FORMULATION AND ASSESSMENT OF MONOLITHIC BETA BLOCKER SUSTAINED RELEASE TABLETS PREPARED BY DIRECT COMPRESSION

A Thesis Submitted to Rhodes University in
Fulfilment of the Requirements for the Degree of

MASTER OF SCIENCE

By

Leith Faye Kieser

December 2002

Faculty of Pharmacy
Rhodes University
Grahamstown
South Africa

ABSTRACT

Beta blockers are commonly prescribed for the chronic treatment of hypertension, one of the most prolific disease states worldwide. The beta blockers selected for this study include acebutolol hydrochloride, labetalol hydrochloride, metoprolol tartrate oxprenolol hydrochloride and propranolol hydrochloride. All of these compounds have a short elimination half-life, necessitating multiple dose per day regimens and therefore the development of sustained release dosage forms incorporating these agents was considered beneficial in terms of extending the dosing interval, with the aim of improving patient compliance and subsequent therapeutic outcomes.

Preformulation studies that were conducted included moisture content analysis by Karl Fischer titration, and DSC, a method used to predict potential interactions between the drugs and tablet excipients.

Tablets were manufactured by both wet granulation and direct compression techniques, and the resultant drug release characteristics were evaluated using the USP Apparatus 3 (BIO-DIS). A validated isocratic HPLC method, capable of separating the five drug candidates simultaneously, was developed and used for the analysis of drug samples. Tablet quality was assessed using analyses that included the physical assessment of weight, diameter, thickness, hardness and friability, as well as content uniformity of tablets, before and after dissolution testing.

Direct compression tablet formulations containing each of the five beta blockers were successfully adapted from a prototype wet granulation matrix tablet containing metoprolol tartrate, and various formulation variables were investigated to establish their effect on the rate and extent of drug release from these tablets. The grade and quantity of ethylcellulose used in the wet granulation and direct compression formulae influenced the release rate of some drug candidates. In addition, an alternative formulation method, involving freeze-drying of the drug with an ethylcellulose dispersion, was shown to have potential for altering release rates further. Anti-frictional agents, talc and colloidal silicon dioxide, did not affect drug release from these matrices, however, they affected the physical characteristics such as tablet weight and thickness, of the resultant tablets. All of the matrix tablets formulated were shown to release drug according to square root of time kinetics, in a sustained manner over a 22 hour period.

ACKNOWLEDGEMENTS

I would like to express my sincere thanks to the following people:

My supervisor, Prof. Roderick. B. Walker, for continual support and guidance throughout this project, and for financial aid in enabling me to complete this work and to attend conferences and courses for the development and improvement of my knowledge and academic exposure.

The Dean and Head of the Faculty of Pharmacy, Prof. I. Kanfer, for the use of departmental facilities.

Mr. Andy Soper, for technical support throughout the duration of this project.

Mr. and Mrs. Morley, for technical and administrative assistance.

Emmanual Lamprecht, for assistance with DSC.

The National Research Foundation and the Joint Research Committee (Rhodes University), for financial support.

The Dow Chemical Company (Michigan, USA) and Colorcon (Kent, UK), for financial support and donation of excipients.

My colleagues, Dr. Bharathi Avula, Mary-Jean Dubber, Tracy Wild, Leila Mansoor, Zaynab Lambat, Fathima Patel and in particular Jessica Arjun, for continued help and support.

My family, whose love and support have encouraged and motivated me, not only in this work, but throughout my life.

STUDY OBJECTIVES

Hypertension is one of the most prolific disease states in the world today, and chronic, life-long drug therapy is often required for the maintenance of acceptable blood pressure levels. Beta blockers are a first line treatment for hypertension, as they reduce cardiac output, thereby lowering elevated blood pressure, without exhibiting serious adverse effects. Propranolol, metoprolol, labetalol, acebutolol and oxprenolol are widely used, not only for hypertension, but also for the treatment of disease states such as angina pectoris, anxiety, thyrotoxicosis, cardiac arrhythmias and essential tremor. The cost effectiveness of propranolol has resulted in its inclusion in the Essential Drugs List (1) in South Africa, and it is the most widely prescribed beta blocker in the public sector in this country. These five beta blockers are relatively short acting, and are generally prescribed in a multiple dose per day regimen, therefore it was felt that inclusion into a sustained release dosage form may be beneficial in terms of increasing patient compliance through once daily dosing, and thereby improving therapeutic outcomes. Furthermore, sustained delivery of beta blockers may decrease the incidence of side effects such as postural hypotension and bradycardia, since the initial peak plasma levels seen with immediate release product dosing would be replaced by a more gradual plasma concentration increase and ultimately a sustained blood level.

The study objectives, based on the desired outcome of producing a viable sustained release dosage form for each of these beta blockers were:

1. To develop and validate an isocratic high performance liquid chromatography (HPLC) system for the simultaneous determination and quantitation of the five beta blockers drug candidates,
2. To incorporate each beta blocker into a wet granulation sustained release matrix tablet, based on a prototype formulation designed for metoprolol tartrate,
3. To convert each of the five wet granulation tablet formulations to a direct compression formula and method of manufacture, capable of releasing the active drug at an equivalent rate and to a similar extent to the wet granulation tablets,

4. To investigate the effects of changing formulation variables of both the wet granulation and the direct compression tablets, and in so doing, to manipulate and control drug release characteristics from these dosage forms,
5. To identify key aspects of the dosage forms for further study.

TABLE OF CONTENTS

ABSTRACT ii

ACKNOWLEDGEMENTS iv

STUDY OBJECTIVES v

LIST OF TABLES xi

LIST OF FIGURES xiii

CHAPTER 1 1
REVIEW OF BETA BLOCKER CANDIDATES 1
1.1. Introduction 1
1.2. Physico-Chemical Properties 3
1.2.1. Chemical Names 3
1.2.2. Structures 4
1.2.3. Stereochemistry 5
1.2.4. Melting Point 5
1.2.5. Optical Activity 6
1.2.6. Infra-Red Spectra 6
1.2.7. Ultraviolet Absorption 9
1.2.8. Solubility and Partition Coefficient 9
1.2.9. pH of solution 10
1.2.10. Dissociation Constant 10
1.2.11. Chemical Stability 11
1.2.12. Compatability 12
1.3. Pharmacokinetics 12
1.3.1. Dose 13
1.3.2. Absorption 14
1.3.3. Bioavailability 14
1.3.4. Distribution 14
1.3.5. Metabolism 16
1.3.6. Elimination 17
1.4. Clinical Pharmacology 18
1.4.1. Mode of Action 18
1.4.2. Indications 19
1.4.3. Contra-Indications 19
1.4.4. High Risk Patient Groups 19
1.4.5. Drug Interactions 21
1.4.6. Side Effects 21
1.4.7. Adverse Drug Reactions 21

CHAPTER 2 23
DEVELOPMENT AND VALIDATION OF AN HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC METHOD FOR THE DETERMINATION OF FIVE BETA BLOCKER CANDIDATES 23
2.1. Introduction 23
2.2. Experimental 24
2.2.1. Reagents 24
2.2.2. Preparation of Stock Solutions 25
2.2.3. Preparation of Buffers 25
2.3. Literature Review 25

2.4. Chromatographic Conditions..... 27
2.5. Method Development..... 29
2.5.1. Introduction..... 29
2.5.2. Mobile Phase Selection..... 30
2.5.2.1. Overview..... 30
2.5.2.2. Effect of Buffer Molarity..... 31
2.5.2.3. Addition of an Ion-Pair Reagent..... 32
2.5.2.4. Effect of Acetonitrile Content..... 34
2.5.2.5. Effect of Buffer pH..... 35
2.5.2.6. Mobile Phase Selection..... 36
2.5.3. Column Selection..... 36
2.5.4. Method of Detection..... 37
2.6. Method Validation..... 39
2.6.1. Introduction..... 39
2.6.2. Linearity..... 40
2.6.3. Precision..... 42
2.6.3.1. Repeatability..... 42
2.6.3.2. Intermediate Precision..... 43
2.6.4. Accuracy..... 44
2.6.5. Limit of Detection and Limit of Quantitation..... 45
2.6.6. Range..... 46
2.6.7. Specificity and Selectivity..... 47
2.6.8. Stability of the Analyte..... 47
2.7. Conclusion..... 50

CHAPTER 3..... 51
DOSAGE FORM ANALYSIS..... 51
3.1. Introduction..... 51
3.2. Moisture content Analysis..... 52
3.2.1. Method..... 52
3.2.2. Results and Discussion..... 53
3.2.3. Conclusion..... 55
3.3. Differential Scanning Calorimetry..... 55
3.3.1. Method..... 56
3.3.2. Results and Discussion..... 56
3.3.3. Conclusion..... 64
3.4. Physical Assessment of Tablets..... 65
3.4.1. Methods..... 65
3.4.2. Results and Discussion..... 66
3.4.2.1. Tablet Diameter, Thickness and Weight..... 66
3.4.2.2. Tablet Hardness and Friability..... 69
3.5. Content Uniformity and Residual Content Assay..... 71
3.5.1. Method..... 71
3.5.2. Results and Discussion..... 72
3.5.3. Conclusion..... 75
3.6. Dissolution Testing..... 76
3.6.1. Preliminary Selection of Dissolution Testing Apparatus..... 76
3.6.1.1. Method..... 77
3.6.1.2. Results and Discussion..... 78
3.6.1.3. Conclusion..... 80
3.6.2. Selected Dissolution Test Conditions..... 80
3.6.3. Sample Treatment..... 80
3.6.4. Statistical Comparison of Dissolution Rate Profiles..... 81

CHAPTER 4..... 84

FORMULATION OF FIVE BETA BLOCKER SUSTAINED RELEASE MATRIX TABLETS BY WET GRANULATION 84
4.1. Sustained Drug Delivery 84
4.1.1. Introduction 84
4.1.2. Oral Sustained Release Dosage Forms 85
4.1.2.1. Matrix Devices 86
4.1.3. Rationale for Sustained Delivery of Beta Blockers 91
4.2. Tablet Manufacture 92
4.2.1. Wet Granulation 92
4.3. Experimental 93
4.3.1. Overview 93
4.3.2. Materials Used 94
4.3.2.1. Drugs 94
4.3.2.2. Excipients 94
4.3.2.2.1. Hydroxypropyl Methylcellulose 94
4.3.2.2.2. Dibasic Calcium Phosphate 95
4.3.2.2.3. Microcrystalline Cellulose 95
4.3.2.2.4. Ethylcellulose 96
4.3.2.2.5. Magnesium Stearate 96
4.3.4. Methods 97
4.3.4.1. Wet Granulation Tablet Formula 97
4.3.4.2. Method of Manufacture 97
4.3.4.3. Effect of Surelease® Load 100
4.4. Results and Discussion 101
4.4.1. Comparison of Dissolution Rates of Drug Candidates 101
4.4.2. Effect of Surelease® Load 102

CHAPTER 5 108
THE DEVELOPMENT AND OPTIMISATION OF FIVE DIRECT COMPRESSION SUSTAINED RELEASE BETA BLOCKER TABLET FORMULATIONS 108
5.1. Introduction 108
5.1.1. Direct Compression Tableting 108
5.2. Experimental 109
5.2.1. Overview 109
5.2.2. Direct Compression Excipients 110
5.2.2.1. Ethocel® 110
5.2.2.2. Purified Talc 110
5.2.2.3. Colloidal Silicon Dioxide 111
5.2.3. Methods 111
5.2.3.1. Direct Compression Formula 111
5.2.3.2. Method of Manufacture 112
5.2.3.3. Formulation Variables Investigated 114
5.2.3.3.1. Anti-Frictional Composition 114
5.2.3.3.2. Ethocel® Grade 114
5.2.3.3.3. Ethocel® Load 115
5.2.3.3.4. Freeze-Dried Method of Manufacture 115
5.3. Results and Discussion 117
5.3.1. Comparison of Release of the Five Drug Candidates 117
5.3.2. Conversion of a Wet Granulation to a Direct Compression Formulation 121
5.3.3. Effect of Anti-Frictional Composition 125
5.3.4. Effect of Ethocel® Grade 130
5.3.5. Effect of Ethocel® Load 137
5.3.6. Effect of Freeze-Drying 140
5.3.7. Mechanism of Release of Beta Blockers from the Sustained

Release Matrix Tablets..... 144

CHAPTER 6..... 151
CONCLUSIONS..... 151

APPENDIX 1 – DSC Thermograms..... 157

APPENDIX 2 – Batch Formulation Records..... 216

APPENDIX 3 – Official Batch Records..... 243

REFERENCES..... 296

LIST OF TABLES

Table 1.1. Melting Points of the Five Selected Beta Blocker Candidates..... 6
Table 1.2. Optical Rotation of the Five Drug Candidates..... 6
Table 1.3. UV Absorption Maxima for the Selected Drug Molecules..... 9
Table 1.4. Solubility and Partition Coefficients of the Five Drug Candidates..... 10
Table 1.5. pH of Solution for Five Beta Blockers..... 10
Table 1.6. Dissociation Constants of the Five Beta Blocker Candidates..... 11
Table 1.7. Recommended Dose for Hypertension, Time to Peak Plasma Concentrations and Bioavailability of Five Beta Blockers..... 13
Table 1.8. Parameters Influencing the Distribution of Five Beta Blockers..... 16
Table 1.9. Elimination Half-lives and Elimination Mechanisms of the Five Beta Blockers..... 17
Table 1.10. Cardioselectivity, Membrane Stabilising Effects and Intrinsic Sympathomimetic Activity of Five Beta Blockers..... 18

Table 2.1. Chromatographic Conditions of HPLC Methods Cited in the Literature..... 26
Table 2.2. Effects of Ion-Pair Reagents (0.01M) on Beta Blocker Retention Time and Peak Resolution..... 33
Table 2.3. Calibration Functions Calculated for Linearity Assessment..... 40
Table 2.4. %RSD Values for Repeatability and Reproducibility Assessment..... 43
Table 2.5. Slope and %RSD Values for an Indication of Precision..... 43
Table 2.6. Recovery Results in the Assessment of Accuracy..... 44
Table 2.7. Results of LOD and LOQ Determination..... 46
Table 2.8. LOQ and ULQ for all Five Beta Blocker Candidates..... 46
Table 2.9. Recovery Values for the Analysis of Tablets Containing the Beta Blocker Candidates..... 47

Table 3.1. Moisture Content of Raw Materials for Matrix Tablet Manufacture..... 54
Table 3.2. Moisture Content of Selected MPT and PROP Powder Blends..... 54
Table 3.3. Summary of DSC Results for Thermal Analysis of ACE Alone and in Combination with Excipients..... 61
Table 3.4. Summary of DSC Results for Thermal Analysis of PROP Alone and in Combination with Excipients..... 61
Table 3.5. Summary of DSC Results for Thermal Analysis of OXP Alone and in Combination with Excipients..... 62
Table 3.6. Summary of DSC Results for Thermal Analysis of LAB Alone and in Combination with Excipients..... 62
Table 3.7. Summary of DSC Results for Thermal Analysis of MPT Alone and in Combination with Excipients..... 63
Table 3.8. Summary of DSC Results for Thermal Analysis of the Excipients Used Alone..... 63
Table 3.9. Mean Tablet Weight, Thickness and Diameter Values for Wet Granulation Batches..... 67
Table 3.10. Mean Tablet Weight, Thickness and Diameter Values for Direct Compression Batches..... 68
Table 3.11. Hardness and Friability Values for all Batches Tested..... 70
Table 3.12. Content Uniformity Assay Results for the Five Beta Blocker Drug Candidates..... 73
Table 3.13. Residual Content After Dissolution for the Five Beta Blocker Drug Candidates..... 74
Table 3.14. Content, Residual Content and Percent Drug Released After 22 Hours Dissolution..... 75
Table 3.15. Dissolution Test Conditions for USP Apparatus 2 and 3..... 77

Table 3.16. f_1 and f_2 Fit Values for Comparison Between the BIO-DIS and the USP Apparatus 2 79
Table 3.17. Dissolution Test Conditions Used for All Tablet Batches 80

Table 4.1. Increased Surelease® Loads for Wet Granulation Formulae (500 g batch size) 100
Table 4.2. Statistical Values for Comparison of Curves for Tablet Batches Containing Different Quantities of Surelease® 104

Table 5.1. Direct Compression Formula with Corresponding Wet Granulation Quantities 112
Table 5.2. Formulae for Glidant Component Selection 114
Table 5.3. Direct Compression Batches Manufactured Using Different Grades of Ethocel® at a 2.8% Load 115
Table 5.4. Formulae for the Assessment of Increased Ethocel® Load 115
Table 5.5. Ethylcellulose (EC) Loads Incorporated into Freeze-Dried Batches. 116
Table 5.6. Formulae for Freeze-Dried Batches 116
Table 5.7. Statistical Values for Comparisons of Wet Granulation and Direct Compression Curves 122
Table 5.8. Statistical Comparison Values for Glidant Component Comparisons. 127
Table 5.9. Physical Properties of Tablets Manufactured using Different Anti-Frictional Components 128
Table 5.10. Uniformity of Tablet Weight for MPT and PROP Batches 129
Table 5.11. Statistical Comparison Values for Ethocel® Grade Comparisons 136
Table 5.12. Statistical Comparison Values for 2.8% and 20% Ethocel® Load Comparisons 137
Table 5.13. Calculated Values for Statistical Comparisons of Batches Manufactured using Freeze-drying and those Manufactured Conventionally 142
Table 5.14. Nominal Values for Drug Release from Selected MPT and PROP Batches 142
Table 5.15. Results for Plot of Cumulative Percent Drug Released versus Time for Selected Batches 145
Table 5.16. Results of Korsmeyer Peppas Calculation 150

LIST OF FIGURES

Figure 1.1. Structures of the five beta blocker candidates, as the free base..... 4
Figure 1.2. Infrared spectra representing each of the five drug molecules as the free base..... 8

Figure 2.1. Representative chromatogram of all five beta blockers using a mobile phase of 0.01M phosphate buffer pH 4 with OSA (0.01M), acetonitrile, methanol (80:36:7)..... 28
Figure 2.2. PROP retention time versus buffer molarity for three different mobile phase compositions..... 32
Figure 2.3. PROP retention time versus concentration of OSA in the aqueous portion of the mobile phase 0.01M phosphate buffer pH 3, acetonitrile and methanol (80:22:7 v/v/v)..... 33
Figure 2.4. PROP retention time versus percentage acetonitrile in the mobile phase 0.01M phosphate buffer pH 3 with OSA 0.01M, acetonitrile and methanol (80:22:7 v/v/v)..... 34
Figure 2.5. PROP retention time versus buffer pH for a mobile phase of 0.01M phosphate buffer with OSA 0.01M, acetonitrile and methanol (80:42:7 v/v/v)..... 35
Figure 2.6. Plots of response : concentration ratio versus concentration for each of the drug candidates..... 41
Figure 2.7. Percent recovery in response (60 µg/ml) for the five beta blocker candidates during storage..... 49
Figure 2.8. Percentage recovery in response (120 µg/ml) for the five beta blocker candidates during storage..... 49

Figure 3.1. Plot of heat flow versus temperature for DSC analysis of ACE..... 58
Figure 3.2. Plot of heat flow versus temperature for DSC analysis of PROP..... 59
Figure 3.3. Plot of heat flow versus temperature for DSC analysis of OXP..... 59
Figure 3.4. Plot of heat flow versus temperature for DSC analysis of LAB..... 60
Figure 3.5. Plot of heat flow versus temperature for DSC analysis of MPT..... 60
Figure 3.6. Dissolution rate profiles of MPT tablet batches manufactured by wet granulation..... 78
Figure 3.7. Dissolution rate profiles of MPT tablet batches manufactured by direct compression..... 79

Figure 4.1. Schematic of drug release from matrix controlled release systems..... 87
Figure 4.2. Schematic diagram of moving fronts during swelling and dissolution of a matrix tablet..... 89
Figure 4.3. Dynamic gel thickness development in a swellable matrix tablet..... 90
Figure 4.4. Schematic diagram of the wet granulation tableting process..... 99
Figure 4.5. Plot of cumulative percent drug released versus time for each of the five beta blockers manufactured by wet granulation..... 101
Figure 4.6. Plot of cumulative percent drug released versus time for MPT batches manufactured using Surelease® loads of 2.5-3.5%, 5% and 10% ethylcellulose solids as a percentage of the final formulation..... 105
Figure 4.7. Plot of cumulative percent drug released versus time for OXP batches manufactured using Surelease® loads of 2.5-3.5%, 5% and 10% ethylcellulose solids as a percentage of the final formulation..... 105
Figure 4.8. Plot of cumulative percent drug released versus time for ACE batches manufactured using Surelease® loads of 2.5-3.5%, 5% and 10% ethylcellulose solids as a percentage of the final formulation..... 106

Figure 4.9. Plot of cumulative percent drug released versus time for PROP batches manufactured using Surelease® loads of 2.5-3.5%, 5% and 10% ethylcellulose solids as a percentage of the final formulation..... 106
Figure 4.10. Plot of cumulative percent drug released versus time for LAB batches manufactured using Surelease® loads of 2.5-3.5%, 5% and 10% ethylcellulose solids as a percentage of the final formulation..... 107

Figure 5.1. Schematic diagram showing the direct compression tabletting process..... 113
Figure 5.2. Plot of cumulative percent drug released versus time for each beta blocker, manufactured by direct compression using Ethocel® FP10 in the formula..... 119
Figure 5.3. Plot of cumulative percent drug released versus time for each beta blocker, manufactured by direct compression using Ethocel® FP100 in the formula..... 119
Figure 5.4. Plot of cumulative percent drug released versus time for each beta blocker, manufactured by direct compression using Ethocel® Std 10 in the formula..... 120
Figure 5.5. Plot of cumulative percent drug released versus time for each beta blocker, manufactured by wet granulation..... 120
Figure 5.6. Plot of cumulative percent drug released versus time for MPT batches manufactured by wet granulation and direct compression..... 122
Figure 5.7. Plot of cumulative percent drug released versus time for PROP batches manufactured by wet granulation and direct compression..... 123
Figure 5.8. Plot of cumulative percent drug released versus time for ACE batches manufactured by wet granulation and direct compression..... 123
Figure 5.9. Plot of cumulative percent drug released versus time for OXP batches manufactured by wet granulation and direct compression..... 124
Figure 5.10. Plot of cumulative percent drug released versus time for LAB batches manufactured by wet granulation and direct compression..... 124
Figure 5.11. Plot of cumulative percent drug released versus time for MPT batches manufactured with different anti-frictional agent combinations..... 126
Figure 5.12. Plot of cumulative percent drug released versus time for PROP batches manufactured with different anti-frictional agent combinations..... 126
Figure 5.13. Relationship between percent purified talc and mean tablet weight for MPT and PROP formulations..... 128
Figure 5.14. Plot of cumulative percent drug released versus time for MPT batches manufactured with different grades of Ethocel®..... 132
Figure 5.15. Plot of cumulative percent drug released versus time for PROP batches manufactured with different grades of Ethocel®..... 132
Figure 5.16. Plot of cumulative percent drug released versus time for ACE batches manufactured with different grades of Ethocel®..... 133
Figure 5.17. Plot of cumulative percent drug released versus time for LAB batches manufactured with different grades of Ethocel®..... 134
Figure 5.18. Plot of cumulative percent drug released versus time for OXP batches manufactured with different grades of Ethocel®..... 135
Figure 5.19. Plot of cumulative percent drug released versus time for PROP batches manufactured with two different grades and two different loads of Ethocel®..... 139
Figure 5.20. Plot of cumulative percent drug released versus time for MPT batches manufactured with two different grades and two different loads of Ethocel®..... 139
Figure 5.21. Dissolution rate profiles of freeze-dried MPT batches and other MPT batches for comparison..... 143

Figure 5.22. Dissolution rate profiles of freeze-dried PROP batches and other PROP batches for comparison..... 143
Figure 5.23. Photograph of three MPT tablets after various dissolution times..... 146
Figure 5.24. Plots of cumulative percent drug released versus time for selected wet granulation batches..... 146
Figure 5.25. Plots of cumulative percent drug released versus time for selected direct compression batches..... 147

CHAPTER ONE
REVIEW OF BETA BLOCKER DRUG CANDIDATES

1.1. INTRODUCTION

Five beta-adrenergic antagonists, or beta blockers, were selected for inclusion into a sustained release matrix tablet formulation, to create five formulations, each with a different active principle, and all capable of releasing the active in a sustained manner. The matrix tablet formulation, manufactured by direct compression, was adapted from a prototype wet granulation formulation containing metoprolol tartrate as the active. Selection of the four other drug candidates was based on various physico-chemical properties, as well as clinical treatment guidelines. The candidates selected were acebutolol hydrochloride (ACE), labetalol hydrochloride (LAB), metoprolol tartrate (MPT), oxprenolol hydrochloride (OXP) and propranolol hydrochloride (PROP). The given abbreviations are used for each listed beta blocker salt, however, the drug name itself is used when referring to the free base molecule.

Drug molecules that exhibit rapid elimination kinetics, and hence short plasma half-lives, lend themselves to sustained delivery, since the sustained therapeutic effect is then a function of the dosage form rather than the drug molecule and can be manipulated by formulation adjustment. To achieve prolonged therapeutic benefits of short acting drugs, inclusion into sustained release dosages form is a favourable alternative to repeated dosing. A physico-chemical characteristic common to all drug candidates for this sustained release matrix tablet formulation, including MPT, was a short elimination half-life, such as those reported in Table 1.9.

A second consideration was the solubility of each drug candidate. Molecules with a high water solubility afford challenges with respect to sustained drug delivery, and all of the drug candidates are, at least, freely soluble in water, as depicted in Table 1.4, with the active in the prototype formulation, MPT, having a solubility greater than 1000:1 in

water. A range of drugs with slightly different solubilities were selected for comparative purposes.

In addition, the usual prescribed dose of each drug candidate was considered, with the selected candidates being those in the dosing range of approximately 100-200 mg daily, shown in Table 1.7. Once again, selection was based on the most commonly prescribed dose of MPT, for the maintenance treatment of hypertension, of 100-200 mg per day (2, 3, 4, 5). The driving force created within the tablet matrix for drug delivery is due to the osmotic effects of the drug and the concentration gradient established between the tablet matrix and the dissolution medium, each of which may be affected by the dose of the active incorporated. It was for this reason that all drugs selected have similar dosing regimens and that the dose per tablet was kept constant throughout the study. All drug candidates selected for this study are orally administered and well absorbed from the gastro-intestinal tract (GIT).

1.2. PHYSICO-CHEMICAL PROPERTIES

1.2.1. Chemical Names

Each drug candidate may be given by the following chemical names:

Acebutolol hydrochloride:

- Butanamide, *N*-[3-acetyl-4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]-, monohydrochloride, (±)-.
- (±)-3'-Acetyl-4'-[2-hydroxy-3-(isopropylamino)propoxy]—butyranilide monohydrochloride.

Labetalol hydrochloride:

- Benzamide, 2-hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]-, monohydrochloride.
- 5-[1-Hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]-salicylamide monohydrochloride.

Metoprolol tartrate:

- 2-Propanol, 1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-, (±)-, [R-(R*,R*)]-2,3-dihydroxybutanedioate (2:1) (salt)
- (±)-1-(Isopropylamino)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanol L-(+)-tartrate (2:1) (salt)
- 1-(Isopropylamino)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanol (2:1) *dextro*-tartrate salt.

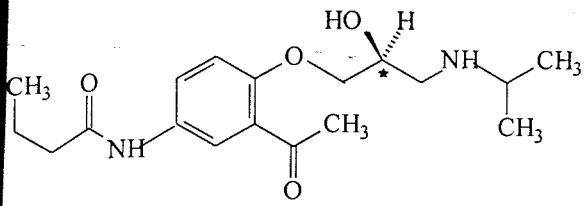
Oxprenolol hydrochloride:

- 2-Propanol, 1-(*o*-allyloxyphenoxy)-3-isopropylamino-, hydrochloride.
- 1-(*o*-allyloxyphenoxy)-3-isopropylamino-2-propanol hydrochloride.

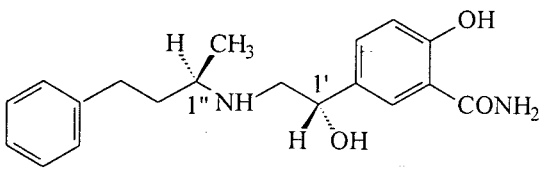
Propranolol hydrochloride:

- 2-Propanol, 1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-, hydrochloride, (±)-.
- (±)-1-(Isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride.

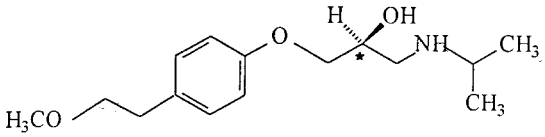
1.2.2. Structures



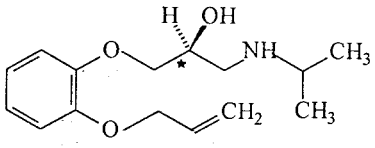
Acebutolol (S-enantiomer)
$C_{18}H_{28}N_2O_4$ MM 336.44



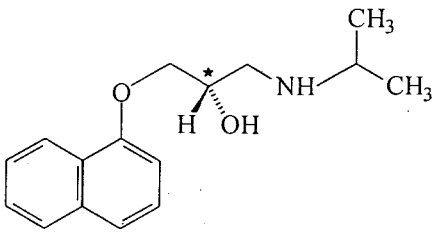
Labetalol (1′ R, 1″ R-isomer)
$C_{19}H_{24}N_2O_3$ MM 328.42



Metoprolol (S-enantiomer)
$C_{15}H_{25}NO_3$ MM 684.82)



Oxprenolol (S-enantiomer)
$C_{15}H_{23}NO_3$ MM 271.73



Propranolol (S-enantiomer)
$C_{16}H_{21}NO_2$ MM 259.36

Figure 1.1: Structures of the five beta blocker candidates, as the free base.

The structures of the five drug candidates, as depicted in Figure 1.1, are related to one another, and are all made up of an aromatic group with one or more side chains. Each compound contains one asymmetric carbon atom, situated on the side chain at the positions depicted by * or the numerals 1′and 1″.

1.2.3. Stereochemistry

The presence of at least one asymmetric carbon atom in each of the molecules of interest, results in the existence of stereoisomers. In acebutolol, metoprolol, oxprenolol and propranolol, one asymmetric center gives rise to two enantiomers, one of which, the S-entantiomer, exhibits the beta-antagonistic effect (6, 7, 8). For example, the S-enantiomer of propranolol is 60 to 100 times more potent in its beta blocking activity than the R-enantiomer (9). For acebutolol, the stereospecificity results in the pharmacologically active S-enantiomer undergoing hepatic first pass metabolism to a lesser degree than the R-enantiomer (6, 8), therefore increasing the therapeutic effect of a given dose, since acebutolol is administered as a racaemic mixture, as are the other drug candidates (10).

Labetalol has two asymmetric centers resulting in the existence of four stereoisomers (11, 12), two of which act at adrenoreceptor sites (12, 13). The SS- and RS-isomers are inactive while the RR-isomer mediates $beta_1$-receptor blockade and possible $beta_2$-agonistic activity, and the SR-isomer is responsible for $alpha_1$-blockade (2, 12). Labetalol is administered as a mixture of the four isomers, in approximately equal proportions (12).

1.2.4. Melting Point

The melting range of each drug candidate is above 100°C, and all are presented in Table 1.1. It is important that the crystalline state of the drugs remains intact during the manufacturing process, which may involve heat due to friction and high compaction pressures.

Table 1.1: Melting Points of the Five Selected Beta Blocker Candidates

Drug	Melting Point Range	Reference
ACE	141 - 144°C	14, 15, 16, 17
LAB	187 - 189°C	15
MPT	120 - 124°C	18, 19, 17
OXP	107 - 109°C	15, 19, 17
PROP	162 - 166°C	19, 20, 16, 15, 17

1.2.5. Optical Activity

The presence of asymmetric centres in each of these molecules, as well as the absence of a plane of symmetry, imparts optical activity to varying degrees. The angle of optical rotation of three of the drug molecules are presented in Table 1.2. Values for ACE and OXP were not found in the literature.

Table 1.2: Optical Rotation of the Three Drug Candidates

Drug	Optical Rotation	Reference
LAB	+0.05° - -0.05°	19
MPT	+6.5° - +10.5°	16
PROP	-1.0° - +1.0°	16

There are two asymmetric carbons in the tartaric acid portion of MPT, and *dextro*-tartaric acid, the isomer used to synthesize metoprolol tartrate, is optically active, therefore this drug candidate's optical activity is a function of both the free base and the salt portion of the molecule (18).

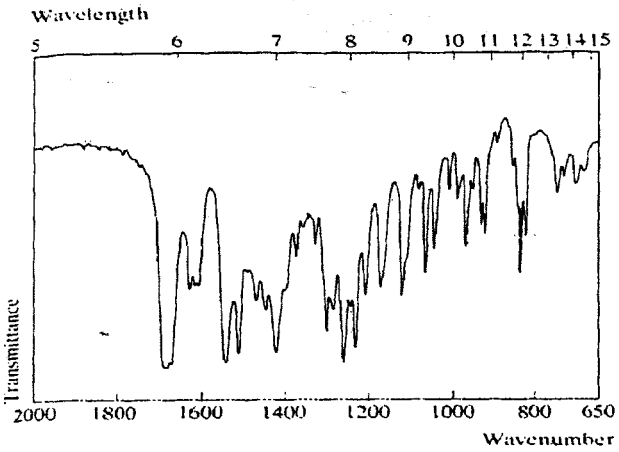
1.2.6. Infra-Red Spectra

The infrared spectra representing the five drug molecules have similar features, which correspond to common structural arrangements. The spectrum for each structure in Figure 1.1, is shown in Figure 1.2.

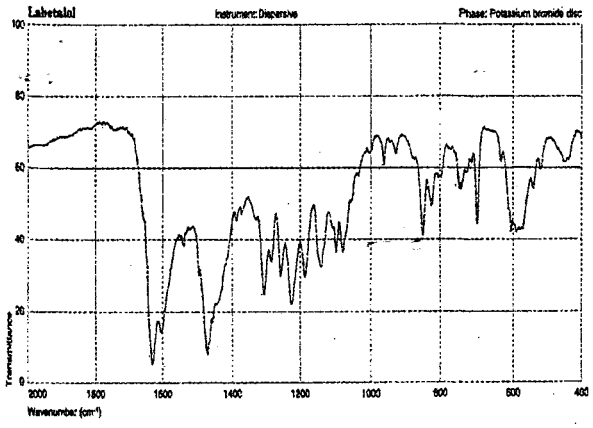
Functional groups such as amine, hydroxyl and methyl substituents are present in these molecules, however, their spectral assignments occur between 3600 and 2300 cm^{-1} (18), and are therefore not represented. All of the drug candidates have an aromatic ring, represented by a peak in the region of 1600 cm^{-1}, as well as a secondary alcohol,

producing a peak at approximately 1100 cm^{-1}. Other substituents that produce peaks in these areas are carboxylic acid salts and aliphatic ethers, at 1600 cm^{-1} and 1100 cm^{-1}, respectively, however not all of the drug candidates contain these groups.

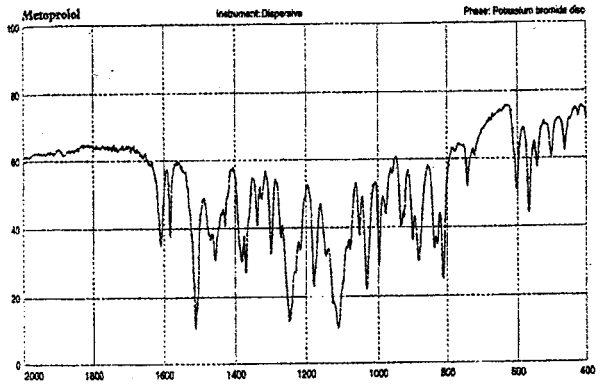
Of the five drug molecules, all except labetalol produce peaks at 1200 cm^{-1} and 1250 cm^{-1}, indicating the presence of an isopropyl group and an aromatic ether, respectively. The 1,4-disubstituted benzene ring, common to acebutolol, metoprolol and labetalol, is represented in each respective infrared spectrum by the peak around 800 cm^{-1}.



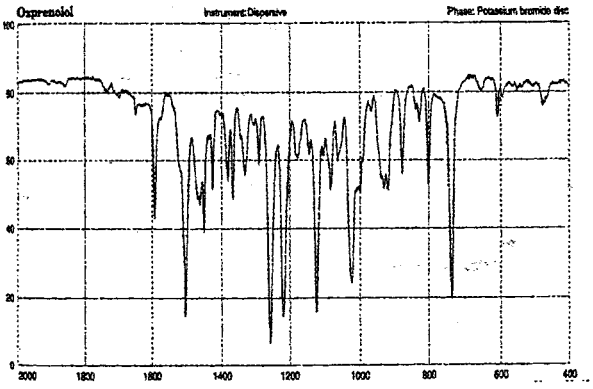
Acebutolol



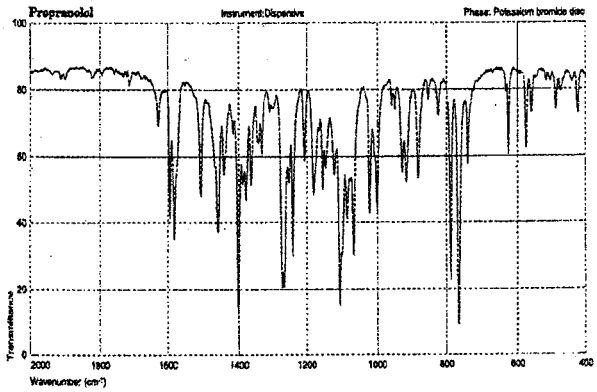
Labetalol



Metoprolol



Oxprenolol



Propranolol

Figure 1.2: Infrared spectra representing each of the five drug molecules as the free base (19, 21).

1.2.7. Ultraviolet Absorption

Acebutolol appears to have two absorption maxima, of approximately 240 and 328 nm as reported in Table 1.3, while all the other beta blockers have one absorption maximum, which falls between 200 and 350 nm. Molar absorptivities at the wavelengths shown are not included, since such values are dependent not only on the absorption capacity of the analyte, but also on the temperature and the solvent system used (22).

Table 1.3: UV Absorption Maxima for the Selected Drug Molecules

Drug	λ_{max} (nm)	Reference
ACE	234 and 320	14, 23
LAB	302	19
MPT	223	15
OXP	272	23, 24
PROP	288	23

1.2.8. Solubility and Partition Coefficient

All drug candidates have a high degree of aqueous solubility, with the least hydrophilic drug, LAB, classified as being 'soluble' in water (19). The high solubility is primarily due to the hydrochloride salt moiety, or the tartrate salt in the case of metoprolol. These salts have relatively high oil-water partition coefficients and therefore also show some degree of lipid solubility (25), although this varies (10, 26). The lipophilicity of these compounds is an important factor and may promote absorption throughout the small and large intestine (3, 10, 27, 28, 29). A correlation between the oil-water partition coefficients and the relative lipophilicity is evident in Table 1.4, with ACE, which has the lowest reported lipophilicity, exhibiting the lowest preference for oil to water partitioning.

Table 1.4: Solubility and Partition Coefficients of the Five Drug Candidates

Drug	Aqueous Solubility (mg/ml water)	Relative Lipid Solubility of the Free Base [10]	Oil / water Partition Coefficient	
			α [30]	β [26]
ACE	200 [14, 15]	Low	59.0	0.17
LAB	17 [3]	Moderate-high	-	4.6
MPT	>1000 [27]	Moderate	76.0	0.15
OXP	Very soluble [19, 27]	Moderate	235.0	0.51
PROP	50 [35]	High	1640	5.4

α Sorensen's phosphate buffer (pH 7.38) and octanol, at 35°C (30).
β *n*-octanol/buffer pH 7.0, at 20°C (26).
Superscripted values refer to literature sources cited.

1.2.9. pH of Solution

The pH value of a solution containing each of these compounds individually, falls within the slightly acidic range of 4.0 - 7.0, as indicated in Table 1.5.

Table 1.5: pH of Solution for Five Beta Blockers

Drug Candidate	Solution Strength (w/v)	pH	Reference
ACE	1%	4.5 - 7.0	16
LAB	1%	4.0 - 5.0	3, 19
MPT	10%	6.0 - 7.0	3, 19, 27
OXP	5%	4.0 - 6.0	3, 16, 19
PROP	1%	5.0 - 6.0	3

1.2.10. Dissociation Constant

The beta blockers in this study are all weak bases with most having pKa values in the region of 9.5 (see Table 1.6) Consequently, they are likely to be highly ionized in the acidic contents of the stomach and the more neutral small intestine (10), but largely unionised in the more alkaline environment of the colon, in particular, the descending colon, in which the pH of the contents may be greater than 7 (31). It is possible that it is in this region that the dosage form can reside for the majority of its transit through the GIT.

Table 1.6: Dissociation Constants of the Five Beta Blocker Candidates

Drug	pKa	Reference
ACE	9.7	10, 23
LAB	7.4	10
MPT	9.7	10, 23
OXP	9.5	10, 23, 32
PROP	9.45	10, 23, 33

1.2.11. Chemical Stability

In general, beta blocking agents are suitable substrates for oxidative degradation (34). In an aqueous environment, the isopropylamine side chain of propranolol undergoes oxidation and a discoloration of the solution is seen, with a reduction in pH (3, 27, 35). The presence of this side-chain in metoprolol, acebutolol and oxprenolol makes these molecules equally susceptible to oxidation.

All five compounds undergo photodegradation (3, 16, 19, 27, 36), and it has been reported that their oxidative degradation is accelerated by irradiation (34). These compounds must therefore be stored protected from light, in well-sealed, airtight containers, and their stability is greatly improved if maintained at 5°C (3, 16, 19, 27, 36).

In the solid state, MPT can be stored at room temperature or at 35°C for five years without chemical degradation, and at 50°C for up to thirty months with no detectable degradation, despite a slight change in colour (18).

Solution stability is defined as the retention of not less than 90% of the original drug concentration (37), hence the time taken to reach this concentration can be considered the shelf-life. Both LAB and PROP show maximum stability in solutions of pH 3.0-4.0 (3, 27, 35, 38), while MPT in solutions buffered to pH 4.0, 7.0 or 9.0 display optimum stability (37). An aqueous OXP solution is reported to have a degradation half-life of 46 weeks and a shelf-life of 48 days when stored at room temperature (39).

1.2.12. Compatibility

Literature sources cite the use of differential scanning calorimetry (DSC) to expose various incompatibilities between beta blockers and tablet excipients (40, 41, 42). Both OXP and PROP were found to be compatible with starch, Sta-Rx 1500®, Avicel PH 101®, Elcema G250® and Ac-Di-Sol®. In addition to these, OXP was compatible with Sterotex® and cross-linked PVP. Interactions were reported for both drugs with Primojel®, lactose, Emcompress®, stearic acid and magnesium stearate (40, 41, 42). OXP was also found to interact with Explotab®, PVP and Precirol Ato 5® (40, 41) and PROP with calcium phosphate monohydrate and Avicel® (42). A DSC study carried out on MPT indicated potential incompatibilities with dibasic calcium phosphate and magnesium stearate, however, no interactions were reported with microcrystalline cellulose or hydroxypropylmethyl cellulose (43).

The implications of the reported incompatibilities, in terms of pharmaceutical formulation, are not known, however, no literary source suggested that any such interactions would impact on tablet behaviour or manufacture.

A DSC study was performed in our laboratory to expose any incompatibilities between the drug candidates and the tablet excipients used in this study, and to confirm those that have already been reported. This is presented in Chapter 3.

1.3. PHARMACOKINETICS

Pharmacokinetics is a discipline involving the study of the time course of drug absorption, distribution, metabolism and excretion, and it considers the relationship of each of these to the magnitude and time course of a therapeutic effect (34). It is generally accepted that the therapeutic effect is proportional to the amount of drug at the site of action, and there is a definite relationship between pharmacologic effects and pharmacokinetics (34), therefore blood plasma levels are commonly used as therapeutic indicators.

1.3.1. Dose

Dosing of beta blockers is adjusted according to the pharmacological response and therapeutic benefit experienced by individual patients (3). The recommended dosing requirements for each drug are therefore considered as guidelines. Once daily dosing is adequate for antihypertensive therapy, although most recommendations include a twice daily administration regimen (2, 4, 5, 44, 45). Recommended doses for maintenance treatment of hypertension using these five beta blockers are presented in Table 1.7. The normal dosing range is approximately 100 – 200 mg per day, however, doses of 400 – 800 mg per day have been prescribed (13).

Dosing regimens vary for other disease states such as angina pectoris, anxiety states, thyrotoxicosis and cardiac arrythmias, and for different drug candidates (3, 4, 5, 27) and these agents may be dosed intravenously for conditions such as acute myocardial infarction and hypertensive crisis (4, 27).

Metabolic anomalies may necessitate alteration of dose levels, for example, patients with liver disease may require a reduction of the usual dose, since all five drug candidates undergo extensive hepatic metabolism (3, 27). In addition, particular racial populations have been shown to respond favourably to unusual labetalol dosing regimens (13).

Table 1.7: Recommended Dose for Hypertension, Time to Peak Plasma Concentrations and Bioavailability of Five Beta Bockers

Drug	Dose (mg/day)	Time to Peak (t_{max}) (hours)	Bioavailability (F) (%)
ACE	200-400 [3, 2, 5]	2 [3, 8]	60 [2, 3, 10]
LAB	200 [3]	1-2 [3, 46, 47]	30 [2, 10] 33 [13, 47]
MPT	100-200 [2, 3, 4, 5]	1.5-2 [3, 27]	50 [2, 10]
OXP	160-320 [3, 4]	1-2 [3, 27]	25-60 [10]
PROP	160-320 [3, 2, 4, 5]	2 [3]	30 [2, 10]

1.3.2. Absorption

The relatively high lipophilicity of these compounds ensures rapid and near complete absorption from the GIT, hence the oral route of administration is most often used for therapy (3, 10, 27, 28, 29). Peak plasma levels are obtained within 3 hours following oral dosing (3, 10), as shown in Table 1.7.

1.3.3. Bioavailability

All five beta blockers are rapidly and almost completely absorbed from the GIT, however, their systemic bioavailability is reduced by hepatic first pass metabolism (2, 3, 10, 27). Pre-systemic elimination of these compounds is a function of their lipophilicity (26), consequently acebutolol, being the least lipophilic compound, is affected to the smallest extent, having a bioavailability of up to 60% (8, 10). The bioavailability of labetalol is substantially lower, at approximately 30% (2), as is the bioavailability value reported for propranolol (2, 10), which has been found to be dose dependant (2), through saturation of hepatic enzyme binding sites (48). The bioavailabilities of metoprolol and oxprenolol are slightly higher, at 50% (2, 3, 10) and 25-60% (10) respectively, and all values are listed in Table 1.7. Variations in reported bioavailability values may be due to concurrent intake of food (11, 49, 50, 51), differences in hepatocellular function or changes in liver blood flow (50), since these beta blockers are high extraction ratio drugs, and thus display flow-dependent kinetics (47).

1.3.4. Distribution

The tissue distribution of all five candidates is typical of moderately lipophilic, basic compounds. Following oral absorption they are rapidly and extensively distributed throughout the body (18, 28). Their lipophilic nature enables ease of distribution across the blood-brain barrier and into the breast milk (2, 3, 10, 26, 27), although this occurs to a lesser degree for acebutolol and labetalol, when compared with metoprolol, propranolol and oxprenolol (10). These differences are more than likely a function of lipophilicity (3,

10, 27, 47). Although all five compounds cross the placental barrier, this is apparently not only a function of their lipophilic character (10).

The apparent volume of distribution for each beta blocker is presented in Table 1.8. The relationship between volume of distribution and plasma protein binding is evident, in that a lower degree of plasma protein binding allows for increased distribution of free drug beyond the systemic circulation, resulting in an increased apparent volume of distribution. High volume of distribution values indicate a large degree of binding at extravascular sites (10).

The weakly basic nature of these drugs facilitates binding to alpha$_1$-acid glycoproteins, albumin and lipoproteins in blood plasma (10, 26). The degree of such plasma protein binding varies greatly with changes in the blood composition and, more specifically, in the range and concentration of plasma proteins present. This phenomenon is evident in the variety of estimated protein binding values for acebutolol, such as 11-20% (14, 10), 50% (3), and 84% (32). Values reported for propranolol are more consistent, with a consensus of greater than 90% (3, 10, 32, 52), as are those for labetalol, of 50% (3, 10, 32,). The lack of agreement of acebutolol values suggests that this drug is in fact, not as highly bound as 84%, when determined in healthy volunteers. Reported values for metoprolol binding are approximately 12% (3, 10, 32), and those for oxprenolol are greater than 80% (10, 27). These values are summarised in Table 1.8.

As the degree of plasma protein binding has an impact on the potential for dialysis of these compounds, this factor has also been incorporated into Table 1.8.

Table 1.8: Parameters Influencing the Distribution of Five Beta Blockers

Drug	Volume of Distribution (L/kg)	Plasma Protein Binding*	Dialysibility
Acebutolol	1.0-1.2 [10, 14]	11-19 [14] 50 [3] 84 [32]	Good
Labetalol	5.6 [10] 9 [47]	50 [3, 4, 11, 32, 47]	None
Metoprolol	5.6 [18] 5.5 [10]	13 [32] 12-14 [3] 8 [10]	Good
Oxprenolol	1.3 [10]	80 [27] 92 [10]	Not significant
Propranolol	4 [4] 2.8-5.5 [10]	>90 [3, 32, 52]	Not significant

*plasma protein binding expressed as the percent of administered drug that is bound to proteins

1.3.5. Metabolism

Propranolol is primarily metabolised in the liver (2, 53) to form at least eighteen metabolites (54). At least four of these metabolites show biological activity (54), although the full extent of their pharmacological contribution has not yet been verified (27, 53). Metoprolol undergoes extensive biotransformation (18, 28), with only 3% of the administered dose being excreted unchanged via the kidneys (10, 18). Similarly, labetalol, oxprenolol and acebutolol are hepatically converted to a large extent (3). Compounds with a high extraction ratio, such as propranolol and labetalol, are significantly affected, in terms of the rate and extent of metabolism, by factors such as hepatic disease, smoking and compounds that alter hepatic enzyme activity (10,11, 47, 55). The decrease in hepatocellular functioning and plasma protein binding, and the change in hepatic blood flow associated with liver disease contribute to a reduction in hepatic clearance, however, it has been reported that no change in acebutolol clearance was observed in patients with liver disease (56).

Reported metabolic pathways of these agents, include hydrolysis (8, 10), acetylation (8, 10), oxidation (3, 10, 27, 49), N- and O-dealkylation (3, 27, 57), aliphatic and aromatic hydroxylation (3, 27, 57) and O-glucuronidation (57). The only metabolites of known

pharmacological activity are diacetalol, from the oxidation and acetylation of labetalol (8, 10, 56), and 4-hydroxypropranolol from propranolol (4). Like all beta blocker metabolites, these active compounds are excreted renally, hence care must be taken when dosing patients, not only with hepatic disease, but with impaired kidney function as well.

1.3.6. Elimination

All the beta blockers of interest are relatively short acting, with elimination half-lives ($t_{1/2}$) ranging from 1 to 8 hours. The $t_{1/2}$ values are summarised in Table 1.9. A small percentage of the parent compounds and all metabolites are excreted in the urine (10, 27), although acebutolol, due to its lower lipid solubility, exhibits renal clearance to a greater extent than the other candidates (10). Elimination of some beta blockers is complicated by genetic polymorphism, in particular due to fast and slow hydroxylators (3, 10), however, the elimination half-lives of the drug candidates appear to be unaffected by age (10).

Table 1.9: Elimination Half-lives and Elimination Mechanisms of the Five Beta Blockers

Drug Candidate	Elimination Half-life ($t_{1/2}$) (hours)	Degree of Hepatic Metabolism [10]
Acebutolol	3-4 [2, 3, 4]	60%
Labetalol	5 [2, 3] 8 [13, 47]	90%
Metoprolol	3-4 [2, 28] 3-7 [18]	90%
Oxprenolol	1-3 [3, 27] 2-4 [26, 53]	90%
Propranolol	3.5-6 [2, 3, 4]	90%

1.4. CLINICAL PHARMACOLOGY

Oxprenolol, labetalol and acebutolol exhibit intrinsic sympathomimetic activity in addition to membrane stabilising activity (negative inotropic effects) by modification of the cell membrane, causing quinidine-like effects (53) such as non-specific cardiac depression and a decline in myocardial conduction velocity, as well as local anaesthesia (53, 58). Metoprolol lacks both of these activities, while propranolol shows only membrane stabilising activity, with no evidence of any intrinsic sympathomimetic action (2, 27, 53).

Metoprolol exhibits the highest degree of cardioselectivity of these compounds, having an affinity for the $beta_1$-receptors of the heart, with acebutolol showing some selectivity between $beta_1$- and $beta_2$-receptors, and propranolol, labetalol and oxprenolol being completely non-selective (2). A summary of these properties, as well as the previously discussed drug activities, is presented in Table 1.10.

Table 1.10: Cardioselectivity, Membrane Stabilising Effects and Intrinsic Sympathomimetic Activity of Five Beta Blockers (4, 2, 3, 53)

Drug Candidate	Intrinsic Sympathomimetic Activity	Membrane Stabilising Effects	Cardioselectivity
Acebutolol	+	+	+
Labetalol	0 / -	0	0
Metoprolol	0 / -	0	+
Oxprenolol	+	+	0
Propranolol	0 / -	++	0

+ = positive effect, - = negative effect and 0 = zero effect.

1.4.1. Mode of Action

Beta blockers exert their effect by competitive antagonism of the $beta_1$-receptors, which are most prolific in the muscle tissue of the heart (2, 3), thereby inhibiting the effects of endogenous catecholamines acting at these sites. Inhibition of these catecholamines results in a decrease in heart rate and cardiac output (52). In addition, by virtue of their $beta_1$-receptor blocking effect, these agents also inhibit renin production (2) causing inhibition of angiotensin II, a potent pressor agent through contraction of vascular smooth

muscle and stimulation of release of epinephrine and nor-epinephrine (2). Since the selectivity of these drugs for the $beta_1$-receptors varies, some antagonism at $beta_2$-receptors may be observed at therapeutic doses.

1.4.2. Indications

In general, beta blockers are used in the treatment of conditions that are characterized by excessive sympathetic nervous activity, such as hypertension, angina pectoris and cardiac arrhythmias (3, 4, 5, 27, 47, 52, 59, 60). They are also prescribed orally, for the initial, and long-term management of myocardial infarctions (3, 5, 47, 60), as well as in alcohol withdrawal (3), anxiety states (3, 4, 5, 27), migraine prophylaxis (4, 3), hyperthyroidism (3, 4, 5) and essential tremor (3, 4). Topically, they may be used for ocular hypertension and chronic open-angle glaucoma (3, 5, 10, 27, 47, 61).

1.4.3. Contra-Indications

As is the case with any medication, a known hypersensitivity to these beta blockers is an absolute contra-indication. In addition, contra-indications include atrioventricular block, heart failure, severe bradycardia (less than 50 beats per minute), sick-sinus syndrome, cardiogenic shock, moderate to severe heart failure, a systolic blood pressure of less than 100 mmHg and myocardial infarct patients with a heart rate of less than 45 beats per minute (3, 4, 45).

1.4.4. High Risk Patient Groups

As some beta blockers are non-selective and cardioselectivity is frequently dose-dependent, antagonism of $beta_2$-receptors, located in the lung, is often seen during beta blocker therapy, as mentioned previously. Beta blockers must therefore be used with caution in patients with asthma, bronchitis and chronic respiratory disease, due to the tendency of these agents to cause bronchial constriction, and subsequent airway

resistance (2, 3, 5, 45, 52). Metoprolol is an exception, as it is the most cardioselective of all beta blockers (3, 28).

Caution with beta blocker therapy is also advised in patients with Raynaud's syndrome and peripheral vascular disease, due to the hypotensive effects of these drugs (4, 45).

Beta blockers affect carbohydrate metabolism (2, 52), although the mechanism is not entirely clear and this is known to impair recovery from hypoglycaemia. In addition, they mask the symptoms of hypoglycaemia such as peripheral tremor, therefore these agents must be used with therapeutic monitoring in patients suffering from type 1 diabetes mellitus (2, 5, 45).

As these drugs are primarily metabolised in the liver, caution must be exercised when prescribing for patients with hepatic impairment. In such cases doses should be reduced (27), although a study conducted by Zaman et al (56) suggests that the pharmacokinetics of acebutolol are not significantly affected by liver disease. Elderly patients have been shown to exhibit reduced liver blood flow and a reduction in functional hepatic cells, and therefore have a slower clearance rate of beta blockers (47). This effect however, is not deemed to be clinically significant (47) although caution in these populations is suggested.

Similarly, patients with renal impairment may exhibit reduced hepatic enzyme activity due to uraemia, and since some renally cleared metabolites exhibit therapeutic activity, doses may need to be reduced (10).

Although these drugs have the potential to cross the placenta, they are acceptable for use during pregnancy (4, 47, 62).

1.4.5. Drug Interactions

Drug interactions of a pharmacodynamic and a pharmacokinetic nature have been reported (3, 10, 32, 55), although the latter is deemed to be of less clinical importance due to the reportedly weak *in vitro / in vivo* correlation (IV/IVC) between average population plasma concentrations and therapeutic outcomes (3).

Pharmacodynamic interactions arise either from the modification of the beta blocking effect, or from increased toxic effects of the selected drugs (3). Cimetidine and other enzyme inhibitors impair the hepatic metabolism of various beta blockers and therefore increase plasma concentrations (3, 55), whereas compounds such as rifampicin, an enzyme inducer, will lower plasma levels by inducing enzymatic breakdown of these agents (3). Calcium channel blockers, such as verapamil and diltiazem, through antihypertensive effects of their own, may potentiate the beta blocking effects, resulting in suppression of heart rate, A-V conduction and myocardial contractility (5).

1.4.6. Side Effects

The most commonly encountered adverse effects of beta blockers are postural hypotension (4), bronchospasm (4, 5), fatigue (3, 4, 5), headache (45), dizziness (4, 45), vertigo (45), coldness of the extremities (45), sleep disturbances (4) and bradycardia (4, 3). Nausea, vomiting and gastralgia have also been observed (4, 45). Such reactions are more commonly associated with intravenous dosing, than with oral therapy, however, these have also been reported with ocular dosing (2, 3, 63).

1.4.7. Adverse Drug Reactions

Serious adverse effects associated with these agents are generally related to their beta antagonistic effect, and hence involve the cardiovascular and respiratory system (2, 3). Examples of these reactions may include heart failure, heart block and bronchospasm (2, 3, 4), and are most prevalent in patients with underlying cardiac disorders (2, 3).

Other undesirable reactions may include central nervous system effects, particularly with highly lipophilic compounds (2, 26), and include depression, hallucinations, confusion and sleep disturbances (3, 45). Further reactions may include pulmonary disease (3, 45), gastro-intestinal disturbances, dermatological conditions (3, 45, 64, 65, 66, 67), ocular symptoms (3, 45), urogenital disturbances (45, 67), haematological reactions (43, 5), metabolic changes (3, 45), and a possible association with auto-antibody production (65).

Overdose with beta blockers may cause coma and convulsions (3). Isoprenaline has been proven effective against bradycardia and hypotension associated with overdosing of acebutolol (10).

Abrupt withdrawal of these agents may precipitate attacks of angina, and can lead to sudden death. This occurs most frequently in patients with ischaemic heart disease, possibly due to up-regulation of beta-receptors (2, 3, 5). Following withdrawal, rebound hypertension and overshoot hypertension may occur (3), thus tapering of doses or controlled withdrawal is recommended (2).

CHAPTER TWO

DEVELOPMENT AND VALIDATION OF AN HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC METHOD FOR THE DETERMINATION OF FIVE BETA BLOCKER DRUG CANDIDATES

2.1. INTRODUCTION

High performance liquid chromatography (HPLC) is an analytical tool for separating and isolating compounds based, in part, on their physico-chemical properties. It is advantageous over thin layer chromatography as it offers a wide variety of stationary phases and thus has a broader analytical capability. In addition, the technique enables complete control over mobile phase flow rate and analyte elution, a high degree of resolution of compounds, and is compatible with a variety of detection methods (68). HPLC is applicable to compounds such as macromolecules or thermolabile substances, that cannot be determined using gas chromatography (GC), for which volatility of the analyte is a prerequisite (68), as this is not required with HPLC, which can be carried out at room temperature. Liquid chromatography techniques that have been developed include reversed-phase, ion-exchange, hydrophilic-interaction, hydrophobic-interaction and size-exclusion chromatography (69). Reversed-phase HPLC (RP-HPLC) brings about separation of compounds according to their polarity, with relatively non-polar molecules having a high affinity for the non-polar stationary phase, thus being retained on the column for longer, and those of a high polarity eluting more rapidly with the mobile phase (68, 70). RP-HPLC is the most widely used liquid chromatographic procedure for the analysis of drug molecules (70).

HPLC stationary phases include adsorbents such as silica, polymeric subtances, alumina, styrene-divinylbenzene, methacrylate and graphitised carbon, with silica the most commonly used for analytes of low molecular weight (less than 1000 g/mol) (69). The physical structure of the stationary phase comprises molecules that are covalently bound to the surface of the silica particles forming a uniform monomolecular layer, which is chemically stable. This binding process, called silanisation, results in a variety of

stationary bonded phases, and produces long chain aliphatic silane groups, of which several derivatisations are possible, affording the analyst a multiplicity of options to solve analytical issues (68, 69).

Mobile phase compositions usually include an aqueous phase, that may or may not be buffered, and an organic modifier, such as methanol or acetonitrile, to alter the eluting strength of the solvent (68). The retention of compounds on the column may be controlled by manipulation of the ratio of these components, and by the addition of other agents, such as ion-pair salts. Generally, isocratic systems make use of a single mobile phase, while gradient methods vary the mobile phase composition as elution proceeds.

2.2. EXPERIMENTAL

2.2.1. Reagents

All reagents used were at least of analytical grade. HPLC grade water was obtained from a Milli-Ro® 15 water purification system (Millipore, Bedford, USA) that consisted of a Super-C® Carbon cartridge, two Ion-X® ion-exchange cartridges and an Organex-Q® cartridge. Two brands of acetonitrile, distilled in glass, were used, Acetonitrile 200 far UV Romil-SpS® Super Purity Solvent (Romil LTD, Waterbeach, Cambridge) and Acetonitrile B&J ACS/HPLC Certified Solvent (Burdick and Jackson, Michigan, USA). Ortho-phosphoric acid (85%) was purchased from Merck, and Sodium hydroxide pellets from Vivid Air. All solvents, both organic and aqueous, were filtered through a 0.45 μm Durapore® HVLP membrane filter (Millipore, Ireland) before use.

Standards were purchased from Sigma Chemical Co. (St. Louis, MO) and included metoprolol tartrate, labetalol hydrochloride, acebutolol hydrochloride, propranolol hydrochloride, pentanesulfonic acid, heptanesulfonic acid and octanesulfonic acid, and since no analytical standard for oxprenolol hydrochloride was obtained, the bulk drug

purchased for tablet manufacture from Sifavitor s.p.a. (Italy) was used for HPLC analyses.

2.2.2. Preparation of Stock Solutions

Approximately 37.5 mg of the analyte of interest was accurately weighed into a 250 ml volumetric flask and made up to volume with water, to produce a stock solution of 150 µg/ml. This was covered in foil and left to stand for 10 minutes, to ensure complete dissolution, after which, the required standard solutions (30, 60, 90 and 120 µg/ml) were prepared by dilution of this stock solution. An internal standard solution was then added to each analyte solution, in the ratio of 1 part internal standard to two parts analyte (v/v).

2.2.3. Preparation of Buffers

A 0.01M phosphate buffer was prepared by accurately pipetting 0.68 ml of ortho-phosphoric acid 85% into a 1 L volumetric flask and making up to volume with HPLC grade water. Adjustment to pH 4 was achieved by the addition of sodium hydroxide pellets, while monitoring the pH using a Crison pH meter (Crison, Lasec, RSA).

2.3. LITERATURE REVIEW

A summary of all relevant information extracted from the literature pertaining to the analysis of the compounds of interest is presented in Table 2.1. It is evident from the table that the most commonly used aqueous component is a phosphate buffer, usually of pH 3, making up the major portion of the mobile phase. The organic modifier most often incorporated is acetonitrile, either alone or in combination with methanol. C_{18} phases appear to be the most popular stationary phase for the analysis of these compounds, and those used vary in both the column and particle dimensions. Ultraviolet spectrophotometry is the most commonly used method of detection, at wavelengths between 200 and 300 nm, and almost all methods reported were performed at room temperature.

Table 2.1: Chromatographic Conditions of HPLC Methods Cited in the Literature

Analyte(s)	Column	Mobile Phase	Flow Rate (ml/min)	Detection Method	λ (nm)	T°	Ref.
OXP & PROP	100 x 8 mm 10 µm, µBondapak CN.	0.05M phosphate buffer pH 3, acetonitrile, methanol (76:15.6:8.4 v/v/v).	5	UV abs	272	25°C	36
ACE, LAB, MPT, OXP & PROP	125 x 4 mm 5 µm CN.	Phosphate buffer pH 3 (µ 0.05), acetonitrile (90:10 v/v), or Phosphate buffer pH 3 (µ 0.05), acetonitrile (80:20 v/v).		UV abs	220 224 235	25°C	71
ACE, MPT, OXP & PROP	250 x 4.6 mm 5 µm C_2.	Sodium chloride buffer (0.0005M HCl, 0.05M NaCl), methanol (65:35 v/v).	1.2	UV abs	220 254	25°C	72
ACE, MPT, OXP & PROP	150 x 4 mm 5 µm C_{18}, 250 x 4 mm 5 µm C_{18}, 150 x 3.9 mm 10 µm C_{18}, 150 x 4.1 mm 5 µm PRP-1 and 150 x 3.9 mm 10 µm µBondapak C_{18}.	0.1M Tris buffer pH 7.4, methanol (20:80 v/v).	1	UV abs	326 275 274 290	25°C	73
OXP	125 x 4 mm 5 µm C_{18}.	Sorenson phosphate buffer with 2% triethylamine pH 3, acetonitrile (30:70 v/v).	0.8	UV abs	224	25°C	39
PROP	100 x 6 mm 5 µm C_{18} protein-coated cartridge.	0.1M citrate buffer pH 4, acetonitrile (78:22 v/v).	2	Spec-flourim.	297 347	25°C	74
PROP	300 X 4 mm CN.	0.01, 0.02 and 0.04M sodium acetate buffers pH 4, 5, 6, 7 and acteonitrile (30:70 v/v).	2	Spec-flourim.	276	25°C	75
MPT, OXP & PROP	300 x 3.9 mm 10 µm C_{18} µBondapak.	10mM phosphate buffer pH 3, acetonitrile, methanol (70:15:15 v/v/v).	1	UV abs	254	25°C	76
OXP	100 x 2 mm C_{18} hypersil.	Phosphate buffer pH 3 (20mM sodium laurayl sulphate, 10mM disodium hydrogen phosphate), acetonitrile (50:50 v/v).	0.5	UV abs	220	25°C	77
MPT	SAS hypersil No. 4	0.02M phosphate buffer pH 3 with 1% pentanesulfonic acid, acetonitrile (80:20 v/v).	1	UV abs	230	30°C	78

2.4. CHROMATOGRAPHIC CONDITIONS

The following conditions were selected for the separation and quantitation of the beta blockers under investigation, and a description of the optimisation process for each component is presented in Section 2.5.

Temperature:	25°C
Flow Rate:	1 ml/minute
Sensitivity:	0.1 AUFS
Detection Wavelength:	220 nm
Mobile phase composition:	0.01M phosphate buffer pH 4 with octanesulfonic acid (0.01M), acetonitrile, methanol (80:36:7 v/v/v)
Column:	Merck LiChrospher® 60 RP-Select B, 5 µm, in LiChroCART® 125-4 (Merck, Darmstadt).
Detector:	Spectrachrom® UV-100 absorbance detector (variable wavelength) (Thermo Separation products, San Jose, California).
Pump:	SpectraSERIES® P100 pump (Thermo Separation products, San Jose, California).
Injector:	Waters WISP® 710B autosampler (Waters Associates, Milford, MA, USA).
Recorder:	Perkin-Elmer 561 recorder (Hitachi, Ltd. Tokyo, Japan).

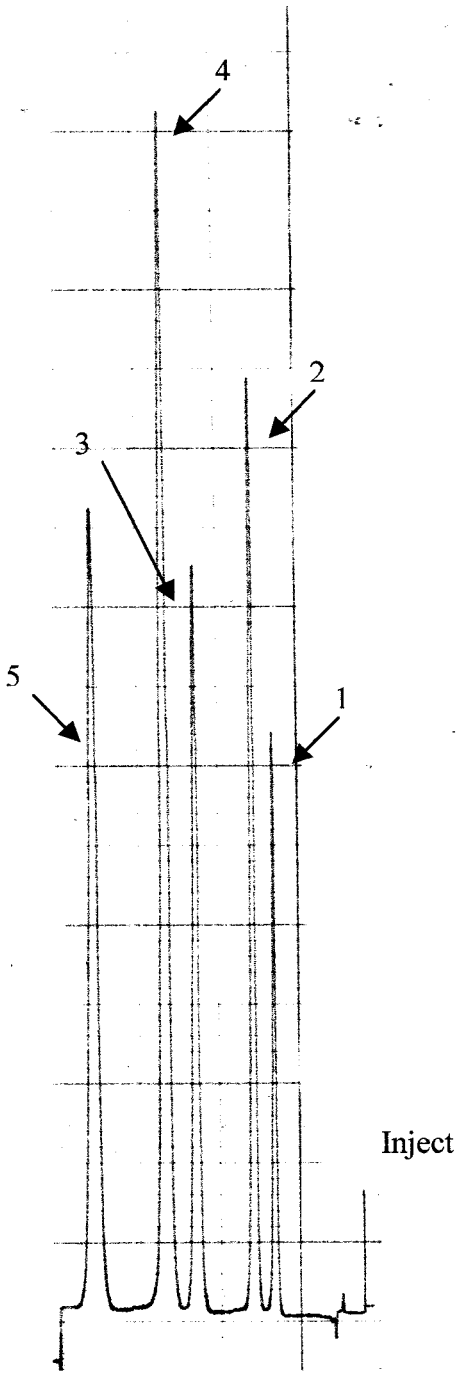


Figure 2.1: Representative chromatogram showing the separation of ACE (1), MPT (2), OXP (3), LAB (4) and PROP (5), with a mobile phase of 0.01M phosphate buffer pH 4 with OSA (0.01M), acetonitrile, methanol (80:36:7 v/v/v).

2.5. METHOD DEVELOPMENT

2.5.1. Introduction

An isocratic RP-HPLC method for the simultaneous determination of the five selected beta blocker candidates was developed and validated. In order to develop an analytical method various issues need to be addressed, such as the intended application of the method and therefore the requirements in terms of sensitivity, selectivity and range amongst others. Parameters such as linearity, precision and accuracy are inconsequential to the method choice since they are fundamental to the success of all analytical methods. Further factors for consideration when selecting chromatographic conditions are the type of analytes and any compounds that may be co-eluted such as degradation products and impurities. In addition, sample pre-treatment may affect the outcome of the analysis.

A description of the contributing variables and the selected HPLC conditions is presented here. The most significant of these variables is the mobile phase composition. The development of a single mobile phase for the detection and quantitation of all drug candidates in this study broadens the practical applicability of the method, as well as improving operating efficiency and simplicity. In seeking FDA approval, analytical methods capable of determining a group of compounds, rather than a single compound, are generally given preference, due to wider applicability (79). In this case, the development of such a method was undertaken in order to accommodate ease of analysis of any of the drug candidates consecutively, therefore minimising analytical downtime caused by switching of columns and mobile phases.

2.5.2. Mobile Phase Selection

2.5.2.1. Overview

Analytical procedures published in the literature include methods to detect and quantitate single beta blockers, or for multiple drug analysis (36, 39, 71, 72, 73, 74, 75, 76, 77, 78). Many documented cases for more than one drug however, used a different mobile phase or detection wavelength for each drug of interest, since they did not achieve satisfactory separation or sensitivity while eluting all compounds using an isocratic method (71, 72, 73). The analytical method developed in this laboratory is applicable to all five drug candidates under investigation, with no alteration of the mobile phase composition or wavelength switching necessary. Resolution between peaks was important for the detection of cross contamination during manufacture, and also to facilitate the use of one drug candidate as an internal standard for another. In this way, the accuracy and precision of the method was also improved.

The initial mobile phase selection was based on the published literary sources. Various buffers have been used as the aqueous component, however, phosphate buffer appeared to be the most common of these, and due to the availability of reagents in our laboratory, a phosphate buffer was selected for this method development. Reports in the literature reveal efficient and successful elution of beta blockers at a variety of different buffer pH's (36, 39, 71, 72, 73, 74, 75), therefore this was investigated during optimisation of this HPLC method and the results are presented in Section 2.5.2.5. Buffer molarity was also found to vary between methods (36, 39, 71, 72, 73, 74, 75), hence this parameter was also assessed, as described in Section 2.5.2.2.

Acetonitrile and methanol have been frequently used as organic modifiers (36, 39, 71, 72, 73, 74, 75, 76, 77, 78), either alone or in combination. Acetonitrile was used in this method to facilitate rapid elution of the compounds of interest. The effect of different proportions of this solvent on the retention time of the beta blockers was assessed, to optimise the mobile phase composition. Silica based columns often produce peaks of poor symmetry for moderately hydrophobic compounds such as these beta blockers when

only acetonitrile is used as the organic modifier, therefore methanol was added, as it tends to improve peak symmetry, and enhance separation (76). Methanol content was kept to a minimum however, due to the retentive effect that it has on the beta blockers studied (76).

Adequate separation of all five candidates was achieved on a Merck LiChrosper® 60 RP-Select B 125 x 4 mm column, and the order of elution was ACE, MTP, OXP, LAB and finally PROP. A typical chromatogram using the optimised mobile phase is shown in Figure 2.1. The extent of retention of these compounds, and the subsequent order of elution, is in part, a function of their lipophilicity and oil/water partition coefficient (25), with which a direct relationship exists (see Table 1.4.). This order of elution is in agreement with other reported HPLC methods (25, 76). Baseline resolution between peaks was poor for the initial mobile phase compositions evaluated, and to improve resolution, alkyl sulfonates were added as ion-pair reagents. In addition, manipulation of the acetonitrile content was used to optimise the overall run time. The aim of these experiments was to optimise separation, such that a practically acceptable retention time for all beta blockers was achieved.

2.5.2.2. Effect of Buffer Molarity

The effect of increasing buffer molarity was evaluated using three different mobile phase compositions. The first contained a phosphate buffer pH 3, acetonitrile and methanol (80:20:7 v/v/v), and the second and third consisted of a buffer of pH 4 with and without an ion pair reagent (octanesulfonic acid 0.01M) respectively, and acetonitrile and methanol in the proportions 80:36:7 (v/v/v). Figure 2.2 shows the retention time of PROP, and therefore the overall retention time of a mixture of the beta blockers, since this compound elutes at the longest retention time of all compounds. It demonstrates that increasing the buffer molarity resulted in subsequent increases in retention time of the beta blocker candidates for all three mobile phase compositions evaluated.

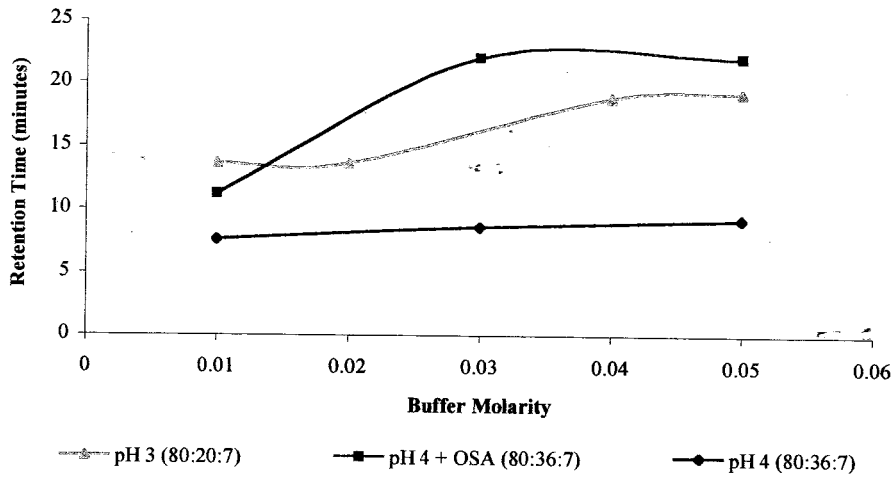


Figure 2.2: PROP retention time versus buffer molarity for three different mobile phase compositions.

Since increasing the buffer molarity resulted in longer run times, the buffer of lowest molarity, 0.01M, was selected for use in this study, to maintain efficiency of the analytical process. All buffer molarities used in the absence of an ion-pair reagent, gave poor resolution of peaks, thus retention time was the only factor considered in the selection of buffer molarity in these experiments.

2.5.2.3. Addition of an Ion-Pair Reagent

Due to poor resolution between ACE and MTP, the first two peaks to elute, an ion-pair agent was introduced to lengthen the retention time of the analytes and improve peak separation. The increased retention time of the analyte is brought about by retention of the ion-pairing agent, which acts as a counter-ion for the charged analyte, binding the analyte by a reversible association (70). In effect the counter-ion neutralises the charge of the analyte and decreases its surface polarity, thus increasing its lipophilicity and potential for binding to hydrophobic stationary phases (70).

Three apolar alkyl sulfonates were assessed for their potential ability to increase retention times. The compounds investigated were pentanesulfonic acid (PSA), heptanesulfonic acid (HSA) and octanesulfonic acid (OSA), each containing a different carbon chain

length, and therefore producing different results with respect to peak resolution and overall retention time. Table 2.2 shows the observed trends in retention time and peak resolution for all beta blocker candidates with different ion-pair reagents compared with the same mobile phase with no ion-pair addition. It is evident that HSA has the greatest retentive effect and therefore produces the most favourable baseline resolution. A short retention time with high resolution was desired, therefore HSA was not an ideal additive, since it produced an unacceptably long run time. Conversely, PSA produced a desirable retention time but lacked adequate baseline resolution, therefore a compromise between peak resolution and a short run time was made, and OSA was selected as the ion-pair reagent of choice.

Table 2.2: Effects of Ion-Pair Reagents (0.01M) on Beta Blocker Retention Time and Peak Resolution

	PSA	HSA	OSA
Run Time	↑	↑↑↑	↑↑
Resolution	↑	↑↑↑	↑↑

To optimise the method further, the impact of the molarity of ion pair reagent was assessed by comparison of retention time. Mobile phases containing 0.00M, 0.005M and 0.01M OSA were prepared comprising 0.01M phosphate buffer pH 3, acetonitrile and methanol (80:22:7 v/v/v). As is evident from Figure 2.3, showing the run time of PROP, increasing the ion-pair molarity caused a marked increase in retention time. Baseline resolution of peaks was achieved at all concentrations studied.

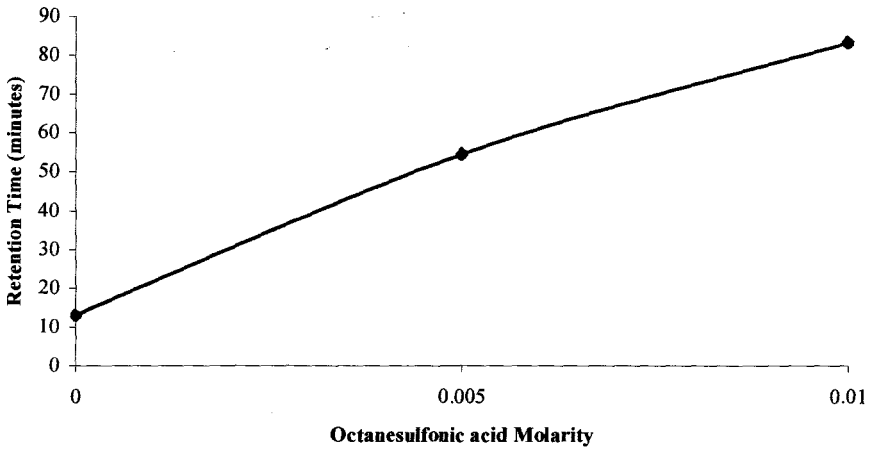


Figure 2.3: PROP retention time versus concentration of OSA in the aqueous portion of the mobile phase 0.01M phosphate buffer pH 3, acetonitrile and methanol (80:22:7 v/v/v).

Although adequate resolution of all peaks of interest was achieved, an analytical run time in excess of 80 minutes (see Figure 2.3) is unacceptable for routine quality control and quality assurance of these compounds in products, therefore the acetonitrile content was adjusted in order to shorten the elution time.

2.5.2.4. Effect of Acetonitrile Content

The effect of acetonitrile content was evaluated and the results show that a substantial increase in the acetonitrile content was required in order to shorten the overall run time of a mixture of all five drug candidates to a practically acceptable time. As seen in Figures 2.3 and 2.4, the mobile phase of (80:22:7 v/v/v) 0.01M phosphate buffer pH 3 with OSA 0.01M, acetonitrile and methanol (ie 20% acetonitrile), eluted PROP, the most retained compound, within 83 minutes. However, when the proportions were changed to 80:36:7 (v/v/v), thus increasing the acetonitrile content to approximately 29%, the retention time decreased to 11 minutes, as shown in Figure 2.4. Further increasing the acetonitrile content to 33%, the proportions 80:42:7 (v/v/v) produced a run time of 7 minutes, however baseline resolution between the first two peaks was not achieved and thus 33% acetonitrile was not acceptable. Consequently, a mobile phase of proportions 80:36:7 (v/v/v) (buffer, acetonitrile, methanol) was selected as the mobile phase of choice for these beta blockers.

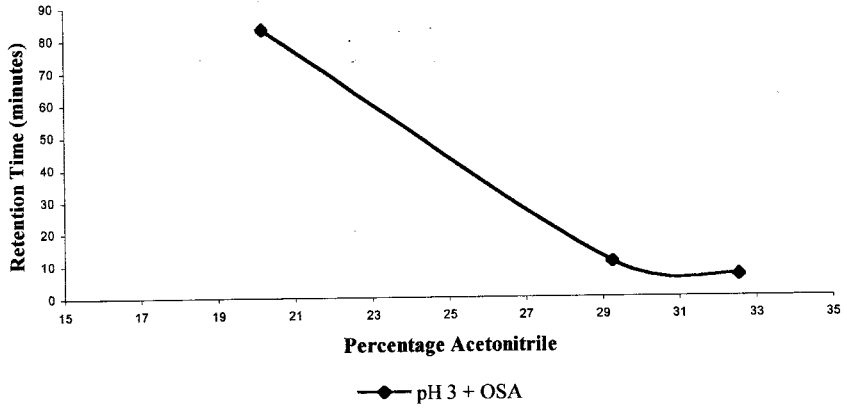


Figure 2.4: PROP retention time versus percentage acetonitrile in the mobile phase 0.01M phosphate buffer pH 3 with OSA 0.01M, acetonitrile and methanol (80:22:7 v/v/v).

2.5.2.5. Effect of Buffer pH

Silica packed columns show optimum stability and performance at pH values above 2 (69). The mobile phase compositions thus far have contained buffers of pH 3, which is near this limit for acceptable maintenance of the column used. Therefore, a variety of higher buffer pH's were investigated. A mobile phase composition of 0.01M phosphate buffer with OSA 0.01M, acetonitrile and methanol (80:42:7 v/v/v), was used at pH's ranging from 3 to 6. At all pH's, poor resolution of the peaks of interest occurred due to the high acetonitrile content, however, despite the poor resolution, an indication of the effect on retention time was obtained, and is depicted in Figure 2.5. At pH 3 and 4 an optimum retention time was achieved, and in general, higher pH's resulted in prolonged retention of all the beta blockers. Since pH 3 and 4 produced equivalent retention times, and since pH 4 is more suitable for optimum maintenance of this column, it was selected as the buffer pH of choice for the mobile phase and for future analyses.

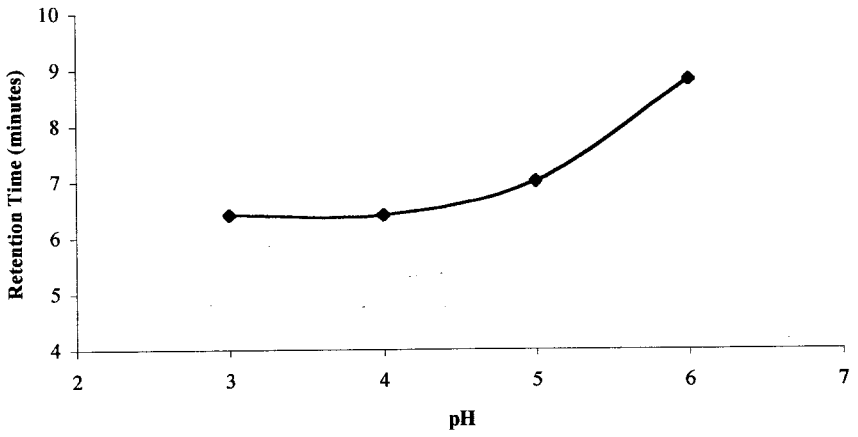


Figure 2.5: PROP retention time versus buffer pH for a mobile phase of 0.01M phosphate buffer with OSA 0.01M, acetonitrile and methanol (80:42:7 v/v/v).

2.5.2.6. Mobile Phase Selection

The final mobile phase selected, that ensured optimum detection and quantitation of the five drug candidates, consisted of an aqueous component of 0.01M phosphate buffer pH 4, with 0.01M octanesulfonic acid, and organic modifiers acetonitrile and methanol, in the proportions 80:36:7 (v/v/v).

2.5.3. Column Selection

The column selected for analysis was the LiChrospher® 60 RP-Select B, 5 µm LiChroCART® 125-4 from Merck. The stationary phase consists of a spherical silica packing, resulting in improved packed bed stability, lower back pressure and superior analytical performance than columns packed with irregular silica particles (69). Silica is termed a general purpose sorbent which is commonly used for RP-HPLC packings, one reason being its compatibility with a broad range of polar and non-polar organic solvents (69). Silica displays more favourable surface chemistry and pressure capabilities than other packings (69), and it is said to be superior due to its porous nature (80). A major disadvantage however, is its limited stability in aqueous alkaline media, thus restricting analysts to using mobile phases of between pH 2 and 8 (69).

A pore volume of 0.5 ml/g is said to be extremely rugged, however 1 ml/g is acceptable for normal analytical applications (69). The specific pore volume of this column is 0.85 ml/g, the specific surface area 700 m^2/g, and the medium pore size is 60 Å or 6 nm (80), which is recommended for molecules with a molecular weight below 3000 g/mol (69) and is therefore suitable for the beta blockers in this study.

The RP-Select B column is an octyl derivative that is specifically designed for the reversed-phase separation of basic compounds (80). The retention time, peak symmetry and selectivity of basic compounds are all affected by the silica matrix, therefore specific column packings are required to prevent secondary interactions (silanophilic interactions) between the positive charge on the basic analyte and the unbound silanol groups of the

stationary phase. The column used in these studies contains an endcapped stationary phase, which contains unreactive trimethylsilyl moieties instead of the charged silanol groups of normal silica packed columns, therefore it is suitable for the analysis of basic compounds. Tailing of peaks is minimised with these types of columns (69) and as the beta blockers included in this study have been reported to show tailing and poor separation of peaks with normal silica packed columns (76), the use of this RP-Select B column was likely to enhance the method of analysis of the drugs of interest.

Silica packings of 5 μm particle size are standard for routine HPLC applications due to short equilibration and analysis times (80), and the LiChroCART® is a standard cartridge that can be applied to most analytical methods. The column length to particle size ratio may be used to give an indication of the performance of a column, with a ratio of approximately 30000 recommended for normal analysis (69). In this case the column length is 125 mm, resulting in a column length to particle size ratio of 25000, in which elution is slightly faster than average. The column length not only has an impact on the analysis time, but also on the back pressure and column efficiency. Generally, the longer the column, or the smaller the particle size diameter, the greater the maximum plate count, and therefore the efficiency (69). This is due to an increase in the surface area of the stationary phase available for interaction with eluting compounds (68). This column has an internal diameter of 4 mm and a column volume of 1,571 ml (80).

2.5.4. Method of Detection

Selection of an optimum detection system for any analytical method depends, to a large extent, on the physicochemical properties of the analyte(s) of interest, as well as the required sensitivity of the system (68). For HPLC analysis, UV-spectrophotometric, fluorescence, refractive index and electrochemical detectors are most often used (68).

The most commonly used methods of detection for analysis of beta blockers include UV-spectrophotometric and fluorescence detection (36, 39, 71, 72, 73). Since none of the compounds of interest are reported to display photoluminescence, spectroflourimetry was

eliminated and ultraviolet (UV) spectrophotometry was selected as the detection method of choice.

The beta blockers selected for this study all absorb energy in the presence of UV irradiation, as described in Section 1.2.7, with absorption maxima between 200 and 300 nm. The molecular structure of each analyte, in particular the phenyl ring, results in the occurrence of electronic transitions, and thus substantial UV absorption when exposed to light of 220 nm (22), such that adequate sensitivity was achieved for all drug candidates at this wavelength. A wavelength of 220 nm was therefore selected as the detection wavelength for all five beta blockers.

2.6. METHOD VALIDATION

2.6.1. Introduction

According to current Good Manufacturing Practice (cGMP) regulations, any analytical method must meet the proper standards of accuracy and reliability (16) and must therefore be appropriately validated prior to use. Validation has been defined as the process of determining the suitability of a measurement system for providing useful analytical data (79), and is essential in order to ensure that the method meets the requirements for its intended application, with the necessary reliability and reproducibility (16, 81).

For an HPLC method to be accepted as a useful analytical tool, it must be validated according to international scientific standards. Standard guidelines apply to all analytical systems, however, the requirements for validation may vary depending on the origin and the intended application of the method. Various protocol guidelines are in place for validation procedures as recommended by bodies such as the International Conference on Harmonisation (ICH), IUPAC, and the Food and Drug Administration (FDA) (79).

Approval of an analytical method by the FDA requires a demonstration of accuracy, precision, sensitivity, specificity, linearity and recovery (81), however, the USP 24 (16) differs slightly in that it recommends the establishment of accuracy, precision, specificity, linearity and range, for compounds that fall into "Category 1" (Analytical methods for quantitation of major components of bulk drug substances or active ingredients in finished pharmaceutical products), such as these drug candidates (29). This analytical method was validated according to the recommendations of both of these bodies, instead of a full collaborative trial, as is recommended for methods developed in-house (79). In addition to the parameters listed above, limit of detection and quantitation, as well as the stability of the analyte in the dissolution media, were established, however recovery was not assessed, since samples required minimal pre-treatment. Validation was carried out using another beta blocker as an internal standard, added one part to two parts analyte

solution, and the ratio of peak height of the analyte of interest to that of the internal standard response was used to interpolate a concentration value.

2.6.2. Linearity

Linearity is a test that demonstrates the direct proportionality of a quantitative response to the concentration of analyte within the range of analysis (16, 82, 83) and was therefore assessed over the range of concentrations expected for analysis, using a standard calibration curve. In UV spectrophotometry it is important that the absorptive response follows the Beer-Lambert law over the range of concentrations analysed, therefore linearity must be shown.

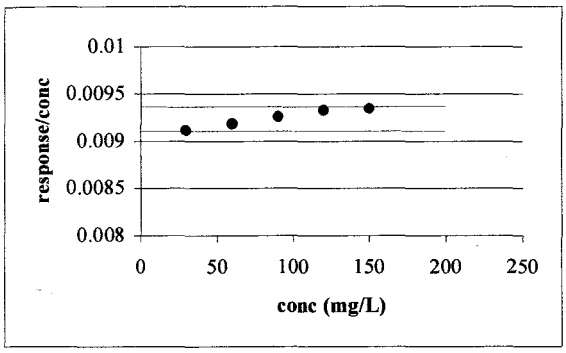
In keeping with ICH recommendations (16), five calibration standards containing one drug and an internal standard were injected in ascending order of concentration, using five repeated samples, and the responses obtained were compared with the theoretical concentrations of the prepared standard solutions, using linear regression analysis. This analysis was performed for each beta blocker. Correlation coefficients between 0.999 and 1 may be used to state that linearity exists and to show the presence of a direct response-concentration relationship (82). Correlation coefficients obtained in this study are presented in Table 2.3, demonstrating that a linear relationship exists for these beta blockers over the concentration range studied.

Table 2.3: Calibration Functions Calculated for Linearity Assessment

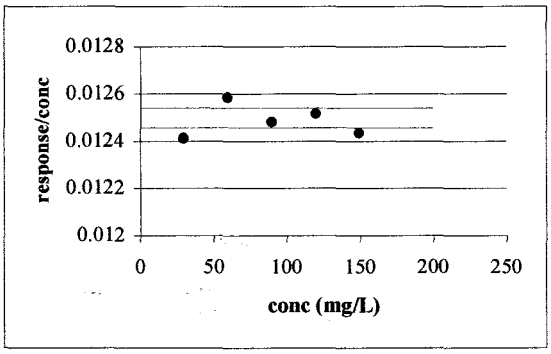
Drug	Internal Standard	Slope	Intercept	R^2 value
ACE	MPT	0.0094	-0.0117	0.9999
LAB	ACE	0.0157	-0.0113	0.9999
MPT	ACE	0.0213	0.0162	0.9999
OXP	ACE	0.0124	0.0039	0.9999
PROP	ACE	0.0110	-0.0239	0.9999

Using the data presented in Table 2.3, a second graph was plotted, in which the theoretical concentration, and the ratio of response to corresponding concentration was plotted for each drug. This type of plot is reported to give a better indication of linearity over the concentration range studied, than linear regression analysis (83). These plots are

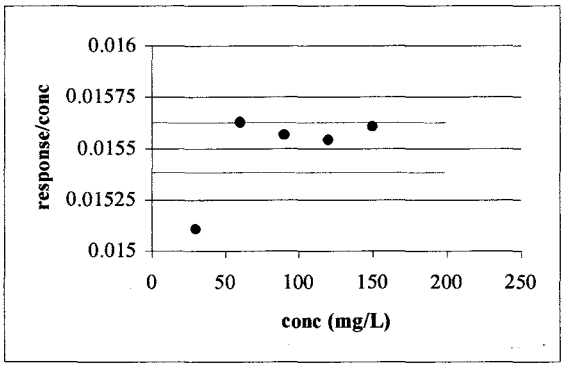
represented in Figure 2.6, with the region of significant similarity indicated by the limits shown. The region of interest is calculated using the standard deviation and the average response : concentration ratio of the calibration standards. For all drug candidates except OXP, at least three data points fall within this region, showing acceptable similarity. For OXP, the standard deviation was comparably smaller than for the other drugs, resulting in these values lying outside of this region, therefore in spite of this, the values obtained were considered acceptable, since their outlying nature is a function of a small standard error, rather than decreased linearity.



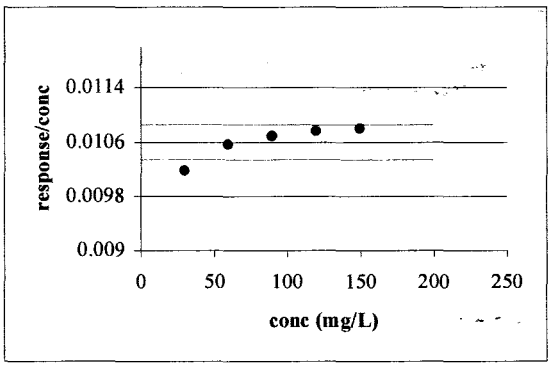
Acebutolol hydrochloride



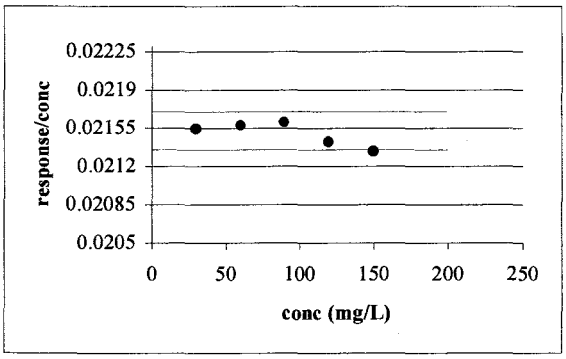
Oxprenolol hydrochloride



Labetalol hydrochloride



Propranolol hydrochloride



Metoprolol tartrate

Figure 2.6: Plots of response : concentration ratio versus concentration for each of the drug candidates.

2.6.3. Precision

Precision is a measure of the extent of agreement between repeated injections of a homogenous sample (16, 83). The precision or trueness of results is a fundamental validation test for any analysis since all official or approved methods of analysis are required to include the assessment and quantification of precision, which is an indication of the repeatability and reproducibility of a method (79).

2.6.3.1. Repeatability

Repeatability, a measure of intra-day variation, demonstrates the ability of a method to withstand experimental variation to a small degree and over a short time interval (82), and was therefore carried out within one day. Repeatability was assessed for each drug candidate separately. Five known standards were injected with an internal standard, in ascending order of concentration, for each drug, over a concentration range of 30 to 150 µg/ml, and this procedure was repeated five times. The ratio of analyte to internal standard peak height was determined and the percent relative standard deviation (%RSD) at each concentration was calculated and used to provide an indication of the repeatability of the system.

A reported acceptance criterion for both repeatability and reproducibility of biological assays is less than or equal to 15% RSD (82), therefore, considering that samples for analysis in this study are not subject to as high a degree of sample matrix pre-treatment and interference, the threshold for acceptability of both parameters was set at less than or equal to 5% RSD. The results reported in Table 2.4. indicate that, according to this limit, the method is acceptable in terms of intra-day variability.

Table 2.4: %RSD Values for Repeatability and Reproducibility Assessment.

Drug	Repeatability Highest %RSD Value	Reproducibility Highest %RSD Value
ACE	1.4258	1.7028
LAB	1.0553	1.6134
MPT	1.6337	1.5385
OXP	0.8861	1.5829
PROP	1.4519	2.7476

2.6.3.2. Intermediate Precision

Intermediate precision, or inter-day variability, reflects the reproducibility of an analytical method and was assessed over five days, in order to introduce a larger variety of experimental conditions over a longer time period than used to ascertain repeatability. Intermediate precision was demonstrated by injecting solutions of five different concentrations of each drug separately, with an internal standard, on five consecutive days. The %RSD values were calculated and are presented in Table 2.4. These results fall within acceptable limits of reproducibility for this method.

The slope of each group of calibrators used in the linearity assessment, and its variance, may also be used to demonstrate the reproducibility of the detector signal in time (82). The slope of each set of standards injected for both the repeatability test and the reproducibility test were calculated and the mean value for each of the two assessments, as well as the %RSD, were calculated. Within-day and between-day variation due to detector signal are reported in Table 2.5, and show that all %RSD values fell below 2%, and although no official acceptance criteria were found, the results reveal that these data were acceptable for reproducibility.

Table 2.5: Slope and %RSD Values for an Indication of Precision

Drug	Repeatability		Reproducibility	
	mean slope	slope %RSD	mean slope	slope %RSD
ACE	0.0094	1.12	0.0093	1.74
LAB	0.0157	0.87	0.0158	0.96
MPT	0.0213	1.56	0.0052	0.94
OXP	0.0124	0.83	0.0123	1.37
PROP	0.0110	1.16	0.0398	1.65

2.6.4. Accuracy

Many literary sources imply that accuracy and precision are the two most important validation tests for demonstrating the quality of an analytical method (82, 84, 79). Accuracy reflects the closeness of analytical results to known standards or reference values within the established range of a method (82, 16, 83).

As recommended by the ICH (16), accuracy of the method for each beta blocker was assessed by injecting three solutions of known concentration in triplicate, and comparing experimentally determined values with nominal theoretical values. For approval of analytical methods, the FDA requires that recovery values greater than 90% be demonstrated for biological samples (84), and as can be seen from the results in Table 2.6, recovery values for this method fell within 1% of the theoretical concentration, thus showing acceptable accuracy of the method, as the recovery was in the region of 98-100%.

Table 2.6: Recovery Results in the Assessment of Accuracy

Drug	Theoretical conc. (µg/ml)	Mean Exper. conc. (µg/ml)	% Recovery	%RSD
ACE	50	50.44	100.87	0.19
	100	99.43	99.43	0.14
	125	126.2	100.98	0.09
LAB	40	39.93	99.82	0.22
	75	75.10	100.14	0.38
	100	100.28	100.28	0.28
MPT	45	44.60	99.10	0.13
	100	100.41	100.41	0.32
	125	125.64	100.51	0.31
OXP	45	44.66	99.15	0.17
	80	79.59	99.49	0.01
	125	124.31	99.45	0.33
PROP	40	40.24	100.61	0.70
	80	79.30	99.12	0.31
	140	139.23	99.45	0.14

2.6.5. Limit of Detection (LOD) and Limit of Quantitation (LOQ)

The LOD is the lowest concentration that can be detected without quantification using the validated analytical method (16, 82, 83), whereas the LOQ, also known as the lower limit of quantitation (LLQ), is the lowest concentration of analyte that can be measured with acceptable accuracy and precision.

The LOD has also been described as the lowest concentration to produce a peak that is distinguishable from the background noise (82), therefore the signal-to-noise ratio of the analyte peak is commonly used to determine the LOD and LOQ, which are given to produce a 3:1 and 10:1 signal-to-noise ratio, respectively (16, 83, 85). There are, however, other methods of determining these values, for example, the lowest concentration to produce a response with a %RSD below 5%, after multiple injections, may be accepted as the LOQ, with the LOD taken as 0.3 times this value (85). Another method, which has gained favour with the ICH, involves a plot of the standard deviation versus the concentration for a group of calibration standards, and the use of a virtual standard deviation at zero concentration on the graph, to calculate the LOQ and LOD, being 10 times and 3 times this concentration, respectively (85).

For the determination of the LOD of this analytical method, 10 blank injections of HPLC grade water were injected with the calibration standards for each drug, to assess the level of background noise. No baseline noise was observed, and this parameter could not be determined using the signal-to-noise ratio, therefore an estimate of the LOD for each drug candidate was made using the experimentally determined LOQ, and these values are reported in Table 2.7.

The LOQ was determined by injecting 3 different dilute solutions of each analyte, four times over, and calculating the mean concentration and percent recovery of each sample, in addition to the %RSD. The results are listed in Table 2.7. A mean response equal to or greater than three times the standard deviation, or a response falling within 80 to 120% of the theoretical concentration, with a %RSD below 5%, may be reported as an acceptable

LOQ (82, 85). From these results, the LOQ for each beta blocker was selected, as shown in Table 2.7.

Table 2.7: Results of LOD and LOQ Determination

Drug	Theoretical conc. (µg/ml)	Mean Experimental conc. (µg/ml)	% Recovery	Standard Deviation	%RSD	Selected LOQ	Calc. LOD
ACE	2	4.19	209.29	0.163	3.89		
	5	6.92	138.44	0.258	3.73	10 µg/ml	3.33
	10	11.94	119.42	0.623	5.21		µg/ml
LAB	2	2.98	59.59	0.355	11.91		
	5	7.12	71.17	0.346	4.86	10 µg/ml	3.33
	10	14.14	94.29	0.501	3.54		µg/ml
MPT	2	1.28	63.98	0.149	11.65		
	5	4.22	84.48	0.094	2.23	5 µg/ml	1.67
	10	9.29	92.86	0.166	1.79		µg/ml
OXP	2	0.20	10.13	0.017	8.24		
	5	2.97	59.40	0.046	1.55	10 µg/ml	3.33
	10	8.69	86.91	0.345	3.97		µg/ml
PROP	5	5.89	117.83	0.139	2.36		
	10	8.53	85.32	0.117	1.37	5 µg/ml	1.67
	15	13.31	88.71	0.082	0.61		µg/ml

2.6.6. Range

The range may be defined as the interval between the upper limit of quantitation (ULQ) and the LOQ (16, 82), and must include the expected concentrations for analysis using the method. It can be said, with confidence, that any concentration within the reported range can be measured with the necessary precision and accuracy for the reliable quantitation of analyte concentrations in drug development studies (16, 82, 83). The range for each drug candidate in this study is presented in Table 2.8, and is indicated by the LOQ and ULQ values.

Table 2.8: LOQ and ULQ for all Five Beta Blocker Candidates

Drug	Range		
	LOQ (µg/ml)	to	ULQ (µg/ml)
ACE	10		150
LAB	10		150
MPT	5		150
OXP	10		150
PROP	5		150

2.6.7. Specificity and Selectivity

Specificity is a measure of the ability of a method to produce a definite response to only the analyte of interest and no other compounds that may be present in the sample, such as tablet excipients, related substances or impurities (16, 82, 83). Selectivity differs slightly in that a method is selective if it produces a distinguishable response for the chosen analyte, from any secondary compounds that are detectable (82).

In this case selectivity was assessed for each drug candidate, except OXP, since tablets were not commercially available, by dissolving a tablet or capsule in water and, after removal of particulate matter by centrifugation at 12000 rpm for 3 minutes, injecting the sample onto the HPLC system. The resultant chromatogram was compared with that of a pure standard. No additional peaks were observed, and all recovery values for the dissolved tablets fell within ± 10% of the stated content, as shown in Table 2.9.

Table 2.9: Recovery Values for the Analysis of Tablets Containing the Beta Blocker Candidates

Drug	Brand Product	% Recovery	%RSD
ACE	Sectral® 100 mg	109.88	0.06
LAB	Trandate® 100 mg	99.29	0.83
MPT	Lopressor® 100 mg	90.09	0.96
PROP	PurBloka® 40 mg	101.63	0.86

2.6.8. Stability of the Analyte

It is important that samples to be analysed are stable throughout the duration of processing and analysis time. Insight into the storage and handling requirements for these samples may be gained by conducting stability studies, whereby samples are compared, after various storage times and conditions, with freshly prepared samples (82). The aim of these studies is to detect the presence of any degradation products that may form during sample collection, processing, analysis and storage prior to analysis (82). Therefore normal experimental conditions were applied to all samples during stability testing.

Two quality control samples were injected at various time intervals after storage, and measured sample concentrations higher than 90% of a freshly prepared sample were considered stable (82).

For each drug candidate, a high (120 μg/ml) and a low (60 μg/ml) concentration marker were prepared and a 1 ml aliquot was removed, mixed with 0.5 ml of an internal standard, and injected immediately. The stock solutions were stored protected from light, and aliquots were withdrawn at various time intervals, as indicated in Figures 2.7. and 2.8. Each aliquot was mixed with a freshly prepared internal standard solution, and injected. The ratio of drug peak height to internal standard peak height, of each injection was expressed as a percentage of the ratio for the first injection (at time zero), to give an indication of the loss in analyte concentration due to degradation. No additional peaks were observed during analysis of these standards, and as depicted in Figures 2.7. and 2.8, all solutions remained stable over the period of testing, with recovery values greater than 90% in all cases.

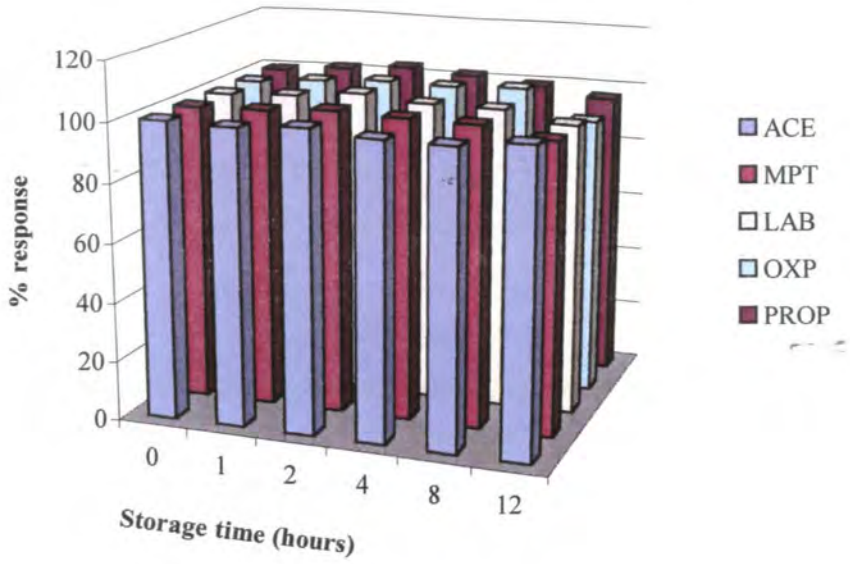


Figure 2.7: Percent recovery in response (60 μg/ml) for the five beta blocker candidates during storage.

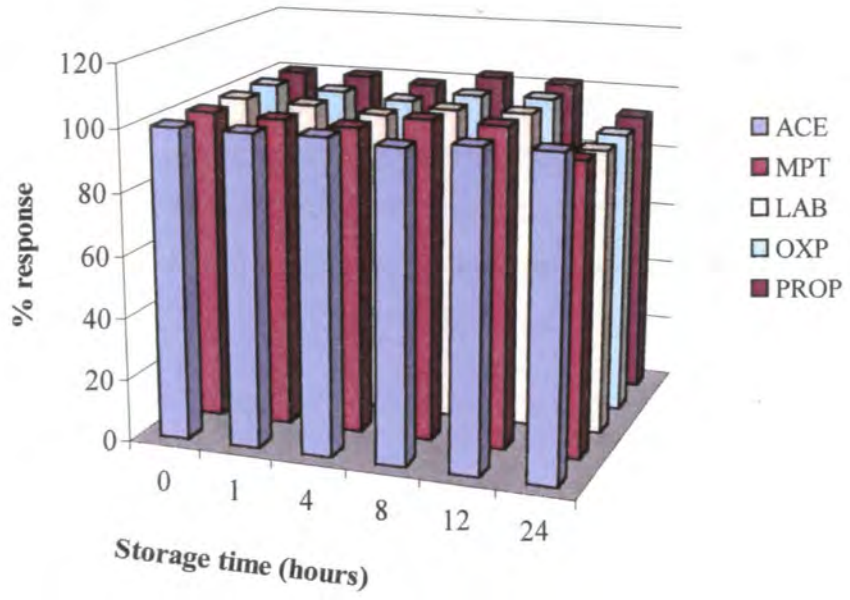


Figure 2.8: Percentage recovery in response (120 μg/ml) for the five beta blocker candidates during storage.

2.7. CONCLUSION

An isocratic modular HPLC system for the simultaneous analysis and quantitation of five beta blockers was developed and validated according to scientifically established acceptability criteria.

The method was optimised by manipulation of mobile phase composition and appropriate selection of analytical column and detection wavelength. Various components of the mobile phase that may influence the rate of elution of the analytes of interest, or that may affect baseline resolution, were assessed for the effects on the drug candidates in this study. It was found that buffer molarity and pH, acetonitrile content, and the addition of ion-pair agents all had a marked effect on the elution of the beta blockers, therefore these variables were manipulated, in order to achieve the desired retention time and baseline resolution.

Validation was carried out by demonstration of acceptable performance with respect to linearity, accuracy, precision, specificity, selectivity and stability of the analyte, and by defining the range of the analytical method, as well as the LOD and LOQ. These parameters were established in accordance with recognised scientific guidelines, and therefore this analytical method may be used with confidence of its validity for precise and accurate scientific studies.

CHAPTER THREE
DOSAGE FORM ANALYSIS

3.1. INTRODUCTION

Pharmaceutical products routinely undergo analytical testing, both during and after the product development phase and during a commercial campaign. This is important for quality assurance of finished products, as well as for the successful launch of new dosage forms onto the market.

Analytical testing was employed in this study as a tool during dosage form design, optimisation and finally, for tablet evaluation and assessment. Moisture content analyses were performed using the Karl Fischer titration method, which is a standard recognised analytical procedure. Potential solid-solid interactions between the drug candidates and tablet excipients were investigated using differential scanning calorimetry, a thermal analytical method routinely employed for these purposes. Following manufacture, tablets were assessed physically, in terms of uniformity of weight, hardness, diameter, thickness and friability, all of which are used for quality control purposes in the pharmaceutical industry during large scale production. In addition to this, content uniformity assays were performed on selected batches, as well as residual content assays. Finally, dissolution rate studies were performed on every batch of tablets manufactured. This was a means of assuring acceptable behaviour *in vitro*, according to the intended purpose of the dosage forms, as well as a means of evaluating the effects of changing formulation variables, which affords the formulator control over the drug release rates achieved.

3.2. MOISTURE CONTENT ANALYSIS

The Karl Fischer titration method is a sensitive analytical technique for measuring the quantity of water present in solvents or adsorbed onto the surface of particulate solids, as well as crystalline bound (hydrate) water (86, 87). In the past, the reagents used consisted of I_2, pyridine and SO_2 in a 1:10:3 mole ratio dissolved either in methanol or 2-methoxyethanol ($CH_3OCH_2CH_2OH$) (86, 87) however, newer Karl Fischer reagents tend to be pyridine free. When the analyte is mixed with the reagent, the presence of water results in a sequence of reactions that is driven by the alcoholic solvent, which must first be standardised by titrating with the Karl Fischer reagent, prior to dissolving the analyte and commencing the assay (86). During the reaction process, one molecule of iodine is removed for each molecule of water (87), and the end point of the reaction is determined electrometrically. A current is applied across two platinum electrodes and as long as iodine is present in the sample to depolarise the cathode, the current will flow (87). The end point is reached when the iodine is depleted and the current flow decreases to zero. The moisture content is then calculated based on the amount of reagent used.

The Karl Fischer titration method was used in this investigation to determine the moisture content of the five beta blocker drug candidates and of all the tablet excipients used for the manufacture of matrix tablets in this study. The excipients included Methocel® K4M and K100M (hydroxypropyl methylcellulose (HPMC)), Emcompress® (dibasic calcium phosphate), Emcocel® 90M (microcrystalline cellulose), Ethocel® (ethylcellulose), magnesium stearate, Cab-O-Sil® M5 (colloidal silicon dioxide) and purified talc.

3.2.1. Method

Moisture content was determined using a Mettler D18 Karl Fischer titrator (Mettler Toledo, Switzerland) with Hydranal® Composite 5 (Riedel-de Haën, Germany) as the one-component reagent, and the HPLC grade methanol was used as the solvent for the analysis. In addition, to gain insight into the compression and tabletting properties of the powder blends, a Karl Fischer titration was carried out on selected batches prior to

compression. A stirring time of 10 minutes was allowed before starting the assay for all powder blends and excipients, whereas the beta blockers were titrated immediately.

3.2.2. Results and Discussion

Table 3.1 provides a summary of the values obtained for each drug candidate. All five drug candidates contained a negligible quantity of water with respect to how this may affect their physical behaviour during the tabletting process. This was an interesting result, as certain drug candidates presented with filming and sticking of tablets during manufacture, which was thought to be a function of the moisture content of different active agents. This however, was not the case, as the results in Table 3.1 indicate. It was thought that the ambient humidity may play a role in the tableting properties of the powder blends, and these tableting properties are discussed further in Section 3.4.2.

Most of the excipient materials contained less than 5% water, which is low and is therefore favourable to avoid sticking to the press tooling, however, some moisture is required, particularly for direct compression tableting, to ensure adequate binding of the powders during compaction and it was found that all batches compressed successfully into tablets. HPMC and microcrystalline cellulose are hygroscopic and therefore adsorb moisture from the atmosphere, thus they typically contain higher moisture levels than other excipients, as demonstrated in this study.

Table 3.1: Moisture Content of Raw Materials for Matrix Tablet Manufacture

Raw Material	Moisture Content
ACE	0.71%
LAB	0.74%
MPT	0.78%
OXP	0.84%
PROP	0.79%
Methocel® K4M	11.86%
Methocel® K100M	24.30%
Emcompress®	3.43%
Emcocel® 90M	13.32%
Ethocel® Std 10	1.75%
Ethocel® Std 20	2.54%
Ethocel® Std 45	2.29%
Ethocel® FP 7	1.68%
Ethocel® FP 10	1.84%
Ethocel® FP 100	1.43%
Magnesium stearate	10.69%
Cab-O-Sil® M5	4.71%
Purified talc	2.02%

The moisture content of ten powder blends prior to compaction are presented in Table 3.2. Of these batches, the MPT formulations incorporating the fine particle (FP) grades of Ethocel® resulted in sticking during compaction, therefore it was expected that their moisture content would be higher than the other batches, however, this was not the case, as indicated by the results in Table 3.2. Instead, it was noted that the relative humidity under which the manufacture of these batches took place varied, and may have contributed to the sticking observed with the MPT batches. As Table 3.2 shows, the humidity levels during compression of the MPT blends were approximately 10% higher than those recorded during manufacture of the PROP tablets, possibly causing adherence of the powders to the surfaces of the press tooling, resulting in sticking of MPT tablets.

Table 3.2: Moisture Content of Selected MPT and PROP Powder Blends

Drug	Batch #	Ethocel® Grade	Moisture Content (%)	Relative Humidity (%)
MPT	M0151	FP 100	10.51	64
	M0153	Std 45	8.96	61
	M0155	Std 10	5.81	61
	M0157	Std 20	6.06	61
	M0159	FP 100	7.76	62
PROP	P0161	FP 7	3.71	52
	P0163	FP 10	5.73	52
	P0165	FP 100	3.90	52
	P0167	Std 45	3.54	52
	P0169	Std 10	5.00	52
	P0171	Std 20	4.79	52

3.2.3. Conclusion

The moisture content of the beta blockers, excipients and tablet blends were accurately determined using the standard Karl Fischer titration. This determination provides valuable information regarding the physical nature of raw materials prior to compaction, and to predict potential formulation behaviour during the tabletting process.

3.3. DIFFERENTIAL SCANNING CALORIMETRY

Thermal analysis of materials is used as a means of measuring thermal events that are characteristic of a material, and occur under applied heat. Differential Scanning Calorimetry (DSC) is a method in which two samples are heated by separate energy sources, one sample being the material of interest, and the other a control or a blank. The difference between the heat that is required by each of the samples to maintain them both at the same temperature is recorded. In this way, endothermic or exothermic thermal events are reported as deviations from the baseline, with endothermic transitions producing deviations in a positive direction, since more energy is required during an endothermic event. In comparison, less energy is supplied to the reference sample, to achieve the desired sample temperature (88).

DSC may be used to predict potential incompatibilities between drugs and excipients for inclusion into tablets, or other pharmaceutical dosage forms, and although excipients are considered medically inert, physical and chemical interactions with drugs may occur, and must be identified (89). In this study, each of the five drug candidates were analysed for potential interactions with the excipient materials to be used. It was expected that the endotherm peaks characteristic of the drug powders would show a shift in position or a significant change in area, in the presence of a solid-solid interaction between the drug and excipient in the mixture analysed. It is important to note, however, that these deviations do not necessarily indicate an incompatibility (40), but alert the formulator to

potential difficulties and thus further chemical and physical analyses should be performed during the product development process.

3.3.1. Method

Samples were prepared for analysis by mixing one part drug to one part excipient (1:1) together using a pestle and mortar. In addition, pure drug powders as well as finely ground tablets were also analysed following grinding. All samples were analysed in powder form, in order to eliminate the potential effects of compaction on the physical properties. Powders were accurately weighed (between 2 and 5 mg) and sealed in flat-bottomed aluminium pans prior to analysis. Each sample was analysed using an empty aluminium pan as the reference, under an atmosphere of nitrogen gas. Heating of the sample took place at a rate of 10°C per minute from 25°C to a temperature exceeding the melting point of the active drug to be analysed. All pure excipient samples were analysed from 25°C to 210°C. A Perkin-Elmer DSC 7® Differential Scanning Calorimeter (The Perkin-Elmer Corp. Norwalk, Connecticut) was used with the Perkin-Elmer Pyris® software for all samples.

3.3.2. Results and Discussion

Figures 3.1 to 3.5 show the heat flow required to maintain each sample and reference pan at equal temperatures, and the thermal events shown occur at or around the melting point of each drug. The thermograms produced for the analysis of each material under investigation are presented in Appendix 1. ACE (Figure 3.1) appears to be compatible with all of the excipients, with the possible exception of dibasic calcium phosphate (DCP). All peaks occur at approximately equal temperatures, and the decreased area of each mixture compared with the pure drug may be attributed to the 1:1 mixture containing approximately 50% drug compared with the pure sample. The peak areas are reported in Table 3.3, and as can be seen, the Δ H values (difference in heat required) that have been corrected for the drug fraction are similar to those for the pure drug substance, indicating no potential interactions. The peak for the ACE:DCP mixture occurs from 142.4°C to 144.9°C, as opposed to 143.0°C to 150.0°C for ACE alone, indicating a

interaction, however this endotherm shift is minor and may be due to a reduction in purity of the sample (41). Analysis of PROP (Figure 3.2) produced similar results, with the DCP mixture producing the only identifiable event. The OXP thermogram (Figure 3.3) was also similar in nature, with a slight shift in the OXP:DCP (1:1) peak observed, as well as an increase in peak area as seen for PROP. Nominal values for PROP and OXP are presented in Tables 3.4 and 3.5, respectively. A potentially weak interaction may be evident between OXP and magnesium stearate, indicated by the erratic baseline seen with this mixture, however, almost no change in peak area or position, as shown in Table 3.5, was observed, hence a potential interaction was not conclusively demonstrated.

LAB tends to show more incompatibilities with tablet excipients than does ACE, PROP or OXP, as is immediately apparent from Figure 3.4. Once again, there appears to be a possible interaction between this drug and DCP, shown by the broadened peak in the figure. Magnesium stearate, being of acidic origin, typically exhibits incompatibilities with various other materials. The DSC trace for the LAB:magnesium stearate (1:1) mixture in Figure 3.4 shows that the LAB endotherm has been replaced by various new peaks lower down the temperature scale. This indicates a potential chemical interaction between LAB and magnesium stearate (40, 41), as was expected with this excipient. However, it cannot be conclusively stated that such an interaction would occur during the blending and compaction processes of tablet manufacture, and long-term stability studies of the manufactured product would be necessary to provide evidence of such an interaction.

The LAB tablet trace is significantly higher than that for the pure drug, and it contains a broader peak that is shifted slightly to the left. Broadening of peaks, associated with decreased peak height, may be indicative of volatilisation of absorbed water (41), as may be the case for this tablet. The tablet contains excipients such as HPMC, which have been shown to contain as much as 24% moisture, as determined in Section 3.2, however, it is unlikely that this moisture loss is the origin of the change in the tablet peak, since such an effect was not observed with HPMC analysed alone, nor with any HPMC-drug mixture. The lowering of peak height may be attributed, more simply, to the lower drug content, at

13.5% of the formulation, compared with 100% drug in the pure sample. Changes in peak shape and height-to-width ratio may also be a result of differences in the sample mixture geometry (40, 41).

The analysis of MPT revealed an incompatibility with magnesium stearate, as shown in Figure 3.5, which is in agreement with results obtained by Arjun (90). The MPT endotherm peak is almost completely reduced, with no other peaks visible from the erratic baseline, indicating a potential interaction. In addition, the MPT:DCP (1:1) mixture produced a peak of greater height and slightly lower temperature, as was the case for ACE and PROP, indicating a possible interaction.

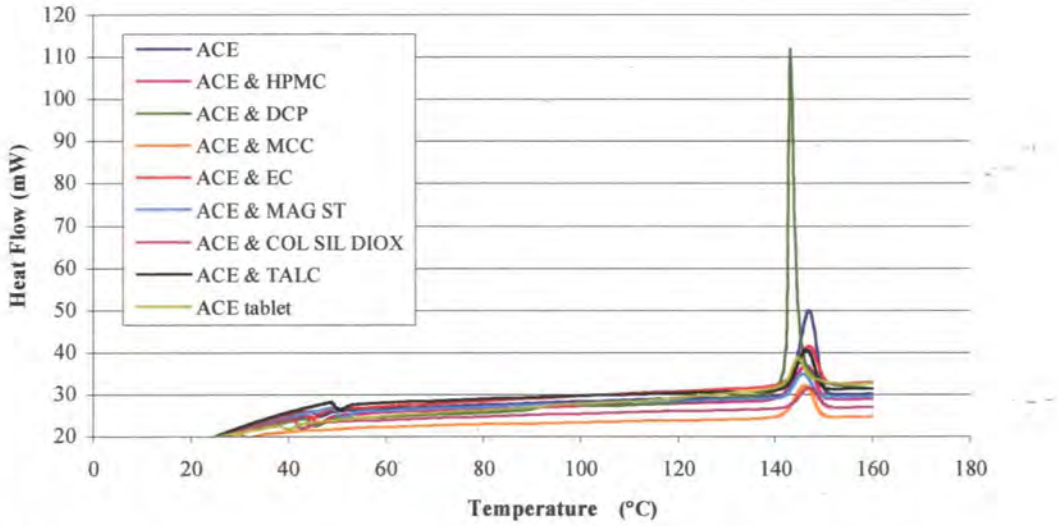


Figure 3.1: Plot of heat flow versus temperature for DSC analysis of ACE.

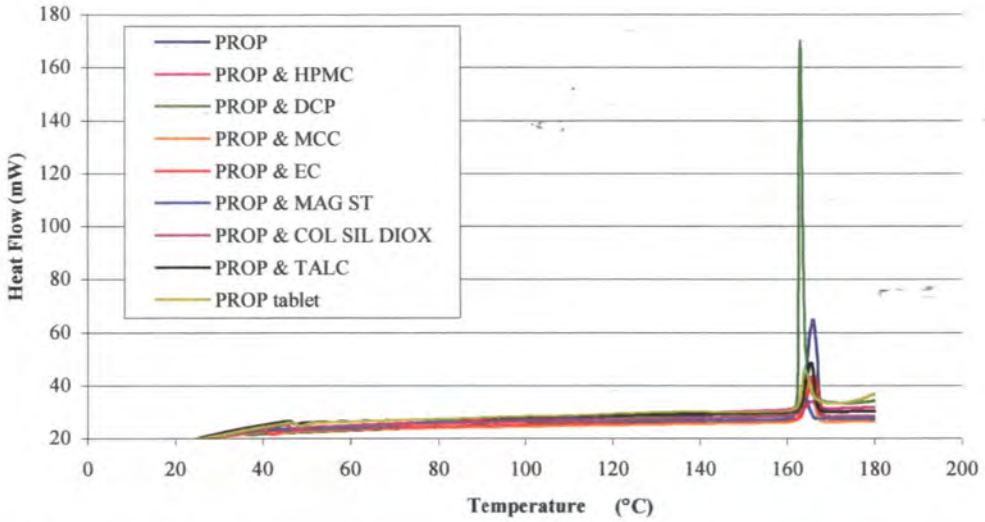


Figure 3.2: Plot of heat flow versus temperature for DSC analysis of PROP.

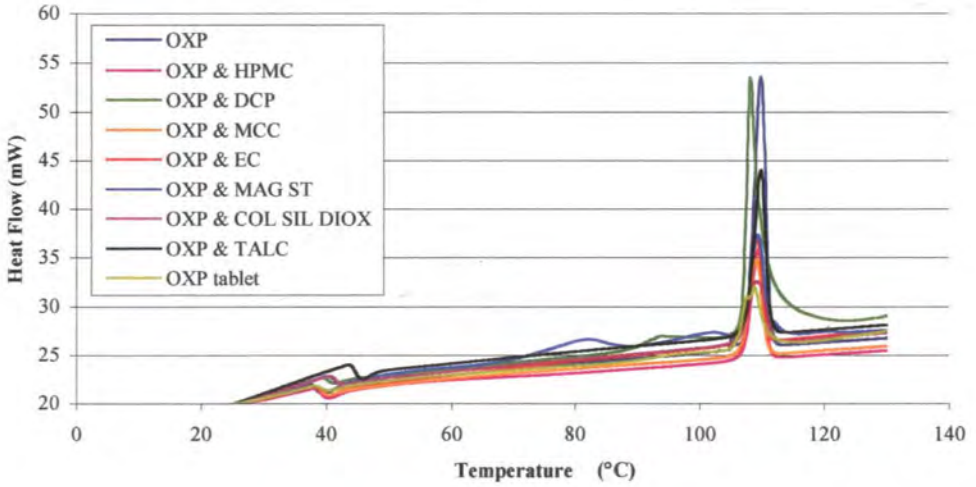


Figure 3.3: Plot of heat flow versus temperature for DSC analysis of OXP.

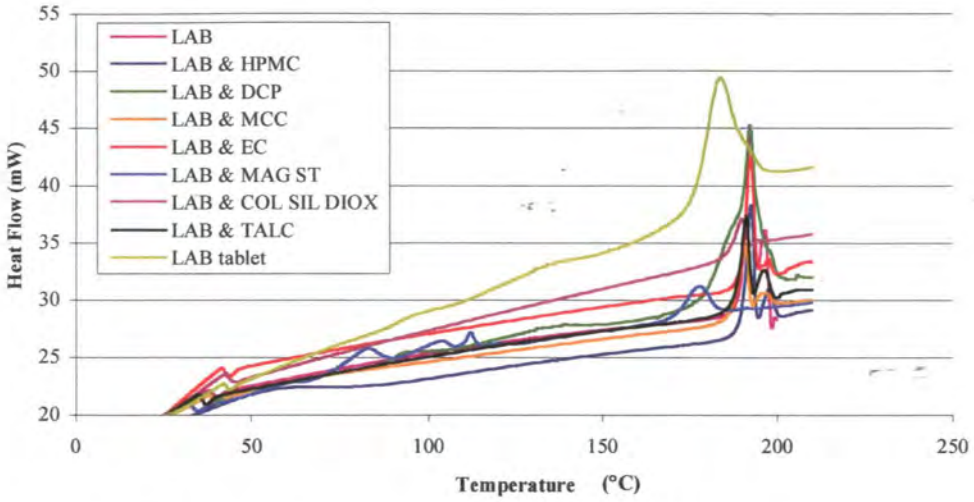


Figure 3.4: Plot of heat flow versus temperature for DSC analysis of LAB.

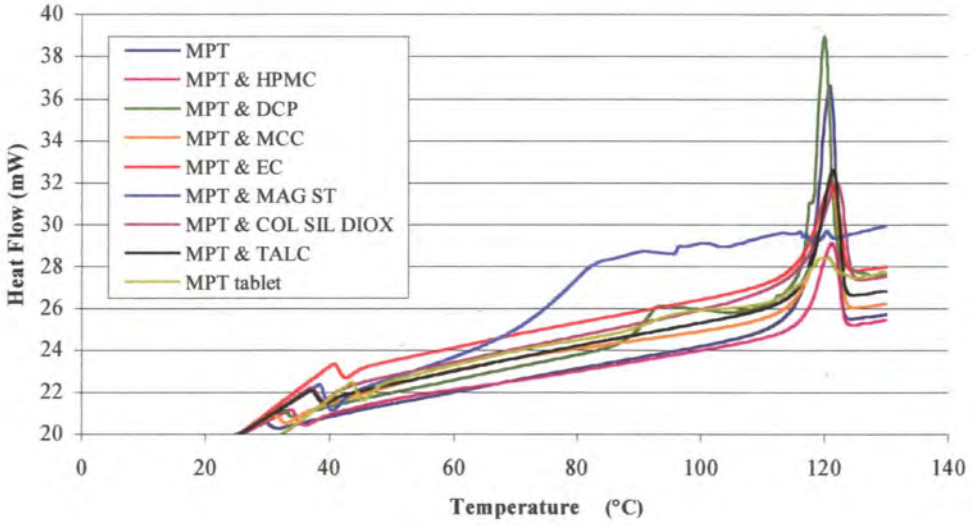


Figure 3.5: Plot of heat flow versus temperature for DSC analysis of MPT.

Table 3.3: Summary of DSC Results for Thermal Analysis of ACE Alone and in Combination with Excipients

Drug	Excipient	Drug Fraction	Peak (°C)	Peak Onset (°C)	Peak End (°C)	Peak Area (mJ)	Δ H (J/g)	Δ H corrected for Drug Fraction (J/g)
ACE	-	1	147.00	143.01	149.99	513.53	117.65	117.65
	HPMC	0.503	146.50	141.60	149.87	260.51	55.46	110.26
	DCP	0.494	143.33	142.44	144.88	893.513	202.52	409.96
	MCC	0.492	146.17	142.04	149.51	217.91	52.76	107.24
	EC	0.506	147.00	142.56	150.33	277.53	61.35	121.25
	Mag Stearate	0.503	145.83	142.25	149.02	147.60	65.31	129.84
	Col sil diox	0.497	147.00	142.99	150.41	133.71	53.51	107.67
	Talc	0.504	146.50	142.55	149.50	254.22	59.24	117.54
	ACE Tablet	0.135	144.66	142.17	147.82	190.72	38.70	286.67

Table 3.4: Summary of DSC Results for Thermal Analysis of PROP Alone and in Combination with Excipients

Drug	Excipient	Fraction Drug	Peak (°C)	Peak Onset (°C)	Peak End (°C)	Peak Area (mJ)	Δ H (J/g)	Δ H corrected for Drug Fraction (J/g)
PROP	-	1	166.17	163.44	167.64	850.99	126.83	126.83
	HPMC	0.486	165.33	162.60	167.31	216.59	56.14	115.51
	DCP	0.505	163.17	162.58	164.37	983.34	204.22	404.40
	MCC	0.503	165.33	162.73	167.24	242.28	62.40	124.06
	EC	0.520	166.33	163.40	168.15	298.54	65.80	126.54
	Mag Stearate	0.508	164.00	161.60	166.11	145.69	60.10	118.31
	Col sil diox	0.493	165.67	162.85	167.85	116.32	45.02	91.32
	Talc	0.506	165.50	163.12	167.00	272.87	84.43	166.86
	PROP Tablet	0.135	164.17	162.92	166.64	228.65	52.66	390.07

Table 3.5: Summary of DSC Results for Thermal Analysis of OXP Alone and in Combination with Excipients

Drug	Excipient	Fraction Drug	Peak (°C)	Peak Onset (°C)	Peak End (°C)	Peak Area (mJ)	Δ H (J/g)	Δ H corrected for Drug Fraction (J/g)
OXP	-	1	109.83	107.69	111.32	389.17	130.68	130.68
	HPMC	0.493	109.50	107.30	111.09	167.60	55.48	112.54
	DCP	0.508	108.17	106.94	110.11	489.65	146.25	287.89
	MCC	0.507	109.17	106.97	110.81	148.98	56.24	110.93
	EC	0.511	109.17	107.02	110.90	161.23	64.00	125.24
	Mag Stearate	0.514	109.33	107.17	111.22	168.66	69.24	134.71
	Col sil diox	0.486	109.17	106.66	111.66	131.79	57.93	119.20
	Talc	0.502	109.83	107.54	111.35	242.25	65.02	129.52
	OXP Tablet	0.135	108.83	106.00	110.96	134.96	34.93	258.74

Table 3.6: Summary of DSC Results for Thermal Analysis of LAB Alone and in Combination with Excipients

Drug	Excipient	Fraction Drug	Peak (°C)	Peak Onset (°C)	Peak End (°C)	Peak Area (mJ)	Δ H (J/g)	Δ H corrected for Drug Fraction (J/g)
LAB	-	1	192.67	189.68	194.62	438.85	119.58	119.58
	HPMC	0.508	192.50	190.02	194.17	240.98	50.57	99.55
	DCP	0.494	192.33	188.53	195.27	681.62	258.78	523.85
	MCC	0.502	190.83	187.59	192.68	167.30	46.82	93.27
	EC	0.512	192.50	189.72	194.24	225.51	51.06	99.73
	Mag Stearate	0.490	177.67	171.05	183.00	120.57	44.33	90.47
	Col sil diox	0.493	189.83	186.51	192.00	57.10	24.53	49.76
	Talc	0.492	191.67	188.07	192.97	217.50	48.82	99.23
	LAB Tablet	0.135	183.67	176.35	191.75	700.72	157.15	1164.07

Table 3.7: Summary of DSC Results for Thermal Analysis of MPT Alone and in Combination with Excipients

Drug	Excipient	Fraction Drug	Peak (°C)	Peak Onset (°C)	Peak End (°C)	Peak Area (mJ)	Δ H (J/g)	Δ H corrected for Drug Fraction (J/g)
MPT	-	1	121.03	117.52	122.84	245.03	87.54	87.54
	HPMC	0.532	121.33	117.15	123.26	98.57	42.69	80.24
	DCP	0.519	120.17	117.55	122.06	246.95	61.26	118.03
	MCC	0.481	121.17	116.71	123.35	162.76	40.26	83.70
	EC	0.482	121.33	115.98	123.61	135.12	44.04	91.37
	Mag Stearate	0.500	No discernable peak					
	Col sil diox	0.501	122.00	116.60	124.42	151.31	43.87	87.56
	Talc	0.495	121.50	117.37	123.62	146.15	44.57	90.04
	MPT Tablet	0.135	121.03	119.50	116.37	122.61	38.59	285.85

Table 3.8: Summary of DSC Results for Thermal Analysis of the Tablet Excipients Used Alone

Excipient	Peak (°C)	Peak Onset (°C)	Peak End (°C)	Peak Area (mJ)	Δ H (J/g)
HPMC	No discernable peak				
DCP	196.00	186.76	200.11	1567.20	360.28
MCC	No discernable peak				
EC	No discernable peak				
Mag Stearate	No discernable peak				
Col sil diox	No discernable peak				
Talc	No discernable peak				

3.3.3. Conclusion

The thermograms presented in Figures 3.1 to 3.5 reveal that ACE and PROP were consistently the most stable of the five drug candidates tested in the presence of the tablet excipients used in this study. OXP also showed relatively few incompatibilities, when compared with MPT and LAB, which showed potential interactions with a variety of excipients.

In summary, all five beta blockers showed possible solid-solid interactions with DCP, however these were not conclusively proven, but are in agreement with results obtained for PROP and OXP by Gerber and Lötter (42), and Botha and Lötter (41), respectively. All drug candidates were expected to interact with magnesium stearate, however, only LAB and MPT underwent thermal transition changes, despite the lubricant's reactive nature. Interactions with magnesium stearate have been demonstrated by Arjun (90) for MPT, by Gerber and Lötter (42) for PROP, and by Botha and Lötter (40, 41) for OXP. Analyses of tablets by DSC for most drug candidates revealed no unexplained transitions, however, as was expected from the 1:1 mixture thermograms, the LAB tablet exhibited effects of potential drug-excipient interactions.

It is difficult to conclusively state that any of the potential interactions observed here can and do occur during the manufacturing process or during storage of the product thereafter, since the conditions of the thermal analysis employed during the DSC screening are different from those of conventional manufacture and storage of products (89). DSC and other methods of thermal analysis provide valuable information during preformulation studies for the selection of materials for use in dosage form design and development. However, it is only with long-term stability studies that actual solid-solid interactions, arising from the formulation process, can be conclusively identified.

3.4. PHYSICAL ASSESSMENT OF TABLETS

Physical tests are routinely carried out on randomly selected portions of batches of tablets after large-scale manufacture in the pharmaceutical industry. These tests are used as indicators of potential areas of difficulty in the manufacturing process and in product approval for marketing. In this study, physical assessment of tablets was performed to improve and optimise the formulation design and manufacturing process, and to provide an indication of ultimate product quality.

3.4.1. Methods

Physical assessment of all tablets manufactured during formulation development was carried out in accordance with USP specifications where applicable, with tests performed to determine the uniformity of weight, thickness, diameter and hardness. Friability is not an official USP test, however, it was determined for each batch of tablets. Twenty tablets from each batch were individually weighed, and the thickness of each measured using vernier callipers. The hardness and diameter were then determined using a PharmaTest® PTB 311E Automated Tablet Testing Instrument (Hainburg, Germany). Friability was assessed according to the guidelines in the USP 24 (16) on ten tablets from each batch, or on 11 tablets for batches with a mean tablet mass less than 650 mg, with a rotation speed of 33 r.p.m. for 3 minutes using an Erweka® friabilator (Heusenstamm, Germany).

3.4.2. Results and Discussion

3.4.2.1. Tablet Diameter, Thickness and Weight

Tablet tooling used in this study was kept constant in order to minimise variation in tablet size and shape from one batch to another, and therefore to reduce the manufacturing variables that may impact on the release characteristics of drugs from these dosage forms. Consequently, minimal variation in tablet diameter for all batches, manufactured both by wet granulation and direct compression, was seen. The small variation, as can be seen in Tables 3.9 and 3.10, may be attributed to the behaviour of different powder blends under compaction pressures, resulting in varying degrees of elastic and/or plastic deformation of materials and their subsequent behaviour on release of stress during compaction.

The bulk density of formulation blends varies with the inclusion of different materials, particularly those formulations manufactured by direct compression. During compression into tablets, different masses of powder fill the die cavity, which remains constant in volume, and since tablets in this study were compressed to a constant target hardness, this mass variation was reflected, not only in the mean tablet weight, but also in the mean thickness values. It is evident from the data presented in Tables 3.9 and 3.10, that a direct relationship exists between these two tablet properties, in which heavier tablets tend to produce tablets with larger mean thickness values.

A target weight of 740 mg per tablet was desired for the direct compression formulations in this study, and of 720 mg for the wet granulation tablets, in order to incorporate 100 mg of active drug. Certain formulation variables investigated for the direct compression matrix tablets, as outlined in Chapter 5, had a considerable effect on the mean tablet weight. In particular, the inclusion of Cab-O-Sil® M5, a low density colloidal silicon dioxide material, as glidant, resulted in a significant decrease in tablet weight, compared with batches containing talc as the glidant. These data are shown in Table 3.10, and are discussed further in Chapter 5.

Table 3.9: Mean Tablet Weight, Thickness and Diameter Values for Wet Granulation Batches

Drug	Batch #	Ethylcellulose Load (%)	Tablet Weight (mg)	Tablet Thickness (mm)	Tablet Diameter (mm)
ACE	A0231	2.5-3.5	760.4 ± 14.8	7.96 ± 0.06	11.27 ± 0.01
	A0219	5	783.3 ± 13.5	7.93 ± 0.05	11.26 ± 0.01
	A0247	10	742.1 ± 23.1	7.63 ± 0.12	11.23 ± 0.02
LAB	L0223	2.5-3.5	742.7 ± 15.6	8.03 ± 0.03	11.27 ± 0.01
	L0251	5	708.9 ± 28.9	7.60 ± 0.10	11.24 ± 0.01
	L0249	10	702.5 ± 35.9	7.59 ± 0.21	11.23 ± 0.01
MPT	M0233	2.5-3.5	667.1 ± 3.7	7.19 ± 0.04	11.26 ± 0.01
	M0213	5	679.9 ± 8.4	7.25 ± 0.06	11.25 ± 0.01
	M0211	10	759.0 ± 29.3	7.86 ± 0.21	11.24 ± 0.01
OXP	O0221	2.5-3.5	782.2 ± 25.6	8.00 ± 0.15	11.24 ± 0.01
	O0253	5	676.3 ± 16.2	7.14 ± 0.11	11.23 ± 0.01
	O0255	10	736.6 ± 21.9	7.71 ± 0.15	11.22 ± 0.01
PROP	P0133	2.5-3.5	685.1 ± 26.4	7.28 ± 0.11	11.21 ± 0.01
	P0217	5	655.9 ± 10.57	7.13 ± 0.05	11.24 ± 0.01
	P0215	10	693.0 ± 8.33	7.40 ± 0.04	11.24 ± 0.01

Table 3.10: Mean Tablet Weight, Thickness and Diameter Values for Direct Compression Batches

Drug	Batch #	Ethocel® Grade	Ethocel® Load	Glidant Component	Tablet Weight (mg)	Tablet Thickness (mm)	Tablet Diameter (mm)
ACE	A0225	FP 10	2.8%	Talc 3%	611.3 ± 31.3	7.14 ± 0.03	11.24 ± 0.01
	A0235	FP 100	2.8%	Talc 3%	640.7 ± 22.6	6.84 ± 0.08	11.21 ± 0.01
	A0237	Std 10	2.8%	Talc 3%	634.9 ± 26.8	6.88 ± 0.08	11.22 ± 0.01
LAB	L0229	FP 10	2.8%	Talc 3%	721.1 ± 23.4	7.92 ± 0.06	11.27 ± 0.01
	L0239	FP 100	2.8%	Talc 3%	694.7 ± 35.2	7.39 ± 0.06	11.22 ± 0.01
	L0241	Std 10	2.8%	Talc 3%	691.1 ± 38.6	7.77 ± 0.03	11.23 ± 0.01
MPT	M0119	FP 100	2.8%	CabOSil® 3%	602.0 ± 10.0	7.07 ± 0.02	11.29 ± 0.03
	M0135	FP 100	2.8%	CabOSil® 1.5%	607.4 ± 26.5	6.95 ± 0.07	11.31 ± 0.03
	M0143	FP 100	2.8%	Talc 2.5%	654.1 ± 19.0	7.15 ± 0.04	11.26 ± 0.01
	M0151	FP 100	2.8%	Talc 3%	691.5 ± 17.4	7.60 ± 0.09	11.27 ± 0.02
	M0147	FP 10	2.8%	Talc 3%	677.3 ± 11.3	7.65 ± 0.04	11.27 ± 0.01
	M0149	FP 7	2.8%	Talc 3%	687.8 ± 23.5	7.81 ± 0.05	11.28 ± 0.03
	M0155	Std 10	2.8%	Talc 3%	686.3 ± 7.8	7.56 ± 0.13	11.27 ± 0.01
	M0157	Std 20	2.8%	Talc 3%	703.6 ± 29.1	7.70 ± 0.06	11.28 ± 0.03
	M0153	Std 45	2.8%	Talc 3%	712.8 ± 15.7	7.79 ± 0.10	11.28 ± 0.02
	M0207	FP 10	20%	Talc 3%	638.3 ± 17.5	7.99 ± 0.11	11.25 ± 0.02
	M0205	Std 20	20%	Talc 3%	702.7 ± 7.5	7.96 ± 0.04	11.25 ± 0.01
	M0259	Freeze-dried	2.8%	Talc 3%	729.7 ± 2.7	7.55 ± 0.02	11.24 ± 0.01
	M0261	Freeze-dried	14%	Talc 3%	672.4 ± 3.8	7.27 ± 0.02	11.22 ± 0.01
OXP	O0227	FP 10	2.8%	Talc 3%	647.6 ± 11.6	7.12 ± 0.03	11.24 ± 0.01
	O0243	FP 100	2.8%	Talc 3%	667.0 ± 17.6	6.93 ± 0.12	11.20 ± 0.00
	O0245	Std 10	2.8%	Talc 3%	650.2 ± 23.8	6.93 ± 0.12	11.21 ± 0.01
PROP	P0125	FP 100	2.8%	CabOSil® 3%	602.2 ± 25.2	6.97 ± 0.06	11.29 ± 0.04
	P0139	FP 100	2.8%	CabOSil® 1.5%	639.2 ± 7.2	7.12 ± 0.05	11.25 ± 0.02
	P0141	FP 100	2.8%	Talc 2.5%	696.9 ± 22.1	7.64 ± 0.02	11.23 ± 0.01
	P0165	FP 100	2.8%	Talc 3%	718.9 ± 18.5	7.88 ± 0.03	11.25 ± 0.01
	P0163	FP 10	2.8%	Talc 3%	737.5 ± 17.5	8.06 ± 0.04	11.25 ± 0.01
	P0161	FP 7	2.8%	Talc 3%	741.4 ± 19.8	8.05 ± 0.02	11.24 ± 0.01
	P0169	Std 10	2.8%	Talc 3%	713.8 ± 5.9	7.77 ± 0.12	11.25 ± 0.01
	P0171	Std 20	2.8%	Talc 3%	713.2 ± 20.5	7.66 ± 0.03	11.24 ± 0.01
	P0167	Std 45	2.8%	Talc 3%	719.9 16.5	7.78 ± 0.05	11.24 ± 0.01
	P0201	FP 10	20%	Talc 3%	629.6 ± 35.1	7.75 ± 0.05	11.24 ± 0.01
	P0203	Std 20	20%	Talc 3%	707.5 ± 18.6	8.04 ± 0.12	11.24 ± 0.01
	P0257	Freeze-dried	2.8%	Talc 3%	526.4 ± 60.0	6.53 ± 0.18	11.20 ± 0.01
	P0263	Freeze-dried	14%	Talc 3%	653 ± 27.9	6.89 ± 0.19	11.23 ± 0.01

3.4.2.2. Tablet Hardness and Friability

The target tablet hardness for all batches was 120 to 160 N, and in general, the mean tablet hardness for all tablets tested for all drug candidates falls between 100 and 160 N. These data are listed in Table 3.11. During compaction of some powder blends, the tablet press experienced excessive strain, necessitating a decrease in compaction force to maintain optimum functioning of the press, thus a lower actual hardness value was achieved, when compared with the target hardness.

It has been shown, for a highly water soluble drug in a sustained release tablet, that drug release is independent of tablet hardness (91, 92, 93), and Ford et al (94) showed that compaction pressures ranging from 93 to 1395 MNm^{-2}, producing tablets of varying hardness, did not impact on the release rate profiles obtained from another highly water soluble drug, promethazine hydrochloride, from polymeric matrices. Therefore, this factor was not considered to contribute markedly to the results of dissolution testing that are presented in Chapters 4 and 5.

The friability results shown in Table 3.11 are acceptable according to the USP 24 guidelines (16), since not more than 1% of the tablet mass was lost for all batches tested. This is an indication that the tablets are adequately resistant to any abrasion that may be encountered during handling, transport or storage of tablets following manufacture.

Table 3.11: Hardness and Friability Values for all Batches Tested

Drug	Direct Compression			Wet Granulation		
	Batch #	Hardness (N)	Friability	Batch #	Hardness (N)	Friability
ACE	A0225	95.87 ± 38.4	0.16%	A0219	138.5 ± 5.8	0.04%
	A0235	183.6 ± 29.5	0.07%	A0231	105.7 ± 10.2	0.08%
	A0237	159.5 ± 35.1	0.07%	A0247	139.3 ± 12.6	0.00%
LAB	L0229	145.1 ± 33.8	0.12%	L0223	100.4 ± 13.9	0.15%
	L0239	223.5 ± 68.4	0.06%	L0249	134.7 ± 32.2	0.00%
	L0241	131.7 ± 48.4	0.12&	L0251	126.2 ± 24.0	0.01%
MPT	M0119	107.9 ± 13.6	0.09%	M0211	119.5 ± 9.1	0.00%
	M0135	112.2 ± 35.7	0.01%	M0213	131.9 ± 7.0	0.00%
	M0137	111.4 ± 11.6	0.11%	M0233	124.0 ± 4.2	0.00%
	M0143	140.1 ± 25.7	0.06%			
	M0147	97.93 ± 11.8	0.06%			
	M0149	101.1 ± 24.6	0.17%			
	M0151	121.5 ± 18.7	0.04%			
	M0153	97.8 ± 14.3	0.05%			
	M0155	100.1 ± 6.0	0.05%			
	M0157	105.4 ± 26.5	0.07%			
	M0159	115.8 ± 19.8	0.06%			
	M0205	105.6 ± 8.1	0.04%			
	M0207	116.7 ± 27.7	0.03%			
	M0259	98.41 ± 3.1	0.09%			
	M0261	72.5 ± 4.4	-			
OXP	O0227	138.7 ± 16.5	0.09%	O0221	87.2 ± 9.0	0.14%
	O0243	167.7 ± 13.7	0.02%	O0253	118.0 ± 5.9	0.00%
	O0245	160.0 ± 20.6	0.06%	O0255	99.27 ± 7.5	0.00%
PROP	P0125	116.1 ± 34.6	0.05%	P0133	168.6 ± 12.8	0.09%
	P0139	158.0 ± 12.2	0.07%	P0215	121.9 ± 4.3	0.01%
	P0141	146.9 ± 22.5	0.07%	P0217	121.8 ± 13.1	0.02%
	P0161	123.1 ± 21.7	0.01%			
	P0163	118.3 ± 22.4	0.16%			
	P0165	115.6 ± 21.2	0.10%			
	P0167	118.7 ± 19.6	0.08%			
	P0169	112.0 ± 11.4	0.10%			
	P0171	123.9 ± 12.0	0.09%			
	P0201	151.4 ± 56.2	0.09%			
	P0203	105.5 ± 13.9	0.07%			
	P0257	60.1 ± 50.2	-			
	P0263	93.6 ± 11.7	0.04%			

3.5. CONTENT UNIFORMITY AND RESIDUAL CONTENT ASSAY

The USP 24 (16) describes two means of demonstrating uniformity of dosage units. For certain dosage forms, uniformity of weight may be used an indicator, however, for the tablets manufactured in this study, a content uniformity assay was required. A content uniformity analysis was performed on selected batches of tablets of all drug candidates, manufactured by wet granulation and direct compression. The results obtained for the selected batches containing each drug candidate were used to correct for the amount of drug released from all dosage forms during dissolution studies. The percent drug released from each formulation, as shown in the figures, was calculated by expressing the amount (mg) released, as a percent of the total amount incorporated in the dosage form, as determined by the content uniformity assay, rather than the theoretical value. The calculated content of each active drug, manufactured into tablets by direct compression or wet granulation, was used for correction of content of all other batches of the same drug manufactured using the same method.

3.5.1. Method

A content uniformity assay was performed on twenty tablets, randomly selected from each batch. Each tablet was individually weighed and crushed in a mortar and pestle, and quantitatively transferred to a 100 ml volumetric flask. The sample was made up to volume with HPLC grade methanol and sonicated for 10 minutes. Residual solids were removed by centrifugation for 3 minutes at 12000 r.p.m, and a 1 ml aliquot was withdrawn and analysed using the validated HPLC system described in Chapter 2. Content uniformity was expressed as the mean percent drug recovered for the twenty tablets assayed. Following the 22 hour dissolution period, the same procedure was used on each remaining tablet core, to determine the percent drug retained in the dosage form for mass balance purposes.

3.5.2. Results and Discussion

The results of the content uniformity assays are presented in Table 3.12. It is evident that the direct compression tablets have higher active content recovery values than the wet granulation tablets. This may be explained, in part, by the method of blending of each formula. The direct compression powder blends were sealed in a cube blender, whereas the bowl used with the planetary mixer when blending the wet granulation component was open. As a result, a large amount of powder was lost to the atmosphere during the granulation procedure. This may introduce variability into the tablets produced by wet granulation. Another factor that may contribute to the lower recovery values obtained from the wet granulation tablets is the Surelease® used in these formulations. The extraction method used may not dissolve all of the ethylcellulose that has potentially coated portions of the wet granulation powder blend, therefore drug may not be liberated from the solid dosage form or the powder, resulting in decreased recovery values during the assay. This would not occur with the directly compressed tablets, as the ethylcellulose should be liberated as dry powder on destruction of the tablet.

Batches M0119 and M0135, containing MPT, showed lower recovery values than the other MPT batches, due to the inclusion of Cab-O-Sil® M5 into these formulae. The colloidal silicon dioxide has an extremely low bulk density compared with the other excipients, therefore it imparts a low bulk density to the entire tablet blend, resulting in an unpredictable loss of powder on the tablet press during compaction. There is an inverse correlation between the Cab-O-Sil® M5 content in these batches and the percent recovery, with decreasing levels of Cab-O-Sil® M5, and subsequent increases in talc, resulting in recovery values closer to 100%. Table 3.12 shows this trend, with the talc component increasing from batch M0119 to M0135, and further, to M0147. The formulae for these batches are presented in Section 5.2.3.3.1.

Table 3.12: Content Uniformity Assay Results for the Five Beta Blocker Drug Candidates

Drug	Direct Compression		Wet Granulation	
	Batch #	% Recovery	Batch #	% Recovery
ACE	A0225	99.18 ± 3.26	A0231	79.62 ± 6.21
LAB	L0229	99.59 ± 4.04	L0223	86.72 ± 3.84
MPT	M0119	90.88 ± 3.45	M0233	97.36 ± 3.76
	M0135	94.85 ± 2.49		
	M0147	99.20 ± 4.41		
	M0155	96.49 ± 4.51		
OXP	O0227	96.44 ± 3.51	O0221	75.15 ± 4.72
PROP	P0163	96.50 ± 5.01	P0133	91.54 ± 9.97

The percent recovered by the residual content analysis performed at the end of each dissolution test is presented in Table 3.13. All values for ACE, MPT and OXP fell below 5%, indicating that almost all of the active drug was released during the 22 hour dissolution period. LAB and PROP values are consistently higher, and correspond to the consistently lower final amount of drug released from these formulations during dissolution testing, as shown in Table 3.14. The rate and amount of drug released from these formulations is discussed in further detail in Chapter 5.

Table 3.13: Residual Content After Dissolution for the Five Beta Blocker Drug Candidates

Drug	Direct Compression		Wet Granulation	
	Batch #	% Recovery		Batch #
ACE	A0225	1.26 ± 0.14	A0219	2.76 ± 1.59
	A0235	0.20 ± 0.09	A0231	4.16 ± 0.60
	A0237	0.63 ± 0.20	A0247	4.37 ± 1.45
LAB	L0229	12.42 ± 1.52	L0223	18.41 ± 1.22
	L0239	10.70 ± 4.03	L0249	26.50 ± 1.41
	L0241	6.95 ± 5.58	L0251	17.93 ± 1.01
MPT	M0135	0.50 ± 0.23	M0211	3.02 ± 0.47
	M0137	2.07 ± 0.39	M0213	1.15 ± 0.13
	M0143	0.59 ± 0.24	M0233	1.26 ± 0.94
	M0147	1.53 ± 0.43		
	M0149	2.12 ± 0.65		
	M0151	1.96 ± 0.20		
	M0153	2.26 ± 0.27		
	M0155	2.51 ± 0.20		
	M0157	2.73 ± 0.33		
	M0159	2.18 ± 0.29		
	M0205	2.20 ± 0.28		
	M0207	2.66 ± 0.49		
OXP	O0227	0.80 ± 0.12	O0221	2.87 ± 0.42
	O0243	0.30 ± 0.28	O0253	2.12 ± 1.47
	O0245	0.53 ± 0.07	O0255	4.23 ± 0.95
PROP	P0161	12.16 ± 1.88	P0215	10.64 ± 1.04
	P0163	11.50 ± 0.77	P0217	12.85 ± 3.10
	P0165	9.74 ± 1.18		
	P0167	9.20 ± 0.90		
	P0169	10.31 ± 1.04		
	P0171	10.21 ± 0.78		
	P0201	8.14 ± 5.28		
	P0203	9.71 ± 0.78		

Table 3.14: Content, Residual Content and Percent Drug Released After 22 Hours Dissolution

Drug	Batch #	Method of Manufacture	Content (%)	Residual Content (%)	Final % Released	Res. Content + Total Rel. (%)
ACE	A0225	Direct Compression	99.18 ± 3.26	1.26 ± 0.14	92.57 ± 3.71	93.83
	A0231	Wet Granulation	79.62 ± 6.21	4.16 ± 0.60	93.86 ± 2.80	98.02
LAB	L0229	Direct Compression	99.59 ± 4.04	12.42 ± 1.52	76.25 ± 3.86	88.67
	L0223	Wet Granulation	86.72 ± 3.84	18.41 ± 1.22	81.13 ± 1.99	99.54
MPT	M0135	Direct Compression	94.85 ± 2.49	0.50 ± 0.23	96.19 ± 2.49	96.69
	M0147	Direct Compression	99.20 ± 4.41	1.53 ± 0.43	104.64 ± 1.17	106.17
	M0155	Direct Compression	96.49 ± 4.51	2.51 ± 0.20	99.52 ± 1.22	102.03
	M0233	Wet Granulation	97.36 ± 3.76	1.26 ± 0.94	91.04 ± 1.12	92.30
OXP	O0227	Direct Compression	96.44 ± 3.51	0.80 ± 0.12	79.27 ± 3.34	80.07
	O0221	Wet Granulation	75.15 ± 4.72	2.87 ± 0.42	104.99 ± 4.71	107.86
PROP	P0163	Direct Compression	96.50 ± 5.01	11.50 ± 0.77	98.30 ± 2.12	109.80

3.5.3. Conclusion

The recovery for these formulations was relatively high, particularly for the direct compression formulations. Table 3.12 indicates that all direct compression tablets contained greater than 90% of the desired dose per tablet, with most values exceeding 95%.

The residual content assay, which measures the amount of drug remaining in the tablet core after dissolution, revealed that LAB and PROP are retained to a greater extent than ACE, MPT and OXP, possibly due to their lower aqueous solubility. These results correspond with the total percent drug released at the end of the dissolution period, as shown by the dissolution rate profiles obtained throughout this study, with LAB and PROP, in general, being released to a lesser extent than the other drug candidates from the manufactured dosage forms.

3.6. DISSOLUTION TESTING

For any new product intended to be marketed, it is important that bioequivalence with an accepted reference product be demonstrated in order for that product to be marketed. This is achieved by obtaining similar *in-vivo* plasma concentration profiles for the test and reference product, showing that there is no significant difference between the rate and extent of absorption under the same conditions of administration. As a preliminary step to *in-vivo* studies, *in-vitro* dissolution tests are well accepted as general indicators of the behaviour of the product *in-vivo*, since the absorption of any drug is subject to liberation from the administered dosage form. For this reason, dissolution studies are valuable tools for increasing the success rate of costly *in-vivo* bioequivalence tests.

In addition to aiding in the optimisation of new products, dissolution tests are applicable during studies to demonstrate dosage form stability and batch-to-batch uniformity, as well as in assessing the effects of a change in formulation variables. In this study, dissolution tests were conducted in order to ascertain whether selected batches were similar, in order to gain insight into the behaviour of the tablets *in vitro* and to assess the effects of formulation variables, as discussed in Chapters 4 and 5.

3.6.1. Preliminary Selection of Dissolution Testing Apparatus

The objective of this study was to select the most appropriate apparatus for dissolution testing of the sustained release matrix tablets developed. Although the USP Apparatus 2 (paddles) is used extensively for sustained release dosage forms, it has become increasingly accepted that the Apparatus 3 (BIO-DIS) is the preferred apparatus for dissolution rate studies of long-acting dosage forms (95, 96). Some advantages of the BIO-DIS, when compared with Apparatus 2, include the closeness with which the gastro-intestinal environment may be simulated, both in terms of the pH range and the turbulence encountered during transit of the dosage form *in vivo*, and the absence of undesirable phenomena usually associated with Apparatus 2, such as coning caused by the laminar flow of the dissolution medium (95).

With Apparatus 3, the tablet may be exposed to as many as six different dissolution media, over a variable time interval for each medium. Usually the dosage form will be advanced from an acid medium, upwards in pH, to that of a more alkaline nature, thus simulating transit through the GIT. In contrast, Apparatus 2 uses only one dissolution vessel per tablet, hence one pH is usually selected for the entire experiment.

3.6.1.1. Method

In order to determine which apparatus was suitable for these studies, an evaluation was carried out using two batches of MPT tablets, one manufactured by wet granulation and the other by direct compression, as both methods of manufacture were employed in this study.

The dissolution conditions for both apparatus used are listed in Table 3.15, with receptor media being buffer of the same molarity for both testing systems, differing only in pH for the USP Apparatus 3.

Table 3.15: Dissolution Test Conditions for USP Apparatus 2 and 3.

Parameter	USP 2 (Paddle)	USP 3 (BIO-DIS)
Temperature	37.5°C	37.5°C
n =	4	6
Test Period	24 hours	22 hours
Agitation Rate	100 r.p.m.	20 dips per minute
Dissolution Media	0.1M phosphate buffer pH 7.2 (900ml)	0.1M phosphate buffers of varying pH (185ml)
Sampling Schedule	1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, 12 hours, 16 hours, 20 hours, 24 hours	**Dissolution medium #** / **pH** / **Dissolution time**: 1 / 1.6 / 1 hour; 2 / 3.4 / 1 hour; 3 / 4.7 / 4 hours; 4 / 6.8 / 4 hours; 5 / 7.2 / 4 hours; 6 / 7.2 / 8 hours

Samples were collected periodically at predetermined times throughout the 24 hour period from Apparatus 2, and at the end of the 22 hour period from each receptor vessel of the BIO-DIS. All samples were analysed by HPLC, and the cumulative percent drug released was plotted versus time, to generate dissolution rate profiles for each formulation. Curves were compared using the f_1 and f_2 difference and similarity factors, defined by Moore and Flanner (97), as described in Section 3.6.4. The percent drug released at times 1, 2, 6, 10, 14 and 22 hours were used to calculate these fit values, and the data at times 14 and 22 hours for Apparatus 2 were graphically interpolated, since data collection was not performed at these time points.

3.6.1.2. Results and Discussion

It is evident from Figures 3.6. and 3.7 that release from the wet granulation formulation was more susceptible to changes in dissolution apparatus when compared with the direct compression tablets. A statistical analysis revealed that a significant difference existed between the apparatus used for the wet granulation tablets, however, acceptable similarity was demonstrated for tablets manufactured by direct compression, as shown by the f_1 and f_2 values reported in Table 3.16.

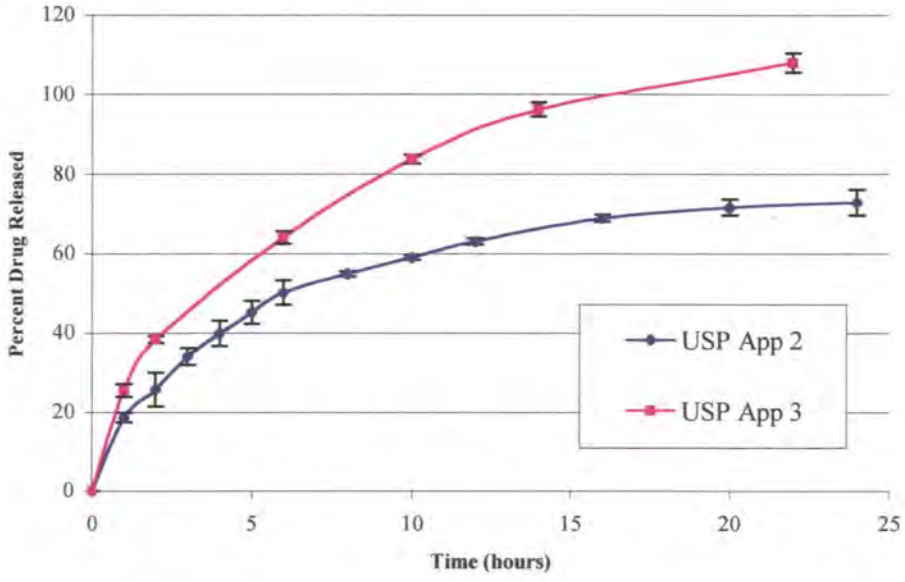


Figure 3.6: Dissolution rate profiles of MPT tablet batches manufactured by wet granulation.

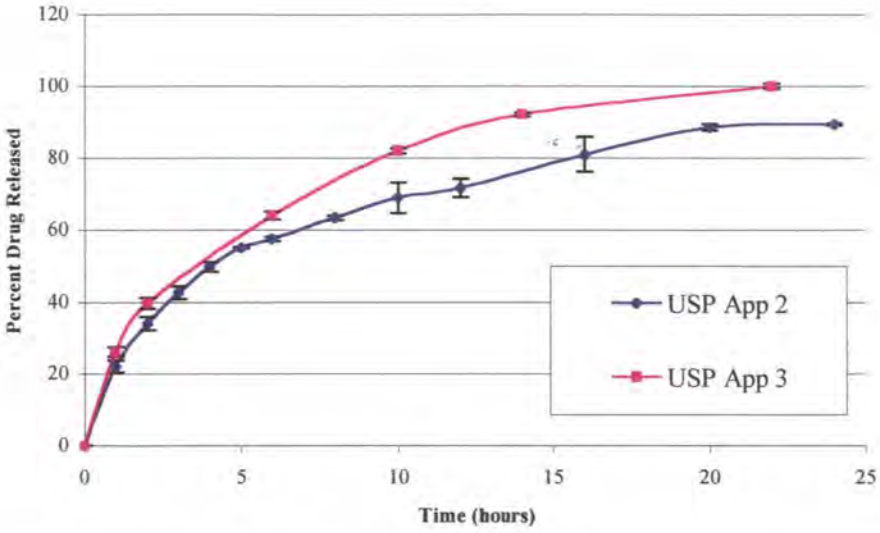


Figure 3.7: Dissolution rate profiles of MPT tablets manufactured by direct compression.

Table 3.16: f_1 and f_2 Fit Values for Comparison Between the BIO-DIS and the USP Apparatus 2.

Method of Manufacture	f_1	f_2
Direct Compression	14.5	51.8
Wet Granulation	42.1	31.9

The more turbulent dissolution environment brought about by reciprocation of the inner cylinders in the BIO-DIS resulted in a greater degree of mechanical erosion or abrasion of tablets, and more than likely contributed to the greater rate and extent of drug release, as seen from tablets prepared by both methods of manufacture, although statistical significance was only verified for the wet granulation tablets. The pH variations of the BIO-DIS may also play a role, in that the lower pH's may result in increased ionisation of the basic drugs, therefore increasing their solubility in the dissolution medium, which is known to influence the rate of drug release (98, 99, 100, 101). The results imply that the BIO-DIS offers a more vigorous dissolution test for the tablets under investigation. In addition, the standard deviations for each batch of tablets (shown by the error bars in the figures) were greater for Apparatus 2 than for Apparatus 3, suggesting that, despite more vigorous experimental conditions, a higher level of precision of data may be generated using the BIO-DIS (96).

3.6.1.3. Conclusion

The USP Apparatus 3 was selected for dissolution testing of the beta blocker tablets manufactured during this study. It provides a more stringent testing procedure, a higher degree of precision, and a more realistic dissolution environment through simulation of the pH range and turbulence encountered in the GIT (96).

3.6.2. Selected Dissolution Test Conditions

Dissolution testing for all batches was carried out using the BIO-DIS, with the conditions as outlined in Table 3.17.

Table 3.17: Dissolution Test Conditions Used for All Tablet Batches.

Apparatus:	USP Apparatus 3 (BIO-DIS)		
Temperature:	37.5°C		
Sample size (n):	6		
Test length:	22 hours		
Agitation rate:	20 dips per minute		
Dissolution media pH (0.1M phosphate buffers, 185ml):	Dissolution medium #	pH	Dissolution time
	1	1.6	1 hour
	2	3.4	1 hour
	3	4.7	4 hours
	4	6.8	4 hours
	5	7.2	4 hours
	6	7.2	8 hours

3.6.3. Sample Treatment

Following dissolution, 2 ml samples were removed from the receptor vessels and analysed by HPLC, with another drug candidate as the internal standard (Section 2.6.1). Sample concentrations were converted to the mass of drug released after each sampling interval, and used to generate a plot of cumulative percent drug released versus time, producing a dissolution rate profile for each batch of tablets manufactured.

3.6.4. Statistical Comparison of Dissolution Rate Profiles

An important feature in the development of any pharmaceutical product is that it meets the required scientific and therapeutic standards of acceptance. For new drug entities full scale clinical trials are unavoidable, however, for the incorporation of accepted drugs into new dosage forms, it is more cost effective to demonstrate similarity between the new application and an existing approved product, hence bioequivalence studies have gained popularity, and scientific recognition, in recent years, and these studies rely on accurate comparisons of dissolution rate profiles. In addition, comparisons with a reference product provide valuable information during the product development process, therefore it is important that these comparisons are made with scientific confidence, and that they are based on sound statistical models or mathematical relationships.

There are numerous methods for comparing dissolution rate profiles, each with various advantages and disadvantages, and any number of the described methods may be used in combination or alone for ascertaining difference and similarity between curves. In general, complications arise with simple comparative methods, such as statistical testing for significant difference in response at individual time points ($t_{x\%}$ approach), since the profiles are generally non-linear, and differences between curves are a function not only of the magnitude of response, but also of the shape of the curve. Simple comparisons of this nature also contribute nothing to the complete characterisation of curves.

For comparison of curves, the data may be fitted to polynomial equations using least square analysis (102) and the resultant profiles compared. The drawback in this case however, is that the actual data generated is not used for the comparison, but rather the regression trend. The Weibull distribution is another method that has been used, in which the curves are linearised and compared, however, it has been reported that problems with the linearity may arise toward the end of the dissolution test, if 100% of the drug is not released (97). This method is also reliant on estimated values for parameters, such as lag time, which may bias the results obtained. The Rescigno index provides a different approach, whereby the concentrations of drug at various time points are used to calculate

a dimensionless number between 0 and 1, the bioequivalence index (103). This index is a measure of the dissimilarity between curves, however it has been shown to bias curves of higher assay than the reference product (97).

Mean dissolution time (MDT) is a commonly used approach for comparing the rate of drug release using dissolution data, and is said to be more accurate than the $t_{x\%}$ approach (104).

Moore and Flanner (97) devised two mathematical relationships that can be used to evaluate the difference between the percent drug released per unit time for two sets of dissolution data. These values indicate the closeness of the curves with respect to both the height and shape, taking into account the different variance at each time point. Moore and Flanner defined the fit factors f_1 and f_2, which represent the difference and similarity between the curves, respectively, and are shown as Equations 3.1 and 3.2.

$$f_1 = \{\frac{[\sum | R_t - T_t |]}{[\sum R_t]} * 100\} \qquad \text{Equation 3.1}$$

$$f_2 = 50 * \log\{[1 + \frac{1}{n} * \sum w_t (R_t - T_t)^2]^{-0.5} * 100\} \qquad \text{Equation 3.2}$$

f_1 represents the relative error incurred in fitting the two data sets, and must fall below 15 for statistical confidence of similarity to exist. f_2 is the average sum of the square of the difference between the data points, therefore it also comments on the difference between curves, however, it is accepted as an indicator of similarity of profiles. Values for f_2 are mathematically scaled to fit between 0 and 100, with values approaching 100 indicating increasing similarity of the resultant dissolution data. The lower threshold value for statistical similarity is 50, as defined in the FDA's Guidance for Industry (105). Although the FDA accepts this method of comparison, it recommends that the %RSD be less than 20% for early samples and less than 10% for the rest. The f_2 value is reported to be sensitive to measurements obtained after 85% dissolution from either the test or reference formulations, therefore it is recommended that data falling above this point be omitted

(105). It has also been suggested that f_2 has complicated statistical properties, which may jeopardise the validity of this comparison of results (105).

Gohel and Panchal (106) have recently introduced a new mathematical comparative method using a similarity factor, S_d, which reveals the percentage difference between two dissolution profiles, by using the area under the curve as a measure of dissolution efficiency. This method offers a high degree of flexibility, since either percent or amount released can be used, as well as simplicity and ease of interpretation (107, 106). S_d is calculated using the following mathematical relationship:

$$S_d = \frac{\sum_{t=1}^{n-1} \left| \text{Log}((AUC_{Rt})/(AUC_{Tt})) \right|}{n-1} \qquad \text{Equation 3.3}$$

f_2 was calculated for comparisons of curves in this study, as it is recommended by the FDA, and f_1 was used as a supplementary indicator, with $f_2 \geq 50$ and $f_1 \leq 15$ showing similarity of data. In light of the reported drawbacks of using f_2, it was felt that verification of the results achieved using this parameter was required, thus the similarity factor S_d was calculated for each comparison.

CHAPTER FOUR
FORMULATION OF FIVE BETA BLOCKER SUSTAINED RELEASE MATRIX TABLETS BY WET GRANULATION

4.1. SUSTAINED DRUG DELIVERY

4.1.1. Introduction

The pharmacokinetic and pharmacodynamic effects of an administered drug *in vivo* may be effectively altered by manipulation of drug release rates from the administered dosage form. There are various advantages to controlling drug delivery, for example, a drug may be sequestered from regions in the body where it does not exert optimum activity, or where it is deactivated (108), therefore improving the safety and efficacy of drug therapy. This may involve either delayed or targeted drug delivery. Economically, controlled delivery devices may be advantageous since fewer applications may result in more cost effective dosage regimens (108). In addition, a reduction in side effects and adverse drug reactions may be achieved through site-specific delivery or through sustained drug release.

Sustained drug release is one of the most broadly applicable and practically feasible means of controlling drug delivery. In general, a sustained release dosage form is designed to release an initial dose, usually approximately 25% of the drug load, to achieve a therapeutic plasma concentration, and then to continue releasing the active in a sustained manner (remaining 75%), to maintain the therapeutic effect (109, 107). This is generally referred to as bimodal release (78, 110, 111), in which the objective is to achieve plasma levels approximating those of an intravenous infusion (77). For this reason, the drug load incorporated into the dosage form may be several times greater than that of a single dose product. Ideally, sustained delivery achieves a rate of drug release that is independent of time (zero order kinetics), whereby drug is delivered in a constant manner. In practice, however, zero-order kinetics are difficult to achieve (78, 108).

4.1.2. Oral Sustained Release Dosage Forms

All orally administered dosage forms are required to release the entire active dose during transit through the GIT. By altering the formulation composition or mechanical structure of the dosage form, the rate and time course of this release process may be manipulated, to achieve a desired therapeutic outcome (111).

In developing a dosage form for sustained release purposes, the physico-chemical properties of the drug molecule must be considered (109, 112). Different drugs behave differently in the GIT and throughout the body, as well as in different vehicles that may be used for drug delivery. In general, drugs that are suited to sustained delivery are absorbed uniformly from all mucosae of the GIT and rapidly metabolised and eliminated, and drugs that are prescribed in small doses, for chronic conditions (109). In sustained release applications, it is desirable that the rate of absorption be a function of the dosage form rather than the drug itself, since this affords the formulator greater control over the resultant pharmacokinetics of the molecule.

Sustained release dosage forms include ion-exchange resins, slow dissolving chemical complexes, osmotically controlled devices, reservoir devices and monolithic (matrix) systems (108, 109). Although osmotic systems have gained popularity in recent years, the most common sustained release dosage forms are the diffusion-controlled devices, which may include reservoir and matrix systems.

Reservoir systems (membrane systems) include tablets that are coated with an encapsulating film (108, 113), multiparticulate systems with various levels of polymeric coatings, microencapsulated products such as microspheres (109) and osmotically-controlled devices such as the OROS® systems (108). Film coatings used for sustained release purposes are generally made of long chain polymers, which coalesce to form a continuous layer on the surface of the tablet, through which the drug must diffuse, thus limiting the rate of release, which may be affected by the thickness of the polymer coat, as well as the solubility of the drug in the coating material (114). Drug release from these

dosage forms occurs by Fickian diffusion, and a constant rate of release can be achieved (114, 100), thus zero order kinetics may be observed with this technology, as long as the reservoir system is in tact. If the dose incorporated is high enough that penetration of water produces a drug concentration higher than its saturation solubility, a concentration gradient will be maintained and the rate of drug diffusion across the polymer membrane may be constant.

A matrix system was formulated in this study, therefore this type of device and drug release from these systems is described in greater detail.

4.1.2.1. Matrix Devices

Matrix devices are one of the most commonly used sustained release dosage forms, due to their relatively simple fabrication, when compared with coated systems, and due to their high level of efficacy and low potential for toxicity that may be caused by dose dumping (115, 116).

Matrix systems consist of the active ingredient dispersed within a solid matrix material, which can be insoluble plastic type materials, waxes, or hydrophilic polymers, the latter being the most commonly used in recent years (113). Various polymers are suited to this application, such as the high viscosity grade cellulose derivatives, acrylic resins, polyethylene, polyvinyl chloride and many others. Matrices are produced either by granulation and compression or by directly compressing the rate-controlling polymer with the active drug. Compaction results in the formation of multiple inter-particulate bonds between polymer molecules, which inhibit disintegration, and between drug and polymer molecules, which may contribute to the slow rate of release (111).

Matrix systems may release the drug by a single or combination of mechanisms, involving diffusion, dissolution, swelling, erosion, polymer relaxation or hydrolysis, and non-uniform drug distribution (115). In systems that rely primarily on diffusion, drug release is dependent on the rate of diffusion through the matrix and into the surrounding

medium (113, 114), or alternatively through pores in the matrix, or both (89). An initial burst effect may be seen, with drug being released in a sustained manner thereafter, producing the previously mentioned bimodal response. Drugs incorporated at a low dose (0-5% w/w) tend to be released by simple diffusion through the polymer matrix, whereas drugs of a higher load (5-10% w/w) present with more complex release mechanisms due to the introduction of cavities as drug molecules dissolve (108). Regardless of the mechanism, these systems do not generally release drug according to zero order kinetics. For zero order drug release to occur, the rate of release is independent of time or concentration, and the amount released is directly proportional to dissolution time. Instead, matrix systems typically display square root of time dependency (22, 98, 113, 114, 117, 118), where the release rate decreases with time, and is thus usually dependent on the rate of water uptake and drug diffusion through the matrix (119). Figure 4.1 is a simple schematic of the process of drug release from these systems.

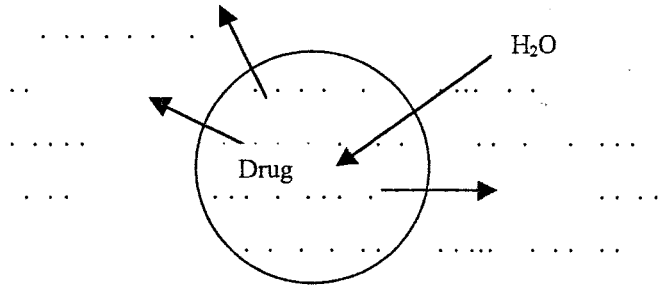


Figure 4.1: Schematic of drug release from matrix controlled release systems.

To gain an understanding of drug release from these systems, one must consider the behaviour of a solute in the matrix. The drug molecule undergoes Fickian diffusion within the matrix vehicle as described by the following derivation of Fick's first law (22):

$$dQ/dt = DC_s/h \qquad \text{Equation 4.1.}$$

where dQ/dt is the rate of drug release per unit surface area of the matrix, D and C_s are the diffusion coefficient and solubility of the drug molecule in the diffusion medium (polymer matrix) respectively, and h is the diffusional pathlength (22). This model requires the assumptions that D is independent of time and drug concentration and that

dissolution is the primary process, and that a pseudo-steady state exists during the controlled release process (120). Considering that drug is continuously diffusing out of the dosage form, resulting in the formation of a depletion zone, it follows that the diffusional pathlength (*h*) is effectively increasing with time, therefore the right hand side of Equation 4.1. is continuously changing, suggesting that a constant rate of release may not be achieved.

Using Fick's first law of diffusion, Higuchi defined the following relationship to describe the release of drugs from matrix tablet formulations (22):

$$Q = [\, D\varepsilon / \tau \,(\, 2A - \varepsilon C_s \,)\, C_s\, t \,]^{1/2} \qquad \text{Equation 4.2.}$$

where Q is the weight (g) of drug released per unit surface area, D and C_s are the diffusion coefficient and solubility of the drug in the polymer matrix, respectively, ε and τ are the porosity and tortuosity constants of the matrix, respectively, and A is the concentration of the drug in the tablet in g/ml. For this model, to describe drug release effectively, it is assumed that a pseudo steady-state is maintained during release, that A is greater than C_s, that perfect sink conditions are maintained, that the drug molecules are smaller than the polymer molecules, that D remains constant and that no interaction between the drug and polymer occurs (113).

From Equation 4.2, it can be said that the amount of drug released is proportional to the square root of time, hence non-linear drug release is observed. This model incorporates a negligible degree of matrix erosion, therefore deviations from the square root of time dependent relationship in the latter part of dissolution may be attributed to erosion (117), in which instance Case II transport is commonly observed. The porosity and tortuosity terms have been included in order to account for drug leaching out via pores in the polymer matrix filled with GIT fluid or dissolution medium, as the case may be (22).

Use of the Higuchi equation allows for identification of parameters that may influence the rate of drug release from a dosage form, such as the drug load (A), the choice of

polymer, since this will affect D, and the tableting process, which has an impact on ε and τ. The desired release rate may be acquired through manipulation of these components, for example, decreasing the porosity of the tablet, by using excipients of higher bulk density (111), would decrease the mass of drug released at any given time point, resulting in a slower release rate.

It has been established that zero order release is not characteristic of matrix devices, however, linear release has been reported with specially designed swelling-controlled devices made from hydrogels or hydrophilic polymers, or both (118, 121, 122). These polymers may be natural, such as guar gum, but are more commonly synthetic, and include substances such as hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), methylcellulose (MC), sodium carboxymethylcellulose (SCMC), ethylene vinyl alcohol (EVA) and polymethacrylate (107, 108), and they are often used in combination, to achieve a desired release rate (78, 107). In such systems, the aqueous dissolution medium penetrates the polymer matrix, which subsequently becomes hydrated and swells. Drug diffuses outwards through the polymer in a counter-current fashion (99). This results in mixed release mechanisms, incorporating swelling/erosion control and diffusion control (115). The interface between the swelling polymer and the medium is called the dissolution/erosion front, while the interface moving towards the centre of the tablet between the gel layer and the unhydrated polymer is called the swelling front, as shown in Figure 4.2. The position and rate of movement of these fronts determines the release rate of drugs from the matrix (115).

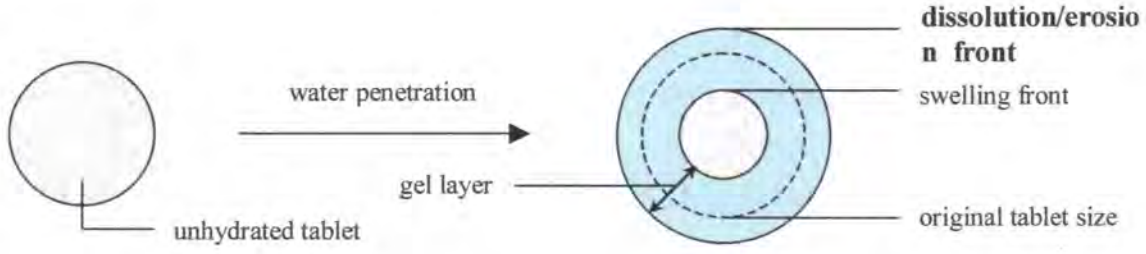


Figure 4.2: Schematic diagram of moving fronts during swelling and dissolution of a matrix tablet (115).

High molecular weight polymers may undergo dissolution to a minor extent, although attrition may also contribute to drug release, which occurs primarily by diffusion through the swollen gel layer (123). Release from these systems may be both Fickian or Non-Fickian, depending on the diffusive mobility of the drug in relation to the penetrating dissolution medium (121). Case II transport may also be observed, and this involves polymer relaxation and disentanglement (123), thus accounting for matrix erosion. When the rate of drug diffusion through the gel layer is faster than the rate at which the swelling front is penetrating into the tablet, zero order release may be observed (121). Zero order release may also occur if the advancement of the swelling front and the attrition of the dissolution/erosion front are synchronised, thus holding the diffusional pathlength constant (62, 115, 123). Figure 4.3 shows that eventually the diffusional pathlength will decrease, due to polymer erosion, however, the release rate will not increase as a consequence, since this is compensated for by the decreased size of the matrix and lower drug concentration remaining in the core (62, 122).

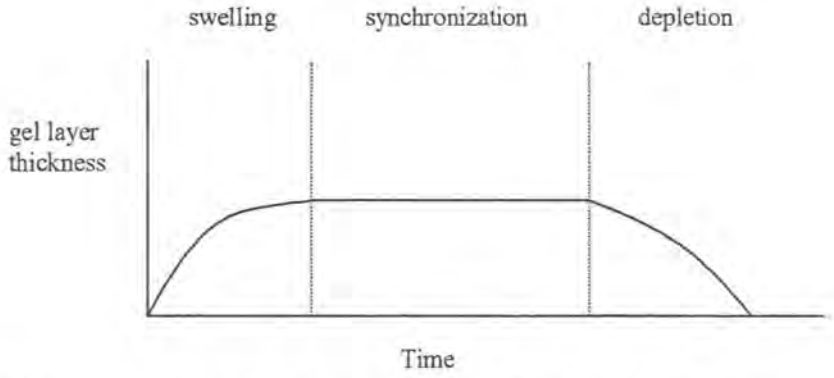


Figure 4.3: Dynamic gel thickness development in a swellable matrix tablet (115).

Release from matrix systems is among the most difficult to model, due to the complexity of the processes that occur. However, various models have been presented, and one method involves fitting the data from drug release rate studies to the following semi-empirical equation derived by Peppas (86):

$$M_t/M_\infty = kt^n \qquad \text{Equation 4.3.}$$

where M_t/M_∞ is the fraction of drug released at time t, k is a constant incorporating both structural and geometric characteristics of a dosage form, and n is the diffusional exponent indicative of the release mechanism (117). It is desirable to have a value of n=1, since this indicates a linear relationship between the fraction released and time, thus depicting zero order release. For most matrix systems, however, square root of time dependency is seen, thus n=0.5 (122). Values between 0.5 and 1 indicate non-Fickian or anomalous diffusion, possibly due to drug release via pores in the matrix, and values for n greater than 1 indicate Case II transport (122).

Other means by which drug release can be altered and slowed include modification of geometry of the drug delivery device (91, 98, 111), as well as excipient interactions, such as ionic polymers that slow the release of charged species (78, 92). In addition, hybrid systems exist, which include combinations of the diffusion-controlled systems described previously. Hybrid systems may include, for example, coated beads that are compressed into a tablet or, alternatively, a matrix tablet core that is coated with a polymer film. These systems may afford further control over drug release, and have been shown to release drug by zero order kinetics (43, 115).

4.1.3. Rationale for Sustained Delivery of Beta Blockers

Beta blockers, one of the most widely administered classes of drugs worldwide, are usually prescribed as chronic therapy for the treatment of hypertension, often in a multiple doses per day regimen. Multiple dosing of the five beta blocker candidates is usually required, since therapeutic plasma levels cannot be maintained on a once daily dose, due to their short elimination half life. To achieve prolonged therapeutic benefits of short acting drugs, inclusion into a sustained release dosage form is a favourable alternative to repeated dosing. In addition, drugs that exhibit rapid elimination kinetics lend themselves to sustained delivery, since the sustained therapeutic effect is then a

function of the dosage form, rather than the drug molecule itself, and drug delivery can be manipulated by formulation modifications.

4.2. TABLET MANUFACTURE

Tablets are the most popular type of dosage form for oral drug delivery, due to their ease of administration, relatively simple fabrication and low cost. As described previously, they can readily be adapted to produce sustained drug delivery. For sustained release applications, tablets may be manufactured using the same techniques as for immediate release formulations, which include wet granulation, dry granulation and direct compression. A brief introduction to the principles involved in wet granulation is described below, and to direct compression in Chapter 5.

4.2.1. Wet Granulation

Wet granulation is a widely applicable method of tablet manufacture involving an intermediate process, whereby powders are converted to free-flowing granules, for compaction into tablets. This method of tablet preparation includes weighing and sieving of dry powders, blending with the addition of a fluid, screening and drying the damp mass, re-screening the dry granules, addition of a lubricant and/or other excipients, and finally, compression into tablets (109, 124). Figure 4.4 in Section 4.3.4.2 is a schematic diagram of the wet granulation method of manufacture used in this study, and it illustrates these processes.

Incorporation into granules enables almost any dry compound to be compressed into tablets, regardless of the physico-chemical properties inherent in the drug or excipients, since the compressibility of the blend is a function of the granule mass, rather than the individual components.

During the granulation procedure, the powder mass is wetted by the addition of a granulating fluid, in order for the powder particles to be combined into agglomerates. The

agglomerates tend to exhibit improved flow and compression properties after drying, compared with the individual powders. This procedure can be performed, for small scale purposes, in a bowl or mortar, or using twin-shell blenders, double-cone blenders or planetary mixers; and on a large scale, using ribbon blenders, high-speed shear mixers or fluid bed apparatus, in which granulation and drying can take place simultaneously (124).

4.3. EXPERIMENTAL

4.3.1. Overview

A prototype wet granulation formula for a sustained release matrix tablet containing MPT (90) was applied to the four other beta blocker candidates, with all variables held constant, in order to assess the affects of the active agent properties on the *in-vitro* behaviour of the final dosage form.

The success of application of the prototype formula to the other beta blockers was evaluated in terms of *in-vitro* drug release characteristics, physical properties of tablets and suitability of the granule/powder blend for the tableting process.

In addition, various loads of the insoluble polymer ethylcellulose, incorporated as Surelease®, were investigated to determine the effect on drug release from this tablet formulation.

4.3.2. Materials Used

4.3.2.1. Drugs

ACE was purchased from Profarmaco (Italy), MPT from K.A. Malle Pharmaceuticals Ltd. (India) and PROP from Kothari Phytochemicals International (India). Both OXP and LAB were purchased from Sifavitor s.p.a. (Italy).

4.3.2.2. Excipients

All materials used in this study are GRAS listed and appear in the FDA Inactive Ingredients Guide for inclusion into oral formulations (125).

4.3.2.2.1. Hydroxypropyl Methylcellulose (HPMC)

HPMC is a propylene glycol ether of methylcellulose (16), and thus exists as a long chain polymer (43). It is soluble in water and forms a viscous colloidal solution (125). HPMC is routinely used for topical formulations as well as in tablet manufacture, where it is used either as a binder, a film-coating agent or as a sustained release matrix-forming excipient (125). It is available in different grades, depending on the degree of substitution and average molecular weight of the polymer (125). These differences result in varying solution viscosities, the higher of which are used for matrix-type sustained release tablets, due to their increased capability for hydration and swelling (92, 93, 119), and since they alter the diffusion coefficient of the drug in the matrix such that release is retarded (119, 123, 126). In addition, HPMC is commonly used because it is biocompatible, highly compressible, and can accommodate a large percentage of drug. Release characteristics of drugs are also fairly resistant to manufacturing variations when incorporated in HPMC matrices (62, 93, 101, 127). In this study, Methocel® (Colorcon, Kent, UK) was used, grade K4M (4000 cp) during granulation, and K100M, (100 000 cp) as a rate-retarding matrix-forming material.

Release of highly water-soluble drugs from HPMC matrices is generally diffusion controlled, and follows the square root of time model as described by Higuchi (62, 92, 123). The HPMC:drug ratio has been reported to affect drug release rate profiles, whereby increasing the polymer content resulted in slower release (92, 93, 94, 128). The release mechanism of drugs from matrices of HPMC has been shown to be regulated primarily by a swelling-controlled diffusional process, for highly water soluble drugs, with polymer erosion playing an insignificant role, whereas for drugs of lower solubility, the release is predominantly polymer dissolution/erosion controlled (115).

4.3.2.2.2. Dibasic Calcium Phosphate (DCP)

DCP is one of the most widely used tablet diluents for both wet granulation and direct compression, since it is relatively stable and has inherent desirable flow and compression characteristics (125). It may be anhydrous or contain two water molecules of hydration (16). DCP is abrasive to compaction apparatus and therefore requires the addition of a lubricant, such as magnesium stearate (124, 125), and it is insoluble in water, forming tablets that do not readily disintegrate (125), unless used with a disintegrating agent, such as sodium starch glycolate or povidone. Emcompress® (Edward Mendell Co. Inc, NY, USA) was used in this study, and it has a mean granular particle size less than 420 μm (125).

4.3.2.2.3. Microcrystalline Cellulose (MCC)

MCC is a purified, non-fibrous, water-insoluble, partially depolymerised cellulose, which is also available in different particle size grades (125). As described for DCP, MCC is a common diluent used for wet granulation and direct compression tableting, yet unlike DCP, this material has some inherent lubricant properties, and a disintegration capability due to its potential for capillary action in aqueous media (124, 125). In addition to this, MCC has some binding capabilities, and it has been reported to contribute to sustained drug delivery (93). Emcocel® 90M (Edward Mendell Co. Inc, NY, USA) was used in this study, and this grade has a mean particle size of 91 μm, and a moisture content less than

5.0%, however it is hygroscopic, as demonstrated in Chapter 3, and should therefore be stored in well sealed containers (125).

4.3.2.2.4. Ethylcellulose

Ethylcellulose is an ethyl ether of cellulose, consisting of β-anhydroglucose units linked together to form long chain polymers (125). It has broad applications in the pharmaceutical industry including use in topical preparations, microencapsulation, tablet coating and tablet granulation (125). Although its main use in sustained release oral dosage forms is as a hydrophobic coating agent, it is also widely used as a matrix former, incorporated either by dry blending or granulation (125). This cellulose polymer is available in various grades, associated with different particle sizes and solution viscosities, the higher grades producing film coatings of greater strength and durability when compared with the lower viscosity grades (125). All grades are practically insoluble in water, producing hard tablets with poor disintegration characteristics (125). Surelease® (Colorcon, Kent, UK), an aqueous ethylcellulose dispersion, was used as the granulating fluid in all wet granulation formulations. It contains 24.97% ethylcellulose solids dispersed in an ammonium hydroxide vehicle, with dibutyl sebacate as a plasticiser, oleic acid as a stabiliser and fumed silica as an anti-adherent (129). It is a stable system, requiring no preparation or manipulation before use, although dilution or warming of the liquid may be necessary, depending on the desired application.

4.3.2.2.5. Magnesium Stearate

Magnesium stearate is one of the most commonly used lubricants in the tableting industry, despite its incompatibilities with compounds such as strong acids, alkalis and iron salts (125), and process difficulties due to its hydrophobic nature. This material tends to be susceptible to over-blending, resulting in soft tablets, and it is generally used at a tablet load of less than 3% (w/w) (125).

4.3.4. Methods

The wet granulation matrix tablets were manufactured according to the following formula, by the method outlined. Good Manufacturing Practices (GMP) were adhered to at all times, with appropriate documentation of any observations and anomalous events that occurred during the manufacturing process. This documentation is presented for all batches, manufactured both by wet granulation and by direct compression, in Appendix 2, and official batch records for all batches are included in Appendix 3.

4.3.4.1. Wet Granulation Tablet Formula

1. Active	20%
Methocel® K4M	10%
Emcompress®	37.5%
Emcocel® 90M	32.5%
	100%
2. Surelease®	0.14-0.18 g/g
3. Methocel® K100M	20%
Emcompress®	10%
Emcocel® 90M	7%
4. Magnesium stearate	1%

4.3.4.2. Method of Manufacture

All powders in (1) were separately weighed, screened (mesh size 20) and granulated with Surelease® (2), using a Kenwood® planetary mixer (Kenwood, UK) on setting 1. After warming to approximately 25°C, the undiluted Surelease® dispersion was added using a peristaltic pump (Masterflex Easyload, Cole-Palmer Instrument Company, IL, USA) which delivered the fluid at a constant rate of approximately 6 g/minute. The blend was then passed through a sieve (mesh size 10) using an oscillating granulator (Erweka, Germany) set at 50 r.p.m. The resultant granules were dried in an oven at 60°C for 12 hours after which they were rescreened (mesh size 10). The weight of the granule mass was recorded. The matrix excipients (3), expressed in the formula as percentages of the resultant granule mass, were then individually weighed, screened (mesh size 20) and

blended with the granules in a 1 kg capacity cube blender set at an horizontal angle, with rotation at 100 r.p.m. for 20 minutes. The magnesium stearate (4) was then weighed, sieved (mesh size 44) and added to the blender, and blending continued for a further 3 minutes. The blend was compressed into tablets on a Manesty® B3B Rotary press, tooled with two sets of biconcave punches at between 30 and 40 r.p.m, to a target weight of 720 mg and a target hardness of 120-160 Newtons (12-16 Kp). Tablets were dedusted using a vacuum through a sieve, and stored away from light until required for analysis. A schematic diagram is included, in Figure 4.4, to give a visual overview of this process.

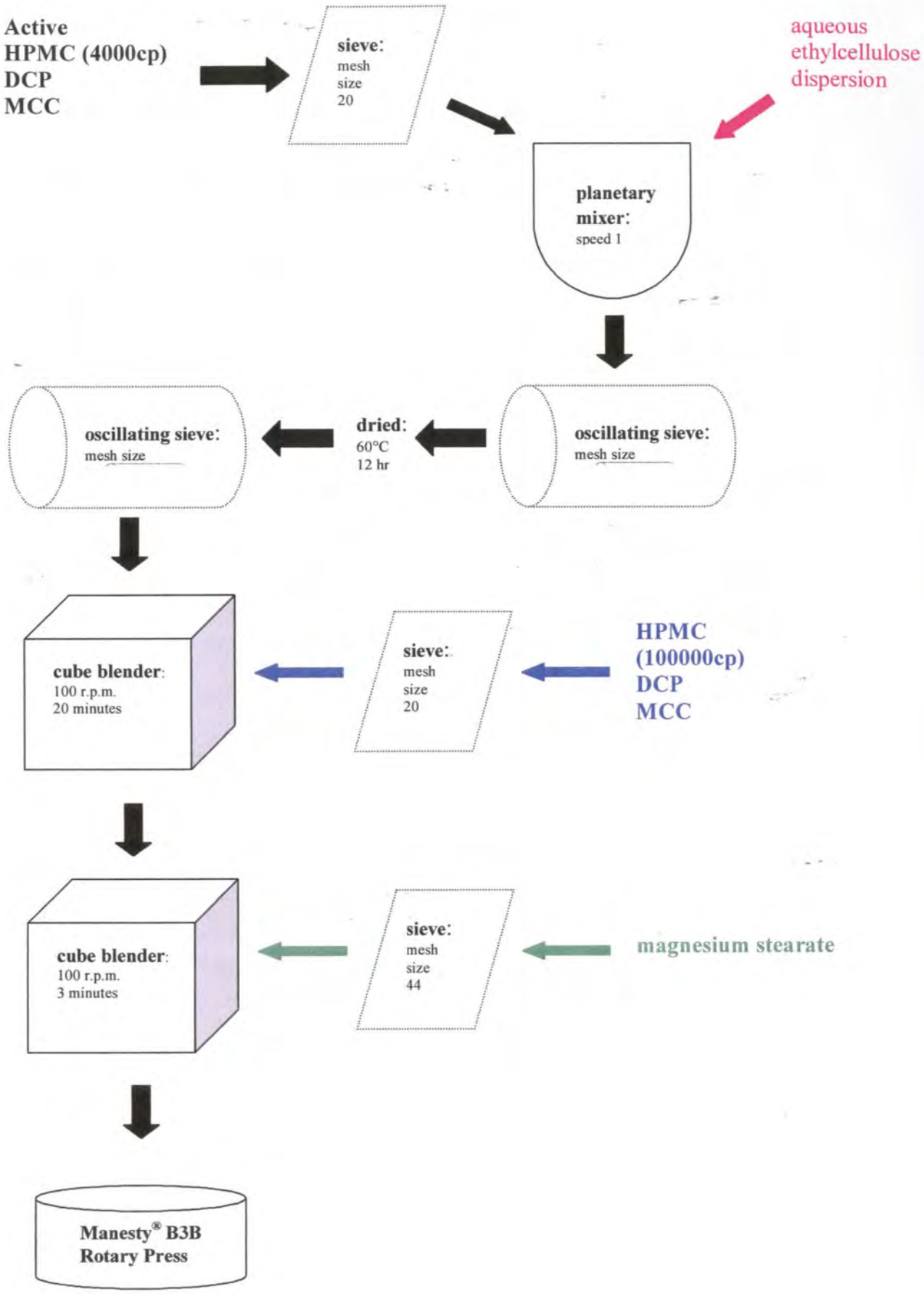


Figure 4.4: Schematic diagram of the wet granulation tabletting process.

4.3.4.3. Effect of Surelease® Load

In an attempt to slow the rate of drug release from these tablets, the granulation fluid, Surelease®, usually incorporated at a load of 2.5-3.5% ethylcellulose solids, was increased to 5% and 10%, by incorporating the additional quantities of Surelease® as indicated in Table 4.1, and the resultant dissolution rate profiles were compared. Blends that became over-wet during granulation, due to excessive addition of fluid, were dried at 40°C for one hour prior to screening.

Table 4.1: Increased Surelease® Loads for Wet Granulation Formulae (500 g batch size)

Batch #	Mass Surelease® added	Mass Ethylcellulose solids	% Ethylcellulose incorporated
M0233	79-90 g	17.5-22.5 g	2.5-3.5%
M0213	100 g	25 g	5%
M0211	200 g	50 g	10%

4.4. RESULTS AND DISCUSSION

4.4.1. Comparison of Dissolution Rates of the Drug Candidates

All five beta blocker candidates selected were successfully incorporated into a prototype matrix tablet formulation, which sustained drug release over a 22 hour dissolution period. Figure 4.5 depicts a typical dissolution profile for each active ingredient, and illustrates the different behaviour of the formulations.

From Figure 4.5 it can be seen that LAB is released at the slowest rate and to the least extent, compared with all other drug candidates. MPT and ACE appear to be released in an almost identical manner, while PROP followed the same release pattern until 10 hours, after which, it's release rate increased. On completion of the dissolution test, PROP was released to a similar extent to OXP, which displayed the highest release rate of all drug candidates from 2 hours onwards.

There are various factors that may contribute to the different release rates observed, such as drug solubility or drug interactions with various excipients. These issues will be addressed further in Chapter 5, and discussed in conjunction with batches of the same active agents, manufactured into tablets by direct compression.

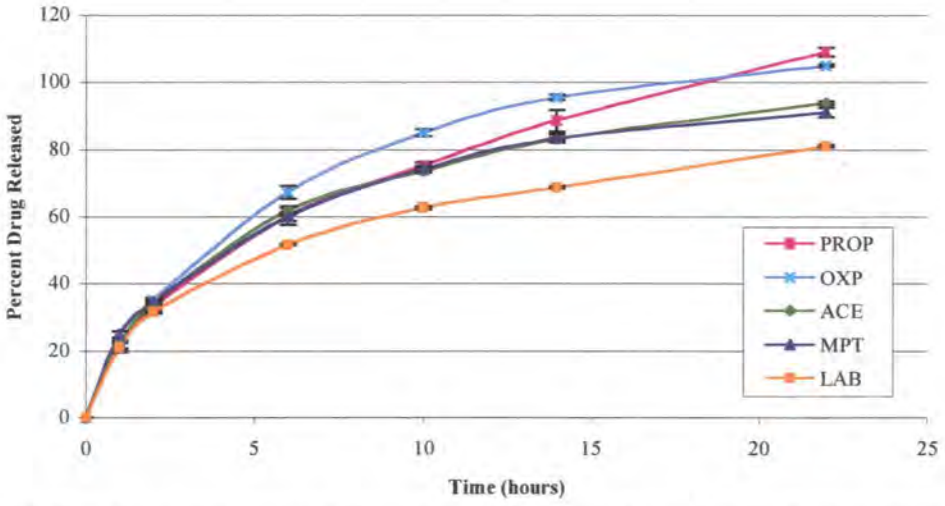


Figure 4.5: Plot of cumulative percent drug released versus time for each of the five beta blockers manufactured by wet granulation.

4.4.2. Effect of Surelease® Load

In this investigation of the Surelease® load effects on drug release, the beta blockers behaved differently from one another, despite their similar physico-chemical characteristics. It was expected that an increase in the quantity of Surelease® used as the granulating fluid would slow the rate and extent of release of each beta blocker from these dosage forms. However, contrary to expectation, this was not the case for all drug candidates under investigation.

The release rates of MPT and OXP were unaffected by the increased Surelease® content, and any further increase in ethylcellulose content. These results are depicted in Figures 4.6 and 4.7, respectively, and may be explained for MPT by the high aqueous solubility of the active, however, OXP is no more soluble than the other drug candidates under investigation, such as ACE, which displayed altered release characteristics. MPT dissolves readily in the ammonium hydroxide vehicle of Surelease®, and therefore drug particles are unlikely to be coated by the ethylcellulose dispersion, since they will dissolve in the liquid and be released at first contact with the aqueous dissolution environment. This may explain why the increased Surelease® load had no significant retardant effect on the release of MPT.

A trend is evident with ACE, PROP and LAB, in that the higher Surelease® loads produced tablets that released drug at a slower rate and to a lower extent than the prototype formulation. This trend is clearly illustrated in Figures 4.8, 4.9 and 4.10, in which one can see a significant difference between the release rate profiles of batches manufactured using different Surelease® loads. The difference between curves was assessed statistically and the results are presented in Table 4.2. As Figures 4.6 and 4.7 suggest, there is no statistically significant difference between batches containing different loads of Surelease® for MPT and OXP, assessed according to the FDA's acceptance criterion for similarity of $f_2 \geq 50$. When comparing the curves for ACE, PROP and LAB, f_2 values less than 50 were expected, in order to verify the dissimilarity of

curves and to demonstrate the retardant effect that Surelease® has on these drugs. As seen in Table 4.2, both ACE formulations manufactured with 5% and 10% Surelease® are statistically dissimilar to their prototype counterpart, and this is clearly evident from Figure 4.8. Although all f_2 values for comparisons of the PROP batches made with different loads of Surelease® were low, not all values fell below 50, however, the trend in drug release characteristics is clearly evident from Figure 4.9. For LAB, none of the comparisons yielded f_2 values less than 50, and although the trend is less obvious when compared with PROP, it is still clearly illustrated in Figure 4.10. This may indicate a degree of insensitivity of the f_1 and f_2 metrics, as has been suggested by Shah et al (105).

The retardant effect of the increased Surelease® load on the release rate of these agents appears to be a function of the complete Surelease® system, rather than merely the addition of more ethylcellulose, since increased levels of ethylcellulose incorporated as a dry powder had no effect on the release profiles of direct compression formulations similar in composition to these wet granulation tablets. These results are presented and discussed further in Chapter 5. It is possible that the rate of drug release from the batches manufactured using Surelease®, as opposed to Ethocel® in the direct compression formulations, is affected by other compounds present in the Surelease® dispersion, such as oleic acid, into which some of the drug may dissolve and may therefore have to partition out during drug release, resulting in altered behaviour of the drug in the dissolution testing environment.

In addition, the Surelease® system may form a coat around portions of the dry powder blend, which may contain drug particles, and produce granules that have a reservoir-like structure, and when compressed into a tablet, form a hybrid-type system, rather than a simple matrix tablet. This may also explain the decreased release rates observed with increased Surelease® loads, since the Surelease®-coated areas would increase in thickness and in mechanical stability, resulting in proportionate decreases in the drug release rate and extent, as seen in the figures presented.

Iqbal et al (130) assessed the effects of different ethylcellulose loads on the release of naproxen (practically insoluble in water) from a wet granulation polymer tablet, and they found that there was a significant decrease in release rates for batches manufactured with greater quantities of ethylcellulose. Their method of manufacture differed however, from the method used in this study, in that dry ethylcellulose powder was incorporated before granulation, rather than in the granulating fluid. In spite of this difference, the results obtained by Iqbal et al show that ethylcellulose has a role to play in determining the rate of release of the active ingredient from these types of dosage forms, although similar results were not expected for this study, since naproxen has a much lower solubility than any of the drug candidates under investigation.

The effects seen in this investigation demonstrate a means by which the release of some of these beta blockers may be controlled, to achieve the desired release rates through manipulation of this formulation variable.

Table 4.2: Statistical Values for Comparison of Curves for Tablet Batches Containing Different Quantities of Surelease®

Drug	Batches Compared	EC Solids Content (%)	f_1	f_2	% Diff.*
ACE	A0231 & A0219	2.5-3.5 vs 5	40.5	28.5	58.73
	A0231 & A0247	2.5-3.5 vs 10	42.4	27.9	68.92
	A0219 & A0247	5 vs 10	4.3	84.0	9.61
LAB	L0223 & L0251	2.5-3.5 vs 5	4.1	78.0	5.03
	L0223 & L0249	2.5-3.5 vs 10	12.5	57.0	16.11
	L0251 & L0249	5 vs 10	8.8	65.6	10.50
MPT	M0233 & M0213	2.5-3.5 vs 5	1.3	92.5	2.34
	M0233 & M0211	2.5-3.5 vs 10	5.1	70.1	3.18
	M0213 & M0211	5 vs 10	5.0	69.3	0.26
OXP	O0221 & O0253	2.5-3.5 vs 5	3.0	77.6	8.52
	O0221 & O0255	2.5-3.5 vs 10	3.2	80.3	2.74
	O0253 & O0255	5 vs 10	2.9	80.6	5.20
PROP	P0133 & P0217	2.5-3.5 vs 5	9.3	55.2	6.31
	P0133 & P0215	2.5-3.5 vs 10	24.4	37.6	29.96
	P0217 & P0215	5 vs 10	16.6	49.2	23.07

*Percent difference between curves was calculated using the similarity factor S_d defined by Gohel (106).

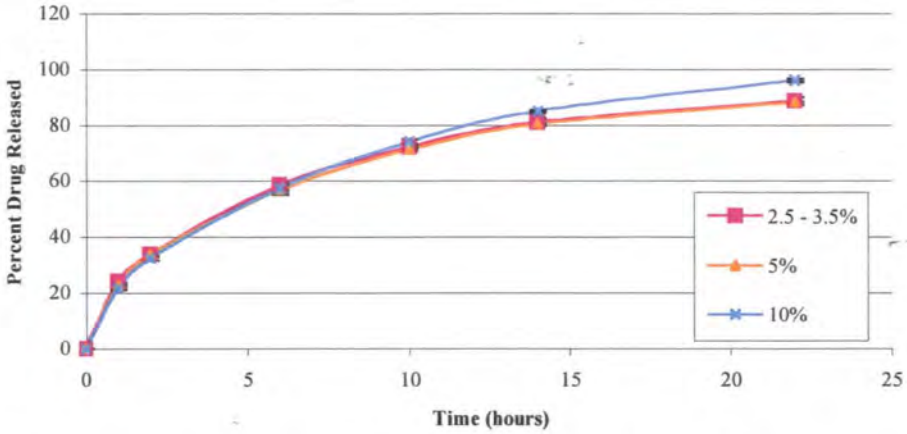


Figure 4.6: Plot of cumulative percent drug released versus time for MPT batches manufactured using Surelease® loads of 2.5-3.5%, 5% and 10% ethylcellulose solids as a percentage of the final formulation.

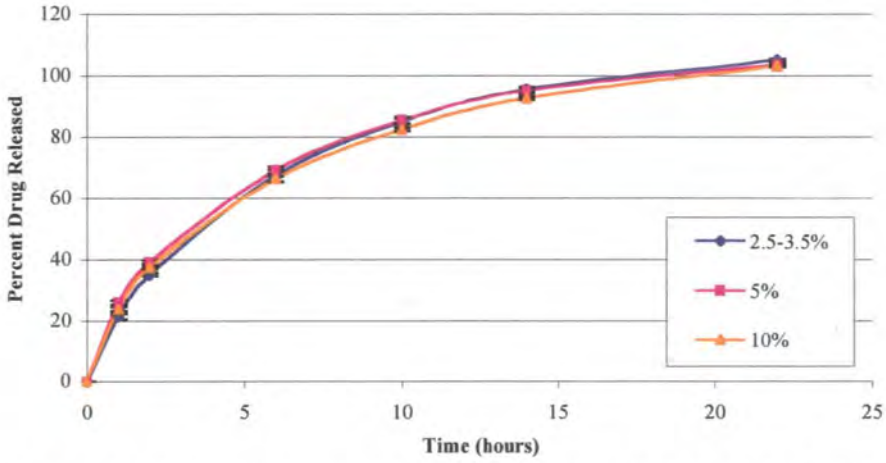


Figure 4.7: Plot of cumulative percent drug released versus time for OXP batches manufactured using Surelease® loads of 2.5-3.5%, 5% and 10% ethylcellulose solids as a percentage of the final formulation.

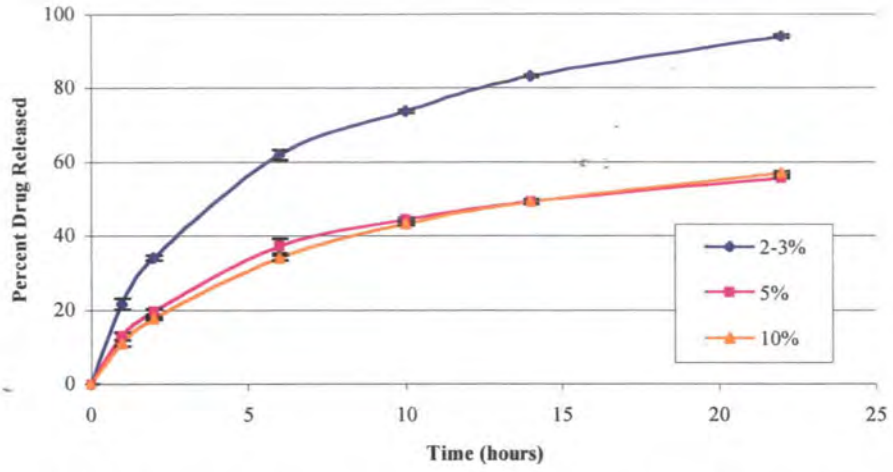


Figure 4.8: Plot of cumulative percent drug released versus time for ACE batches manufactured using Surelease® loads of 2.5-3.5%, 5% and 10% ethylcellulose solids as a percentage of the final formulation.

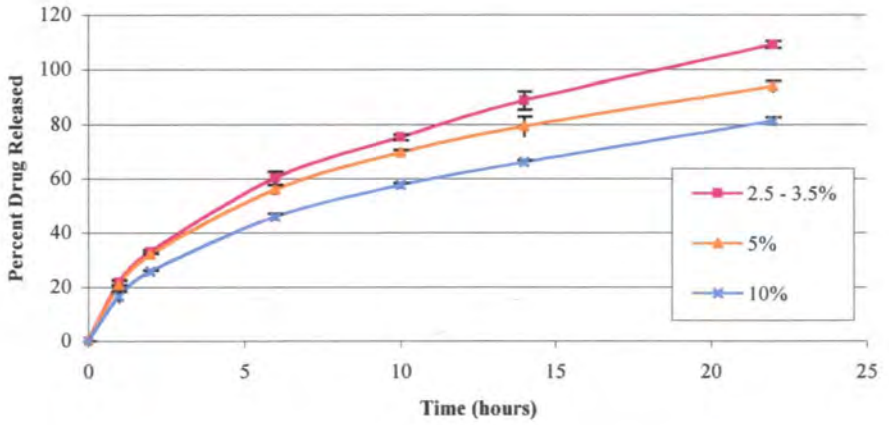


Figure 4.9: Plot of cumulative percent drug released versus time for PROP batches manufactured using Surelease® loads of 2.5-3.5%, 5% and 10% ethylcellulose solids as a percentage of the final formulation.

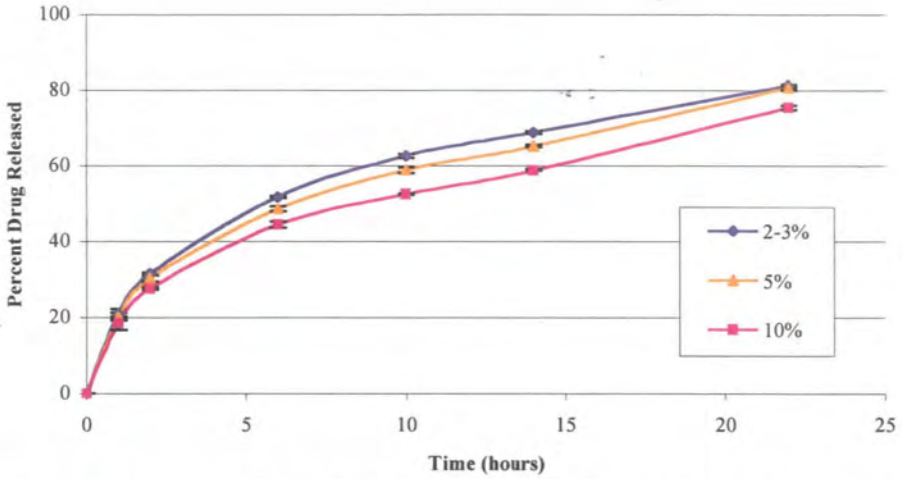


Figure 4.10: Plot of cumulative percent drug released versus time for LAB batches manufactured using Surelease® loads of 2.5-3.5%, 5% and 10% ethylcellulose solids as a percentage of the final formulation.

CHAPTER FIVE
THE DEVELOPMENT AND OPTIMISATION OF FIVE DIRECT COMPRESSION SUSTAINED RELEASE BETA BLOCKER TABLET FORMULATIONS

5.1. INTRODUCTION

5.1.1. Direct Compression Tableting

Wet granulation has traditionally been the preferred method of tablet manufacture, due to its wide applicability in the pharmaceutical industry, however, advances in excipient technology and manufacturing equipment have lead to the increased use of direct compression as a means of manufacture. Direct compression offers improved efficiency, simplicity, and minimisation of potential handling errors during manufacture, and it eliminates the intermediary processes of wet granulation, in that powders are merely weighed, sieved, blended and subsequently compressed.

The simplicity of this method of manufacture is offset by the limited number of excipients with the suitable flow and cohesive properties that may be tableted in this way, and by practical complications that arise due to variables such as ambient temperature and relative humidity. In recent years, a variety of free-flowing, highly compressible excipients have become available as a result of novel methods of preparation. Excipients such as spray-dried lactose and microcrystalline cellulose fall into this category. In addition, tablet presses using forced or induced feeders can ensure adequate and constant filling of die cavities with powders that do not exhibit optimum gravitational flow thus enhancing the tableting process (109, 124).

For drug loads lower than 25% (w/w), suitable diluents may be used in the formulation to impart appropriate flow and compaction properties to the powder blend, however, for higher drug loads, the drug itself must be adequately compressible and have little or no effect on the flowability of the powder blend (124).

Tablets manufactured by direct compression typically show high variability in terms of weight, hardness and thickness, due to sub-optimum flow and compression characteristics of powder blends. Sticking of tablets to die walls and punch faces is also commonly observed, therefore additional anti-frictional agents may be required, not only to perform the role of glidant by enhancing flow properties, but also as a lubricant, to prevent sticking.

5.2. EXPERIMENTAL

5.2.1. Overview

The primary objective of this study was to adapt a previously developed formulation (90) for each of the beta blockers in this study, to a direct compression formula with comparable *in-vitro* drug release characteristics to the wet granulation tablets. Comparisons between direct compression and wet granulation were also made with respect to the physical characteristics of tablets such as uniformity of weight, thickness, diameter, hardness and friability.

A further objective was to optimise the direct compression tableting process by manipulating the anti-frictional component of the formula, without sacrificing the desired release characteristics. Compaction and flow properties of the powder blends were assessed with respect to the anti-frictional agents incorporated into the formula, and dissolution rate profiles of the different batches were compared using the f_1 and f_2 comparative values (97) as well as the percentage difference between the curves, calculated using the similarity factor, *Sd*, defined by Gohel (106).

In addition, in order to gain insight into the behaviour of these tablets *in-vitro*, and to develop an idea of the role of various excipients, the formula was evaluated with respect to changes in the grade and quantity of ethylcellulose incorporated. The HPMC:drug ratio

has been reported to directly affect the rate of drug release from these types of dosage forms (93, 127), therefore the HPMC content, as well as that of the active ingredient, was kept constant throughout the study, in order to isolate the effects of changes in the other components.

Finally, in an attempt to slow the rate and extent of drug release further, an alternative method of manufacture was employed, involving freeze-drying of the drug with an ethylcellulose dispersion. The implication of this is that the formulator may acquire another means of retarding the release rate of those drug candidates that were unaffected by modifications of conventional formulation parameters.

5.2.2. Direct Compression Excipients

As many of the excipients included in the direct compression formulae were used in the wet granulation method, only those that were used exclusively for direct compression have been discussed in this section. All of the materials are included in the FDA Inactive Ingredient Guide, and all except purified talc are GRAS listed.

5.2.2.1. Ethocel®

Ethocel® (Dow Chemical Co.) is a dry ethylcellulose product, and was used as a binding polymer in all direct compression formulations. Six different grades were used, of which three were standard grades (10, 20 and 45), and three were fine particle grades (FP 7, FP 10 and FP 100). The latter have been especially designed for direct compression controlled release applications (131).

5.2.2.2. Purified Talc

Purified talc is a native, anhydrous magnesium silicate (16, 125), mainly used in topical preparations, as a dusting powder, and in solid oral dosage forms, as a lubricant (at 1-10% load) or diluent (at 5-30% load) (125). Talc is not absorbed after oral ingestion and is therefore regarded as non-toxic and is included in the FDA Inactive Ingredient Guide

(125), however, in South Africa, the Medicines Control Council (MCC) requires that talc used for oral preparations be shown to be asbestos free.

5.2.2.3. Colloidal Silicon Dioxide

Colloidal silicon dioxide is a submicroscopic fumed silica, which has a small particle size and large specific surface area, therefore it imparts good flow properties to powder blends, and is subsequently included into tablet formulations as a glidant (125). Other uses for colloidal silicon dioxide are in aerosols that are not intended for inhalation, and in semi-solid preparations, in which it is incorporated as a stabilising or suspending agent (125). Different grades, with different particles sizes, are available. The grade used in this study, Cab-O-Sil® M5 (Cabot Corp, Madras), has a specific surface area of approximately 150 m^2/g and a mean particle diameter of approximately 15 nm (125). All grades are hygroscopic, although, large quantities of water may be absorbed without the powder liquefying, or flowability being compromised (125), and thus it may also behave as a desiccant.

5.2.3. Methods

5.2.3.1. Direct Compression Formula

The final selected direct compression formula for the beta blocker candidates is presented in Table 5.1. The percentage (w/w) of each excipient incorporated in the wet granulation formula has been listed for comparative purposes. As can be seen, the proportion of each component in the direct compression formulation closely approximates that in the wet granulation and thus comparison of tablet batches manufactured by direct compression and wet granulation was easily achieved. The ethylcellulose used was Ethocel® of varying grades, and the values expressed for the ethylcellulose content of the wet granulation formula refer to the solids content of ethylcellulose in the aqueous dispersion Surelease®.

Table 5.1: Direct Compression Formula with Corresponding Wet Granulation Quantities

Ingredient	Direct Compression	Wet Granulation
Active Ingredient	13.5	14
Methocel® K4M (HPMC)	6.8	7
Emcompress®	32.3	33.4
Emcocel® 90M	26.9	28
Ethylcellulose	2.8	2 – 3
Methocel® K100M (HPMC)	14	14
Anti-frictional component	3	-
Magnesium Stearate	0.7	0.7

5.2.3.2. Method of Manufacture

All powders, except for the magnesium stearate and the additional anti-frictional agent, were individually weighed, screened (mesh size 20) and blended together in a cube blender rotating at 100 r.p.m for 20 minutes, at an horizontal angle, as presented in the schematic diagram in Figure 5.1. The anti-frictional agents were then weighed, screened (mesh size 44) and added, and blending continued, for a further 3 minutes. The powder blend was subsequently transferred to the Manesty® B3B rotary press, set at between 30 and 40 r.p.m and tooled with two sets of biconcave punches, and compressed into tablets, to a target weight of 740 mg and a target hardness of 120 to 160 Newtons (12-16 Kp). Tablets were dedusted by a vacuum through a screen, and stored away from light. A schematic diagram has been included in Figure 4.3, to give a visual overview of the direct compression manufacturing process.

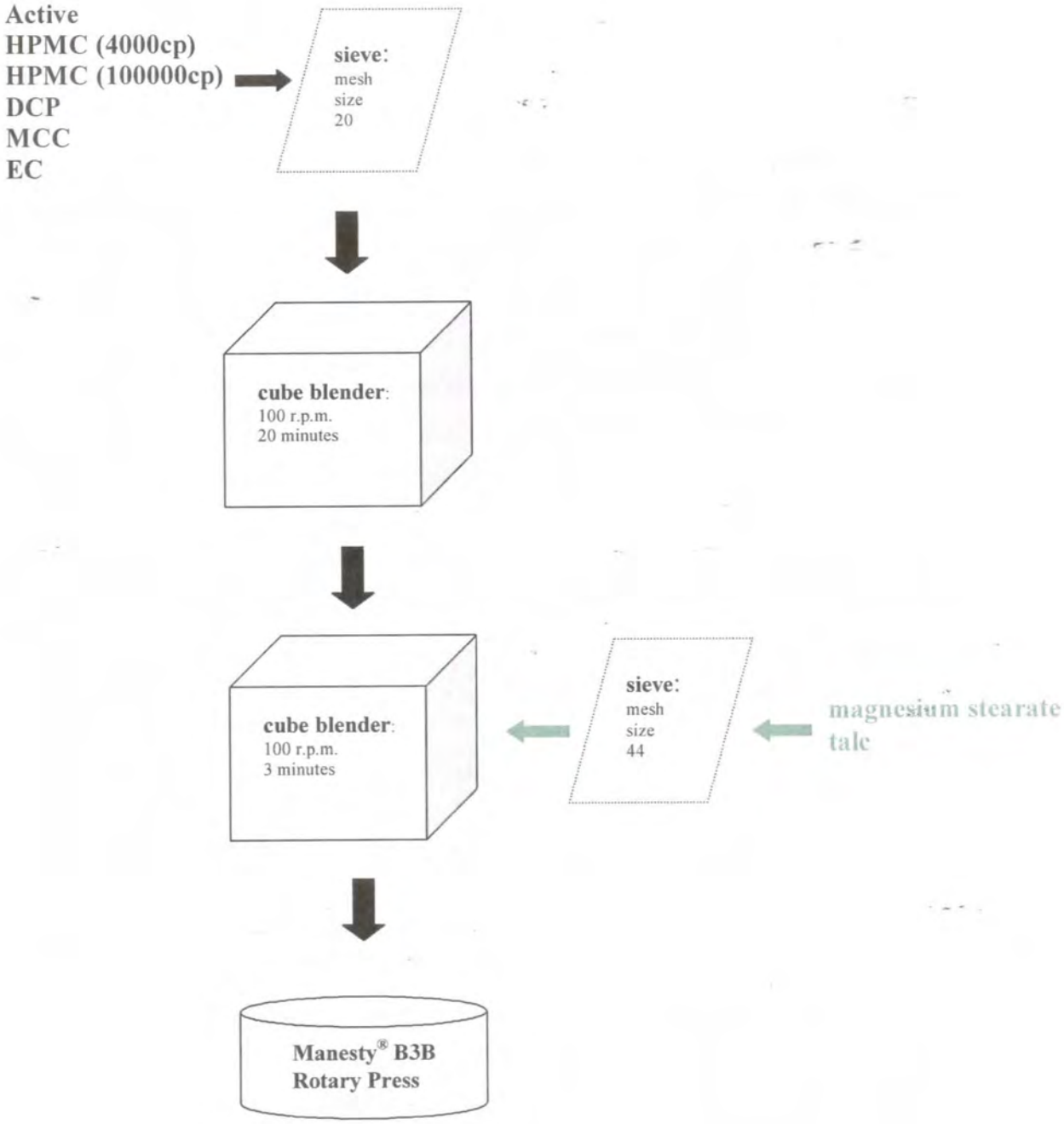


Figure 5.1: Schematic diagram showing the direct compression tableting process

5.2.3.3 Formulation Variables Investigated

5.2.3.3.1. Anti-Frictional Composition

During adaptation of the prototype wet granulation formula to a direct compression method, an additional anti-frictional agent was required to prevent sticking of the tablets to the punches and to improve the flowability of the powder blend whilst running the press. MPT and PROP were used as model drugs, and the anti-frictional agents, purified talc and Cab-O-Sil® M5, were considered as additional glidants. The effects of incorporating each of these, as well as various combinations of these, were assessed. Table 5.2. provides a summary of the various batches manufactured during optimisation of the formula with respect to the anti-frictional component.

Table 5.2: Formulae for Glidant Component Selection

	M0119	**M0135**	**M0143**	**M0137**	**P0125**	**P0139**	**P0141**	**P0165**
MPTA	13.5	13.5	13.5	13.5	-	-	-	-
PHCl	-	-	-	-	13.5	13.5	13.5	13.5
Methocel® K4M	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8
Emcompress®	32.3	32.3	32.3	32.3	32.3	32.3	32.3	32.3
Emcocel® 90M	26.9	26.9	26.9	26.9	26.9	26.9	26.9	26.9
Ethocel® FP 100	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8
Methocel® K100M	14	14	14	14	14	14	14	14
Talc	**-**	**1.5**	**2.5**	**3**	**-**	**1.5**	**2.5**	**3**
Cab-O-Sil® M5	**3**	**1.5**	**0.5**	**-**	**3**	**1.5**	**0.5**	**-**
Magnesium stearate	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7

5.2.3.3.2. Ethocel® Grade

The effects of using different particle sizes and solution viscosities of both the standard and the fine particle grades of the dry ethylcellulose component Ethocel® were evaluated. This was carried out using six different grades for inclusion into both the MPT and PROP tablets, and using three different grades for the evaluation of the other three drug candidates, as presented in Table 5.3. Purified talc was used in all cases as the glidant.

Table 5.3: Direct Compression Batches Manufactured Using Different Grades of Ethocel® at a 2.8% Load

	Ethocel® Grades					
Drug	**Std 10**	**Std 20**	**Std 45**	**FP 7**	**FP 10**	**FP 100**
ACE	A0237				A0225	A0235
LAB	L0241				L0229	L0239
MPT	M0155	M0157	M0153	M0149	M0147	M0137
OXP	O0245				O0227	O0243
PROP	P0169	P0171	P0167	P0161	P0163	P0165

5.2.3.3.3. Ethocel® Load

In light of the decreased drug release rate from the matrix tablets manufactured by wet granulation with increased quantities of Surelease®, it was considered beneficial to ascertain whether an increase in the dry ethylcellulose component of the direct compression formulation would yield a similar result. This was assessed for MPT and PROP, using the FP 10 and the standard 20 grade of Ethocel® at a load of 20%, with a compensatory reduction in the other formulation components, except the active agents, as depicted in Table 5.4.

Table 5.4: Formulae for the Assessment of Increased Ethocel® Load

	M0207	**M0205**	**P0201**	**P0203**
MPTA	13.5	13.5	-	-
PHCl	-	-	13.5	13.5
Methocel® K4M	5.8	5.8	5.8	5.8
Emcompress®	25	25	25	25
Emcocel® 90M	20	20	20	20
Ethocel® FP 10	20	-	20	-
Ethocel® Std 20	-	20	-	20
Methocel® K100M	12	12	12	12
Talc	3	3	3	3
Magnesium stearate	0.7	0.7	0.7	0.7

5.2.3.3.4. Freeze-Drying Method of Manufacture

MPT and PROP were used in these batches wherein a portion of drug powder was dissolved or dispersed in the aqueous ethylcellulose dispersion, Surelease®. This was performed such that two different levels of ethylcellulose were incorporated for each drug, as indicated in Table 5.5. The drug and Surelease® were mixed, frozen in liquid nitrogen, and exposed to a vacuum for 24 hours, to facilitate freeze-dying of the solids

through sublimation. The dried matter was then sieved (mesh size 20), and tableted by direct compression, as outlined in the formulae given in Table 5.6, with quantities of freeze-dried matter incorporated such that a 13.5% drug load was maintained for all formulations.

Table 5.5: Ethylcellulose (EC) Loads Incorporated into Freeze-Dried Batches

Drug	Drug Mass	Surelease® Mass	EC Solids	Drug:EC Ratio	Batch #	EC Load
MPT	90 g	75 g	17.6 g	4.8:1	M0259	2.8%
MPT	90 g	360 g	90 g	1:1	M0261	14%
PROP	90 g	75 g	17.6 g	4.8:1	P0263	2.8%
PROP	90 g	360 g	90 g	1:1	P0257	14%

Table 5.6: Formulae for Freeze-Dried Batches

	M0259	M0261	P0263	P0257
Freeze-dried matter	16.3%	27.5%	16.3%	27.5%
Methocel® K4M	6.8%	6%	6.8%	6%
Emcompress®	32.3%	26%	32.3%	26%
Emcocel® 90M	26.9%	22.8%	26.9%	22.8%
Methocel® K100M	14%	14%	14%	14%
Talc	3%	3%	3%	3%
Magnesium stearate	0.7%	0.7%	0.7%	0.7%

5.3 RESULTS AND DISCUSSION

5.3.1. Comparison of Release of the Five Drug Candidates

The five drug candidates under investigation were incorporated into four formulations containing the same excipients, *viz.* one wet granulation formulation, and three direct compression formulations using three different grades of Ethocel®. Drug release profiles from these four formulations with each of the five active ingredients are presented in Figures 5.2 to 5.5. It is clear that the release characteristics of each drug in each formulation differ, and this may be attributed to the different ways in which these beta blockers are affected by formulation changes.

Drug release from matrix systems has been shown to be influenced by the aqueous solubility of the active species (98, 99, 100, 101) and drugs of lower water solubility are more likely to produce release profiles that follow zero-order kinetics, than highly water soluble compounds (101). Although all five beta blocker candidates are relatively soluble in water, the variation in solubility between drug candidates may have contributed to the range of release profiles obtained. Figure 5.2 depicts drug release curves for tablets manufactured by direct compression using Ethocel® FP 10, and the extent of release of the drugs shown partially correlates with the individual drug solubilities. MPT (solubility 1000:1 of water) is shown to release the highest amount of drug at the fastest rate, while LAB (lowest solubility), released drug at the slowest rate and to the least extent. The residual content of this LAB batch was 12.42% indicating that a significant amount of drug was retained in the dosage form at the end of dissolution testing, compared with lower residual values for the other drug candidates (Table 3.14).

Figures 5.3 and 5.4 depict release rate profiles for tablet batches manufactured in the same way as previously described, using Ethocel® FP 100 and Std 10, respectively, instead of Ethocel® FP 10. These graphs present results that are in contrast to those for the Ethocel® FP 10 grades, however, they are in agreement with one another, showing very little variation between batches incorporating the different beta blockers. These figures suggest that drug release is controlled more by the design of the dosage form,

which is a favourable attribute for sustained release devices, rather than by the physical and chemical properties inherent in the drug under investigation.

Figure 5.5, shows drug release from the wet granulation tablets previously discussed in Chapter 4. Unlike Figures 5.3 and 5.4, Figure 5.5 shows a greater variation between the curves generated, however, the rates of release of the different beta blockers relative to one another are different from the trend observed in Figure 5.2. This also suggests that drug release from the wet granulation formulation is a function of the dosage form rather than a dependence on the drug solubility alone, as was more than likely the case for the direct compression batches manufactured with Ethocel® FP 10 and depicted in Figure 5.2. It is interesting to note however, that LAB was released at the slowest rate in Figure 5.5 as well as in Figure 5.2. Release of highly water soluble drugs from matrix systems is dependent on their diffusion characteristics through the polymer matrix, whereas drugs of lower solubility are released predominantly by polymer disentanglement and dissolution (116). Release of LAB therefore, being of the lowest solubility, would be more dependent on erosion of the dosage form, than are the other drug candidates, and its release would increase in the latter part of dissolution, compared with the other beta blockers, due to erosion of the tablet. This may explain why the curves for LAB do not plateau towards the end of the dissolution test, as did those for the other drug candidates, and provide a possible reason for the slower release rate towards the beginning of dissolution testing.

It is likely that the wet granulation and direct compression formulations behave differently in terms of drug release characteristics, despite containing most of the same excipients. The Surelease® dispersion, used only in the wet granulation formula, may be responsible for influencing the rate and extent of drug release for some of these beta blockers, as discussed previously in Chapter 4, therefore affecting the relative position of the curves to one another, as depicted in Figure 5.5.

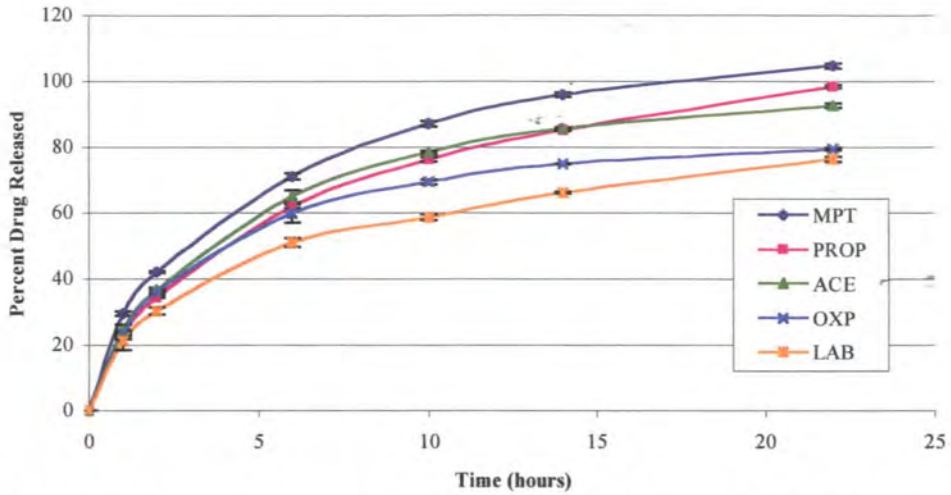


Figure 5.2: Plot of cumulative percent drug released versus time for each beta blocker, manufactured by direct compression using Ethocel® FP10 in the formula.

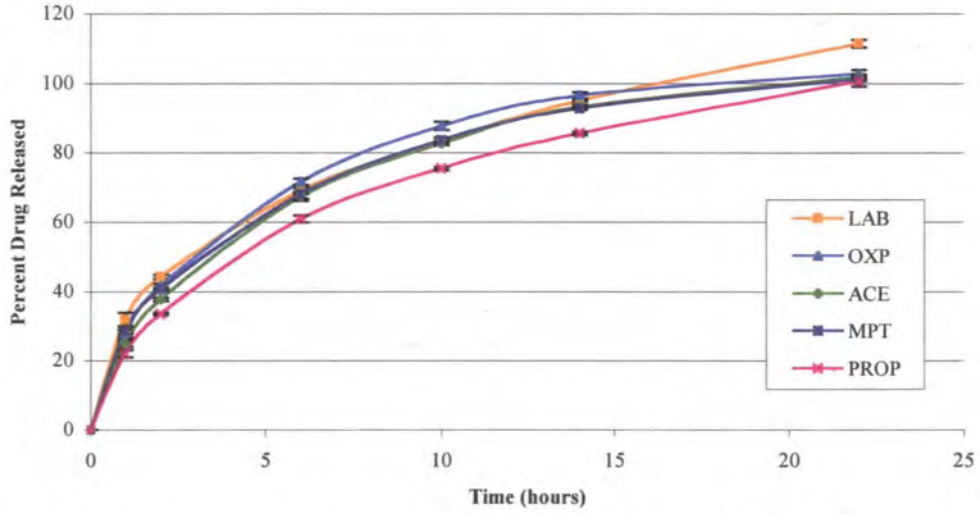


Figure 5.3: Plot of cumulative percent drug released versus time for each beta blocker, manufactured by direct compression using Ethocel® FP100 in the formula.

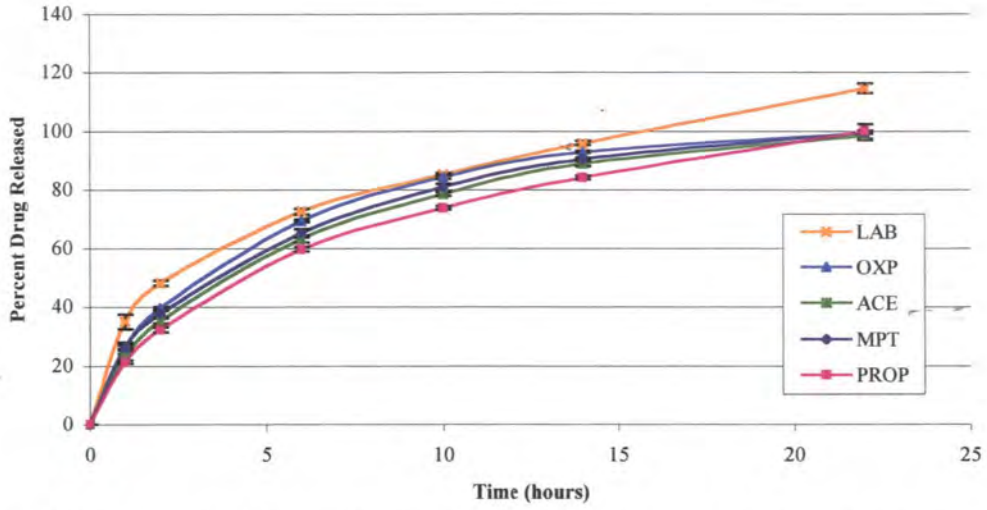


Figure 5.4: Plot of cumulative percent drug released versus time for each beta blocker, manufactured by direct compression using Ethocel® Std 10 in the formula.

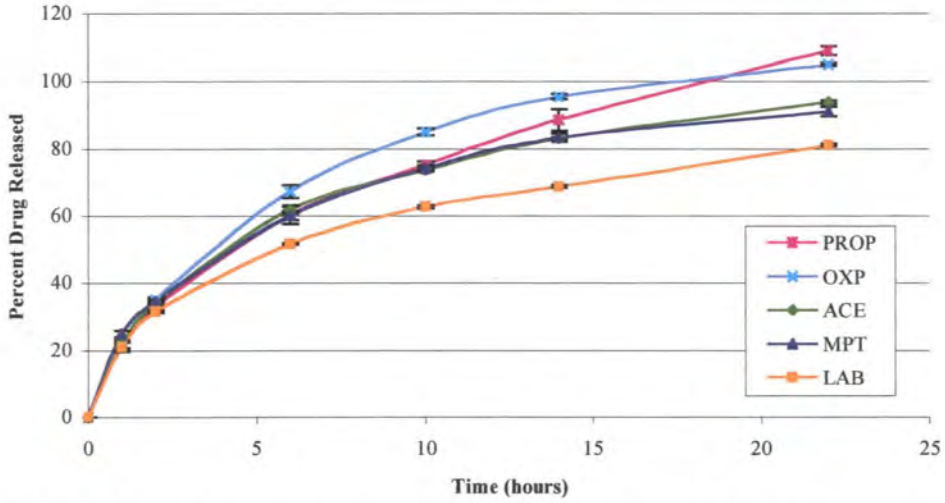


Figure 5.5: Plot of cumulative percent drug released versus time for each beta blocker manufactured by wet granulation.

5.3.2. Conversion of a Wet Granulation to Direct Compression Formulation

The aim of this study was to achieve dissolution rate profiles, using a direct compression method of manufacture, that closely approximate those of the wet granulation formulation containing the same active ingredient. Figures 5.6 to 5.10 show two direct compression dissolution curves and one wet granulation curve for each drug, MPT, PROP, ACE, OXP and LAB, respectively. Each figure contains the two direct compression batches that most closely reproduce the profile of the wet granulation formulation, with the grade of Ethocel® used in the selected direct compression formulae indicated on each graph. In general, the grades most likely to produce the desired release rate profiles were Ethocel® FP 100 and Ethocel® Std 10.

The wet granulation formula for all drug candidates was successfully adapted to a direct compression formula, producing highly comparable release rate profiles. For all drugs except LAB, at least two of the direct compression formulations released drug in a similar manner, whilst only one was successful for LAB. Statistical comparisons between the direct compression curves and each wet granulation profile are presented in Table 5.7, and show that these newly developed direct compression formulations are all similar in release characteristics to the wet granulation tablets, except for one of the LAB profiles. As can be seen, all f_2 values except one fall above 50, thus satisfying the requirement for similarity as described by Moore and Flanner (97). Gohel's similarity factor S_d (106) was used to calculate the percent difference between the curves and these data are presented in the same table.

The formulation developed for PROP was found to be the most robust of all the beta blockers studied, with respect to manufacturing and formulation variables, and this drug candidate resulted in the most successful conversion of the wet granulation formula to a direct compression formulation and manufacturing process. PROP produced six direct compression formulations with different grades of Ethocel®, all of which released PROP in a precise and similar manner to that of the wet granulation formulation, as shown in

Figure 5.7, and in a similar manner to one another, as discussed in the Ethocel® grade assessment studies described in Section 5.3.4.

MPT, ACE and OXP produced batches with good correlation to the wet granulation, in terms of drug dissolution rate profiles, and, although only one of the LAB batches showed statistically significant similarity, the likeness of the profiles is evident. This study demonstrates that it is possible, not only to mimic the wet granulation profiles of all drug candidates, but also to manipulate the drug release characteristics by simple alterations of the direct compression formulae.

Table 5.7: Statistical Values for Comparisons of Wet Granulation and Direct Compression Curves

Drug	Batches Compared	Comparison	f_1	f_2	% Diff.*
MPT	M0233 & M0151	WG & DC (FP100)	12.8	54.3	14.2
	M0233 & M0155	WG & DC (Std 10)	8.6	61.5	8.2
PROP	P0133 & P0165	WG & DC (FP100)	3.5	70.4	0.3
	P0133 & P0169	WG & DC (Std 10)	4.3	68.1	1.6
ACE	A0231 & A0225	WG & DC (FP10)	4.5	75.2	7.8
	A0231 & A0237	WG & DC (Std 10)	5.2	70.8	5.1
OXP	O0221 & O0243	WG & DC (FP100)	5.7	67.3	13.9
	O0221 & O0245	WG & DC (Std 10)	5.0	70.0	8.7
LAB	L0223 & L0229	WG & DC (FP10)	4.3	75.8	2.2
	L0223 & L0239	WG & DC (FP100)	37.3	34.0	38.1

*Percent difference between curves was calculated using the similarity factor S_d defined by Gohel (106).

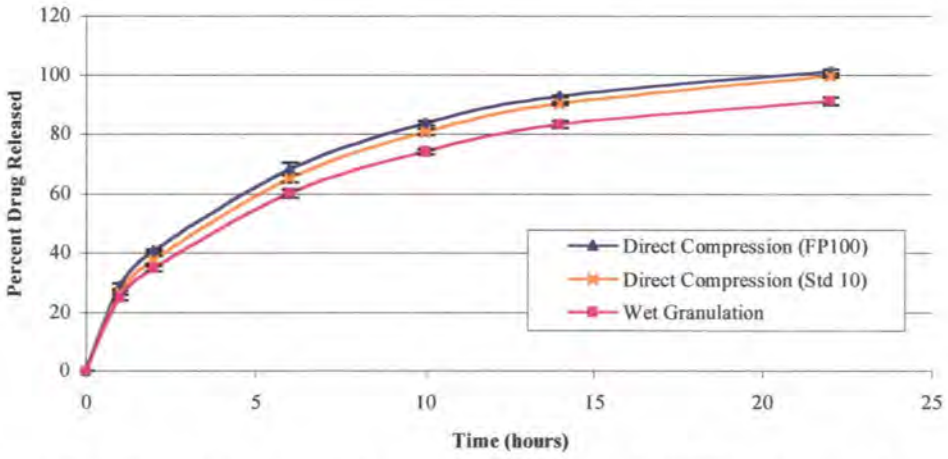


Figure 5.6: Plot of cumulative percent drug released versus time for MPT batches manufactured by wet granulation and direct compression.

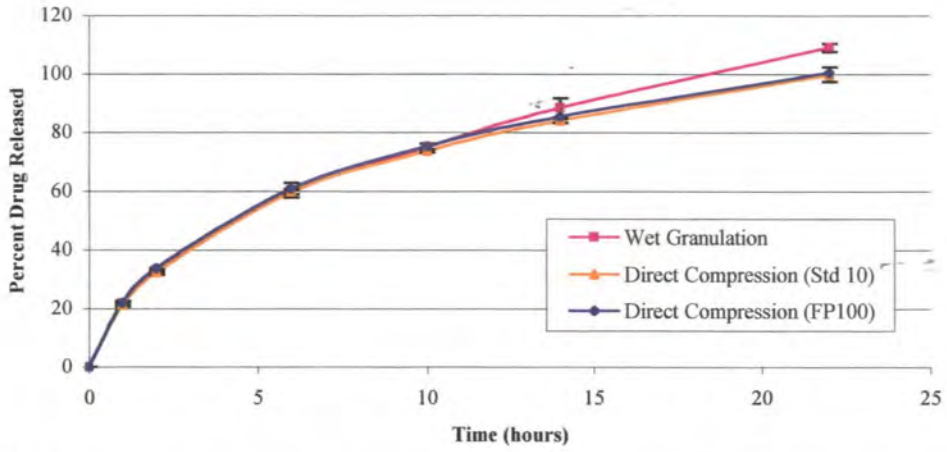


Figure 5.7: Plot of cumulative percent drug released versus time for PROP batches manufactured by wet granulation and direct compression.

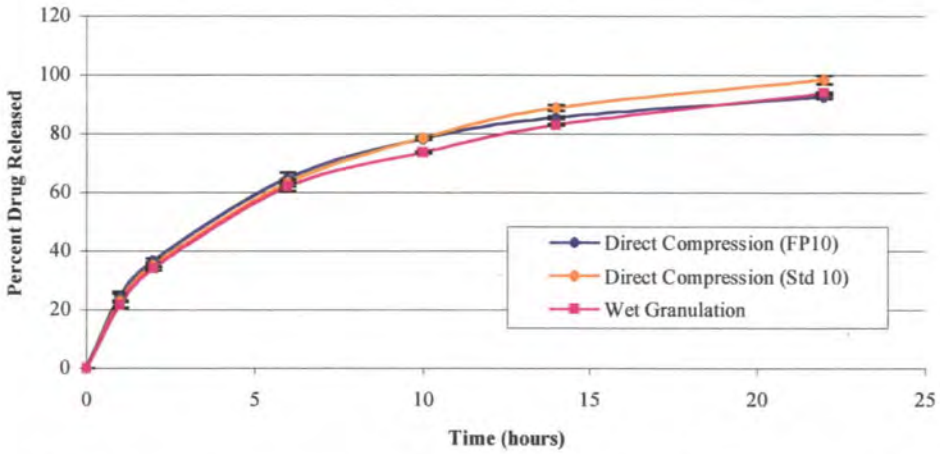


Figure 5.8: Plot of cumulative percent drug released versus time for ACE batches manufactured by wet granulation and direct compression.

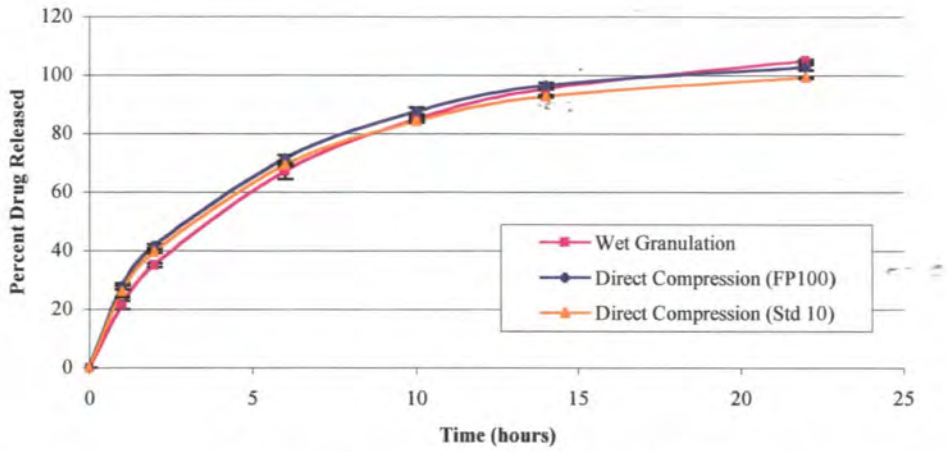


Figure 5.9: Plot of cumulative percent drug released versus time for OXP batches manufactured by wet granulation and direct compression.

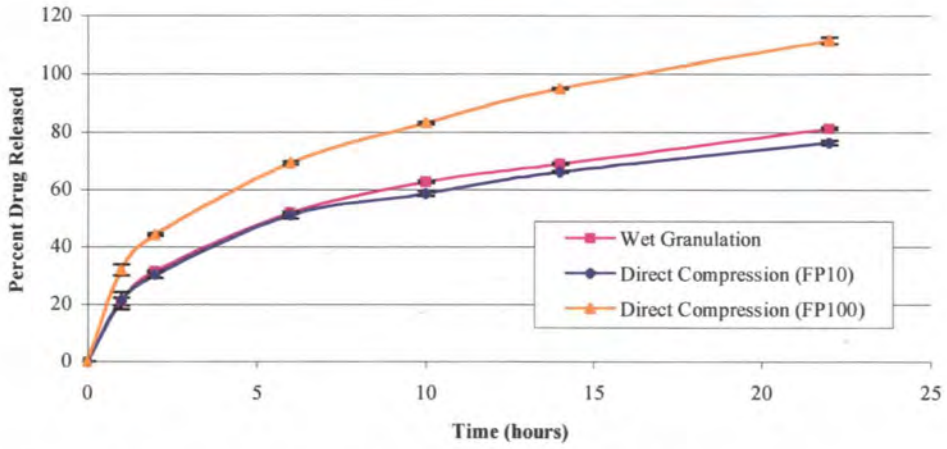


Figure 5.10: Plot of cumulative percent drug released versus time for LAB batches manufactured by wet granulation and direct compression.

5.3.3. Effect of Anti-Frictional Composition

MPT and PROP were selected as the model drugs for this experiment, and the results of changing the anti-frictional component on dissolution rates are presented in Figures 5.11 and 5.12. Initially the results for each active drug appear to differ, with PROP being unaffected by the anti-frictional component and MPT showing a large degree of variation. However, it can be seen from Figure 5.11, that the release rate profiles for MPT batches manufactured using 3% Cab-O-Sil® M5 and those using 3% purified talc, are similar, releasing the drug to almost exactly the same extent at the end of the dissolution test. The curves for 1.5%:1.5% and 2.5%:0.5% talc:Cab-O-Sil® M5 are anomalous, with no trend in drug release evident, and this variation appears to be an artefact of the manufacturing process, rather than the glidant used. It is unlikely that an interaction between Cab-O-Sil® M5 and talc has resulted in altered release profiles, compared with profiles generated using either glidant alone, since the two combinations appear to have an opposite effect on the rate of release. An interaction would shift both curves in the same direction, since the same materials are used for both formulations. In addition to this, shifting of curves was not observed for the same tablets manufactured with PROP, suggesting no interaction between these components. DSC studies carried out on these two excipients individually, as described in Section 3.3, revealed thermograms which indicated no thermal events for either excipient when heated up to 210°C, suggesting that these materials are stable throughout the manufacturing process employed in this study, therefore a significant interaction between these compounds was not expected.

Although the curves in Figure 5.11 appear to be different from one another, f_1 and f_2 values show that they are all not significantly different except for the two batches containing 1.5% and 2.5% talc. Statistical values presented in Table 5.8 reveal that the f_2 value for this comparison is 49.8, thus these curves are in fact deemed similar, with an f_2 value of approximately 50. According to the calculated S_d similarity factor, these two curves are only 13% different from one another. All PROP curves are statistically similar, with 8.53% the largest difference between any two of the curves, as indicated in Table 5.8.

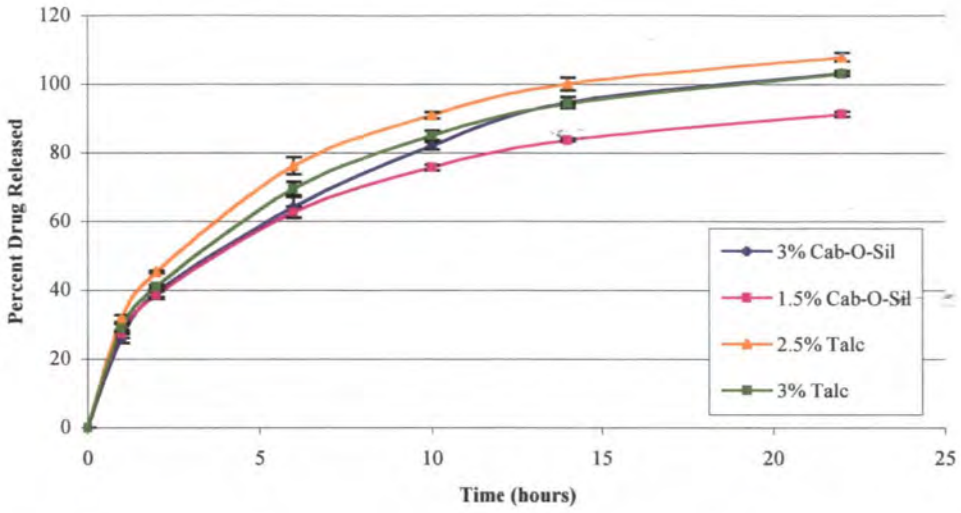


Figure 5.11: Plot of cumulative percent drug released versus time for MPT batches manufactured with different anti-frictional agent combinations.

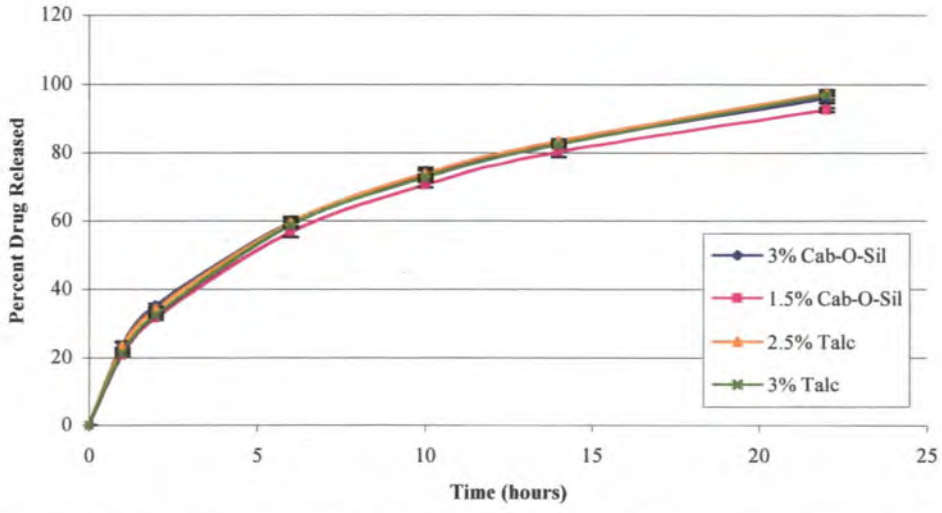


Figure 5.12: Plot of cumulative percent drug released versus time for PROP batches manufactured with different anti-frictional agent combinations.

Table 5.8: Statistical Comparison Values for Glidant Component Comparisons

Drug	Batches Compared	Glidant Comparison*				f_1	f_2	% Diff.**
		3% C	1.5% T	2.5% T	3% T			
MPT	M0159 & M0143			X	X	7.1	63.9	8.97
	M0159 & M0135		X		X	6.0	64.2	3.45
	M0159 & M0119	X			X	3.3	75.3	6.79
	M0159 & M0135		X	X		12.2	49.8	13.00
	M0143 & M0119	X		X		9.5	55.6	16.34
	M0135 & M0119	X	X			5.8	66.1	2.76
PROP	P0165 & P0141			X	X	1.8	89.3	4.18
	P0165 & P0139		X		X	3.4	78.5	2.70
	P0165 & P0125	X			X	2.3	85.5	5.25
	P0141 & P0139		X	X		5.1	72.6	7.46
	P0141 & P0125	X		X		0.8	95.1	0.49
	P0139 & P0125	X	X			5.3	73.6	8.53

* C = Cab-O-Sil® M5, T = talc

** Percent difference between curves was calculated using the similarity factor S_d defined by Gohel (106).

Lee et al (93) achieved zero order release of melatonin, a poorly water soluble drug, over 10 hours, from a matrix formulation of high viscosity grade HPMC, magnesium stearate and colloidal silicon dioxide. As can be seen from Figures 5.11 and 5.12, neither Cab-O-Sil® M5 nor talc produced zero order release profiles when used with HPMC in the batches manufactured in this study. The low water solubility of melatonin is likely to have contributed to the achievement of zero order release in that study, and may account for the different release profiles obtained in this study, with water-soluble drug candidates.

With respect to the resultant physical properties of the manufactured tablets, talc appeared to be of more benefit than Cab-O-Sil® M5, for achieving the desired tablet weight. Table 5.9 provides a summary of the effects of the different anti-frictional agents on various physical properties of the tablets. As can be seen, there is a strong correlation between the percent talc incorporated and the mean tablet weight and thickness. As the talc load was increased, the tablet thickness increased, with a corresponding increase in tablet weight, and a one tailed t-test comparing batches with 3% Cab-O-Sil® M5 to those with 3% talc revealed a significant difference between the mean tablet weight for both MPT and PROP. This increase in weight may be a result of the densifying action of talc on the powder blend, due to its greater bulk density when compared with the colloidal

silicon dioxide. The target tablet weight for these direct compression products, incorporating a dose of 100 mg of active drug, was 740 mg. Consequently, talc was preferred as a glidant to Cab-O-Sil® M5, as it improved the likelihood of achieving the desired target weight. The relationship between the talc component and mean tablet weight is shown in Figure 5.13, for both MPT and PROP, illustrating the desifying effect that talc has on the powder blend.

Table 5.9: Physical Properties of Tablets Manufactured using Different Anti-Frictional Components

Drug	Batch #	Anti-Frictional (%Cab-O-Sil®: %talc)	Weight (mg)	Thickness (mm)	Hardness (N)	Diameter (mm)
MPT	M0119	3:0	602.0 ± 10.0	7.07 ± 0.02	107.9 ± 13.6	11.29 ± 0.03
	M0135	1.5:1.5	607.4 ± 26.5	6.95 ± 0.07	112.2 ± 35.7	11.31 ± 0.03
	M0143	0.5:2.5	654.1 ± 19.0	7.15 ± 0.04	140.1 ± 25.7	11.26 ± 0.01
	M0159	0:3	701.1 ± 19.0	7.69 ± 0.04	115.8 ± 19.8	11.27 ± 0.01
PROP	P0125	3:0	602.2 ± 25.2	6.97 ± 0.06	116.1 ± 34.6	11.29 ± 0.04
	P0139	1.5:1.5	639.3 ± 7.2	7.12 ± 0.05	158.0 ± 12.2	11.25 ± 0.02
	P0141	0.5:2.5	696.9 ± 22.1	7.64 ± 0.02	146.9 ± 22.5	11.23 ± 0.01
	P0165	0:3	718.9 ± 18.5	7.88 ± 0.03	115.6 ± 21.2	11.25 ± 0.01

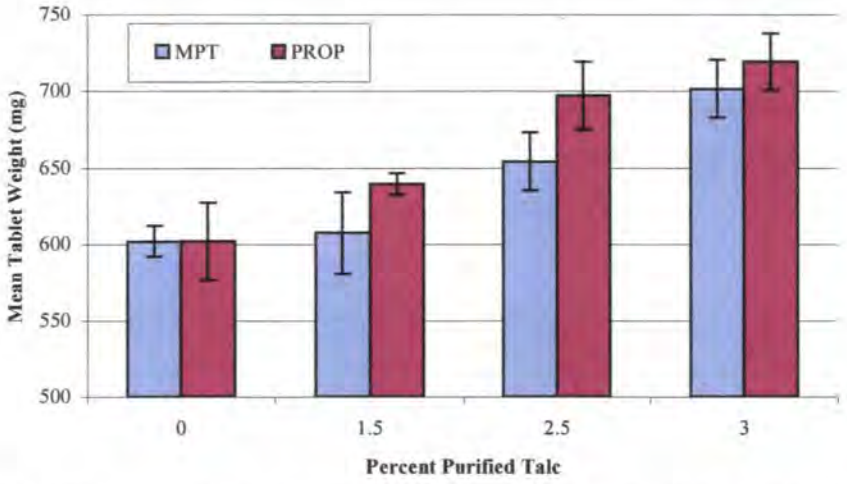


Figure 5.13: Relationship between percent purified talc and mean tablet weight for MPT and PROP formulations.

The primary function of a glidant is to improve the flow properties of a powder blend, and in this case the glidant(s) used, Cab-O-Sil® M5 and/or talc, worked in a complementary fashion with the lubricant magnesium stearate, which acts on the surfaces of the punch faces and die walls, to prevent sticking of the formulation during compaction. No sticking or filming was observed during this investigation, and all glidant

compositions appeared to facilitate satisfactory compression of the blends into tablets. Flow of the powder blends from the hopper into the die was assessed using uniformity of tablet weight as an indicator, expressed as %RSD, and these values are presented in Table 5.10. Cab-O-Sil® is known to improve flow properties due to its small particle size and large specific area (93), therefore it was expected that the powder blends with higher colloidal silicon dioxide loads would display improved flowability, and hence more uniform tablet weight. Laicher and Profitlich (78) reported that colloidal silicon dioxide did not improve the flow of a direct compression powder blend which contained cellulose polymers such as hyrdoxypropylcellulose and methylcellulose, and as can be seen from Table 5.10, neither Cab-O-Sil® nor talc appeared to alter the flow properties of the powder blend in this study.

Content uniformity analyses were performed on batches of tablets containing 3% Cab-O-Sil®, 1.5%:1.5% Cab-O-Sil®:talc, and 3% talc, and, as presented in Chapter 3, the content uniformity improved for batches with increasing quantities of talc in the formula. Demonstration of content uniformity is important for regulation and approval of a dosage form, therefore these results indicate that talc is more favourable than Cab-O-Sil® M5 in this respect, as tablets with a higher talc loading are more likely to achieve the desired recovery levels during content uniformity analysis.

Table 5.10: Uniformity of Tablet Weight for MPT and PROP Batches

Drug	Batch #	Anti-Frictional (%Cab-O-Sil®: %talc)	%RSD of Mean Tablet Weight
MPT	M0119	3:0	1.66
	M0135	1.5:1.5	4.36
	M0143	0.5:2.5	2.90
	M0159	0:3	2.71
PROP	P0125	3:0	4.19
	P0139	1.5:1.5	1.12
	P0141	0.5:2.5	3.17
	P0165	0:3	2.58

In summary, the inclusion of different glidants appeared to have little or no effect on the release profiles of either MPT or PROP from this formulation, and all anti-frictional components prevented sticking and promoted adequate flow of powder blends into die cavities, such that tablets of uniform weight and thickness were produced. Talc appeared

to be better than colloidal silicon dioxide in terms of densification of tablets, so that the desired target weight of 740 mg may be achieved. The tablets of lower thickness, however, are favourable for swallowing and would therefore improve patient compliance, thus Cab-O-Sil® M5 may be better in this respect. The tablets manufactured using 3% talc, although thicker than those manufactured using 3% Cab-O-Sil® M5, were of an acceptable thickness, and in light of the higher density of the powder blends prior to compaction, 3% talc was selected as the glidant component of choice for this formulation, and was used for all further batches manufactured in these studies.

5.3.4. Effect of Ethocel® Grade

Different grades of Ethocel® are made of ethylcellulose polymers of different molecular weight, and produce different solution viscosities (131). The fine particle grades used in this study are specifically designed for direct compression purposes (131), and while they produce a solution of similar viscosity to their standard grade counterparts, they have a much finer particle size. It was expected that this property would allow for greater distribution of the ethylcellulose particles throughout the powder blend, therefore imparting increased hydrophobicity to the tablet core, since ethylcellulose is hydrophobic in nature. For this reason, a slower drug release rate was expected with the fine particle grades than with the standard grades, however, this trend was not observed. Figures 5.14 to 5.16 show the dissolution rate profiles for batches containing MPT, PROP and ACE, respectively, manufactured using various grades of Ethocel® (Table 5.3) as indicated in the figures. All three figures suggest that the type and grade of Ethocel® incorporated into the tablet batches had no significant effect on the rate or extent of drug release, and no trends in drug release characteristics were evident for standard or fine particle grades. f_1 and f_2 values verify statistically that these curves are similar, and the resultant values for all comparisons are presented in Table 5.11 (pg 136). In this case, all comparisons revealed that the curves are less than 12% different in terms of area under the curve for each pair tested, as shown in the same table.

A study conducted by Makhija and Vavia (119) revealed that the viscosity grade of ethylcellulose incorporated into a direct compression matrix tablet had no significant effect on the release rate of venlafaxine, which is of a similar aqueous solubility to MPT. In another study, Lee et al (93) reported that increasing the viscosity of a polymer resulted in a decreased drug release rate, however, this was with reference to the rate-controlling polymer, which, in the matrix tablets of this study, was HPMC rather than ethylcellulose. In light of this, the results shown in Figures 5.14 to 5.16, depicting similar release profiles, were as expected. It is reasonable to say that since ethylcellulose is insoluble in the aqueous environment of the dissolution apparatus and in that of the GIT, the polymer would not dissolve and hence solution viscosity would play little or no role in altering the rate of drug release.

Pollock and Sheskey (132) showed that the fine particle Ethocel® grades produced significantly slower drug release from ethylcellulose matrix tablets, for a drug that is freely soluble in water, than the granular standard grades, however, this Ethocel® was used at a load of approximately 50% of the formulation, whereas in the matrix tablets in this study, Ethocel® comprised only 2.8%, hence such effects were not observed. The high ethylcellulose load in the former case suggests that Ethocel® was the rate-controlling polymer in those formulations, as opposed to HPMC, which was the rate-controlling polymer in the tablets manufactured for this study.

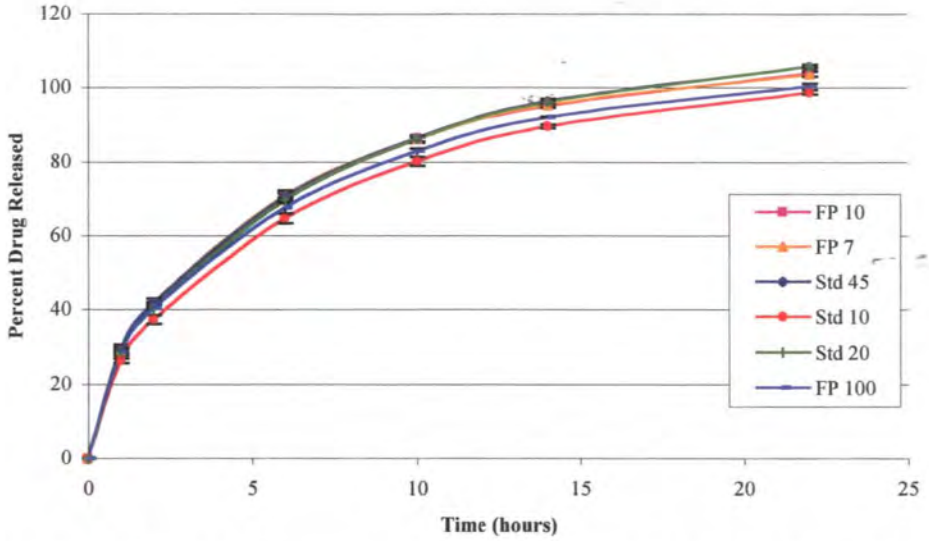


Figure 5.14: Plot of cumulative percent drug released versus time for MPT batches manufactured with different grades of Ethocel®.

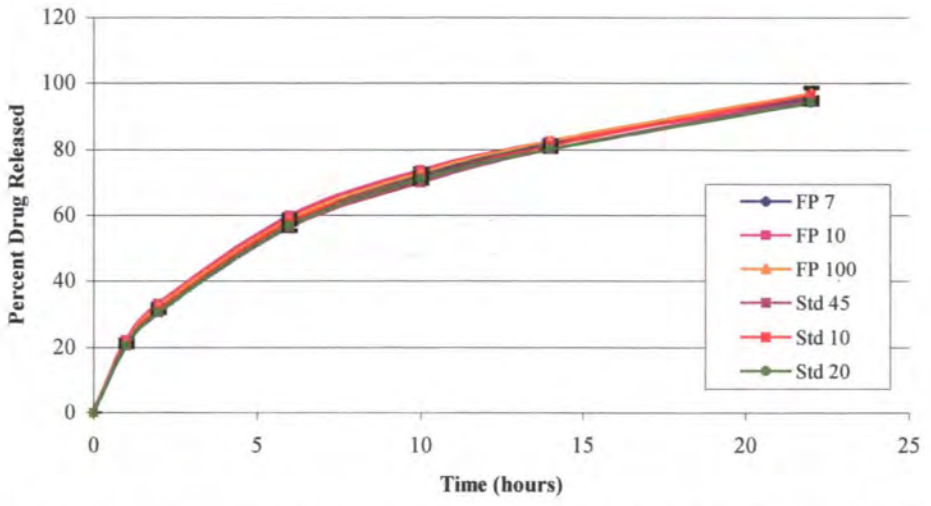


Figure 5.15: Plot of cumulative percent drug released versus time for PROP batches manufactured with different grades of Ethocel®.

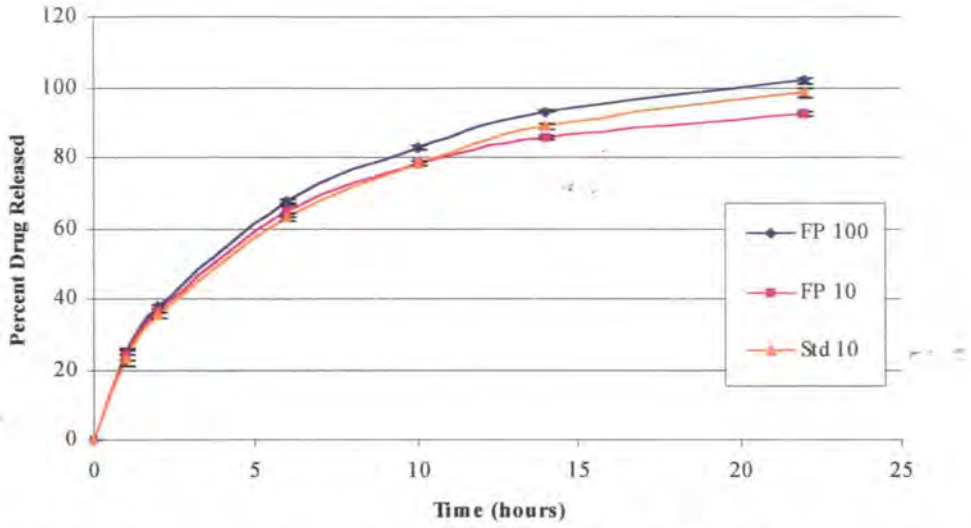


Figure 5.16: Plot of cumulative percent drug released versus time for ACE batches manufactured with different grades of Ethocel®.

In contrast to these results, Figures 5.17 and 5.18, that depict the release of LAB and OXP respectively, show a change in release rate for one of the Ethocel® grades investigated. Ethocel® FP 10 appears to retard drug release such that less than 80% was released after 22 hours, for both LAB and OXP, and these figures show a difference of up to 47.74% between batches manufactured with Ethocel® FP 10 and the other grades, as indicated in Table 5.11. These results were unexpected, since they are not in agreement with those obtained for the other drug candidates. The slower release of the FP 10 grade may be attributed to the smaller particle size resulting in a lower degree of porosity of tablets, which, according to the Higuchi equation (equation 4.2), would result in a decreased release rate. This however, is unlikely, since it was not observed for the other drug candidates, and since the quantity of ethylcellulose incorporated in these formulations is low (2.8%), and is therefore not expected to have a significant effect on tablet porosity. Alternatively, a factor that may contribute to the decreased release rates observed for these drug candidates manufactured into tablets using Ethocel® FP 10 is the hydrophobicity that ethylcellulose imparts to the tablet during blending. The finer particle size of the FP 10 grade, compared with the standard 10 or FP 100 grades, may result in the ethylcellulose being distributed within the tablet matrix to a greater degree, thus imparting a higher level of hydrophobicity to the resultant tablets. This may result in a

slower rate of hydration of the tablet during dissolution testing, thus having a retardant effect on the drug release characteristics of the dosage form.

It has been reported that drugs of lower solubility are affected by manufacturing variables to a greater extent than highly water soluble drugs (133), and since LAB is of a lower solubility than ACE, MPT and PROP, it may be affected to a greater degree by altered ethylcellulose levels. No nominal value was found for the aqueous solubility of OXP, therefore this explanation could apply to OXP as well, since it is known to be less soluble than ACE and MPT (19), however no conclusion can be reached from this information.

Additional studies on a variety of formulations may be required to further characterise the effects of the grade of Ethocel® on the release of each drug candidate from these matrix systems and to evaluate any trends in drug release.

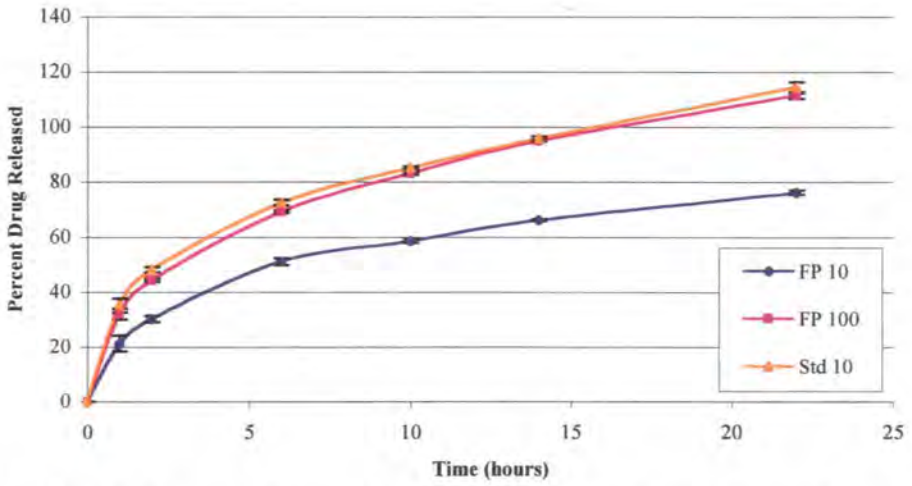


Figure 5.17: Plot of cumulative percent drug released versus time for LAB batches manufactured with different grades of Ethocel®.

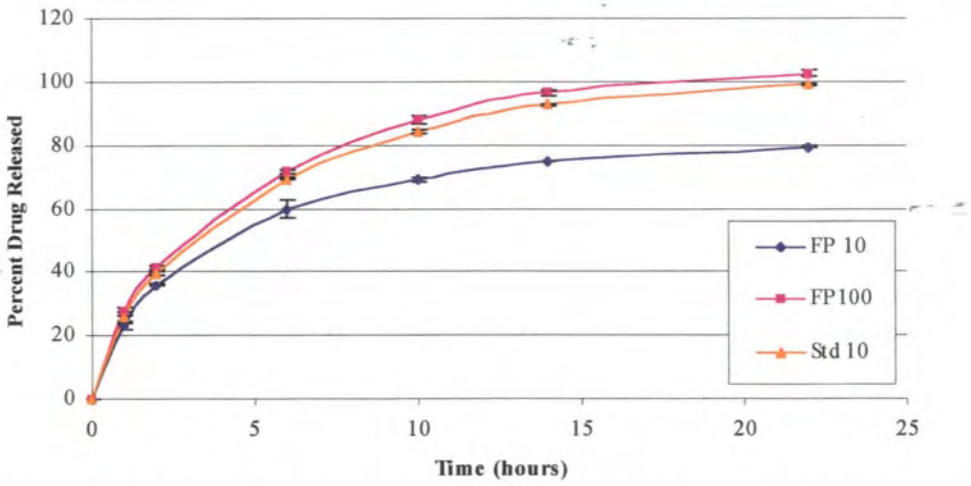


Figure 5.18: Plot of cumulative percent drug released versus time for OXP batches manufactured with different grades of Ethocel®.

Table 5.11: Statistical Comparison Values for Ethocel® Grade Comparisons

Drug	Batches Compared	Ethocel® Grades Compared	f_1	f_2	% Diff.*
MPT	M0147 & M0151	FP10 & FP100	3.4	77.2	3.16
	M0147 & M0155	FP10 & Std 10	7.5	64.2	9.80
	M0147 & M0149	FP10 & FP7	0.3	99.4	0.00
	M0147 & M0157	FP10 & Std 20	1.3	91.6	0.69
	M0147 & M0153	FP10 & Std 45	0.9	93.2	0.00
	M0151 & M0155	FP100 & Std 10	3.8	77.9	6.06
	M0151 & M0149	FP100 & FP7	3.4	77.1	3.11
	M0151 & M0157	FP100 & Std 20	3.7	73.8	1.89
	M0151 & M0153	FP100 & Std 45	4.2	72.5	3.72
	M0155 & M0149	Std 10 & FP7	7.5	64.1	9.75
	M0155 & M0157	Std 10 & Std 20	7.6	63.3	8.53
	M0155 & M0153	Std 10 & Std 45	8.4	61.7	10.36
	M0149 & M0157	FP7 & Std 20	1.4	90.3	0.64
	M0149 & M0153	FP7 & Std 45	1.0	92.4	0.03
	M0157 & M0153	Std 20 & Std 45	0.7	95.4	1.25
PROP	P0163 & P0165	FP10 & FP100	1.6	91.4	1.88
	P0163 & P0169	FP10 & Std 10	2.9	84.2	4.93
	P0163 & P0161	FP10 & FP7	1.7	91.5	3.33
	P0163 & P0171	FP10 & Std 20	3.7	79.6	6.69
	P0163 & P0167	FP10 & Std 45	3.7	78.1	6.59
	P0165 & P0169	FP100 & Std 10	1.8	90.9	2.47
	P0165 & P0161	FP100 & FP7	1.1	95.1	0.87
	P0165 & P0171	FP100 & Std 20	3.4	81.4	4.23
	P0165 & P0167	FP100 & Std 45	3.4	81.1	4.13
	P0169 & P0161	Std 10 & FP7	1.3	94.5	1.02
	P0169 & P0171	Std 10 & Std 20	1.6	90.7	1.18
	P0169 & P0167	Std 10 & Std 45	1.7	91.4	1.08
	P0161 & P0171	FP7 & Std 20	2.4	87.2	2.78
	P0161 & P0167	FP7 & Std 45	2.4	85.7	2.68
	P0171 & P0167	Std 20 & Std 45	0.7	97.5	0.00
ACE	A0225 & A0235	FP10 & FP100	6.2	63.3	4.04
	A0225 & A0237	FP10 & Std 10	3.5	75.4	2.16
	A0235 & A0237	FP100 & Std 10	5.0	71.7	6.78
LAB	L0229 & L0239	FP10 & FP100	43.3	31.5	40.95
	L0229 & L0241	FP10 & Std 10	48.7	29.3	47.74
	L0239 & L0241	FP100 & Std 10	3.7	75.5	6.22
OXP	O0227 & O0243	FP10 & FP100	24.9	39.7	21.28
	O0227 & O0245	FP10 & Std 10	20.1	43.8	16.06
	O0243 & O0245	FP100 & Std 10	3.8	76.1	4.64

* Percent difference between curves was calculated using the similarity factor S_d defined by Gohel (106).

5.3.5. Effect of Ethocel® Load

Drug release profiles of PROP and MPT manufactured with 2.8% and 20% Ethocel® of two different grades are depicted in Figures 5.19 and 5.20, respectively. It is evident from both figures that no significant decrease in the rate or extent of drug release was observed for either active principle, and this was verified by the statistics presented in Table 5.12. f_1 and f_2 values calculated for comparison of the batches manufactured with 2.8% and 20% of each grade of Ethocel®, for each drug, fell below 15 and above 50, respectively, indicating that the curves are similar, when compared using this method. The percent difference between the respective curves, as calculated from the similarity factor S_d (106), are all less than 12%, as shown in Table 5.12, thus emphasising the relative similarity of the curves under investigation.

Table 5.12: Statistical Comparison Values for 2.8% and 20% Ethocel® Load Comparisons

Drug	Batches Compared	Ethocel® Grade	f_1	f_2	% Diff.*
MPT	M0205 & M0157	Std 20	3.1	76.1	1.42
	M0207 & M0147	FP 10	4.3	71.8	11.94
PROP	P0203 & P0171	Std 20	5.2	72.2	10.83
	P0201 & P0163	FP 10	2.7	81.6	5.47

* Percent difference between curves was calculated using the similarity factor S_d defined by Gohel (106).

Makhija and Vavia (119) reported a decrease in drug release rate with increasing ethylcellulose loads of between 30% and 45% incorporated into a similar direct compression matrix tablet, therefore a similar result was expected in this study. This however, was not observed, since the quantities of ethylcellulose incorporated into these tablets were substantially lower, at 2.8% and 20%, bearing less of an impact on the drug release characteristics of the dosage form. Similary, Iqbal et al (130) reported a decreased release rate for naproxen from tablets containing elevated levels of ethylcellulose, however the method of manufacture involved the formulation of a solid-dispersion of ethylcellulose with the drug, and then drying to form granules. This may have altered the physical state of the drug and the polymer, producing different results to those obtained from batches manufactured by a conventional direct compression procedure, as was employed for the manufacture of these batches. Additionally, the low water solubility of naproxen may have contributed to its sustained release.

The effect of increasing the ethylcellulose content of the wet granulation formulation was investigated and described in Chapter 4, and the results lead to the expectation that increasing the ethylcellulose content would result in a decreased release rate for PROP, but not for MPT. Therefore, a reduction in the rate of release of PROP from the 20% Ethocel® formulations was expected, due to the increased ethylcellulose content. As this was not the case, it may be said that the ethylcellulose content of the wet granulation formulation is not acting as a rate controlling polymer by virtue of its physical properties, but rather by a mechanism involving binding and coating of drug particles during granulation with the Surelease®.

Drug release is reported to be affected, not only by the drug load, but also the drug:polymer ratio for rate-controlling polymers such as HPMC (127, 94). The drug load was held constant for the formulations assessed, and only minor adjustments to the drug:HPMC ratio were made to accommodate the increased Ethocel® load. Therefore this variable was eliminated as a rate altering factor, and the similarity of the release profiles seen is in fact a result of the ethylcellulose behaving as a binder and not a rate-controlling polymer.

In contrast, the curves for MPT (Figure 5.20) reveal a trend in the drug release rate, albeit a non-statistically significant trend. Unlike the PROP curves in Figure 5.19, there is a small decrease in the rate and extent of drug release for the 20% Ethocel® batches from six hours onwards. In the figure, the green and violet curves represent the batches manufactured with 2.8% ethylcellulose, and the blue and yellow curves with 20% ethylcellulose. This slight decrease is possibly due to the increased hydrophobicity of tablets manufactured with a larger quantity of the hydrophobic polymer, ethylcellulose. The more hydrophobic nature of the tablets acts in opposition to the high osmotic potential of MPT itself, whose solubility is greater than 1000:1 in water. This may result in a slightly slower rate and extent of water uptake, and the minor reduction in drug release rate that is seen in Figure 5.20. This was not observed for PROP, and may be explained by its lower water solubility, at 50:1, since an increase in hydrophobicity due to

ethylcellulose addition may be insignificant, compared with the hydrophobic nature imparted by the PROP itself.

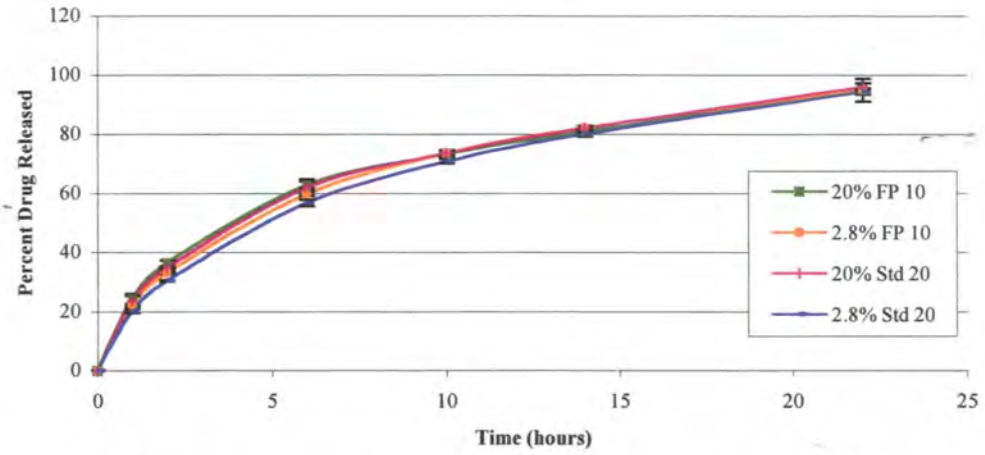


Figure 5.19: Plot of cumulative percent drug released versus time for PROP batches manufactured with two different grades and two different loads of Ethocel®.

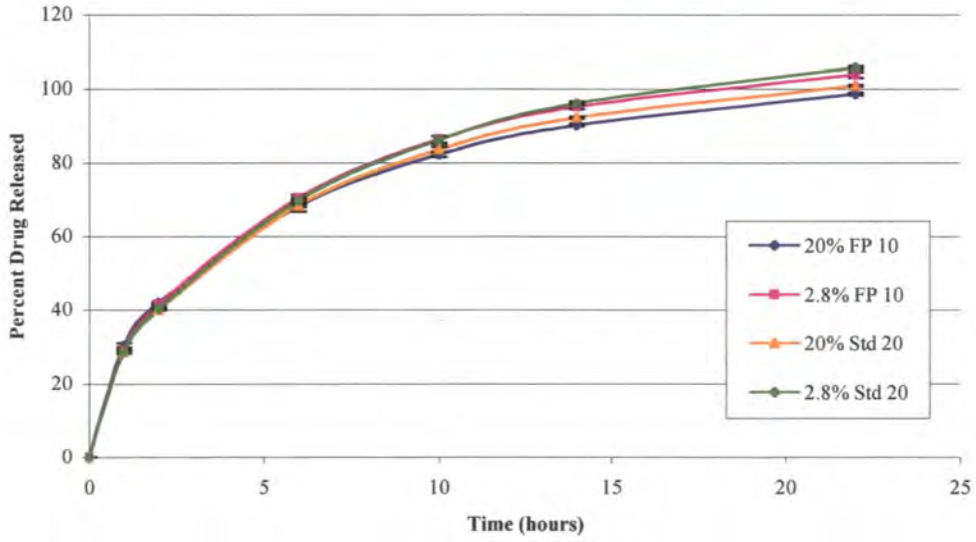


Figure 5.20: Plot of cumulative percent drug released versus time for MPT batches manufactured with two different grades and two different loads of Ethocel®.

5.3.6 Effect of Freeze-Drying

Freeze-drying, or lyophylisation, is a process in which the aqueous portion of a mixture is removed by sublimation, under a vacuum. The mixture, in this case consisting of drug and Surelease®, was frozen in liquid air, and the frozen water subsequently removed by vacuum. The rapid freezing of the mixture and the freeze-drying process limits the growth of ice crystals, making this process less destructive to the crystalline structure of the material than slower freezing processes. The process conditions, such as temperature and vacuum strength, determine the physical structure of the dry cake formed (134).

The results obtained for each active ingredient tested differed, both in terms of drug release characteristics from the directly compressed tablets, and in terms of the physical properties of the freeze-dried material. When the drug powder was mixed with the Surelease® dispersion, the MPT dissolved to form a solution, whereas the PROP produced a suspension, more than likely due to its lower aqueous solubility. After the 24 hour freeze-drying period, the MPT had formed a hard cake whereas the PROP was present as a more granular-type cake, which was more easily ground up and size-reduced through a sieve (mesh size 20).

The release rate profiles for MPT manufactured in this way are presented in Figure 5.21, and the quantity of ethylcellulose solids, present in the amount of Surelease® used for each batch, is specified. In addition, batches manufactured by a conventional direct compression method have been included, with the grade and percent ethylcellulose, incorporated as Ethocel®, indicated on the graph. The original prototype wet granulation batch has also been included in the figure, for comparative purposes. It was expected that the freeze-drying process would result in an intimate association between the drug and the ethylcellulose polymer molecules, resulting in a decreased rate of release from the tablet matrix. The physical nature of the dried cake suggested that an intimate association had occurred, since it was harder and more mechanically robust than the raw drug powder, however this was not reflected in the dissolution rate profiles obtained, as can be seen in Figure 5.21. It is interesting to note that both freeze-dried batches released drug at

the same rate and to the same extent as the original wet granulation batch, rather than the direct compression batches, which released drug slightly faster. This suggests that the ethylcellulose incorporated in the Surelease® dispersion may be acting in a slightly different manner to that incorporated as the dry Ethocel® powder, possibly due to the other constituents in the Surelease®, such as the plasticiser, dibutyl sebacate, or the stabiliser, oleic acid. Statistical comparisons of these curves show that both freeze-dried batches, with 2.8% and 20% ethylcellulose, are similar to the direct compression and wet granulation formulations, with f_2 values as high as 76.4. The calculated values are presented in Table 5.13. The lack of effect on drug release rate that the freeze-drying process appears to have had on MPT, may be attributed in part to the high water solubility of MPT, and its virtually instantaneous dissolution in an aqueous environment.

Figure 5.22 depicts the dissolution of PROP from formulations manufactured in the same way as the MPT formulations shown in Figure 5.21. The retardant effect of the freeze-drying process on the release of this drug from these dosage forms is clearly evident, and statistically verified as shown in Table 5.13. Increasing the ethylcellulose content incorporated by freeze-drying caused a resultant decrease in the rate and extent of drug release. PROP did not completely dissolve in the Surelease® dispersion prior to freeze-drying, therefore it is possible that the dispersed ethylcellulose molecules aggregated around the drug particles during mixing, resulting in a hydrophobic polymer coat surrounding drug particles. Therefore, the release rate may be decreased by the introduction of a polymer coat through which the drug would have to diffuse prior to being released into the hydrated gel matrix, for diffusion out of the dosage form. The insoluble nature of ethylcellulose may impart mechanical stability to these coats, which may cause a portion of the active drug to be retained in the dosage form throughout the dissolution test, hence a lower overall percent drug released would result. The numerical values for the final amount released and percent drug retained are presented in Table 5.14. Contrary to expectation, the residual content values for the freeze-dried batches did not indicate that PROP was retained in the matrix, since they were not greater than those for the conventionally manufactured tablets.

Content uniformity analyses were not performed on the batches manufactured using freeze-dried material, therefore it is possible that the low rate and extent of drug release observed with these PROP batches may be due to low content, rather than a retarding effect of the freeze-drying of drug with Surelease®. Residual content values for PROP in these batches are low, suggesting that the PROP content of each batch is below 100% of the intended dose. It is not known whether PROP is lost during the freeze-drying process, and further investigation would be necessary for complete explanation of the effects seen in Figure 5.22.

Table 5.13: Calculated Values for Statistical Comparisons of Batches Manufactured using Freeze-drying and those Manufactured Conventionally

Drug	Batches Compared	Batch Descriptions	f_1	f_2	% Diff.
MPT	M0147 & M0259	FP10 & FD 2.8%	12.4	52.7	11.97
	M0147 & M0261	FP10 & FD 14%	11.4	55.4	13.08
	M0233 & M0259	WG & FD 2.8%	3.9	76.4	6.02
	M0233 & M0261	WG & FD 14%	4.8	73.9	4.91
	M0259 & M0261	FD 2.8% & FD 14%	2.5	80.9	0.53
PROP	P0163 & P0263	FP10 & FD 2.8%	21.0	44.1	18.63
	P0163 & P0257	FP10 & FD 14%	31.7	37.5	27.63
	P0133 & P0263	WG & FD 2.8%	20.8	38.5	15.27
	P0133 & P0257	WG & FD 14%	27.3	33.3	24.27
	P0263 & P0257	FD 2.8% & FD 14%	8.2	65.7	8.42

Table 5.14: Nominal Values for Drug Release from Selected MPT and PROP Batches

Drug	Batch #	Description	Final % Drug Released	% Residual Content
MPT	M0233	Wet Granulation	91.04 ± 1.12	1.26 ± 0.93
	M0147	Direct Compression (2.8% FP10)	104.64 ± 1.17	1.53 ± 0.43
	M0207	Direct Compression (20% FP10)	99.51 ± 1.16	2.66 ± 0.49
	M0259	Direct Compression (2.8% Freeze-dried)	91.32 ± 10.11	0.56 ± 0.16
	M0261	Direct Compression (14% Freeze-dried)	95.99 ± 2.30	2.44 ± 0.09
PROP	P0133	Wet Granulation	109.05 ± 6.90	Not done
	P0163	Direct Compression (2.8% FP10)	98.30 ± 2.12	11.50 ± 0.77
	P0201	Direct Compression (20% FP10)	98.25 ± 6.80	8.14 ± 5.28
	P0263	Direct Compression (2.8% Freeze-dried)	78.61 ± 0.28	5.35 ± 1.88
	P0257	Direct Compression (14% Freeze-dried)	72.47 ± 10.36	3.44 ± 1.53

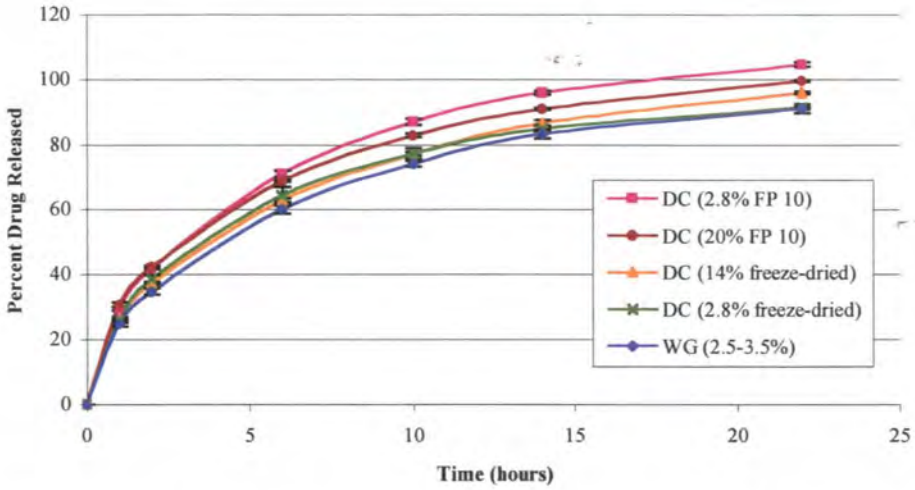


Figure 5.21: Dissolution rate profiles of freeze-dried MPT batches and other MPT batches for comparison.

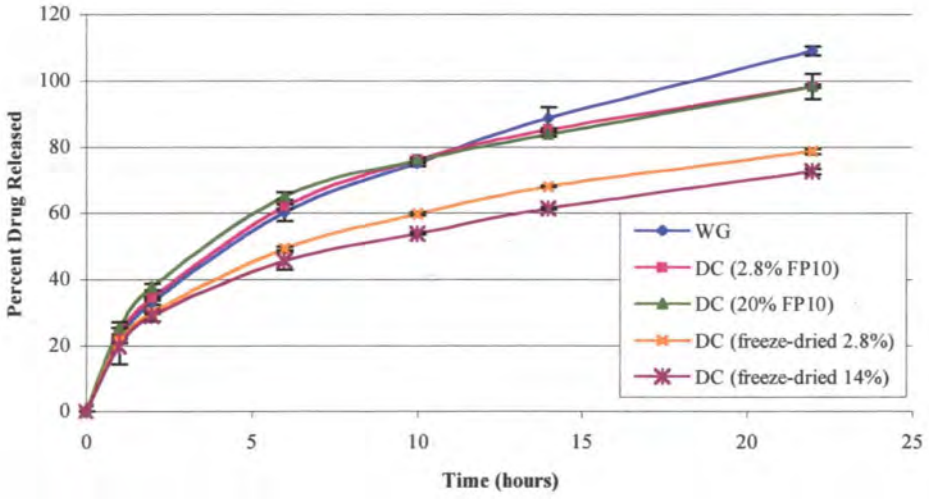


Figure 5.22: Dissolution rate profiles of freeze-dried PROP batches and other PROP batches for comparison.

5.3.7. MECHANISM OF RELEASE OF BETA BLOCKERS FROM THE SUSTAINED RELEASE MATRIX TABLETS

The release of each beta blocker from the matrix systems developed in this study differed, both in the rate and extent of release. Figures 5.24 and 5.25 depict representative wet granulation and direct compression drug release profiles for all drug candidates, and have been included in order to illustrate the concepts discussed.

Typically observed drug release characteristics of hydrophilic matrices were described, and the general behaviour of high viscosity grades of HPMC was outlined in Chapter 4. The tablets formulated in this study contained a large proportion of the hydrophilic polymer HPMC, therefore it was expected that release from these tablets would follow square root of time dependent kinetics as described by Higuchi (22), in which drug is released by diffusion through the polymer matrix. In addition, it was expected that zero order release throughout the dissolution test period was not likely to be achieved. Observation during the dissolution process revealed that, initially, swelling took place, resulting in a substantial increase in tablet size, followed by erosion in the latter part of the test period. This is illustrated in Figure 5.23, which depicts three MPT tablets, the first prior to dissolution, one after three hours hydration and the third at the end of the 22 hour dissolution test. Similar observations were made for tablets manufactured using the drug candidates in this study.

In order to characterise the drug release kinetics, the values for cumulative percent drug released for selected batches of each drug candidate were plotted against the square root of time, up to 80% drug release. According to Higuchi (22), if data plotted in this manner produces a straight line then the drug release is diffusion-controlled. The latter region of the curve was eliminated, since the contribution of erosion and polymer attrition in this region skews the data thus leading to inappropriate conclusions. Tablet erosion may also account for the release patterns observed, and will be discussed.

One wet granulation and one direct compression batch was plotted in this way for each drug candidate, as well as any batches whose release profiles deviated significantly from these, in order to expose any change in release mechanism due to altered formulation variables. The straight line parameters for the Higuchi plots are presented in Table 5.15, and the consistent closeness to 1, of the correlation coefficients that were generated for all curves, verifies that the release of each beta blocker, from tablets manufactured using different formulation variables, follows the square root of time dependency described by Higuchi (22), and therefore occurs primarily via diffusion of drug molecules through the hydrophilic matrix, for up to 80% drug released.

The slope of each square root of time plot gives an indication of the rate of release during the first 80% drug dissolution, and the values presented in Table 5.15 correlate with the order of height of the dissolution rate profiles in Figures 5.24 and 5.25.

Table 5.15: Results for Plot of Cumulative Percent Drug Released versus Time for Selected Batches

Drug	Batch #	Method of Manufacture	Slope (hr^{-1})	r^2
ACE	A0231	Wet Granulation (2.5-3.5%)	24.08	0.997
	A0225	Direct Compression (FP 10)	25.35	0.998
	A0247	Wet Granulation (10%)	12.79	0.995
LAB	L0223	Wet Granulation (2.5-3.5%)	17.39	0.992
	L0229	Direct Compression (FP 10)	16.29	0.989
	L0239	Direct Compression (FP 100)	28.27	0.997
MPT	M0223	Wet Granulation (2.5-3.5%)	23.61	0.999
	M0151	Direct Compression (FP 100)	27.86	0.999
OXP	O0221	Wet Granulation (2.5-3.5%)	27.64	0.994
	O0243	Direct Compression (FP 100)	29.35	0.999
	O0227	Direct Compression (FP 10)	17.57	0.970
PROP	P0133	Wet Granulation (2.5-3.5%)	24.28	0.999
	P0165	Direct Compression (FP 100)	24.36	0.999
	P0215	Wet Granulation (10%)	17.60	0.999
	P0263	Freeze-dried DC (2.8%)	16.84	0.993

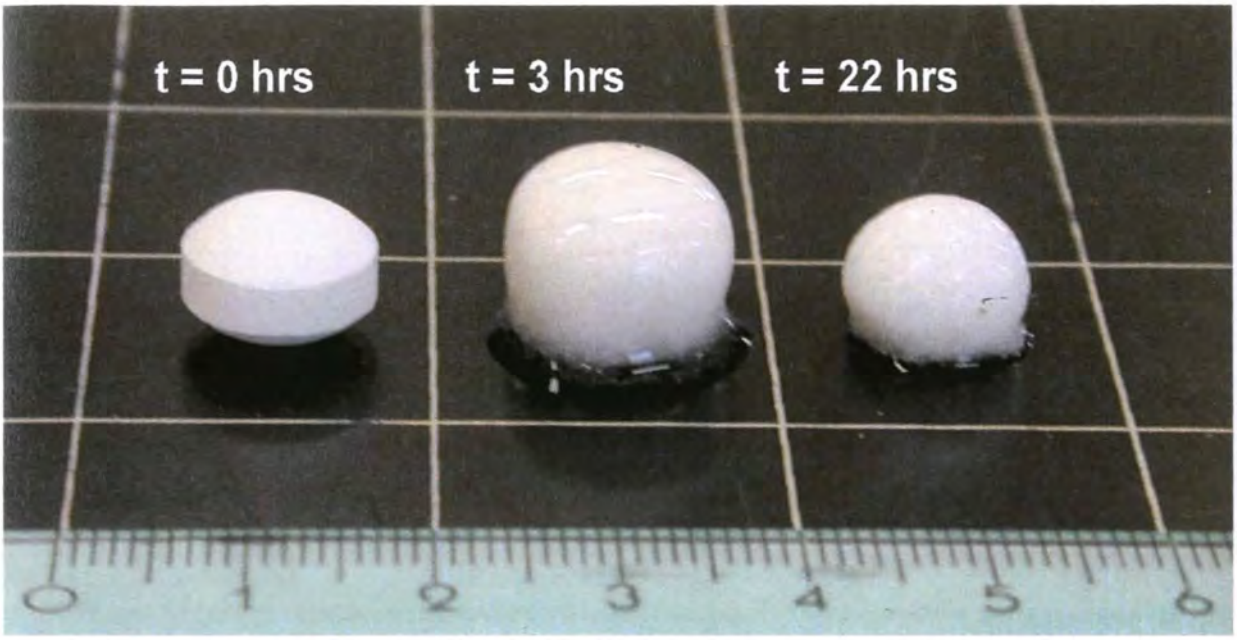


Figure 5.23: Photograph of three MPT tablets after various dissolution times.

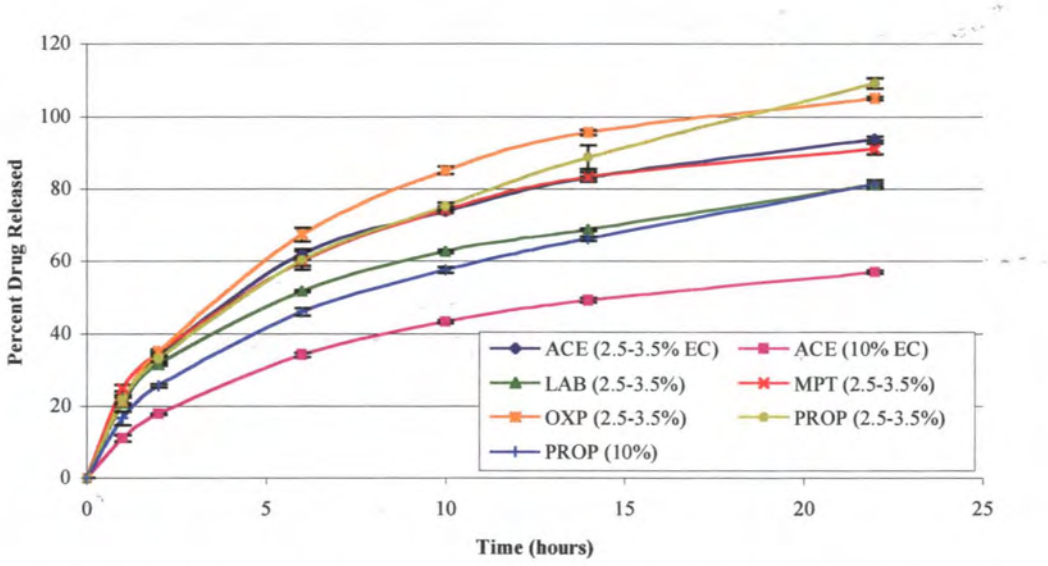


Figure 5.24: Plots of cumulative percent drug released versus time for selected wet granulation batches.

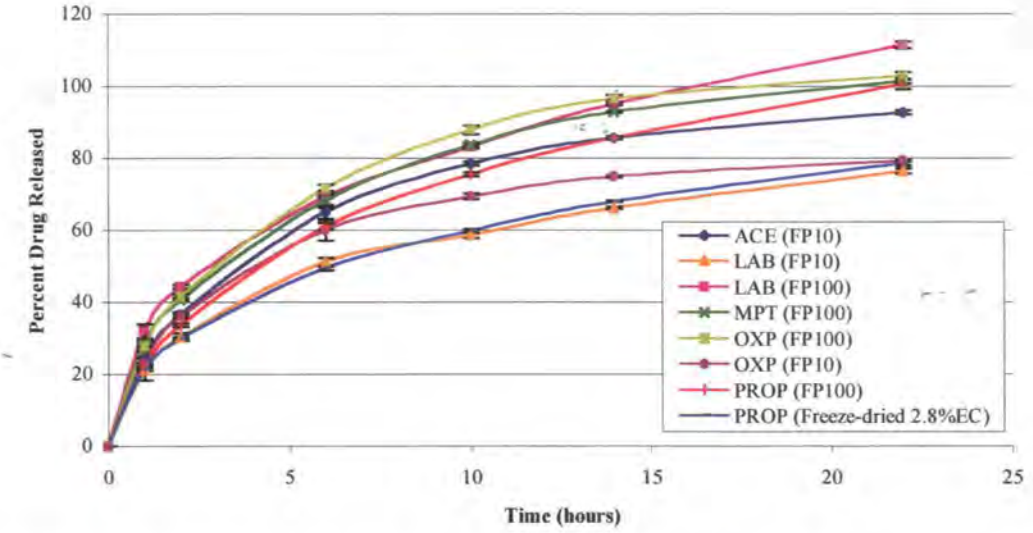


Figure 5.25: Plots of cumulative percent drug released versus time for selected direct compression batches.

Baveja et al (126) presented hydrophilic matrix tablets containing either MPT or PROP as the active ingredients, which released these drugs according to zero order kinetics, which they attributed to synchronisation between the penetration of the swelling front and the attrition of the dissolution/erosion front. In that study, the release was described by fitting the data to the Korsmeyer Peppas equation (86), as shown in Chapter 4, Equation 4.3. This equation was used in this study, to aid in describing the release of MPT and PROP from these dosage forms. Only two drug candidates were assessed using this equation, since values for *k*, the constant accounting for structural and geometric characteristics of the dosage form, could not be found in the literature for ACE, LAB and OXP. Baveja et al (126) published *k* values for hydrophilic matrices with various combinations of MPT:HPMC and PROP:HPMC. The formulations in this study included a drug:polymer ratio of 1:1.5, therefore the closest combination used by Baveja et al, 1:2, was used to calculate the exponent *n* in this study. The constant *k* is affected by the partitioning of the drug from the polymer into the dissolution medium (100), and it is therefore dependent on the relative solubility of the drug in the aqueous medium and in the polymer matrix. As the drug candidates have different water solubilities, it is impossible to extrapolate the results obtained for MPT and PROP to the other beta

other beta blockers, however, predictions regarding the general release mechanism from the ACE, LAB and OXP tablets may be made.

The exponent n is descriptive of the release mechanism, and as discussed in Chapter 4, a value of n=0.5 is expected for diffusion controlled systems, where the drug release shows square root of time dependency. In such a case the Korsmeyer Peppas equation would appear as follows:

$$M_t/M_\infty = kt^{0.5} \qquad \text{Equation 5.1}$$

In systems whose drug release data fits Equation 5.1, the fraction released is proportional to the square root of time, and release is primarily diffusion-controlled, as was expected for these beta blockers. One can also see from the above equation that as n approaches 1, zero order release is observed, with the fraction of drug released being directly proportional to time, indicating a constant rate of release, and therefore a straight line on plots such as those in Figures 5.24 and 5.25. Values for n between 0.5 and 1 indicate non-Fickian or anomalous diffusion and values greater than 1 indicate Case II transport (122).

The calculated n values, using data obtained from the dissolution studies performed on selected batches in this study, are presented in Table 5.16. It is evident that the calculated values reveal little about the drug release mechanism, since they are not accounted for by the guidelines for interpretation given by Korsmeyer and Peppas, as described above. This may be a result of the use of published k values for MPT and PROP in HPMC matrices. The k values obtained from the literature were calculated by Baveja et al for flat-faced tablets comprising only HPMC and drug. The tablets in this study were more complex in composition, and biconvex in shape, which may have contributed to the anomalous results obtained, since the constant k incorporates structural and geometric aspects of the dosage form. Although the drug release mechanism was not successfully described using the published k values, information regarding the drug release may be obtained. Baveja et al stated that n values which decrease with time indicate that the mode of drug release approaches Fickian type diffusion (126). Table 5.16 shows that,

apart from the calculated values at the first time point used, the *n* values for the tablets manufactured in this study decreased with time, possibly indicating Fickian type diffusion. The low values calculated at the early time point may be a result of the burst effect seen in Figures 5.24 and 5.25, which is characteristic of the HPMC that is used in the formulations (135). It is clear that erosion of these dosage forms occurs during *in vitro* dissolution studies, as can be seen in Figure 5.23, and this erosion is more than likely contributing to the mechanism by which these drugs are released from these dosage forms, however, this cannot be conclusively determined by the calculation used. The overall mechanism of release from these monolithic devices is likely to involve Case II transport, since this includes polymer relaxation and erosion of the dosage form, as observed in this study. Although the mechanism of drug release cannot be determined from the results obtained in this investigation, it is feasible to state that a complex mixed mechanism, involving drug diffusion and polymer erosion, governed the release of the beta blockers from the matrix tablets in this study.

Table 5.16: Results of Korsmeyer Peppas Calculation

Drug	Batch #	Method of Manufacture	Dissolution Time (Hrs)	*n*
MPT	M0223	Wet Granulation (2.5-3.5%)	2	0.266
			6	0.413
			10	0.409
			14	0.391
	M0147	Direct Compression (FP 100)	2	0.537
			6	0.506
			10	0.478
			14	0.444
PROP	P0133	Wet Granulation (2.5-3.5% EC)	2	0.367
			6	0.480
			10	0.467
			14	0.462
	P0165	Direct Compression (FP 100)	2	0.394
			6	0.486
			10	0.469
			14	0.449
	P0215	Wet Granulation (10% EC)	2	0.005
			6	0.329
			10	0.351
			14	0.352
	P0263	Freeze-dried DC (2.8% EC)	2	0.229
			6	0.369
			10	0.367
			14	0.362

CHAPTER SIX
CONCLUSIONS

A primary objective of this study was to incorporate five different beta blockers into the prototype wet granulation formulation, which was successfully achieved. All drug candidates were suitable for granulation and all formulations compressed well into tablets. No sticking and/or excessive strain on the tablet press was observed during the compaction process. The physical characteristics of the developed dosage forms including uniformity of tablet weight, hardness, diameter and thickness, as well as friability, fell within the specifications normally set for solid oral dosage forms. All five beta blockers were released in a sustained manner over the 22 hour dissolution testing period, however, each drug candidate behaved differently from one another, in terms of drug release from the wet granulation matrices. PROP and OXP appeared to be released fastest, followed by MPT and ACE, with the formulation containing LAB releasing drug slowest, and to the least extent. The order of the rates of release of these compounds does not correlate with their aqueous solubility, suggesting that the release of these agents is controlled, in part, by the dosage form, rather than only by properties of the drug, such as solubility. This was thought to be a positive attribute, since it highlights an area of opportunity for manipulation of the release of these drugs by formulation modification.

Preformulation studies were carried out to aid in optimisation of the dosage form during the development process. Moisture content analyses revealed relatively low moisture associated with the five drug candidates and higher water content for hygroscopic excipients such as HPMC and microcrystalline cellulose. DSC studies performed on drugs and excipients revealed potential interactions with excipients such as dibasic calcium phosphate and magnesium stearate for both LAB and MPT, however no definite conclusions were drawn from this investigation. The thermal analysis was used rather as a tool for predicting potential areas of incompatibilities, and further stability studies would be necessary to determine any actual solid-solid interactions that may occur during manufacture and/or subsequent storage of these tablets.

The assessment of drug release from tablets was performed using USP Apparatus 3 (BIO-DIS), which was determined to be the most appropriate dissolution test apparatus for the matrix tablets developed and produced in this study (96). Sample aliquots collected during dissolution studies were analysed using HPLC. The development of an isocratic HPLC method capable of determining all five beta blockers simultaneously was undertaken as an intermediate objective, and a single method was developed for analysis of all drug candidates. The analytical method allowed for the use of one compound as an internal standard for another, and any cross-contamination of beta blockers that may occur during the development and manufacturing process, would be readily determined. The HPLC method was optimised by manipulation of system variables, and validated according to standards specified by recognised scientific bodies such as the ICH and FDA.

In addition, content uniformity assays were performed on selected batches manufactured by both direct compression and wet granulation techniques for each drug candidate. The content uniformity was used in calculating the percent drug released from each formulation during dissolution testing, and residual content analysis was performed on each tablet core at the conclusion of each dissolution period using the same extraction method. The percent recovered in these tablets correlated relatively well with the total percent drug released from the tablets tested for content uniformity. A mass balance of the total amount released and the amount remaining in the tablet resulted in approximately 100% of the dose incorporated being accounted for in most cases.

The wet granulation formulation was converted to a direct compression formulation, in order to improve the efficiency and to simplify the manufacturing process. Successful conversion was achieved for all drug candidates, and the drug release profiles obtained for each beta blocker manufactured into tablets by wet granulation and direct compression were statistically similar.

In order to assess the robustness of the direct compression formulation, various formulation changes were made, and the effects on drug release from the altered systems

determined. The formulations containing different active ingredients responded differently to the alterations made, and additional research involving each of the drug candidates would be required to gain a further understanding of the performance of the dosage forms *in vitro*.

Purified talc and Cab-O-Sil® M5 were both used, either alone or in combination, as glidants in the direct compression formulations, and it was found that no significant change in drug release characteristics resulted from the use of either material. It was found, however, that talc was more favourable than Cab-O-Sil® M5 in terms of achieving the desired active pharmaceutical content, and the target weight, since Cab-O-Sil® M5 produced tablets of low weight, due to its inherent low bulk density.

The grade and load of ethylcellulose, incorporated into the direct compression batches, as Ethocel®, was assessed and the effects on drug release evaluated. ACE, MPT and PROP release appeared to be unaffected by the grade of ethylcellulose used, whilst OXP and LAB showed a marked decrease in the rate and extent of drug release when the fine particle FP 10 grade was used at a 2.8% (w/w) load. In addition, PROP and MPT both showed no significant change in release from batches manufactured using increased amounts of Ethocel®, up to 20% (w/w). This was attributed to the fact that Ethocel® was incorporated as a small proportion of the formulation, and that it was not acting as the rate-controlling polymer, but primarily as a binding agent in these tablets.

The effect of the ethylcellulose load incorporated into the wet granulation tablets as Surelease®, on the drug release characteristics was also investigated. Ethylcellulose was found to influence the rate of release of some of the beta blockers to a larger extent than others, with PROP, ACE and LAB being released at substantially slower rates from formulations manufactured using higher loads of Surelease®. This decrease in release rate was possibly due to the Surelease® coalescing and forming an ethylcellulose coat around drug particles, thus inhibiting or slowing the rate of diffusion of these molecules through the matrix. A decrease in release rate with increasing Surelease® loads was not observed with tablets containing OXP and MPT as the active ingredients.

In addition, a different approach was attempted for preparing MPT and PROP for inclusion into sustained release matrix tablets. In this technique, drug powder was mixed with the Surelease® dispersion and freeze-dried prior to inclusion into a direct compression formulation. The amounts of Surelease® and drug used were consistent with those used in the conventional direct compression method of manufacture. Contrasting results were achieved for the two beta blockers under investigation, and whilst PROP showed an expected decrease in release rate for the batches manufactured using the freeze-dried material, MPT remained unaffected. This may be attributed to the high aqueous solubility of MPT when compared with PROP, and subsequent physical differences in the freeze-dried material that was harvested for compaction into tablets.

The mechanism of release of beta blockers from these products was assessed. It is evident from the resultant dissolution rate profiles for each batch assesed, that zero-order drug release kinetics were not achieved, but rather diffusion-controlled release predominated, and thus the release rate profiles followed square root of time kinetics. HPMC was used in these formulations as the rate-controlling polymer, and this material typically displays square root of time dependency, therefore the release patterns seen from these dosage forms were as expected.

The MPT prototype wet granulation matrix tablet (90) was successfully used for *in vitro* sustained delivery of four additional beta blocker drugs, and the resultant formulations were successfully converted to direct compression formulae, capable of producing comparable drug release characteristics. This study has demonstrated that the rate of delivery of drugs from these formulations may be controlled by manipulation of formulation variables, in order to achieve the desired release characteristics.

Further development is required to optimise these formulations, and additional studies may provide an understanding of the processes involved in controlling drug release from these monolithic matrix dosage forms.

There is potential for further investigation of the effects of changes in the ethylcellulose grade and quantity for all five of the beta blockers manufactured by wet granulation and direct compression in this study. Further analyses on a variety of different formulations may produce more conclusive results, and enable better prediction of the behaviour of these drugs *in vitro*. Novel methods of inclusion of this excipient, such as the freeze-drying process used in this study, may contribute further to an understanding of the role of ethylcellulose as a rate-controlling or binding excipient in these dosage forms.

The rate-controlling polymer in the tablets manufactured in this study was predominantly HPMC. Therefore, the quantity of this excipient may be manipulated, to alter the rate and extent of drug release. The grade and quantity of this excipient used has been shown to affect the release of many different drugs from hydrophilic matrices (92, 119, 126, 128, 116), therefore its use provides an excellent opportunity for further research, not only into controlling drug release, but also for modelling of drug release and elucidation of release mechanisms of drugs from swellable matrix systems.

Geometry modification has been shown to produce altered drug release rate profiles for polymeric matrix type tablets (98, 111), therefore further development of these formulations with respect to dosage form dimensions may be investigated as a means of further controlling the release of the beta blockers studied. Systems utilising structural changes have been shown to shift the release mechanism towards zero-order kinetics (98, 111), as is desired for sustained release dosage forms, and one system was reported to be suitable for large scale manufacture (98).

Large scale manufacture is an important consideration in the development of any dosage form. The issues associated with batch-size scale-up of sustained release formulations such as these, require investigation in order to optimise the potential of these tablets for large scale production. Compositional changes may affect the success of batch-size scale-up of extended release preparations (137), therefore a beneficial future area of research may be to determine the behaviour of the formulations developed in this study during subsequent scale-up experiments.

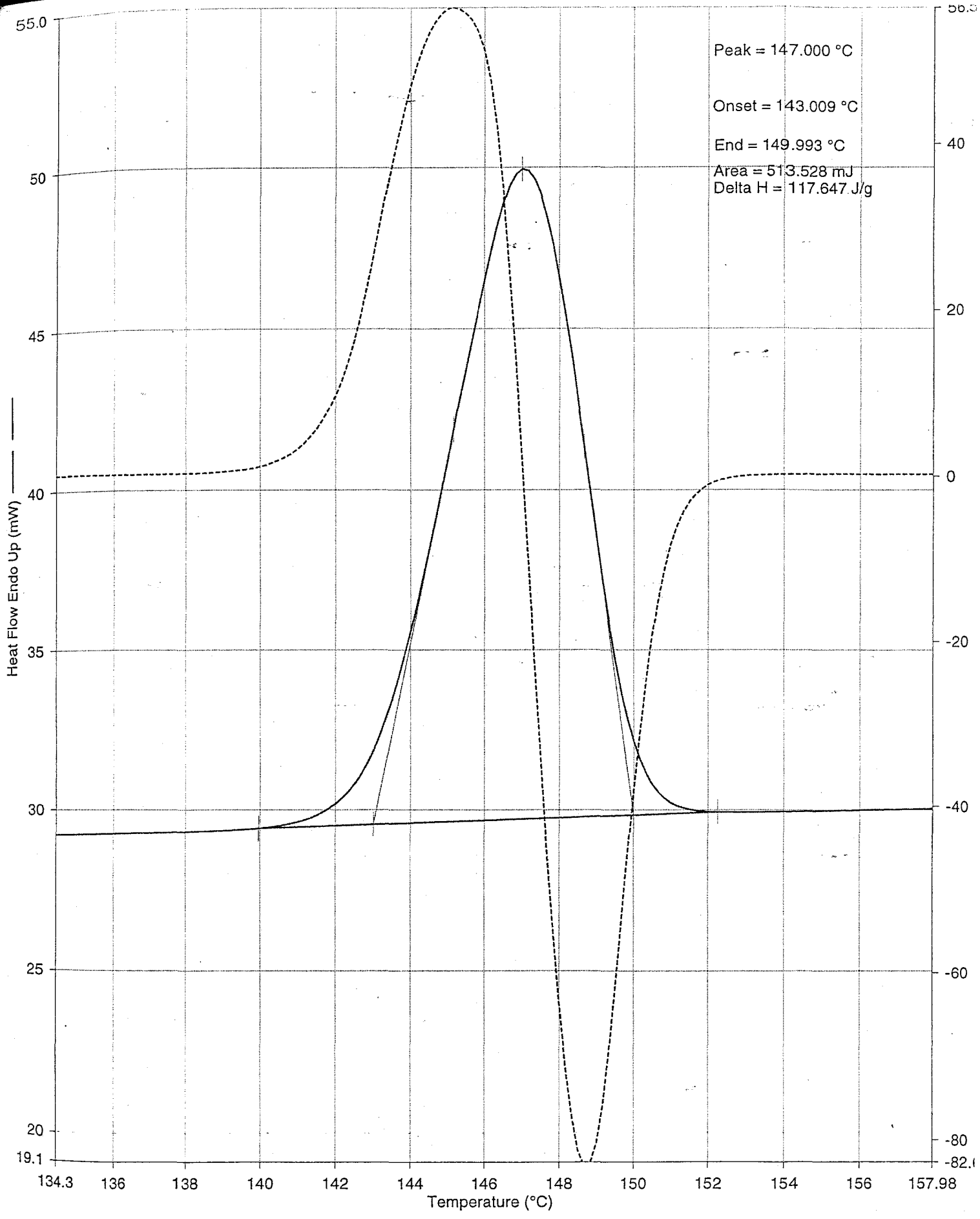
A demonstration of stability is fundamental for the approval of any pharmaceutical product for the marketplace, and, although the DSC results allow the prediction of potential instabilities, it is important that comprehensive stability studies be conducted for the tablets developed, in order to establish whether such preliminary incompatibilities do in fact exist.

The overall intention of sustained release dosage forms is to deliver a drug to the systemic circulation in a sustained manner, therefore it is important that the drug is absorbed and distributed to the target site *in vivo*. *In vitro* studies are valuable as tools for predicting *in vivo* behaviour of these dosage forms, however, accurate *in vitro / in vivo* correlations (IV/IVC) are necessary for interpreting *in vitro* results in a meaningful manner. An IV/IVC was demonstrated for sustained release preparations of MPT, PROP and OXP using mongrel dogs (101), however further *in vivo* studies would be required for characterisation of the behaviour of these beta blocker tablets in humans, such as those carried out for MPT by Eddington et al (136, 138), which demonstrate a positive correlation between sustained delivery of MPT *in vitro* and blood plasma levels *in vivo*. Factors such as hepatic first pass metabolism must be considered, as this is likely to affect the bioavailability of these agents *in vivo*, as has been shown for PROP (48).

This study has presented a preliminary investigation and product development process for beta blocker matrix tablet formulations, by both a wet granulation and direct compression manufacturing process, with the objective of providing sustained drug delivery over a 22 hour period achieved. In addition, it has provided a base for a number of potential areas of research, to increase and expand on the information resulting from this work.

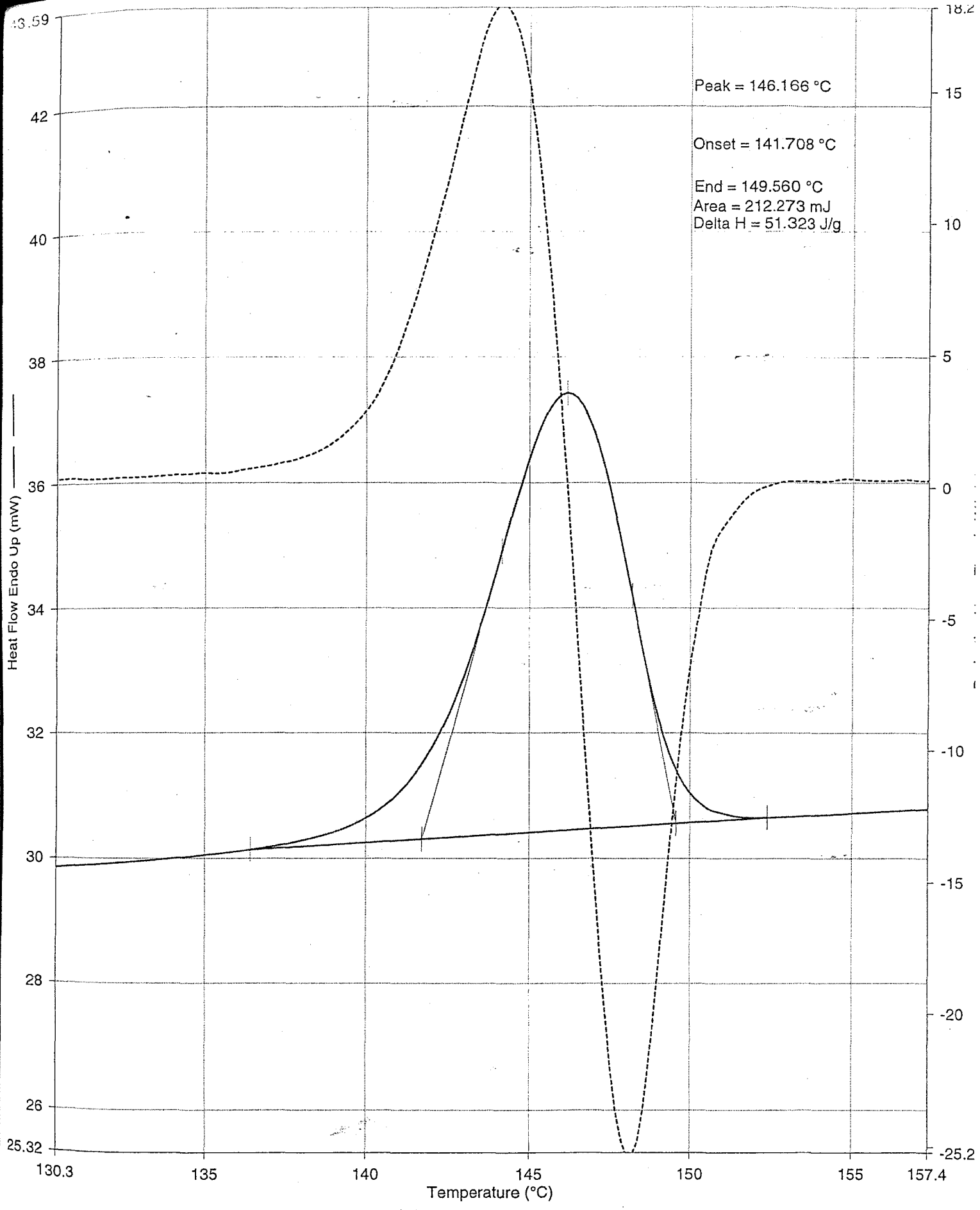
APPENDIX ONE

DCS THERMOGRAMS



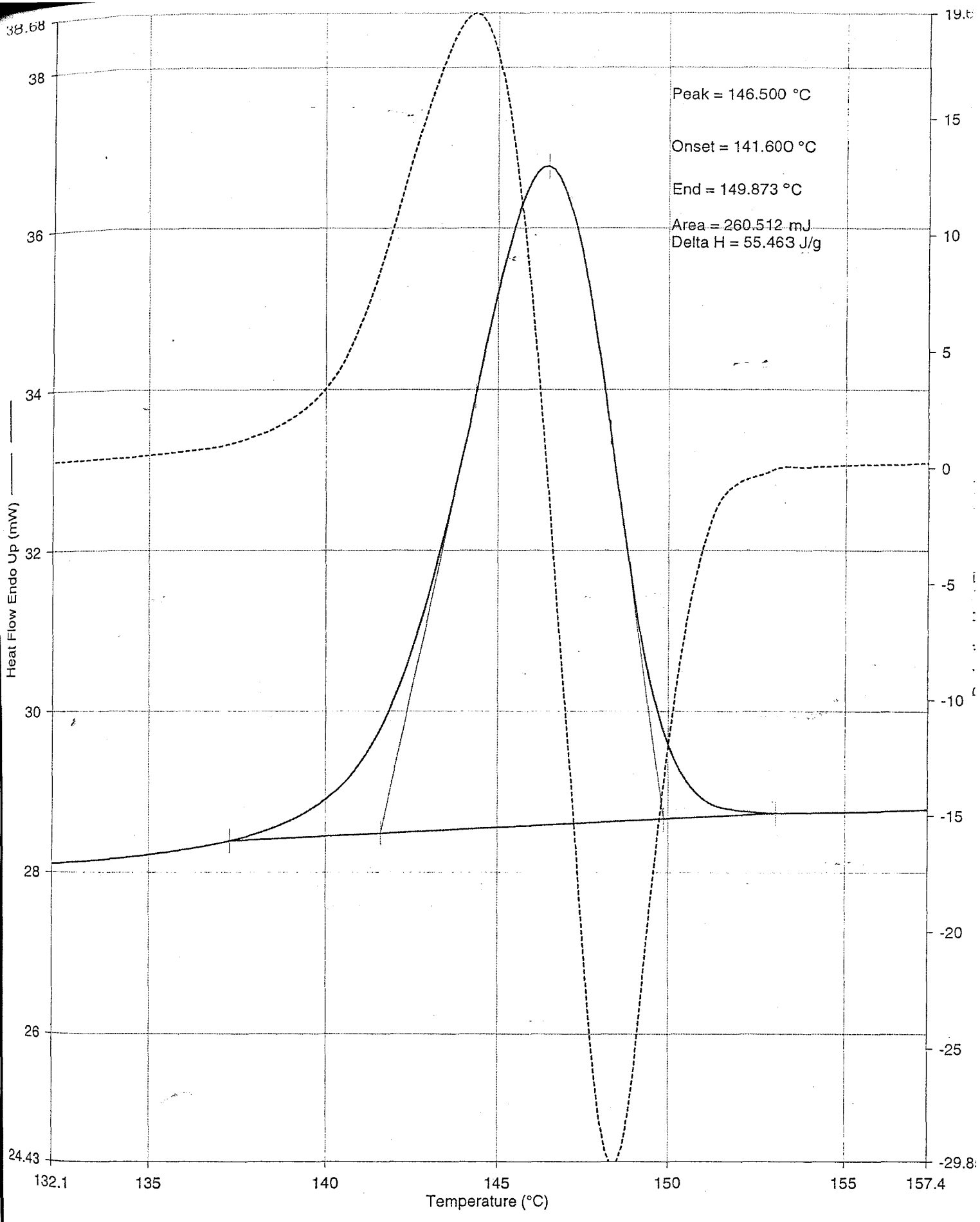
11/29/2002 12:37:33 PM

1) Heat from 25.00°C to 160.00°C at 10.00°C/min



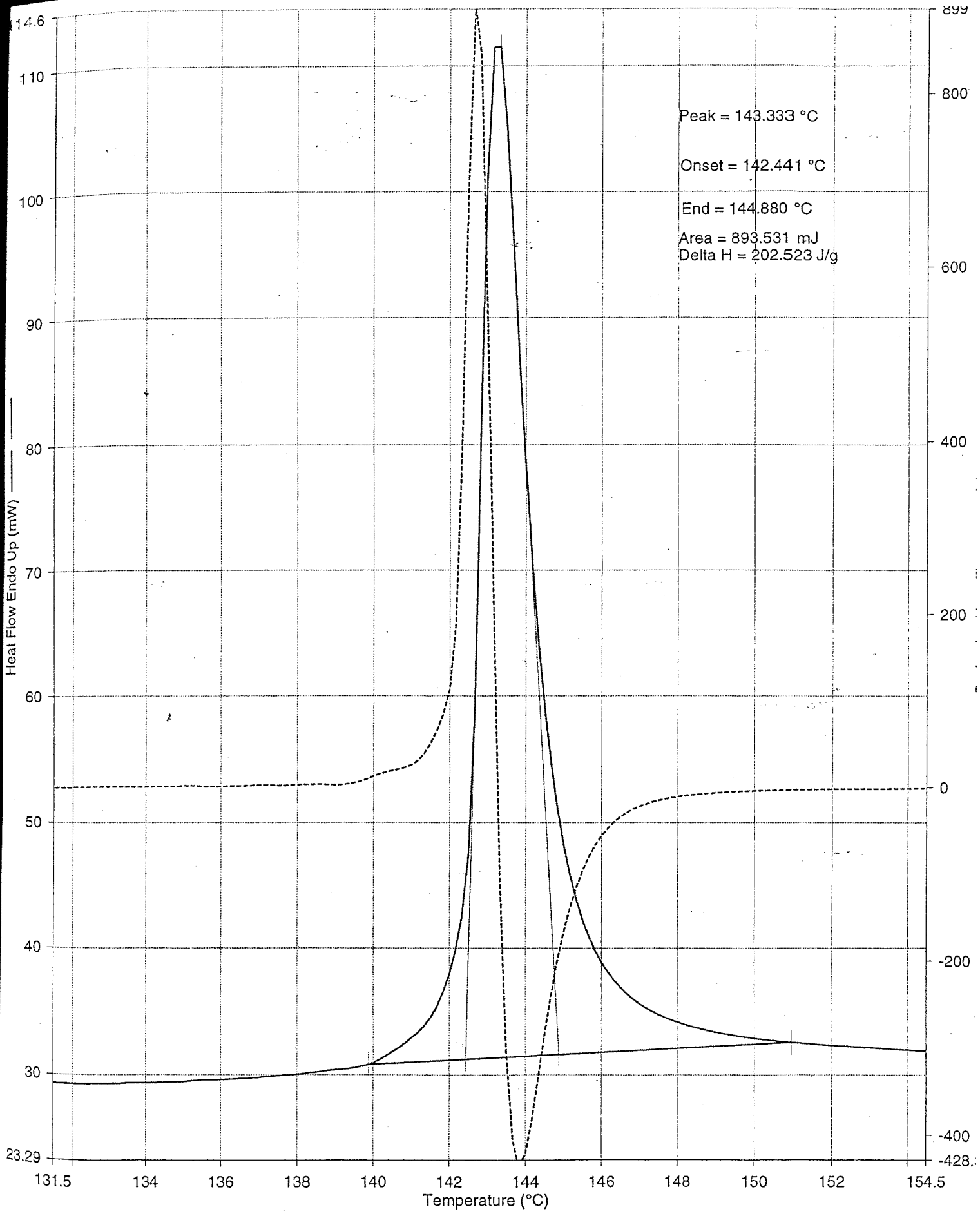
11/29/2002 12:30:33 PM

1) Heat from 25.00°C to 160.00°C at 10.00°C/min



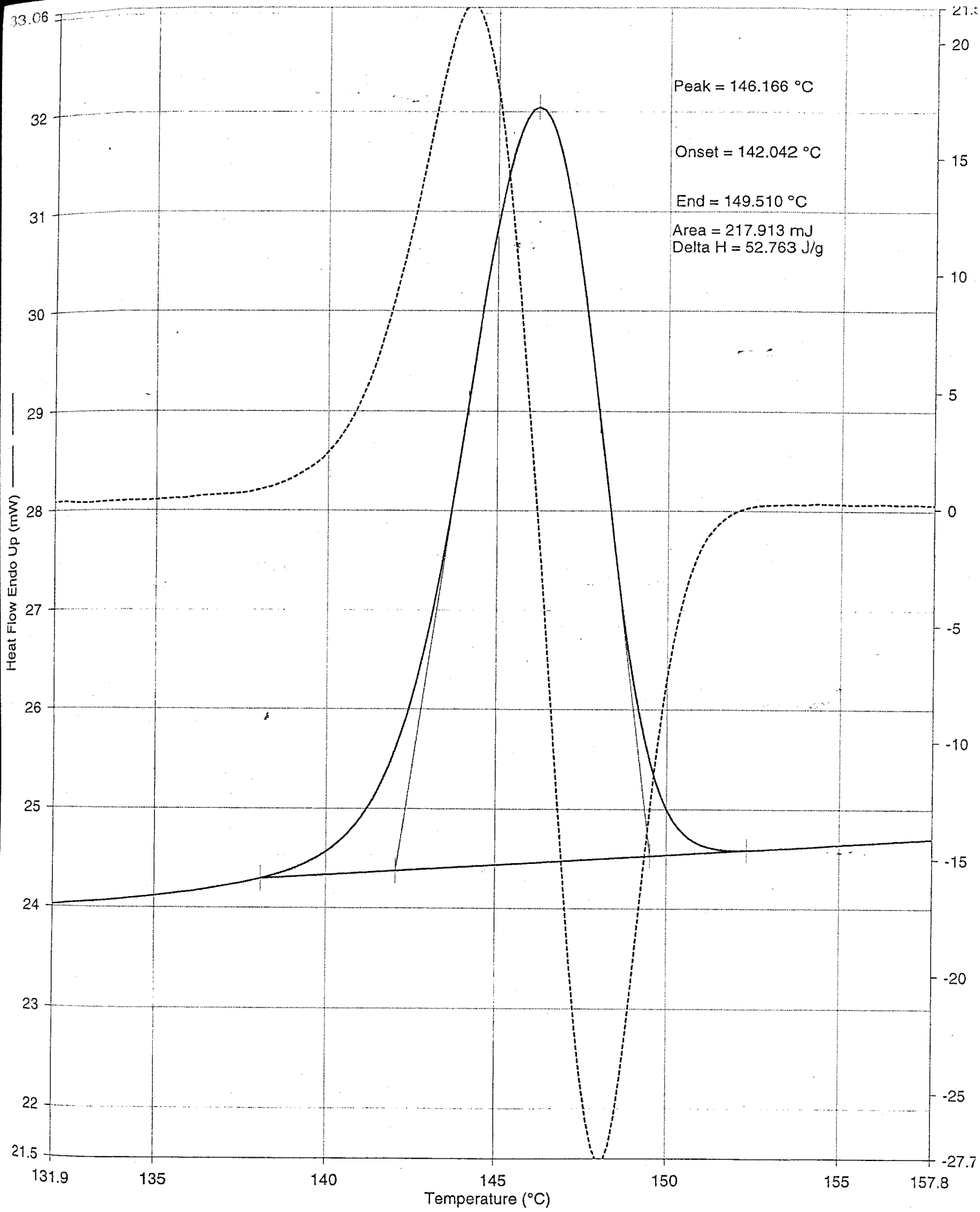
11/29/2002 12:32:04 PM

1) Heat from 25.00°C to 160.00°C at 10.00°C/min



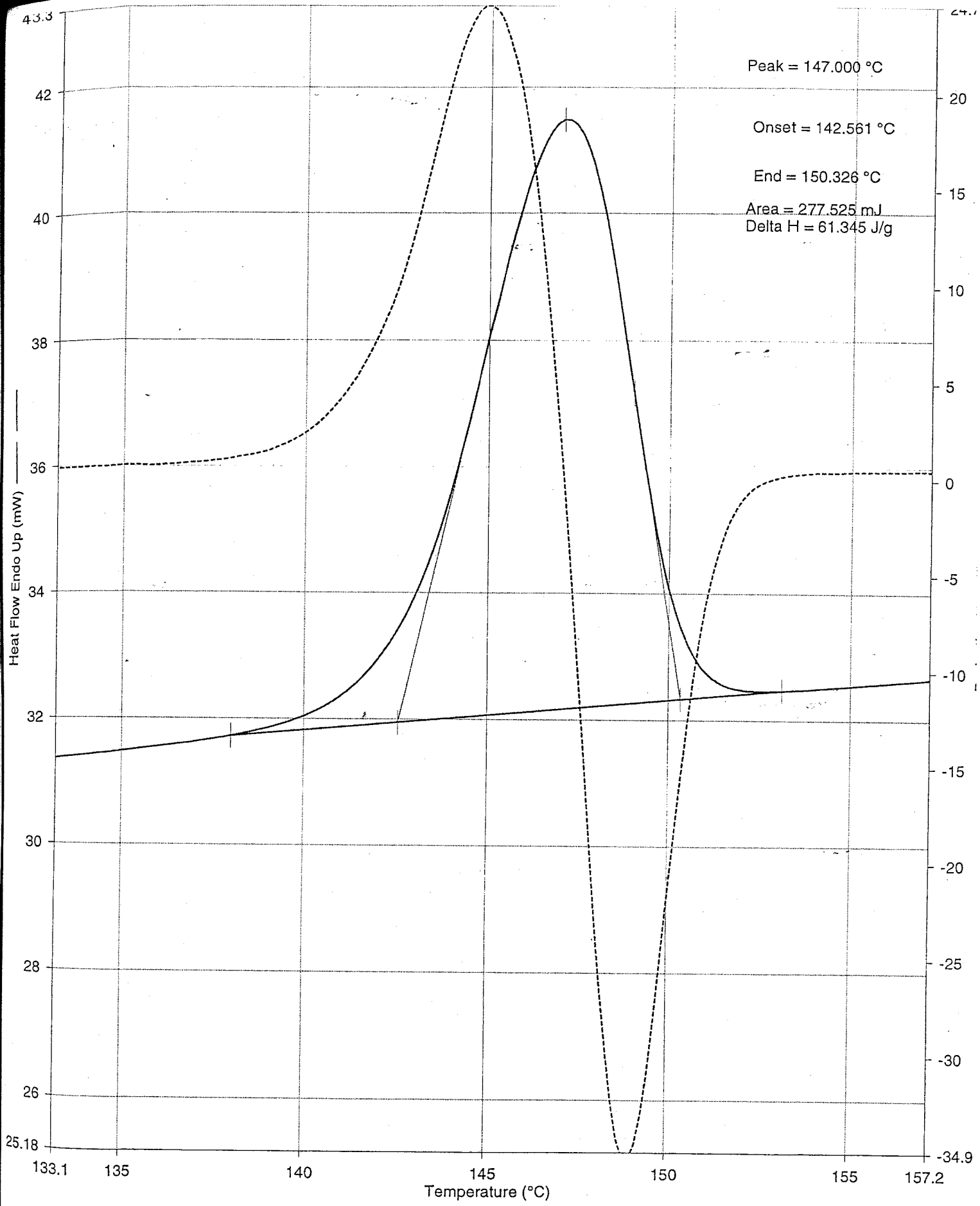
11/29/2002 12:42:59 PM

1) Heat from 25.00°C to 160.00°C at 10.00°C/min



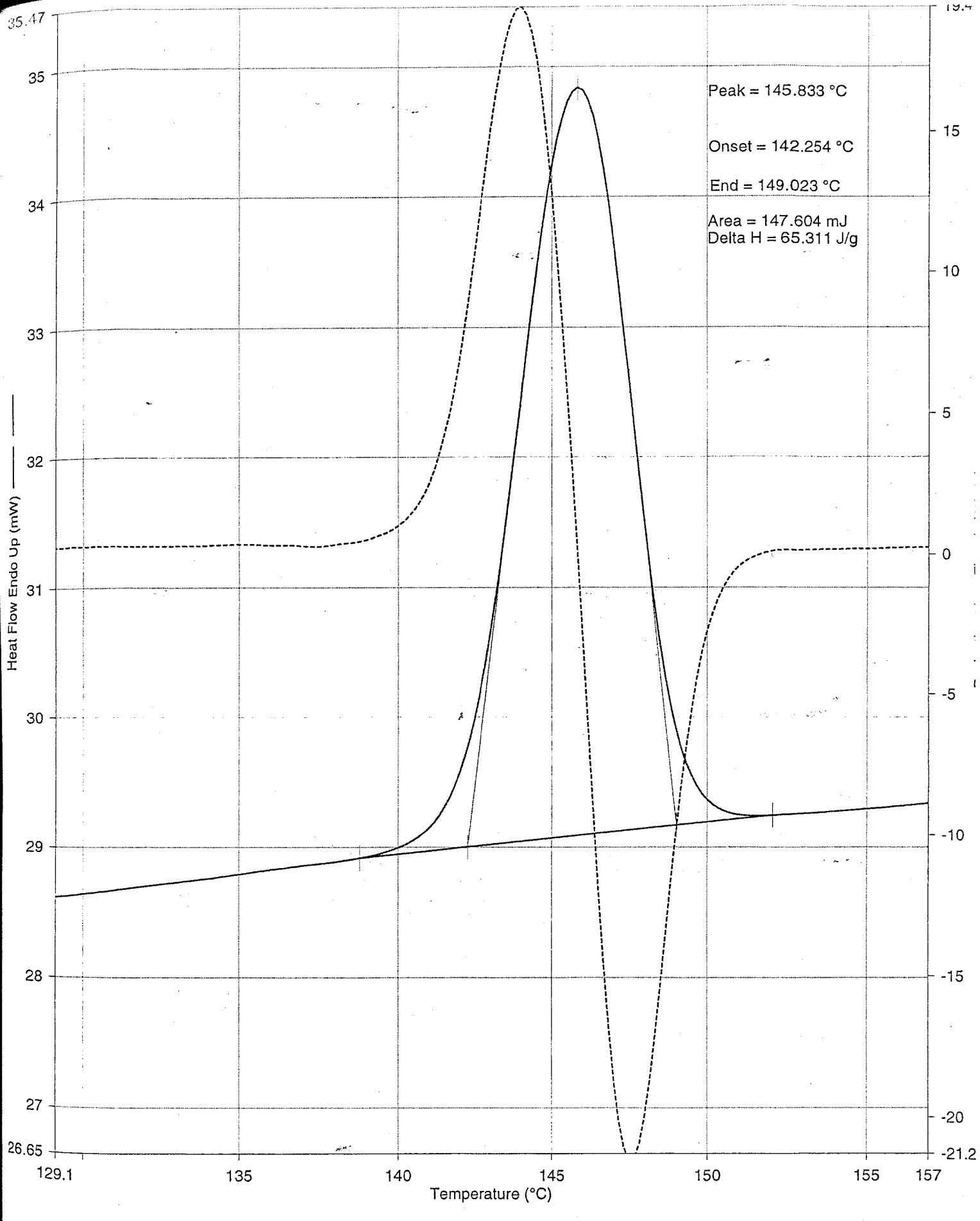
11/29/2002 12:33:29 PM

1) Heat from 25.00°C to 160.00°C at 10.00°C/min



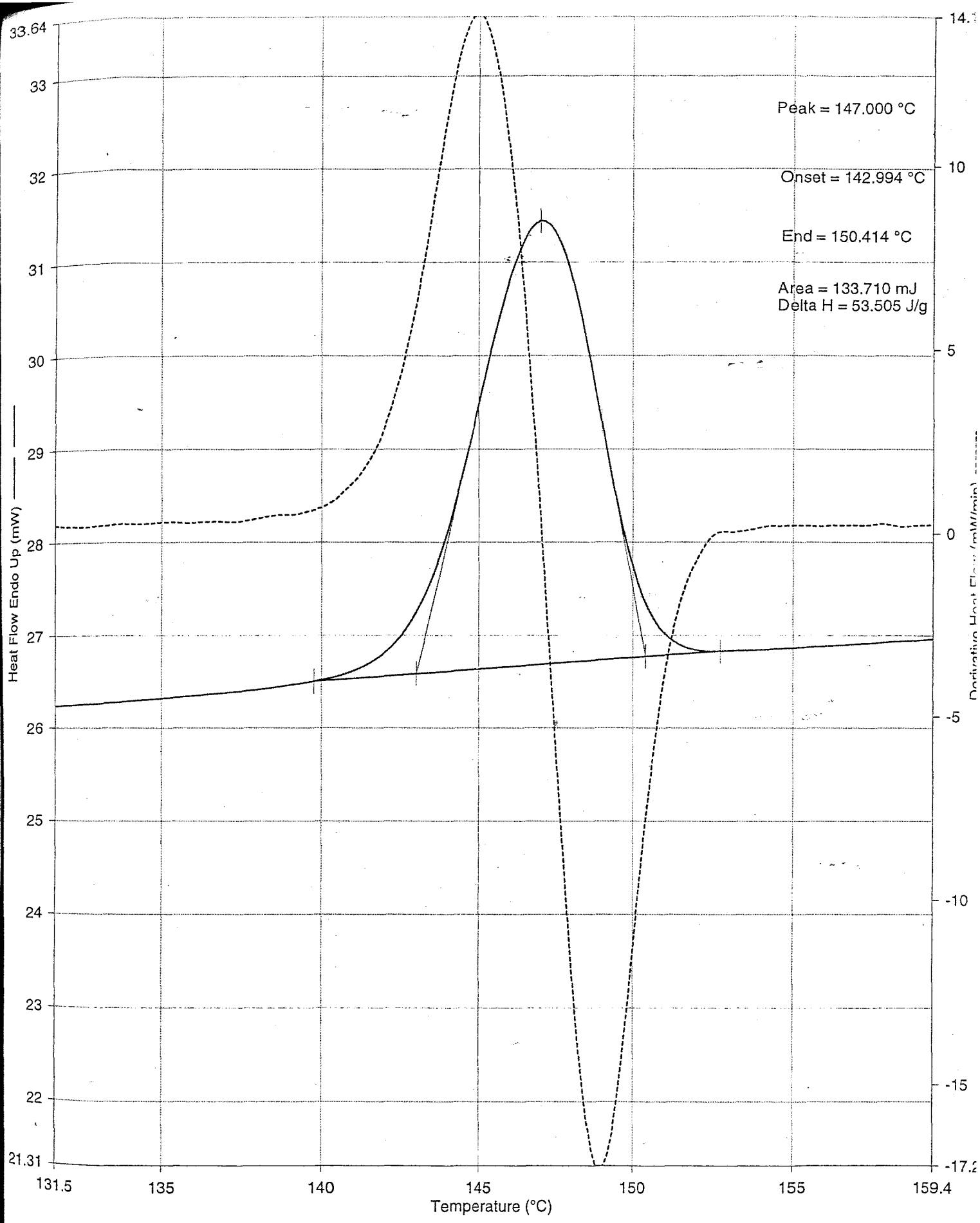
11/29/2002 12:28:02 PM

1) Heat from 25.00°C to 160.00°C at 10.00°C/min



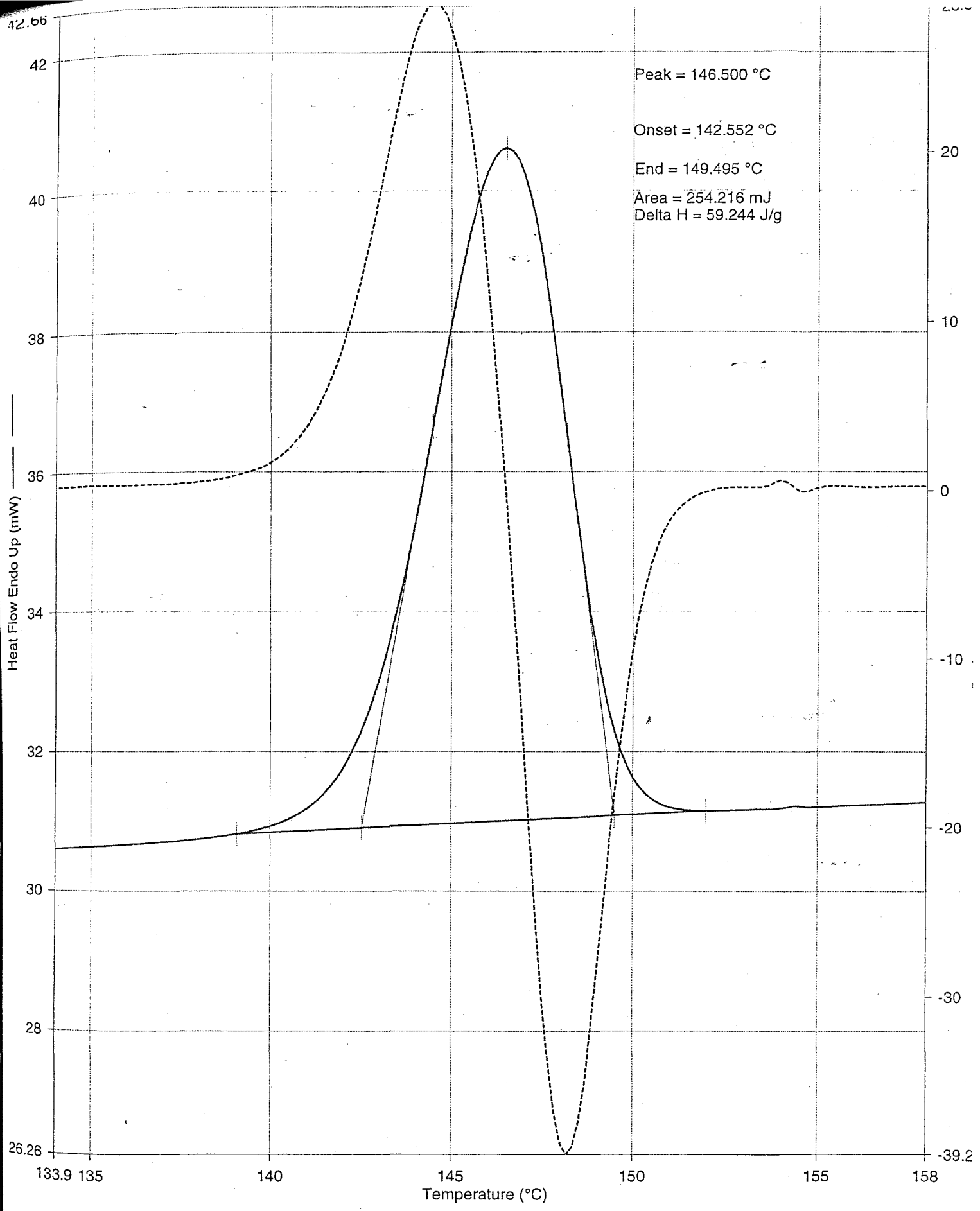
11/29/2002 12:34:54 PM

1) Heat from 25.00°C to 160.00°C at 10.00°C/min



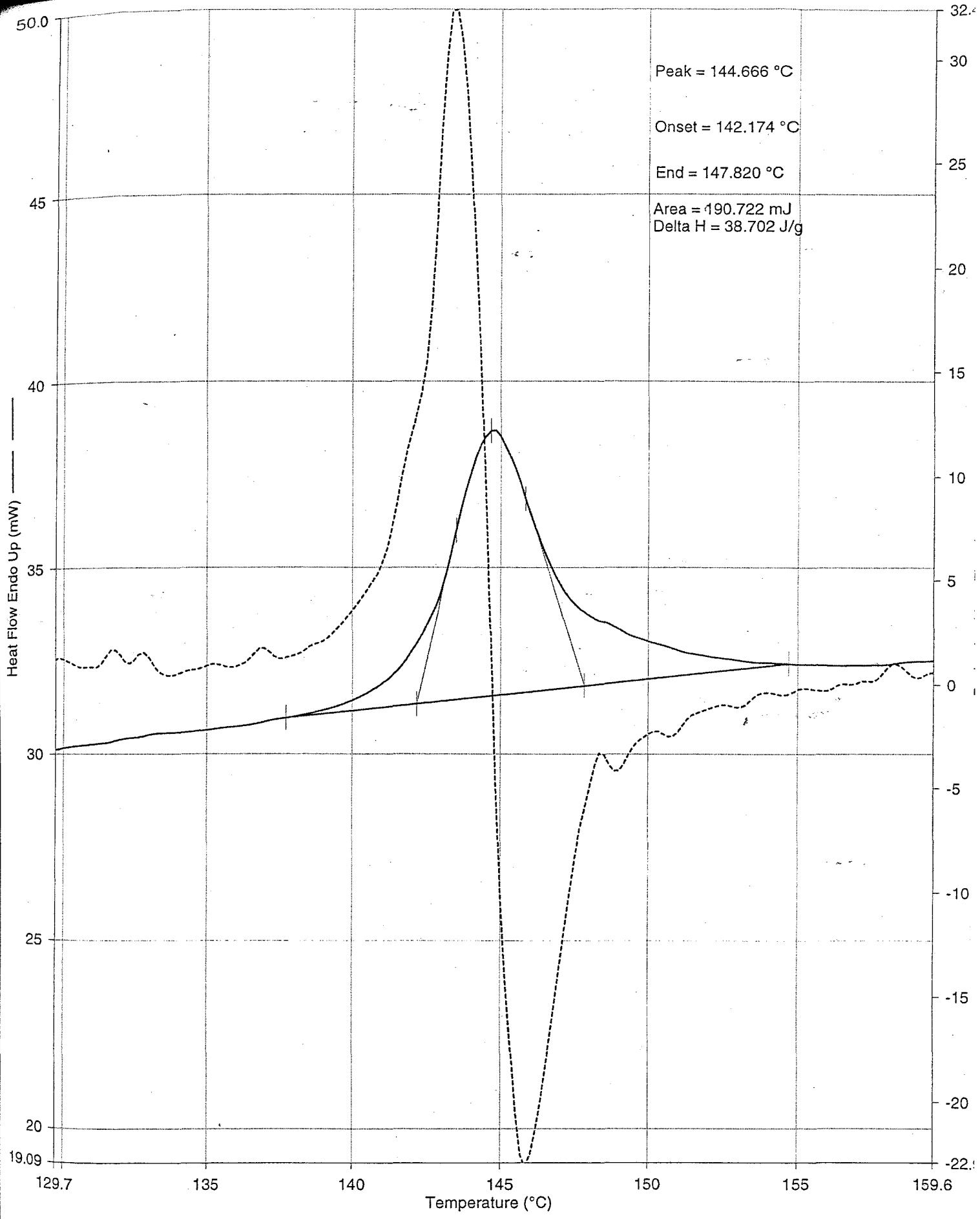
11/29/2002 12:20:17 PM

1) Heat from 25.00°C to 160.00°C at 10.00°C/min



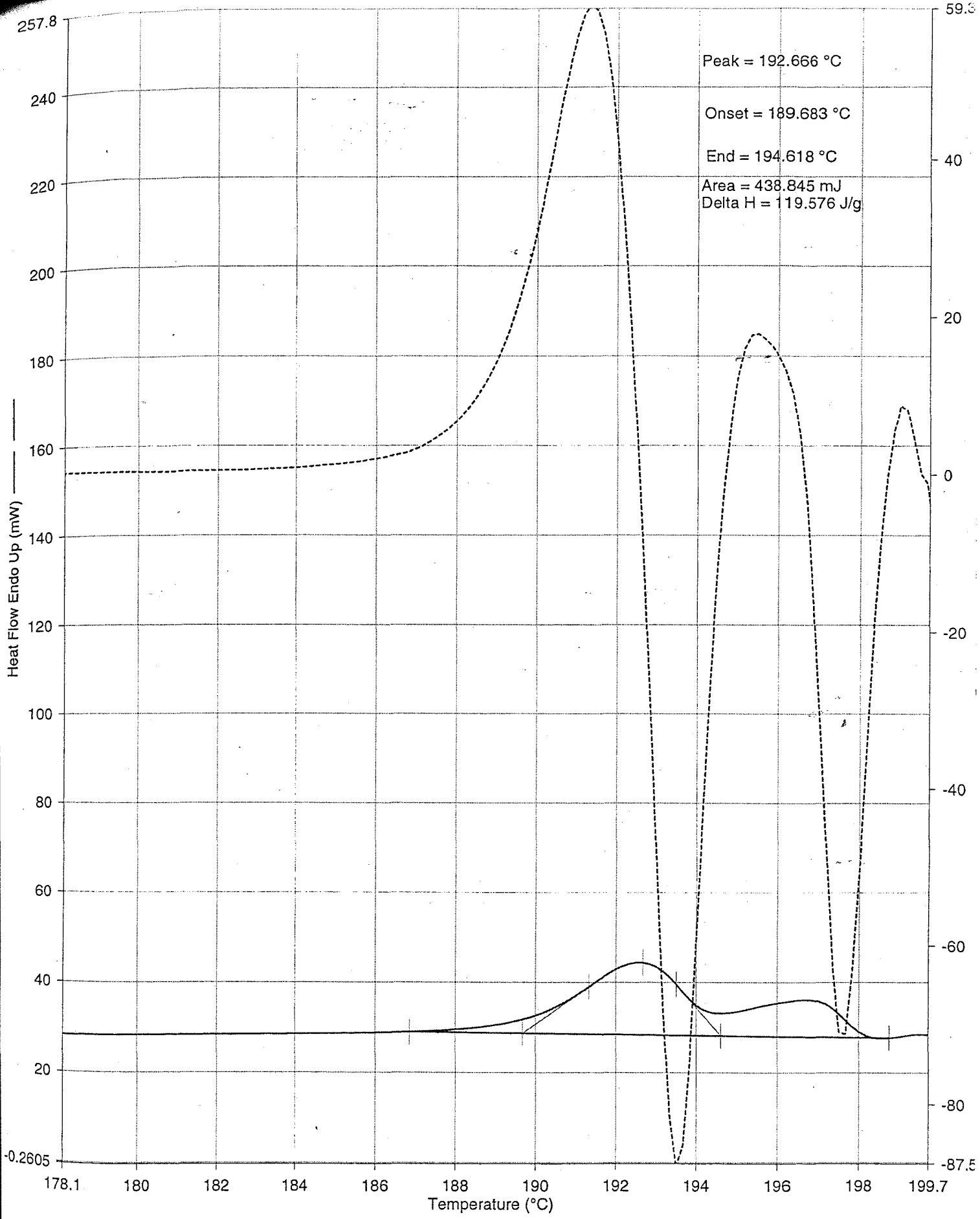
11/29/2002 12:36:16 PM

1) Heat from 25.00°C to 160.00°C at 10.00°C/min



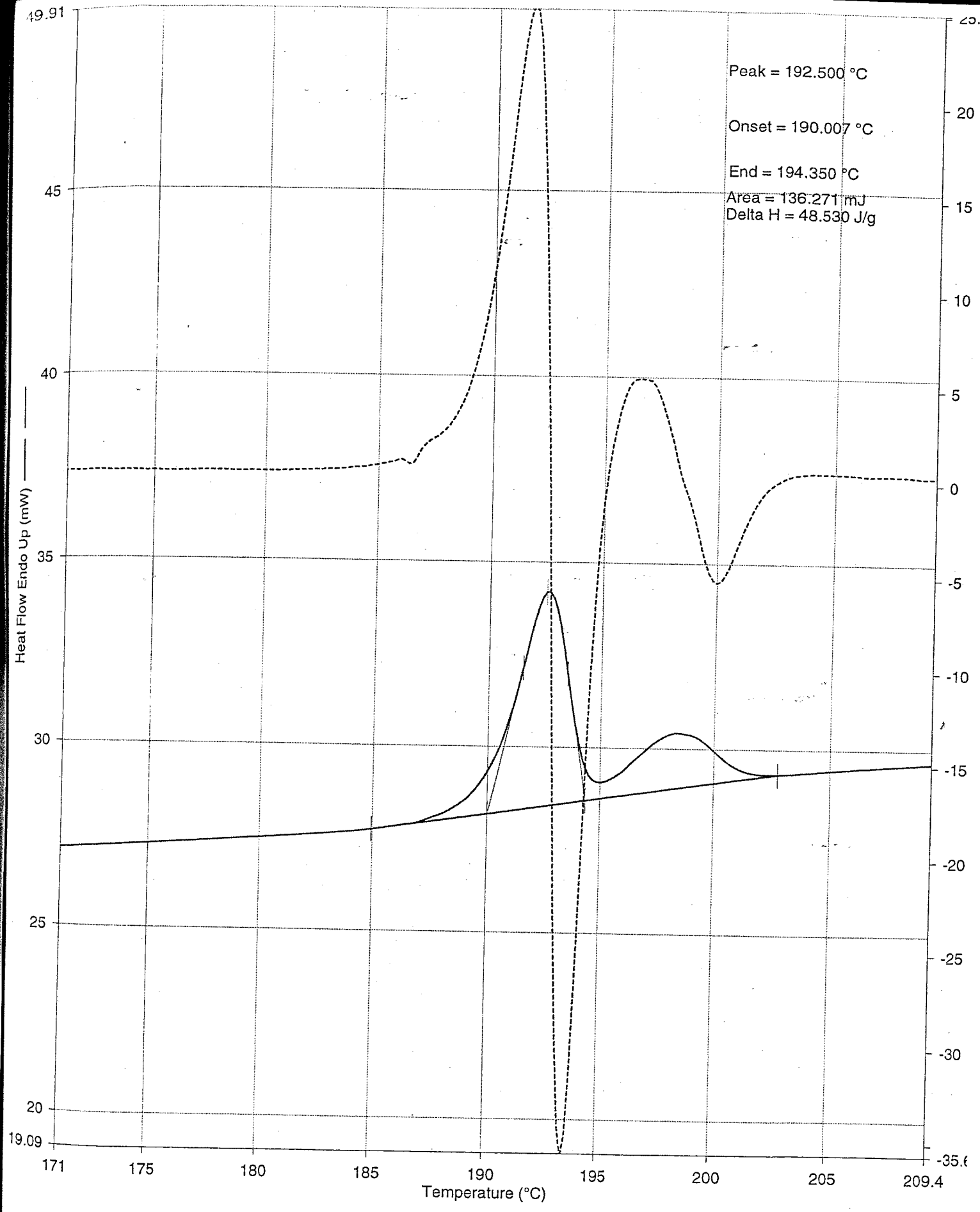
11/29/2002 12:39:42 PM

1) Heat from 25.00°C to 160.00°C at 10.00°C/min



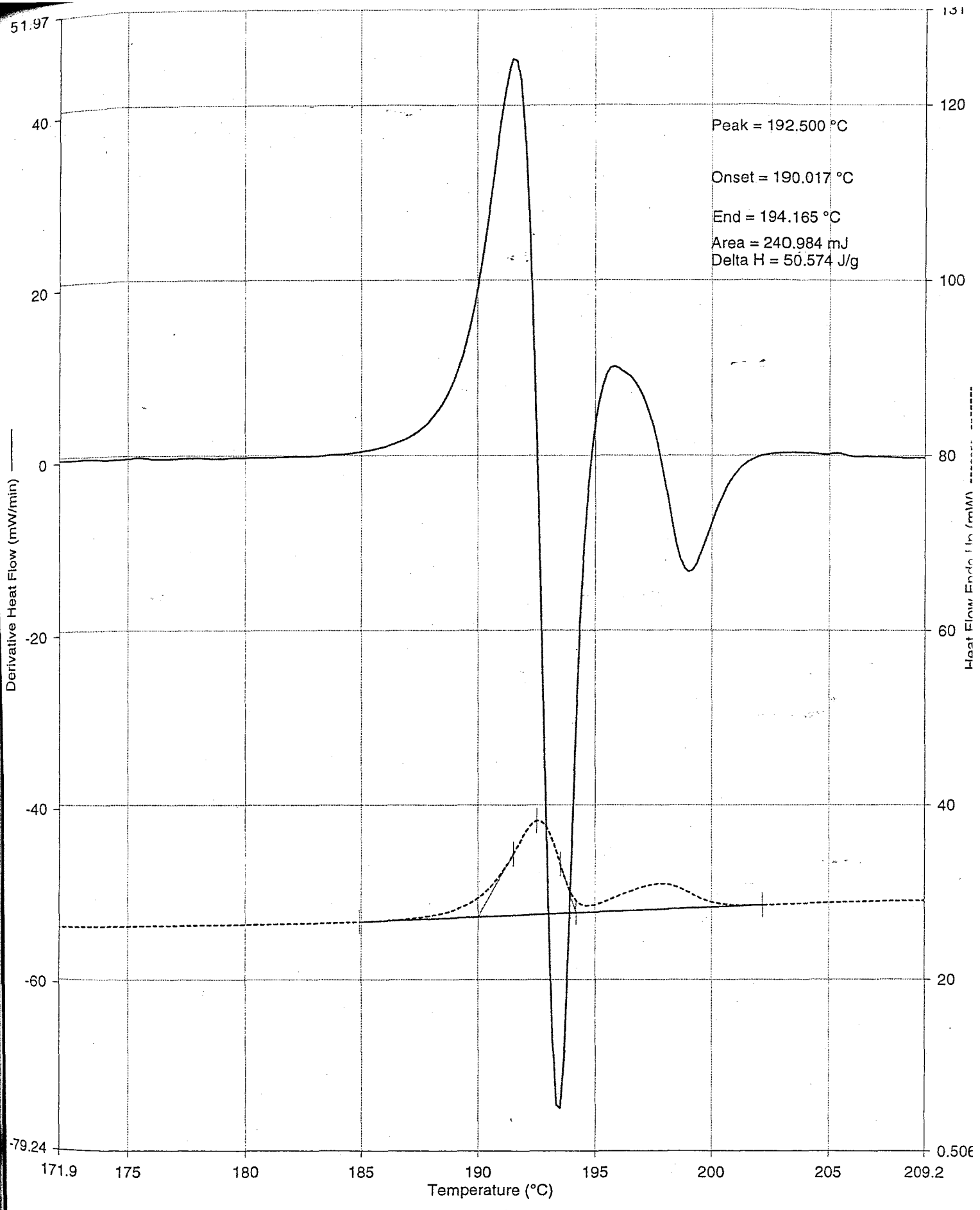
11/29/2002 1:05:31 PM

1) Heat from 25.00°C to 200.00°C at 10.00°C/min



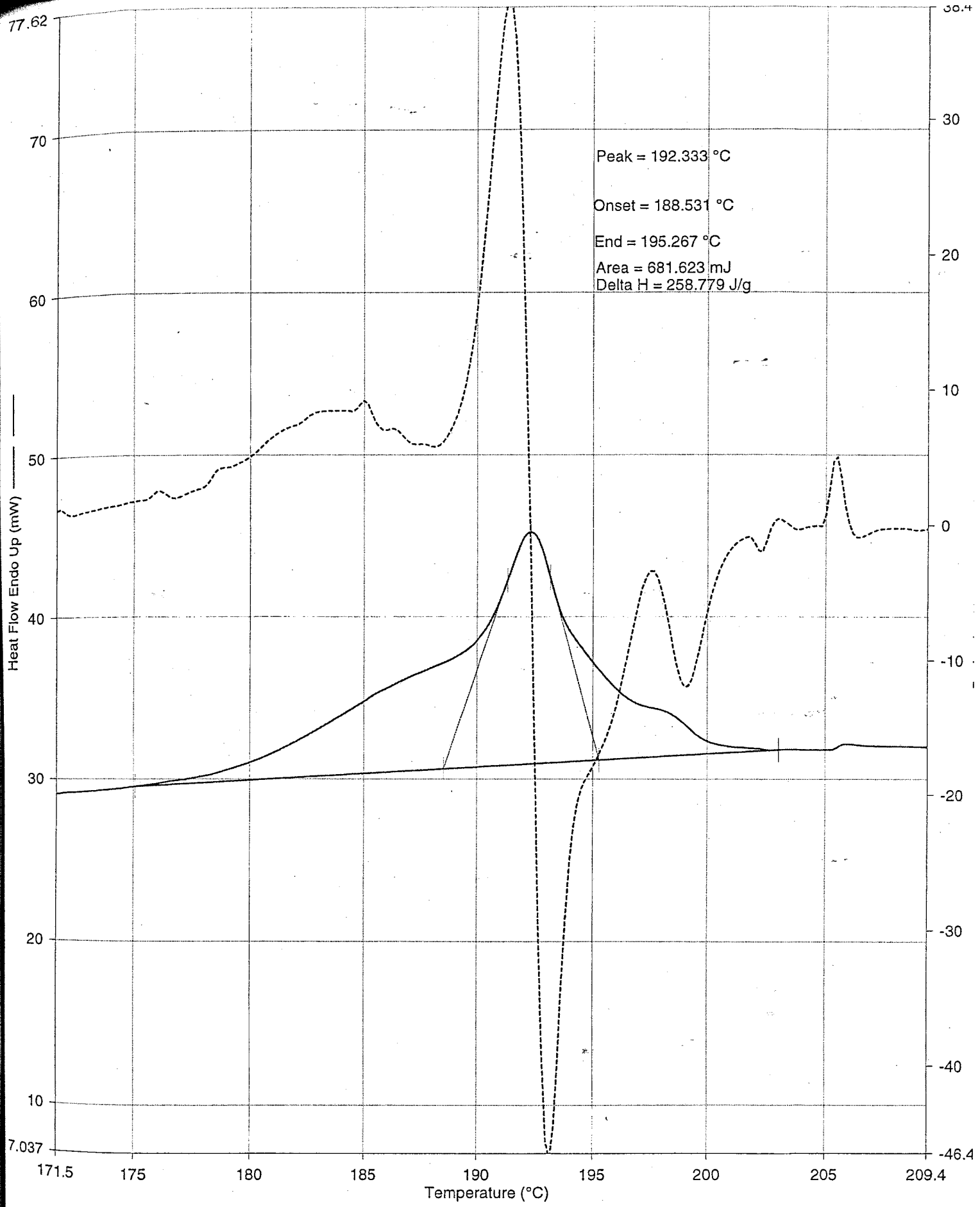
1) Heat from 25.00°C to 210.00°C at 10.00°C/min

11/29/2002 12:57:43 PM



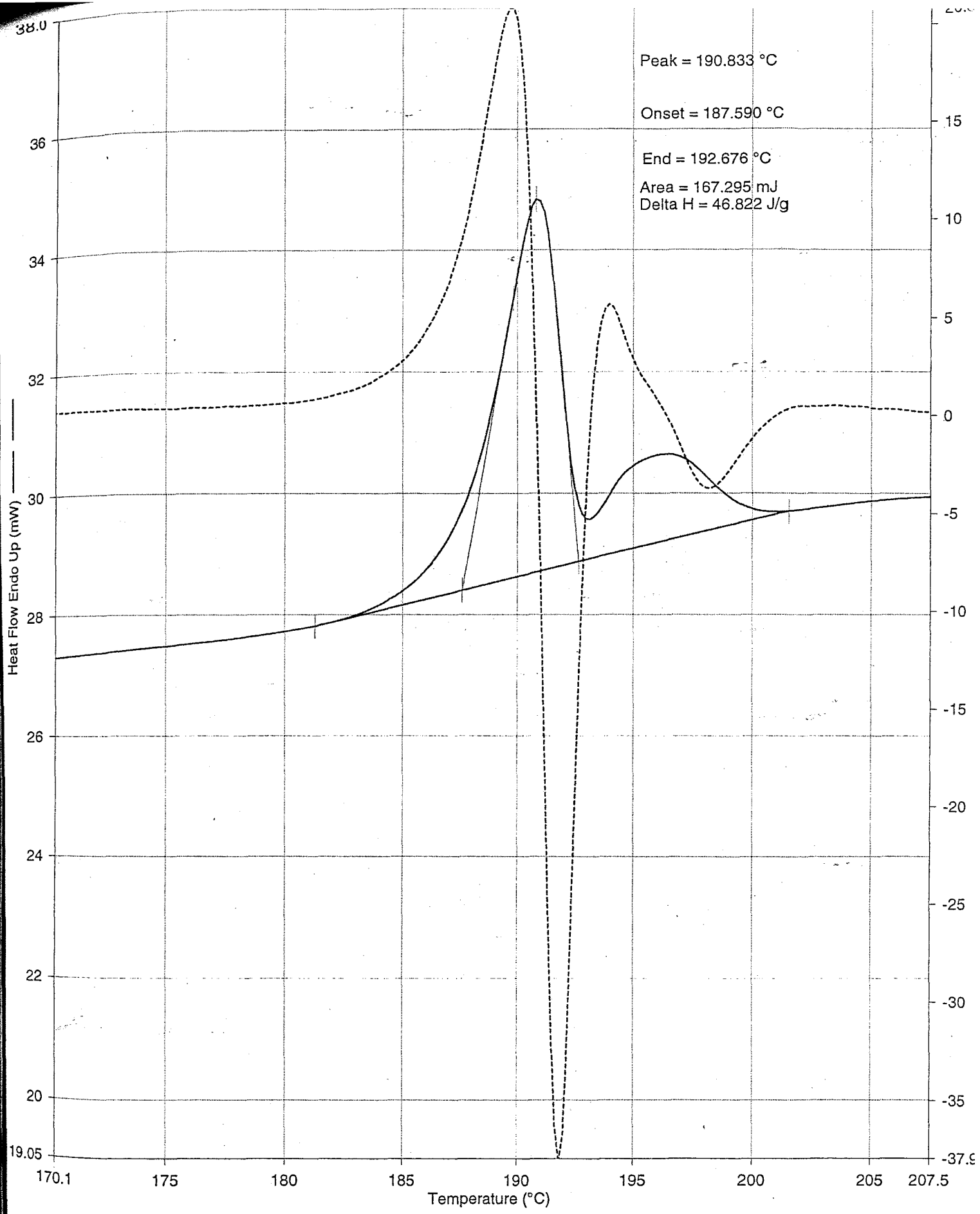
12/2/2002 10:42:35 AM

1) Heat from 25.00°C to 210.00°C at 10.00°C/min



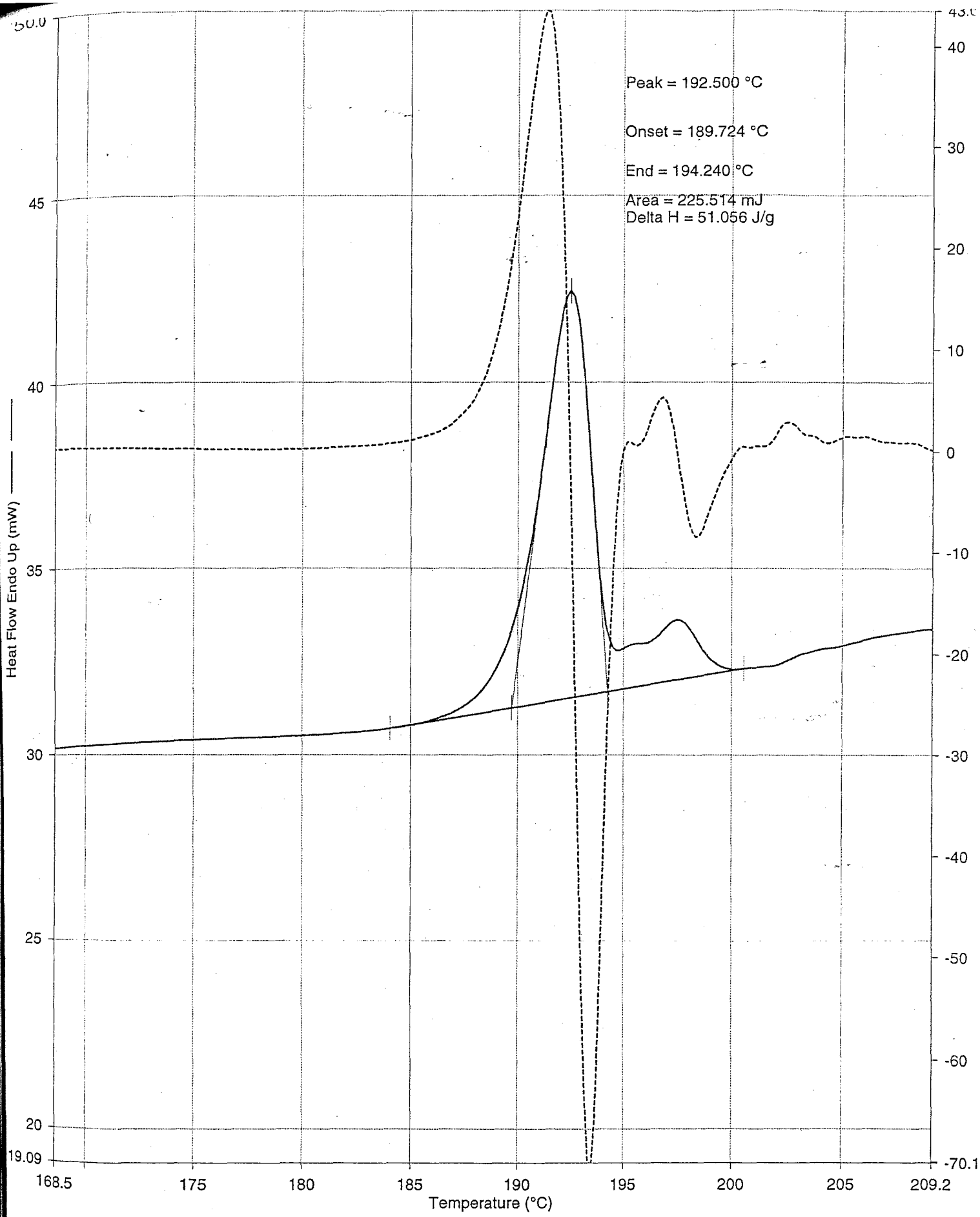
11/29/2002 12:54:53 PM

1) Heat from 25.00°C to 210.00°C at 10.00°C/min



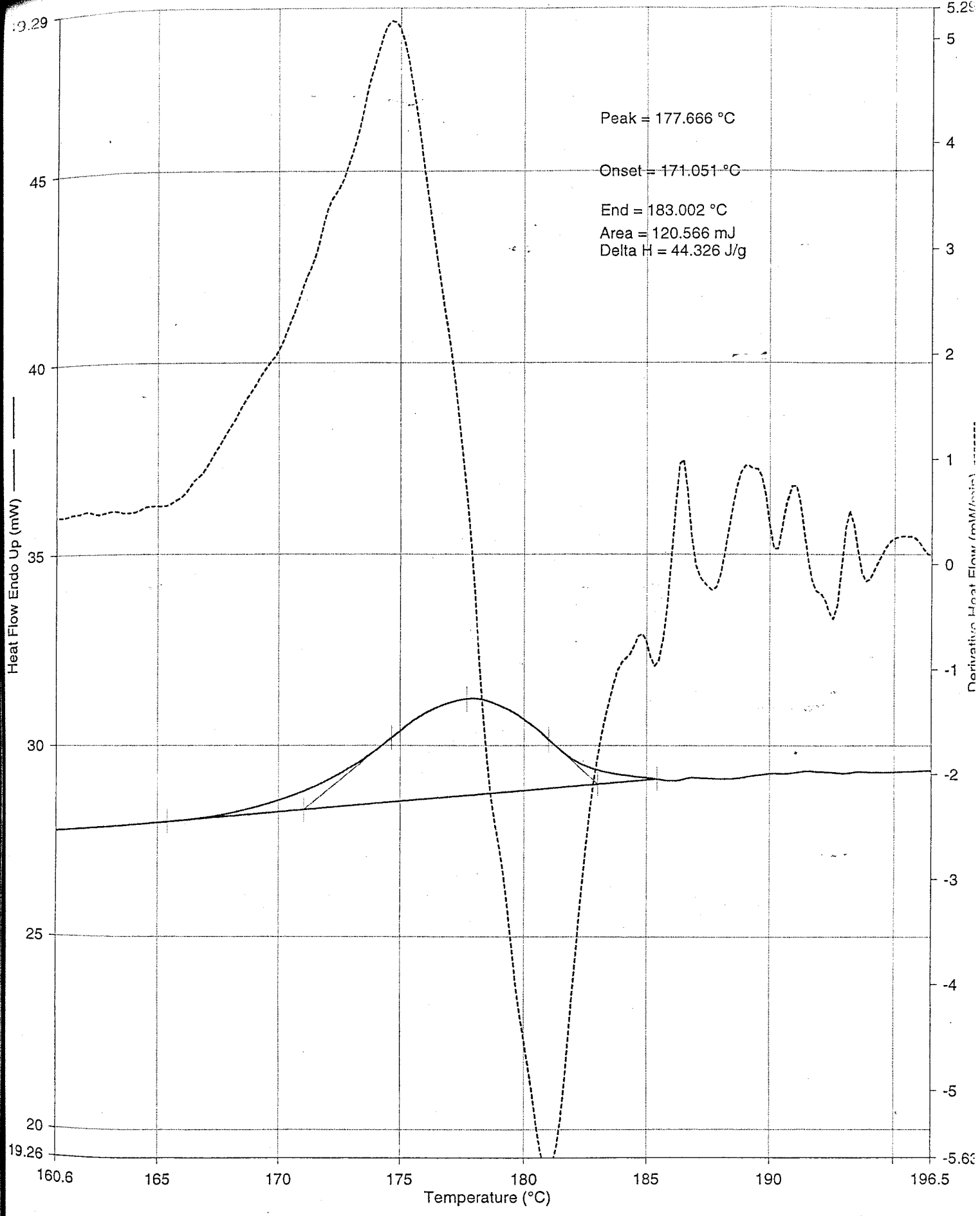
11/29/2002 1:00:53 PM

1) Heat from 25.00°C to 210.00°C at 10.00°C/min



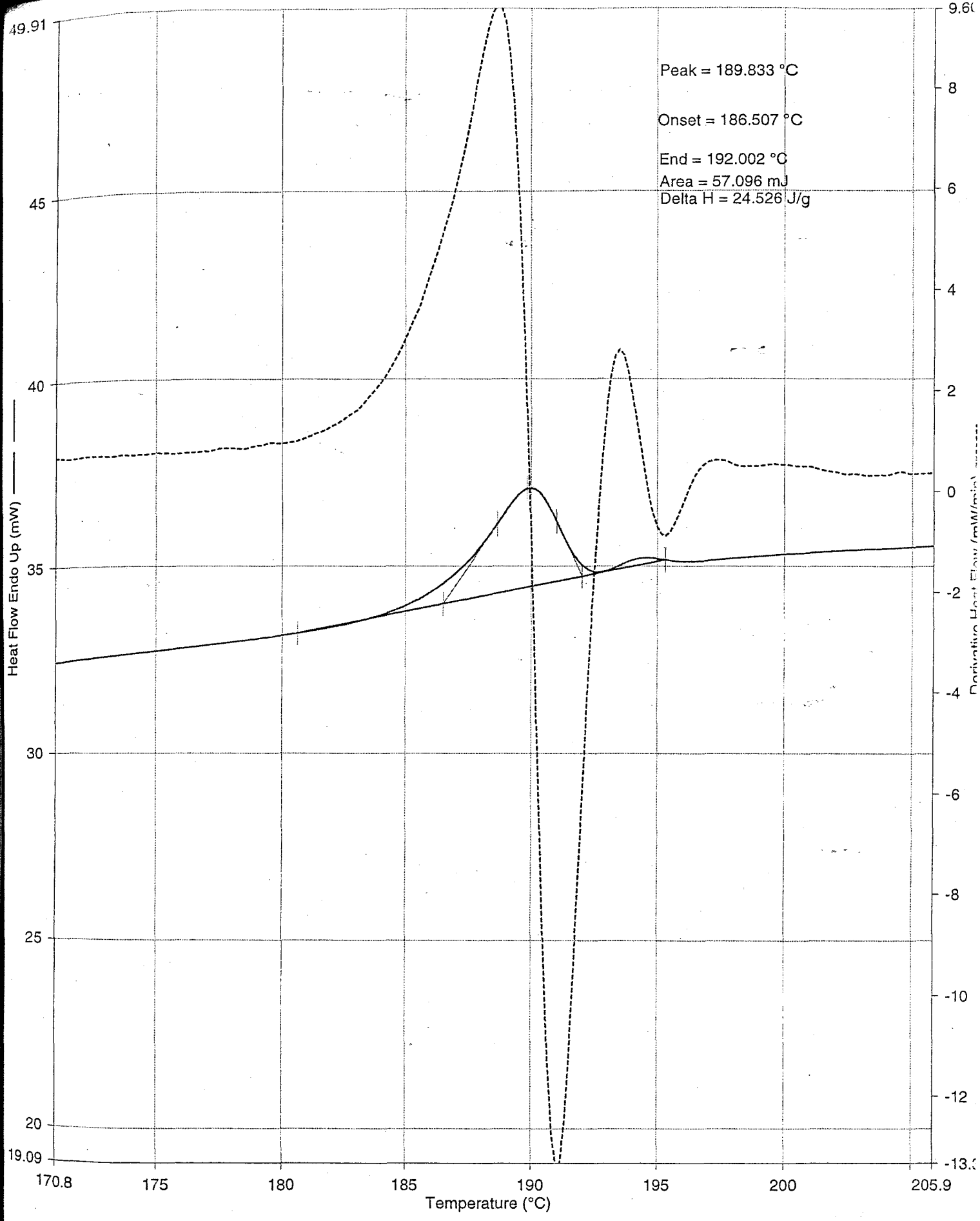
11/29/2002 12:56:18 PM

1) Heat from 25.00°C to 210.00°C at 10.00°C/min



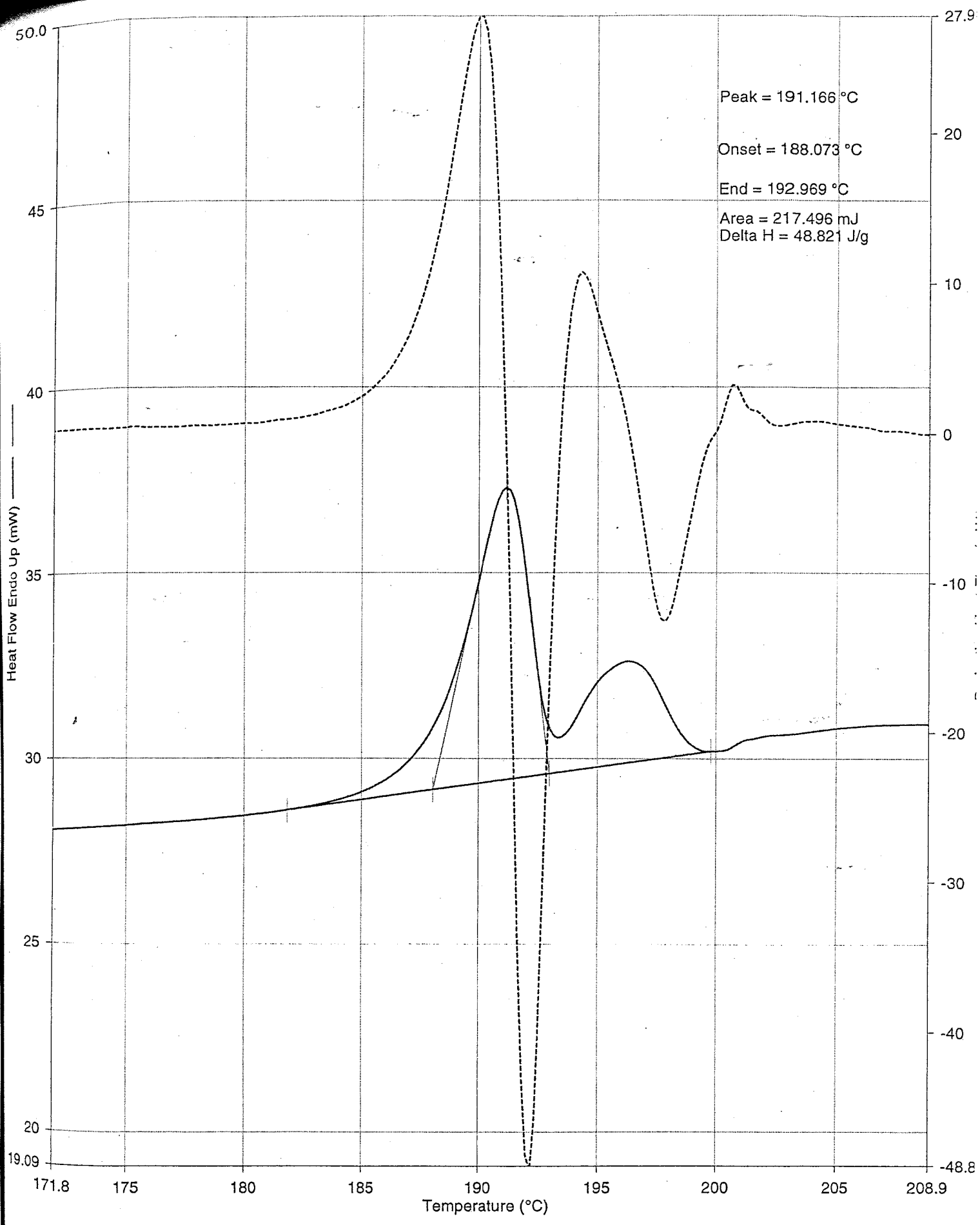
11/29/2002 1:02:31 PM

1) Heat from 25.00°C to 210.00°C at 10.00°C/min



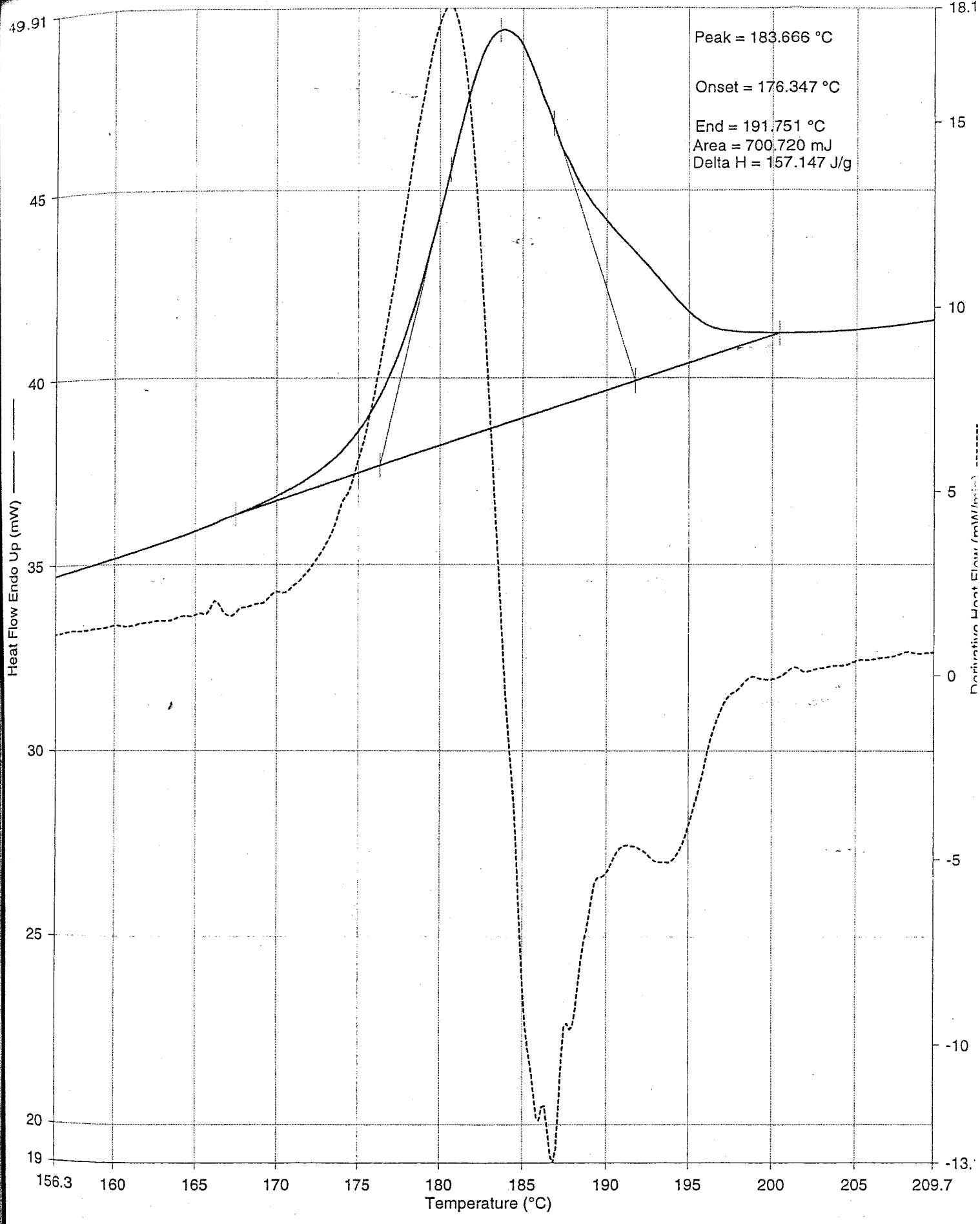
11/29/2002 12:53:05 PM

1) Heat from 25.00°C to 210.00°C at 10.00°C/min



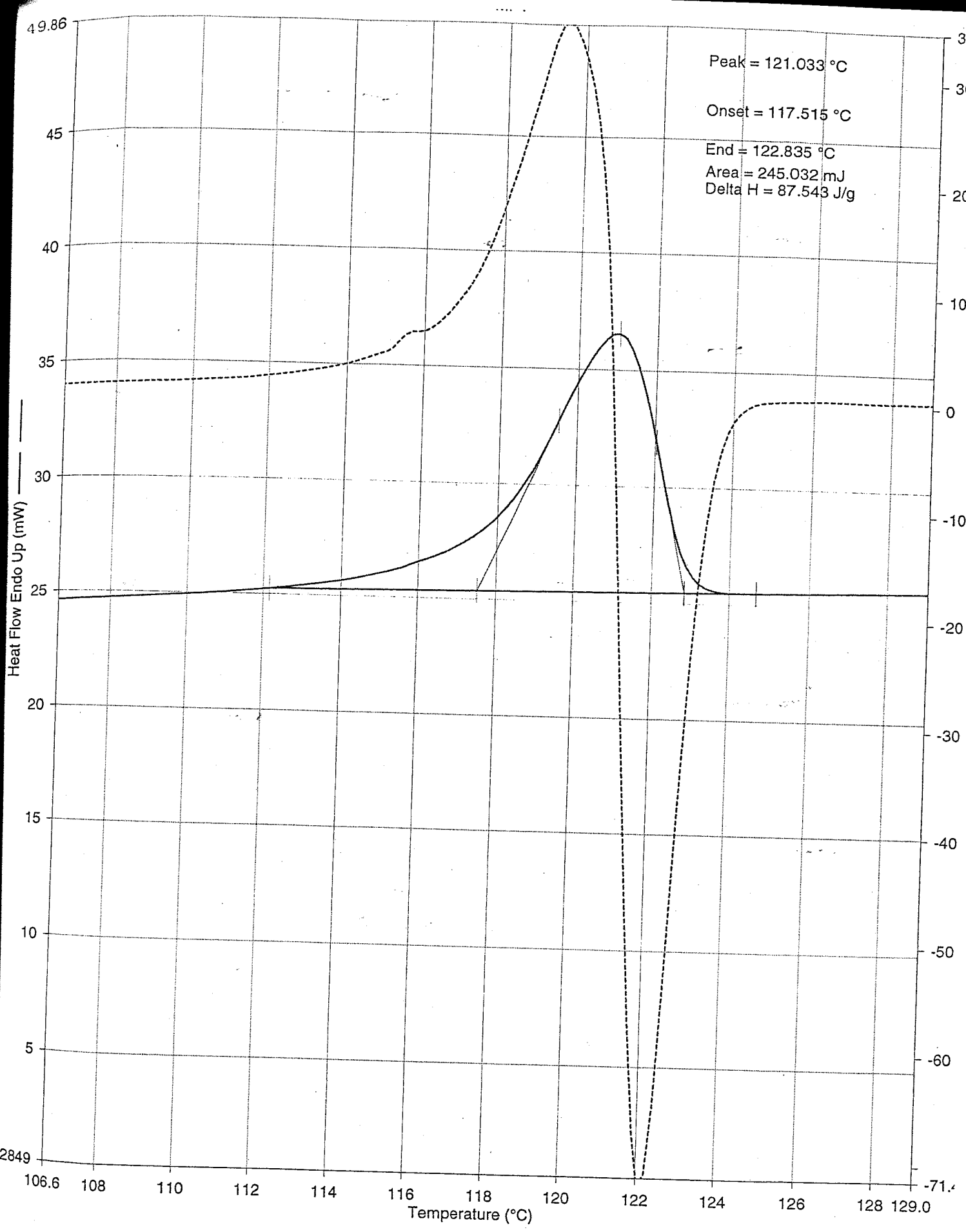
11/29/2002 1:03:57 PM

1) Heat from 25.00°C to 210.00°C at 10.00°C/min



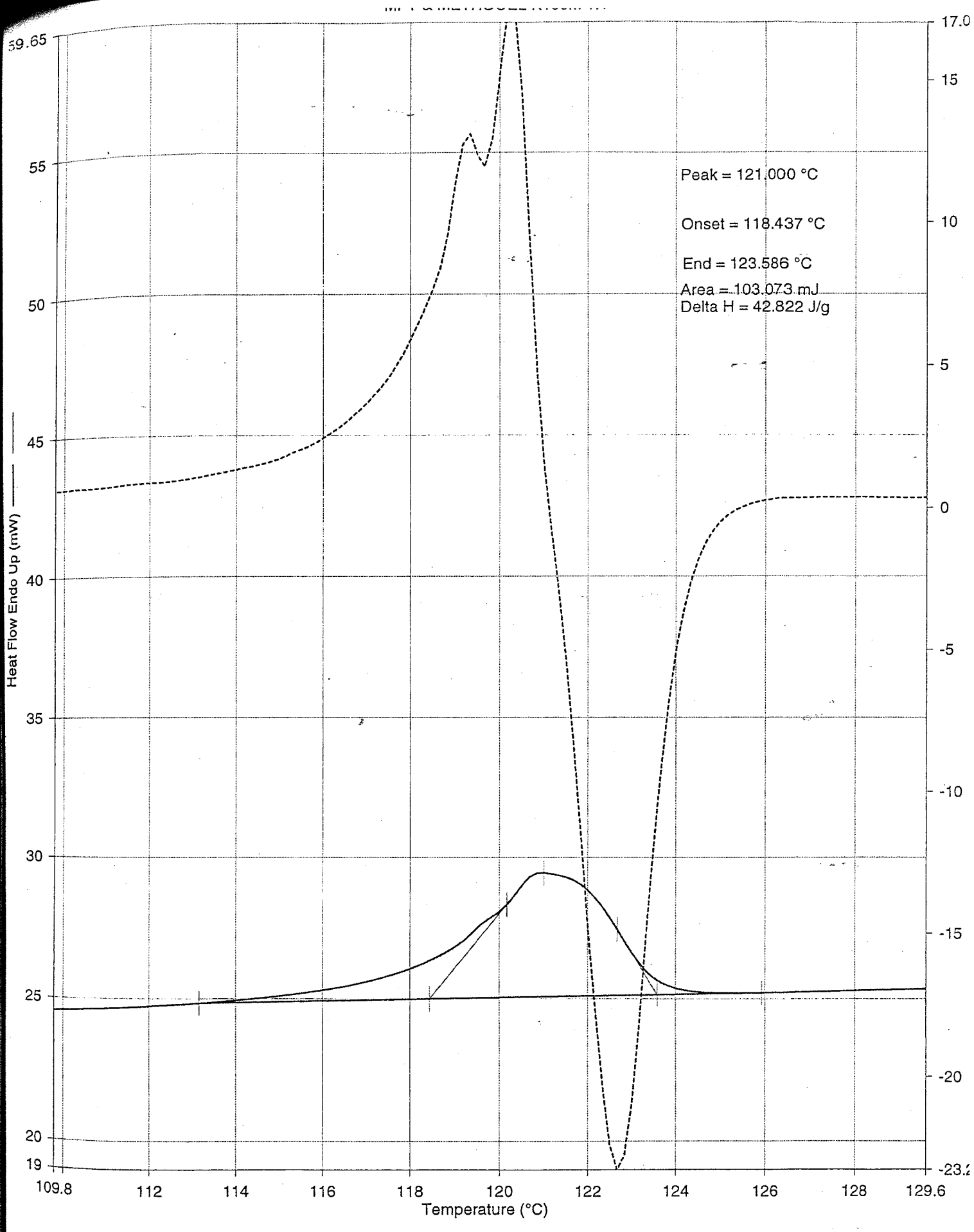
11/29/2002 1:06:56 PM

1) Heat from 25.00°C to 210.00°C at 10.00°C/min



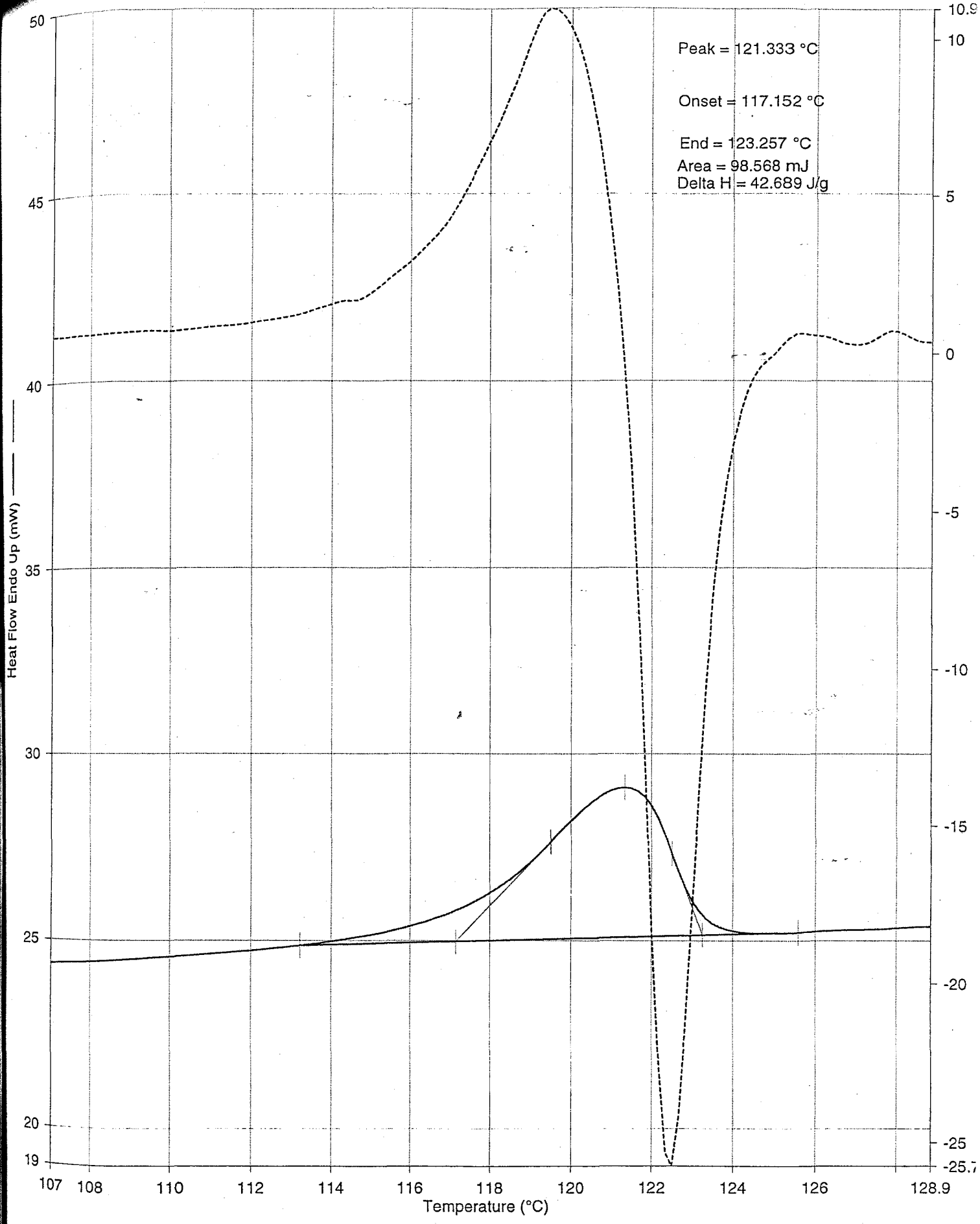
1) Heat from 25.00°C to 130.00°C at 10.00°C/min

11/29/2002 1:30:23 PM



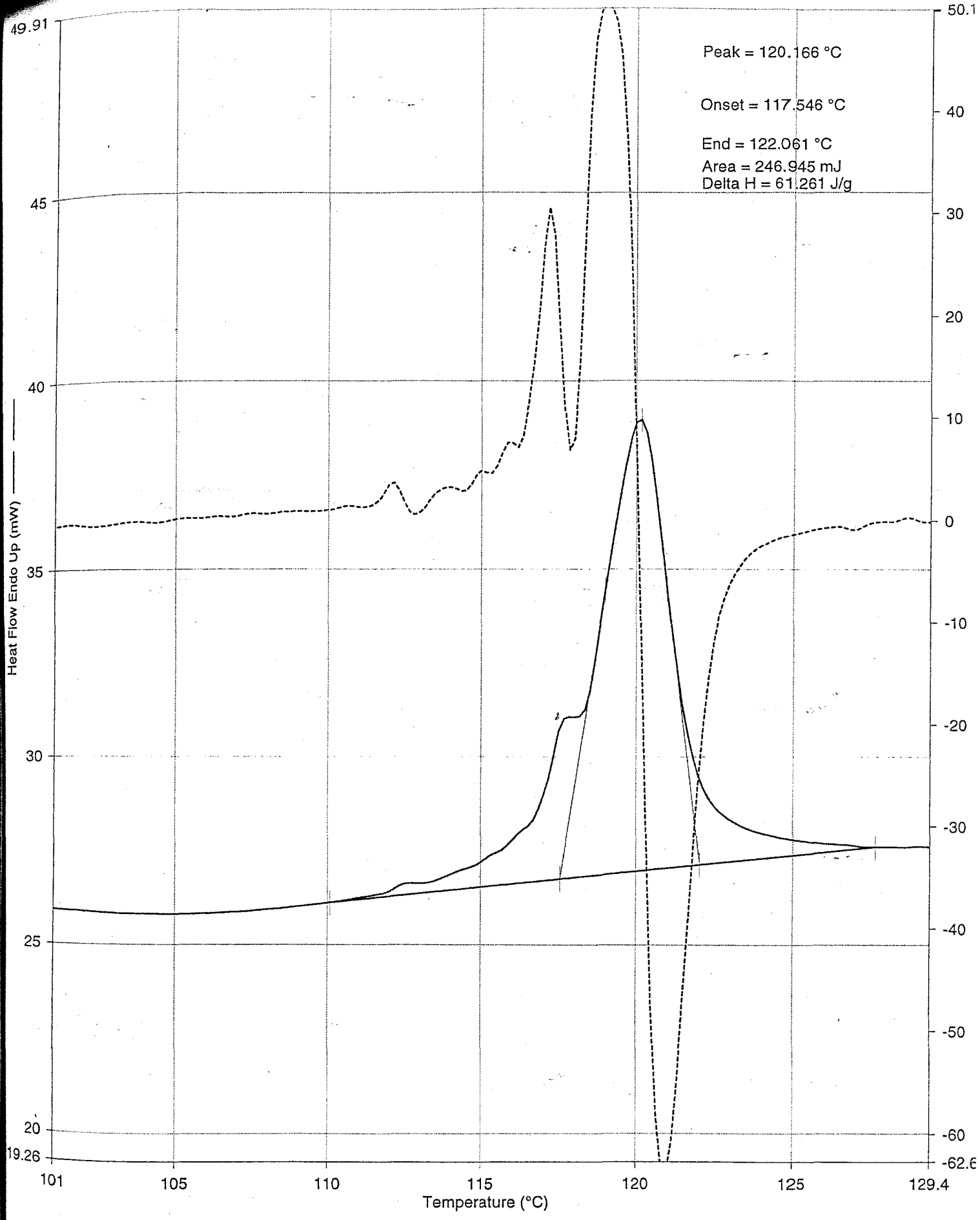
11/29/2002 1:24:26 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



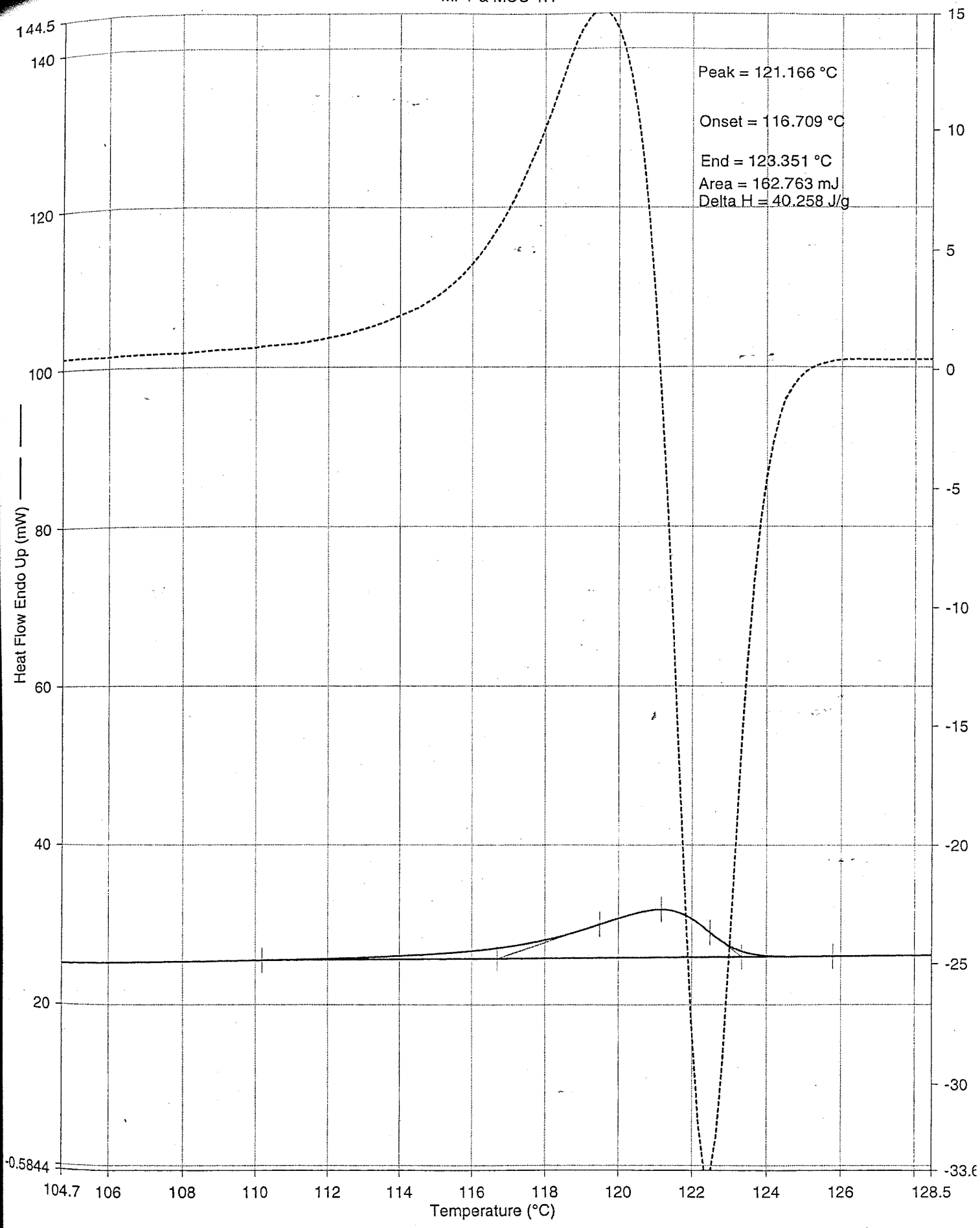
11/29/2002 1:25:34 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



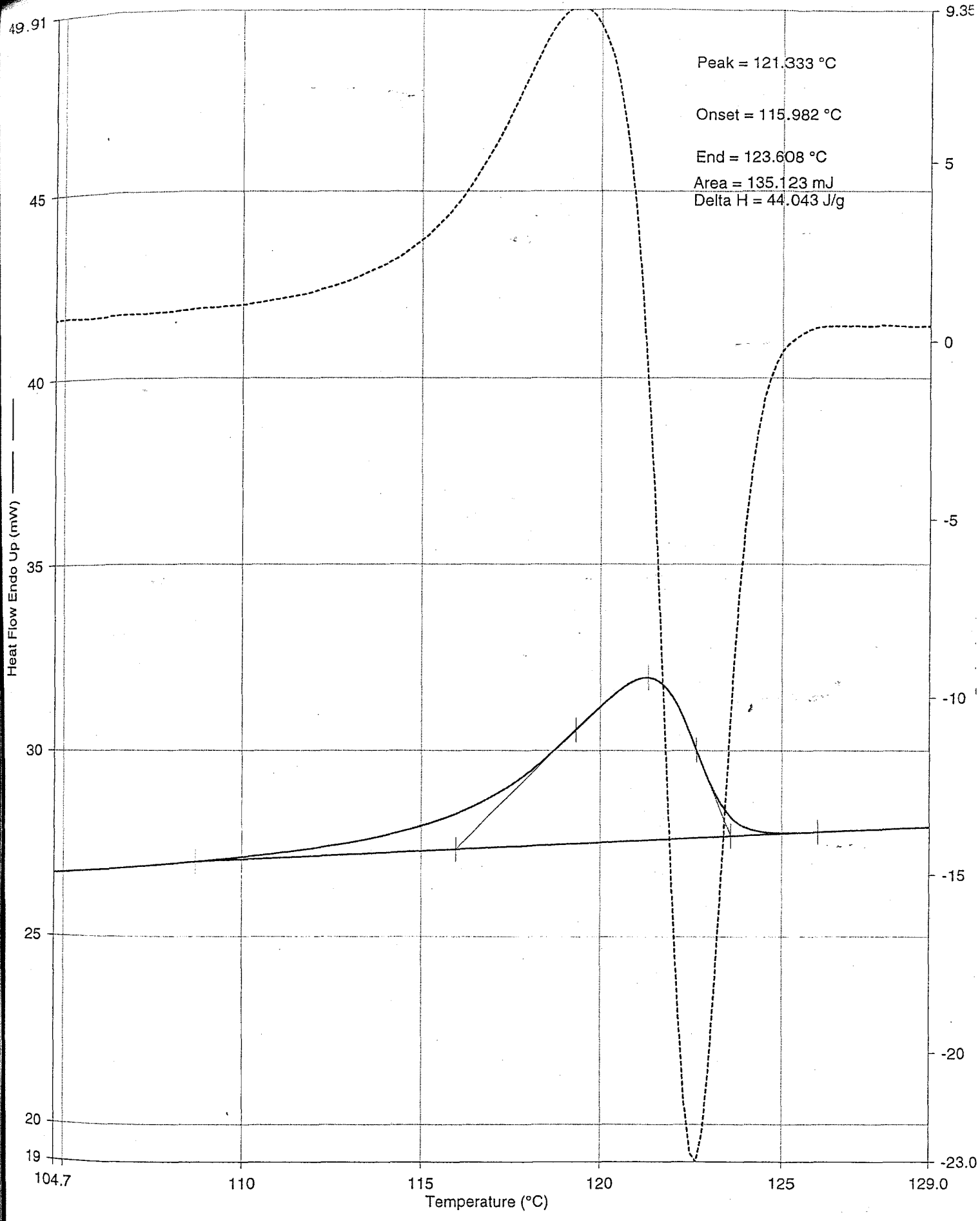
11/29/2002 1:19:29 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



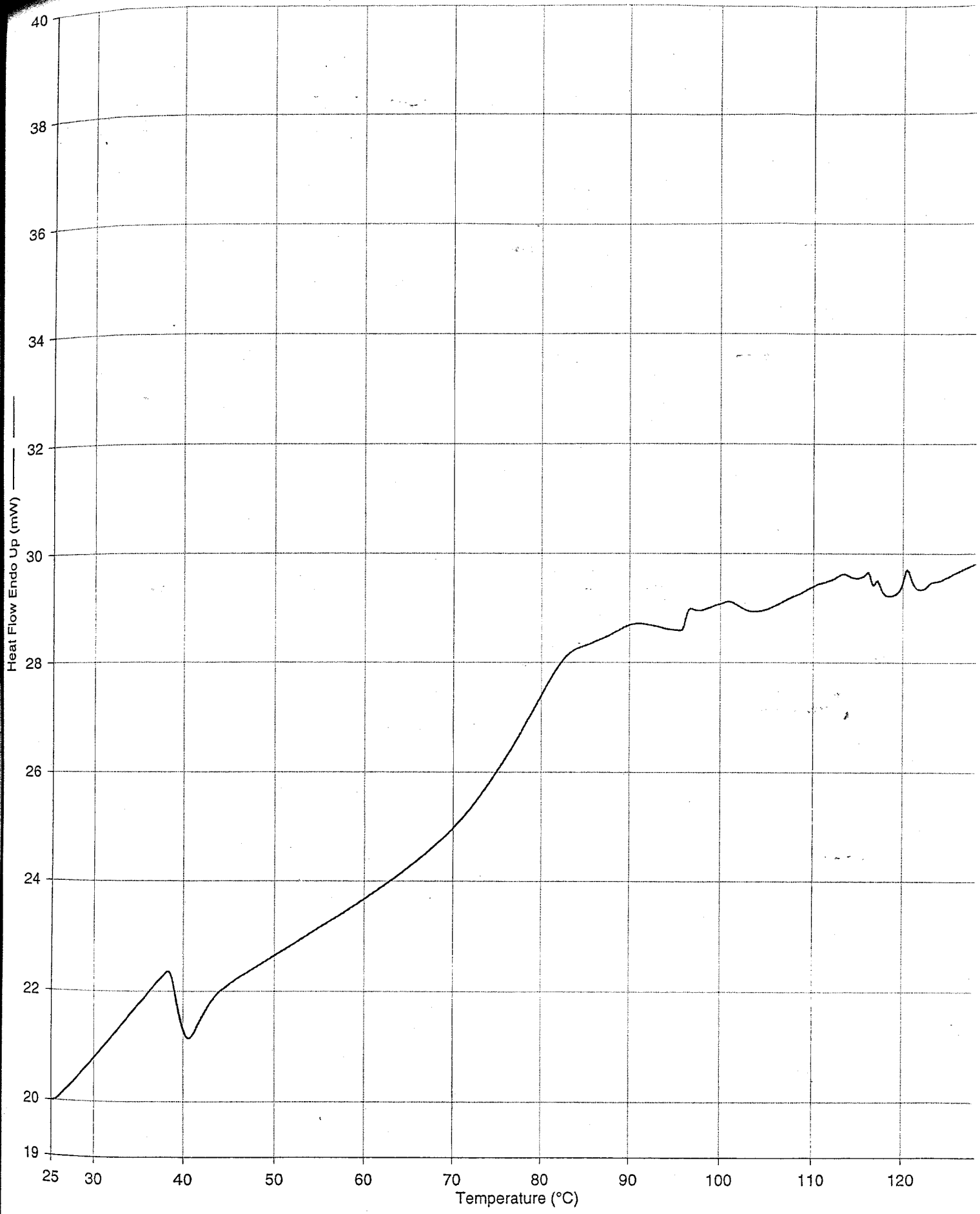
11/29/2002 1:26:53 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



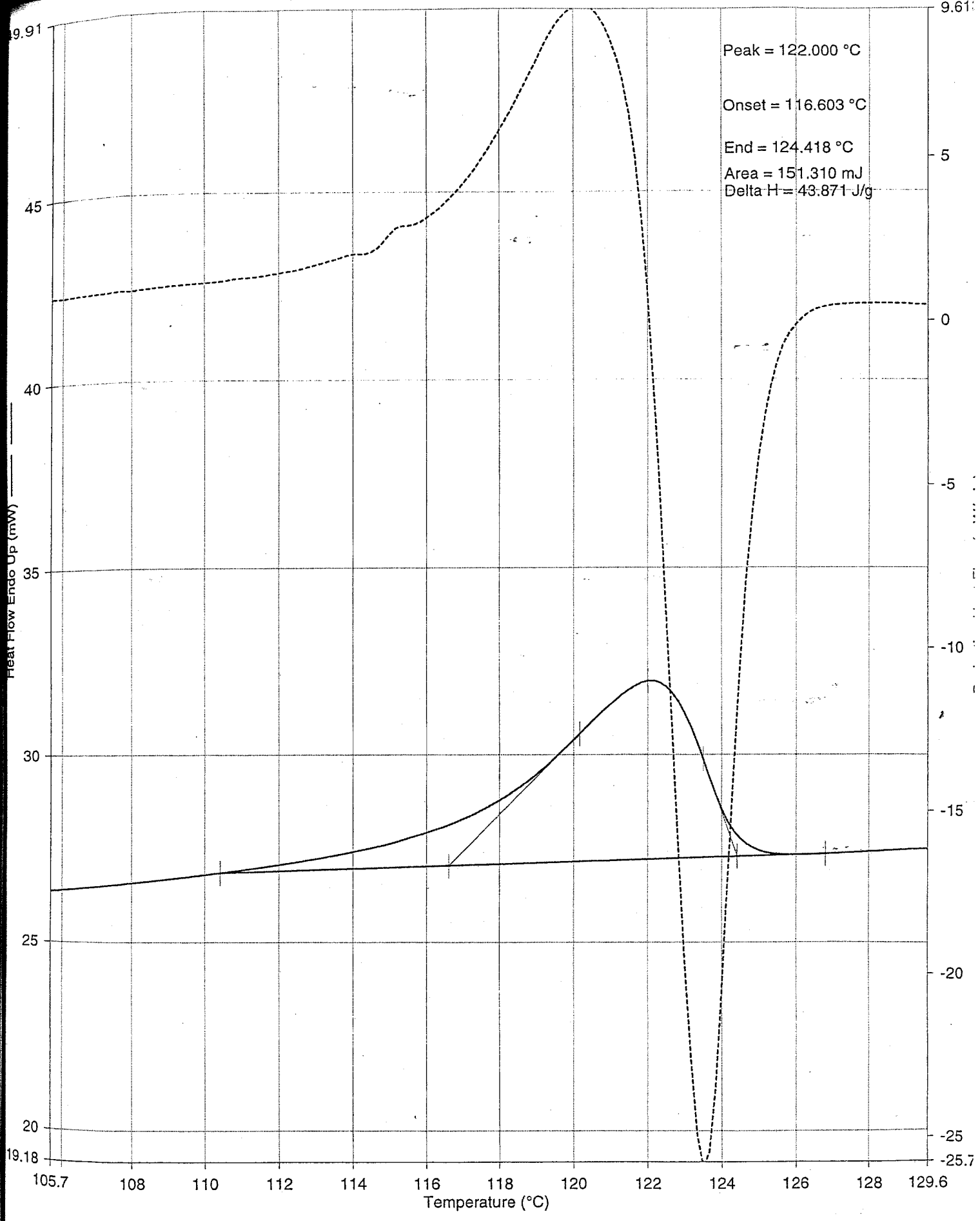
11/29/2002 1:16:43 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



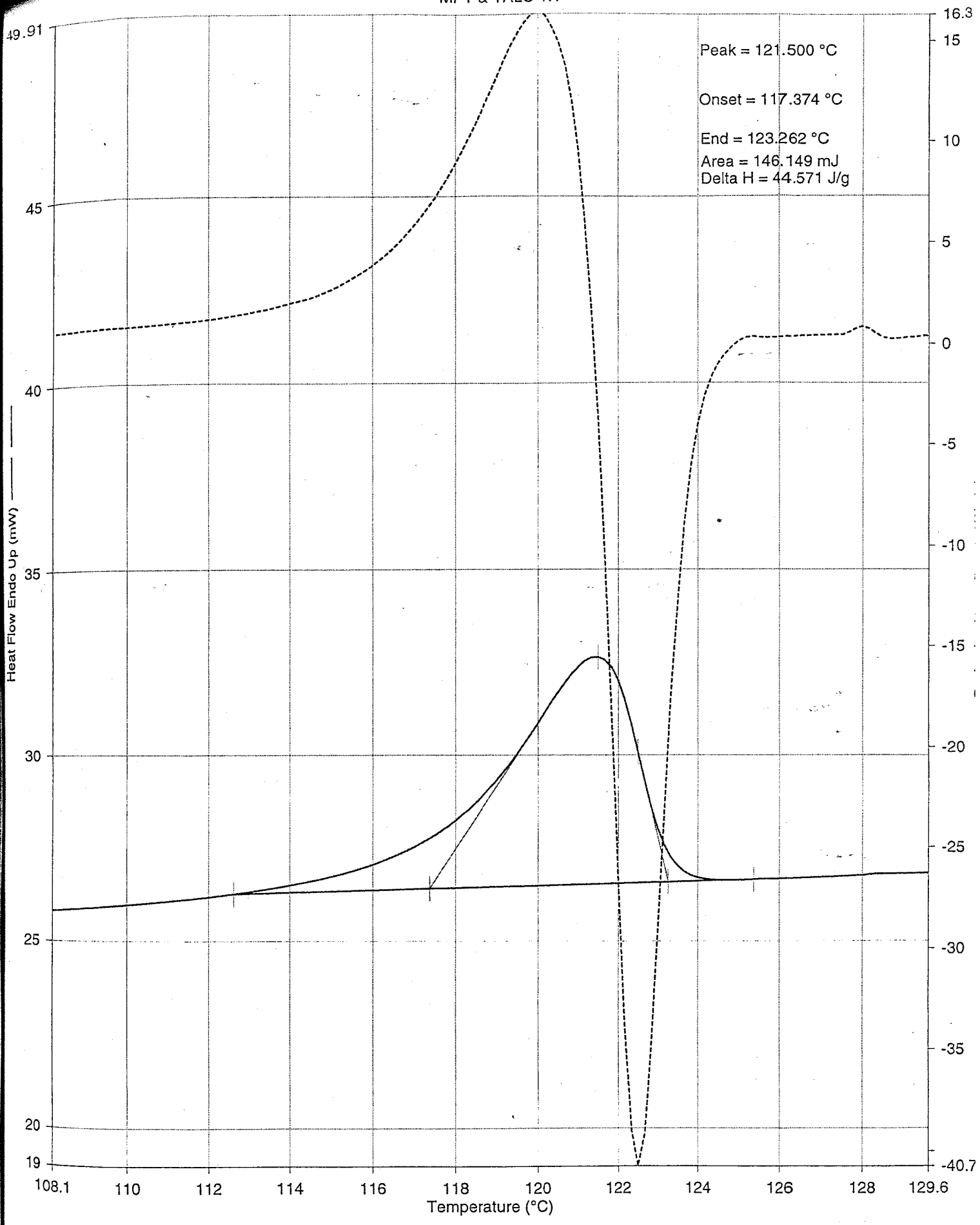
11/29/2002 1:27:59 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



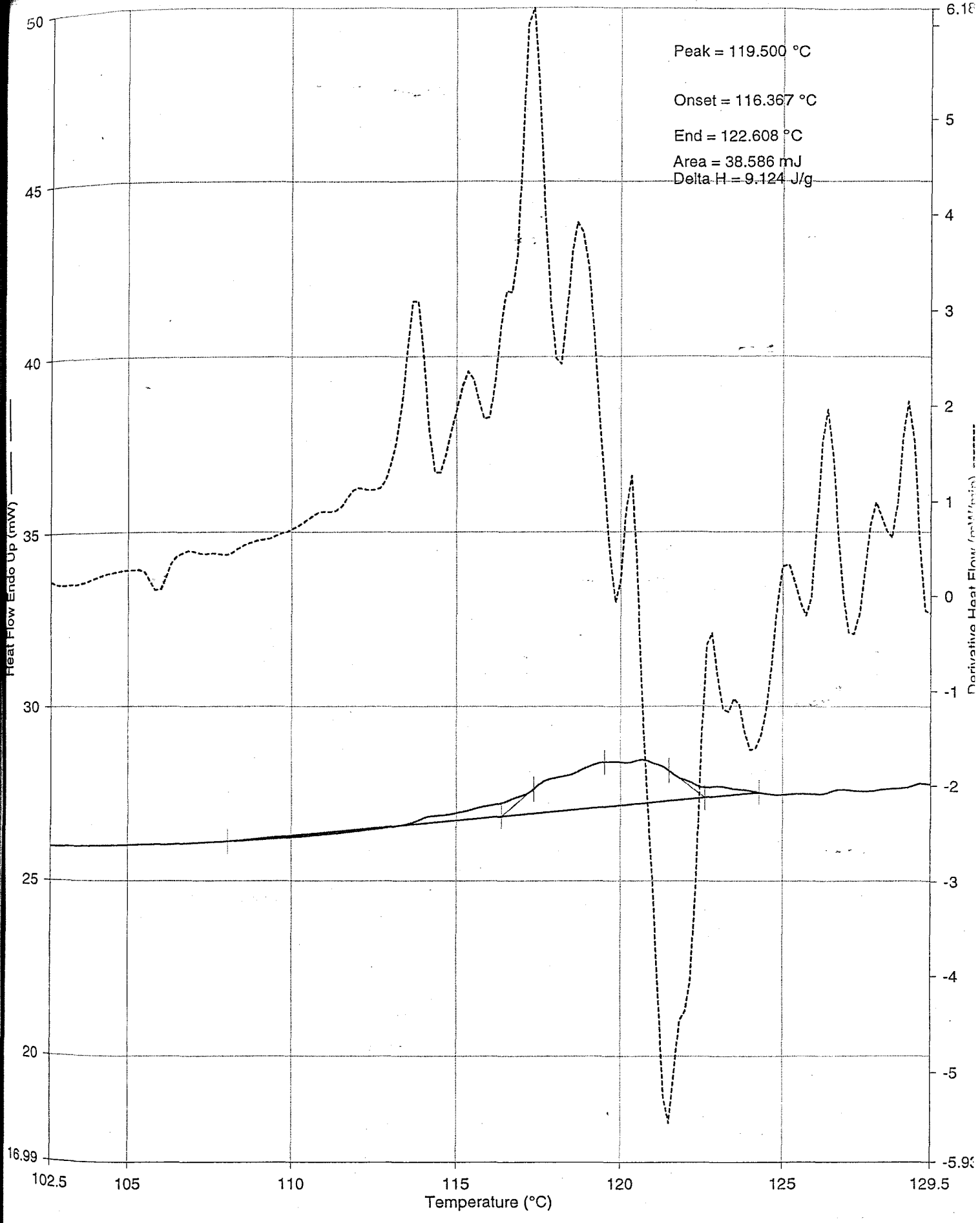
11/29/2002 1:18:18 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



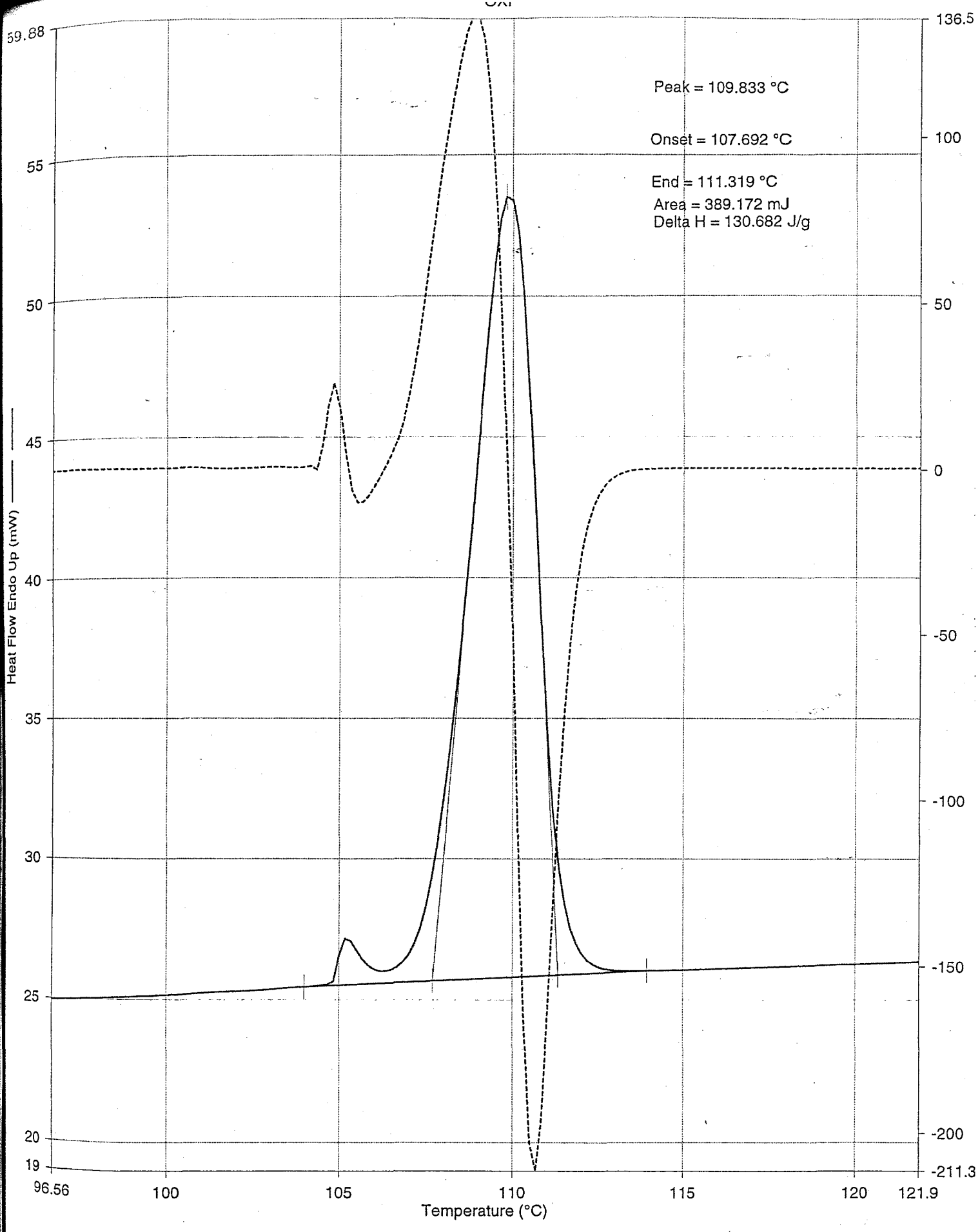
11/29/2002 1:29:14 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



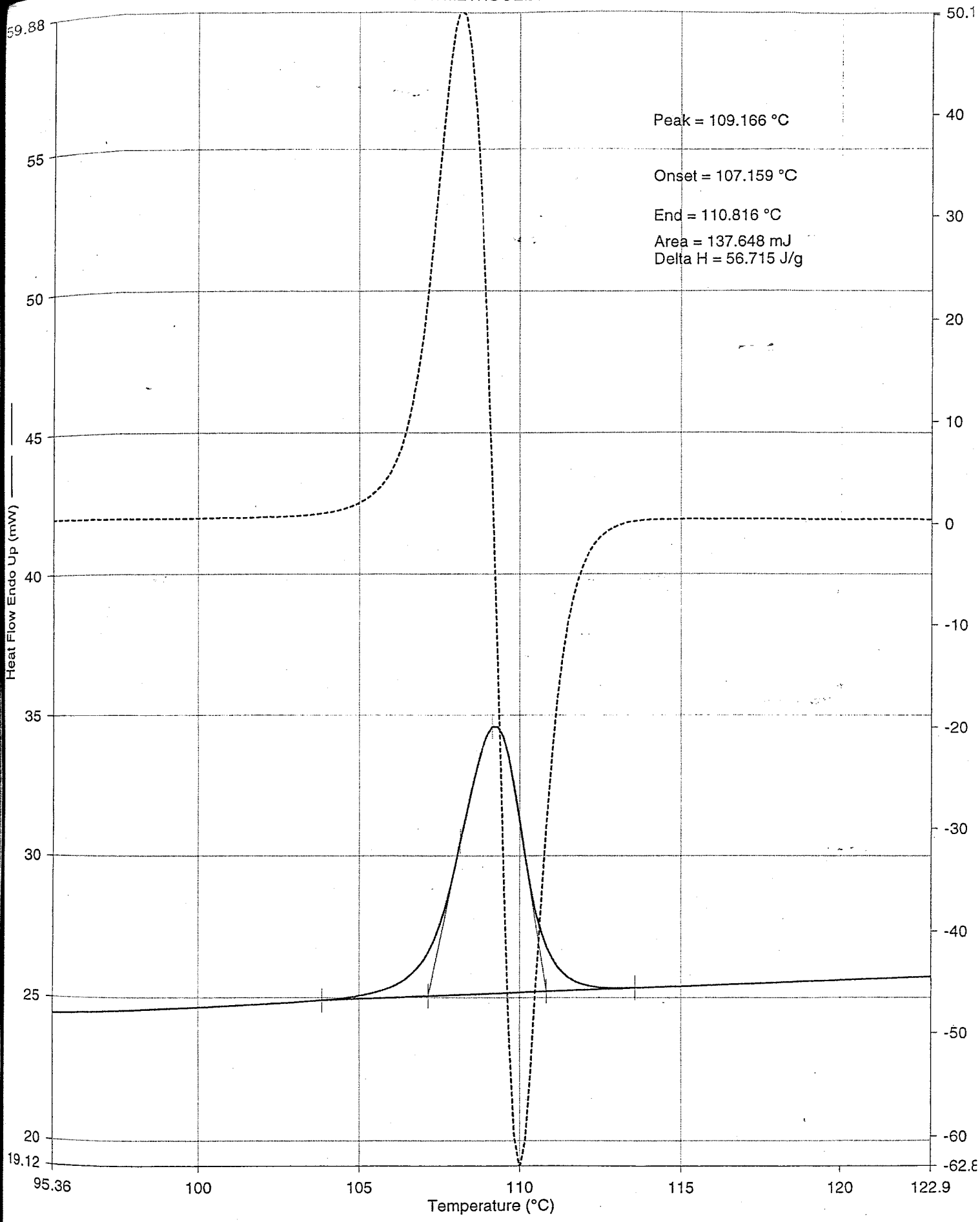
11/29/2002 1:32:16 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



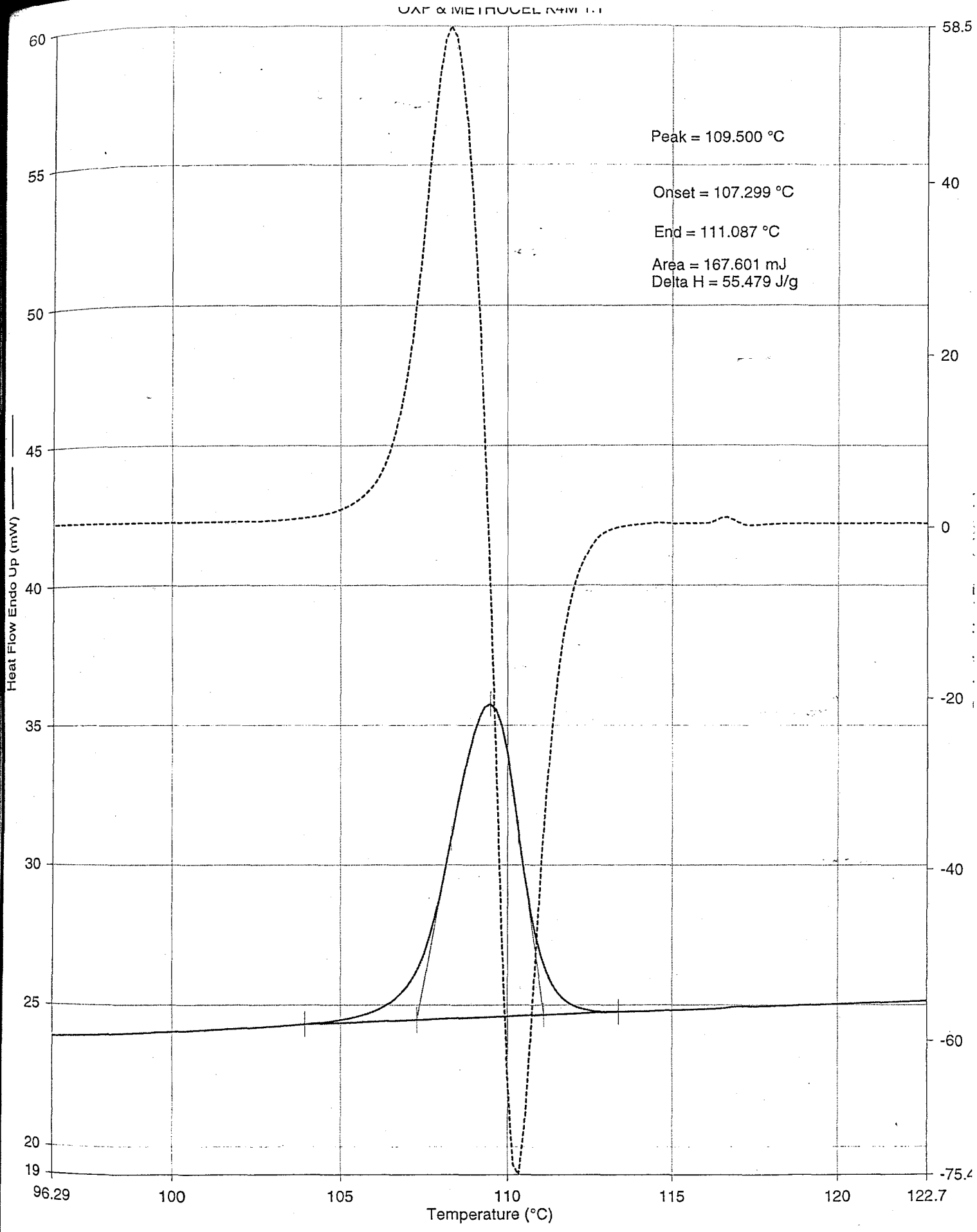
11/29/2002 1:48:04 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



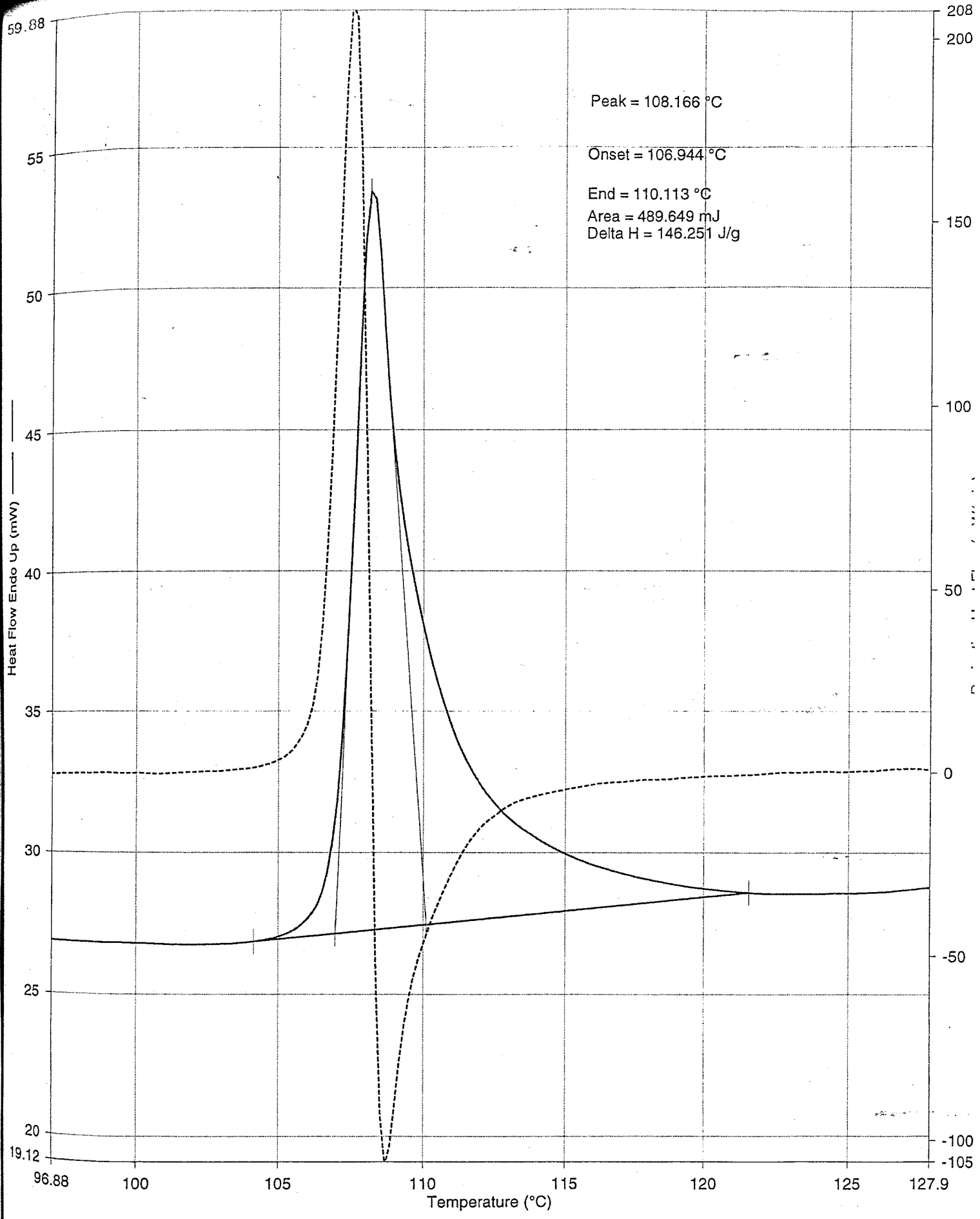
11/29/2002 1:40:31 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



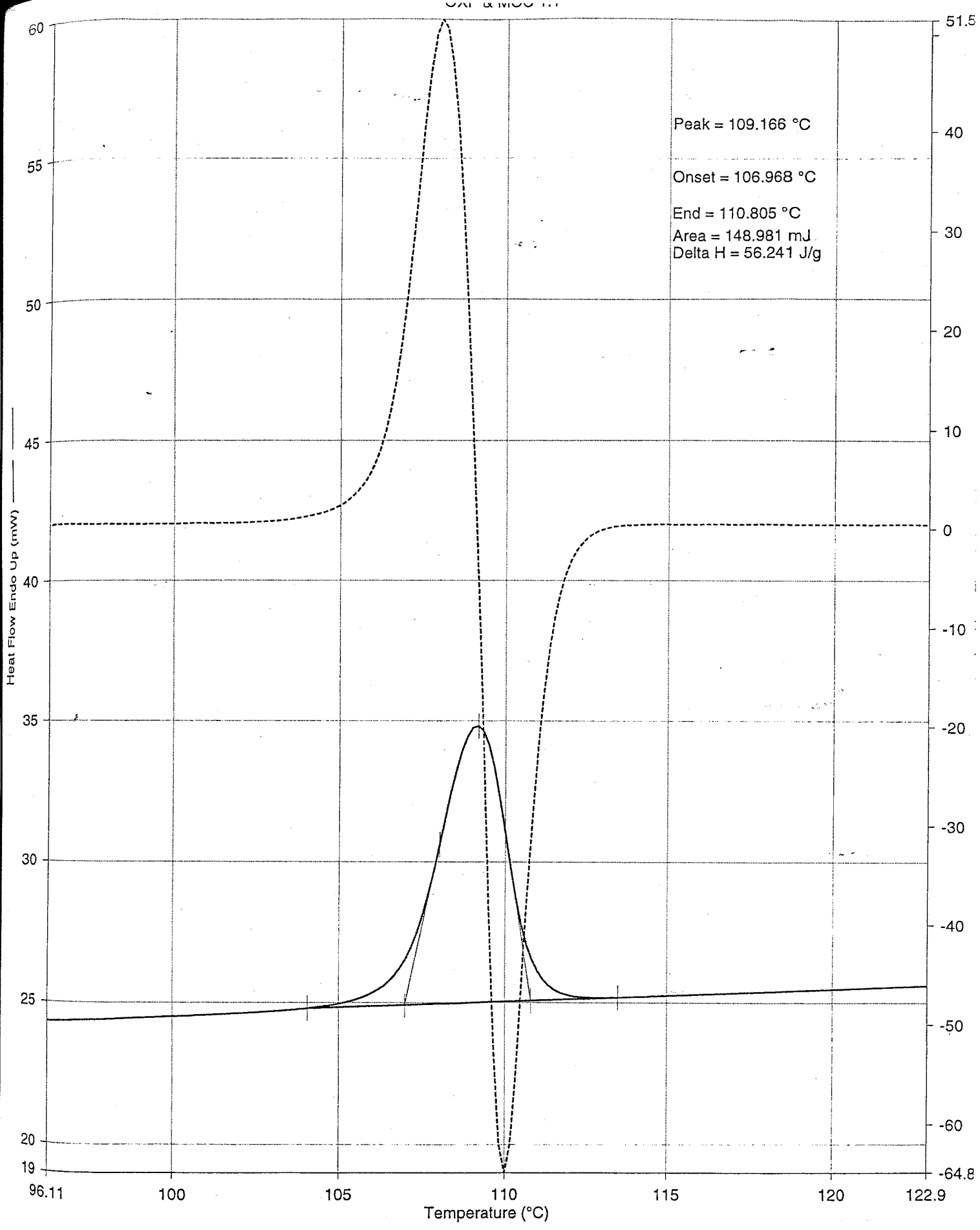
11/29/2002 1:41:40 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



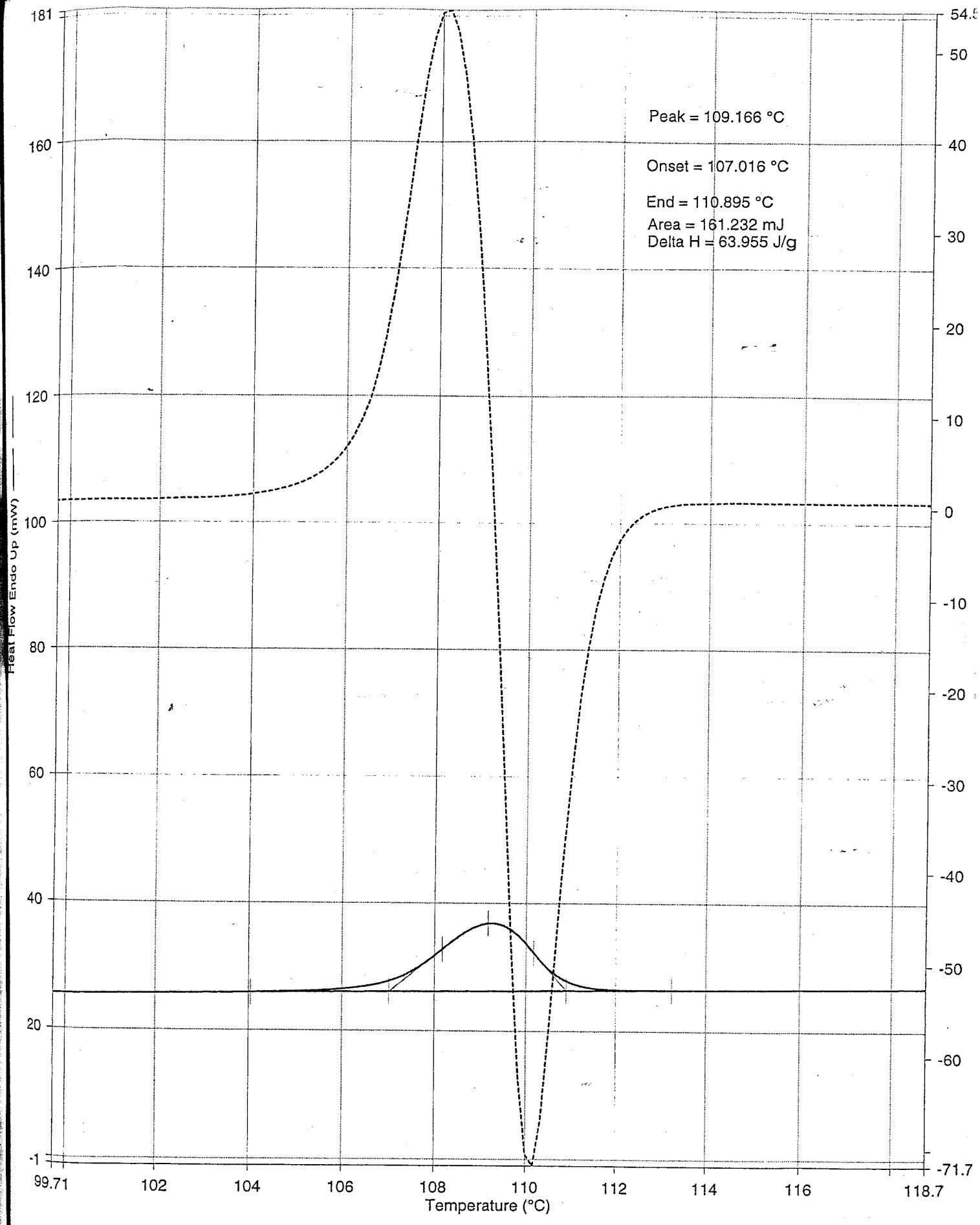
11/29/2002 1:36:21 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



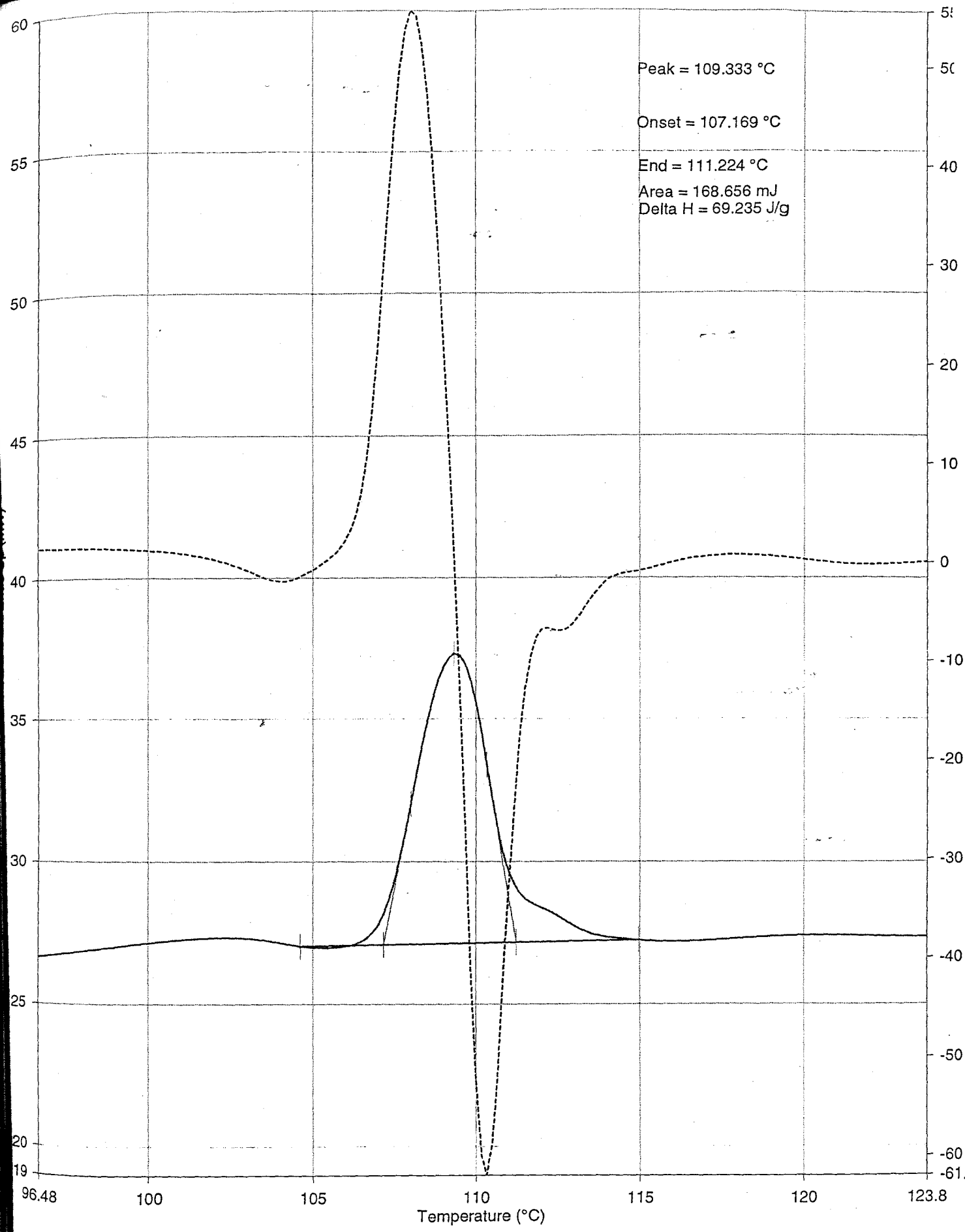
11/29/2002 1:42:56 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



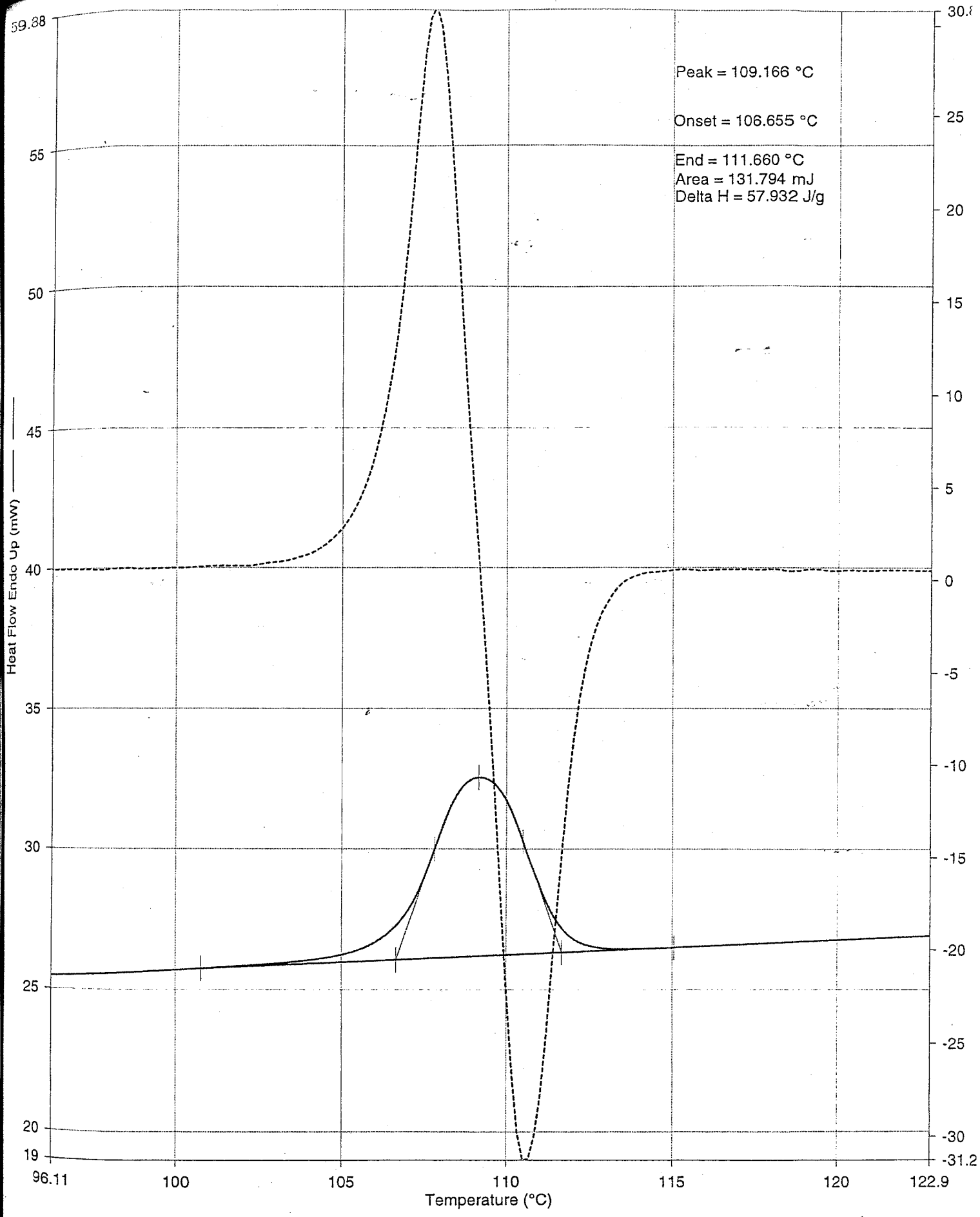
11/29/2002 1:37:52 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



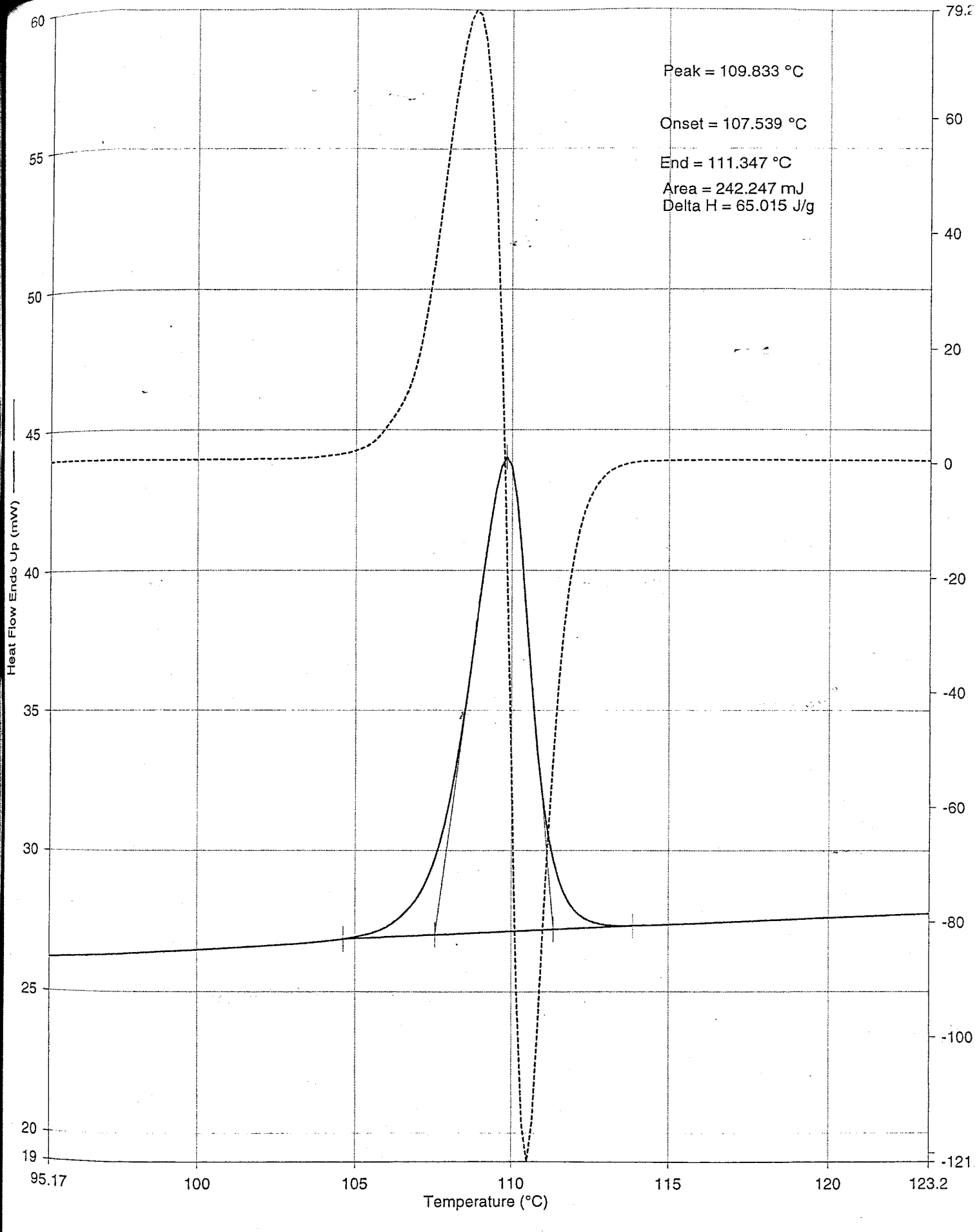
11/29/2002 1:44:54 PM

Heat from 25.00°C to 130.00°C at 10.00°C/min



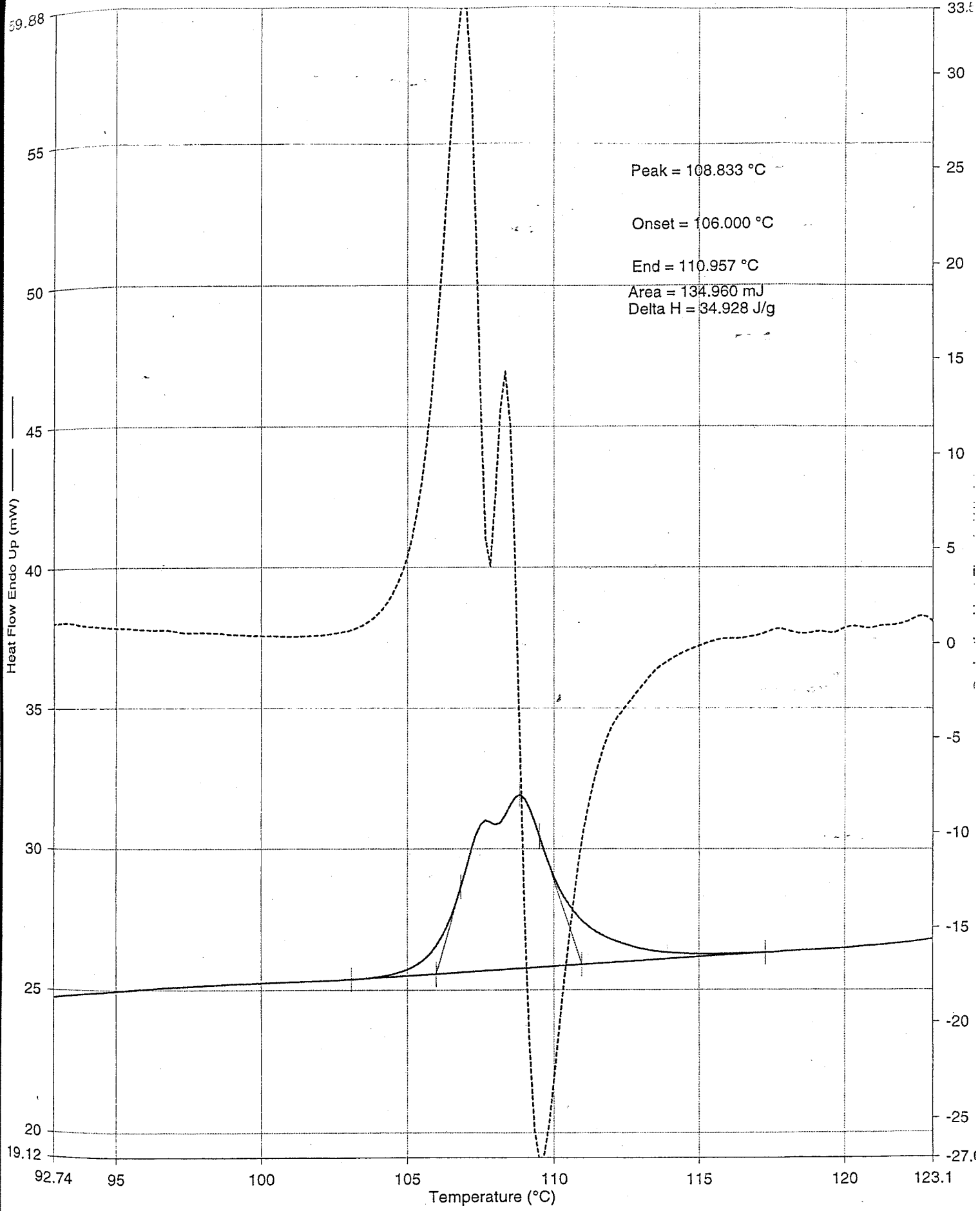
11/29/2002 1:34:08 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



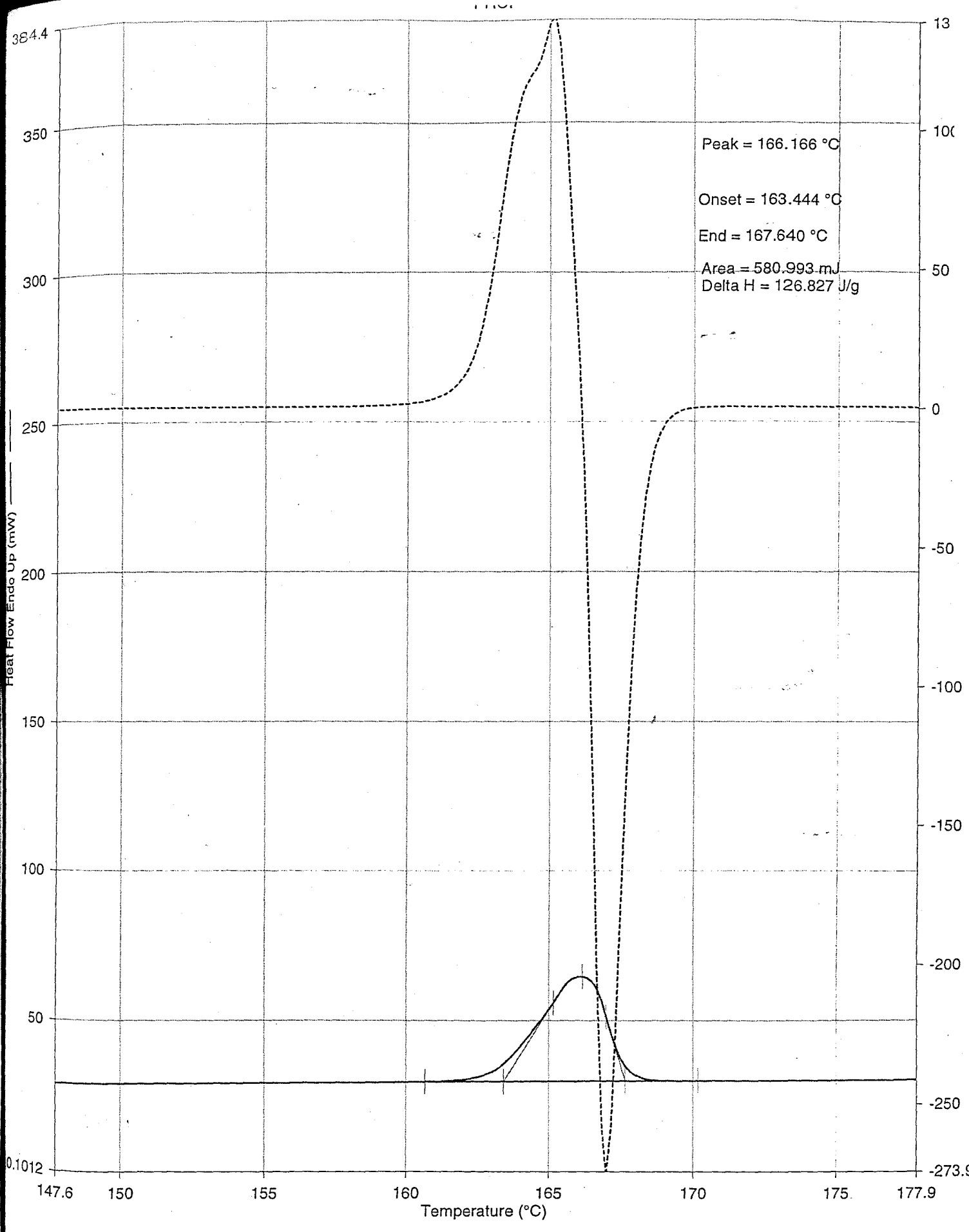
11/29/2002 1:46:04 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



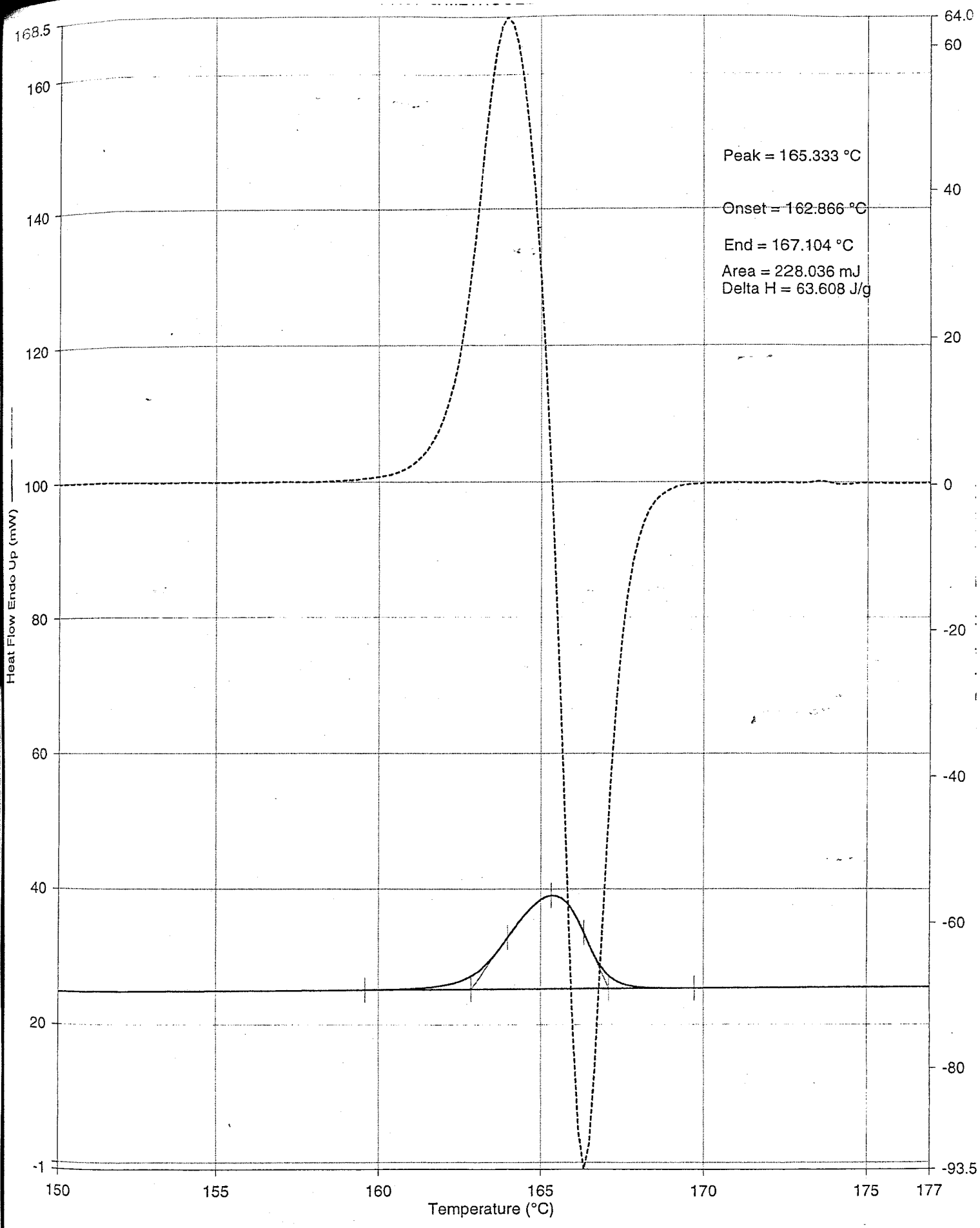
11/29/2002 1:49:05 PM

1) Heat from 25.00°C to 130.00°C at 10.00°C/min



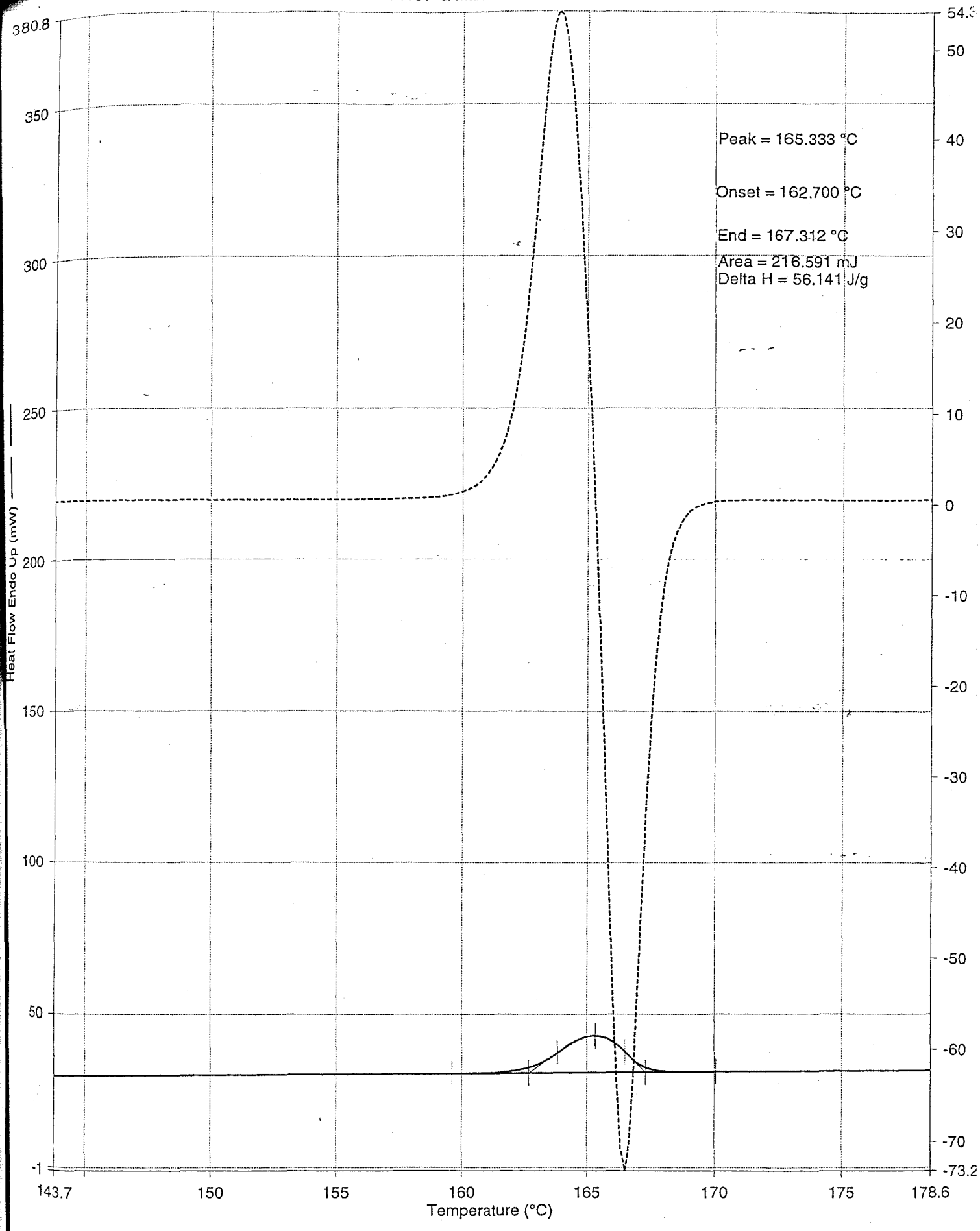
11/29/2002 1:59:43 PM

1) Heat from 25.00°C to 180.00°C at 10.00°C/min



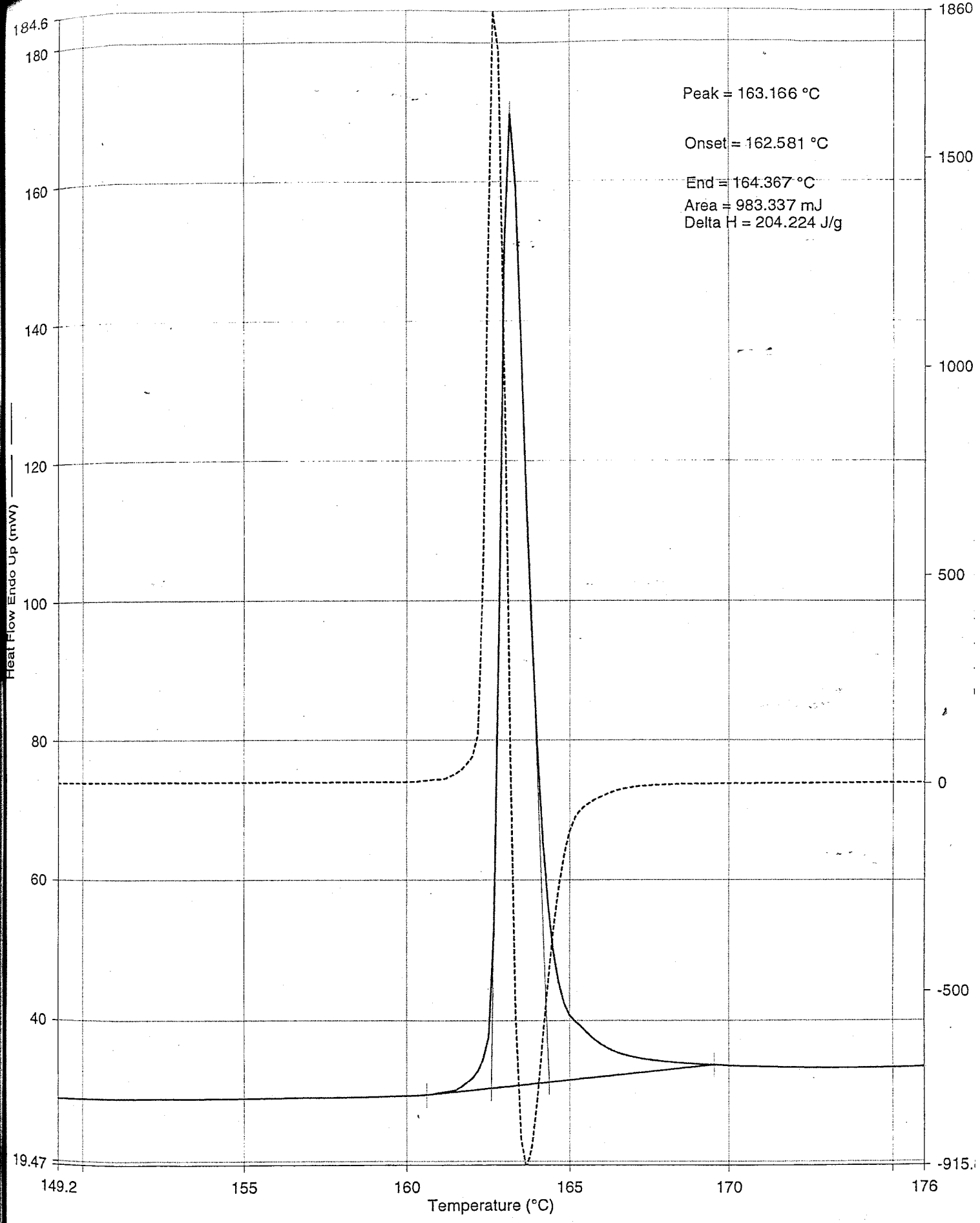
11/29/2002 1:53:43 PM

1) Heat from 25.00°C to 180.00°C at 10.00°C/min



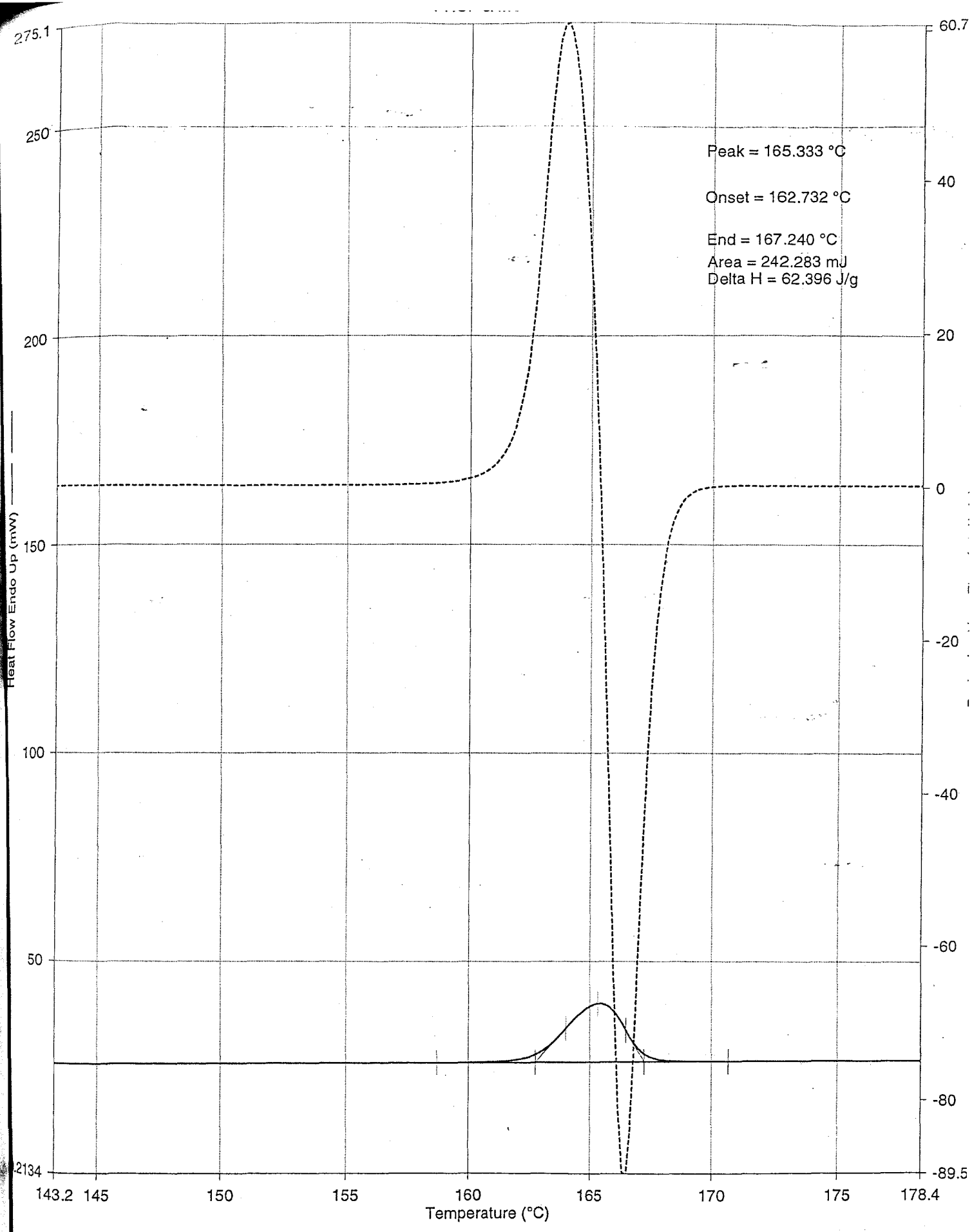
11/29/2002 1:54:48 PM

1) Heat from 25.00°C to 180.00°C at 10.00°C/min



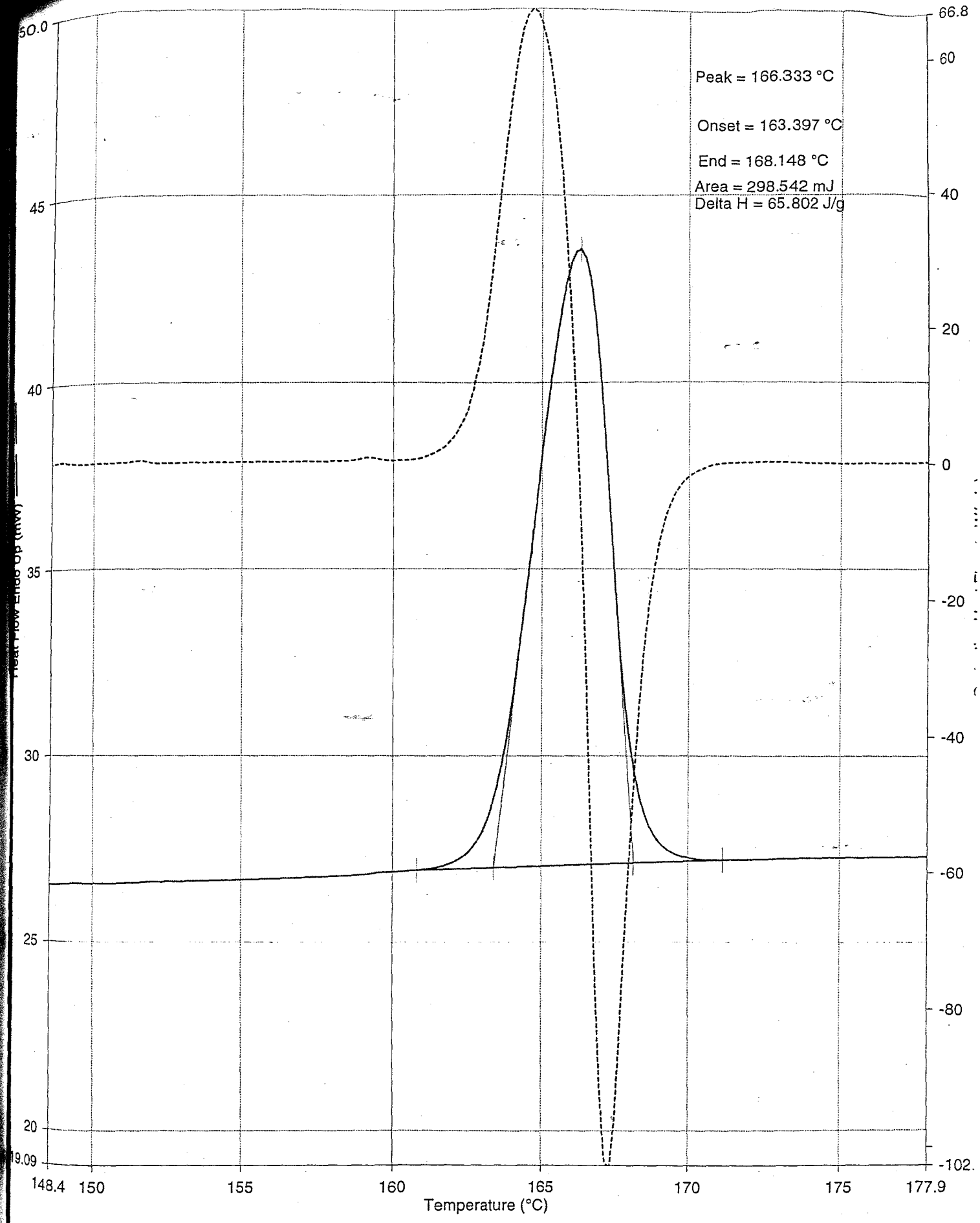
11/29/2002 1:51:29 PM

1) Heat from 25.00°C to 180.00°C at 10.00°C/min



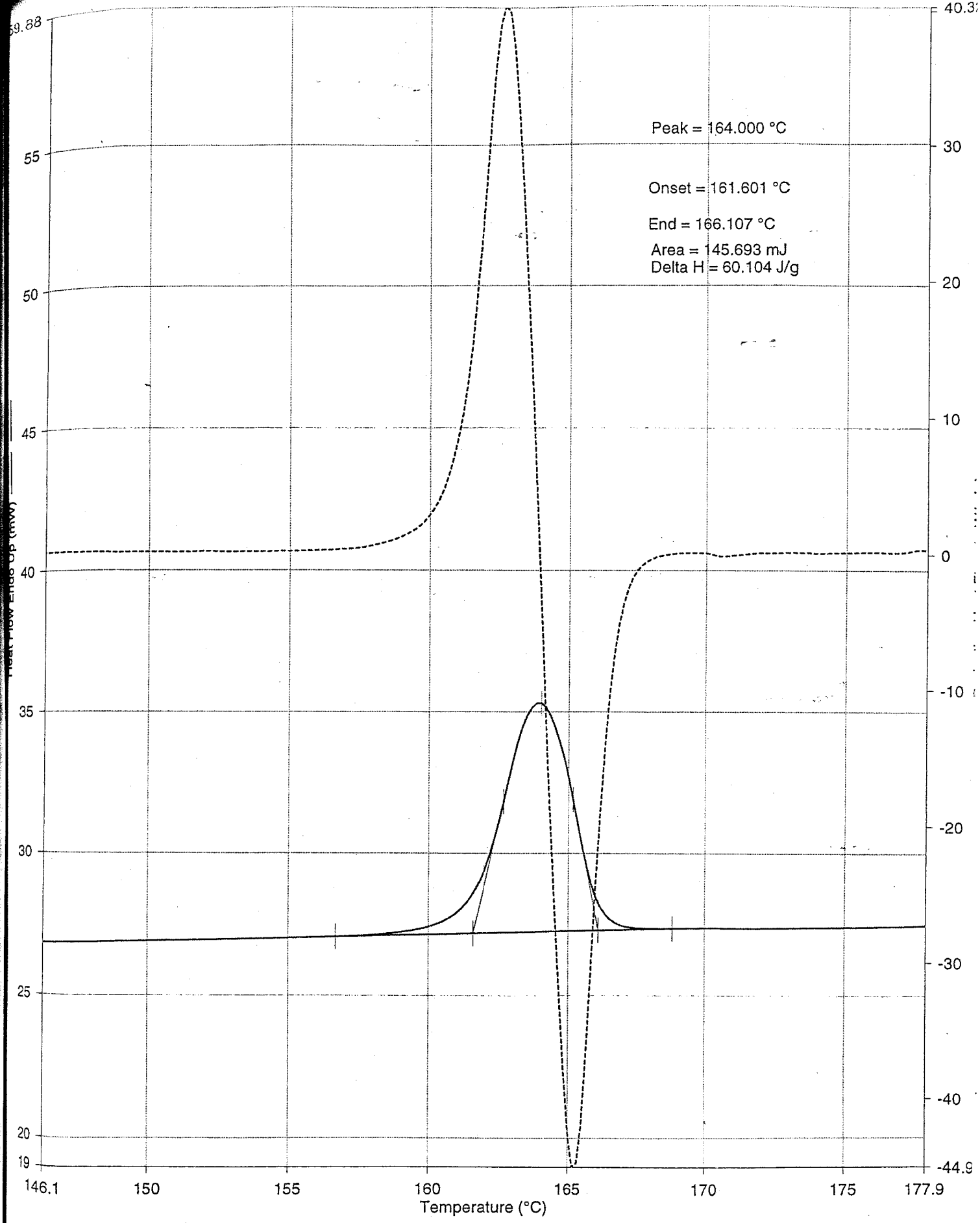
11/29/2002 1:55:54 PM

) Heat from 25.00°C to 180.00°C at 10.00°C/min



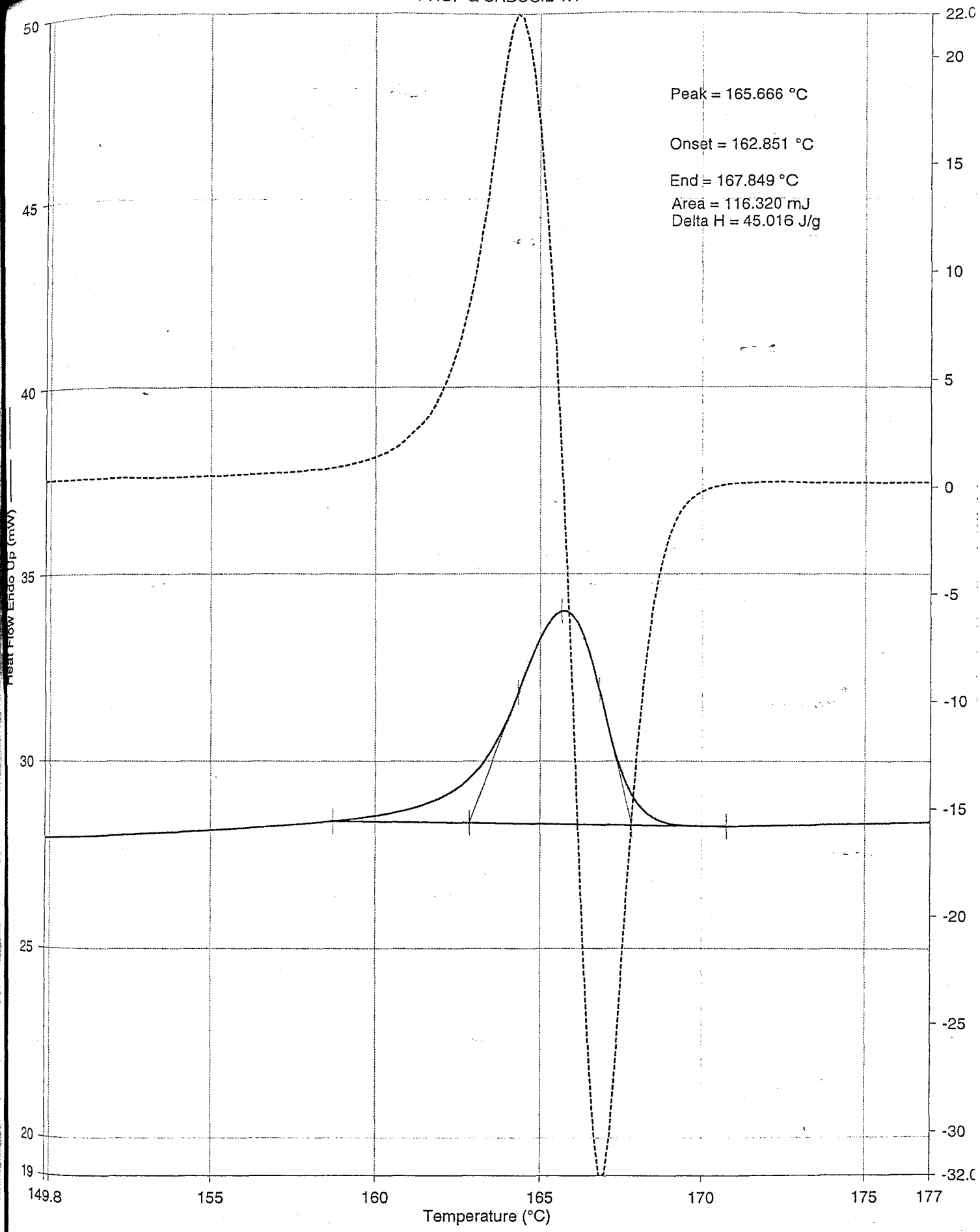
11/29/2002 1:52:34 PM

1) Heat from 25.00°C to 180.00°C at 10.00°C/min



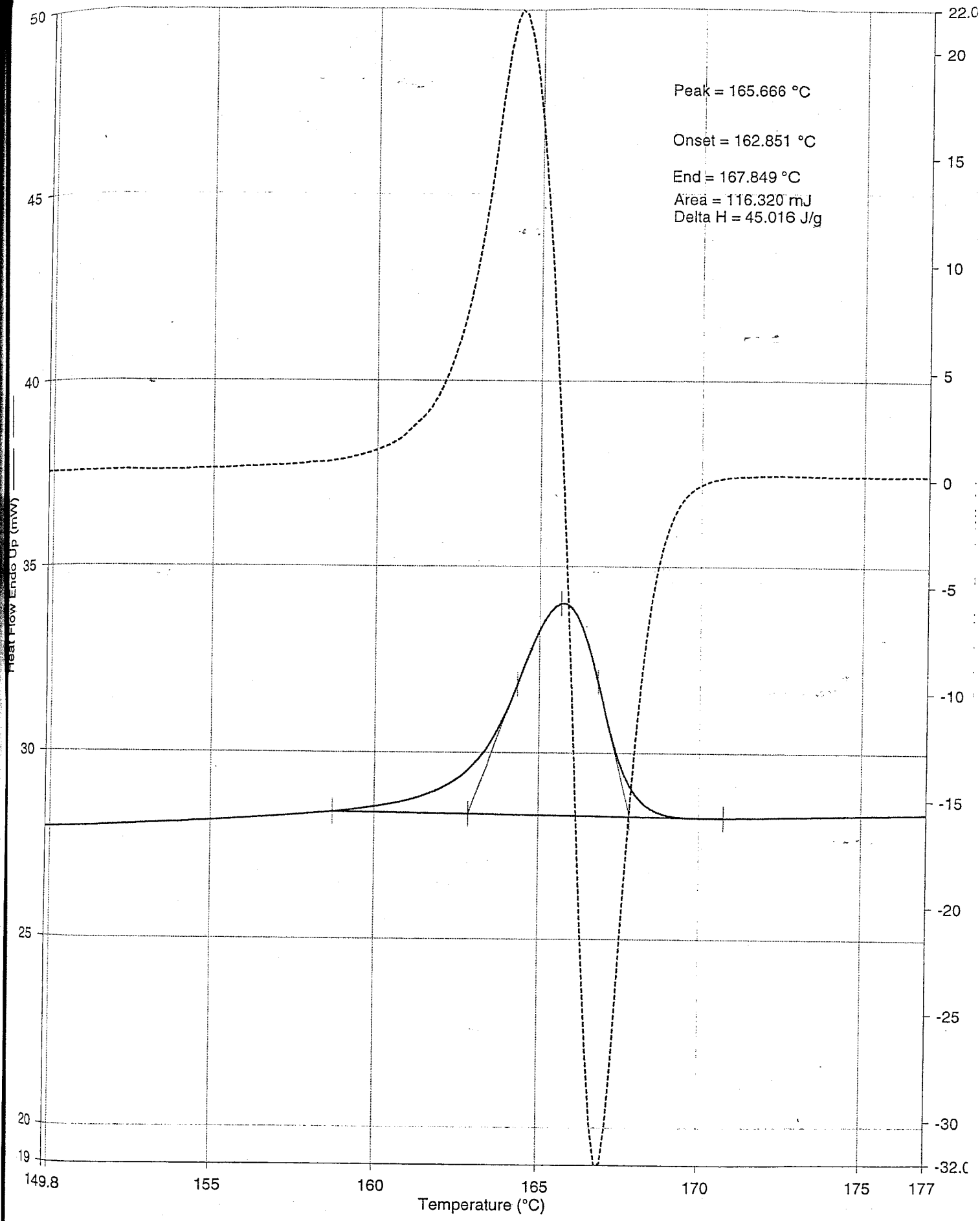
11/29/2002 1:57:30 PM

1) Heat from 25.00°C to 180.00°C at 10.00°C/min



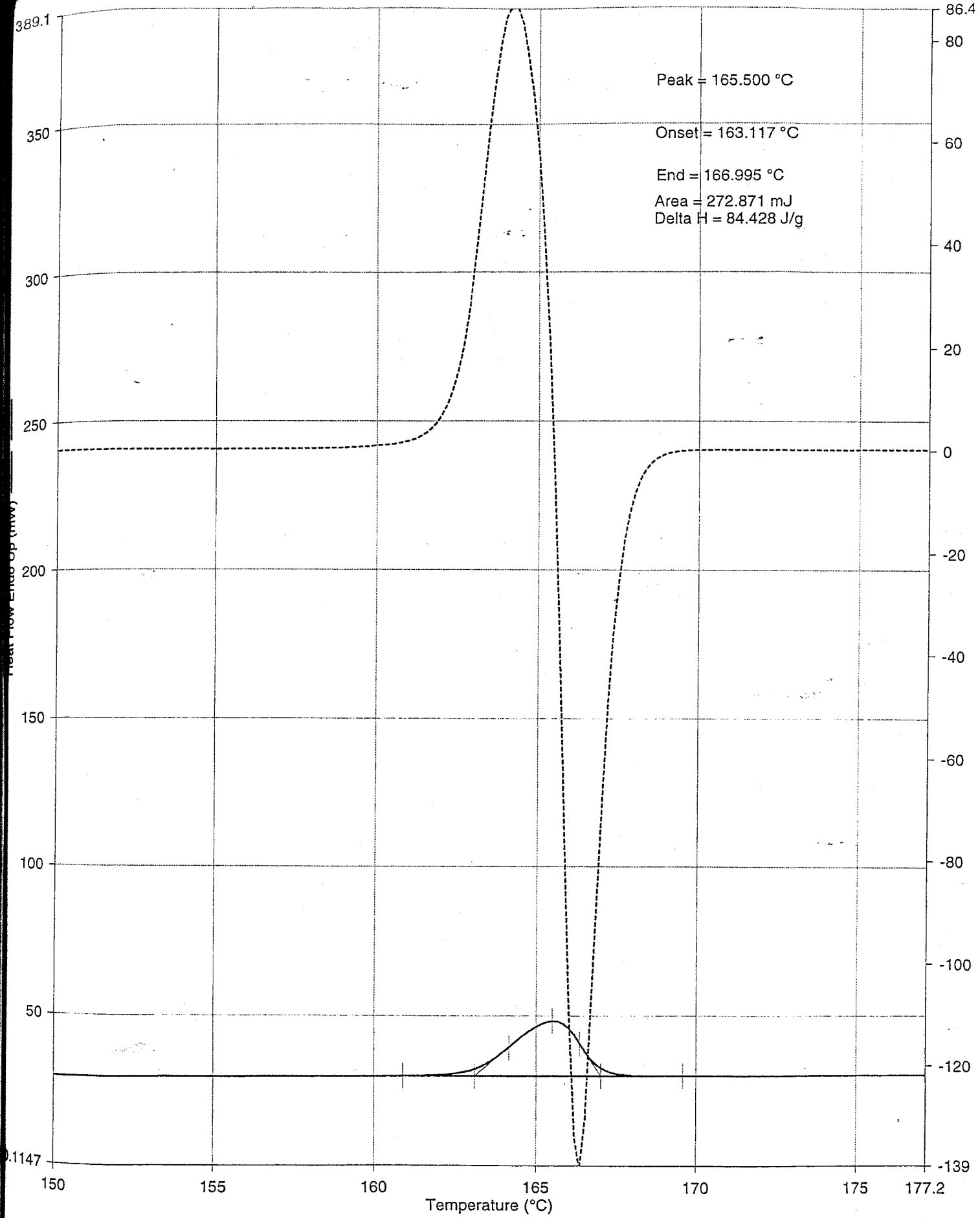
11/29/2002 1:50:18 PM

1) Heat from 25.00°C to 180.00°C at 10.00°C/min



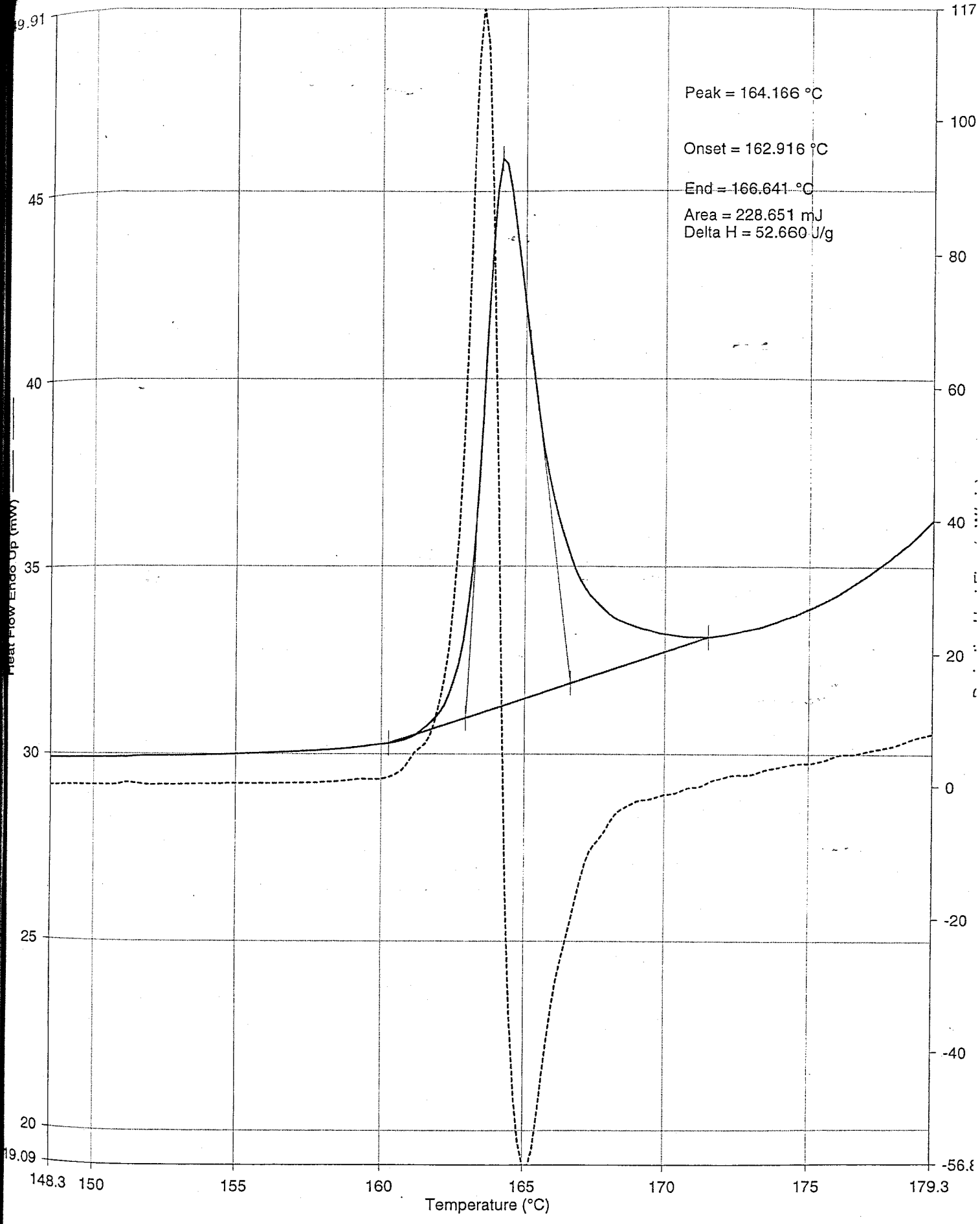
1) Heat from 25.00°C to 180.00°C at 10.00°C/min

11/29/2002 1:50:18 PM



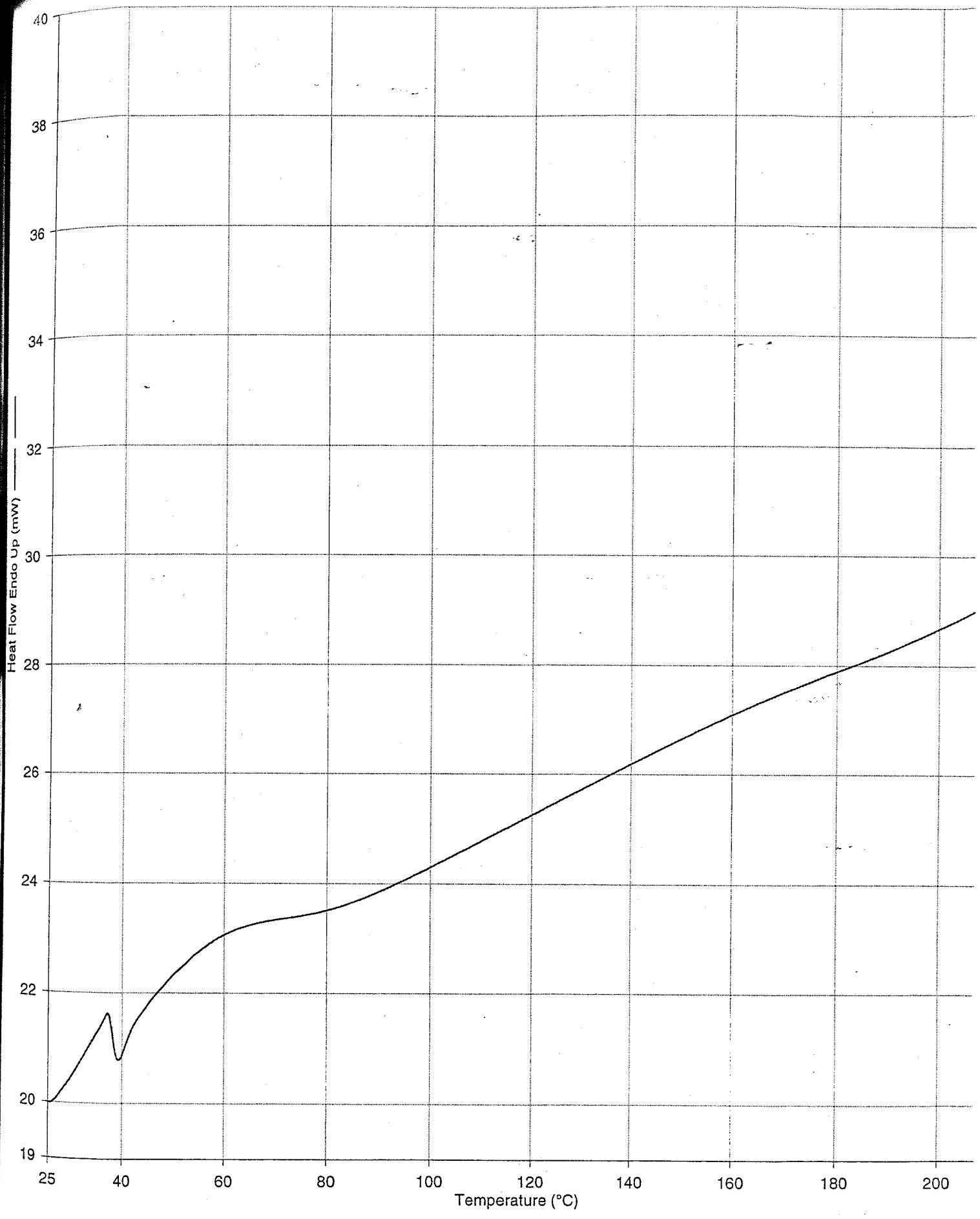
11/29/2002 1:58:35 PM

1) Heat from 25.00°C to 180.00°C at 10.00°C/min



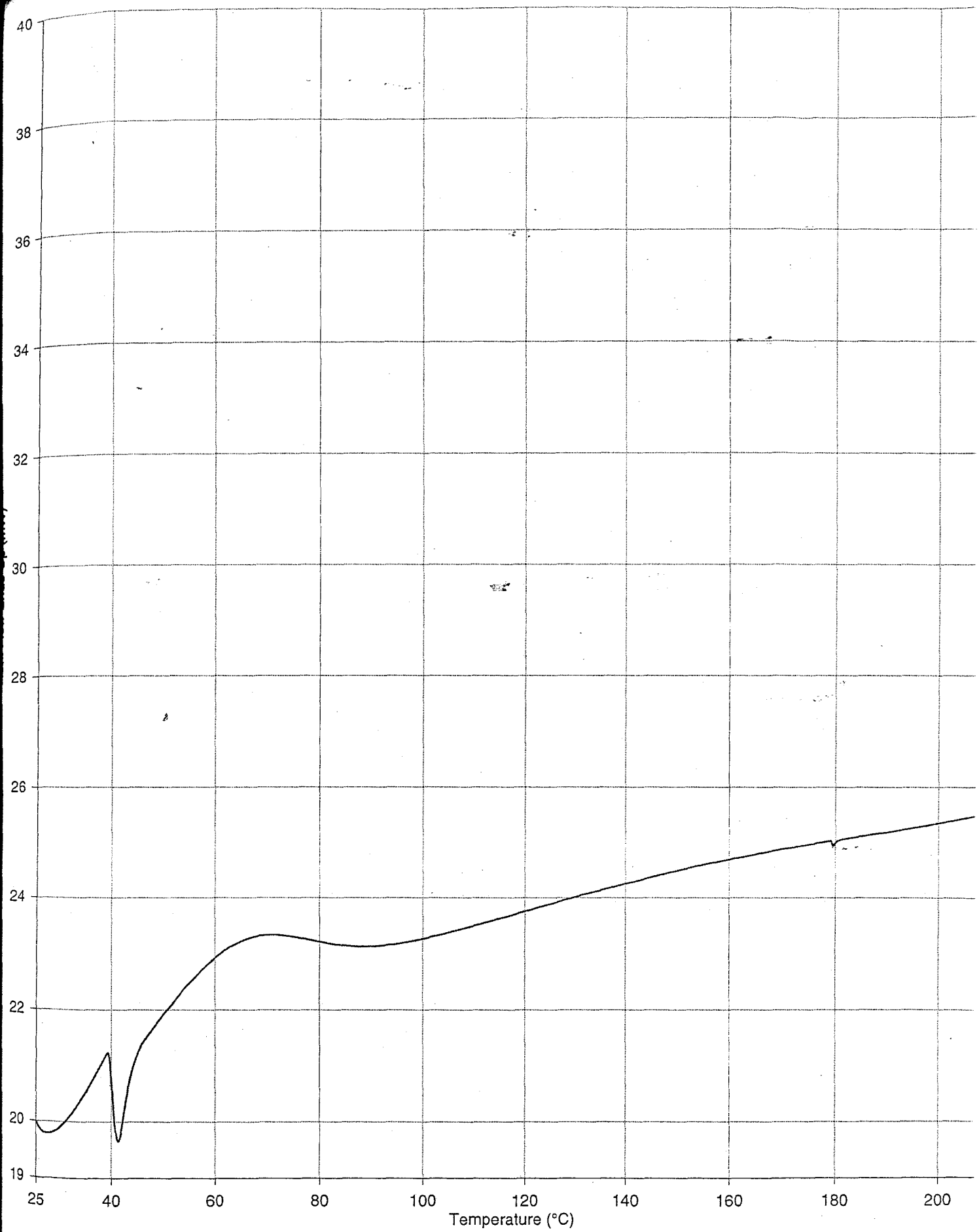
11/29/2002 2:00:50 PM

1) Heat from 25.00°C to 180.00°C at 10.00°C/min



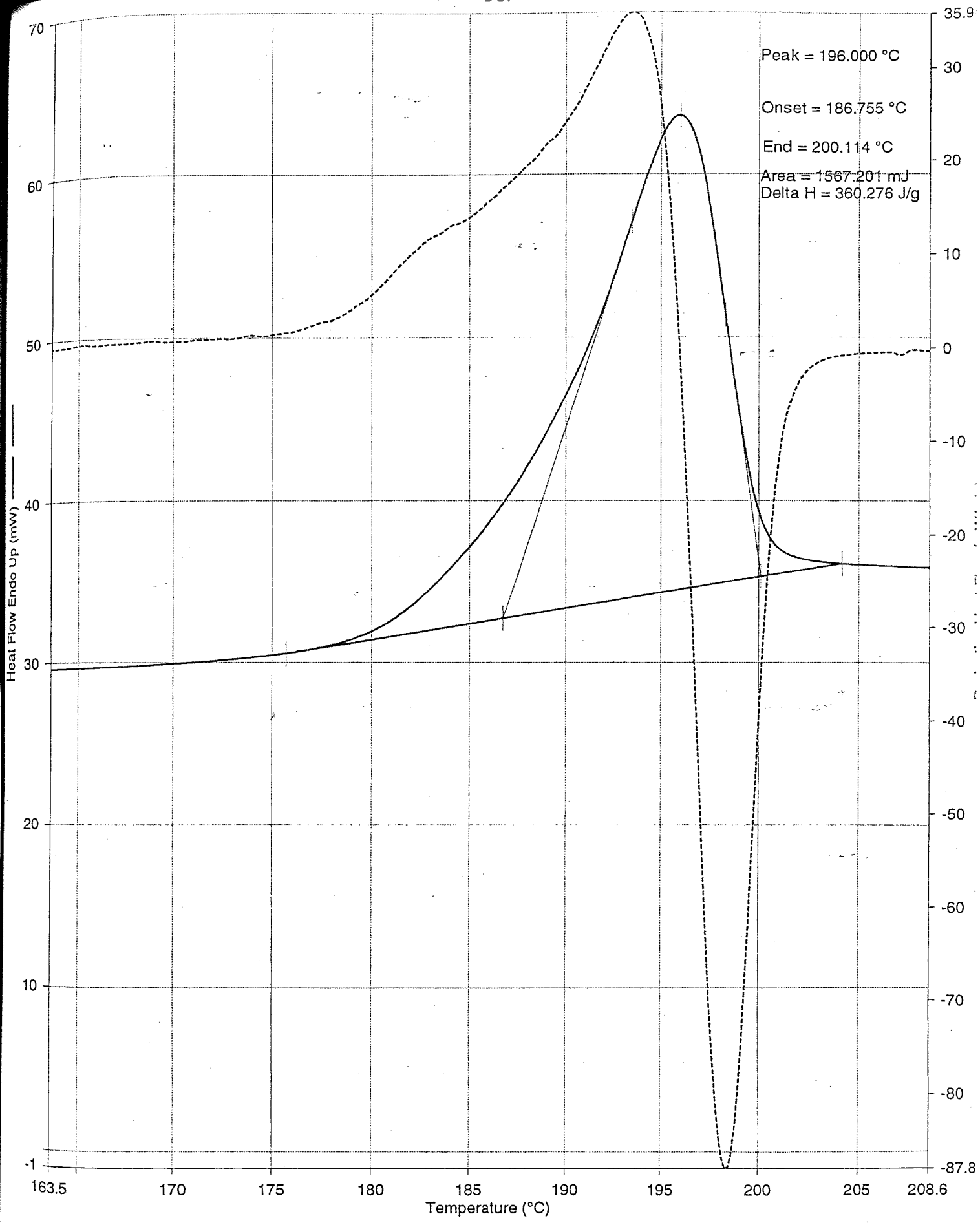
11/29/2002 12:50:41 PM

1) Heat from 25.00°C to 210.00°C at 10.00°C/min



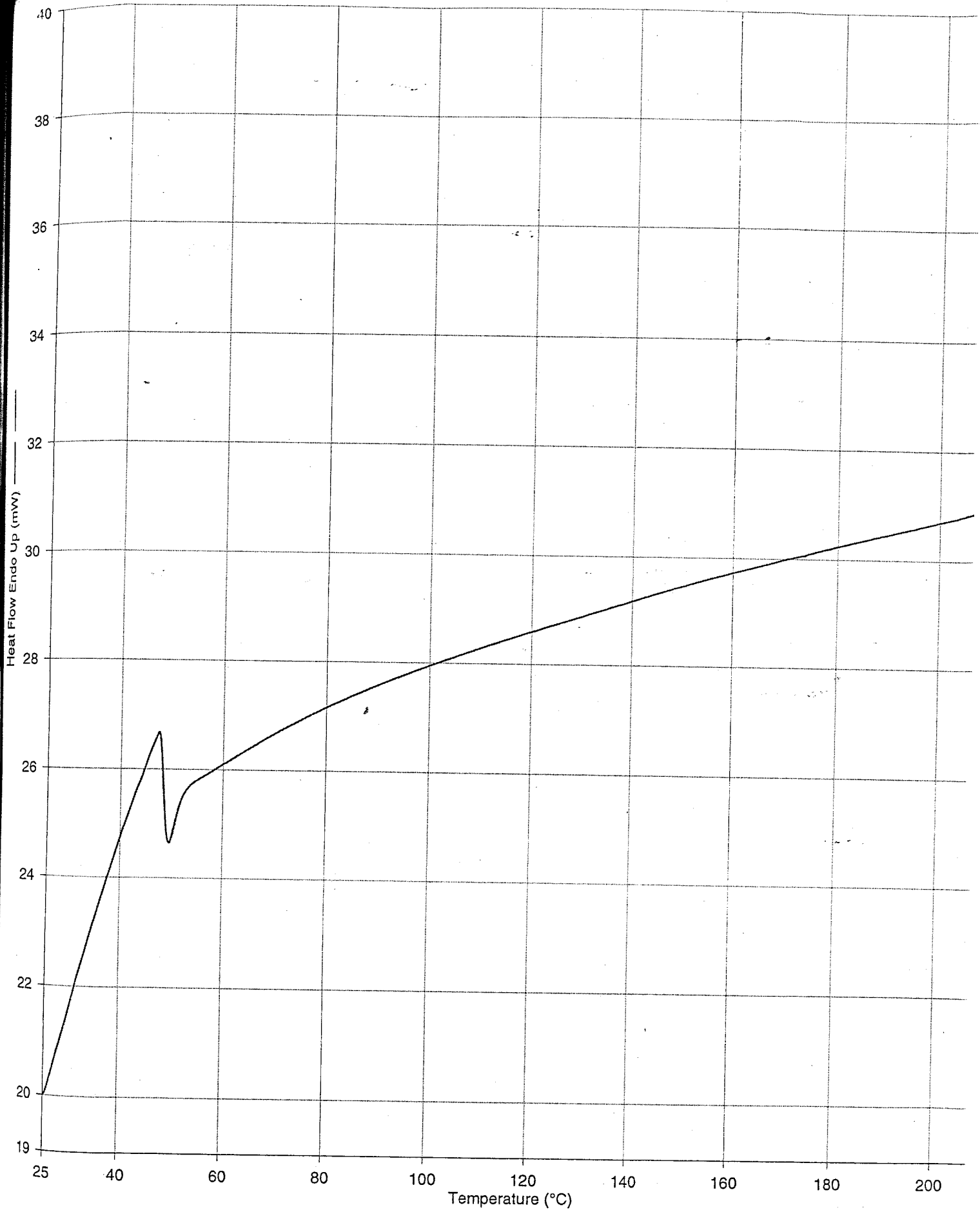
11/29/2002 12:51:17 PM

) Heat from 25.00°C to 210.00°C at 10.00°C/min



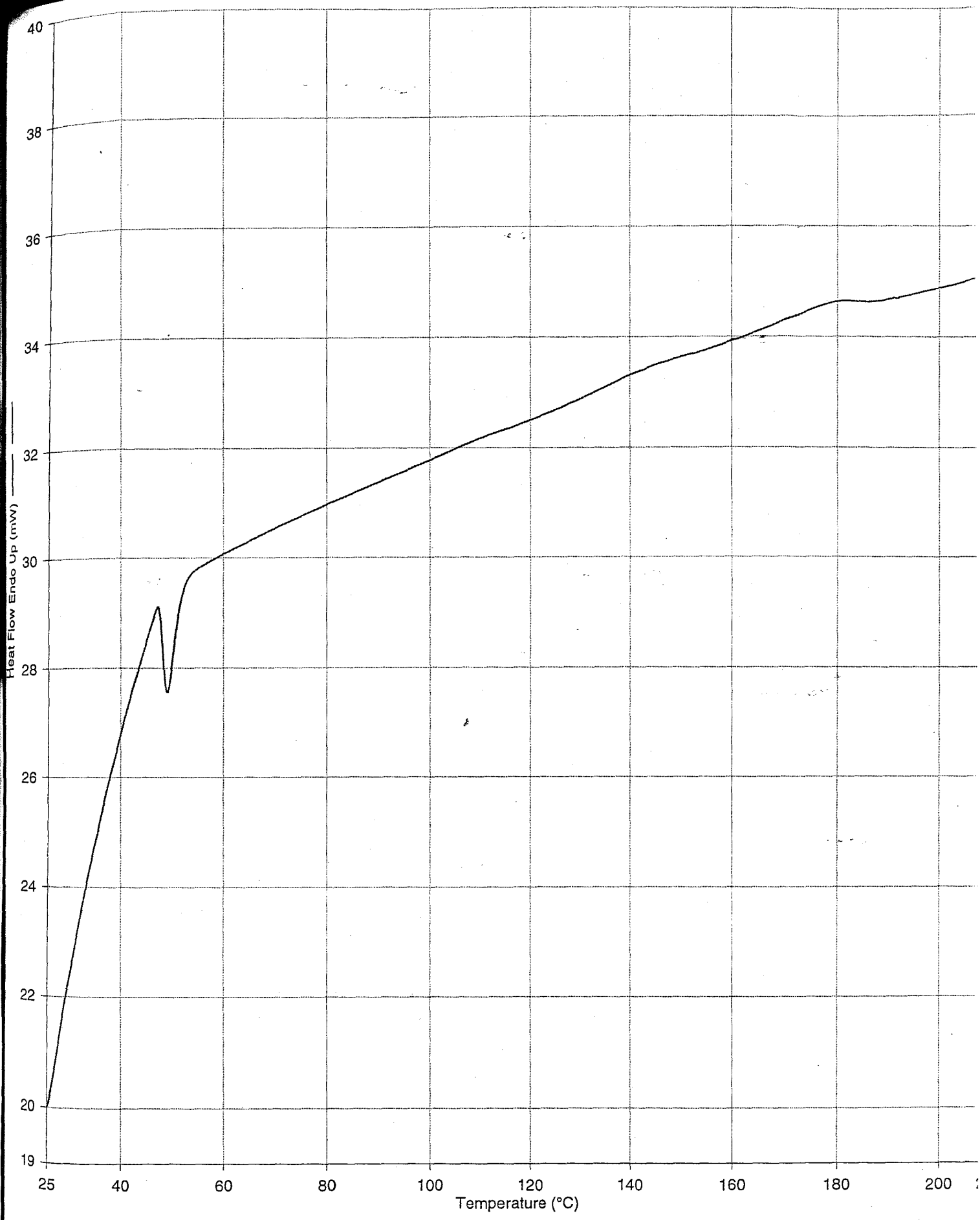
11/29/2002 12:47:11 PM

1) Heat from 25.00°C to 210.00°C at 10.00°C/min



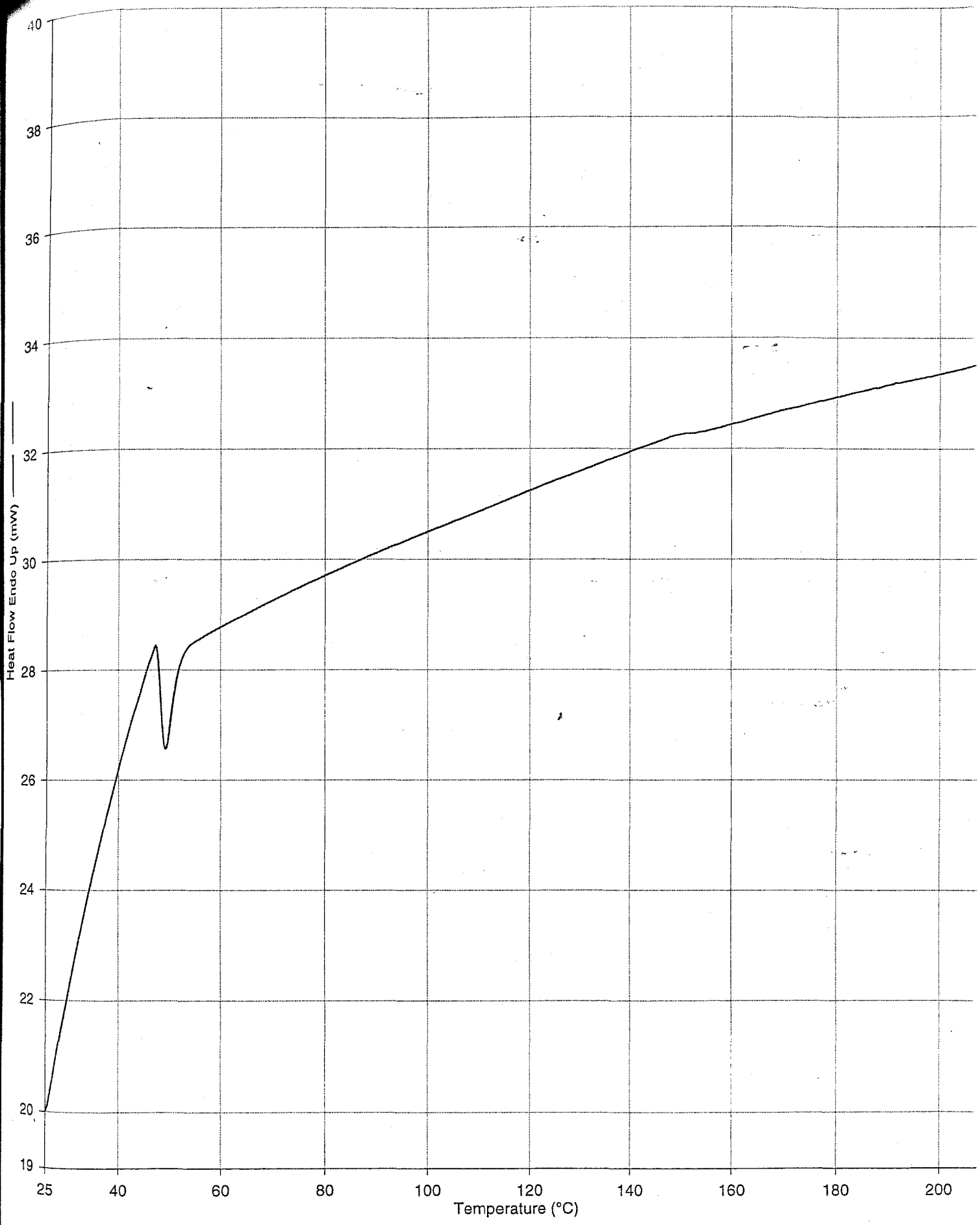
1) Heat from 25.00°C to 210.00°C at 10.00°C/min

11/29/2002 1:13:13 PM



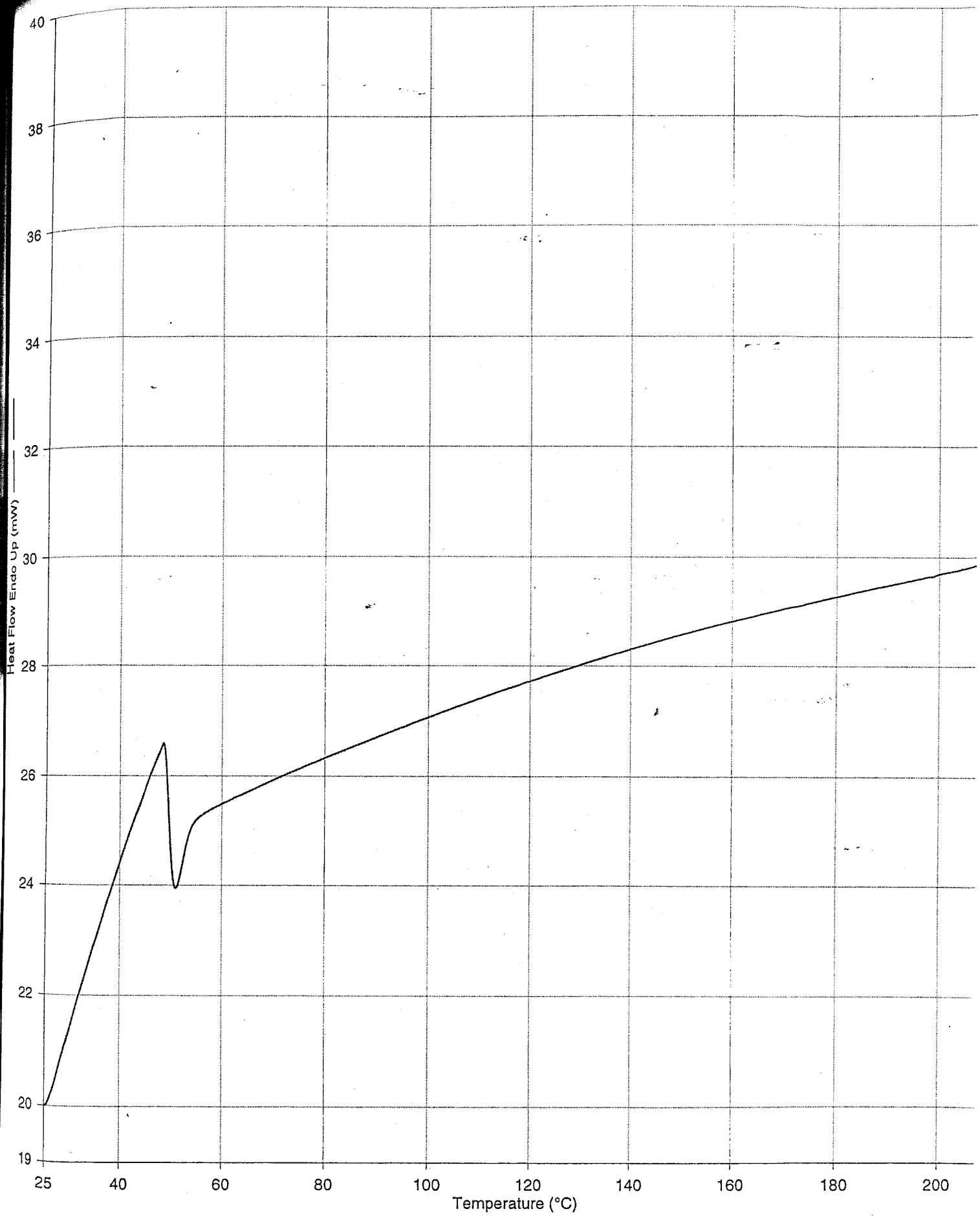
11/29/2002 12:48:40 PM

1) Heat from 25.00°C to 210.00°C at 10.00°C/min



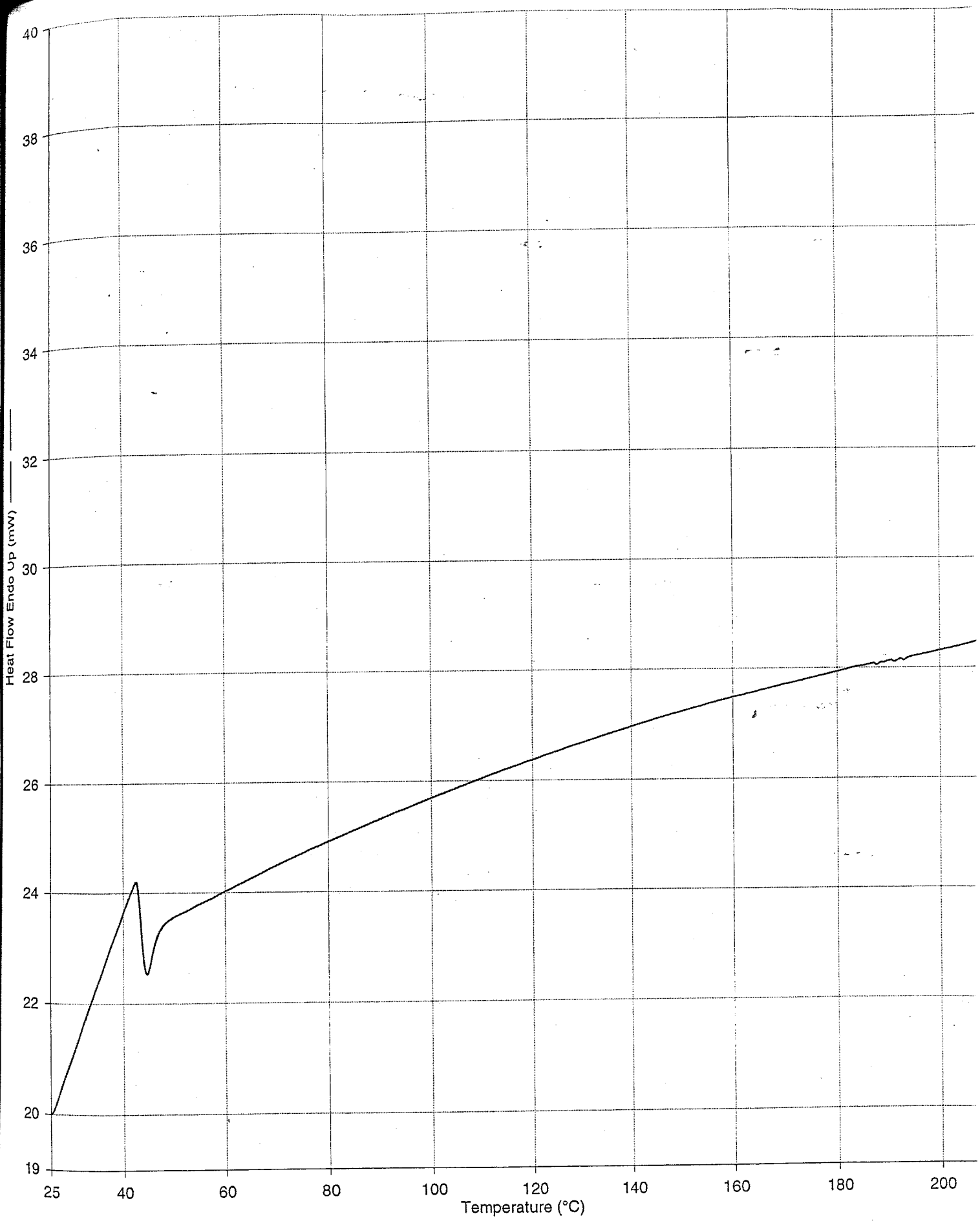
11/29/2002 1:14:38 PM

1) Heat from 25.00°C to 210.00°C at 10.00°C/min



11/29/2002 12:45:45 PM

1) Heat from 25.00°C to 210.00°C at 10.00°C/min



11/29/2002 2:01:21 PM

1) Heat from 25.00°C to 210.00°C at 10.00°C/min

APPENDIX TWO

BATCH PRODUCTION RECORDS

WET GRANULATION – ALL BETA BLOCKERS

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: A0219 Batch Size: 580 mg Granulation Date: 30/09/2002
Formulator: Leith Kieser Tabletting Date: 01/10/2002

Material	Formula	Quantity Added	Done By	Checked By
ACE	20	100 g	LK	
Methocel K4M	10	50 g	LK	
Emcompress	37.5	187.5g	LK	
Emcocel 90M	32.5	162.5g	LK	
Surelease	0.2g/g	100g	LK	
Methocel K100M	20	84g	LK	
Emcocel 90M	7	29.4g	LK	
Emcompress	10	42g	LK	
Mag Stearate	1	4.2g	LK	

Target weight: 720 mg Granule mass: 420 g Temperature: 16.6 °C
Target hardness: 120-160 N Relative Humidity: 43 %

Surelease® mass before granulation: 559.98 g
Surelease® mass after granulation: 452.11 g
Surelease® mass added: 107.87 g

Granulation time (start): 10 h 31
Granulation time (stop): 10 h 58
Granulation time: 27 mins

Drying Temperature: 60 °C
Drying Time: 12 hours

Tablet Press: Manesty B3B
Tooling: 11Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: No sticking during tabletting. Weights and Hardness values relatively constant between two punches.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: A0231 Batch Size: 635 mg Granulation Date: 30/09/2002
Formulator: Leith Kieser Tabletting Date: 01/10/2002

Material	Formula	Quantity Added	Done By	Checked By
ACE	20	100 g	LK	
Methocel K4M	10	50 g	LK	
Emcompress	37.5	187.5 g	LK	
Emcocel 90M	32.5	162.5 g	LK	
Surelease	0.14-0.18 g/g	70-90 g	LK	
Methocel K100M	20	92 g	LK	
Emcocel 90M	7	32.2 g	LK	
Emcompress	10	46 g	LK	
Mag Stearate	1	4.6 g	LK	

Target weight: 720 mg Granule mass: 460 g Temperature: 16.8 °C
Target hardness: 120-160 N Relative Humidity: 42 %

Surelease® mass before granulation: 570.46 g
Surelease® mass after granulation: 494.02 g
Surelease® mass added: 76.44 g

Granulation time (start): 10 h 05
Granulation time (stop): 10 h 35
Granulation time: 30 mins

Drying Temperature: 60 °C
Drying Time: 12 hours

Tablet Press: Manesty B3B
Tooling: Ø 11mm biconcave
Press Speed: 30-40 r.p.m.

Observations: Granule mass was too wet therefore dried for 1 hour before screening.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: A0247 Batch Size: 538 mg Granulation Date: 05/11/2002
Formulator: _____ Tabletting Date: 06/11/2002

Material	Formula	Quantity Added	Done By	Checked By
ACE	20	100 g	LK	
Methocel K4M	10	50 g	LK	
Emcompress	37.5	187.5 g	LK	
Emcocel 90M	32.5	162.5 g	LK	
Surelease	0.4 g/g	200 g	LK	
Methocel K100M	20	78 g	LK	
Emcocel 90M	7	27.3 g	LK	
Emcompress	10	39 g	LK	
Mag Stearate	1	3.9 g	LK	

Target weight: 720 mg Granule mass: 390 g Temperature: 16.9 °C
Target hardness: 120-160 N Relative Humidity: 41 %

Surelease® mass before granulation: 325.66 g
Surelease® mass after granulation: 127.19 g
Surelease® mass added: 198.19 g

Granulation time (start): 11 h 29
Granulation time (stop): 12 h 20
Granulation time: 51 mins

Drying Temperature: 60 °C
Drying Time: 12 hours

Tablet Press: Manesty B3B
Tooling: Ø 11mm Biconcave
Press Speed: 30-40 r.p.m.

Observations: Granulation required drying before screening. No sticking during tabletting. Relatively even hardnesses but varied weights between two punches. (730-780 mg)

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: L0223 Batch Size: 593 mg Granulation Date: 30/09/2002
Formulator: Leith Kieser Tabletting Date: 01/10/2002

Material	Formula	Quantity Added	Done By	Checked By
LAB	20	100g	LK	
Methocel K4M	10	50g	LK	
Emcompress	37.5	187.5g	LK	
Emcocel 90M	32.5	162.5g	LK	
Surelease	0.14–0.18g/g	70–90g	LK	
Methocel K100M	20	86g	LK	
Emcocel 90M	7	30.1g	LK	
Emcompress	10	43g	LK	
Mag Stearate	1	4.3g	LK	

Target weight: 720 mg Granule mass: 430 g Temperature: 15.6°C
Target hardness: 120–160 N Relative Humidity: 40 %

Surelease® mass before granulation: 492.74 g
Surelease® mass after granulation: 415.64 g
Surelease® mass added: 77.10 g

Granulation time (start): 14 h 13
Granulation time (stop): 14 h 38
Granulation time: 25 mins

Drying Temperature: 60 °C
Drying Time: 12 hours

Tablet Press: Manesty B3B
Tooling: 11mm Ø Biconcave
Press Speed: 30–40 r.p.m.

Observations: Granules required drying prior to screening.
No sticking during tabletting.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: L0249 Batch Size: 725 mg Granulation Date: 05/11/2002
Formulator: Leith Kieser Tabletting Date: 06/11/2002

Material	Formula	Quantity Added	Done By	Checked By
LAB	20	100g	LK	
Methocel K4M	10	50g	LK	
Emcompress	37.5	187.5g	LK	
Emcocel 90M	32.5	162.5g	LK	
Surelease	0.4 g/g	200g	LK	
Methocel K100M	20	105g	LK	
Emcocel 90M	7	36.8g	LK	
Emcompress	10	52.5g	LK	
Mag Stearate	1	5.3g	LK	

Target weight: 720 mg Granule mass: 525 g Temperature: 17.3°C
Target hardness: 120–160 N Relative Humidity: 39 %

Surelease® mass before granulation: 513.39 g
Surelease® mass after granulation: 306.21 g
Surelease® mass added: 207.18 g

Granulation time (start): 12 h 30
Granulation time (stop): 13 h 05
Granulation time: 35 mins

Drying Temperature: 60 °C
Drying Time: 12 hours

Tablet Press: Manesty B3B
Tooling: 11mm Ø Biconcave
Press Speed: 30–40 r.p.m.

Observations: No sticking during tableting.
Even hardness values but weight values varied between punch sets (approx. 690–730 mg).

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: L0251 Batch Size: 547 mg Granulation Date: 05/11/2002
Formulator: Leith Kieser Tabletting Date: 06/11/2002

Material	Formula	Quantity Added	Done By	Checked By
LAB	20	100g	LK	
Methocel K4M	10	50 g	LK	
Emcompress	37.5	187.5g	LK	
Emcocel 90M	32.5	162.5g	LK	
Surelease	0.2g/g	100g	LK	
Methocel K100M	20	79.2g	LK	
Emcocel 90M	7	27.7g	LK	
Emcompress	10	39.6g	LK	
Mag Stearate	1	4 g	LK	

Target weight: 720 mg Granule mass: 396 g Temperature: 17.3°C
Target hardness: 120-160 N Relative Humidity: 39 %

Surelease® mass before granulation: 450.55 g Granulation time (start): 15 h10
Surelease® mass after granulation: 342.42 g Granulation time (stop): 15 h27
Surelease® mass added: 108.13 g Granulation time: 17 mins

Drying Temperature: 60 °C Tablet Press: Manesty B3B
Drying Time: 12 hours Tooling: 11mm Ø Bi concave
Press Speed: 30-40 r.p.m.

Observations: No sticking during tableting.
Variation in tablet hardness (approx. 120-170 N)
and weight (approx. 710-750 mg) between punch sets.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0211 Batch Size: 690 mg Granulation Date: 02/10/2002
Formulator: Leith Kieser Tabletting Date: 04/10/2002

Material	Formula	Quantity Added	Done By	Checked By
MPT	20	100 g	LK	
Methocel K4M	10	50 g	LK	
Emcompress	37.5	187.5g	LK	
Emcocel 90M	32.5	162.5 g	LK	
Surelease	0.4 g/g	200 g	LK	
Methocel K100M	20	100 g	LK	
Emcocel 90M	7	35g	LK	
Emcompress	10	50 g	LK	
Mag Stearate	1	5g	LK	

Target weight: 720 mg Granule mass: 500 g Temperature: 18.1°C
Target hardness: 120-160 N Relative Humidity: 51 %

Surelease® mass before granulation: 657.68 g Granulation time (start): 09h08
Surelease® mass after granulation: 453.42 g Granulation time (stop): 09h40
Surelease® mass added: 204.26 g Granulation time: 32 mins

Drying Temperature: 60 °C Tablet Press: Manesty B3B
Drying Time: 12 hours Tooling: 11mm Ø Bi concave
Press Speed: 30-40 r.p.m.

Observations: Granules required drying prior to screening.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0213 Batch Size: 676 mg Granulation Date: 03/10/2002
Formulator: Leith Kieser Tabletting Date: 04/10/2002

Material	Formula	Quantity Added	Done By	Checked By
MPT	20	100 g	LK	
Methocel K4M	10	50 g	LK	
Emcompress	37.5	187.5 g	LK	
Emcocel 90M	32.5	162.5 g	LK	
Surelease	0.2 g/g	100 g	LK	
Methocel K100M	20	98 g	LK	
Emcocel 90M	7	34.3 g	LK	
Emcompress	10	49 g	LK	
Mag Stearate	1	4.9 g	LK	

Target weight: 720 mg Granule mass: 490 g Temperature: 16.9°C
Target hardness: 120-160 N Relative Humidity: 39%

Surelease® mass before granulation: 532.81 g
Surelease® mass after granulation: 425.26 g
Surelease® mass added: 107.55 g

Granulation time (start): 10 h10
Granulation time (stop): 10 h25
Granulation time: 15 mins

Drying Temperature: 60 °C
Drying Time: 12 hours

Tablet Press: Manesty B3B
Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Tablets weights were low (approx. 670 mg) therefore ran press on maximum weight. No sticking and hardness values relatively constant between punch sets.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0233 Batch Size: 662 mg Granulation Date: 03/10/2002
Formulator: Leith Kieser Tabletting Date: 04/10/2002

Material	Formula	Quantity Added	Done By	Checked By
MPT	20	100 g	LK	
Methocel K4M	10	50 g	LK	
Emcompress	37.5	187.5 g	LK	
Emcocel 90M	32.5	162.5 g	LK	
Surelease	0.14-0.18 g/g	70-90 g	LK	
Methocel K100M	20	96 g	LK	
Emcocel 90M	7	33.6 g	LK	
Emcompress	10	48 g	LK	
Mag Stearate	1	4.8 g	LK	

Target weight: 720 mg Granule mass: 480 g Temperature: 17 °C
Target hardness: 120-160 N Relative Humidity: 38 %

Surelease® mass before granulation: 564.58 g
Surelease® mass after granulation: 482.06 g
Surelease® mass added: 82.52 g

Granulation time (start): 11 h15
Granulation time (stop): 11 h35
Granulation time: 20 mins

Drying Temperature: 60 °C
Drying Time: 12 hours

Tablet Press: Manesty B3B
Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: No sticking during tabletting. Uniform hardness and weights between punches but weights low (approx. 670 mg) therefor ran press on max setting.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: 00221 Batch Size: 635 mg Granulation Date: 30/09/2002
Formulator: Leith Kieser Tabletting Date: 04/10/2002

Material	Formula	Quantity Added	Done By	Checked By
OXP	20	100 g	LK	
Methocel K4M	10	50 g	LK	
Encompress	37.5	187.5 g	LK	
Emcocel 90M	32.5	162.5 g	LK	
Surelease	0.14–0.18 g/g	70–90 g	LK	
Methocel K100M	20	92 g	LK	
Emcocel 90M	7	32.2 g	LK	
Encompress	10	46 g	LK	
Mag Stearate	1	4.6 g	LK	

Target weight: 720 mg Granule mass: 460 g Temperature: 16.4°C
Target hardness: 120–160 N Relative Humidity: 43 %

Surelease® mass before granulation: 575.72 g
Surelease® mass after granulation: 505.13 g
Surelease® mass added: 70.59 g

Granulation time (start): 14 h 48
Granulation time (stop): 15 h 09
Granulation time: 21 mins

Drying Temperature: 60 °C
Drying Time: 12 hours

Tablet Press: Manesty B3B
Tooling: 11mm Ø Biconcave
Press Speed: 30–40 r.p.m.

Observations: No sticking during tableting. Press under strain therefore could not get hardness values higher than approx. 110 N.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: 00253 Batch Size: 566 mg Granulation Date: 05/11/2002
Formulator: Leith Kieser Tabletting Date: 06/11/2002

Material	Formula	Quantity Added	Done By	Checked By
OXP	20	100 g	LK	
Methocel K4M	10	50 g	LK	
Encompress	37.5	187.5 g	LK	
Emcocel 90M	32.5	162.5 g	LK	
Surelease	0.2 g/g	100 g	LK	
Methocel K100M	20	82 g	LK	
Emcocel 90M	7	28.7 g	LK	
Encompress	10	41 g	LK	
Mag Stearate	1	4.1 g	LK	

Target weight: 720 mg Granule mass: 410 g Temperature: 17 °C
Target hardness: 120–160 N Relative Humidity: 41 %

Surelease® mass before granulation: 449.80 g
Surelease® mass after granulation: 347.78 g
Surelease® mass added: 102.02 g

Granulation time (start): 09 h 35
Granulation time (stop): 10 h 00
Granulation time: 25 mins

Drying Temperature: 60 °C
Drying Time: 12 hours

Tablet Press: Manesty B3B
Tooling: 11mm Ø Biconcave
Press Speed: 30–40 r.p.m.

Observations: No sticking seen during tableting. Constant hardness values between punch sets but weights varied between approximately 660 and 700 mg.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: 00255 Batch Size: 711 mg Granulation Date: 05/11/2002
Formulator: Leith Kieser Tabletting Date: 06/11/2002

Material	Formula	Quantity Added	Done By	Checked By
OXP	20	100g	LK	
MethocelK4M	10	50 g	LK	
Emcompress	37.5	187.5 g	LK	
Emcocel 90M	32.5	162.5 g	LK	
Surelease	0.4g/g	200 g	LK	
MethocelK100M	20	103 g	LK	
Emcocel 90M	7	36.1 g	LK	
Emcompress	10	51.5 g	LK	
Mag Stearate	1	5.2 g	LK	

Target weight: 720 mg Granule mass: 515 g Temperature: 17.3°C
Target hardness: 120-160 N Relative Humidity: 41 %

Surelease® mass before granulation: 508.20 g
Surelease® mass after granulation: 315.12 g
Surelease® mass added: 193.08 g

Granulation time (start): 15 h14
Granulation time (stop): 15 h38
Granulation time: 24 mins

Drying Temperature: 60 °C
Drying Time: 12 hours

Tablet Press: Manesty B3B
Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Granules required drying before rescreening. Hardness values low as press under strain. Weights low (approx. 690 mg) but press run on max setting. No sticking seen.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: P0133 Batch Size: 531 mg Granulation Date: 22/01/2002
Formulator: Leith Kieser Tabletting Date: 23/01/2002

Material	Formula	Quantity Added	Done By	Checked By
PROP	20	100 g	LK	
MethocelK4M	10	50 g	LK	
Emcompress	37.5	187.5 g	LK	
Emcocel 90M	32.5	162.5 g	LK	
Surelease	0.14-0.18g/g	70-90 g	LK	
MethocelK100M	20	77 g	LK	
Emcocel 90M	7	27 g	LK	
Emcompress	10	38.5 g	LK	
Mag Stearate	1	3.9 g	LK	

Target weight: 720 mg Granule mass: 385 g Temperature: 24.9°C
Target hardness: 120-160 N Relative Humidity: 80 %

Surelease® mass before granulation: 324.42 g
Surelease® mass after granulation: 249.14 g
Surelease® mass added: 75.28 g

Granulation time (start): 13 h45
Granulation time (stop): 14 h20
Granulation time: 35 mins

Drying Temperature: 60 °C
Drying Time: 12 hours

Tablet Press: Manesty B3B
Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: No sticking during tableting.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: P0215 Batch Size: 690 mg Granulation Date: 03/10/2002
Formulator: Leith Kieser Tabletting Date: 04/10/2002

Material	Formula	Quantity Added	Done By	Checked By
PROP	20	100 g	LK	
Methocel K4M	10	50 g	LK	
Emcompress	37.5	187.5 g	LK	
Emcocel 90M	32.5	162.5 g	LK	
Surelease	0.4 g/g	200 g	LK	
Methocel K100M	20	100 g	LK	
Emcocel 90M	7	35 g	LK	
Emcompress	10	50 g	LK	
Mag Stearate	1	5 g	LK	

Target weight: 720 mg Granule mass: 500 g Temperature: 17.2°C
Target hardness: 120-160 N Relative Humidity: 49 %

Surelease® mass before granulation: 655.21 g
Surelease® mass after granulation: 455.69 g
Surelease® mass added: 199.52 g

Granulation time (start): 16 h00
Granulation time (stop): 16 h45
Granulation time: 45 mins

Drying Temperature: 60 °C
Drying Time: 12 hours

Tablet Press: Manesty B3B
Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Ran press on max weight setting but weights only up to approx 700mg. No sticking seen. Hardness values relatively constant in target range.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: P0217 Batch Size: 662 mg Granulation Date: 03/10/2002
Formulator: Leith Kieser Tabletting Date: 04/10/2002

Material	Formula	Quantity Added	Done By	Checked By
PROP	20	100 g	LK	
Methocel K4M	10	50 g	LK	
Emcompress	37.5	187.5 g	LK	
Emcocel 90M	32.5	162.5 g	LK	
Surelease	0.2 g/g	100 g	LK	
Methocel K100M	20	96 g	LK	
Emcocel 90M	7	33.6 g	LK	
Emcompress	10	48 g	LK	
Mag Stearate	1	4.8 g	LK	

Target weight: 720 mg Granule mass: 480 g Temperature: 17.2°C
Target hardness: 120-160 N Relative Humidity: 50 %

Surelease® mass before granulation: 539.77 g
Surelease® mass after granulation: 437.52 g
Surelease® mass added: 102.25 g

Granulation time (start): 15 h05
Granulation time (stop): 15 h25
Granulation time: 20 mins

Drying Temperature: 60 °C
Drying Time: 12 hours

Tablet Press: Manesty B3B
Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Weights low (approx 640-650 mg) therefor ran press on max setting. Constant hardness values obtained and no sticking during tableting.
LK

BATCH PRODUCTION RECORDS

DIRECT COMPRESSION – ALL BETA BLOCKERS

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: A0225 Batch Size: 500 mg Blending Date: 28/08/2002
Formulator: Leith Kieser Tabletting Date: 28/08/2002

Material	Formula	Quantity Added	Done By	Checked By
ACE	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel FP10	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 17.8 °C
Target Hardness: 120-160 N Relative Humidity: 77 %

Blender: Cube blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11 mm Ø bi-concave
Press Speed: 30-40 r.p.m.

Observations: No sticking seen during tableting but weights and hardness values varied between punch sets. Blend flowed poorly from hopper. Tablet weights very low therefore ran press on max weight setting.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: A0235 Batch Size: 500 mg Blending Date: 18/10/2002
Formulator: Leith Kieser Tabletting Date: 18/10/2002

Material	Formula	Quantity Added	Done By	Checked By
ACE	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel FP 100	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mg Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 22.6°C
Target Hardness: 120-160 N Relative Humidity: 47 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: No sticking seen during tableting. Tablet weights low therefore ran press on max weight setting. Large variation seen between hardness and weight values for two punch sets.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: A0237 Batch Size: 500 mg Blending Date: 18/10/2002
Formulator: Leith Kieser Tabletting Date: 18/10/2002

Material	Formula	Quantity Added	Done By	Checked By
ACE	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel Std 10	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 22.7°C
Target Hardness: 120-160 N Relative Humidity: 45 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: No sticking seen during tableting. Uneven hardness and weight values between two punch sets (approx 610 mg @ 130 N & 710 mg @ 210 N.)

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: L0229 Batch Size: 500 mg Blending Date: 28/08/2002
Formulator: Leith Kieser Tabletting Date: 28/08/2002

Material	Formula	Quantity Added	Done By	Checked By
LAB	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel FP10	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 18.5°C
Target Hardness: 120-160 N Relative Humidity: 76 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Hardness varied throughout compression but values were consistent between two sets of punches.
No sticking observed.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: L0239 Batch Size: 500 mg Blending Date: 18/10/2002
Formulator: Leith Kieser Tabletting Date: 18/10/2002

Material	Formula	Quantity Added	Done By	Checked By
LAB	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel FP 100	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 22.8°C
Target Hardness: 120-160 N Relative Humidity: 42 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: No sticking during compaction.
Uneven weights and hardnesses between two punch sets (approx. 650 mg @ 130N and 740 mg @ greater than 220N.)

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: 20241 Batch Size: 500 mg Blending Date: 18/10/2002
Formulator: Leith Kieser Tabletting Date: 18/10/2002

Material	Formula	Quantity Added	Done By	Checked By
LAB	13.5	67.5 g	LK	
Methocel K4M	6-8	34 g	LK	
Encompress	32.3	161.5 g	LK	
Encocel 90M	26.9	134.5 g	LK	
Ethocel Std 10	2-8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 23.2°C
Target Hardness: 120-160 N Relative Humidity: 47%

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Large variation in hardness values throughout compression. Weights were uneven between the two punches (approx 650mg & 740mg). No sticking during compaction.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0119 Batch Size: 500 mg Blending Date: 29/10/2001
Formulator: Leith Kieser Tabletting Date: 29/10/2001

Material	Formula	Quantity Added	Done By	Checked By
MPT	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Encompress	32.3	161.5g	LK	
Encocel 90M	26.9	134.5g	LK	
Ethocel FP100	2-8	14 g	LK	
Methocel K100M	14	70 g	LK	
Cab-O-Sil M5	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 22.4°C
Target Hardness: 120-160 N Relative Humidity: 68 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Tablet weights were low therefore ran press on max setting but still could not reach target weight.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0135 Batch Size: 500 mg Blending Date: 27/02/2002
Formulator: Leith Kieser Tabletting Date: 27/02/2002

Material	Formula	Quantity Added	Done By	Checked By
MPT	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32-3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel FP100	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Cab-O-Sil M5	1.5	7.5 g	LK	
Talc	1.5	7.5 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 24.4°C
Target Hardness: 120-160 N Relative Humidity: 67 %

Blender: Cube Blender Tablet Press: Manesty 83B
Blend Time: 20 mins Tooling: 11mm @ Biconcave
Press Speed: 30-40 r.p.m.

Observations: Tablet weights inconsistent between two punch sets (approx. 580 mg and 650 mg). Press run on max setting for weight but tablets still underweight.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0137 Batch Size: 500 mg Blending Date: 21/03/2002
Formulator: Leith Kieser Tabletting Date: 21/03/2002

Material	Formula	Quantity Added	Done By	Checked By
MPT	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32-3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel FP100	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 24.1°C
Target Hardness: 120-160 N Relative Humidity: 65 %

Blender: Cube blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm @ Biconcave
Press Speed: 30-40 r.p.m.

Observations: No sticking seen during tableting. Hardness values relatively consistent between two punch sets.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0143 Batch Size: 500 mg Blending Date: 21/03/2002
Formulator: Leith Kieser Tabletting Date: 21/03/2002

Material	Formula	Quantity Added	Done By	Checked By
MPT	13.5	67.5g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5g	LK	
Ethocel FP100	2.8	14 g	LK	
Methocel K100M	14	70g	LK	
Cab-O-Sil M5	0.5	2.5g	LK	
Talc	2.5	12.5g	LK	
Mag Stearate	0.7	3.5g	LK	

Target Weight: 740 mg Temperature: 23 °C
Target Hardness: 120-160 N Relative Humidity: 62 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11 mm Ø Bicancave
Press Speed: 30-40 r.p.m.

Observations:

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0147 Batch Size: 500 mg Blending Date: 03/05/2002
Formulator: Leith Kieser Tabletting Date: 03/05/2002

Material	Formula	Quantity Added	Done By	Checked By
MPT	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5g	LK	
Emcocel 90M	26.9	134.5g	LK	
Ethocel FP10	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15g	LK	
Mag Stearate	0.7	3.5g	LK	

Target Weight: 740 mg Temperature: 19.8 °C
Target Hardness: 120-160 N Relative Humidity: 64 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11 mm Ø Bicancave
Press Speed: 30-40 r.p.m.

Observations: Sticking was observed to both upper and lower punch faces. Same weight variation between punch sets observed.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0149 Batch Size: 500 mg Blending Date: 03/05/2002
Formulator: Leith Kieser Tabletting Date: 03/05/2002

Material	Formula	Quantity Added	Done By	Checked By
MPT	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel FP7	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 19.1°C
Target Hardness: 120-160 N Relative Humidity: 63 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Sticking to both upper and lower punch faces of both sets of punches. Hardness values relatively constant between punch sets.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0151 Batch Size: 500 mg Blending Date: 03/05/2002
Formulator: Leith Kieser Tabletting Date: 03/05/2002

Material	Formula	Quantity Added	Done By	Checked By
MPT	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel FP100	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 20 °C
Target Hardness: 120-160 N Relative Humidity: 64 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Sticking observed but only to one punch face of one set of punches. Hardness values relatively constant throughout run.

Powder left on press after tableting was kept, sieved, and tested for moisture content.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0153 Batch Size: 500 mg Blending Date: 03/05/2002
Formulator: Leith Kieser Tabletting Date: 03/05/2002

Material	Formula	Quantity Added	Done By	Checked By
MPT	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Encacel 90M	26.9	134.5 g	LK	
Ethocel Std 45	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 20 °C
Target Hardness: 120-160 N Relative Humidity: 61 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Sticking seen (surface blemishes on tablets from both upper and lower punch faces) from approx one third of the way through the run. Hardness values and weights relatively constant and able to get weights up to approx 740 mg. Powder from press was sieved and tested for moisture content.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0155 Batch Size: 500 mg Blending Date: 03/05/2002
Formulator: Leith Kieser Tabletting Date: 03/05/2002

Material	Formula	Quantity Added	Done By	Checked By
MPT	13.5	67.5g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Encacel 90M	26.9	134.5 g	LK	
Ethocel Std 10	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15g	LK	
Mag Stearate	0.7	3.5g	LK	

Target Weight: 740 mg Temperature: 20.3°C
Target Hardness: 120-160 N Relative Humidity: 61 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Sticking seen only towards the end of the batch on the lower punch faces only. Hardness values and tablet weights relatively constant between the two punch sets, however tablet weights below 700mg therefor press run on maximum weight setting. Powder from press sieved and kept for Karl Fischer analysis.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0157 Batch Size: 500 mg Blending Date: 03/05/2002
Formulator: Leith Kieser Tabletting Date: 03/05/2002

Material	Formula	Quantity Added	Done By	Checked By
MPT	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel Std 20	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 20 °C
Target Hardness: 120-160 N Relative Humidity: 61 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Hardness values varied between two punch sets (approx. 100 N & 180 N). Weight variation not as pronounced.
Slight blemishes seen on tablets compressed in latter third of run.
Powder from press following compaction collected, sieved and analysed for moisture content.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0159 Batch Size: 500 mg Blending Date: 03/05/2002
Formulator: Leith Kieser Tabletting Date: 03/05/2002

Material	Formula	Quantity Added	Done By	Checked By
MPT	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel FP 100	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 20 °C
Target Hardness: 120-160 N Relative Humidity: 62 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Weights and hardnesses relatively constant between two punch sets. Slight sticking seen towards end of run.
Powder left on the press after compaction was removed, sieved (size 20) and analysed for moisture content by Karl Fischer analysis.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0205 Batch Size: 500 mg Blending Date: 07/08/2002
Formulator: Leith Kieser Tabletting Date: 07/08/2002

Material	Formula	Quantity Added	Done By	Checked By
MPT	13.5	67.5 g	LK	
Methocel K4M	5.8	29 g	LK	
Emcompress	25	125 g	LK	
Emcocel 90M	20	100 g	LK	
Ethocel Std 20	20	100 g	LK	
Methocel K100M	12	60 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 13.3 °C
Target Hardness: 120-160 N Relative Humidity: 41 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: No sticking observed during tableting.
Hardness and weight values very consistent between two punch sets.
Good flow from hopper.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0207 Batch Size: 500 mg Blending Date: 07/08/2002
Formulator: Leith Kieser Tabletting Date: 07/08/2002

Material	Formula	Quantity Added	Done By	Checked By
MPT	13.5	67.5 g	LK	
Methocel K4M	5.8	29 g	LK	
Emcompress	25	125 g	LK	
Emcocel 90M	20	100 g	LK	
Ethocel FP10	20	100 g	LK	
Methocel K100M	12	60 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 13.3 °C
Target Hardness: 120-160 N Relative Humidity: 41 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Small blemishes seen on one surface of tablets produced in latter part of run.
Poor flow from hopper.
Weights and hardnesses relatively even for two punch sets.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0259 Batch Size: 264 mg Blending Date: 06/11/2002
Formulator: Leith Kieser Tabletting Date: 06/11/2002

Material	Formula	Quantity Added	Done By	Checked By
Freeze-dried material	16.3	43 g	LK	
Methocel K4M	6.8	18 g	LK	
Emcompress	32.3	85 g	LK	
Emcocel 90M	26.9	71 g	LK	
Methocel K100M	14	37 g	LK	
Talc	3	8 g	LK	
Mag Stearate	0.7	2 g	LK	

Target Weight: 740 mg Temperature: 18.5°C
Target Hardness: 120-160 N Relative Humidity: 45 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Freeze-dried Material : MPT 85g dissolved in 70.5g Surelease ∴ 43g Freeze dried material = 35.6g MPT + 7.4g ethylcellulose ie. 13.5% drug + 2.8% ethylcellulose.

No sticking during tableting. Even hardness and weight values between two punch sets.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: M0261 Batch Size: 116 mg Blending Date: 05/11/2002
Formulator: Leith Kieser Tabletting Date: 05/11/2002

Material	Formula	Quantity Added	Done By	Checked By
Freeze-dried Material	27.5	32 g	LK	
Methocel K4M	6	7 g	LK	
Emcompress	26	30.2 g	LK	
Emcocel 90M	22.8	26.5 g	LK	
Methocel K100M	14	16.2 g	LK	
Talc	3	3.5 g	LK	
Mag Stearate	0.7	0.8 g	LK	

Target Weight: 740 mg Temperature: 20.4°C
Target Hardness: 120-160 N Relative Humidity: 35 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Freeze-dried material : MPT 30g dissolved in 120g Surelease ∴ 32g Freeze-dried material = 16g MPT and 16g ethylcellulose ie. 13.15% drug + 13.15% ethylcellulose.

Sever capping seen throughout run. No sticking to punch faces observed.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: 00227 Batch Size: 500 mg Blending Date: 28/08/2002
Formulator: Leith Kieser Tabletting Date: 28/08/2002

Material	Formula	Quantity Added	Done By	Checked By
OXP	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel FP 10	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 18.1 °C
Target Hardness: 120-160 N Relative Humidity: 77 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Bicon cave
Press Speed: 30-40 r.p.m.

Observations: Tablet weights and hardness values from each punch set relatively constant. Small blemish seen on upper and lower surface of tablets compressed by one set of punches.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: 00243 Batch Size: 500 mg Blending Date: 18/10/2002
Formulator: Leith Kieser Tabletting Date: 18/10/2002

Material	Formula	Quantity Added	Done By	Checked By
OXP	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel FP100	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 23.2 °C
Target Hardness: 120-160 N Relative Humidity: 54 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm diam. Bi concave
Press Speed: 30-40 r.p.m.

Observations: Press under strain therefore reduced compression force slightly. No sticking seen. Hardness and weight values relatively consistent between two punch sets.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: 00245 Batch Size: 500 mg Blending Date: 18/10/2002
Formulator: Leith Kieser Tabletting Date: 18/10/2002

Material	Formula	Quantity Added	Done By	Checked By
OXP	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel Std 10	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 23.4°C
Target Hardness: 120-160 N Relative Humidity: 51 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Hardness values relatively constant. Tablet weights varied between punch sets (approx. 610 and 700 mg). No sticking observed during compression.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: P0125 Batch Size: 500 mg Blending Date: 08/11/2001
Formulator: Leith Kieser Tabletting Date: 08/11/2001

Material	Formula	Quantity Added	Done By	Checked By
PROP	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel FP100	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
CabOSil M5	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 18.9°C
Target Hardness: 120-160 N Relative Humidity: 62 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Could not get tablet weights up to target weight even with press run on max weight setting. (max die fill volume).

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: P0139 Batch Size: 500 mg Blending Date: 21/03/2002
Formulator: Leith Kieser Tabletting Date: 21/03/2002

Material	Formula	Quantity Added	Done By	Checked By
PROP	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel FP100	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
CabOSil M5	1.5	7.5 g	LK	
Talc	1.5	7.5 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 23.1 °C
Target Hardness: 120-160 N Relative Humidity: 61 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: No sticking during compression. Uniform hardness values between two punch sets.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: P0141 Batch Size: 500 mg Blending Date: 21/03/2002
Formulator: Leith Kieser Tabletting Date: 21/03/2002

Material	Formula	Quantity Added	Done By	Checked By
PROP	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel FP100	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
CabOSiM5	0.5	2.5 g	LK	
Talc	2.5	12.5 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 23.6°C
Target Hardness: 120-160 N Relative Humidity: 58 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11 mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: No sticking and relatively uniform hardness values seen throughout run.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: P0161 Batch Size: 500 mg Blending Date: 17/05/2002
Formulator: Leith Kieser Tabletting Date: 17/05/2002

Material	Formula	Quantity Added	Done By	Checked By
PROP	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel FP 7	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mg Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 14.7°C
Target Hardness: 120-160 N Relative Humidity: 52 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm @ bicurve
Press Speed: 30-40 r.p.m.

Observations: No sticking seen during tableting process. Small variation between punch sets for hardness values.

Powder collected after compaction, for Karl Fischer analysis.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: P0163 Batch Size: 500 mg Blending Date: 17/05/2002
Formulator: Leith Kieser Tabletting Date: 17/05/2002

Material	Formula	Quantity Added	Done By	Checked By
PROP	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel FP 10	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mg Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 14.5°C
Target Hardness: 120-160 N Relative Humidity: 52 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm @ bicurve
Press Speed: 30-40 r.p.m.

Observations: No sticking seen. Achieved target weight with uniformity between two punch sets for weight and hardness values.

Kept powder off press and sieved (size 20) for moisture content analysis.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: P0165 Batch Size: 500 mg Blending Date: 17/05/2002
Formulator: Leith Kieser Tabletting Date: 17/05/2002

Material	Formula	Quantity Added	Done By	Checked By
PROP	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel FP100	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 14.5°C
Target Hardness: 120-160 N Relative Humidity: 52 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Variation in weights and hardness seen (approx 700 - 740 mg and 100 - 180 N).
No sticking observed during compaction.
Powder kept for Karl Fischer Analysis

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: P0167 Batch Size: 500 mg Blending Date: 17/05/2002
Formulator: Leith Kieser Tabletting Date: 17/05/2002

Material	Formula	Quantity Added	Done By	Checked By
PROP	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emcocel 90M	26.9	134.5 g	LK	
Ethocel Std 45	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 15.1°C
Target Hardness: 120-160 N Relative Humidity: 52 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: No sticking observed.
Tablet hardness values varied throughout compression.
Tablet weights varied between two punch sets (approx. 690 and 730 mg).
Powder kept and analysed for moisture content.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: P0169 Batch Size: 500 mg Blending Date: 17/05/2002
Formulator: Leith Kieser Tabletting Date: 17/05/2002

Material	Formula	Quantity Added	Done By	Checked By
PROP	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emocel 90M	26.9	134.5 g	LK	
Ethocel Std 10	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 15.5°C
Target Hardness: 120-160 N Relative Humidity: 52 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30 -40 r.p.m.

Observations: No sticking seen throughout run.
Hardness values showing good consistency at approx 130N and good tablet weights of approx 730mg achieved.

Powders kept and served for moisture content analysis.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: P0171 Batch Size: 500 mg Blending Date: 17/05/2002
Formulator: Leith Kieser Tabletting Date: 17/05/2002

Material	Formula	Quantity Added	Done By	Checked By
PROP	13.5	67.5 g	LK	
Methocel K4M	6.8	34 g	LK	
Emcompress	32.3	161.5 g	LK	
Emocel 90M	26.9	134.5 g	LK	
Ethocel Std 20	2.8	14 g	LK	
Methocel K100M	14	70 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 15.5°C
Target Hardness: 120-160 N Relative Humidity: 52 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: No sticking seen.
Hardness and weight values consistently close to target values.

Powders left on press kept for Karl Fischer analysis of moisture content.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: P0201 Batch Size: 500 mg Blending Date: 07/08/2002
Formulator: Leith Kieser Tabletting Date: 07/08/2002

Material	Formula	Quantity Added	Done By	Checked By
PROP	13.5	67.5 g	LK	
Methocel K4M	5.8	29 g	LK	
Emcompress	25	125 g	LK	
Emcocel 90M	20	100 g	LK	
Ethocel FP10	20	100 g	LK	
Methocel K100M	12	60 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 12-5°C
Target Hardness: 120-160 N Relative Humidity: 40 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm diam Biconcave
Press Speed: 30-40 r.p.m.

Observations: Poor flow from Hopper.
No sticking seen. No blemishes on tablet surfaces but a small amount of powder residue remained on both lower punch faces.
Weights and hardness values varied between two punch sets. Hardness values approx 100N & 200N.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: P0203 Batch Size: 500 mg Blending Date: 07/08/2002
Formulator: Leith Kieser Tabletting Date: 07/08/2002

Material	Formula	Quantity Added	Done By	Checked By
PROP	13.5	67.5 g	LK	
Methocel K4M	5.8	29 g	LK	
Emcompress	25	125 g	LK	
Emcocel 90M	20	100 g	LK	
Ethocel Std 20	20	100 g	LK	
Methocel K100M	12	60 g	LK	
Talc	3	15 g	LK	
Mag Stearate	0.7	3.5 g	LK	

Target Weight: 740 mg Temperature: 12.5°C
Target Hardness: 120-160 N Relative Humidity: 41 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: Better flow from hopper than P0201.
Relatively even tablets and hardness values and weights showed little variation between punch sets. Approx. 710 & 730 mg and 110N and 150N.
No sticking observed.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: P0257 Batch Size: 182 mg Blending Date: 05/11/2002
Formulator: Leith Kieser Tabletting Date: 05/11/2002

Material	Formula	Quantity Added	Done By	Checked By
Freeze-dried material	27.5	50 g	LK	
Methocel K4M	6	11 g	LK	
Emcompress	26	47.3 g	LK	
Emcocel 90M	22.8	41.5 g	LK	
Methocel K100M	14	25.5 g	LK	
Talc	3	5.5 g	LK	
Mag Stearate	0.7	1.3 g	LK	

Target Weight: 740 mg Temperature: 20.1°C
Target Hardness: 120-160 N Relative Humidity: 35 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: No sticking occurred during compaction. Press under strain therefore maximum hardness values achieved were approximately 90N and many tablets capped during compression. Tablet weights very low (approx 500mg) with press run on max setting.

RHODES UNIVERSITY, FACULTY OF PHARMACY, GRAHAMSTOWN, 6140
BATCH PRODUCTION RECORD

Batch Number: P0263 Batch Size: 362 mg Blending Date: 06/11/2002
Formulator: Leith Kieser Tabletting Date: 06/11/2002

Material	Formula	Quantity Added	Done By	Checked By
Freeze-dried material	16.3	59 g	LK	
Methocel K4M	6.8	24.6 g	LK	
Emcompress	32.3	117g	LK	
Emcocel 90M	26.9	97.4g	LK	
Methocel K100M	14	50.7g	LK	
Talc	3	11 g	LK	
Mag Stearate	0.7	2.5g	LK	

Target Weight: 740 mg Temperature: 18.2°C
Target Hardness: 120-160N Relative Humidity: 42 %

Blender: Cube Blender Tablet Press: Manesty B3B
Blend Time: 20 mins Tooling: 11mm Ø Biconcave
Press Speed: 30-40 r.p.m.

Observations: No sticking seen, and no capping but press under strain therefore terminated run approximately half way through.

APPENDIX THREE

OFFICIAL BATCH RECORDS – ALL BETA BLOCKERS

Batch Identification: Wet Granulation (5% EC) **Batch Number: A0219**
Date of Manufacture: 30 September & 01 October 2002
Batch size: 580 g **Temperature:** 16.6°C
Relative Humidity: 43%

Formula:

Acebutolol hydrochloride	20	100 g	Final Granule mass: 420 g
Methocel® K4M	10	50 g	
Emcompress®	37.5	187.5 g	
Emcocel® 90M	32.5	162.5 g	
Surelease®	0.2 g/g	100 g	
Methocel® K100M	20	84 g	
Emcocel® 90M	7	29.4 g	
Emcompress®	10	42 g	
Magnesium stearate	1	4.2 g	

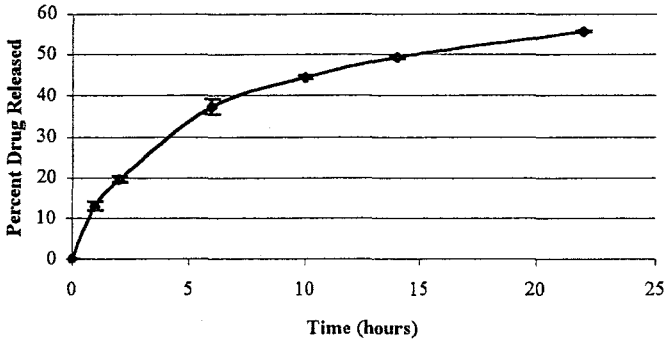
Target Weight: 720 mg
Target Hardness: 120 –160 N

Physical Assessment:

	Mean	%RSD
Weight	783.3	1.69
Thickness	7.93	0.66
Diameter	11.26	0.04
Hardness	138.5	4.18

Friability (10 tablets)	
Mass before test:	7.8329 g
Mass after test:	7.8295 g
Mass lost:	0.0034 g
Percentage lost:	0.0434%

Dissolution Rate Profile:



Residual Content: 2.76 ± 1.59 %

Batch Identification: 3% Talc, Ethocel® FP 10 **Batch Number: A0225**
Date of Manufacture: 28 August 2002
Batch size: 500 g **Temperature:** 17.8°C
Relative Humidity: 77%

Formula:

Acebutolol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 10	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

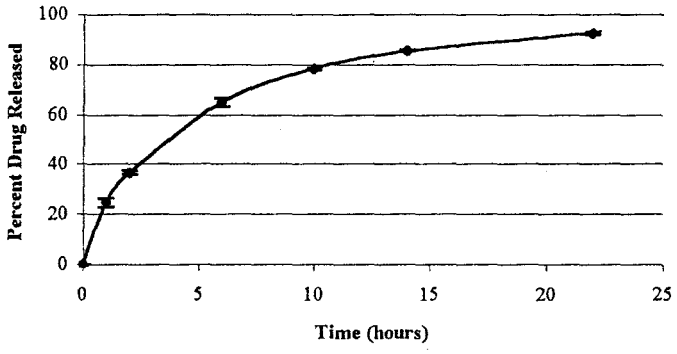
	Mean	%RSD
Weight	611.3	5.12
Thickness	7.14	0.44
Diameter	11.24	0.09
Hardness	95.87	40.09

Friability (11 tablets)

Mass before test:	6.8492 g
Mass after test:	6.8385 g
Mass lost:	0.0107 g
Percentage lost:	0.1562%

Content Uniformity: 99.18 ± 3.26 %

Dissolution Rate Profile:



Residual Content: 1.26 ± 0.14 %

Batch Identification: Wet Granulation (2.5-3.5% EC) **Batch Number: A0231**
Date of Manufacture: 30 September & 01 October 2002
Batch size: 635 g **Temperature:** 16.8°C
Relative Humidity: 42%

Formula:

Acebutolol hydrochloride	20	100 g	Final Granule mass: 460 g
Methocel® K4M	10	50 g	
Emcompress®	37.5	187.5 g	
Emcocel® 90M	32.5	162.5 g	
Surelease®	0.14-0.18 g/g	70-90 g	
Methocel® K100M	20	92 g	
Emcocel® 90M	7	32.2 g	
Emcompress®	10	46 g	
Magnesium stearate	1	4.6 g	

Target Weight: 720 mg
Target Hardness: 120 –160 N

Physical Assessment:

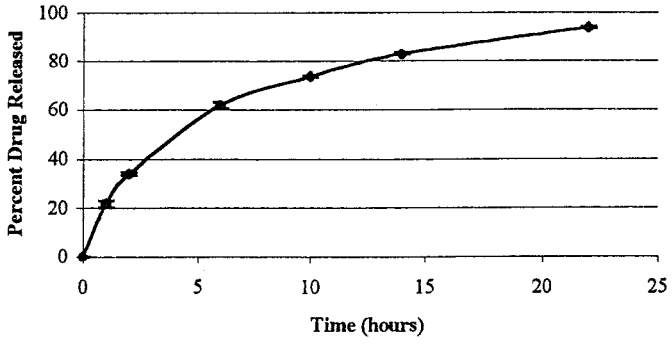
	Mean	%RSD
Weight	760.4	1.95
Thickness	7.96	0.71
Diameter	11.27	0.09
Hardness	105.7	9.69

Friability (10 tablets)

Mass before test:	7.6476 g
Mass after test:	7.6412 g
Mass lost:	0.0064 g
Percentage lost:	0.0837%

Content Uniformity: 79.62 ± 6.21 %

Dissolution Rate Profile:



Residual Content: 4.16 ± 0.60 %

Batch Identification: 3% Talc, Ethocel® FP 100 **Batch Number: A0235**
Date of Manufacture: 18 October 2002
Batch size: 500 g **Temperature:** 22.6°C
Relative Humidity: 47%

Formula:

Acebutolol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 100	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

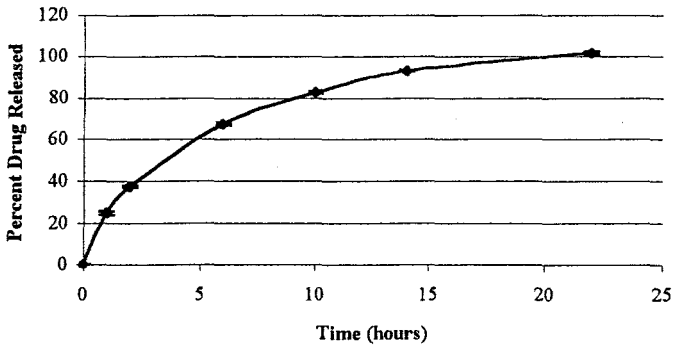
Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

	Mean	%RSD
Weight	640.7	3.53
Thickness	6.84	1.16
Diameter	11.21	0.08
Hardness	183.6	16.08

Friability (11 tablets)	
Mass before test:	6.9930 g
Mass after test:	6.9880 g
Mass lost:	0.0050 g
Percentage lost:	0.0715%

Dissolution Rate Profile:



Residual Content: 0.20 ± 0.09 %

Batch Identification: 3% Talc, Ethocel® Std 10 **Batch Number: A0237**
Date of Manufacture: 18 October 2002
Batch size: 500 g **Temperature:** 22.7°C
Relative Humidity: 45%

Formula:

Acebutolol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® Std 10	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

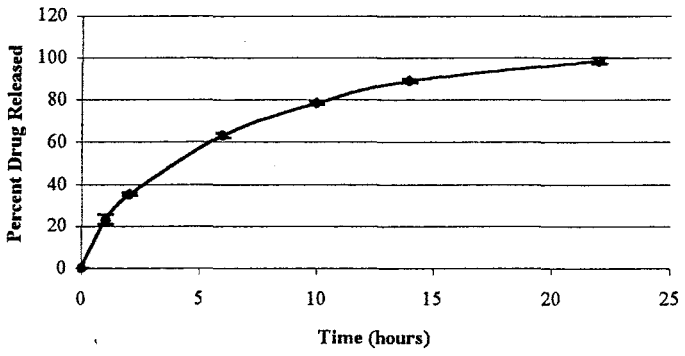
Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

	Mean	%RSD
Weight	634.9	4.23
Thickness	6.88	1.19
Diameter	11.22	0.07
Hardness	159.5	21.99

Friability (11 tablets)	
Mass before test:	7.0046 g
Mass after test:	6.9995 g
Mass lost:	0.0051 g
Percentage lost:	0.0728%

Dissolution Rate Profile:



Residual Content: 0.63 ± 0.20 %

Batch Identification: Wet Granulation (10% EC) **Batch Number: A0247**
Date of Manufacture: 05 & 06 November 2002
Batch size: 538 g **Temperature:** 16.9°C
Relative Humidity: 41%

Formula:

Acebutolol hydrochloride	20	100 g	Final Granule mass: 390 g
Methocel® K4M	10	50 g	
Emcompress®	37.5	187.5 g	
Emcocel® 90M	32.5	162.5 g	
Surelease®	0.4 g/g	200 g	
Methocel® K100M	20	78 g	
Emcocel® 90M	7	27.3 g	
Emcompress®	10	39 g	
Magnesium stearate	1	3.9 g	

Target Weight: 720 mg
Target Hardness: 120 –160 N

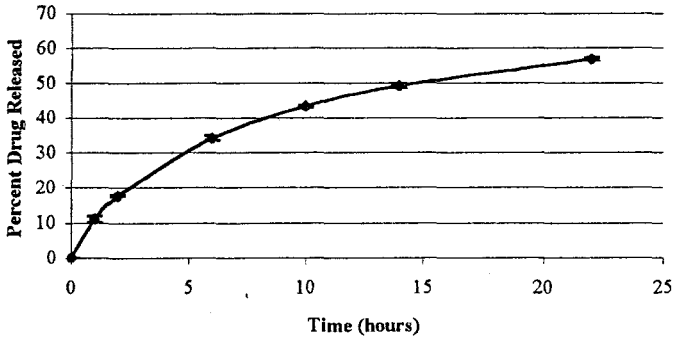
Physical Assessment:

	Mean	%RSD
Weight	742.1	3.11
Thickness	7.63	1.61
Diameter	11.23	0.05
Hardness	139.3	9.03

Friability (10 tablets)

Mass before test:	7.3637 g
Mass after test:	7.3637 g
Mass lost:	0.0000 g
Percentage lost:	0.0000%

Dissolution Rate Profile:



Residual Content: 4.37 ± 1.45 %

Batch Identification: Wet Granulation (2.5-3.5% EC) **Batch Number: L0223**
Date of Manufacture: 30 September & 01 October 2002
Batch size: 593 g **Temperature:** 15.8°C
Relative Humidity: 40%

Formula:

Labetalol hydrochloride	20	100 g	Final Granule mass: 430 g
Methocel® K4M	10	50 g	
Emcompress®	37.5	187.5 g	
Emcocel® 90M	32.5	162.5 g	
Surelease®	0.14-0.18 g/g	70-90 g	
Methocel® K100M	20	86 g	
Emcocel® 90M	7	30.1 g	
Emcompress®	10	43 g	
Magnesium stearate	1	4.3 g	

Target Weight: 720 mg
Target Hardness: 120 –160 N

Physical Assessment:

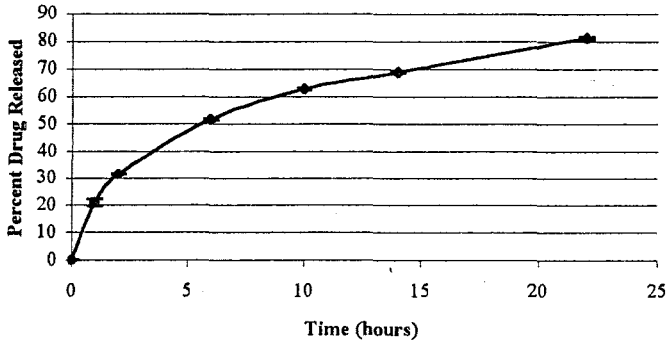
	Mean	%RSD
Weight	742.7	2.09
Thickness	8.03	0.33
Diameter	11.27	0.07
Hardness	100.4	13.83

Friability (10 tablets)

Mass before test:	7.3432 g
Mass after test:	7.3324 g
Mass lost:	0.0108 g
Percentage lost:	0.1471%

Content Uniformity: 86.72 ± 3.84 %

Dissolution Rate Profile:



Residual Content: 18.41 ± 1.22 %

Batch Identification: 3% Talc, Ethocel® FP 10 **Batch Number: L0229**
Date of Manufacture: 28 August 2002
Batch size: 500 g **Temperature:** 18.5°C
Relative Humidity: 76%

Formula:

Labetalol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 10	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

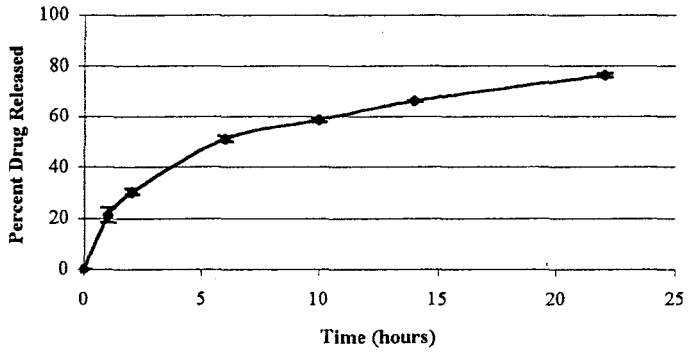
	Mean	%RSD
Weight	721.1	3.24
Thickness	7.92	0.75
Diameter	11.23	0.05
Hardness	145.1	23.30

Friability (10 tablets)

Mass before test:	7.2152 g
Mass after test:	7.2065 g
Mass lost:	0.0087 g
Percentage lost:	0.1206%

Content Uniformity: 99.59 ± 4.04 %

Dissolution Rate Profile:



Residual Content: 12.42 ± 1.52 %

Batch Identification: 3% Talc, Ethocel® FP 100 **Batch Number: L0239**
Date of Manufacture: 18 October 2002
Batch size: 500 g **Temperature:** 22.8°C
Relative Humidity: 42%

Formula:

Labetalol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 100	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

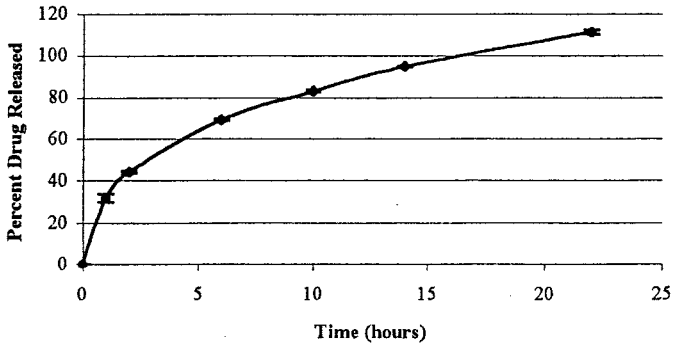
Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

	Mean	%RSD
Weight	694.7	5.06
Thickness	7.39	0.80
Diameter	11.22	0.11
Hardness	223.5	30.59

Friability (10 tablets)	
Mass before test:	6.8889 g
Mass after test:	6.8851 g
Mass lost:	0.0038 g
Percentage lost:	0.0552%

Dissolution Rate Profile:



Residual Content: 10.70 ± 4.03 %

Batch Identification: 3% Talc, Ethocel® Std 10 **Batch Number: L0241**
Date of Manufacture: 18 October 2002
Batch size: 500 g **Temperature:** 22.8°C
Relative Humidity: 42%

Formula:

Labetalol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® Std 10	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

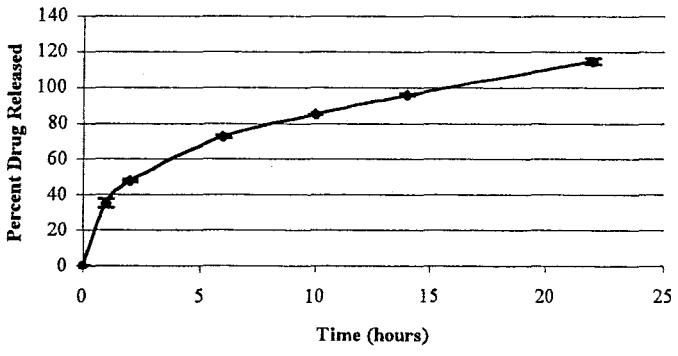
Physical Assessment:

	Mean	%RSD
Weight	691.1	5.59
Thickness	7.77	0.34
Diameter	11.23	0.11
Hardness	131.7	35.21

Friability (10 tablets)

Mass before test:	6.9880 g
Mass after test:	6.9797 g
Mass lost:	0.0083 g
Percentage lost:	0.1188%

Dissolution Rate Profile:



Residual Content: 6.95 ± 5.58 %

Batch Identification: Wet Granulation (10% EC)
Date of Manufacture: 05 & 06 November 2002
Batch size: 725 g

Batch Number: L0249

Temperature: 17.3°C
Relative Humidity: 39%

Formula:

Labetalol hydrochloride	20	100 g	Final Granule mass: 525 g
Methocel® K4M	10	50 g	
Emcompress®	37.5	187.5 g	
Emcocel® 90M	32.5	162.5 g	
Surelease®	0.4 g/g	200 g	
Methocel® K100M	20	105 g	
Emcocel® 90M	7	36.75 g	
Emcompress®	10	52.5 g	
Magnesium stearate	1	5.3 g	

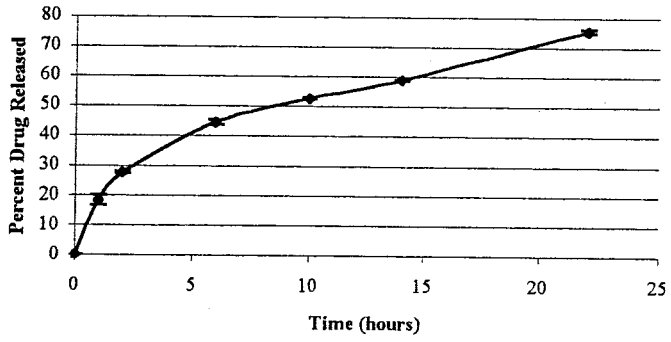
Target Weight: 720 mg
Target Hardness: 120 –160 N

Physical Assessment:

	Mean	%RSD
Weight	702.5	5.10
Thickness	7.59	2.74
Diameter	11.23	0.12
Hardness	134.7	23.92

Friability (10 tablets)	
Mass before test:	7.1523 g
Mass after test:	7.1523 g
Mass lost:	0.0000 g
Percentage lost:	0.0000%

Dissolution Rate Profile:



Residual Content: 26.50 ± 1.41 %

Batch Identification: Wet Granulation (5% EC) **Batch Number: L0251**
Date of Manufacture: 05 & 06 November 2002
Batch size: 547 g **Temperature:** 17.3°C
Relative Humidity: 39%

Formula:

Labetalol hydrochloride	20	100 g	
Methocel® K4M	10	50 g	Final Granule mass: 396 g
Emcompress®	37.5	187.5 g	
Emcocel® 90M	32.5	162.5 g	
Surelease®	0.2 g/g	100 g	
Methocel® K100M	20	79.2 g	
Emcocel® 90M	7	27.7 g	
Emcompress®	10	39.6 g	
Magnesium stearate	1	4 g	

Target Weight: 720 mg
Target Hardness: 120 –160 N

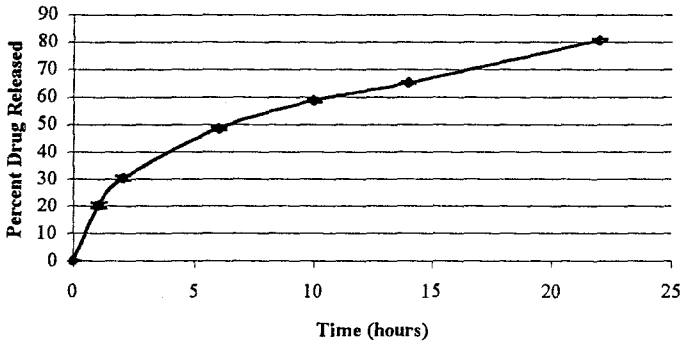
Physical Assessment:

	Mean	%RSD
Weight	708.9	4.08
Thickness	7.60	1.28
Diameter	11.24	0.07
Hardness	126.2	19.05

Friability (10 tablets)

Mass before test:	7.0844 g
Mass after test:	7.0839 g
Mass lost:	0.0005 g
Percentage lost:	0.0071%

Dissolution Rate Profile:



Residual Content: 17.93 ± 1.01 %

Batch Identification: 3% Cab-O-Sil®, Ethocel® FP 100 **Batch Number: M0119**
Date of Manufacture: 29 October 2001
Batch size: 500 g **Temperature:** 22.4°C
Relative Humidity: 68%

Formula:

Metoprolol tartrate	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 100	2.8	14 g
Methocel® K100M	14	70 g
Cab-O-Sil® M5	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

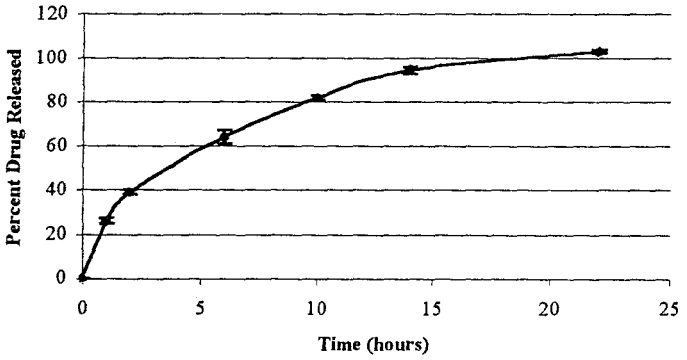
	Mean	%RSD
Weight	602.0	1.66
Thickness	7.07	0.25
Diameter	11.29	0.31
Hardness	107.9	12.6

Friability (11 tablets)

Mass before test:	6.5879 g
Mass after test:	6.5820 g
Mass lost:	0.0059 g
Percentage lost:	0.0896%

Content Uniformity: 90.88 ± 3.45 %

Dissolution Rate Profile:



Batch Identification: 1.5% Cab-O-Sil®, 1.5% Talc
Batch Number: M0135
Date of Manufacture: 27 February 2002
Batch size: 500 g
Temperature: 24.4°C
Relative Humidity: 67%

Formula:

Metoprolol tartrate	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 100	2.8	14 g
Methocel® K100M	14	70 g
Cab-O-Sil® M5	1.5	7.5 g
Purified talc	1.5	7.5 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

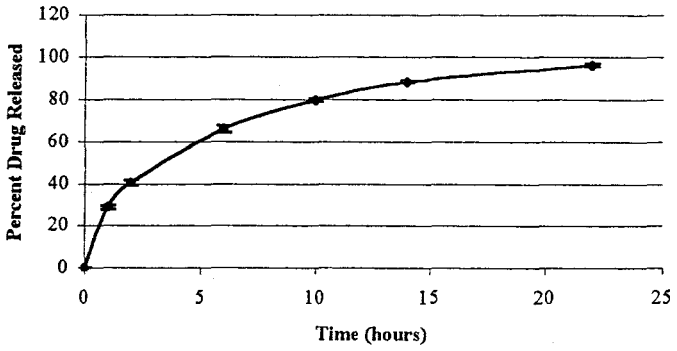
	Mean	%RSD
Weight	607.4	4.36
Thickness	6.95	0.95
Diameter	11.31	0.24
Hardness	112.2	31.87

Friability (11 tablets)

Mass before test:	6.7431 g
Mass after test:	6.7421 g
Mass lost:	0.0010 g
Percentage lost:	0.0148%

Content Uniformity: 94.85 ± 2.49 %

Dissolution Rate Profile:



Residual Content: 0.501 ± 0.23 %

Batch Identification: 3% Talc, Ethocel® FP 100 **Batch Number: M0137**
Date of Manufacture: 21 March 2002
Batch size: 500 g **Temperature:** 24.1°C
Relative Humidity: 65%

Formula:

Metoprolol tartrate	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 100	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

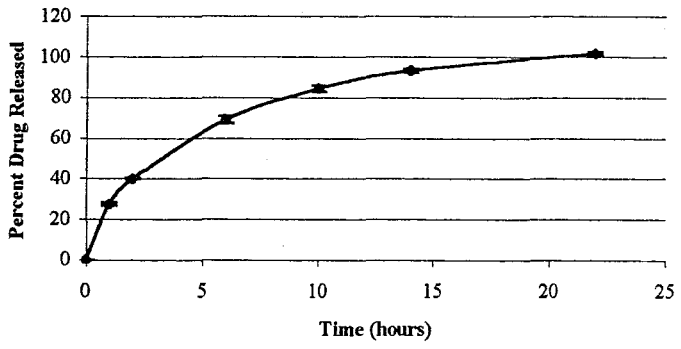
Physical Assessment:

	Mean	%RSD
Weight	701.9	2.28
Thickness	7.85	0.68
Diameter	11.31	0.24
Hardness	111.4	10.4

Friability (10 tablets)

Mass before test:	7.0143 g
Mass after test:	7.0067 g
Mass lost:	0.0076 g
Percentage lost:	0.1084%

Dissolution Rate Profile:



Residual Content: 2.07 ± 0.39 %

Batch Identification: 0.5% Cab-O-Sil®, 2.5% Talc **Batch Number: M0143**
Date of Manufacture: 21 March 2002
Batch size: 500 g **Temperature:** 23.0°C
Relative Humidity: 62%

Formula:

Metoprolol tartrate	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 100	2.8	14 g
Methocel® K100M	14	70 g
Cab-O-Sil® M5	0.5	2.5 g
Purified talc	2.5	12.5 g
Magnesium stearate	0.7	3.5 g

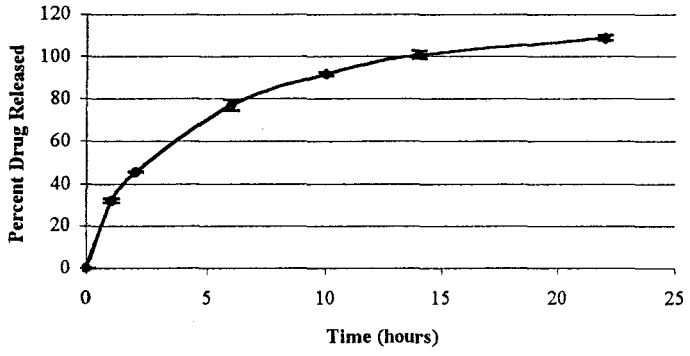
Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

	Mean	%RSD
Weight	654.1	2.90
Thickness	7.15	0.56
Diameter	11.26	0.09
Hardness	140.1	18.34

Friability (10 tablets)	
Mass before test:	6.6402 g
Mass after test:	6.6362 g
Mass lost:	0.0040 g
Percentage lost:	0.0602%

Dissolution Rate Profile:



Residual Content: 0.509 ± 0.24 %

Batch Identification: 3% Talc, Ethocel® FP 10 **Batch Number: M0147**
Date of Manufacture: 03 May 2002
Batch size: 500 g **Temperature:** 19.8°C
Relative Humidity: 64%

Formula:

Metoprolol tartrate	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 10	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

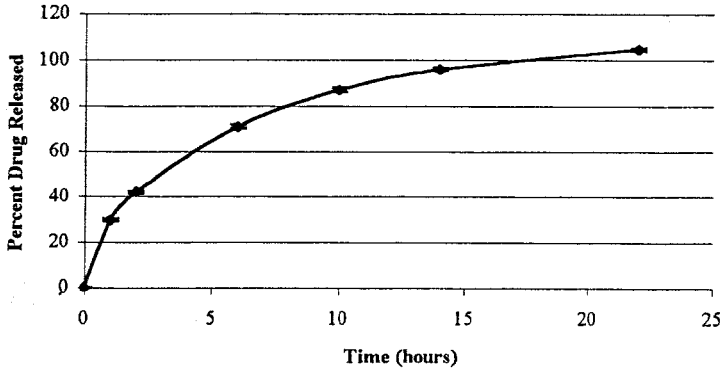
	Mean	%RSD
Weight	677.3	1.67
Thickness	7.65	0.53
Diameter	11.27	0.08
Hardness	97.93	12.02

Friability (10 tablets)

Mass before test:	6.7896 g
Mass after test:	6.7853 g
Mass lost:	0.0043 g
Percentage lost:	0.0633%

Content Uniformity: 99.20 ± 4.41 %

Dissolution Rate Profile:



Residual Content: 1.53 ± 0.43 %

Batch Identification: 3% Talc, Ethocel® FP 7 **Batch Number: M0149**
Date of Manufacture: 03 May 2002
Batch size: 500 g **Temperature:** 19.7°C
Relative Humidity: 63%

Formula:

Metoprolol tartrate	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 7	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

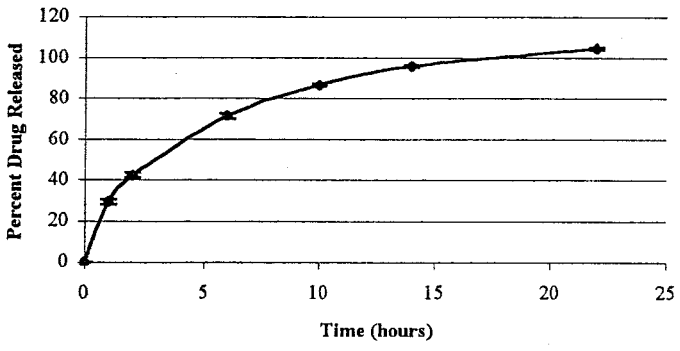
Physical Assessment:

	Mean	%RSD
Weight	687.8	3.41
Thickness	7.81	0.65
Diameter	11.28	0.27
Hardness	101.1	24.3

Friability (10 tablets)

Mass before test:	6.7200 g
Mass after test:	6.7086 g
Mass lost:	0.0114 g
Percentage lost:	0.1696%

Dissolution Rate Profile:



Residual Content: 2.12 ± 0.65 %

Batch Identification: 3% Talc, Ethocel® FP 100 **Batch Number: M0151**
Date of Manufacture: 03 May 2002
Batch size: 500 g **Temperature:** 20.0°C
Relative Humidity: 64%

Formula:

Metoprolol tartrate	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 100	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

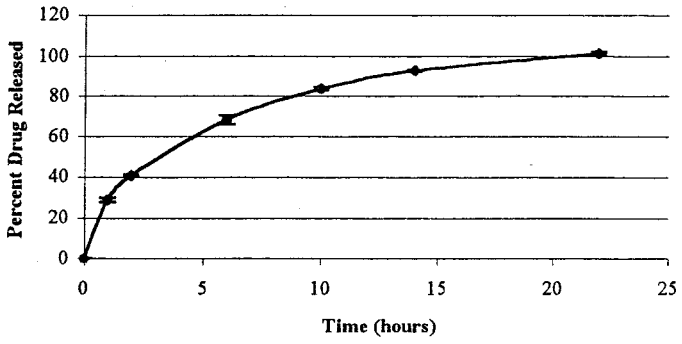
Physical Assessment:

	Mean	%RSD
Weight	691.5	2.51
Thickness	7.60	1.19
Diameter	11.27	0.08
Hardness	121.5	15.36

Friability (11 tablets)

Mass before test:	6.9700 g
Mass after test:	6.9670 g
Mass lost:	0.0030 g
Percentage lost:	0.0430%

Dissolution Rate Profile:



Residual Content: 1.96 ± 0.20 %

Batch Identification: 3% Talc, Ethocel® Std 45 **Batch Number: M0153**
Date of Manufacture: 03 May 2002
Batch size: 500 g **Temperature:** 20.0°C
Relative Humidity: 61%

Formula:

Metoprolol tartrate	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® Std 45	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

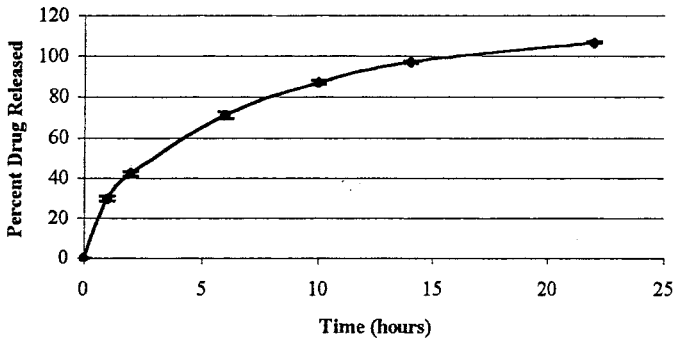
Physical Assessment:

	Mean	%RSD
Weight	712.8	2.20
Thickness	7.79	1.33
Diameter	11.28	0.14
Hardness	97.8	14.6

Friability (10 tablets)

Mass before test:	7.1017 g
Mass after test:	7.0981 g
Mass lost:	0.0036 g
Percentage lost:	0.0507%

Dissolution Rate Profile:



Residual Content: 2.26 ± 0.27 %

Batch Identification: 3% Talc, Ethocel® Std 10 **Batch Number: M0155**
Date of Manufacture: 03 May 2002
Batch size: 500 g **Temperature:** 20.3°C
Relative Humidity: 61%

Formula:

Metoprolol tartrate	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® Std 10	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

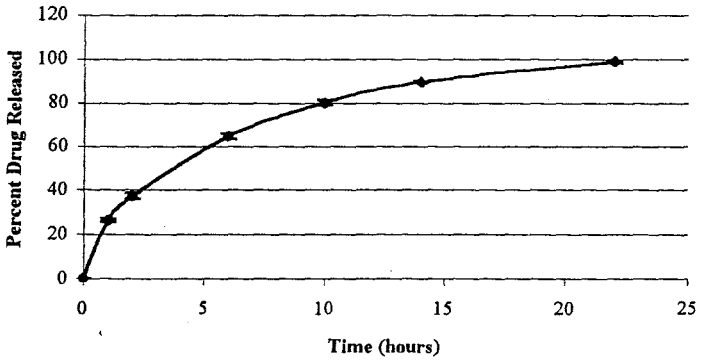
Physical Assessment:

	Mean	%RSD
Weight	686.3	1.14
Thickness	7.56	1.66
Diameter	11.27	0.07
Hardness	100.1	5.99

Friability (10 tablets)

Mass before test:	6.9042 g
Mass after test:	6.9007 g
Mass lost:	0.0035 g
Percentage lost:	0.0507%

Dissolution Rate Profile:



Residual Content: 2.51 ± 0.20 %

Batch Identification: 3% Talc, Ethocel® Std 20 **Batch Number: M0157**
Date of Manufacture: 03 May 2002
Batch size: 500 g **Temperature:** 20.0°C
Relative Humidity: 61%

Formula:

Metoprolol tartrate	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® Std 20	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

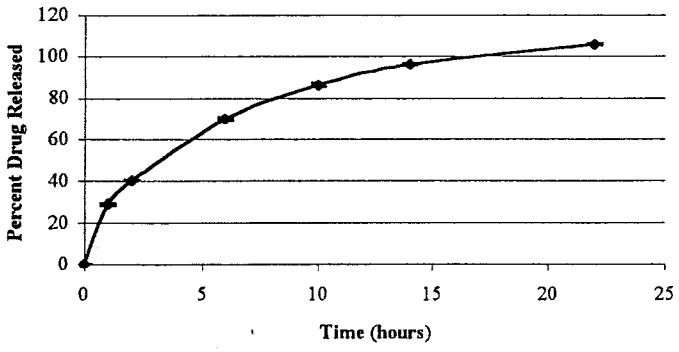
Physical Assessment:

	Mean	%RSD
Weight	703.6	4.13
Thickness	7.70	0.78
Diameter	11.28	0.24
Hardness	105.4	25.16

Friability (10 tablets)

Mass before test:	7.0402 g
Mass after test:	7.0351 g
Mass lost:	0.0051 g
Percentage lost:	0.0724%

Dissolution Rate Profile:



Residual Content: 2.73 ± 0.33 %

Batch Identification: 3% Talc, Ethocel® FP 100 **Batch Number: M0159**
Date of Manufacture: 03 May 2002
Batch size: 500 g **Temperature:** 20.0°C
Relative Humidity: 62%

Formula:

Metoprolol tartrate	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 100	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

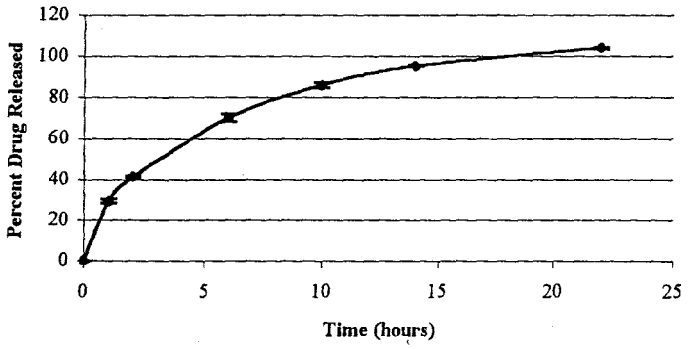
Physical Assessment:

	Mean	%RSD
Weight	701.1	2.71
Thickness	7.69	0.55
Diameter	11.27	0.15
Hardness	115.8	17.1

Friability (10 tablets)

Mass before test:	6.8391 g
Mass after test:	6.8348 g
Mass lost:	0.0043 g
Percentage lost:	0.0628%

Dissolution Rate Profile:



Residual Content: 2.18 ± 0.29 %

Batch Identification: Std 20 (20% Ethocel®) **Batch Number: M0205**
Date of Manufacture: 07 August 2002
Batch size: 500 g **Temperature:** 13.3°C
Relative Humidity: 41%

Formula:

Metoprolol tartrate	13.5	67.5 g
Methocel® K4M	5.8	29 g
Emcompress®	25	125 g
Emcocel® 90M	20	100 g
Ethocel® Std 20	20	100 g
Methocel® K100M	12	60 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

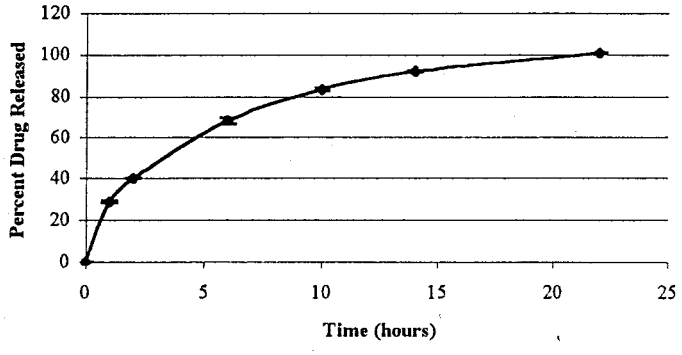
Physical Assessment:

	Mean	%RSD
Weight	702.7	1.07
Thickness	7.96	0.49
Diameter	11.25	0.09
Hardness	105.6	7.67

Friability (10 tablets)

Mass before test:	7.0420 g
Mass after test:	7.0395 g
Mass lost:	0.0025 g
Percentage lost:	0.0355%

Dissolution Rate Profile:



Residual Content: 2.20 ± 0.28 %

Batch Identification: FP 10 (20% Ethocel®) **Batch Number: M0207**
Date of Manufacture: 07 August 2002
Batch size: 500 g **Temperature:** 13.3°C
Relative Humidity: 41%

Formula:

Metoprolol tartrate	13.5	67.5 g
Methocel® K4M	5.8	29 g
Emcompress®	25	125 g
Emcocel® 90M	20	100 g
Ethocel® FP 10	20	100 g
Methocel® K100M	12	60 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

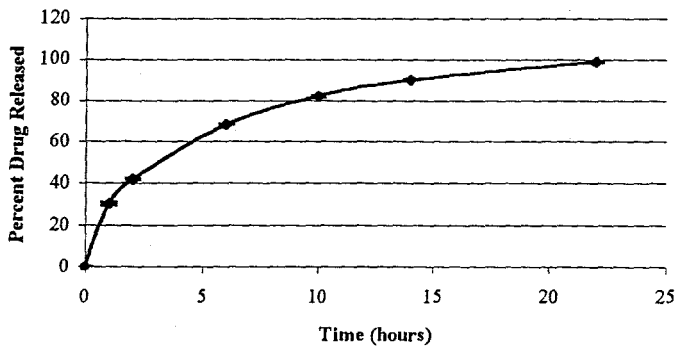
Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

	Mean	%RSD
Weight	638.3	2.74
Thickness	7.99	1.44
Diameter	11.25	0.15
Hardness	116.7	23.72

Friability (11 tablets)	
Mass before test:	7.1046 g
Mass after test:	7.1025 g
Mass lost:	0.0021 g
Percentage lost:	0.0296%

Dissolution Rate Profile:



Residual Content: 2.66 ± 0.49 %

Batch Identification: Wet Granulation (10% EC)
Batch Number: M0211
Date of Manufacture: 03 & 04 October 2002
Batch size: 690 g

Temperature: 18.1°C
Relative Humidity: 51%

Formula:

Metoprolol tartrate	20	100 g	
Methocel® K4M	10	50 g	Final Granule mass: 500 g
Emcompress®	37.5	187.5 g	
Emcocel® 90M	32.5	162.5 g	
Surelease®	0.4 g/g	200 g	
Methocel® K100M	20	100 g	
Emcocel® 90M	7	35 g	
Emcompress®	10	50 g	
Magnesium stearate	1	5 g	

Target Weight: 720 mg
Target Hardness: 120 –160 N

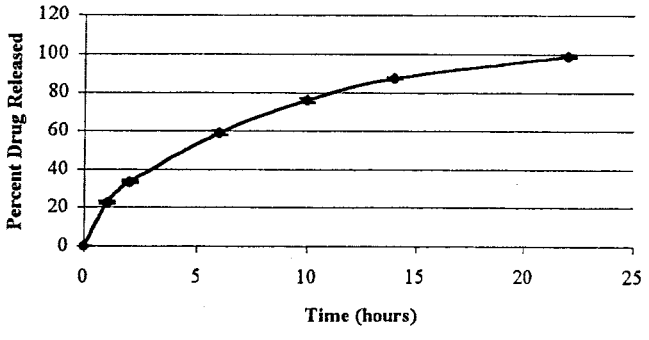
Physical Assessment:

	Mean	%RSD
Weight	759.0	3.86
Thickness	7.86	2.72
Diameter	11.24	0.06
Hardness	119.5	7.64

Friability (10 tablets)

Mass before test:	7.4943 g
Mass after test:	7.4943 g
Mass lost:	0.0000 g
Percentage lost:	0.0000%

Dissolution Rate Profile:



Residual Content: 3.02 ± 0.47 %

Batch Identification: Wet Granulation (5% EC)
Date of Manufacture: 03 & 04 October 2002
Batch size: 676 g

Batch Number: M0213

Temperature: 16.9°C
Relative Humidity: 39%

Formula:

Metoprolol tartrate	20	100 g	Final Granule mass: 490 g
Methocel® K4M	10	50 g	
Emcompress®	37.5	187.5 g	
Emcocel® 90M	32.5	162.5 g	
Surelease®	0.2 g/g	100 g	
Methocel® K100M	20	98 g	
Emcocel® 90M	7	34.3 g	
Emcompress®	10	49 g	
Magnesium stearate	1	5 g	

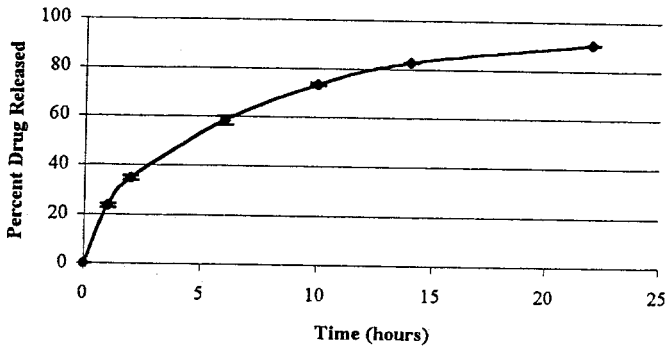
Target Weight: 720 mg
Target Hardness: 120 –160 N

Physical Assessment:

	Mean	%RSD
Weight	679.9	1.23
Thickness	7.25	0.83
Diameter	11.25	0.05
Hardness	131.9	5.29

Friability (10 tablets)	
Mass before test:	6.8488 g
Mass after test:	6.8485 g
Mass lost:	0.0003 g
Percentage lost:	0.0044%

Dissolution Rate Profile:



Residual Content: 1.15 ± 0.13 %

Batch Identification: Wet Granulation (2.5-3.5% EC) **Batch Number: M0233**
Date of Manufacture: 03 & 04 October 2002
Batch size: 662 g

Temperature: 17°C
Relative Humidity: 38%

Formula:

Metoprolol tartrate	20	100 g	Final Granule mass: 480 g
Methocel® K4M	10	50 g	
Emcompress®	37.5	187.5 g	
Emcocel® 90M	32.5	162.5 g	
Surelease®	0.14-0.18 g/g	70-90 g	
Methocel® K100M	20	96 g	
Emcocel® 90M	7	33.6 g	
Emcompress®	10	48 g	
Magnesium stearate	1	4.8 g	

Target Weight: 720 mg
Target Hardness: 120 –160 N

Physical Assessment:

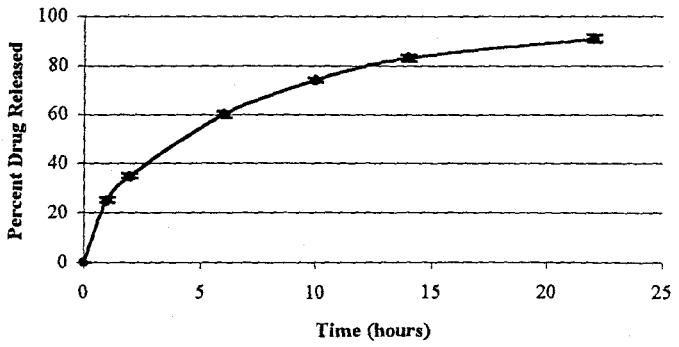
	Mean	%RSD
Weight	667.1	0.55
Thickness	7.19	0.49
Diameter	11.26	0.05
Hardness	124.0	3.42

Friability (10 tablets)

Mass before test:	6.6919 g
Mass after test:	6.6919 g
Mass lost:	0.0000 g
Percentage lost:	0.0000%

Content Uniformity: 97.36 ± 3.76 %

Dissolution Rate Profile:



Residual Content: 1.26 ± 0.94 %

Batch Identification: Freeze-dried (2.8% EC solids) **Batch Number: M0259**
Date of Manufacture: 06 November 2002
Batch size: 264 g

Temperature: 18.5°C
Relative Humidity: 45%

Formula:

Freeze-dried material	16.3	43 g
Methocel® K4M	6.6	18 g
Emcompress®	32.3	85 g
Emcocel® 90M	26.9	71 g
Methocel® K100M	14	37 g
Purified talc	3	8 g
Magnesium stearate	0.7	2 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

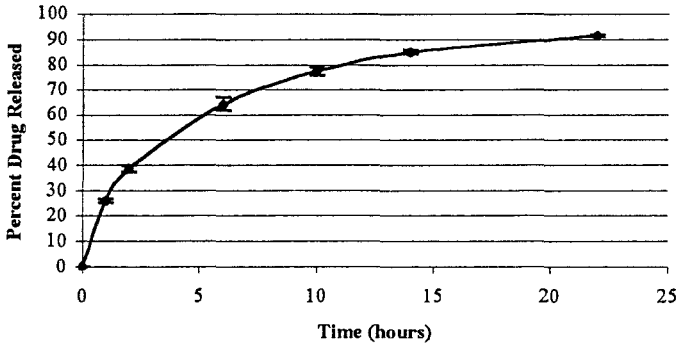
	Mean	%RSD
Weight	729.7	0.37
Thickness	7.55	0.24
Diameter	11.24	0.06
Hardness	98.41	3.18

Freeze-dried Material: Metoprolol tartrate 85 g
Surelease® 70.5 g (17.6 g ethylcellulose solids)

Friability (10 tablets)

Mass before test:	7.2716 g
Mass after test:	7.2651 g
Mass lost:	0.0065 g
Percentage lost:	0.0894%

Dissolution Rate Profile:



Residual Content: 0.56 ± 0.16 %

Batch Identification: Freeze-dried (14% EC solids)
Date of Manufacture: 05 November 2002
Batch size: 116 g

Batch Number: M0261

Temperature: 20.4°C
Relative Humidity: 35%

Formula:

Freeze-dried material	27.5	32 g
Methocel® K4M	6	7 g
Emcompress®	26	30.2 g
Emcocel® 90M	22.8	26.5 g
Methocel® K100M	14	16.2 g
Purified talc	3	3.5 g
Magnesium stearate	0.7	0.8 g

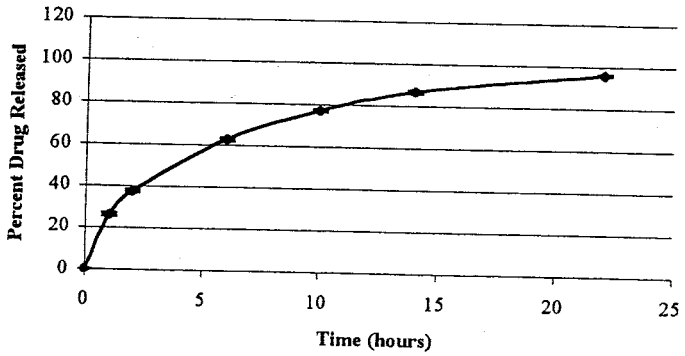
Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

	Mean	%RSD
Weight	672.4	0.56
Thickness	7.27	0.31
Diameter	11.22	0.05
Hardness	72.54	6.13

Freeze-dried Material: Metoprolol tartrate 30 g
Surelease® 120 g (30 g ethylcellulose solids)

Dissolution Rate Profile:



Residual Content: 2.44 ± 0.09 %

Batch Identification: Wet Granulation (2.5-3.5%EC) **Batch Number: O0221**
Date of Manufacture: 30 September & 01 October 2002
Batch size: 635 g **Temperature:** 16.4°C
Relative Humidity: 43%

Formula:

Oxprenolol hydrochloride	20	100 g	
Methocel® K4M	10	50 g	Final Granule mass: 460 g
Emcompress®	37.5	187.5 g	
Emcocel® 90M	32.5	162.5 g	
Surelease®	0.14-0.18 g/g	70-90 g	
Methocel® K100M	20	92 g	
Emcocel® 90M	7	32.2 g	
Emcompress®	10	46 g	
Magnesium stearate	1	4.6 g	

Target Weight: 720 mg
Target Hardness: 120 –160 N

Physical Assessment:

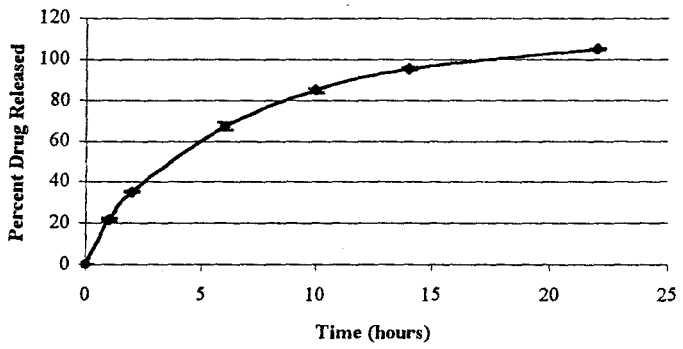
	Mean	%RSD
Weight	782.2	3.27
Thickness	8.00	1.85
Diameter	11.24	0.08
Hardness	87.2	10.27

Friability (10 tablets)

Mass before test:	7.8064 g
Mass after test:	7.7957 g
Mass lost:	0.0107 g
Percentage lost:	0.1371%

Content Uniformity: 75.15 ± 4.72 %

Dissolution Rate Profile:



Residual Content: 2.87 ± 0.42 %

Batch Identification: 3% Talc, Ethocel® FP 10 **Batch Number: O0227**
Date of Manufacture: 28 August 2002
Batch size: 500 g **Temperature:** 18.1°C
Relative Humidity: 77%

Formula:

Oxprenolol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 10	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

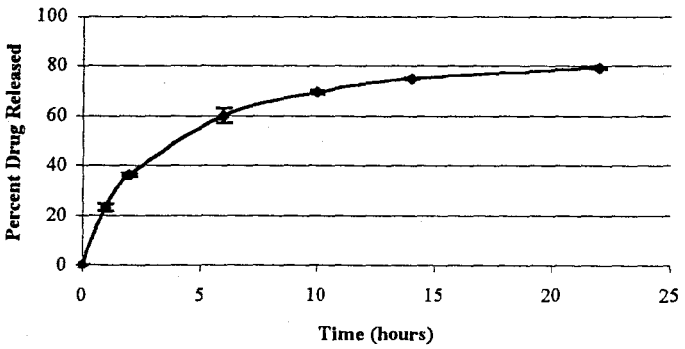
Physical Assessment:

	Mean	%RSD
Weight	647.6	1.79
Thickness	7.12	0.36
Diameter	11.23	0.06
Hardness	138.7	11.93

Friability (10 tablets)	
Mass before test:	6.5086 g
Mass after test:	6.5027 g
Mass lost:	0.0059 g
Percentage lost:	0.0906%

Content Uniformity: 96.44 ± 3.51 %

Dissolution Rate Profile:



Residual Content: 0.80 ± 0.12 %

Batch Identification: 3% Talc, Ethocel® FP 100 **Batch Number: O0243**
Date of Manufacture: 18 October 2002
Batch size: 500 g

Temperature: 23.2°C
Relative Humidity: 54%

Formula:

Oxprenolol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 100	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

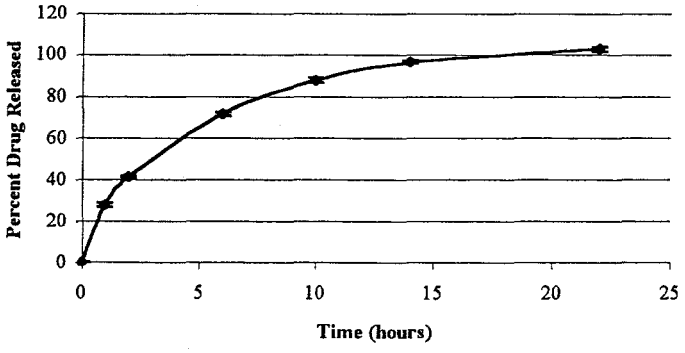
Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

	Mean	%RSD
Weight	667.0	2.63
Thickness	6.93	1.68
Diameter	11.20	0.04
Hardness	167.7	8.17

Friability (10 tablets)	
Mass before test:	6.7017 g
Mass after test:	6.7001 g
Mass lost:	0.0016 g
Percentage lost:	0.0239%

Dissolution Rate Profile:



Residual Content: 0.30 ± 0.28 %

Batch Identification: 3% Talc, Ethocel® Std 10 **Batch Number: O0245**
Date of Manufacture: 18 October 2002
Batch size: 500 g **Temperature:** 23.4°C
Relative Humidity: 51%

Formula:

Oxprenolol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® Std 10	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

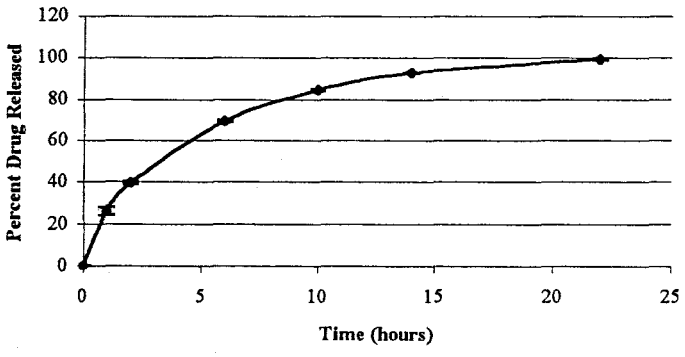
Physical Assessment:

	Mean	%RSD
Weight	650.2	3.67
Thickness	6.93	1.74
Diameter	11.21	0.08
Hardness	160.0	12.88

Friability (11 tablets)

Mass before test:	6.9935 g
Mass after test:	6.9894 g
Mass lost:	0.0041 g
Percentage lost:	0.0586%

Dissolution Rate Profile:



Residual Content: 0.53 ± 0.07 %

Batch Identification: Wet Granulation (5%EC) **Batch Number: O0253**
Date of Manufacture: 05 & 06 November 2002
Batch size: 566 g

Temperature: 17.0°C
Relative Humidity: 41%

Formula:

Oxprenolol hydrochloride	20	100 g	Final Granule mass: 410 g
Methocel® K4M	10	50 g	
Emcompress®	37.5	187.5 g	
Emcocel® 90M	32.5	162.5 g	
Surelease®	0.2 g/g	100 g	
Methocel® K100M	20	82 g	
Emcocel® 90M	7	28.7 g	
Emcompress®	10	41 g	
Magnesium stearate	1	4.1 g	

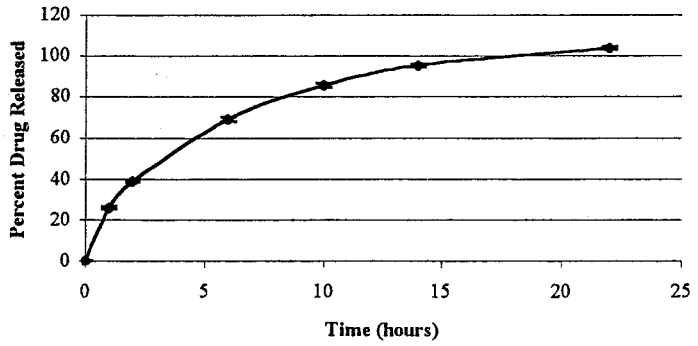
Target Weight: 720 mg
Target Hardness: 120 –160 N

Physical Assessment:

	Mean	%RSD
Weight	676.3	2.40
Thickness	7.14	1.50
Diameter	11.23	0.05
Hardness	118.0	5.02

Friability (10 tablets)	
Mass before test:	6.7735 g
Mass after test:	6.7735 g
Mass lost:	0.0000 g
Percentage lost:	0.0000%

Dissolution Rate Profile:



Residual Content: 2.12 ± 1.47 %

Batch Identification: Wet Granulation (10%EC)
Batch Number: O0255
Date of Manufacture: 05 & 06 November 2002
Batch size: 711 g

Temperature: 17.3°C
Relative Humidity: 41%

Formula:

Oxprenolol hydrochloride	20	100 g	Final Granule mass: 515 g
Methocel® K4M	10	50 g	
Emcompress®	37.5	187.5 g	
Emcocel® 90M	32.5	162.5 g	
Surelease®	0.4 g/g	200 g	
Methocel® K100M	20	103 g	
Emcocel® 90M	7	36.05 g	
Emcompress®	10	51.5 g	
Magnesium stearate	1	5.2 g	

Target Weight: 720 mg
Target Hardness: 120 –160 N

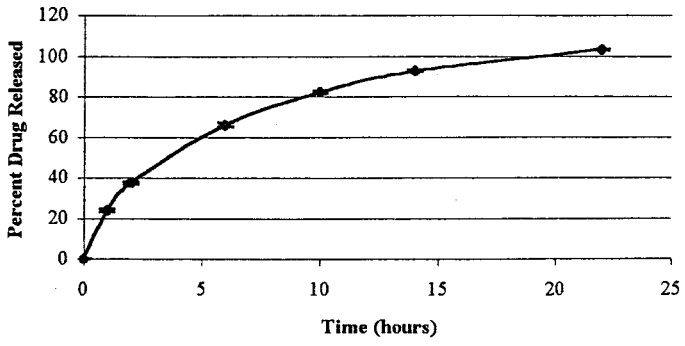
Physical Assessment:

	Mean	%RSD
Weight	736.6	2.98
Thickness	7.71	1.97
Diameter	11.22	0.06
Hardness	99.27	7.60

Friability (10 tablets)

Mass before test:	7.3733 g
Mass after test:	7.3733 g
Mass lost:	0.0000 g
Percentage lost:	0.0000%

Dissolution Rate Profile:



Residual Content: 4.23 ± 0.95 %

Batch Identification: 3% Cab-O-Sil®, Ethocel® FP 100 **Batch Number: P0125**
Date of Manufacture: 11 November 2001
Batch size: 500 g **Temperature:** 18.9°C
Relative Humidity: 62%

Formula:

Propranolol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 100	2.8	14 g
Methocel® K100M	14	70 g
Cab-O-Sil® M5	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

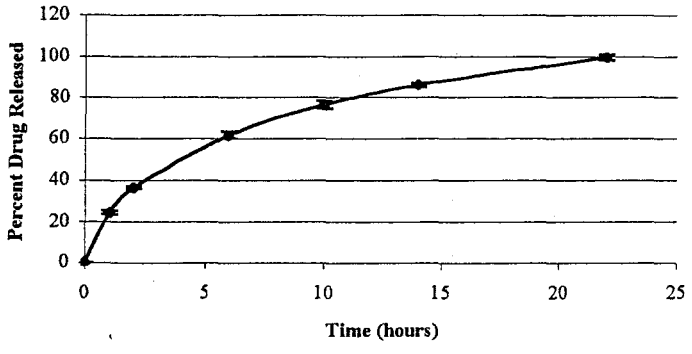
Physical Assessment:

	Mean	%RSD
Weight	602.2	4.15
Thickness	6.97	0.90
Diameter	11.29	0.34
Hardness	116.1	29.79

Friability (11 tablets)

Mass before test:	6.8150 g
Mass after test:	6.8116 g
Mass lost:	0.0034 g
Percentage lost:	0.0499%

Dissolution Rate Profile:



Batch Identification: Wet Granulation (2.5-3.5%EC) **Batch Number: P0133**
Date of Manufacture: 22 & 23 January 2002
Batch size: 531 g

Temperature: 24.9°C
Relative Humidity: 80%

Formula:

Propranolol hydrochloride	20	100 g	Final Granule mass: 385 g
Methocel® K4M	10	50 g	
Emcompress®	37.5	187.5 g	
Emcocel® 90M	32.5	162.5 g	
Surelease®	0.14-0.18 g/g	70-90 g	
Methocel® K100M	20	77 g	
Emcocel® 90M	7	27 g	
Emcompress®	10	38.5 g	
Magnesium stearate	1	3.9 g	

Target Weight: 720 mg
Target Hardness: 120 –160 N

Physical Assessment:

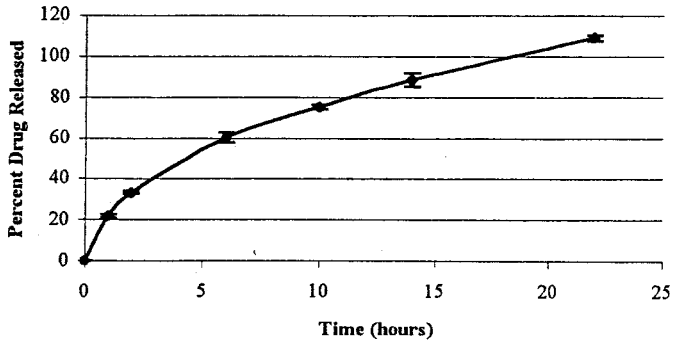
	Mean	%RSD
Weight	685.1	3.86
Thickness	7.28	1.55
Diameter	11.21	0.05
Hardness	168.6	7.56

Friability (10 tablets)

Mass before test:	6.9250 g
Mass after test:	6.9186 g
Mass lost:	0.0064 g
Percentage lost:	0.0924%

Content Uniformity: 91.54 ± 9.97 %

Dissolution Rate Profile:



Batch Identification: 1.5% Cab-O-Sil®, 1.5% Talc
Batch Number: P0139
Date of Manufacture: 21 March 2002
Batch size: 500 g
Temperature: 23.1°C
Relative Humidity: 61%

Formula:

Propranolol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 100	2.8	14 g
Methocel® K100M	14	70 g
Cab-O-Sil® M5	1.5	7.5 g
Purified talc	1.5	7.5 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

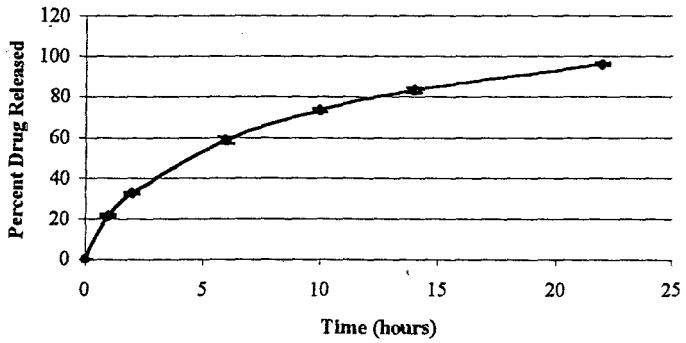
Physical Assessment:

	Mean	%RSD
Weight	639.2	1.12
Thickness	7.12	0.65
Diameter	11.25	0.17
Hardness	158.0	7.74

Friability (11 tablets)

Mass before test:	7.0083 g
Mass after test:	7.0032 g
Mass lost:	0.0051 g
Percentage lost:	0.0728%

Dissolution Rate Profile:



Batch Identification: 0.5% Cab-O-Sil®, 2.5% Talc **Batch Number: P0141**
Date of Manufacture: 21 March 2002
Batch size: 500 g **Temperature:** 23.6°C
Relative Humidity: 58%

Formula:

Propranolol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 100	2.8	14 g
Methocel® K100M	14	70 g
Cab-O-Sil® M5	0.5	2.5 g
Purified talc	2.5	12.5 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

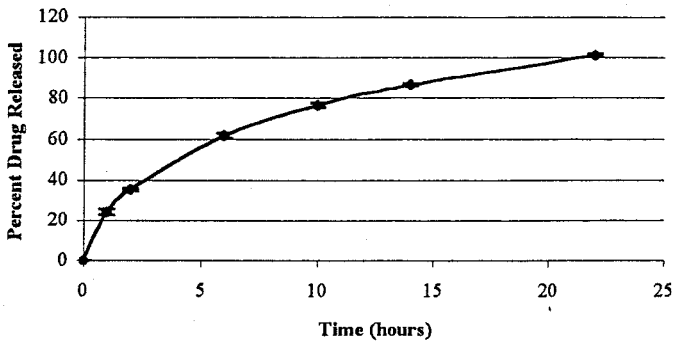
Physical Assessment:

	Mean	%RSD
Weight	686.9	3.17
Thickness	7.64	0.32
Diameter	11.23	0.08
Hardness	146.9	15.34

Friability (10 tablets)

Mass before test:	6.8749 g
Mass after test:	6.8704 g
Mass lost:	0.0045 g
Percentage lost:	0.0655%

Dissolution Rate Profile:



Batch Identification: 3% Talc, Ethocel® FP 7 **Batch Number: P0161**
Date of Manufacture: 17 May 2002
Batch size: 500 g **Temperature:** 14.7°C
Relative Humidity: 52%

Formula:

Propranolol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 7	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

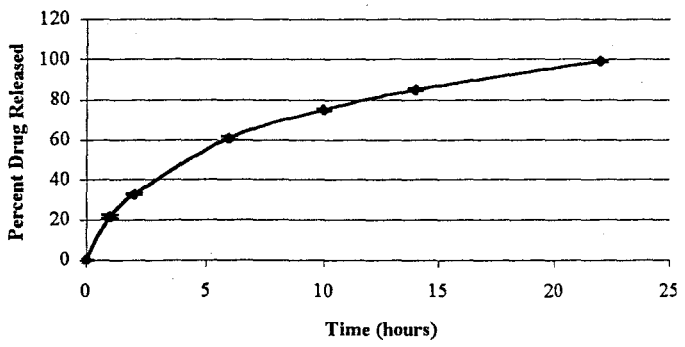
Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

	Mean	%RSD
Weight	741.4	2.67
Thickness	8.05	0.24
Diameter	11.24	0.07
Hardness	123.1	17.6

Friability (10 tablets)	
Mass before test:	7.4747 g
Mass after test:	7.4741 g
Mass lost:	0.0006 g
Percentage lost:	0.0080%

Dissolution Rate Profile:



Residual Content: 12.16 ± 1.88 %

Batch Identification: 3% Talc, Ethocel® FP 10 **Batch Number: P0163**
Date of Manufacture: 17 May 2002
Batch size: 500 g **Temperature:** 14.5°C
Relative Humidity: 52%

Formula:

Propranolol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 10	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

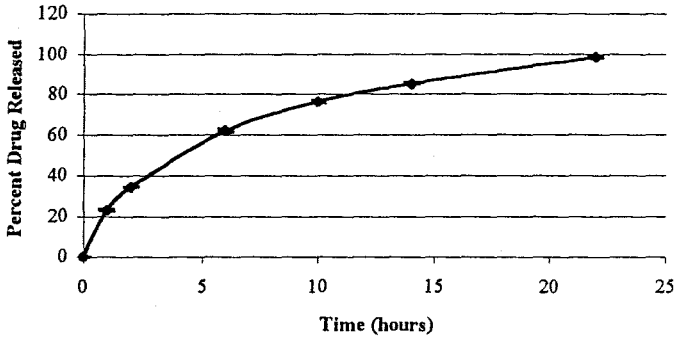
Physical Assessment:

	Mean	%RSD
Weight	737.5	2.37
Thickness	8.06	0.44
Diameter	11.25	0.07
Hardness	118.3	18.93

Friability (10 tablets)	
Mass before test:	7.2625 g
Mass after test:	7.2512 g
Mass lost:	0.0113 g
Percentage lost:	0.1556%

Content Uniformity: 96.50 ± 5.01 %

Dissolution Rate Profile:



Residual Content: 11.50 ± 0.77 %

Batch Identification: 3% Talc, Ethocel® FP 100
Date of Manufacture: 17 May 2002
Batch size: 500 g

Batch Number: P0165

Temperature: 14.5°C
Relative Humidity: 52%

Formula:

Propranolol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® FP 100	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

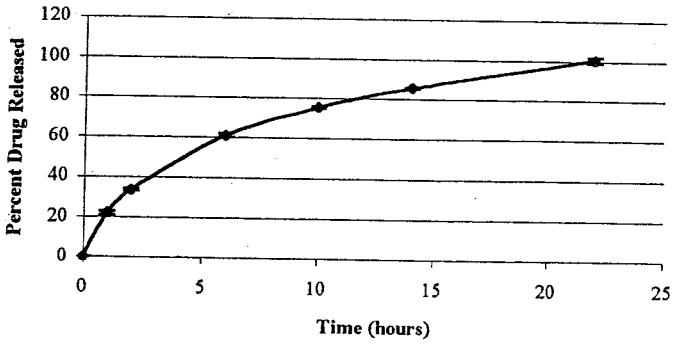
Physical Assessment:

	Mean	%RSD
Weight	718.9	2.58
Thickness	7.88	0.37
Diameter	11.25	0.08
Hardness	115.6	18.30

Friability (10 tablets)

Mass before test:	7.1088 g
Mass after test:	7.1015 g
Mass lost:	0.0073 g
Percentage lost:	0.1027%

Dissolution Rate Profile:



Residual Content: 9.74 ± 1.18 %

Batch Identification: 3% Talc, Ethocel® Std 45 **Batch Number: P0167**
Date of Manufacture: 03 May 2002
Batch size: 500 g **Temperature:** 15.1°C
Relative Humidity: 52%

Formula:

Propranolol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® Std 45	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

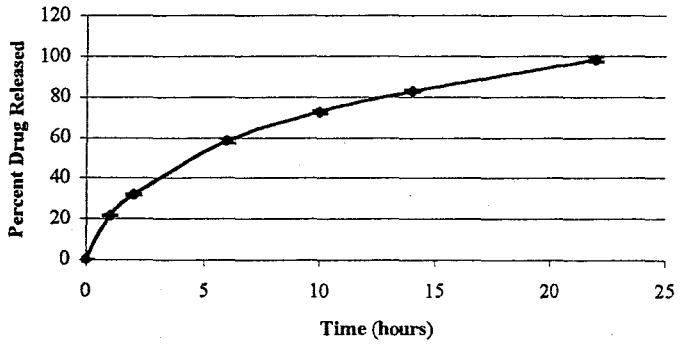
Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

	Mean	%RSD
Weight	719.9	2.29
Thickness	7.78	0.59
Diameter	11.24	0.08
Hardness	118.7	16.5

Friability (10 tablets)	
Mass before test:	7.1621 g
Mass after test:	7.1565 g
Mass lost:	0.0056 g
Percentage lost:	0.0782%

Dissolution Rate Profile:



Residual Content: 9.20 ± 0.90 %

Batch Identification: 3% Talc, Ethocel® Std 10 **Batch Number: P0169**
Date of Manufacture: 17 May 2002
Batch size: 500 g

Temperature: 15.5°C
Relative Humidity: 52%

Formula:

Propranolol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® Std 10	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

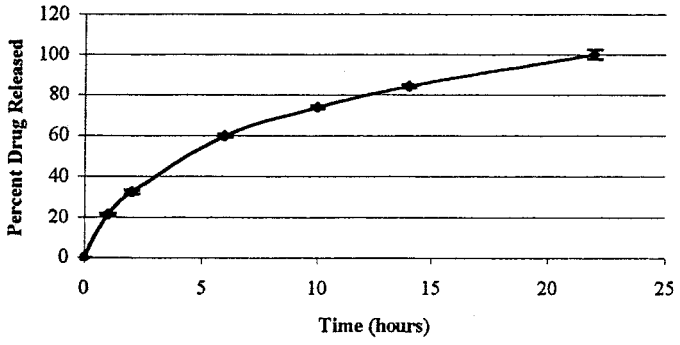
Physical Assessment:

	Mean	%RSD
Weight	713.8	0.82
Thickness	7.77	1.59
Diameter	11.25	0.05
Hardness	112.0	10.16

Friability (10 tablets)

Mass before test:	7.1826 g
Mass after test:	7.1756 g
Mass lost:	0.0070 g
Percentage lost:	0.0975%

Dissolution Rate Profile:



Residual Content: 10.31 ± 1.04 %

Batch Identification: 3% Talc, Ethocel® Std 20 **Batch Number: P0171**
Date of Manufacture: 17 May 2002
Batch size: 500 g **Temperature:** 15.5°C
Relative Humidity: 52%

Formula:

Propranolol hydrochloride	13.5	67.5 g
Methocel® K4M	6.8	34 g
Emcompress®	32.3	161.5 g
Emcocel® 90M	26.9	134.5 g
Ethocel® Std 20	2.8	14 g
Methocel® K100M	14	70 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

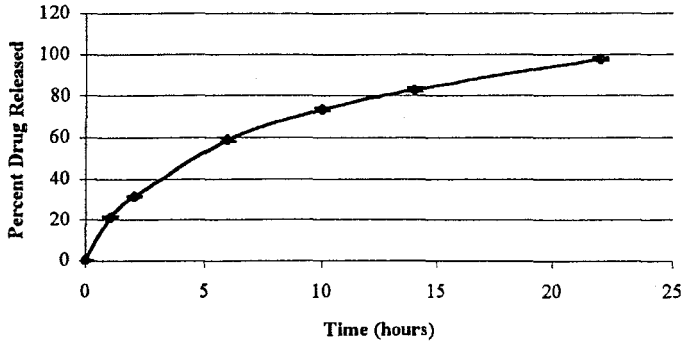
Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

	Mean	%RSD
Weight	713.2	2.88
Thickness	7.66	0.42
Diameter	11.24	0.05
Hardness	123.9	9.68

Friability (10 tablets)	
Mass before test:	6.9978 g
Mass after test:	6.9914 g
Mass lost:	0.0064 g
Percentage lost:	0.0915%

Dissolution Rate Profile:



Residual Content: 10.21 ± 0.78 %

Batch Identification: FP 10 (20% Ethocel®) **Batch Number: P0201**
Date of Manufacture: 07 August 2002
Batch size: 500 g **Temperature:** 12.5°C
Relative Humidity: 40%

Formula:

Propranolol hydrochloride	13.5	67.5 g
Methocel® K4M	5.8	29 g
Emcompress®	25	125 g
Emcocel® 90M	20	100 g
Ethocel® FP 10	20	100 g
Methocel® K100M	12	60 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

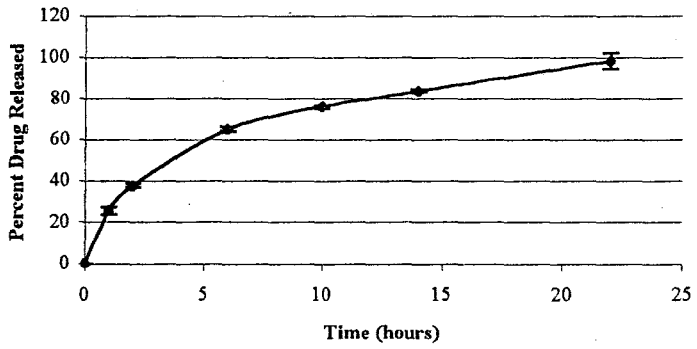
Physical Assessment:

	Mean	%RSD
Weight	629.6	5.57
Thickness	7.75	0.65
Diameter	11.24	0.08
Hardness	151.4	37.14

Friability (11 tablets)

Mass before test:	6.6083 g
Mass after test:	6.6025 g
Mass lost:	0.0058 g
Percentage lost:	0.0878%

Dissolution Rate Profile:



Residual Content: 8.14 ± 5.28 %

Batch Identification: Std 20 (20% Ethocel®) **Batch Number: P0203**
Date of Manufacture: 07 August 2002
Batch size: 500 g **Temperature:** 12.5°C
Relative Humidity: 41%

Formula:

Propranolol hydrochloride	13.5	67.5 g
Methocel® K4M	5.8	29 g
Emcompress®	25	125 g
Emcocel® 90M	20	100 g
Ethocel® Std 20	20	100 g
Methocel® K100M	12	60 g
Purified talc	3	15 g
Magnesium stearate	0.7	3.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

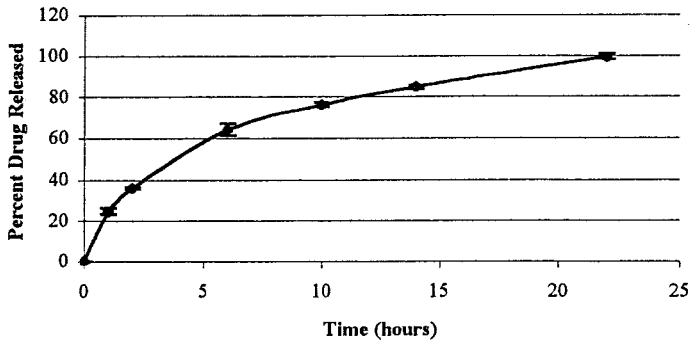
Physical Assessment:

	Mean	%RSD
Weight	707.5	2.62
Thickness	8.04	1.48
Diameter	11.24	0.08
Hardness	105.5	13.20

Friability (10 tablets)

Mass before test:	7.0495 g
Mass after test:	7.0447 g
Mass lost:	0.0048 g
Percentage lost:	0.0681%

Dissolution Rate Profile:



Residual Content: 9.71 ± 0.78 %

Batch Identification: Wet Granulation (10% EC) **Batch Number: P0215**
Date of Manufacture: 03 & 04 October 2002
Batch size: 690 g **Temperature:** 17.2°C
Relative Humidity: 49%

Formula:

Propranolol hydrochloride	20	100 g	
Methocel® K4M	10	50 g	Final Granule mass: 500 g
Emcompress®	37.5	187.5 g	
Emcocel® 90M	32.5	162.5 g	
Surelease®	0.4 g/g	200 g	
Methocel® K100M	20	100 g	
Emcocel® 90M	7	35 g	
Emcompress®	10	50 g	
Magnesium stearate	1	5 g	

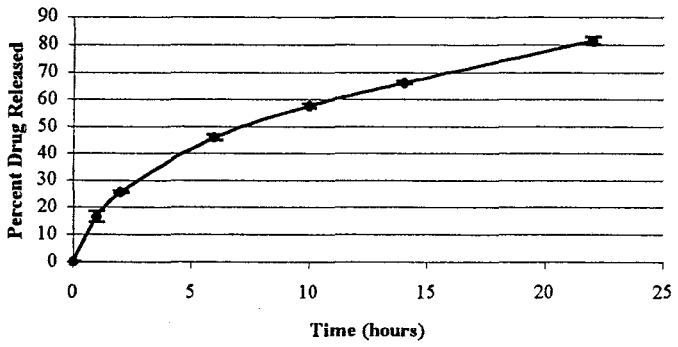
Target Weight: 720 mg
Target Hardness: 120 –160 N

Physical Assessment:

	Mean	%RSD
Weight	693.0	1.20
Thickness	7.40	0.52
Diameter	11.24	0.06
Hardness	121.9	3.57

Friability (10 tablets)	
Mass before test:	7.0084 g
Mass after test:	7.0080 g
Mass lost:	0.0004 g
Percentage lost:	0.0057%

Dissolution Rate Profile:



Residual Content: 10.64 ± 1.04 %

Batch Identification: Wet Granulation (5% EC) **Batch Number: P0217**
Date of Manufacture: 03 & 04 October 2002
Batch size: 662 g

Temperature: 17.2°C
Relative Humidity: 50%

Formula:

Propranolol hydrochloride	20	100 g	Final Granule mass: 480 g
Methocel® K4M	10	50 g	
Emcompress®	37.5	187.5 g	
Emcocel® 90M	32.5	162.5 g	
Surelease®	0.2 g/g	100 g	
Methocel® K100M	20	96 g	
Emcocel® 90M	7	33.6 g	
Emcompress®	10	48 g	
Magnesium stearate	1	4.8 g	

Target Weight: 720 mg
Target Hardness: 120 –160 N

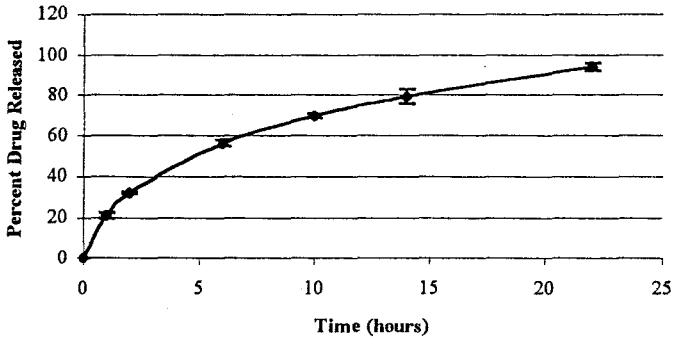
Physical Assessment:

	Mean	%RSD
Weight	655.9	1.61
Thickness	7.7.13	0.77
Diameter	11.24	0.08
Hardness	121.8	10.80

Friability (11 tablets)

Mass before test:	6.6194 g
Mass after test:	6.6184 g
Mass lost:	0.0010 g
Percentage lost:	0.0151%

Dissolution Rate Profile:



Residual Content: 12.85 ± 3.10 %

Batch Identification: Freeze-dried (14% EC solids) **Batch Number: P0257**
Date of Manufacture: 05 November 2002
Batch size: 182 g **Temperature:** 20.1°C
Relative Humidity: 35%

Formula:

Freeze-dried material	27.5	50 g
Methocel® K4M	6	11 g
Emcompress®	26	47.3 g
Emcocel® 90M	22.8	41.5 g
Methocel® K100M	14	25.5 g
Purified talc	3	5.5 g
Magnesium stearate	0.7	1.3 g

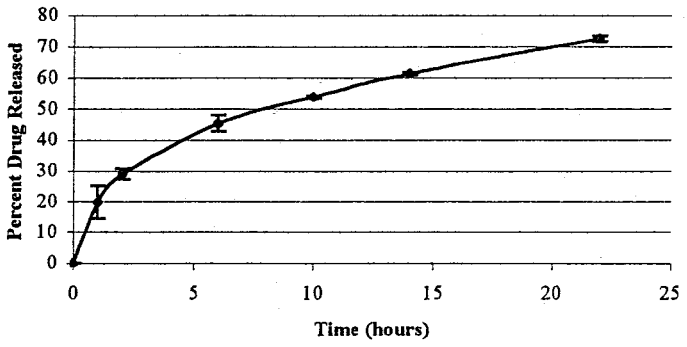
Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

	Mean	%RSD
Weight	526.4	12.54
Thickness	6.53	2.68
Diameter	11.20	0.09
Hardness	60.09	50.22

Freeze-dried Material: Propranolol hydrochloride 30 g
Surelease® 120 g (30 g ethylcellulose solids)

Dissolution Rate Profile:



Residual Content: 3.44 ± 1.53 %

Batch Identification: Freeze-dried (2.8% EC solids) **Batch Number: P0263**
Date of Manufacture: 06 November 2002
Batch size: 362 g **Temperature:** 18.2°C
Relative Humidity: 42%

Formula:

Freeze-dried material	16.3	59 g
Methocel® K4M	6.6	24.6 g
Emcompress®	32.3	117 g
Emcocel® 90M	26.9	97.4 g
Methocel® K100M	14	50.7 g
Purified talc	3	11 g
Magnesium stearate	0.7	2.5 g

Target Weight: 740 mg
Target Hardness: 120 –160 N

Physical Assessment:

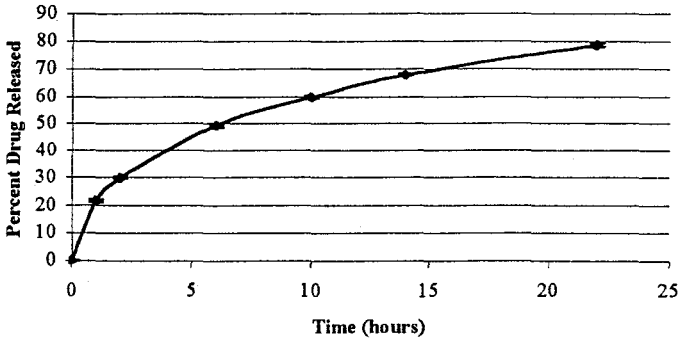
	Mean	%RSD
Weight	653.0	4.28
Thickness	6.87	2.78
Diameter	11.23	0.05
Hardness	93.66	12.55

Freeze-dried Material: Propranolol hydrochloride 70 g
Surelease® 58 g (14.5 g ethylcellulose solids)

Friability (11 tablets)

Mass before test:	7.0192 g
Mass after test:	7.0163 g
Mass lost:	0.0029 g
Percentage lost:	0.0413%

Dissolution Rate Profile:



Residual Content: 5.35 ± 1.88 %

REFERENCES

1. *Standard Treatment Guidelines and Essential Drugs List*, Essential Drugs Programme, South Africa, Hospital Level, Adults, 1998.

2. *Basic and Clinical Pharmacology*, Bertram G. Katzung (ed.), Appleton and Lange, 7th Edition 1998, pp 140-166.

3. *Martindale: The Extra Pharmacopoeia*, J.E.F Reynolds (ed.), The Royal Pharmaceutical Society, London, 30th Ed, 1993, pp 624-641.

4. *The South African Medicines Formulary*, C.J. Gibbon (ed.), South African Medical Association, Health and Medical Publishing Group, 2000, pp 136-141.

5. *The Merck Manual*, Donald F. de Korte (ed.), Merck and Co., 1992, pp 420-423, 469, 505, 513, 519, 1078, 1113, 1634, 2673.

6. S.A. Mostafavi, R.T. Foster. Pharmacokinetics of acebutolol enantiomers after intravenous administration of racemate in a rat model: a dosing range comparison. *Biopharm. Drug. Dispos.* **18**(5): 397-408 (1997)

7. C.G.M. Jordan. A study of the Relationship between the structure and Physicochemical Parameters of a homologous Series of Oxprenolol Esters at Various pH Values and Temperatures. *J. Pharm. Sci.* **86**(10): 1085-1091 (October 1997)

8. M. Piquette-Miller, R.T. Foster, C.T. Kappagoda. Pharmacokinetics of Acebutolol Enantiomers in Humans. *J. Pharm. Sci.* **80**(4): 313-316 (April 1991)

9. A. Karlsson, C. Pettersson. Determination of (R)- and (S)-propranolol in plasma by high-performance liquid chromatography using N-benzoxycarbonylglycyl-L-proline as chiral selector in the mobile phase. *J. Chromatography.* **494**: 157-171 (1989)

10. J.G. Riddell, D.W.G. Harron, R.G. Shanks. Clinical Pharmacokinetics of β-Adrenoceptor Antagonists. *Clin. Pharmacokinet.* **12**: 305-320 (1987)

11. J.J. McNeil, W.J. Louis. Clinical Pharmacokinetics of Labetalol. *Clin. Pharmacokin.* **9**: 157-167 (1984)

12. E. Gold, W. Chang, M. Cohen, T. Baum, S. Ehrreich, G. Johnson, N. Prioli and E.J. Sybertz. Synthesis and Comparison of Some Cardiovascular Properties of the stereoisomers of labetalol. *J. Med. Chem.* **25**: 1363-1370 (1982)

13. I. Darmansjah, A. Setiawati, P. Prabowo, E. Sukandar, I. Parsoedi, Ardaya, B. Bahry, J. Jusman and E. Anggraeni. A dose-ranging study of labetalol in moderate to moderately severe hypertension. *J. Clin. Pharm. Ther.* **33**(4): 226-231 (1995)

14. R.T. Foster, R.A. Carr. Acebutolol. *Analytical Profiles of Drug Substances.* **Volume 19,** K. Florey (ed.) Academic Press, New York, USA, pp 1-26.

15. *The Merck Index*, S. Budavari, M.J. O'Neil, A. Smith, P.E. Heckelman, J.F. Kinneary (eds.), Merck and Co., 1996 pp 4-5, 910, 1050, 1193, 1347-1348.

16. *United States Pharmacopoeia incorporating 'The National Formulary'*, United States Pharmacopoeial Convention, Maryland, 24th Ed, 1999, pp 15, 290, 843, 949, 1101, 1228, 1428, 1586, 2000, 2148-2152.

17. *Dictionary of Drugs, Chemical Data, Structures and Bibliographies*. J. Elks and C.R. Ganellin (eds.) Chapman and Hall Ltd., 1990, pp 2, 723, 817, 922, 1034.

18. J.R. Luch. Metoprolol Tartrate. *Analytical Profiles of Drug Substances*. **Volume 12,** K. Florey (ed.) Academic Press, New York, USA, pp 325-356.

19. *The British Pharmacopoeia*, The Stationery Office, London, 1998, pp 32, 768, 889, 971, 1103.

20. Propranolol Hydrochloride B.P/U.S.P. Http://www.chemicals-india.com/propranolol.html Retrieved 13/11/2001.

21. *Clark's Isolation and Identification of Drugs* 2nd Ed. A.C. Moffat (ed.) The Pharmaceutical Press, London, 1986, pp 309.

22. *Physical Pharmacy*, 4th Ed. A. Martin. Lea and Febiger, Philladelphia London, 1993, pp 399-418.

23. G.V. Betageri, J.A. Rogers. Thermodynamics of partitioning of β-blockers in the *n*-octanol-buffer and liposome systems. *Int. J. Pharm.* **36**: 165-173 (1987)

24. M.H. Barary, M.A. Elsayed, S.M. Mohamed. Spectrophotometric determination of hydralazine hydrochloride, oxprenolol hydrochloride and chlorthalidone in combination and for oxprenolol hydrochloride as single component dosage form. *Drug. Dev. Ind. Pharm.* **16**(9): 1539-1554 (1990)

25. P. Saha, K-J. Kim, H. Yamanara, E.D. Crandall and V.H. Lee. Influence of Lipophilicity on Beta Blocker Penetration Across Alveolar Epithelial Cell Monolayers. *J. Contr. Rel.* **32**(Dec 1): 191-200 (1994)

26. P.B. Woods, M.L. Robinson, E.R. Squibb & Sons Ltd. An investigation of the comparative liposolubilities of β-adrenoceptor blocking agents. *J. Pharm. Pharmacol.* **33**: 172-173 (1981)

27. *Martindale: Pharmaceutical Press*, K. Parfitt (ed.), The Royal Pharmaceutical Society, London, 32nd Ed, 1999, pp 809, 896, 907, 926, 937.

28. C.G. Regardh et al. Pharmacokinetic Studies on the Selective β_1-Receptor Antagonist Metoprolol in Man. *J. Pharmacokin. Biopharm.* **2**(4): 347-364 (1974)

29. http://www.pharmscitech.com/volume1issue2/013/manuscript.htm Retrieved 19/10/2002.

30. R.D. Schoenwald, H. Huang. Corneal Penetration Behavior of β-Blocking Agents I: Physicochemical Factors. *J. Pharm. Sci.* **72**(11): 1266-1272 (November 1983)

31. A-L Ungell. Personal Communication, August 2002.

32. W.A. Ritschel. Compilation of Pharmacokinetic Parameters of Beta-Adrenergic Blocking Agents. *Drug. Intel. Clin. Pharm.* **14**: 746-756 (November 1980)

33. R.J. Ruane, I.D. Wilson. The use of C_{18} bonded silica in the solid phase extraction of basic drugs – possible role for ionic interactions with residual silanols. *J. Pharm. Biomed. Anal.* **5**(7): 723-727 (1987)

34. *Applied Clinical Pharmacokinetics*. Dennis R. Mungall (ed.), Raven Press, New York, 1983, pp 1.

35. *British Pharmaceutical Codex*, The Pharmaceutical Society of Great Britain, The Pharmaceutical Press, London, 1973, pp 412.

36. A. El-Yazigi. Analysis of Oxprenolol in Formulations by High-Performance Liquid Chromatography. *J. Pharm. Sci.* **73**(6): 571-574 (June 1984)

37. L.V. Allen, Jr., M.A. Erickson III. Stability of labetalol, metoprolol tartrate, verapamil hydrochloride, and spironolactone with hydrochlorthiazide in extemporaneously compounded oral liquids. *Am. J. Health-Syst. Pharm.* **53**: 2304-2309 (October 1996)

38. P.C. Yuen, C.R. Taddei, B.E. Wyka and I.A. Chaudry. Compatibility and Stability of Labetalol Hydrochloride in Commonly used Intravenous Solutions. *Am. J. Hosp. Pharm.* **40**: 1007-1009 (1983)

39. P. Modamio, O. Montejo, C.F. Lastra and E.L. Marino. A valid high-performance liquid chromatography method for oxprenolol stability studies. *Int. J. Pharm.* **112**: 93-96 (1994)

40. S.A. Botha, A.P. Lotter. Compatibility study between oxprenolol hydrochloride, temazepam and tablet excipients using differential scanning calorimetry. *Drug. Dev. Ind. Pharm.* **16**(2): 331-345 (1990)

41. S.A. Botha, A.P. Lotter. Compatibility study between oxprenolol hydrochloride and tablet excipients using differential scanning calorimetry. *Drug. Dev. Ind. Pharm.* **15**(11): 1843-1853 (1989)

42. J.J. Gerber and A.P. Lötter. Compatability Study Between Propranolol Hydrochloride and Tablet Exciepients Using Differential Scanning Calorimetry. *Drug Dev. Ind. Pharm.* **19**(5): 623-629 (1993)

43. E.K. Iyer and H.P. Tipnis. Preformulation compatibility study between metoprolol tartrate and tablet excipients using differential scanning calorimetry(DSC). *Indisn J. Pharm. Sci.* **58**(1): 22-24 (1996)

44. M.H. Frick, R. Kala. Once Daily Versus Twice Daily Beta-blockers: Effects on Arrhythmias and Hypertension. *The Lancet.* September 13th: 588 (1980)

45. Package Insert, Lopressor® 100 Tablets, Novartis, South Africa. Published 22 January 1999.

46. J.J. McNeil et al. Pharmacokinetics and pharmacodynamic studies of labetalol in hypertensive subjects. *Br. J. Clin. Pharmac.* **8**: 157S-161S (1979)

47. R. Donnelly, G.J.A. Macphee. Clinical Pharmacokinetics and Kinetic-Dynamic Relationships of Dilevalol and Labetalol. *Clin. Pharmacokinet.* **21**(2): 95-109 (1991)

48. F. Jamali. Personal Communication. September 2002.

49. S.K. Yamashita, S.E. Walker, T. Choudhury and J. Iazzetta. Compatibility of selected critical care drugs during simulated Y-site administration. *Am. J. Health-Syst. Pharm.* **53**: 1048-1051 (May 1996)

50. R. Zaman, M.R. Wilkins, M.J. Kendall and D.B. Jack. The Effect of Food and Alcohol on the Pharmacokinetics of Acebutolol and its Metabolite, Diacetolol. *Biopharm. Drug. Dispos.* **5**: 91-95 (1984)

51. J. Kanto, H. Allonen, T. Kleimola and R. Mäntlyä. Pharmacokinetics of labetalol in healthy volunteers. *Int. J. Clin. Pharm. Ther. Tox.* **19**(1): 41-44-478 (1981)

52. *The Pharmacologic Basis of Therapeutics* 6th Ed. A. G. Gilman, L.S. Goodman and A. Goodman. MacMillan Publishing Co. Inc, London, 1980.

53. M. L'Estrange Orme. Clinical pharmacology and therapeutic uses of beta adrenergic blocking drugs. *Hosp. Formulary.* May: 366-383 (1978)

54. B.M. Silber, N.H.G. Holford, S. Riegelman. Dose-Dependent Elimination of Propranolol and its Major Metabolites in Humans. *J. Pharm. Sci.* **72**(7): 725-732 (July 1983)

55. A. Somogyi, R. Gugler. Drug Interactions with Cimetidine. *Clin. Pharmacokin.* **7**: 23-41 (1982)

56. R. Zaman, D.B. Jack, M.R. Wilkins and M.J. Kendall. Lack of Effect of Liver Disease on the Pharmacokinetics of Acebutolol and Diacetolol: a single dose study. *Biopharm. Drug. Dispos.* **6**: 131-137 (1985)

57. W.L. Nelson, M.J. Bartels. *N*-Dealkylation of Oxprenolol: Formation of 3-Aryloxypropane-1,2-diol, 3-Aryloxylactic Acid, and 2-Aryloxyacetic Acid Metabolites in the Rat. *J. Pharm. Sci.* **74**(1): 33-36 (January 1985)

58. D. Attwood, S.P. Agarwal. The surface activity and self-association of some β-adrenoceptor blocking agents in aqueous solution. *J. Pharm. Pharmacol.* **31**: 392-395 (1979)

59. S.S. Gottlieb. Underuse of Beta-Blockers in Cardiovascular Meds. *Am. J. Managed Care.* **6**(April Suppl. 6): S229-S302 (2000)

60. P. Modamio, C.F. Lastra, E.L. Marino. Error Structure for the HPLC analysis for atenolol, metoprolol and propranolol: a useful weighting method in parameter estimation. *J. Pharm. Biomed. Anal.* **17**: 507-513 (1998)

61. J.T. Collett, J.A. Hendrickson, Ch.Y.C. Chew, P.M. Shah, A.R. Laddu and B.N. Singh. Comparative beta-blocking potencies of acebutolol and propranolol relative to plasma drug levels. *Int. J. Clin. Pharm. Ther. Tox.* **19**(11): 473-478 (1981)

62. K.P. Devi, K.V. Ranga Rao, S. Baveja, M. Fathi and M. Roth. Zero-Order Release Formulation of Oxprenolol Hydrochloride with Swelling and Erosion Control. *Pharm. Res.* **6**(4): 313-317 (1989)

63. C.G.M. Jordan. How an Increase in the Carbon Chain Length of the Ester Moiety Affects the Stability of a Homologous Series of Oxprenolol Esters in the Presence of Biological Enzymes. *J. Pharm. Sci.* **87**(7): 880-885 (July 1998)

64. R. Gabriel. Circumoral paraesthesiae and labetalol. *Br. Med. J.* March 4th: 580 (1978)

65. R. Staughton, R. Stutton, M. Farrell. β-blockers, Autoimmunity and Rashes. *The Lancet.* September 13th: 581 (1980)

66. A.Y. Finlay, E. Waddington. Cutaneous reactions to labetalol. *Br. Med. J.* April 15th: 987 (1978)

67. R.W. Grange and E. Wilson Jones. Bullous lichen planus caused by labetalol. *Br. Med. J.* April 1st: 816-817 (1978)

68. *Encyclopedia of Pharmaceutical Technology, Vol. 2.* J. Swarbrick and J.C. Boylan. Marcell Dekker Inc., New York and Basel, 1990, pp 437-445.

69. *Waters Chromatography Columns and Supplies Catalogue 1999-2000.* Waters Corporation, USA, pp 44-55.

70. *Instrumental Methods of Analysis* 7th Ed. H.W. Willard, L.L. Merritt Jr, J.A. Dean, F.A. Settle Jr. Wadsworth Publishing Company, Belmont, California, 1988, pp 626-644.

71. G. Musch, Y. Buelens, D.L. Massart. A strategy for the determination of beta blockers in plasma using solid-phase extraction in combination with high-performance liquid chromatography. *J. Pharm. Biomed. Anal.* **7**(4): 483-497 (1989)

72. B.R. Patel, J.J. Kirschbaum, R.B. Poet. High-Pressure Liquid Chromatography of Nadolol and Other β-Adrenergic Blocking Drugs. *J. Pharm. Sci.* **70**(3): 336-338 (March 1981)

73. A.G. González, M.A. Herrador, A.G. Asuero. Hydrophobicity of β-adrenoceptor blocking agents: Study of correlations between retention in reversed-phase HPLC systems and octanol-water partition constants. *Int. J. Pharm.* **120**: 215-220 (1995)

74. G. Tamai, I. Morita, T. Masujima, H. Yoshida and H. Imai. Direct, Simultaneous Determination of Propranolol and its 4-Hydroxy Metabolite by Liquid Chromatography. *J. Pharm. Sci.* **73**(12): 1825-1827 (1984)

75. G. Nygard, W.H. Shelver and S.K. Wahba Khalil. Sensitive High-Pressure Liquid Chromatographic Determination of Propranolol in Plasma. *J. Pharm. Sci.* **68**(3): 379-381 (1979)

76. N.E. Basci, A. Temizer, A. Bozkurt and A. Isimer. Optimization of mobile phase in the separation of β-blockers by HPLC. *J. Pharm. Biomed. Anal.* **18**: 745-750 (1998)

77. P.K. Gupta, J.K.C. Lim, A.R. Zoest, F.C. Lam and C.T. Hung. Relative Bioavailability of Oral Sustained-Release and Regular-Release Oxprenolol Tablets at Steady-state. *Biopharm. Drug. Dispos.* **12**: 493-503 (1991)

78. A. Laicher and T. Profitlich. Influence of Tablet Formulation and Size on the *In-Vitro* Sustained Release Behaviour of Metoprolol tartrate from Hydrophilic Matrices. *Drug Dev. Ind. Pharm.* **21**(17): 1929-1939 (1995)

79. R. Wood. How to validate analytical methods. *Trends in Analytical Chemistry.* **18**(9 & 10): 624-632 (1999)

80. *Merck ChromBook 2000,* Merck, Darmstadt, Germany, pp39-65.

81. J.R. Lang and S. Bolton. A comprehensive method validation strategy for bioanalytical applications in the pharmaceutical industry – 1. Experimental considerations. *J. Pharm. Biomed. Anal.* **9**(5): 357-361 (1991)

82. H. Rosing, W.Y. Man, E. Doyle, A. Bult and J.H. Beijnen. Bioanalytical Liquid Chromatographic Method Validation. A Review of Current Practices and Procedures. *J. Liq. Chrom. & Rel. Technol.* **23**(3): 329-354 (2000)

83. G.C. Hokanson. A life Cycle Approach to the Validation of Analytical Methods during Pharmaceutical Product Development, Part I: The Initial Method Validation Process. *Pharm. Tech.* September: 118-130 (1994)

84. Krull and M. Swartz. Regulatory Review of Method Validation Protocols. *LCGC.* **18**(6): 620-625 (2000)

85. T.C. Paino and A.D. Moore. Determination of the LOD and LOQ of an HPLC Method Using Four Different Techniques. *Pharm. Tech.* October: 86-90 (1999)

86. *Quantitative Chemical Analysis*. Daniel C. Harris. W.H. Freeman and Company, San Francisco, 1982. pp 459-461.

87. *Vogel's Textbook of Quantitative Chemical Analysis* 5th Ed. G.H. Jeffery, J. Bassett, J. Mendham, R.C. Denney. Longman Scientific and Technical. John Wiley and Sons, Inc., New York 1989, pp 637-638.

88. *Introduction to Thermal Analysis, Techniques and Applications* 2nd Ed. M.E. Brown (ed.) Kuwer Academic Publishers, Netherlands, 2001, pp 55-90.

89. M.E. Brown, E.M. Antunes, B.D. Glass, M. Labete and R.B. Walker. DSC Screening of Potential Prochlorperazine-Excipient Interactions in Preformulation Studies. *J. Therm. Anal. Calorimetry.* **56**: 1317-1322 (1999)

90. *The Development and Assessment of Both a Separate, Once-Daily Modified Release Matrix Formulation of Metoprolol Tartrate and a Combination Formulation with Hydrochlorothiazide.* J. Arjun, MSc. Thesis, 2001.

91. S.K. Baveja and K.V. Ranga Rao. Sustained release tablet formulation of centperazine. *Int. J. Pharm.* **31**: 169-174 (1986)

92. J.L. Ford, K. Mitchell, D. Sawh, S. Ramdour, D.J. Armstrong, P.N.C. Elliot, C. Rostron and J.E. Hogan. Hydroxypropylmethylcellulose matrix tablets containing propranolol hydrochloride and sodium dodecyl sulphate. *Int. J. Pharm.* **71**: 213-221 (1991).

93. B.J. Lee, S-G. Ryu and J-H. Cui. Formulation and Release Characteristics of Hydroxypropyl Methylcellulose Matrix Containing Melatonin. *Drug Dev. Ind. Pharm.* **25**(4): 493-501 (1999)

94. J.L. Ford, M.H. Rubinstein and J.E. Hogan. Formulation of sustained release promethazine hydrochloride tablets using hydroxypropylmethylcellulose matrices. *Int. J. Pharm.* **24**: 327-338 (1985)

95. I. Borst, S. Ugwu and A. Beckett. New and Extended Applications for USP Drug Release Apparatus 3. Dissolution Technologies, 4(1) February 1997.

96. L.F. Kieser and R.B. Walker. Dissolution Testing of Metoprolol Tartrate Sustained Release Matrix Tablets: Comparison of USP Apparatus 2 (paddles) and 3 (BIO-DIS). Presented at the Annual Meeting of the Controlled Release Society, Seoul, Korea, July 2002.

97. J.W. Moore and H.H. Flanner. Mathematical Comparison of Dissolution Profiles. *Pharm Tech.* **20**(6): 64-74 (1996)

98. M.E. Sangalli, P. Giunchedi, L. Maggi, U. Conte and A. Gazziniga. Inert Monolithic Device with a Central Hole for Constant Drug Release. *Eur. J. Pharm. Biopharm.* **40**(6):370-373 (1994)

99. B. Gander, R. Gurny and E. Doelker. Crosslinked poloxamers as a versatile monolithic drug delivery system. *Pharmaceutical Technology: Controlled Drug Release, Vol 1.* M.H. Rubinstein (ed.), Ellis Horwood Ltd, 1987, pp 34-40.

100. *Drug Delivery Systems, Characteristics and Biomedical Applications.* R.C. Juliano (ed.). Oxford University Press, Inc. New York, 1980, pp 3-83.

101. K.V. Ranga Rao and K. Padmalatha Devi. Swelling controlled-release systems: recent developments and applications. *Int. J Pharm.* **48**: 1-13 (1988)

102. J.W. Mauger, D. Chilko and S. Howard. On the Analysis of Dissolution Data. *Drug. Dev. Ind. Pharm.* **12**: 969-992 (1986)

103. A. Rescigno. Bioequivalence. *Pharm. Res.* **9**: 925-928 (1992)

104. W.D. Linder and B.C. Lippold. Drug release from hydrocolloid embeddings with high or low susceptibility to hydrodynamic stress. *Pharm. Res.* **12**: 1781-1785 (1995)

105. V.P. Shah et al. In Vitro Dissolution Profile Comparison – Statistics and Analysis of the Similarity Factor f_2. *Pharm. Res.* **15**(6): 889-996 (1998)

106. M.C. Gohel and M.K. Panchal. Comparison of In Vitro Dissolution Profiles Using a Novel Model-Independent Approach. *Pharm. Tech.* **24**(3): 92-102 (2000)

107. M.C. Gohel and M.K. Panchal. Novel Use of Similarity Factors f_2 and S_d for the Development of Diltiazem HCl Modified Release Tablets Using a 3^2 Factorial Design. *Drug Dev. Ind. Pharm.* **28**(1): 77-87 (2002)

108. Review of Pharmaceutical Controlled Release Methods and Devices. Paul A. Steward, 1995, http://www.initium.demon.co.uk/rel_nf.html Retrieved 09/04/2001.

109. *Introduction to Pharmaceutical Dosage Forms* 3rd Ed. Howard C. Ansel. Lea & Febiger, Philladelphia, USA. 1981, pp 189-219.

110. *Oral Sustained Release Formulations, Design and Evaluation*. A. Yacobi and E. Halperin-Walega, Pergamon Press, 1988, pp 39-45.

111. M.L. González-Rodriguez, J.I. Pérez-Martínez, S. Merino, A. Fini and A.M. Rabasco. Channeling Agent and Drug Release from a Central Core Matrix Tablet. *Drug Dev. Ind.Pharm.* **27**(5): 439-446 (2001)

112. *Controlled Drug Delivery, Drugs in the Pharmaceutical Sciences, Vol. 29*. J.R. Robinson and V.H.L. Lee (eds.). Marcell Dekker Inc, New York and Basel, 1987 pp 180-210.

113. H-W. Hui, J.R. Robinson and V.H.L. Lee. Design and Fabrication of Oral controlled Release Systems. Controlled Drug Delivery, 2nd Ed. J.R. Robinson and V.H.L. Lee (eds.) Marcell Dekker Inc, New York and Basel, 1987, pp 373-432.

114. *Rate-Controlled Drug Administration and Action*. H.A.J. Struyker-Boudier. CRC Press Inc, Florida USA, 1986, pp 15-47.

115. *Oral ER Technology: Mechanism of Release*. P.I. Lee. Scientific Foundations for Regulating Drug Product Quality. G.L. Amidon, J.R. Robinson and R.L. Williams (eds.), AAPS Press, USA, 1997, pp 221-230.

116. K. Sako, T Sawada, H. Nakashima, S. Yokohama and T Sonobe. Influence of water soluble fillers in hydroxypropylmethylcellulose matrices on *in vitro* and *in vivo* drug release. *J. Controlled. Rel.* **81**: 165-172 (2002)

117. S. Senel, Y. Capan and A.A. Hncal. Factors affecting the formulation of sustained release potassium chloride tablets. *Pharmaceutical Technology: Controlled Drug Release, Vol 2*. J.I. Wells and M.H. Rubinstein (eds.), Ellis Horwood Ltd, 1991, pp 34-43.

118. A.R. Fassihi and M.S. Parker. Controlled drug release from a compressed heterogenous polymeric matrix: kinetics of release. *Pharmaceutical Technology: Controlled Drug Release, Vol 1*. M.H. Rubinstein (ed.), Ellis Horwood Ltd, 1987, pp 64-71.

119. S.N. Makhija and P.R. Vavia. Once daily sustained release tablets of venlafaxine, a novel antidepressant. *Eur. J. Pharm. & Biopharm.* **54**: 9-15 (2000)

120. *Sustained Release Medications*, Chemical Technology Review, No. 177. J.C. Johnson (ed.). Noyes Data Corporation, New Jersey, USA, 1980, pp 96-113.

121. *Controlled Release Delivery Systems*. T.J. Roseman and S.Z. Mansdorf (eds.) Marcell Dekker Inc, New York and Basel, 1983, pp 77-90.

122. R.W. Korsmeyer, R. Gurny. E.Doelker, P. Buri and N.A. Peppas. Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm.* **15**: 25-35 (1983)

123. J.E. Möckel and B.C. Lippold. Zero-order Drug Release from Hydrocolloid Matrices. *Pharm. Res.* **10**(7): 1066-1070 (1993)

124. *Remington: The Science and Practice of Pharmacy* 9th Ed. Alfonso R. Gennaro (ed.) Mack Publishing Company, Easton, Pennsylvania, 1995, pp 1615-1649.

125. *The Handbook of Pharmaceutical Excipients* 2nd Ed. Ainley Wade and Paul. J. Weller (eds.). London Pharmaceutical Press, 1994, pp 56-60, 84-87, 195-200, 280-282, 229-231, 424-427, 519-521.

126. S.K. Baveja, K.V. Ranga Rao and K. Padmalatha Devi. Zero-order hydrophilic matrix tablets of β-adrenergic blockers. *Int. J. Pharm.* **39**: 39-45 (1987)

127. S.K. Baveja, K.V. Ranga Rao, and K.Padmalatha. Devi. Relationship between gum content and half-life of soluble β-blockers from hydrophilic matrix tablets. *Int. J. Pharm.* **47**: 133-139 (1988)

128. J.L. Ford, M.H. Rubinstein and J.E. Hogan. Propranolol hydrochloride and aminophylline release from matrix tablets containing hydroxypropylmethylcellulose. *Int. J. Pharm.* **24**: 339-350 (1985)

129. Material Safety Data Sheet for Surelease®, 2000, Colorcon.

130. Z. Iqbal, A. Babar and M. Ashraf. Controlled-Release Naproxen Using Micronized Ethyl Cellulose by Wet-Granulation and Solid-Dispersion Method. *Drug Dev. Ind. Pharm.* **28**(2): 129-134 (2002)

131. Ethocel® Premium Polymers for Pharmaceutical Applications Product Information Leaflet. The Dow Chemical Company.

132. D.K. Pollock and P.J. Sheskey. Evaluation of Fine Particle Size Ethocel® polymer for use in Controlled-Release Matrix Drug Delivery. The Dow Chemical Company. Presented at the 23rd International Symposium on Controlled Release of Bio Active Materials, Kyoto, Japan, July 1996.

133. B. Huet de Barochez, J.S. Julien, F. Lapeyre, S. Horvath and A. Cuiné. Influence of drug solubility in the formulation of hydrophilic matrices. *Pharmaceutical Technology: Controlled Drug Release, Vol 2*. J.I. Wells and M.H. Rubinstein (eds.), Ellis Horwood Ltd, 1991, pp 13-22.

134. M. Kramer, B. Sennhenn and G. Lee. Freeze-Drying Using Vacuum-Induced Surface Freezing. *J. Pharm. Sci.* **91**(2): 433-443 (2002)

135. V. Pillay and M.P. Danckwerts. A Novel Approach for Textural Profiling of Polymeric Drug Delivery Systems. Presented at the 3rd International Conference on Pharmaceutical and Pharmacological Sciences, Boksburg, South Africa, September, 2002.

136. H. Mahayni, G.S. Rekhi, R.S. Uppoor, P. Marroum and N.D. Eddington. Evaluation of "External" Predictability of an *In Vitro-In Vivo* Correlation for an Extended Release Formulation Containing Metoprolol Tartrate. *J. Pharm. Sci.* **89**(Oct): 1354-1361 (200)

137. *Scale-Up of Oral Extended-Release Dosage Forms*. AAPS/FDA Workshop Committee Report. *Pharm. Tech.* May: 46-54 (1995)

138. N.D. Eddington, P. Marroum, R. Uppoor, A. Hussain and L. Augsburger. Development and Internal Validation of an *In Vitro-In Vivo* Correlation for a hydrophilic Metoprolol Tartrate Extended Release Tablet Formulation. *Pharm. Res.* **15**(March): 466-473 (1998)