FORMULATION AND ASSESSMENT OF VERAPAMIL SUSTAINED RELEASE TABLETS

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By

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ABSTRACT

The oral route of drug administration is most extensively used due to the obvious ease of administration. Verapamil hydrochloride is a WHO listed phenylalkylamine, L-type calcium channel antagonist that is mainly indicated for cardiovascular disorders such as angina pectoris, supraventricular tachycardia and hypertension. Due to its relatively short half-life of approximately 4.0 hours, the formulation of a sustained-release dosage form is useful to improve patient compliance and to achieve predictable and optimized therapeutic plasma concentrations.

Direct compression and wet granulation were initially used as methods for tablet manufacture. The direct compression method of manufacture produced tablets that exhibited formulation and manufacturing difficulties. Mini-tablets containing verapamil hydrochloride were then prepared by wet granulation using Surelease® E-7-19010 and Eudragit® NE 30D as the granulating agents after which the granules were incorporated with an hydrophilic matrix material, Carbopol® 974P NF. Granule and powder blends were evaluated using the angle of repose, loose and tapped bulk density, Carr's compressibility index, Hausner's ratio and drug content. Granules with good flow properties and satisfactory compressibility were used for further studies.

Tablets were subjected to thickness, diameter and weight variation tests, crushing strength, tensile strength, friability and content uniformity studies. Tablets that showed acceptable pharmaco-technical properties were selected for further analysis. Drug content uniformity and dissolution release rates were determined using a validated isocratic HPLC method.

Initially, USP apparatus 1 and 3 dissolution apparatus were used to determine *in-vitro* drug release rates from the formulations over a 22-hour period. USP apparatus 3 was finally selected as it offers the advantages of mimicking, in part, the changes in the physicochemical environment experienced by products in the gastro-intestinal tract.

Differences in release rates between the test formulations and a commercially available product, Isoptin® SR were observed at different pH's using USP apparatus 1. The release of verapamil hydrochloride from matrix tablets was pH dependent and was markedly reduced at higher pH values. This may be due, in part, to the poor solubility of verapamil hydrochloride

at these pH values and also the possible interaction of verapamil hydrochloride with anionic polymers used in these formulations.

Swelling and erosion behaviour of the tablets were evaluated and differences in behaviour were observed which may be attributed to the physico-chemical characteristics of the polymers used in this study.

In-vitro dissolution profiles were characterized by the difference (f_1) and similarity factor (f_2) and also by a new similarity factor, S_d. In addition, the mechanism of drug release from these dosage forms was mainly evaluated using the Korsmeyer-Peppas model and the kinetics of drug release assessed using other models, including Zero order, First order, Higuchi, Hixson-Crowell, Weibull and the Baker-Lonsdale model.

Dissolution kinetics were best described by application of the Weibull model, and the Korsmeyer-Peppas model. The release exponent, n, confirmed that drug release from these dosage forms was due to the mixed effects of diffusion and swelling and therefore, anomalous release kinetics are predominant.

In conclusion, two test batches were found to be comparable to the reference product Isoptin® SR with respect to their *in-vitro* release profiles.

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STUDY OBJECTIVES

The population of patients with chronic conditions or complications of other disease is increasing [1]. Chronically ill patients take a number of medicines to treat their conditions, which may lead to non-compliance and non-adherence to the prescribed dosage regimen.

Verapamil hydrochloride (VRP) is a World Health Organization (WHO) and South African Medicines Formulary (SAMF) listed drug that is indicated for the treatment of several cardiovascular diseases, particularly angina pectoris, supraventricular tachyarrhythmias and hypertension [2]. These cardiovascular diseases are common and patients with these conditions require constant monitoring. VRP is available in 120-, 180-, and 240 mg extended release tablets. It has a short biological half-life and therefore is suitable for formulation as a sustained-release product in order to reduce the frequency of administration of doses and to improve patient compliance.

The purposes of this study were therefore:

1. To develop and validate a suitable high performance liquid chromatographic (HPLC) method for the determination of verapamil hydrochloride.
2. To investigate the possibility of using Surelease® E-7-19010 and Eudragit® NE 30D as granulating fluids in preparing VRP matrix tablets containing Carbopol® 974P NF and Methocel® K100M as primary matrix polymers.
3. To evaluate the release of VRP from the dosage form developed using an appropriate dissolution test procedure.
4. To study the drug dissolution kinetics and release mechanisms for the matrix tablets prepared using Carbopol® 974P NF.
5. To identify key aspects of the formulation that needs further study.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER ONE

REVIEW OF A CALCIUM CHANNEL BLOCKER CANDIDATE

1.1 INTRODUCTION

Recent advances in cardiovascular drug therapy are unparalleled in medical history. As a result of an increased understanding of the pathophysiology and molecular biology of cardiovascular diseases, new, more effective cardiovascular drugs have been developed and their success in preventing and treating cardiovascular disease is well documented [3].

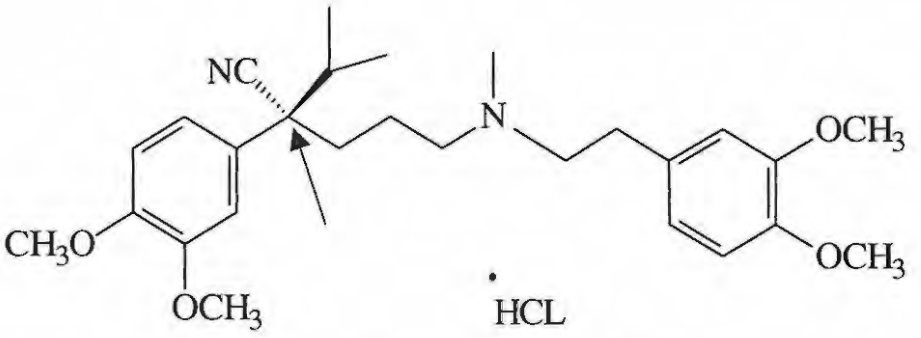
The prevalence of cardiovascular diseases varies with age, race and education, amongst other variables [4]. Therefore, it is essential that today's pharmaceutical scientists keep up-to-date with the latest developments with respect to manufacturing these 'life saving agents'. Verapamil hydrochloride is a WHO listed drug that is indicated for the treatment of several cardiovascular diseases, including angina pectoris, supraventricular tachyarrhythmias and hypertension, amongst others. These cardiovascular diseases are common and they need constant monitoring. Verapamil hydrochloride is available as 40-, 80- and 120 mg immediate release products and as 120-, 180- and 240 mg extended release tablets. It has a short half-life [2] and is therefore suitable for inclusion in a sustained-release formulation. These products would reduce the frequency of administration and improve patient compliance.

1.2 PHYSICO-CHEMICAL PROPERTIES

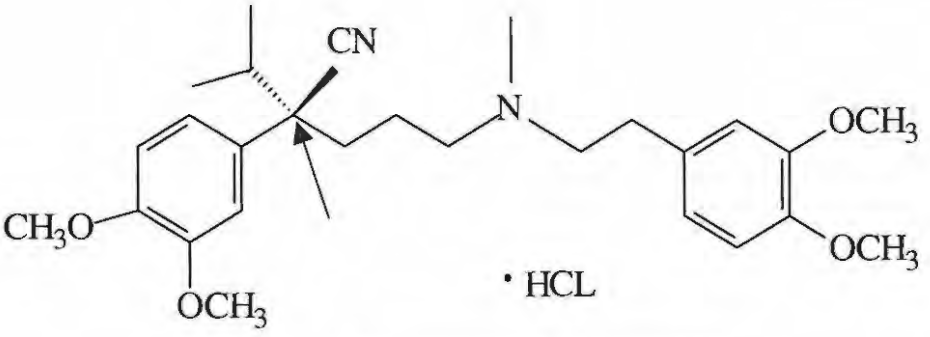
1.2.1 Description

Verapamil hydrochloride (VRP) is a white, practically odourless, crystalline powder [5-7]. It contains not less than 99.0% and not more than 101.0% of racemic VRP, determined with reference to the dried substance [5]. The chemical structures of the two VRP isomers are depicted in Figure 1.1 and the compound is known as;

- 5-[N-(3,4-dimethoxyphenethyl) methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile hydrochloride [7]
- α-[3-[[2-(3,4-Dimethoxyphenyl) ethyl]-methylamino] propyl]-3,4-dimethoxy-α-(1-methylethyl) benzeneacetonitrile hydrochloride [8]
- α-isopropyl-α-[(N-methyl-N-homoveratryl)-γ-aminopropyl]-3,4-dimethoxyphenylacetonitrile hydrochloride [8]



(S) verapamil hydrochloride



(R) verapamil hydrochloride

where ⟶ indicates a chiral carbon.

Figure 1.1. Chemical structure of VRP isomers [($C_{27}H_{38}N_2O_4$, HCl)] (MW = 491.1).

1.2.2 Optical Rotation

A 1% methanolic solution of VRP exhibited no optical activity when measured at 589 nm in a 1dm cell at 25°C [9].

1.2.3 pH of Solution

The pH of a 0.1 % aqueous solution of VRP is 4.5-6.0 [5, 10].

1.2.4 Solubility (21°C)

The solubility of VRP as a function of pH is depicted in Figure 1.2 and Table 1.1 lists the solubility of the compound in a variety of solvents. The solubility is approximately 80-90 mg/ml in solution of pH 2.3 to 6.4, where the ionized species predominates, which decreases rapidly in alkaline pH. The solvent used was water and adjusted to the desired pH using 0.1N NaOH and 0.1N HCl solutions for this study [9].

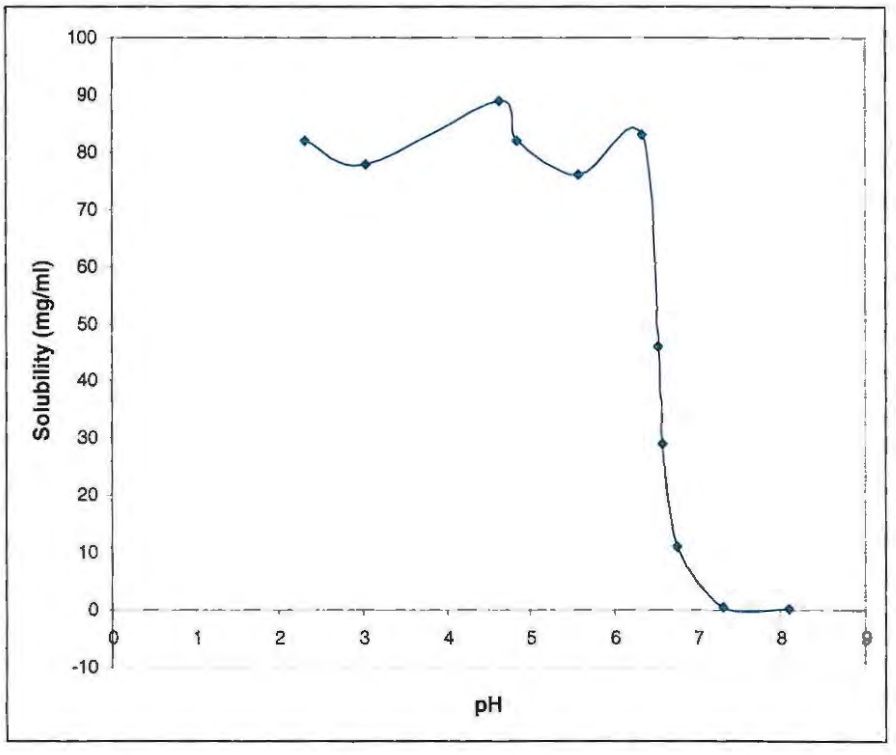


Figure 1.2. Solubility of VRP as a function of pH.

Table 1.1. Solubility of VRP in a variety of solvents.

Solvent	Solubility (mg/ml)	Reference
Water	83	9, 10
Ethanol	26	9, 10
Propylene glycol	93	9
Ethanol	> 100	9, 10
Methanol	> 100	9, 10
2-Propanol	4.6	9
Ethylacetate	1.0	9, 10
Dimethyl formamide	> 100	9, 10
Methylene chloride	> 100	9
Hexane	0.001	9

1.2.5 pK_a

Titration of VRP (dissolved in methanol – water) with 0.1N potassium hydroxide (KOH) in methanol yielded a pK_a value of 8.6 on extrapolation to pure water [9].

1.2.6 Hygroscopicity

A sample of VRP exposed to 79% relative humidity at room temperature for 24 hours, absorbed 0.47% w/w moisture, indicating that VRP is not hygroscopic [9].

1.2.7 Ultraviolet Absorption Spectrum

A 0.002% solution of VRP in methanol yielded two wavelengths of maximum absorption, which occur at 230 nm (ε = 16 700) and 278 nm (ε = 6 090) [9, 10]. Das Gupta [8] reported and measured the lamda max of 278 nm for VRP in water.

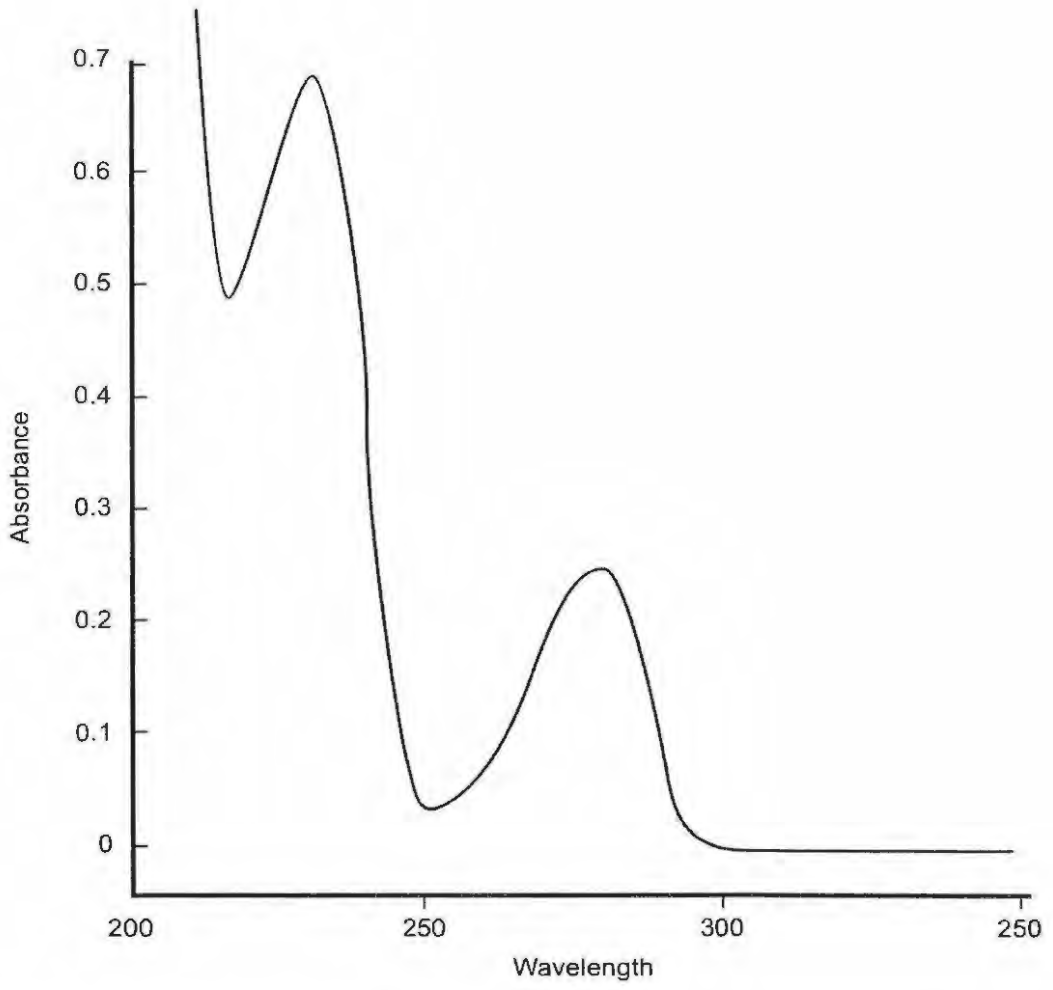


Figure 1.3. UV absorption spectrum of VRP in Methanol [9].

1.2.8 Melting range

VRP melts over a 1-4°C temperature range that occurs between 140-144°C [9].

1.3 SNYTHETIC PATHWAY

1.3.1 Synthetic Procedure

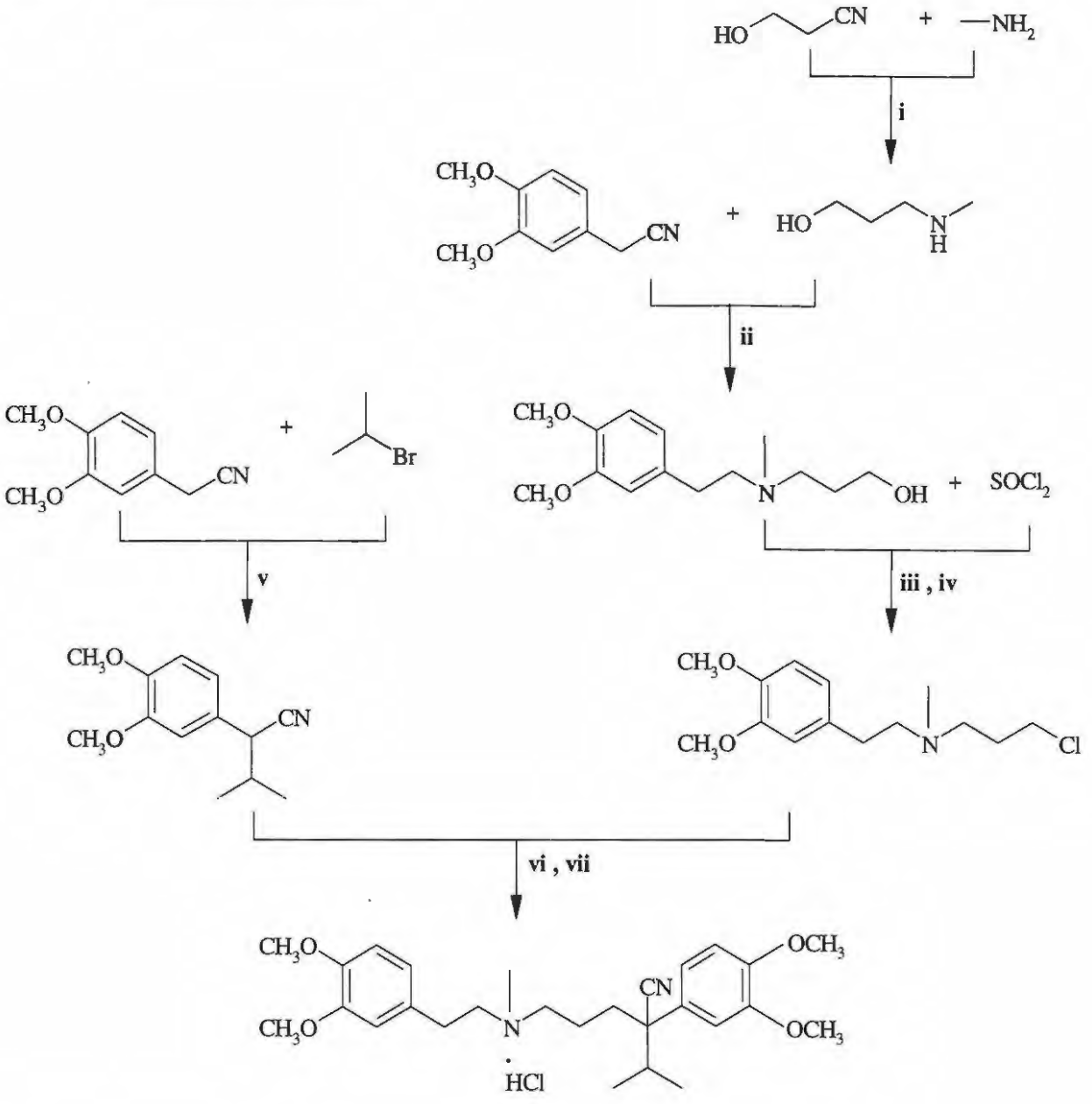


Figure 1.4. Pathway of synthesis of VRP.

where,

i = H_2, 5% Pd /Al_2O_3 ii = H_2, 20% Pd / C iii = CH_2Cl_2

iv = NaOH-H_2O v = Sodium Amide Toluene

vi = Sodium Amide Toluene

vii = Hydrochloric Acid

1.3.2 Stereospecificity

The presence of a chiral centre in VRP (Figure 1.1) results in the presence of stereoisomers, and in all the commercially available formulations, VRP is present as a racemic mixture, *i.e.*, R and S enantiomers [6, 7]. Many of the antiarrhythmic drugs introduced onto the market during the past three decades have a chiral centre in their structures and are consequently made available as racemates [11]. There is substantial stereoselectivity in one or more of the pharmacological actions of VRP, with the activity of each enantiomer differing by as much as 20-fold or more for this drug. Biological absorption of chiral VRP appears to be non-stereoselective, however, distribution, metabolism and renal excretion usually favour one enantiomer over the other [11].

1.3.3 Structure Activity Relationship

There is a dearth of structure-activity relationship (SAR) studies on calcium channel antagonists despite the wealth of data published in the literature [12-15]. Mannhold *et al* [13] reported that the methoxy groups on the benzene ring near the asymmetric carbon atom and the isopropyl group are not essential for the frequency-dependent negative inotropic action of VRP, but do have a strong influence on the potency of the compound. Both the tertiary amino nitrogen and the two benzene rings are essential for the frequency-dependent negative inotropic action of VRP. The molecular importance of the N-methyl group is probably due to its influence on steric effects in the molecule.

1.4 STABILITY

VRP is stable under high-stress thermal and photo-chemical conditions when exposed in the solid state. It is also stable under neutral, acidic and basic aqueous reflux conditions. However, when VRP is dissolved in methanol and subjected to UV irradiation for 2 hours, it degrades rapidly [9].

VRP, in solutions of different pH, did not decompose after 105 days when stored at 50°C. Q_{10} values were used to approximate the long term stability of VRP in solution and it was estimated to be stable for 4.5 years, although 5% w/v decomposition was reported in solutions of pH 1.4, 6.5 and 7.3. The optimum pH range of VRP has been reported to be from 3.2 to 5.6 [8].

Allen and Erickson [16] studied the stability of an oral liquid dosage form of VRP and reported that the solutions were stable for up to 60 days when stored at between 5°C and 25°C in the absence of light.

1.5 CLINICAL PHARMACOLOGY

1.5.1 Mechanism of Action

VRP was the first clinically available calcium-channel blocker, and is a congener of papaverine [17], which is an alkaloid found in the opium poppy and has vasodilator activity [4].

There are four distinct types of voltage-gated calcium channels, *viz.* L, N, T and P. The therapeutic calcium (Ca^{2+}) blockers developed to date have been almost exclusively L-type channel blockers. It is likely that screening methods used to assess activity are able to determine L-type channel blockers only, which is the reason that almost all calcium channel blockers developed to date interact only with the L-channel [4]. However, intensive studies are currently underway to develop selective blockers of neuronal calcium channels in the hope that more effective and selective drugs may be discovered for the prevention of brain injury following stroke [4]. VRP is known to act on the L-voltage-gated calcium channels [4].

Voltage-gated channels are distinguishable mainly on the basis of the voltage range over which they open, their tendency to close and remain inactive during maintained depolarization, their single channel conductance and their prevalence in different types of tissues [6]. The different types of calcium channel undoubtedly represent distinct membrane proteins and at present only a fragmentary knowledge of their physiological functions are understood [6].

The L-type calcium channel is the most dominant type of system found in cardiac and smooth muscle tissues, which are known to contain several receptors. These receptor regions are more than likely stereoselective, as marked differences in the R and S stereoisomer-binding affinity and pharmacologic potency are observed for the R and S enantiomers of VRP respectively [4].

Two groups of drugs, the dihydropyridines and non-dihydropyridines are known to block the L-voltage-gated channels. The dihydropyridines tend to have greater effects on the peripheral

vasculature than on the heart [11], whereas the non-dihydropyridines have greater effects on cardiac myocytes, as well as exhibiting pronounced inhibitory effects on the sinus and AV nodal conducting systems [17].

From a functional point of view, cardiac muscles may be divided into three major masses, *viz.* the atrial muscle, the ventricular muscle, and the specialised muscular tissue, which is adapted to conduct excitation throughout the myocardium rather than to contract [18].

The contractile mechanism of smooth muscle, such as those of the skeletal and cardiac muscle, is dependent on Ca^{2+} activated myosin ATPase [4, 18]. Coronary dilator drugs appear to act by depriving the contractile mechanism of Ca^{2+} ions. VRP acts by blocking the transport of Ca^{2+} ions across the plasma membrane of smooth muscle cells, and also blocks the transport of Ca^{2+} into cardiac muscle cells, therefore, causing cardiac depression [4, 6, 18, 19].

The distribution of free small ions such as sodium (Na^+), calcium (Ca^{2+}) and potassium (K^+), across the membranes of resting cardiac ventricular muscle cells resembles that of other excitable tissues and their internal: external concentration rates are depicted in Table 1.2.

Table 1.2. Distribution of cations across resting cardiac ventricular muscle membranes.

	Concentration mmol/L)	
Ion	**Internal**	**External**
Na^+	18	110
Ca^{2+}	0.0002	2
K^+	90	2.5

The resting membrane is relatively impermeable to Na^+ and Ca^{2+}, but is highly permeable to K^+ [18], which results in an unequal distribution of ions between the internal and external environment. In this instance, K^+ is more concentrated in the intracellular fluid, and Na^+ and Ca^{2+} in the extracellular fluid [18]. Direct measurement of the ventricular fibre resting potential with microelectrodes reveals that there is a potential of approximately -80 to -90 mV. When the membrane of a ventricular muscle cell is depolarised, there is a fall in membrane potential to about -70 mV [18]. The rapid upstroke of the action potential is mainly a consequence of sodium gate opening and the membrane becoming highly permeable to Na^+ ions, which enter the membrane fibres carrying positively charged ions into the cell [4,

18]. There is some evidence that a fast Ca^{2+} current contributes to a small extent to the rapid rise in the action potential. At the peak of the action potential, the membrane potential is reversed to a value of approximately +30 mV. The rapid initial inward sodium current is quickly deactivated, and the sodium gates close, with subsequent membrane repolarization. However, a secondary slower inward current of Ca^{2+} gives rise to a plateau of the action potential and interrupts the repolarization process. The positively charged ions carrying the secondary slower inward current pass through different channels from those carrying the initial rapid inward current and the slow inward current is carried mainly by Ca^{2+} through specific calcium channels [4, 18].

Inactivation of the secondary slow inward current is followed by an increased permeability of the membrane to K^+ and thus the membrane repolarizes. An action potential, once initiated, passes emphatically from cell to cell, and travels throughout the whole of the muscle mass at velocities that range from 0.5 to 4 m/sec in different parts of the myocardium [18].

Metal ions such as manganese (Mn^{2+}), cobalt (Co^{2+}) and indium (In^{3+}) also block the entry of Ca^{2+} during the plateau phase of the action potential, and produce a considerable depression of contractility when given in large doses. Therefore, a large intake of these salts may cause a chronic form of cardiac failure and this has been observed in heavy beer drinkers when cobalt chloride has been used as a foam-stabilising additive in beer [18].

1.5.2 Clinical Use

VRP is a class IV anti-arrhythmic agent primarily used in the control of supraventricular tachyarrhythmias, classical and variant angina pectoris and in the management of hypertension [2, 4, 17, 19, 20]. When VRP is combined with a ß-adrenergic antagonist, therapy is more effective in lowering blood pressure than when either drug is used alone. However, as might be expected, the combination may have synergistic effects on the PR interval of an electrocardiogram and, as a consequence, this combination should be avoided [17].

VRP may be effective in the treatment of sporadic hemiplegic and familial hemiplegic migraine [21]. Cluster headache is an uncommon, yet well-defined neurovascular syndrome occurring in both episodic and chronic varieties for which VRP has been reported to be the cornerstone drug for prophylaxis [22]. It has been used (off label) in post-infarct protection when beta blockade is contraindicated and in the absence of clinical congestive heart failure

[2]. VRP has been shown to be as effective as an angiotensin converting enzyme [ACE] inhibitor, in reducing albumin secretion and therefore has been successfully used in the management of diabetic nephropathy when [ACE] inhibitors and angiotensin receptor blockers [ARB] are contraindicated [23]. In a study by Wisner *et al* [24], VRP was found to be effective in the treatment of bipolar disorders in studies in which out-patients including some pregnant women were subjects, but these findings have not been correlated [25].

1.5.3 Interactions

VRP is known to interact with propranolol and has caused congestive heart failure, severe bradycardia, arteriovenous block, and ventricular asystole [3, 4, 17].

VRP is a cytochrome P450 (CYP) 3A4 and P-glycoprotein inhibitor [26] and this can affect the pharmacokinetic profiles of other co-administered drugs such as Rifampicin [27]. It is extensively metabolised in the liver and interactions may occur with drugs that inhibit or enhance liver metabolism. Increased plasma concentrations of buspirone [28], simvastatin [29], carbamazepine, cyclosporine, digoxin, midazolam and theophylline have been reported, and the plasma concentration of alcohol may also be increased when used in combination with VRP [7, 19].

VRP is displaced from protein binding sites by cefriaxone, clindamycin [7, 30] and other highly protein bound agents, such as non-steroid anti-inflammatory agents, warfarin, phenytoin, sulphonamides and sulphonylureas [2]. In addition, acute VRP toxicity has also been reported [7, 30].

Phenorbabitone has an effect on the disposition of VRP's disposition in humans. It is an hepatic-enzyme inducing drug and has been reported to increase the clearance of oral and intravenous administered VRP and to reduce oral bioavailability of the compound in healthy subjects [7, 19].

Dumestre-Toulet *et al* [31] reported a fatality following co-administering sildenafil and VRP in one patient. An autopsy revealed that severe artery sclerosis, as well as signs of myocardial infarct had occurred. This is the first report of a fatal sildenafil-VRP association, probably caused by hypotension and cardiac dysrrhythmia [31].

Grapefruit juice can markedly affect the oral bioavailability of drugs. The absorption of VRP when administered with grapefruit juice increases peak plasma concentration in humans and the effect seems to be mediated mainly by suppression of the cytochrome P450 enzyme, CYP 3A4 in the small intestine wall [32-34]. Individuals with proportionally higher baseline CYP 3A4 levels had a higher proportional increase in VRP clearance [32]. The components of grapefruit that are the most probable cause of the interaction, are the psoralen derivatives [33], but *in-vitro* findings support the flavonoid, naringin, or the furanocoumarin, 6'7'-dihydroxybergamottin, as being the active ingredients. However, a recent investigation by Bailey *et al* [32] indicated that neither of these substances made a major contribution to grapefruit juice-drug interactions in humans.

Tannergren *et al* [35] reported that repeated administration of St John's Wort can cause a severe herbal-drug interaction with VRP by decreasing the bioavailability of the R- and S-enantiomers. These interactions are thought to be caused by induction of intestinal and hepatic CYP 3A4 or by induction of the transport P-glycoproteins [P-gp and ABCB1] through activation of the steroid X-receptor / pregne X-receptor (SXR / PXR). St John's Wort contains a complex mixture of molecules, but the inducing effects are probably mediated by hyperforin [36], which is also thought to be responsible for the major antidepressant activity of the extract [37].

1.5.4 Contraindications

VRP is contraindicated in patients with any broad QRS complex tachycardia, sick sinus syndrome [2, 7, 17, 19], pre-existing AV nodal disease, severe hypotension, Wolf-Parkinson-White syndrome with anterograde conduction, Lown-Ganong-Levine syndrome, myocardial depression, including those produced by beta blockers, digoxin, quinidine or disopyramide and congestive heart failure [2, 17, 19].

The drug should be used with caution in patients with hypertrophy obstructive cardiomyopathy, aortic stenosis, bradycardia, hepatic or renal impairment and gastro-intestinal bleeding [2].

VRP has been associated with acute attacks of porphyria and is considered unsafe for use in porphyric patients [7].

1.5.5 Precautions

There are a number of patient groups in which VRP should be used with caution.

1.5.5.1 Geriatrics

Total VRP clearance was decreased in elderly hypertensive patients when compared with that in young patients, and the elimination half-life was prolonged [2, 7] as a result of decreased renal clearance [2]. Therefore, lower dosages may be necessary in elderly patients [19].

1.5.5.2 Paediatrics

Pfammatter and Bausersfereld [38] reported in a previous study that paroxysmal supraventricular tachycardia caused by atrio-ventricular re-entry is the most frequent arrhythmia in children of all age groups. It represents the most frequent clinical situation where arrhythmic drug therapy has to be considered in a child [38]. Neonates and infants with paroxysmal supraventricular tachycardia generally present with signs of acute congestive heart failure. Intravenous VRP is contraindicated in neonates and infants because of the high risk of electromechanical dissociation. In children older than 5 years of age and adolescents, VRP may be administered with the same restrictions as in adult patients [39].

1.5.5.3 Pregnancy

The incidence and severity of tachyarrhythymias, including both supraventricular tachycardia and ventricular tachycardia may increase during pregnancy. The causes of these have been proposed to be due to haemodynamic, hormonal, autonomic and emotional changes related to pregnancy, which may also include increases in plasma catecholamine concentrations, adrenergic receptor sensitivity, atrial stretch and increased end-diastolic volumes due to intravascular volume expansions [40].

Nifedipine and VRP are the best-studied calcium antagonists in human pregnancy. Although embryogenesis, the development and integration of embryonic organs, is a highly calcium dependent process, there are no substantiated data to indicate that calcium channel blockers cause a significant increase in fetal toxicity in human pregnancy [2, 41]. VRP crosses the placenta [2, 7, 40] and in the first three months of pregnancy it is considered to be second line therapy [41].

Although VRP administration during the third trimester is generally safe and not considered teratogenic, it must be used with caution as it has been shown that VRP when used for fetal supraventricular tachycardia caused fetal atrioventricular block, bradycardia, reduced contractility and hypotension [40].

1.5.5.4 Lactation

Tan and Lie [40] reported that treatment of tachyarrhythmias during pregnancy and lactation is complicated by concerns regarding safety and tolerability for the fetus and infant. All commonly used antiarrhythmic drugs cross the placenta and are excreted in breast milk. Their plasma concentration in the fetus and infant are partly determined by differences in pH between their serum and that of the mother. Most antiarrhythmic drugs are alkali compounds and accumulate in acidic environments [40]. VRP is excreted in breast milk with reported concentrations in milk [2, 7, 40] varying between 23% and 94% of those in maternal serum [40]. To date, there have been no documented difficulties with respect to VRP's use when breastfeeding, however it is not recommended [2].

1.5.5.5 Renal Impairment

Zacharia *et al* [42] studied the pharmacokinetics of VRP and norverapamil (NVRP) in normal subjects and patients with renal failure undergoing maintenance haemodialysis following IV infusion. Severe renal failure requiring haemodialysis did not change the time course of VRP and NVRP plasma concentrations after either IV or oral doses [42]. The terminal elimination rate constant, clearance, volume of distribution and bioavailability of VRP were not significantly different between the two groups. In addition, the apparent maximal plasma concentration, terminal rate constant and area under the curve for NVRP were similar in patients with renal failure and normal subjects. Therefore, it can be concluded that the plasma disposition of VRP and NVRP is not affected in patients with impaired renal function [42].

1.5.5.6 Smoking

Smoking increases CYP 1A2 activity and as this enzyme contributes to the biotransformation of VRP in the liver, the pharmacokinetic parameters of VRP are different in smokers [26, 34]. There is a decrease in AUC and $C_{\max}^{ss}$ values and therefore patients who are smokers, should abstain from smoking when being treated with VRP [34].

1.5.5.7 Effects of Food

Hoon *et al* [43] studied the effects of food on the bioavailability of a sustained-release (SR) formulation of VRP. Compared with the conventional immediate-release formulations, SR-VRP had a reduced C_{max}, prolonged t_{max}, and unchanged $t_{1/2}$. The AUC was 80% of the conventional preparation. Therefore, concomitant food administration significantly prolonged the t_{max} of SR-VRP [19, 43, 44].

1.5.6 Adverse Effects

Treatment with VRP is generally well tolerated, however, adverse effects associated with the pharmacological effect of VRP on cardiac conduction can arise and may he severe in patients with hypertrophic cardiomyopathies [7].The following adverse reactions have been reported in clinical trials and marketing experience [7, 19]:

Bradycardia, atrioventricular block, worsening heart failure, and transient asystole have been reported [2, 7, 17, 19].

Central nervous system (CNS) effects include confusion, equilibrium disorders, muscle cramps, paresthesia, psychotic symptoms and less commonly headaches, nightmares and insomnia [7, 19].

There has been a report of a patient who had a history of bronchial asthma [7, 19] who developed symptoms of acute asthma following administration of a modified-release preparation. The cause may be attributed to the excipients such as alginate used in the product [7]. The most predominantly reported non-cardiac adverse effect is constipation. Nausea may occur, but is less frequently reported [2, 7, 17, 19] and there have been isolated reports of tinnitus [7] and gingival hyperplasia during chronic therapy of VRP [7, 17, 19, 45]. Hypersensitivity reactions such as rash, pruritis, alopecia and urticaria have also been reported [7, 19] and there have been a few reports of erythema multiforme, Steven-Johnson syndrome and exfoliate dermatitis [7, 19]. Hypertrichosis, over many parts of the body has been reported in a male patient following one-month therapy with VRP [7].

There have been reports of increased frequency of urination, spotty menstruation, oligomenorrhea [19] and recurring impotence in men who were taking VRP [7, 19].

Patients have developed elevated serum-prolactin concentrations when treated with VRP [7]. Hyperglycaemia, metabolic acidosis and hyperkalaemia have occurred following administration of a single dose of modified-release VRP in a non-diabetic patient who had previously tolerated regular VRP [7].

Elevation of transaminase with and without concomitant elevations in alkaline phosphatase and bilirubin has been reported during VRP therapy [17, 19]. Clinical symptoms of hepatotoxicity such as malaise, fever, and/or right upper quadrant pain and darkened urine, have also been reported [17, 19]. These reactions may be due to a hypersensitivity reaction and were reversible on discontinuation of VRP therapy [7].

1.6 CLINICAL PHARMACOKINETICS

1.6.1 Dosage and Administration

The usual initial adult dose for hypertension, angina or arrhythmias is 80-120 mg three times a day [2, 19, 20]. In some cases, the dose may be decreased following clinical improvement [19]. If required, the dose may be increased to a total daily dose of 480 mg [2, 19] and dosages should be individualized by titration depending on patient tolerance and responsiveness to VRP [2]. In the treatment of hypertension using slow release tablets, the usual dosage is 240 mg once daily [2, 3] and the dose may be increased at weekly intervals [3] to a maximum 240 mg 12 hourly [2, 3, 19].

In the treatment of obstructive hypertrophic cardiomyopathy the usual starting dose is 80-120 mg three to four times daily and occasionally patients may require doses up to 600-720 mg/day [2, 19].

Lower doses are usually required in elderly patients [2, 3] and in the treatment of patients with advanced renal or hepatic disease [2]. Constant electrocardiogram (ECG) and blood pressure monitoring should be carried out during intravenous administration [2, 3] for early detection of PR interval prolongation, bradycardia and hypotension [2].

1.6.1.1 Overdosage

Overdosage with VRP generally produces cardiovascular symptoms such as severe bradycardia, heart block, profound hypotension [2, 7,19] and diminished peripheral perfusion with loss of peripheral pulses, cyanosis and resultant cold hands and feet [7].

1.6.1.2 Treatment of Overdosage

Overdoses of orally administered VRP should be treated by gastric lavage with concomitant administration of activated charcoal [7, 19, 46].

It should be noted that VRP is not removed by dialysis [7]. Intravenous infusion of calcium salts is recommended as the specific antagonist to VRP and may reverse the haemodynamic and the electrophysiological effects of the drug. If hypotension persists, intravenous administration of sympathomimetic agents, such as isoprenaline, dopamine or noradrenaline may also be necessary. Bradycardia may be treated by the administration of atropine, isoprenaline, or by use of cardiac pacing [7, 19].

Overdosage with modified-release preparations of VRP may result in prolonged toxicity of delayed onset [7] as drug release and absorption in the intestine may occur over 48 hours [19]. Extensive elimination measures such as induced vomiting, removal of the contents of the stomach and the small intestine under endoscopy, intestinal lavage and high enemas are indicated [19]. The use of charcoal in combination with polyethylene glycol solution (PEG) reduced the absorption of VRP, even when administered 2 hours after ingesting an overdose of VRP [46].

1.6.1.3 Guidelines for Use

Patients should be advised not to crush or chew sustained-release tablets or capsules and if a dose is missed, it should be taken as soon as possible thereafter [19, 45]. If several hours have passed or if the time for the next dose is close, patients should not double the dose to catch up, unless advised by a doctor. If more than one dose is missed, patients are advised to contact a health care provider. Patients are also advised to brush and floss their teeth and see a dentist regularly [30].

1.6.1.4 Incompatibility

VRP was found to be incompatible with solutions of nafcillin sodium [7, 47], aminophylline, and sodium bicarbonate, which is manifested by the formation of a precipitate in alkaline solutions [7].

1.6.2 Absorption

VRP is weakly basic and is poorly absorbed from neutral and alkaline media [48]. It is approximately 90% absorbed from the gastrointestinal tract after oral administration, but is subject to considerable hepatic first-pass metabolism with the result that oral bioavailability is only approximately 20% - 35% [2- 4, 19, 20, 49, 50]. When administered orally, peak effects occur within 1-2 hours with conventional immediate release tablets [2, 3, 19] and within 4-8 hours when extended release preparations are used. Following IV administration, therapeutic effects occur within minutes of dosing and persist for between 30 minutes and 6 hours [3, 7].

1.6.3 Distribution

The steady state hypothetical volume of distribution in healthy adults ranges from 4.5 to 7 L/kg, but may increase to 12 L/kg in patients with hepatic cirrhosis [2]. About 90% of the circulating drug is bound to plasma proteins [2, 7, 19, 20]. VRP crosses the placenta and is distributed into breast milk [2, 7, 40].

1.6.4 Metabolism

In healthy subjects, orally administered VRP undergoes extensive metabolism in the liver [2, 3, 4, 19, 20, 50, 51]. The pharmacology of VRP [52, 53] is complicated by the fact that the R and S enantiomers differ in their pharmacodynamic and kinetic properties. S-Verapamil is pharmacologically more potent than R-verapamil (*i.e.* up to 20 times more potent in terms of negative dromotropic effect [54], but is also preferentially metabolized [55, 56]). As a consequence, serum levels of the S-enantiomer are always lower than those of the less active R-enantiomer and the R to S serum concentration ratio is approximately 2 after intravenous administration and 5 after oral administration, respectively [57, 58]. The higher ratio observed after oral dosing is caused by extensive stereoselective pre-systemic first-pass metabolism in the gut wall mucosa and liver, which may also be the reason for the low oral

bioavailability of about 20% and 50% for the S-verapamil and R-verapamil enantiomers, respectively [52, 55-57].

Twelve metabolites have been isolated and identified in plasma. All compounds except NVRP are present in trace amounts only [19, 50]. Although VRP has been marketed for many years, few studies of its transformation in humans have been reported and only a few of the oxidative (Phase 1) and glucuronide (Phase 2) metabolites have been identified [49].

Borlack *et al* [49] identified 21 Phase I and 16 Phase II metabolites. All the Phase II metabolites (glucuronides) and 11 of the Phase I (oxidative) metabolites had not been reported previously [49]. NVRP, the primary metabolite, has pharmacological activity similar to that of the parent compound [20].The therapeutic range in serum varies from 20 to 500 ng/ml depending on the drug form used [50, 51] and there is considerable inter-individual variation in plasma concentrations [50]. To reach such concentrations, the oral dose should be twelve times higher than the intravenous dose [50]. The activity of class IV anti-arrhythmic drugs such as VRP is usually monitored by observation of their haemodynamic effects, rather than by therapeutic drug monitoring (TDM) [59].

N-dealkylation is the main metabolic pathway of VRP and yields a secondary amine (22%) and primary amine (3-4%). The N-demethylated product, NVRP comprises 6% of the urinary metabolites collected in 48 hours [2]. N-demethylation and N-dealkylation of VRP is catalysed by CYP 34A [60]. The O-demethylated products of all these compounds represent about 16 -17% of the administered dose and are excreted exclusively as inactive conjugates [2]. VRP exhibits non-linear pharmacokinetics and considerable inter- and intra-patient variability [60]. A number of possible explanations for this phenomenon have been suggested, including changes in hepatic blood flow [61], the presence of a deep tissue compartment of drug distribution [62] and a reduction in hepatic clearance and first-pass extraction, possibly due to saturation of metabolic pathways, is frequently cited as the main reason for variability [56, 62-64].

1.6.5 Excretion

VRP exhibits bi- or tri-phasic elimination kinetics [50] and is reported to have an elimination half-life of between 6 to 12 hours [2, 6, 7, 19, 20], but increases to as much as 16 hours in patients with hepatic cirrhosis [2, 19]. In infants, the elimination half-life may increase from 5 to 7 hours [2], as a result of the saturation of hepatic enzyme systems as plasma VRP levels

rise [19]. Approximately 70% of an administered dose is excreted as metabolites in the urine and 16% or more in the faeces within 5 days of the dose. About 3 to 4% of an administered dose is excreted in the urine as unchanged drug [2, 7, 19, 20].

Commercially, VRP is used as a racemic mixture with the S-isomer having 3 - 4 fold greater clearance and a 3-10 fold greater dromotropic effect than the R-isomer following both oral and intravenous administration [60].

Population analyses of pharmacokinetic data in healthy volunteers and in patients with hypertension or angina suggest that the S-isomer has a 4-fold smaller AUC compared to that of the R-isomer when administered as a racemic mixture [60]. The apparent plasma clearance of both R- and S-enantiomers decreases with increasing dose, which is consistent with a non-linear mechanism for clearance [60].

Clearance of the R- and S-enantiomers has also been found to be greater following administration of an immediate-release formulation when compared to a sustained-release or controlled release formulation. This difference in clearance values between formulations may be a result of input rate differences on stereo-selective clearance [60].

It has been previously shown that N-demethylation and N-dealkylation of VRP is catalysed by CYP 34A [60] and mucosal CYP 34A enzymes are less abundant in the jejunum and ileum when compared to the duodenum. Thus, first-pass intestinal metabolism may be reduced when the drug is absorbed from the more distal sites of the small intestine [60].

1.7 CONCLUSION

Despite the vast amount of work that has been correlated in past years on VRP, it can be concluded that a deeper understanding of the complex mechanism of action and an explanation of the potential drug-drug and drug-herb interactions must be determined before the drug is administered to patients. The availability of the drug in a racemate form necessitates that the synthetic pathway be properly understood so that the correct ratio of the enantiomers can be obtained, since the different isomers exhibit different potency in pharmacological effects and this poses formulation challenges. An understanding of the importance of stereochemistry in the biological system and the basic phenomena and concepts associated with the stereochemistry of VRP is necessary. The complex pharmacokinetics of VRP therefore, require that only competent clinicians may prescribe this

A = the width of the peak to the leading edge of the peak at 10% of the peak height and

B = the width of the peak to the tailing edge of the peak at 10% of the peak height.

Symmetrical peaks have an A_s of 1.0 and usable columns produce peaks with A_s values of 0.90 to 1.3. Peak asymmetry was measured at 10% of full peak height [66] and the calculation of column efficiency or number of theoretical plates, *N*, for these columns using equations 2.1 or 2.3 was based on the assumption that the peaks obtained were Gaussian-shaped [66, 71].

During the optimization of the analytical method, an Inertsil® ODS 5 µm, 15 cm x 4.6 mm (Metachem Technologies Inc. Torrance, CA, USA) and Supelcosil® ODS 5 µm, 15 cm x 4.6 mm (Alltech, Deerfield, IL, USA) were tested. The chromatographic conditions used to test the columns are reported in § 2.4. The Inertsil® column had a plate count number of approximately 6000 and the Supelcosil® column gave *N* values of less than 5000. Resolution and retention were affected by the change of these columns. The Inertsil® column was finally selected as a column of choice for this study. The peak tailing factor (PTF) calculated at 5% of full peak height for VRP (n = 3) was 1.17 with % RSD = 1.91 and the peak asymmetric factor measured at 10% of peak full height was 1.33 with % RSD = 1.73. Therefore, chromatographic peaks obtained when using the Inertsil® column were better in terms of peak shape than those obtained using the Supelcosil® column.

Lastly, the effects of ion-pair reagent, organic solvent, buffer molarity and eluent pH were investigated on the retention time of VRP.

2.3.2.2 Internal Standard

Many analysts prefer the use of an internal standard for quantitative analysis [8, 51, 76, 78-80, 82, 83, 87, 88]. The purpose of including an internal standard is to minimise system and procedure variations, thus eliminating variations in precision as a function of sample size [68]. This technique minimises error introduced as a result of sample preparation, apparatus and analytical technique [65, 68, 88]. Lindholm *et al* [88] and Hammerstrand [89] reported that the use of an internal standard is one method used to

improve the accuracy of an analytical method and it compensates for varying injection volumes and day to day instrumental changes, thereby promoting method accuracy.

A known compound of fixed concentration is added to the sample of unknown concentration to give a separate peak in the chromatogram. A plot of ratio of peak area/height to internal standard peak area/height versus concentration may be used to generate a calibration curve from which experimental results can be determined by interpolation. The choice of an internal standard is most important and it must be resolved completely from all other peaks and should elute near peaks of interest. Other important considerations are that it must not react with other components and should not be present in the original sample [65, 68].

To date propranolol [51], imipramine [79], norverapamil [80] and fluoxetine [82] have been used as internal standards for the analysis of VRP. In this study, metoprolol, acebutolol and carbamazepine were selected as possible choices for internal standards, based on their structural similarities to VRP.

Carbamazepine (CBZ) was selected as the internal standard of choice for this assay, based on chromatographic resolution, peak shape and run time.

2.3.2.3 Effect of Ion-Pair Reagent Type

To try and improve the chromatographic peaks of a basic analyte in terms of symmetry, ion-pair reagents of different molecular weights were tested for their suitability for the analysis of VRP. Pentane sulfonic acid (PSA), heptane sulfonic acid (HSA) and octane sulfonic acid (OSA) were assessed for their ability to improve the peak shape and retention characteristic.

The sulfonic acid salts are used as ion-pair reagents to try and achieve an optimum separation by improving the peak shape. Ion-pair reagents with different molecular weight cause different effects with respect to retention and separation. Figure 2.1 shows the effects of the different sulfonic acids on retention time of VRP. The separation is more pronounced when a longer sulfonic alkyl chain was used in the mobile phase due to its hydrophobic nature.

The increased retention time for VRP is a result of the ion-pair reagent acting as a counter-ion for the charged cationic VRP analyte, thus binding it by reversible association [90]. In effect, the counter-ion neutralises the charge of VRP and decreases its surface polarity, thus increasing its lipophilicity and potential for binding to a hydrophobic stationary phase [90]. The retention time (R_t) of CBZ remained relatively unchanged when the sulfonic acid salts were changed as it is a neutral compound and does not contain basic groups suitable for ion-pair formation.

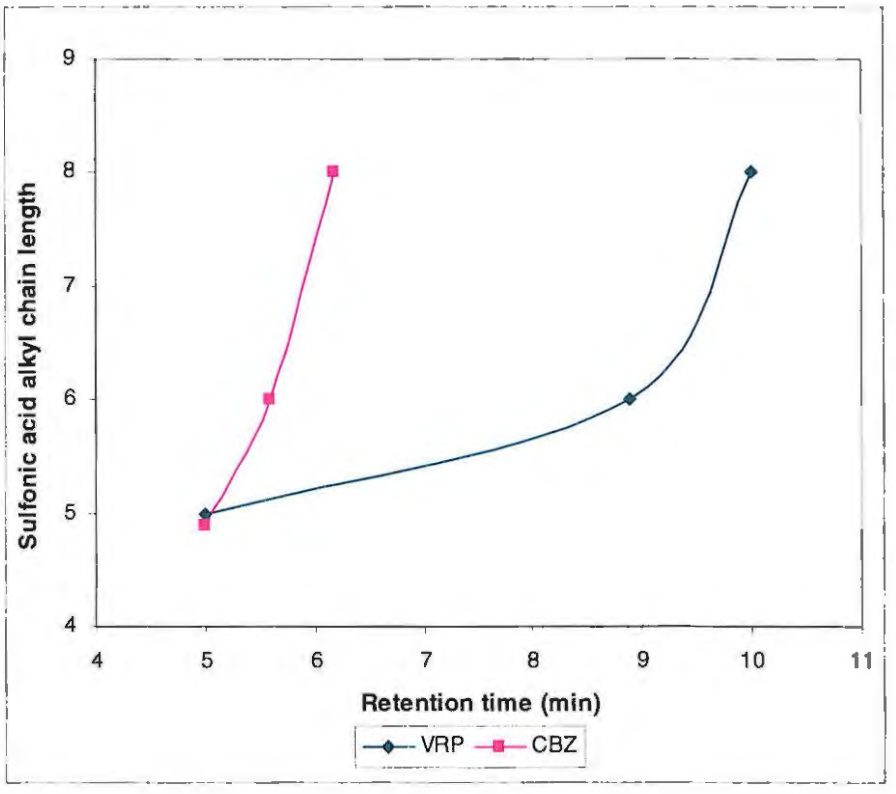


Figure 2.1. Effect of sulfonic acid chain length on retention time of VRP.

2.3.2.4 *Effect of Organic Solvent Composition*

A mobile phase consisting of 75mM Phosphate buffer: Acetonitrile (68:32, v/v) was selected after several trials with mobile phases of high ACN content. At high % v/v ACN (>35%), there was no resolution between CBZ and VRP. When the % v/v ACN was lowered below 30%, the peaks became somewhat broader and a longer R_t was achieved. A 32% v/v ACN, the peaks showed reasonable separation. The results revealed that when the ACN content was lower, the R_t increased rapidly (Figure 2.2) and when ACN content was higher, the R_t time decreased. Therefore, it can be concluded that phosphate buffer: acetonitrile in the proportion (68:32, v/v) is suitable as a final choice of mobile phase and that for the analysis of CBZ, % v/v ACN has a marked influence on both the resolution and the retention of VRP.

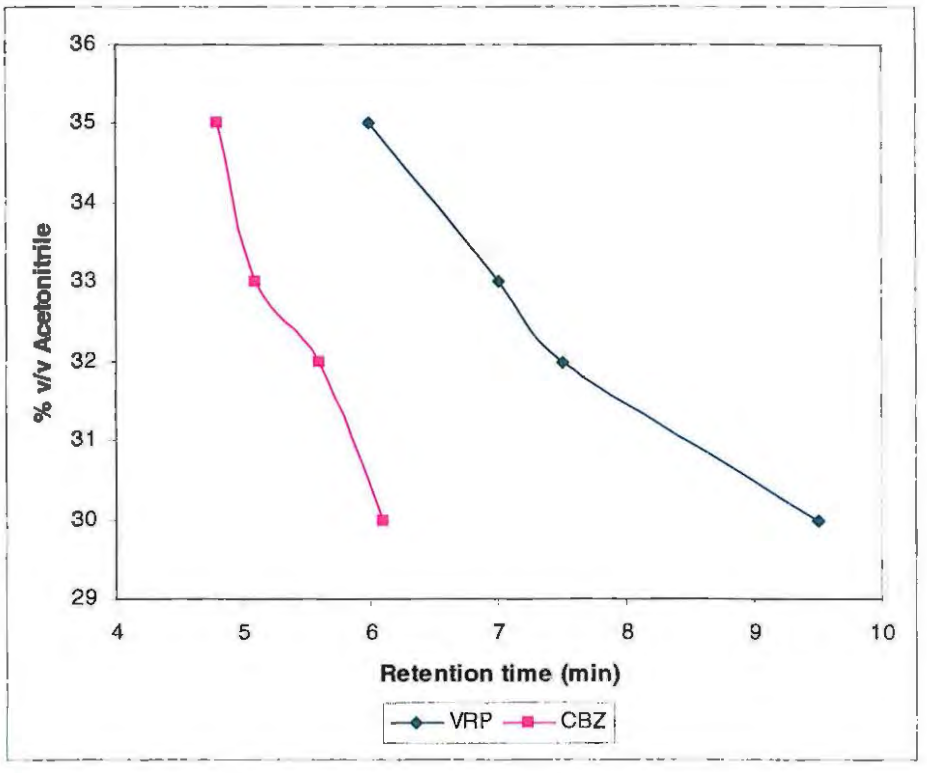


Figure 2.2. Effect of percent acetonitrile on the retention time of VRP.

2.3.2.5 *Effect of Buffer Molarity*

An increase in buffer concentration selectively decreased the R_t of VRP (Figure 2.3), due to increasing competition of buffer cations for silanol sites which are preferentially attached to the column. Since increasing the buffer molarity resulted in shorter run times, a buffer with a molarity of 75mM was selected for use in this study. The results obtained in this study are in agreement with observations made by Marin *et al* [91] that for ionisable compounds an increase in ionic strength can suppress solute and silica ionization, as well as secondary interactions between them.

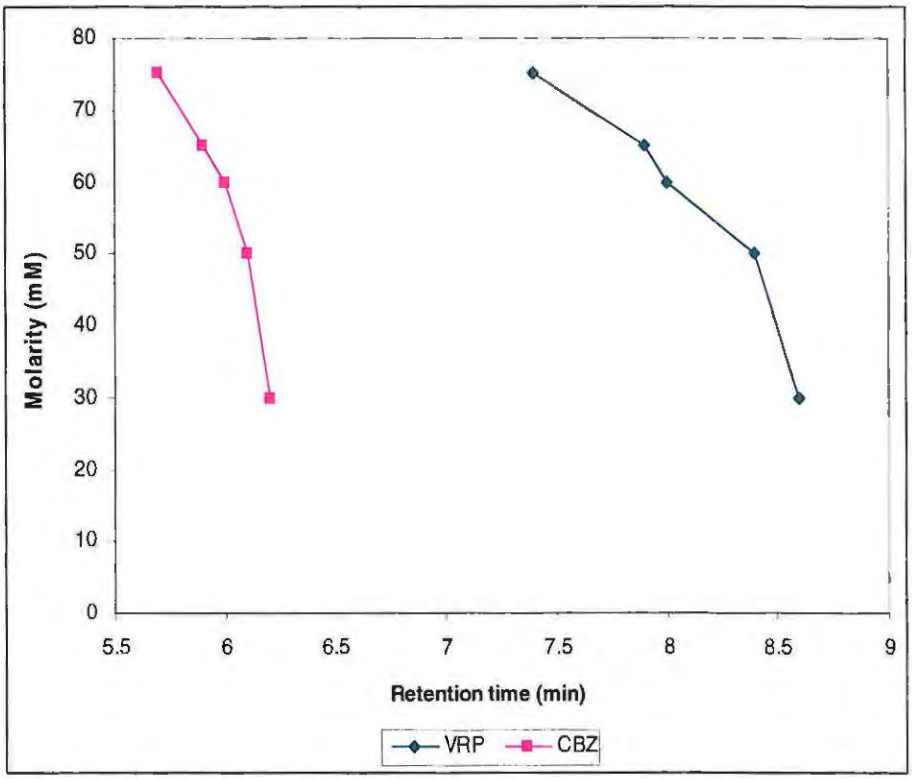


Figure 2.3. Effect of buffer molarity on retention time of VRP.

2.3.2.6 *Effect of Buffer pH*

Silica packed columns show optimum stability and performance at pH values above 2.0 [92]. The effect of eluent pH on the R_t of VRP was therefore investigated in a pH range of 3.0 - 4.6 using ACN as the organic modifier. An increase in buffer pH had a corresponding increase in the R_t of VRP, but the R_t of CBZ remained relatively unchanged (Figure 2.4). Therefore pH 3.0 was selected as the optimum buffer pH for the analysis of VRP. It can be concluded from these studies that an increase in pH had a corresponding effect on the R_t of VRP.

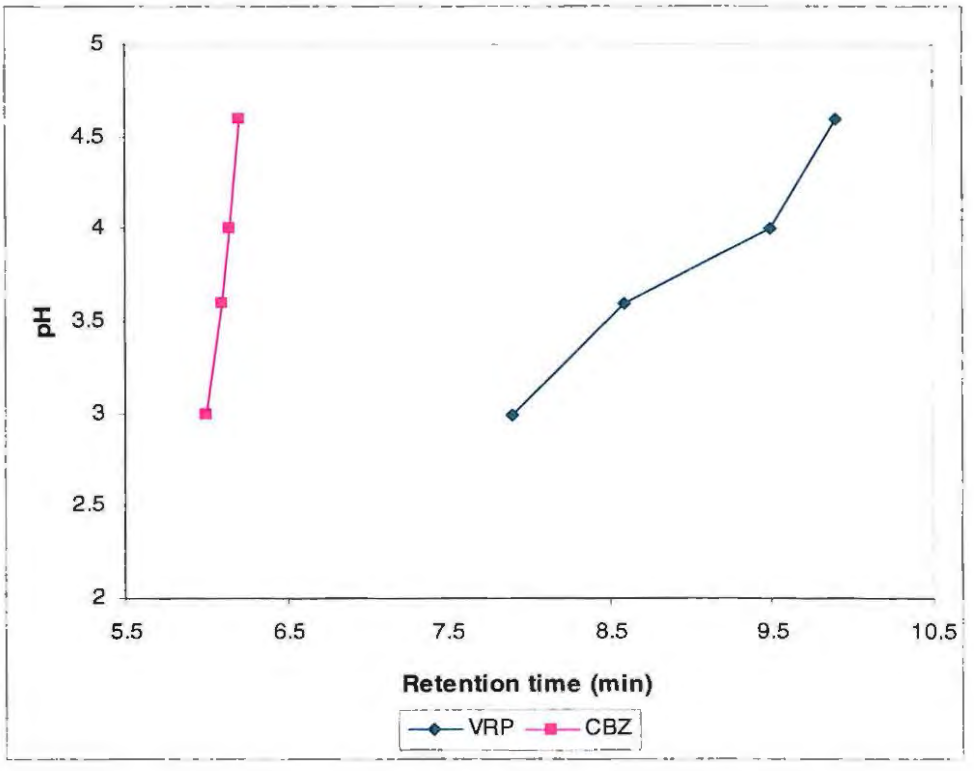


Figure 2.4. Effect of buffer pH on retention time of VRP.

2.4 CHROMATOGRAPHIC CONDITIONS

The following conditions were selected for the quantitation of VRP and Figure 2.5 depicts a typical chromatogram of VRP and internal standard CBZ.

Column	Inertsil® C_{18} (5 µm) Length 150 mm I.D. 4.6 mm
Detector	Linear UVIS 200 (Instruments Corporation, Reno,NV)
Pump	SpectraSERIES P100 pump (Thermoseparation Products, San Jose, California, USA)
Injector	Waters WISP 710B Autosampler (Waters Associates, Milford, MA, USA)
Wavelength	278 nm
Sensitivity	0.05 AUFS
Flow rate	1.5 ml/min
Injection volume	10 µl
Recorder	SpectraPHYSICS SP 4600 Integrator (San Jose, California, USA)
Temperature	Ambient
Mobile phase composition	pH 3.0, 75mM, phosphate buffer: acetonitrile (68:32, v/v)

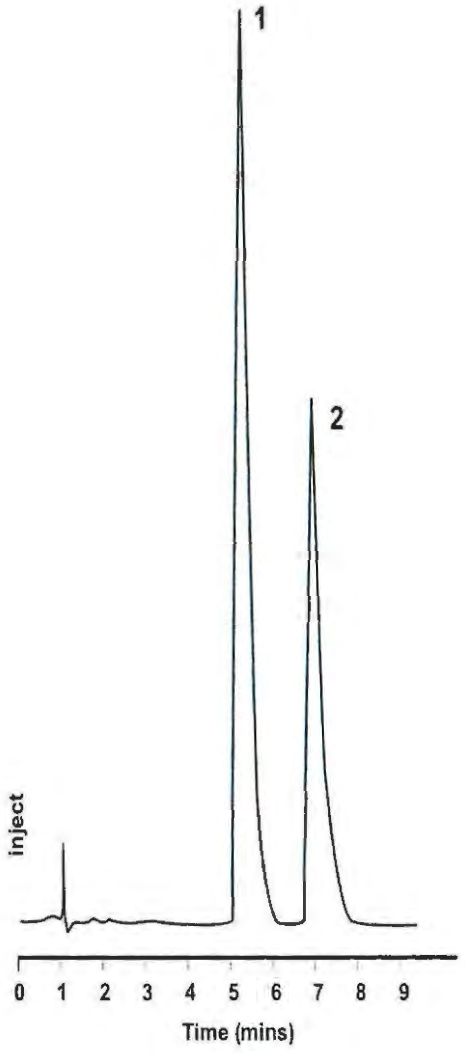


Figure 2.5. Typical chromatogram of CBZ (1) and VRP (2) at 20 μg/ml and 50 μg/ml, respectively, obtained using the chromatographic conditions specified in § 2.4.

2.5 METHOD VALIDATION

2.5.1 Introduction

Various protocol guidelines are recommended by bodies such as the International Conference on Harmonization (ICH), IUPAC, and the Food and Drug Administration (FDA) for the validation of analytical methods [93]. Prior to use, an analytical method for routine analysis must first be validated to demonstrate that it is suitable for its intended purpose [94]. Validation parameters such as selectivity, linearity, accuracy, precision and recovery must be evaluated in every analytical application. The limit of quantitation (LOQ), limit of detection (LOD), stability, and ruggedness/robustness should be investigated, but have been evaluated to a lesser extent in the past [94]. The LOQ is a very stable characteristic and therefore it should be included in the calibration curve, however, the LOD is not a very stable characteristic and therefore it should not be included in the calibration curve. Ruggedness/robustness tests were rarely performed in many of the citations [94].

Validation is often viewed as a test of the acceptability of a specific method. However, the real goal of the validation process is to challenge the method and determine limits of allowed variability for the conditions needed to run the method such that a desired outcome will be achieved [69]. It is best to prioritize the components of validation studies and typically, specificity, linearity, accuracy, and precision studies are needed initially, followed by studies of stability and ruggedness at a later stage [69].

2.5.2 Linearity and Range

The linearity of an analytical method is used to show that test results are either directly, or by a well-defined mathematical transformation, proportional to the concentration of an analyte in samples within a given range [88].

Traditionally, the linear correlation co-efficient is used as a measure of the linearity of a method and according to Lindholm *et al* [88] and Causey *et al* [94] its value should be ≥ 0.99. However, according to Bildlingmeyer [95], a high value for the correlation co-efficient does not necessarily indicate a linear standard curve [95]. The linear co-

efficient should be accompanied by a graph in which the response/sample concentration is plotted versus the logarithmic sample concentrations [95].

The range of an analytical method is the interval between the upper and lower levels of analyte (including these levels) that have been demonstrated to be determined with a suitable level of precision, accuracy and linearity using the method as described [96].

A calibration curve was constructed by plotting (Figure 2.6) the peak height ratios of VRP/CBZ versus VRP concentration and performing least-squares linear regression analysis. The calibration curve had a slope of 0.0103 and a y-intercept of 0.0190 with a correlation co-efficient of 0.9989.

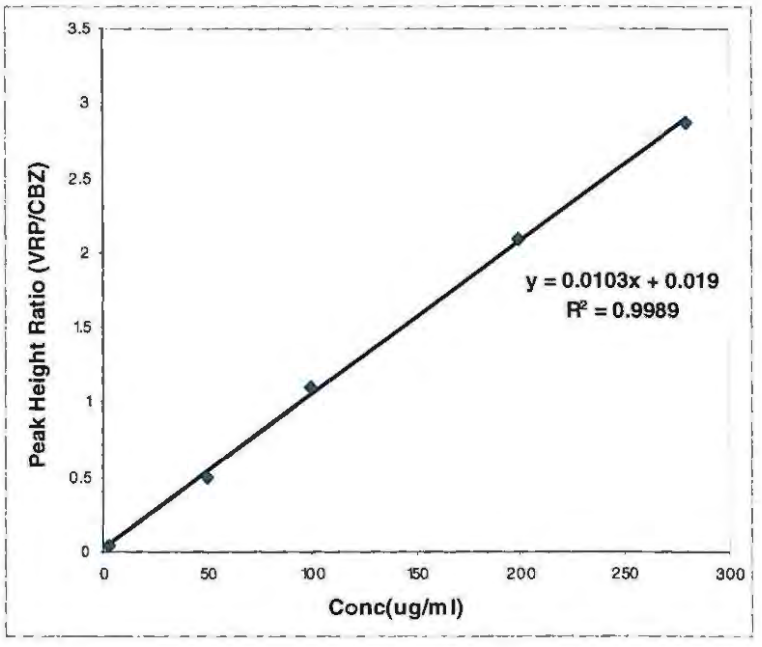


Figure 2.6. Calibration curve constructed after linear regression of peak height ratios versus concentration. Linear regression equation: y = 0.0103x + 0.019.

The linearity of peak height ratios of VRP to CBZ versus concentrations was studied from 3.0 μg/ml to 280 μg/ml for VRP.

2.5.3 Precision

The precision of an analytical method is the degree of agreement among individual tests results when the procedure is applied repeatedly to multiple aliquots of a homogeneous sample [91, 97], or it may also be considered the reproducibility of multiple measurements of an homogenous sample. Reproducibility of results using

different instruments, analysts, sample preparations, laboratories, data obtained on a single day or over multiple days may all constitute an assessment of precision. Different levels of precision are often assessed as part of method development [51, 67, 91].

Precision is usually reported as the percentage relative standard deviation (% RSD). The measured % RSD can be subdivided into three categories, *viz.* repeatability (intra-day precision), intermediate precision (inter-day precision) and reproducibility (between laboratories precision) [98-100].

Precision was considered at two levels for this method, *viz.* repeatability and intermediate precision and the tolerance for % RSD was set at ± 10% for these studies.

2.5.3.1 Repeatability

Repeatability of a method is determined when the analysis is performed in one laboratory by one analyst using the same equipment on the same day. It has been suggested [98] that repeatability be tested by the analysis of a minimum of five determinations at three different concentrations (low, medium and high) in the range of expected concentrations. However, according to ICH [100] repeatability should be assessed by analysis of three determinations at three different concentrations or through six determinations at 100% of the test concentration.

Intra-assay precision involves multiple measurements of the same sample (different preparations) by the same analysts under the same conditions [51, 69, 91, 101]. The intra-day precision obtained for six replicates of standard solutions of VRP with the internal standard, CBZ, which were analyzed on three different days at three different concentrations, are shown in Table 2.2.

Table 2.2. Intra-day precision data for analysis of VRP.

Concentration (µg/ml)	Mean concentration determined (µg/ml)	Standard deviation	Precision (% RSD)
10.00	9.49	0.0035	2.53
100.00	104.97	0.0095	1.22
200.00	202.96	0.0367	1.08

The results reveal that all standard deviation values were within the acceptable range and the % RSD values were less than or equal to 5%, which are within the limits set in our laboratory.

2.5.3.2 Intermediate Precision

Intermediate precision, or inter-day variability is the agreement of complete measurements (including standards) when the same method is applied many times within the same laboratory [91]. Thus determinations may include full analysis on different days with the same or different instruments by the same or different analysts, but would involve multiple preparations of samples and standards.The inter-day variability of this method was assessed over three days at three different concentrations for six replicates of VRP standards. Sample preparation was conducted as detailed in § 2.2.3 and the results are depicted in Table 2.3.

Table 2.3. Inter-day precision data for analysis of VRP.

Concentration (µg/ml)	Mean concentration determined (µg/ml)	Standard deviation	Precision (% RSD)
10.00	9.58	0.0029	3.76
100.00	97.56	0.0013	2.10
200.00	203.41	0.0057	1.73

The results show that all % RSD values determined were less than or equal to 5%, which is within the limits set in our laboratory. Therefore, the method may be precise.

2.5.3.3 Reproducibility

Reproducibility examines the precision between laboratories and is often determined in collaborative studies or method transfer experiments [69]; therefore it was not performed in these studies.

2.5.4 Accuracy and Bias

The accuracy of an analytical method is defined as the closeness of the measured value to the true value of analytes in the sample [69, 91, 97, 99]. A tolerance of 2% was set for % RSD for this parameter. This complies with the limits set by a number of pharmaceutical industries [102]. Bias assesses the influence of the analyst on the performance of the method. Accuracy and bias were determined by making repeat measurements of three samples of varying concentration. The FDA [103] recommends that accuracy studies for drug products be performed at 80, 100 and 120% of the target concentration. Accuracy studies were performed in triplicate on samples representative of high, medium and low concentrations. The results are shown in Table 2.4 and reveal that the largest value obtained for % bias was 2.87%, indicating that no value obtained deviated by greater than approximately 2.90% of the stated value. Values of % RSD obtained all complied with the 2% tolerance test, indicating that the method was accurate for the determination of VRP.

Table 2.4. Accuracy test results of blinded samples.

Theoretical concentration (µg/ml)	Mean concentration determined (µg/ml)	SD	% RSD	% Bias
10.00	10.23	0.0095	1.62	+2.25
100.00	102.96	0.0083	0.44	+2.87
200.00	199.67	0.037	1.08	-0.17

2.5.5 Limit of Detection / Limit of Quantitation

Recent articles in the literature have included much discussion regarding the determination of the limit of quantitation (LOQ) and limit of detection (LOD) values

of an HPLC method [51, 79-82, 91, 97, 104]. Paino and Moore [105] described four techniques to determine the LOD and LOQ of analytic systems:

i) lowest concentration for which % RSD ≤ 5%,
ii) plot of standard deviation versus concentration,
iii) confidence interval of a best-fit line and
iv) signal-to-noise ratio methods.

The LOQ is the lowest amount of analyte in a sample that can be quantitatively determined with precision and accuracy under the stated experimental conditions [91, 97] and the LOD is the lowest amount of an analyte in a sample that can be detected, but not quantitated as an exact value [91, 97]. For chromatographic analysis, LOD may be defined as that concentration giving a peak height response three times greater than the baseline noise level. Although various methods to estimate the LOD have been described, an experimental assessment provides the best measure of the operating limits of the equipment. The LOQ and LOD of the method developed for the analysis of VRP in this study were determined using a precision of ≤ 5.0%. By convention, the LOD value is taken as 0.3 x LOQ [105] and the LOQ was found to be 3.0μg/ml (%RSD = 2.27) and LOD based on the above relationship was 1.0μg/ml.

2.5.6 Specificity

Vessman [106] and Rosing *et al* [107] pointed out that the specificity of a method is a measure of the ability of an analytical method to produce a definite response to only the analyte of interest and no other compounds that may be present in the sample, for example tablet excipients, related substances or impurities. Specificity was assessed by comparing chromatograms obtained from analysis of a standard solution containing the analyte only with a sample mixture obtained by dissolving commercially available tablets of VRP in the dissolution medium. The chromatographic peaks obtained were well resolved from the solvent front and there were no interfering peaks from the excipients. Therefore, the method is deemed to be specific.

2.6 CONCLUSION

A reversed phase HPLC method for the *in-vitro* quantitation of VRP has been developed, validated and subsequently applied to the assessment of dosage form. The linearity of the VRP/CBZ peak height ratio versus VRP concentration was demonstrated. The chromatographic conditions described yielded sharp, symmetrical peaks with a high degree of resolution. CBZ and VRP were well separated and their R_t were approximately 5.5 and 7.5 minutes respectively. Optimisation of the analytical method was achieved by manipulation of mobile phase composition, buffer pH, buffer molarity, ion-pair reagent type and evaluation of a variety of HPLC columns.

The ion-pair reagents, PSA, HSA and OSA, were investigated. However, due to longer retention times and poor equilibration of the column, these compounds were not suitable for use in the routine analysis of VRP and were therefore not used in the final method.

The mobile phase suggested in this method does not require any of the complicated components and can easily be prepared.

The HPLC method developed in these studies is an improvement on the method presented in the USP monograph for VRP, where the latter employs the addition of a competing amine, 2-aminoheptane and acetate buffer to the mobile phase. The ion-pair reagent may lead to shortening of the column life and the use of a volatile buffer may result in an unstable pH. The use of an inorganic buffer, phosphate, in this method results in a relatively stable pH for the buffer, which leads to consistent results.

The described method is simple, selective, accurate, precise, rapid, sensitive and linear. It is appropriate for the assessment of *in-vitro* release and analysis of VRP in pharmaceutical dosage forms.

CHAPTER THREE
FORMULATION AND ASSESSMENT OF POWDER BLENDS FOR SUSTAINED RELEASE TABLETS

3.1 POWDER RHEOLOGY

3.1.1 Introduction

Since more than 80% of pharmaceutical products are available as solid oral dosage forms, powder and processing technologies are important factors to be considered in the pharmaceutical industry. Flowability and compactibility are two essential characteristics that need prior investigation, to ensure successful tablet manufacture [108].

The ultimate specifications of a finished tablet will be a consequence of the compressibility, adhesive/cohesive interactions and mechanical properties of the component materials. Consequently, a poorly compactable drug will result in formulation challenges and possibly formulation failure [109].

The importance of the flowability of a powder in the production of pharmaceutical dosage forms is well-documented in the literature [108]. Powder flowability is influenced by particle size, size distribution, shape, surface texture of particles, surface energy, chemical composition, moisture content and granulation vessel geometry [108]. Numerous methods for measuring powder flowability have been developed, largely based on an empirical understanding of the process. In practice, experimental results of flowability determinations are not always consistent and may be hard to interpret. However, they do give an understanding of the behaviour of powders [109, 110].

Commonly used techniques to assess flowability of powders in the pharmaceutical industry include measurement of the angle of repose (§ 3.2.1), bulk and tapped density determinations (§ 3.2.2) that are used to calculate Carr's compressibility index (§ 3.2.3) and the Hausner ratio (§ 3.2.4) of a powder [108, 109]. These values are obtained from the initial packing density (aerated density) and the final packing density obtained after tapping the powder in a controlled and defined way (tapped density) [109].

Particle compactibility is defined as the ability of a powdered material to be compressed into a tablet of specified strength. Pharmaceutical compacts are required to possess sufficient mechanical strength to withstand normal handling and transport. The mechanical strength of pharmaceutical compacts is characterized by the force required to fracture a specimen across its diameter, which is usually reported as tablet hardness in the pharmaceutical industry. The strength of a compact is a reflection of the bonding that has occurred during compaction [108]. This relates to the type of bonds, a more complicated concept for a mixture, the number of effective bonds, contact surface area and bond distribution in the compact. Since virtually all tablets consist of more than one material, the prediction of the compaction properties of mixtures from those of the individual components is of obvious interest [108].

3.2 EXPERIMENTAL

3.2.1 Angle of Repose (AOR)

The flowability of powders was determined by measuring the angle of repose of the blends listed in Table 3.5. The end of a funnel was placed 2 cm above a flat glass plate. Approximately 20 g of powder, the mass depended on the bulk density of the material, was poured into the funnel. After releasing the powder from the funnel, the top of the resulting cone reached the end of the funnel. The height of the cone, h and the diameter of the base, d, were determined and the angle of repose, α, was calculated [109,110, 111] using equation 3.1.

$$\tan\alpha = \frac{2h}{d} \qquad \text{Eq.3.1}$$

where

α = angle at the base of the cone

h = height of the cone

d = diameter of the base of the cone

Table 3.1 shows the relationship between the AOR and powder flow properties. It is evident that an AOR of less than 25° is indicative of good flow properties whereas an AOR greater than 40° reflects inadequate or poor flow. Adding a glidant may improve the flow of blends that have an AOR of 30 - 40° [112].

Table 3.1. Relationship between angle of repose, α and powder flow.

Angle of repose (α) degrees	**Flow**
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very poor

Alternatively, measuring the angle of the base and the length of the opposite sides of the cone permits calculation of the AOR using equation 3.2 [112].

$$\alpha = \text{arc cos } [\frac{d}{(l_1 + l_2)}] \qquad \text{Eq. 3.2}$$

where

α = angle at the base of the cone,

d = the diameter of the cone and

l_1 and l_2 = the two opposite sides of the cone.

3.2.2 Bulk and Tapped density

The aerated bulk density of the powders was determined by allowing the dispersed powder to settle in a container under the influence of gravity alone [112]. A powder with strong structural strength will resist collapse when dispersed in a container and will have a low bulk density, whilst a structurally weak powder will collapse easily and have a high bulk density [108,109]. The tapped bulk density of a blend is determined by tapping the container holding the aerated sample. The structure of a cohesive powder will collapse significantly on tapping while a weak or free-flowing powder has little scope for further consolidation [109]. The Hausner ratio and Carr's compressibility index have been

developed based on this theory [108,109,113] and are used as an important tool for the characterization properties of powders.

The bulk density of blends was determined by pouring a sample of the powder (20 g) into a 100 ml graduated A-grade measuring glass cylinder and measuring the volume occupied by the powder. The cylinder was lightly tapped to dislodge residual powders from sticking to the wall of the measuring cylinder. The volume was read directly from the cylinder and used to calculate the bulk density. In order to determine the tapped bulk density of the powder, the measuring cylinder was tapped for 500 tap cycles after which the volume was recorded. In all cases, the cylinder was tapped by hand from a height of 2.5 cm on a wooden bench top to attain a constant reading from the cylinder over a period of less than 10 minutes.

The Carr's compressibility index was then calculated from the bulk and tapped densities [109-111,113,114].

3.2.3 Carr's Index (CI)

Carr's compressibility index has been reported in literature as useful for the evaluation of sustained-release and controlled-release blends [109-111,113,114]. Carr's index was calculated using equation 3.3, and Table 3.2 shows the interpretation of Carr's index for powder flow.

$$CI = \left[\frac{\rho_{tap} - \rho_{bulk}}{\rho_{tap}} \right] \text{X } 100 \qquad \text{Eq. 3.3}$$

where

CI = Carr's compressibility index,

ρ_{tap} = tapped density and

ρ_{bulk} = bulk density.

Lower CI's are associated with low cohesiveness and greater fluidity properties. Such properties may enhance good tablet manufacture [112]. The addition of a lubricant enhances powder flow considerably when the CI is above 20%.

Table 3.2. Interpretation of Carr's index.

Carr's Index (%)	Flow
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to passable
23 – 35	Poor
33 – 38	Very poor
> 40	Very very poor

3.2.4 Hausner Ratio (HR)

Hausner ratio has been reported in literature as useful for the evaluation of sustained-release and controlled-release blends [110,111,113]. The Hausner ratio was calculated using equation 3.4 and Table 3.3 shows the interpretation of Hausner's ratio for powder flow.

$$HR = \frac{\rho_{tap}}{\rho_{bulk}} \qquad \text{Eq. 3.4}$$

where

ρ_{tap} = tapped density,

ρ_{bulk} = bulk density.

Lower HR values (< 1.25) are associated with good flow and values greater than 1.5 may lead to cohesiveness of powder particles, resulting in poor flow. When HR is between 1.25 and 1.5, addition of a glidant improves powder flow [115].

Table 3.3. Interpretation of Hausner ratio.

Hausner Ratio	Flow
< 1.25	Good
> 1.50	Poor

3.2.5 Kawakita analysis

Powder flow properties can also be analyzed using Athy-Heckel, Kawakita and Cooper-Eaten analysis [116]. The Kawakita equation is depicted in equation 3.5.

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \qquad \text{Eq. 3.5}$$

where

P = is the applied pressure,

C = is the degree of volume reduction of a powder, the constant,

A = constant, is the total degree of volume reduction for the powder bed and

b = is a constant that is inversely related to the yield strength of the particles.

The constants, a and b, can be evaluated from a plot of the ratio of P and C versus P. This equation describes the relationship between the degree of volume reduction of the powder column and the pressure applied to the powder [116,117].

The basis for the Kawakita equation for powder compression is that particles subjected to a compressive load in a confined space are viewed as a system in equilibrium at all stages of compression, so that the product of the pressure volume term is a constant [116].

It has been reported [118] that the Kawakita constant, a, which quantifies the maximum possible volume reduction, due to tapping or applied load should equal Carr's compressibility index. Thus, the application of the Kawakita equation has no advantage over the use of Carr's compressibility index as an indicator of possible volume reduction.

As the Carr's index gave usable data, the Kawakita constant was not determined in these studies.

3.3 EXCIPIENTS

All materials used in this study are generally recognised as safe (GRAS) and appear in the FDA Inactive Ingredients Guide for inclusion in oral formulations [119].

3.3.1 Carbomer

Carbomers are white-coloured, low density, acidic, hygroscopic powders with a slight odour [119]. They are very high molecular weight synthetic polymers of acrylic acid, which are chemically cross-linked with either allylsucrose or allylethers or pentaerythritol. They contain about 56%-68% of carboxylic acid (COOH) groups calculated on the dry basis [119] and have a pK_a of 6.0 ± 0.5 [120].

Cross-linked carbomer polymers are not soluble in aqueous media, but swell while linear polymers are soluble in polar solvents such as water [119].

Carbomer polymers may be used as rate controlling agents and may enhance the control of release properties of dosage forms at lower concentrations than competitive materials. Carbomer polymers can form strong matrices at low concentrations due to their inherently cross linked structure [120], which is one of the contributing factors to its success as a rate controlling polymer.

The polar form of carbomer has a glass transition temperature of 105°C. However, the glass transition temperature drops dramatically as the polymer comes into contact with water. Plasticization of the carbomer with water causes the polymer chains to start gyrating. As the radius of gyration becomes greater and the end to end distances increase, the polymer swells on a macroscopic level. These polymers swell up to 1000 times their original volume and up to ten times their original diameter in the presence of water to form a gel, when exposed to a pH environment, controlled above its pK_a [120].

It is important to emphasize that as carbomers are already crosslinked, viscosity and molecular weight are not the primary parameters controlling drug release rates, unlike in linear, soluble matrix systems [120], such as hydroxypropyl methylcellulose (HPMC) and sodium carboxymethylcellulose (SCMC), amongst others.

There are currently four carbomer polymers designed for oral application. These are Carbopol® 934P NF, Carbopol®974P NF, Carbopol®971P NF and Carbopol® 71G NF. [119,120]. In tablet formulations, carbomers may be used as dry or wet binders or as rate controlling excipients [119].

3.3.2 Methacrylic Acid Copolymers

Eudragit® RS and Eudragit® RL are bio-compatible copolymers synthesized from acrylic and methacrylic acid esters. The molecular structures of Eudragit® RS and RL differ only in the extent of the quaternary ammonium substitutions, with Eudragit® RS showing a lower degree of substitution than Eudragit® RL. Eudragit® RL has 10% and Eudragit ®RS has 5% of quartenary ammonium functional groups. The ammonium groups are present as salts that impart pH- independent permeability of the polymers [119]. Their permeability to water is unaffected by pH, however, water can permeate more freely into Eudragit® RL than it can into Eudragit® RS, due to the relative hydrophilicity of the RL copolymer. The acrylate-methacrylate polymers have been used in the preparation of matrix tablets for oral sustained release, in tablet coating and in the microencapsulation of drugs [121].

Methacrylic acid copolymer is a fully polymerized copolymer of methacrylic acid and an acrylic or methacrylic ester. Three types of polymers, type A (Eudragit® L, Eudragit® RL), type B (Eudragit® S, Eudragit® RS) and type C (Eudragit® L 30 D-55), have been defined and these vary in their methacrylic acid ester content and solution viscosity [119]. Typically, the molecular weight of these polymers is in excess of 100 000 mass units. Solid polymers may be used in direct compression tabletting in proportions of 10-50% [119].

Eudragit® NE 30D is a neutral aqueous ester dispersion consisting of polymethacrylic acid esters. The dispersions are milky-white liquids of low viscosity and have a weak aromatic odour. This polymer is particularly suitable for granulation processes in the manufacture of matrix tablets [122].

Eudragit® RL 30D and Eudragit® RS 30D are aqueous dispersions of copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups. The dispersions contain 30% w/v polymer [119].

3.3.3 Hydroxypropylmethylcellulose (HPMC)

The use of HPMC (Methocel® K100M) in sustained-release dosage forms has been widely reported [110, 123 - 130]. It is a non-ionic, non-toxic polymer that has been used in topical formulations, as well as in tablet manufacture. It has been used as a binder and as a sustained release matrix-forming excipient [119]. It is available in different grades, depending on the degree of substitution and average weight of the polymer [119].

In tablet formulations containing hydrophilic polymers such as HPMC, the release of the active drug is controlled by the rate of formation of a partially hydrated gel layer of the tablet surface that is formed upon contact between the polymer and aqueous gastric media. The release rate is further controlled by the continuous formation of an additional gel layer [124].

HPMC polymer controlled release dosage forms have been classified as swelling controlled release systems [110,123-129]. Generally, in swelling controlled matrix systems, there are two major factors that control the rate of release of drug from matrix. The factors considered to be important are the rate of aqueous medium infiltration into the matrix and the subsequent relaxation of the polymer, resulting in either hydration or gelation and swelling of the polymer, respectively. As a result of these simultaneous processes, two fronts are evident, a swelling front (glassy polymer/gel interface) and an eroding front (gel/medium interface). The distance between the two fronts depends on the relative rates at which the swelling and eroding fronts move in relation to each other and is termed the diffusion layer [125].

3.3.4 Ethylcellulose

Ethylcellulose is an ethyl ether of cellulose, consisting of β-anhydroglucose units joined together to form long chain polymers [119]. The main use of ethylcellulose in oral formulations is as a hydrophilic coating agent for tablets and granules. Ethylcellulose coatings are used to modify drug release, to mask unpleasant tastes, encapsulate drugs and to improve the overall stability of formulations. Modified-release tablet formulations may also be produced using ethylcellulose as a matrix forming material. Ethylcellulose produces hard tablets with low friability [114, 119].

Surelease® E-7-19010, an aqueous ethylcellulose dispersion, was used as the granulating fluid in wet granulation formulations. It contains approximately 24.9% w/v total solid content dispersed in an ammonium hydroxide vehicle, with dibutyl sebacate as a plasticizer and oleic acid as a stabilizer [131]. 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.

Surelease® E-7-19010 was diluted to 15% w/v dispersion prior to use, by adding distilled water while stirring [131].

3.3.5 Dibasic Calcium Phosphate (DCP)

DCP is widely used as a diluent or filler due to its low hygroscopicity, excellent flow characteristics, compatibilities, low cost and physical and chemical stability. DCP is abrasive and a lubricant such as magnesium stearate is required for successful tableting. Two main particle-size grades of dibasic calcium phosphate dihydrate are used by the pharmaceutical industry. The milled material is used in wet-granulation and the coarse-grade material is used in direct-compression formulations [119]. The coarse-grade was used in direct-compression formulae in this study.

3.3.6 Microcrystalline Cellulose (MCC)

MCC is purified, partially depolymerized cellulose that occurs as white, odourless, tasteless, crystalline powder, composed of particles of different sizes and moisture grades

that have different properties and applications [119]. MCC is widely used as a diluent in oral tablet and capsules formulations prepared by either wet-granulation or direct-compression processes [119]. Emcocel® 90M has a mean particle size of 91 μm and a moisture content less than 5%. It has an angle of repose of 34.4°, a bulk and tapped density of 0.29g/cm^3 and 0.35g/cm^3, respectively [119] and was used as a diluent in combination with DCP and lactose monohydrate.

3.3.7 Lactose Monohydrate

Lactose occurs as a white to off-white crystalline powder. It is odourless and sweet-tasting and is widely used as filler or diluent in tablets and capsules. Generally, the grade of lactose chosen is dependent on the type of dosage form being developed. Direct-compression grades for example, are often used to carry small amounts of drug [119].

Direct-compression grades of lactose are more fluid and more compressible than crystalline or powdered lactose and are generally composed of spray-dried lactose, which contains specially prepared pure α – lactose monohydrate along with a small amount of amorphous lactose. Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics [119].

3.3.8 Talc

Talc is a very fine, white to greyish-white powder. It is commonly referred to as hydrous magnesium silicate and the composition of talc may vary depending on the geographical source of the material used. It is used in solid oral dosage formulations as a glidant and tablet lubricant at 1-10% w/w levels [119].

3.3.9 Magnesium Stearate

Magnesium stearate is a mixture of magnesium and a variety of organic acids that consists chiefly of variable proportions of magnesium stearate and palmitate. It is primarily used as a lubricant in capsule and tablet manufacturing at concentrations of between 0.25 and 0.5% w/w. It is hydrophobic and may retard the dissolution of a drug

from a solid dosage form and therefore, the lowest possible concentration should be used in formulations [119].

3.4 FORMULATION COMPOSITION

Different formulations were prepared by either dry compression or wet granulation method. Formulations VRP001-VRP023 were prepared and the powder blends or granules were subjected to a variety of tests prior to tableting. A summary of the formulation composition is listed in Table 3.4.

Tablets from batches VRP001-VRP019 were prepared by direct compression (DC) and tablets from batches VRP020-VRP023 were prepared by a wet granulation (WG) method.

Table 3.4. Formulation of VRP001 – VRP023.

	FORMULATION (% w/w)												
INGREDIENTS	**VRP001**	**VRP002**	**VRP003**	**VRP004**	**VRP005**	**VRP006**	**VRP007**	**VRP008**	**VRP009**	**VRP010**	**VRP011**	**VRP012**	**VRP013**
VRP	33	33	33	33	33	33	33	33	33	33	33	33	33
Carbopol® 974P NF	10	15	-	-	10	15	-	-	10	10	10	10	10
Carbopol® 971P NF	-	-	10	15	-	-	10	15	-	-	-	-	-
Eudragit® RS PO	-	-	-	-	-	-	-	-	-	-	7.5	-	7.5
Eudragit® RL PO	-	-	-	-	-		-	-	-	-	-	7.5	-
Eudragit® RS 30D	-	-	-	-	-	-	-	-	-	-	-	-	-
Eudragit® NE 30D	-	-	-	-	-	-	-	-	-	-	-	-	-
Methocel® K100M	-	-	-	-	10	10	10	10	-	-	-	-	-
Ethocel® 10PF	-	-	-	-	-	-	-	-	5	5	-	-	7.5
Surelease®	-	-	-	-	-	-	-	-	-	-	-	-	-
Emcompress®	-	-	-	-	-	-	-	-	24.5	-	-	-	-
Lactose	56	51	56	51	46	41	46	41	24.5	51	48.5	48.5	41
Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Mg stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Table 3.4 continued.

	FORMULATION (% w/w)									
INGREDIENTS	**VRP014**	**VRP015**	**VRP016**	**VRP017**	**VRP018**	**VRP019**	**VRP020**	**VRP021**	**VRP022**	**VRP023**
VRP	33	33	33	33	33	33	33	33	33	33
Carbopol® 974P NF	-	10	10	10	7.5	7.5	10	10	10	10
Eudragit® RS PO	15	15	7.5	7.5	20	7.5	13.5	13.5	-	-
Eudragit® RS 30D	-	-	-	-	-	-	-	-	20ml	-
Eudragit® NE 30D	-	-	-	-	-	-	-	-	-	20ml
Methocel® K100M	-	-	-	-	-	-	-	10	-	-
Ethocel® 10PF	5	7.5	7.5	7.5	7.5	20	-	-	16	16
Surelease® E-7-19010	-	5ml	-	-	-	-	10ml	20ml	-	-
Emcompress®	-	-	41	-	-	-	20	20	20	20
Emcocel®	-	-	-	41	-	-	20	20	10	10
Lactose	46	30	-	-	31	31	-	-	-	-
Talc	0.5	0.5	0.5	0.5	0.5	0.5	-	-	-	-
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

3.5 RESULTS AND DISCUSSION

The powders or granules of the different formulations were all tested and the angle of repose, bulk density, tapped bulk density, Carr's compressibility index and Hausner's ratio determined. A summary of the results of these determinations is listed in Table 3.5. The results of the angle of repose and compressibility index (%) ranged between 26.00° ± 2.64 to 36.16° ± 2.49 and 8.90 ± 3.44 to 35.56 ± 3.00, respectively. The results of bulk and tapped density ranged from 0.57 ± 1.25 to 0.74 ± 2.08 and 0.76 ± 2.22 to 0.98 ± 3.10, respectively. The results of angle of repose indicate good flow properties of all the blends except for tablets from batches VRP001- VRP003 and VRP009-VRP011. This was further supported by lower compressibility and Hauser's ratios for all the blends except for the blends that initially did not show good flowability in terms of their angle of repose. All determined results indicate that the blends possessed satisfactory flow properties and compressibility index and hence, tablet manufacture may be considered feasible. Tablets from batches VRP001-VRP003 and VRP009-VRP011, which theoretically would produce tablets of non-uniform weight due to differences in fill weight when the powder flows into the tablet die cavity, were the exception in terms of the results of these tests.

Table 3.5. Results of tests on powder blends or granules for formulations VRP001 – VRP023.

Formulations	Angle of Repose (°)	LBD (g/ml)	TBD (g/ml)	CI (%)	HR
VRP001	32.64 ± 5.45	0.64 ± 1.79	0.88 ± 2.10	27.27 ± 3.37	1.38 ± 1.07
VRP002	34.12 ± 2.04	0.61 ± 0.90	0.92 ± 2.07	33.69 ± 3.44	1.51 ± 1.34
VRP003	33.78 ± 2.52	0.58 ± 1.04	0.89 ± 2.40	34.83 ± 2.06	1.22 ± 1.10
VRP004	29.16 ± 3.88	0.73 ± 1.56	0.89 ± 3.06	17.98 ± 2.00	1.17 ± 2.06
VRP005	27.50 ± 1.37	0.71 ± 1.99	0.83 ± 1.21	14.45 ± 3.08	1.17 ± 1.76
VRP006	29.44 ± 2.00	0.59 ± 1.43	0.79 ± 1.08	25.32 ± 3.15	1.34 ± 1.54
VRP007	30.26 ± 1.25	0.66 ± 2.88	0.77 ± 1.00	14.29 ± 2.11	1.17 ± 1.44
VRP008	29.76 ± 1.23	0.67 ± 3.71	0.78 ± 3.02	14.10 ± 3.66	1.16 ± 1.74
VRP009	36.16 ± 2.49	0.58 ± 4.89	0.90 ± 3.12	35.56 ± 3.00	1.55 ± 0.89
VRP010	33.74 ± 1.87	0.68 ± 1.36	0.87 ± 2.07	21.83 ± 3.96	1.28 ± 2.21
VRP011	32.22 ± 1.55	0.71 ± 2.11	0.98 ± 3.10	27.55 ± 3.55	1.38 ± 1.67
VRP012	28.11 ± 1.37	0.63 ± 2.23	0.79 ± 1.05	20.25 ± 3.82	1.25 ± 0.88
VRP013	26.00 ± 2.64	0.57 ± 1.25	0.77 ± 2.04	25.97 ± 2.37	1.35 ± 0.65
VRP014	29.43 ± 0.98	0.72 ± 3.01	0.82 ± 3.01	24.10 ± 2.09	1.14 ± 0.89
VRP015	27.56 ± 1.77	0.63 ± 3.74	0.83 ± 1.00	24.10 ± 3.57	1.32 ± 0.65
VRP016	30.33 ± 1.62	0.66 ± 3.01	0.79 ± 1.01	16.46 ± 2.33	1.12 ± 1.11

NB: all values are expressed as mean ± % RSD

Table 3.5 continued.

Formulations	Angle of Repose (°)	LBD (g/ml)	TBD (g/ml)	CI (%)	HR
VRP017	26.26 ± 1.84	0.71 ± 1.04	0.85 ± 2.05	16.47 ± 3.21	1.20 ± 2.34
VRP018	27.45 ± 3.05	0.69 ± 2.04	0.78 ± 2.12	11.54 ± 3.67	1.13 ± 3.44
VRP019	26.98 ± 2.04	0.73 ± 3.61	0.79 ± 3.00	8.90 ± 3.44	1.10 ± 2.21
VRP020	27.88 ± 1.82	0.74 ± 2.08	0.84 ± 3.06	11.90 ± 2.05	1.14 ± 4.76
VRP021	27.16 ± 1.04	0.68 ± 4.03	0.79 ± 2.11	14.18 ± 2.32	1.16 ± 2.43
VRP022	28.22 ± 2.02	0.65 ± 3.13	0.76 ± 2.22	14.47 ± 2.04	1.17 ± 2.23
VRP023	30.67 ± 1.52	0.66 ± 2.01	0.76 ± 3.01	12.59 ± 2.41	1.15 ± 2.45

NB: all values are expressed as mean ± % RSD

3.5 CONCLUSION

A dosage form of well defined mechanical strength is produced when powders or granules are compacted. Therefore, a thorough knowledge of powder science is of great importance in formulation studies. The results of testing reveal that flowability and compressibility are two critical factors that are essential in ensuring successful tableting. As a result, granulation procedures (WG) seemed to produce the most appropriate materials for compaction and thus all subsequent batches (VRP019-VRP023) were prepared using this technique.

Furthermore, this study highlighted the vital importance of knowing the behaviour of powders or granules well in advance before attempting to tablet these batches.

CHAPTER FOUR
FORMULATION AND ASSESSMENT OF SUSTAINED RELEASE MATRIX TABLETS

4.1 SUSTAINED DRUG DELIVERY

4.1.1 Introduction

The population of patients with chronic conditions or complications of disease is increasing. These situations necessitate patients having to take drugs for a long period and or taking a number of different medicines simultaneously. This in turn can lead to an increase in non-compliance by the patient. Lack of compliance tends to be serious when using drugs with short biological half-lives because they must be taken more frequently than long half-life compounds, in order to maintain therapeutic blood levels. One method to solve such problems is to find a dosage form capable of releasing the drug gradually over a specific period of time in a controlled manner [132].

There is little or no control over release of drug from immediate-release (IR) dosage forms, which often results in constantly changing, unpredictable fluctuating blood levels. In addition, blood level concentrations may fall below the minimum effective concentration (MEC) or above the maximum therapeutic concentration (MTC) resulting in ineffective therapy or unwanted or untoward side effects [133].

The oral route is the preferred route of administration for drug delivery as it offers several advantages over other potential routes due to the potential for better patient compliance and the flexibility in designing dosage forms [134-136].

VRP is one of many drugs that may be used in the chronic treatment of hypertension and angina. Successful treatment requires the maintenance of blood pressure at normal physiological levels, for which a constant and uniform supply of drug is necessary [137]. VRP has a relatively short half-life [2, 7] and the usual oral dosage regimen is 80mg administered 3 times a day [2, 19, 20]. To reduce the frequency of administration and improve patient compliance, a sustained release formulation of VRP may be preferable to

IR products. The drug has a pK_a value of 8.6 [9], is sparingly soluble in water [9, 10] and is administered as a racemic mixture of the R and S enantiomers [60, 138], hence judicious selection of release-retarding excipients is necessary to achieve constant *in-vivo* release rates and subsequent absorption rates.

4.1.2 Oral Sustained Release Dosage Forms

Various polymers have gained importance in the pharmaceutical industry as both drug coatings and vehicles of drug carriage that either protect an active agent during its passage through the body until it is released or by controlling its release, such that a constant release rate is achieved. A few commonly used technologies cited in literature include reservoir, osmotic pump and matrix systems [139].

4.1.2.1 Reservoir Devices

A reservoir device approach to control drug release relies on the encapsulation of a drug within a polymer film or coating. Film coating [114] and micro-encapsulation [140], are both ideal methods for the production of reservoir type sustained-release dosage forms.

Figure 4.1 depicts a schematic representation of the drug release process from a diffusion based reservoir tablet at different times. Important considerations include the use of different additives, polymer functionality and porosity [139]. Of all aspects that need to be considered, the choice of polymer is an important consideration [139, 141].

In these systems, the drug is encapsulated by a high molecular weight polymer (A). In order for the drug to be released from the reservoir, partitioning from the reservoir into the membrane followed by diffusion through the membrane must first occur. Subsequent partitioning from the membrane in to the dissolution fluids (B) completes the process.

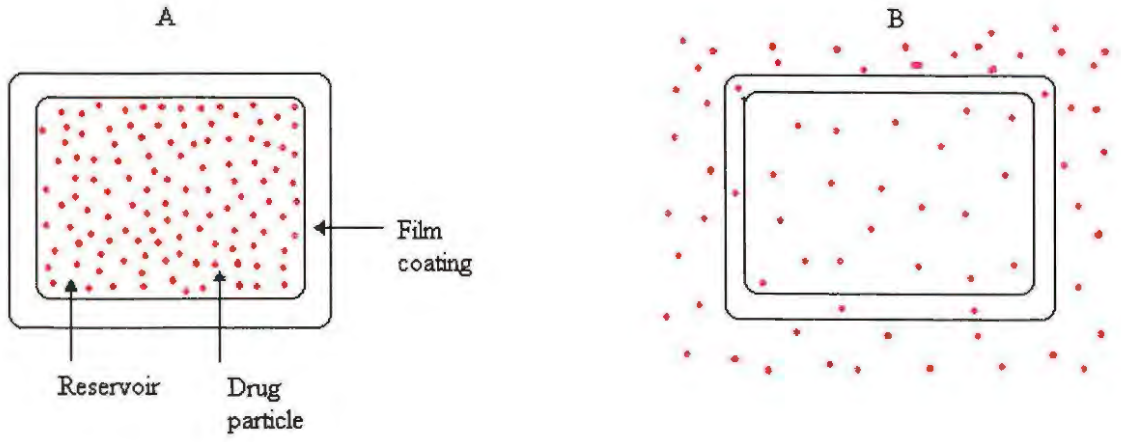


Figure 4.1. Schematic illustration of the mechanism of drug release from a diffusion-based reservoir tablet.

4.1.2.2 Osmotic Devices

Osmotic pump devices are similar to reservoir devices but contain an osmotic agent that generates a suitable osmotic pressure, contained in a tablet and coated with a semi-permeable membrane [139,142]. A small orifice is drilled through the coating by laser or high speed mechanical drill. This system is in essence a coated tablet with an aperture that is exposed to an aqueous environment. A soluble drug or the osmotic agent within the tablet facilitates water uptake through the semi-permeable coating, resulting in the formation of a saturated aqueous drug solution within the device. Hydrostatic pressure is subsequently generated within the device, and the active ingredient is forced out of the device through the orifice that is designed to minimize solute diffusion, whilst preventing the build-up of a hydrostatic pressure head that has the effect of decreasing the osmotic pressure and changing the dimensions of the device [139, 143-45].

Figure 4.2 depicts the mechanism of drug release from an osmotic-controlled release delivery system designed as a single-unit tablet with a single release orifice. The drug is initially encapsulated within a semi-permeable membrane (A). Following the uptake of water into the device, a saturated solution is formed within the device resulting in the build up of pressure which will force the solution out of the device in to the surrounding medium.

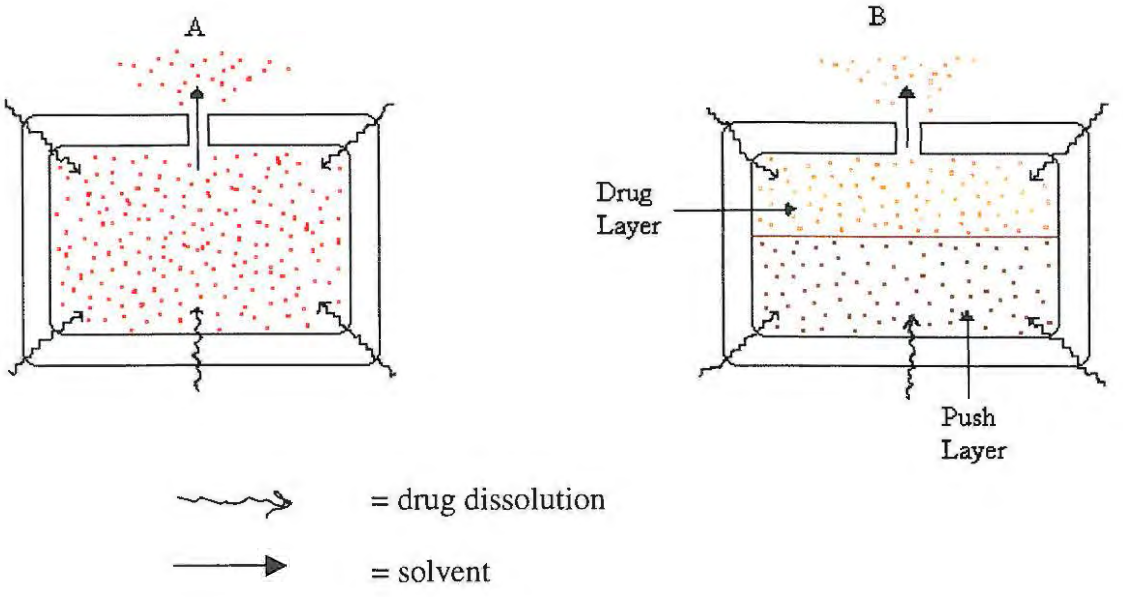


Figure 4.2. Schematic illustration of the mechanism of drug release from an osmotic-controlled release system designed as a single-unit tablet (A) and as a Push-Pull unit (B).

The solubility of a drug in water plays a critical role in the functioning of osmotic pump delivery systems. Typically, the solubility of a drug delivered by these pumps should be at least 10-15% (w/v). The drug is pumped out of the system through the orifice at a controlled rate, which is the product of influx flow rate of water into the core and saturation solubility of the drug as shown in equation 4.1.

$$\frac{dm}{dt} = \left(\frac{dv}{dt} \right) Cs \qquad \text{Eq. 4.1}$$

where

$\frac{dm}{dt}$ = drug flow rate through an orifice,

$\frac{dv}{dt}$ = flow rate of water through an orifice and

Cs = saturation concentration.

In principle, these delivery systems release drug at a zero order rate until the concentration of the osmotically active salt or drug in the system decreases to below its saturation solubility concentration. Deviation from zero order release occurs for the latter part of the *in-vivo* life of the product [143]. Primarily, osmotic systems are suitable for water soluble drugs only and sparingly soluble drugs pose formulation challenges

[139,144,145], such as unexpected or uncontrolled release and inefficient drug dissolution [144].

To overcome this limitation of osmotic devices, an OROS® Push-Pull™ osmotic system has been introduced to deliver insoluble drugs [145]. The Push- Pull™ system (Figure 4.2, B) comprises a bilayer or trilayer tablet core consisting of one push layer and one or more drug layers. The poorly soluble drug is separated from the osmotic agents and suspending agents by a flexible barrier. The push layer contains the osmotic agent(s) and/or water-swellable polymers [145]. A semi-permeable membrane surrounds the tablet core as in the simple osmotic device and an orifice drilled in it on the drug layer side.

4.1.2.3 Matrix Devices

Matrix devices are possibly the most common devices used for controlling the rate of release of drugs. Their abundance is more than likely due to their ease of manufacture compared to reservoir devices and/or osmotic devices. In addition, there is little danger of an accidental high dose due to collapse of delivery system. Monolithic devices, usually consist of an homogeneously dissolved or dispersed therapeutic agent within the polymer matrix, which is then compressed into a tablet/dosage form [139].

Formulation factors, through which the release rate from a matrix system can be modified are by control of the amount of drug in the matrix, the porosity of the release unit, the length and tortuosity of the pores within the release unit, the size of the release unit and the solubility of the drug, which regulates the concentration gradient [141].

Matrix drug delivery systems are usually of two types, *viz.* diffusion/swellable systems or dissolution systems. In diffusion controlled systems, drug release involves solvent penetration, hydration and swelling of the matrix followed by diffusion of the drug molecules from the hydrated layer of the matrix to the surrounding bulk solution. The most common examples of excipients used in matrix systems to sustain/prolong or control drug release include cellulose ethers (*e.g.*, HPMC), methacrylic acid copolymers and carbomers [135]. Figure 4.3 depicts a schematic mechanism of drug release from a

non-eroding diffusion-controlled matrix tablet at different times during dissolution testing.

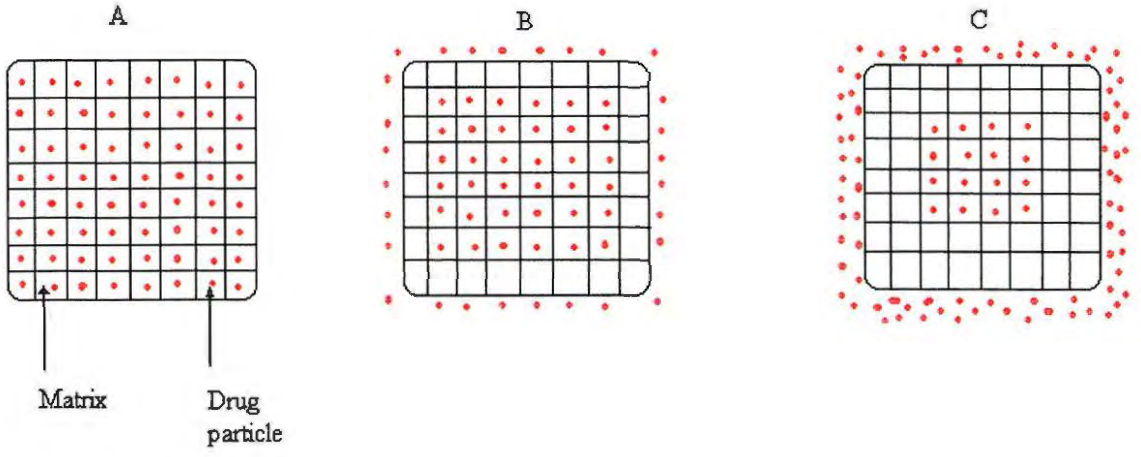


Figure 4.3. Schematic illustration of the mechanism of drug release from a diffusion-controlled matrix tablet.

Initially (A), drug particles located at the surface of the release unit are dissolved and released into the dissolution media (B). As the drug is depleted from the surface of the dosage form, a receding dissolution front is set up within the device (C). Consequently, as the diffusion distance within the dosage form increases the release rate slows down.

Dissolution control systems alter release rates by control of dissolution/erosion of the matrix and hence the attainment of constant rate of drug delivery is easily achieved. Figure 4.4 depicts a schematic of the mechanism of drug release from a dissolution/erosion tablet at different times. Sodium carboxymethylcellulose (SCMC) and natural gums have been the most widely used polymers in such dosage forms [135].

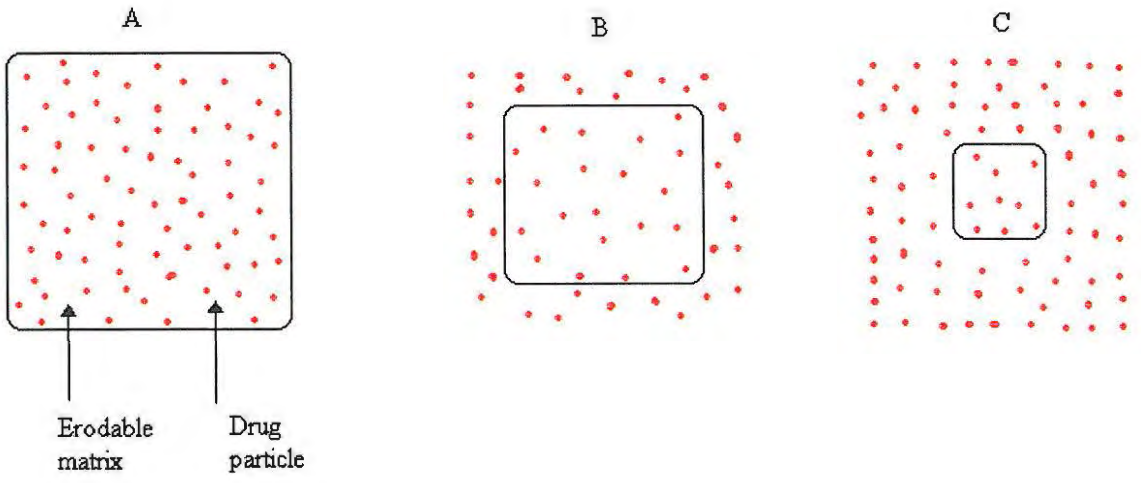


Figure 4.4. Schematic illustration of the mechanism of drug release from an erodable tablet.

In erosion-controlled systems the rate of drug release is controlled by the rate of erosion of the matrix material in which the drug is dispersed. The matrix is normally a tablet and initially (A) drug particles located at the surface of the release unit are dissolved and thereafter, the matrix undergoes erosion. The erosion process involves the continuous liberation of both drug and matrix excipients from the surface of the tablet (B). Further erosion of the dosage form (C) results in a continuous reduction in tablet weight during the course of the release process.

An important stage in the formulation process of a matrix system is the selection of a suitable polymeric material as the matrix forming component, due to the fact that the design of these systems has focused on the concept of polymeric hydration to protect the tablet from rapid disintegration and dissolution in order to delay drug release. Various types of polymers with different sol-gel transitions have been investigated to develop swellable delivery systems. Water penetration capacity, polymer swelling rate, drug dissolution and matrix erosion are the major factors that determine gel layer thickness, which is capable of preventing matrix disintegration and further rapid water penetration [134].

4.2 EXPERIMENT

4.2.1 Proposed Evaluation Design

The tablet formulations were prepared by either direct compression or wet granulation using Carbopol® 974 P NF as the primary matrix polymer for the DC products and either Surelease® E-7-19010 or Eudragit® NE 30D as the granulating fluids for WG. The success of the method of manufacture was determined using comparative dissolution testing of the TEST products versus the commercially available product, Isoptin® SR 240 mg. In addition, physical characteristics such as weight, content uniformity, crushing strength, tensile strength in addition to friability and water uptake studies were performed. The suitability of the granules/powder blend in terms of powder properties such as the angle of repose, bulk density, tapped density, Carr's compressibility index and Hausner's ratio were assessed and have been reported in § 3.2.1, § 3.2.2, § 3.2.3 and § 3.2.4.

4.2.2 Preliminary Studies

Single-unit and multiple-unit monolithic matrix tablets of 7 mm and 11 mm in diameter were manufactured. The active ingredient VRP was obtained from Aspen-Pharmacare (Port Elizabeth, South Africa) and was used as the model drug for these investigations. The other excipients were sourced from different manufacturing companies and are listed in Table 4.1.

Table 4.1. Excipients used in formulation studies.

EXCIPIENTS	MARKET/TRADE NAME	MANUFACTURER / DONOR
Verapamil hydrochloride	Verapamil HCL	Aspen Pharmacare, SA
Carbomer	Carbopol® 971/974 P NF	Noveon, Inc., Brecksville, Cleveland, USA
Hydroxypropylmethylcellulose	Methocel® K100M	Colocorn® LTD, Dartford, Kent, UK
Ammonio methacrylate	Eudragit® RS /RL PO	Rohm Pharma Polymers, Darmstadt, GmBH
Ammonio methacrylate	Eudragit® RS /NE 30D	Rohm Pharma Polymers, Darmstadt, GmBH
Dibasic calcium phosphate USP/Ph.Eur/.JP/BP/	Emcompress®	Penwest Pharmaceutical Co., Mendel, UK
Microcrystalline cellulose	Emcocel® 90M	Penwest Pharmaceutical Co., Mendel, UK
Ethylcellulose NF	Ethocel® 10 FP	Dow Chemical Co., Michigan, USA
Ethylcellulose dispersion	Surelease ® E-7-19010	Colocorn® LTD, Dartford, Kent,UK
Lactose monohydrate USP/NF/BP/EP/JP	Super Tab®	Lactose Co. Hawera, NZ
Talc	Talc	Aspen Pharmacare, SA
Magnesium stearate	Magnesium stearate	Aspen Pharmacare, SA

4.2.3 Preparation of the Sustained-Release Test Formulation

Tablets were manufactured by either direct compression or wet granulation procedures. All batches were subjected to testing and a summary of the results for each manufactured batch including observations made during the tabletting process are shown in appendix 1. An example of a typical executed batch manufacturing record used to record the manufacturing process for all batches produced either by direct compression or wet granulation are included in appendix 2 and 3, respectively. Formulations prepared with different drug/polymer ratios are shown in § 3.4 and Table 3.4. Prior to tabletting, powder flow properties were assessed in order to ensure that all blends possessed good flow properties to prevent non-uniform tablet production.

4.2.4 Method of Manufacture

4.2.4.1 Direct Compression

The simplicity of the direct compression process has positioned it as an ideal starting procedure for tablet manufacture and was used initially in these studies. The initial direct compression formula for VRP is presented in Table 4.2.

Table 4.2. Direct compression formula of tablet batch VRP001.

Formula	% (w/w)
Verapamil hydrochloride	33.0
Carbopol® 974P NF	10.0
Lactose monohydrate	56.0
Talc	0.5
Magnesium stearate	0.5

The batches of tablets that were manufactured using direct compression techniques were VRP001 to VRP019. The following procedure was adopted in the manufacture of batch

VRP001and all other DC batches followed a similar process with minor modifications where appropriate.

4.2.4.1.1 Direct Manufacturing Procedure

All components, except for the magnesium stearate and talc were individually weighed using a top-loading electronic balance Model PM 4600 (Mettler, Zurich, Switzerland), screened (mesh size 20) and blended in a cube blender rotating at 100 rpm for 20 minutes, at a horizontal angle. Magnesium stearate and talc were then weighed, screened (mesh size 40) and added to the mixture. The blending process was continued for a further 3 minutes. A schematic diagram depicting this process is shown in Figure 4.5.

The powder blend was fed from a hopper and tablets were prepared on a 16-station rotary press (Manesty® B3B, England) fitted with 11 mm concave punches. Where necessary, die cavities were blocked with a solid teflon disc to facilitate the preparation of small batches. The target weight and hardness of the tablets were 720mg and 100-140N (10 – 14Kp) respectively. Tablets were de-dusted using a vacuum through a sieve and analyzed after 24 hours.

Batches VRP001 – VRP010 were compressed on the rotary press and batches VRP011 – VRP019 were tabletted using a single punch tablet press (Manesty® F3, England) to prepare tablets of 7 mm diameter. The breaking load of the 7 mm diameter tablets was 80 -110 N (8.0-11.5 Kp) and the target tablet weight was 250 mg.

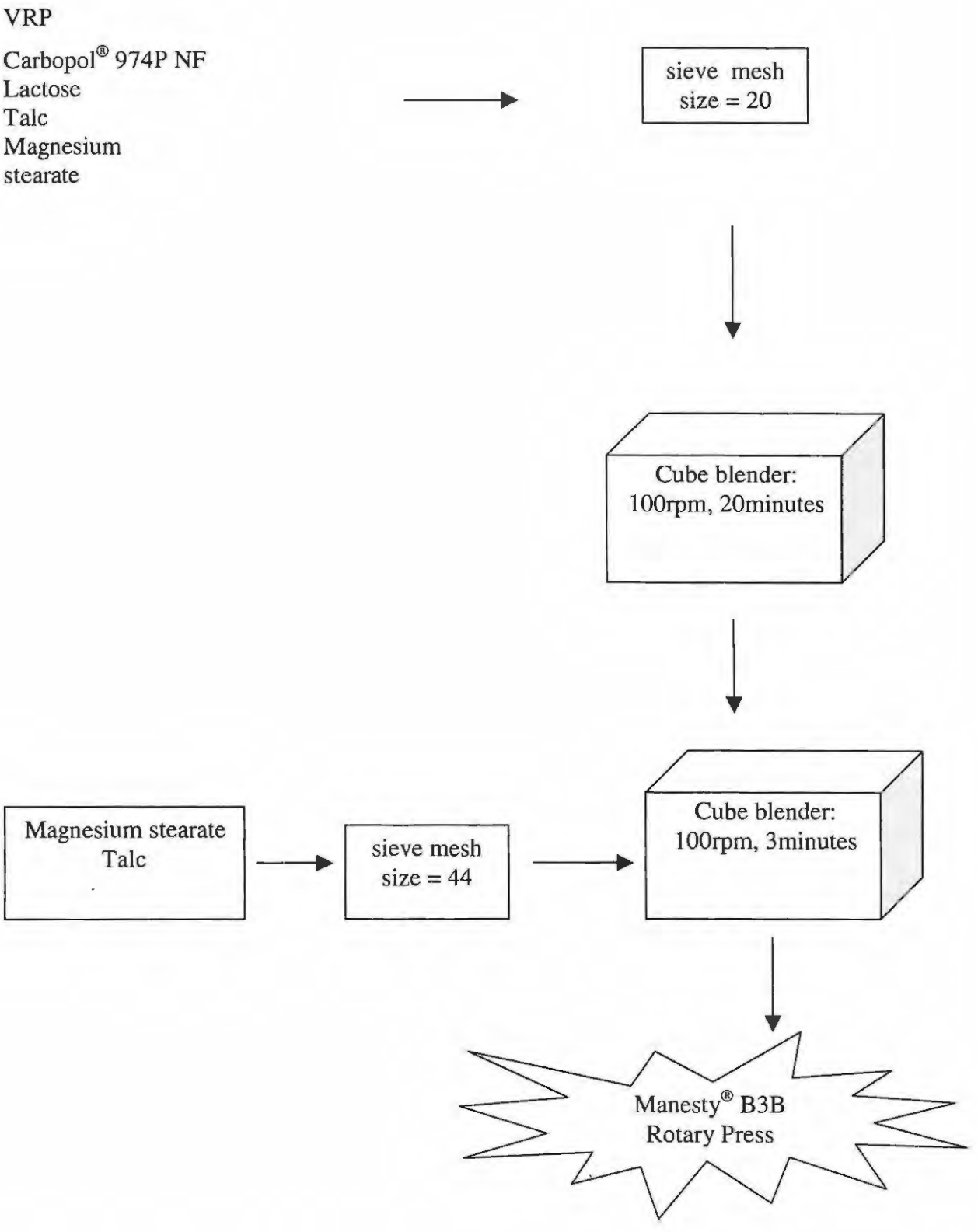


Figure 4.5. A general schematic for direct compression of VRP tablets.

4.2.4.2 Wet Granulation

Wet granulation is a widely applicable and acceptable method of tablet manufacture involving weighing and sieving of dry powders, blending with an appropriate granulating fluid, screening the damp mass, followed by drying and re-screening of the dry granules. The lubricant is added in a similar way to that in the DC method and the granules are finally compressed into tablets. Table 4.3 and Table 4.4 depict the wet granulation formulae of tablet batch VRP021, in which Surelease® E-7-19010 was used as the granulating fluid and tablet batch VRP023, in which Eudragit® NE 30D dispersion was the granulating fluid, respectively. Figure 4.6 depicts a schematic diagram of the wet granulation method of manufacture used in these studies.

Table 4.3. Wet granulation formula of tablet batch VRP021.

Ingredients	**% (w/w)**
(1) VRP	33.0
Carbopol® 974P NF	5.0
Eudragit® RS	7.5
Emcocel® 90M	10.0
(2) Surelease® E-7-19010	20.0 ml
(3) Carbopol® 974P NF	5.0
Eudragit® RS	6.0
Emcocel® 90M	10.0
Emcompress®	20.0
(4) Magnesium stearate	0.5

Table 4.4. Wet granulation formula of tablet batch VRP023.

Ingredients	% (w/w)
(1) VRP	33.0
Carbopol® 974P NF	5.0
Ethocel	10.0
(2) Eudragit® NE 30D	20.0 ml
(3) Carbopol® 974P NF	5.0
Ethocel	6.0
Emcocel® 90M	10.0
Emcompress®	20.0
(4) Magnesium stearate	0.5

The batches of tablets that were manufactured using a wet granulation method were VRP020 to VRP023. The following description refers primarily to the manufacture of batch VRP021 for the formulation presented in Table 4.3. However, a similar procedure was used for the manufacture of batch VRP023.

4.2.4.2.1 Wet Granulation Procedure

The sustained-release test formulations were prepared by blending VRP, Carbopol® 974P NF, Eudragit® RS and Emcocel® 90M (1). The powders were weighed separately using a top-loading electronic balance Model PM 4600 (Mettler, Zurich, Switzerland), screened (mesh screen no.20) and granulated with Surelease® E-7-19010 (2), using a Kenwood planetary mixer (Kenwood, UK) on setting 1. Surelease® E-7-19010 dispersion was diluted to 15% as per manufacture's recommendations. The granulate was then passed through a sieve (mesh screen no. 20) using an oscillating granulator (Erwerka, GmbH, Germany) set at 50 rpm. The granules were dried in an oven maintained at 60°C, for 12 hours, after which, they were re-screened (mesh screen no. 20). The weight of the granule mass was recorded. Carbopol® 974P NF, Eudragit® RS, Emcompress® and Emcocel®

90M (3), was weighed, screened (mesh screen no.20) and blended with the granules in a 1 kg capacity cube blender set at a horizontal angle. Blending was effected at 100 rpm for 30 minutes to ensure adequate mixing. The mixture was lubricated with magnesium stearate (4), which was sieved (mesh screen no. 40) and added to the mixture, which was blended for a further 3 minutes. The blend was fed from a hopper and tablets were prepared on a single punch tablet machine (Manesty® F3, England) as presented in the schematic diagram in Figure 4.5. A set of tablet punches with flat surfaces was used to prepare tablets with a 7 mm diameter.

After compression, the tablets produced by both dry and wet granulation methods were evaluated for weight and content uniformity, crushing strength, tensile strength, friability, swelling index and erosion. The mini-tablets prepared on a single tablet machine were enclosed in a size 00 capsule prior to dissolution testing and liquid uptake studies.

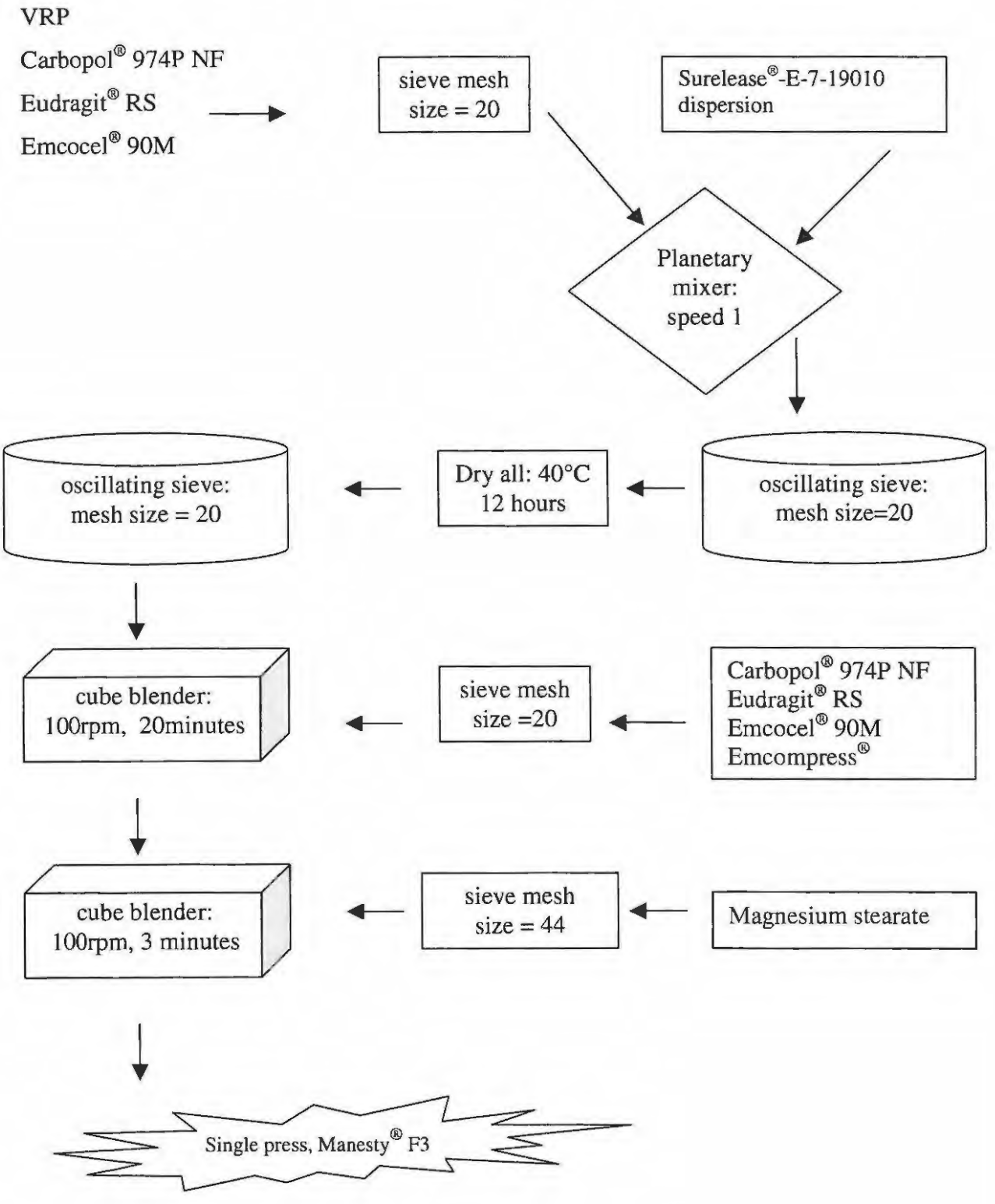


Figure 4.6. A general schematic for wet granulation of VRP tablets.

4.2.5 *In-Vitro* Dissolution Studies

In- vitro dissolution testing has been recognized as an important quality control test for drug products because of its potential association with drug bioavailability [146, 147]. The FDA recommends the use of dissolution as a quality control procedure to ensure lot-to-lot uniformity, to detect manufacturing and/or process variables that could result in variation of product bioavailability, if the test is discriminatory [146].

Furthermore, it can also be employed as a surrogate for assessment of bioequivalence under certain conditions. In view of the significance of dissolution testing, it is therefore essential to investigate drug release characteristics from pharmaceutical preparations. In the development of oral controlled-release products, an ethical or proprietary product, which has been available on the market for some time and that has an established safety and efficacy profile in clinical use is usually selected as a reference. The generic preparation is always formulated so that its dissolution profile is as similar as possible to that of the proprietary product prior to *in-vivo* investigations [147].

Costa and Lobo [148] described dissolution as a process by which a solid of only fair solubility characteristics will enter into solution. The earliest reference to dissolution was made by Noyes-Whitney in 1897 [149], and it was suggested that the dissolution rate of solid substances was determined by the diffusion rate of drug through a very thin layer of saturated solution that forms instantaneously around a solid particle.

Dissolution is the process whereby a solid particle immersed in a liquid undergoes two consecutive steps. Initially, dissolution of the solid at an interface occurs, forming a stagnant layer (or film) with a specific thickness (h) around that particle. Further dissolution results in diffusion of the solute molecules from this stagnant layer to the bulk of the dissolution fluid. The first step is almost instantaneous, but the second is much slower and often becomes the rate limiting step in dissolution. The Noyes-Whitney equation describing dissolution is shown as equation 4.2 and a different version in equation 4.3.

$$\frac{dM}{dt} = \frac{DS}{h}(Cs - C) \qquad \text{Eq. 4.2}$$

or

$$\frac{dC}{dt} = \frac{DS}{Vh}(Cs - C) \qquad \text{Eq. 4.3}$$

where

M = mass of solute dissolved in time t,

$\frac{dM}{dt}$ = mass rate of dissolution,

D = diffusion coefficient of the solute in solution,

S = the surface area of the exposed solid,

h = thickness of the diffusion layer,

Cs = saturation solubility,

C = the concentration of the solute in the bulk solution at time t,

$\frac{dC}{dt}$ = dissolution rate and

V = volume of the dissolution

A number of different dissolution apparatus have been described in the literature [111,133,134,150,151]. The rotating basket (USP apparatus 1) and the paddle (USP apparatus 2) devices are simple, robust and adequately standardized apparatus that are used world wide and thus are supported by the widest experience of experimental use. The paddle and the rotating basket apparatus are recommended in various guidelines as the first choice for *in-vitro* dissolution testing of immediate and controlled/modified-release dosage forms [150].

However, due to the single container nature of the paddle/basket apparatus, experimental difficulties may arise in terms of a change in pH, saturation issues, change in sink conditions or any other test medium parameter change during a specific experiment [150].

The reciprocating cylinder or USP apparatus 3 (Bio-Dis®) has been described [150]. Generally, apparatuses 1-3 can easily be used to characterize the dissolution rate of

almost any drug product. If a drug product cannot be accommodated by one of the apparatus described above, alternative models or appropriate modifications to these apparatus may be developed. However, superiority of the alternative method or the modification must be shown when compared to the well established and standardized equipment [150].

The Bio-Dis® dissolution apparatus has had a relatively short history since its proposal for use as a apparatus by Borst *et al* [151] for drug release testing of extended-release products and as an alternative to the basket (USP apparatus 1) and paddle (USP apparatus 2).

The development of USP apparatus 3 was based on the recognition of the need to establish potential *in-vitro in-vivo* correlations and the fact that the dissolution results obtained with USP apparatus 1 and 2 may be significantly affected by shaft wobble, location, centering and coning [151]. USP apparatus 3 offers the advantages of mimicking in part the changes in the physicochemical environment experienced by products in the gastro-intestinal tract [151].

4.2.5.1 USP Apparatus 1 (Basket)

The dissolution behaviour of VRP from both commercially available and extemporaneously prepared dosage forms was assessed using a fully automated Hanson Research SR 8 PLUS (Chartsworth, CA, USA) dissolution apparatus fitted with an Autoplus™ Multifill™ and Maximizer Syringe Fraction Collector, respectively. The release studies were carried out at 37±0.5°C using USP Apparatus 1 fitted with 8 USP baskets (40-mesh) rotated at 100 rpm. All dosage forms were placed in the baskets that were then lowered into 900 ml of degassed phosphate buffer (0.1 M, pH 7.4). The percent drug released from tablets after a 22-hour tests was determined. Samples (2 ml) were withdrawn and replaced with 2 ml of fresh medium that has automatically been filtered through a 10 μm membrane. Samples were collected at predetermined time intervals after 1, 2, 6, 10, 14 and 22 hours. A summary of the dissolution test conditions for this study is depicted in Table 4.5.

Prior to use, the performance of the Hanson dissolution apparatus was verified by calibration with USP prednisone and salicylic acid calibrator tablets.

4.2.5.2 USP Apparatus 3 (Bio-Dis®)

In addition, a VanKel® Bio-Dis® dissolution tester (VanKel® Industries, New Jersey, USA) was also used for dissolution testing of dosage forms. A model VK 750D digitally controlled water circulation / heater (VanKel® Industries, New Jersey, USA) was used to maintain the temperature of both dissolution media at 37± 0.5°C. Samples were collected at predetermined time intervals at 1, 2, 6, 10, 14 and 22 hours and a summary of the dissolution test conditions for this study is depicted in Table 4.5.

The following parameters were assessed for their impact on drug release rate using this apparatus. The screen mesh sizes supplied with the Bio-Dis® were lahelled as 160, 78, 40 and 20, respectively, corresponding to pore sizes of 74, 177, 405 and 840 μm.

Table 4.5. Summary of general dissolution conditions for basket and reciprocating cylinder dissolution test methods in this study.

Parameter	**USP Apparatus 1**	**USP Apparatus 3**
Dissolution medium	Buffers (pH 1.6, 3.4, 4.6, 6.8 and 7.4)	Buffers (pH 1.6, 3.4, 4.6, 6.8 and 7.4)
Temperature	37.0 ± 0.5°C	37.0 ± 0.5°C
Initial volume	900 ml	180 ml
Basket / dip speed	50 / 100 rpm	10 / 20 dpm
Screen size	405 µm	405 µm top /177 µm bottom
Filter size	0.45 µm	0.45 µm
Volume drawn	2 ml	2 ml
Dissolution time	22 hours each in pH 1.6, 3.4, 4.6, 6.8 and 7.4	1 hour each in pH 1.6 and 3.4 4 hours each in pH 4.6, 6.8, 12 hours in pH 7.4

4.2.6 Physical Characterization of Tablets

4.2.6.1 Weight Uniformity

The weight of each of 20 randomly selected VRP tablets was determined using a top-loading electronic balance Model AG 135 (Mettler Toledo, Switzerland) and the average weight of each manufactured batch established (Table 4.7).

4.2.6.2 Content Uniformity

Twenty randomly selected VRP tablets from each batch were weighed and powdered using a mortar and pestle. An aliquot of powder equivalent to 240 mg of drug was accurately weighed and transferred into a 100 ml volumetric flask containing approximately 70 ml mobile phase. The solution was stirred continuously for 1 hour using a magnetic stirrer (Gallenkamp™, UK) and then made up to volume with mobile phase. The solution was filtered through a 0.45 μm hydrophilic PVDF (Millipore® Millex-HV, Millipore Corporation, Bedford, MA, USA) membrane prior to analysis by HPLC using the chromatographic conditions reported in § 2.4. Individual concentrations were calculated from a calibration curve, and the average values for tablet uniformity calculated for each batch of tablets (Table 4.7).

4.2.6.3 Crushing Strength

The crushing strength of the tablets was measured using an Erweka TB 30 hardness tester (Erweka, GmbH, Heusenstamm, Germany) 24 hours after compaction. Twenty tablets from each batch were tested and the results are shown in Table 4.7. The tablets were oriented the same way in relation to the direction of the applied force to facilitate comparison of the results in all cases.

4.2.6.4 Tensile Strength

The tensile strength of all batches of tablets was calculated using data generated in diametral-compression tests. The relative value of tensile, compressive and shear stress

within a tablet varies, depending on the characteristics of the tablets and the surface providing the applied compression [152]. The tensile strength of tablets from each batch was calculated using equation 4.4 and results are shown in Table 4.7.

$$\sigma_o = \frac{2F}{\pi dT} \qquad \text{Eq. 4.4}$$

where

σ_o = maximum radial tensile strength, N/mm^2,

F = crushing strength, N,

D = tablet diameter, mm and

T = tablet thickness, mm.

4.2.6.5 Friability

The friability of all batches of tablets was measured using an Erweka TA3R friabilator (Erwerka, GmbH, Heusenstamm, Germany). Twenty tablets were de-dusted and weighed on an electronic top-loading balance Model AE 163 (Mettler, Zurich, Switzerland). The tablets were allowed to tumble for 4 minutes at 25 rpm or for 100 drops. Tablets were de-dusted, re-weighed and the percent friability of the tablets calculated (Table 4.7).

4.2.6.6 Water Uptake and Erosion

VRP tablets (n = 3) were weighed individually on a Mettler Model A163 electronic top-loading balance. The tablets were subjected to dissolution test conditions using USP apparatus 1. Tablets were withdrawn at 1, 2, 6 10, 14 and 22 hours, placed on petri dishes and excess surface water removed carefully, using filter paper. The swollen tablets were re-weighed prior to being dried in an oven at 60°C for 12 hours. After drying, the tablets were allowed to cool at ambient temperature and then weighed until a constant weight was achieved (final dry weight). The increase in weight of the wet mass represents the uptake of the dissolution medium and permits the determination of the swelling index (SI) using the method described in equation 4.5 [153].

$$SI = \frac{W_H - Wi}{Wi} \qquad \text{Eq. 4.5}$$

where

Wi = mass of tablet before placing in dissolution media,

W_H = mass of tablet after placing in dissolution media (hydrated).

The percentage increase (Q) or the increase in weight of the tablet that is due to the absorbed medium was calculated using equation 4.6.

$$Q = \left(\frac{W_H - Wi}{Wi}\right) X\ 100 \qquad \text{Eq. 4.6}$$

where

Wi = mass of tablet before placing in dissolution media,

W_H = mass of tablet after placing in dissolution media (hydrated).

Efentakis *et al* [154] established that the degree of erosion (E) of a dosage form may be estimated using equation 4.7.

$$E = \left(\frac{Wi - Wf}{Wi}\right) X100 \qquad \text{Eq. 4.7}$$

where

Wi = mass of tablet before placing in dissolution media,

W_f = final dry weight after erosion.

4.3 RESULTS AND DISCUSSION

4.3.1 Optimization of the Formulation

Figure 4.7 depicts the percent drug released as a function of time for formulation VRP001 and shows the effects of Carbopol® 974P NF the primary matrix polymer, on drug release rate. The drug release profiles for batches VRP002 – VRP004 are shown in appendix 1. It is apparent that carbomer polymers in low polymer/drug ratio do not sustain the release of VRP for a substantial period of time. The release of VRP in the early stages of the 22-hour run is rapid and similar to that observed when testing immediate release dosage forms. Formulations VRP001 and VRP002 release > 90% VRP in 2 hours and batches VRP003 and VRP004 release approximately 60% and 50% of the drug, respectively. Therefore, these formulations were considered inappropriate for further development studies, but served as a starting point for identifying potential formulation compositions for further studies.

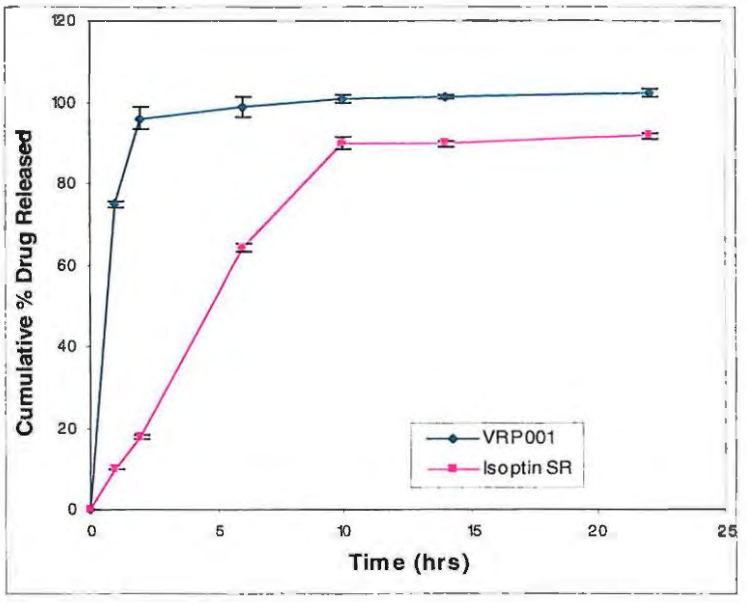


Figure 4.7. Dissolution profile of VRP release from batch VRP001 and Isoptin® SR (n = 6).

Sammani *et al* [128] prepared blends of HPMC and carbomers to formulate a matrix sustained release formulation for diclofenac sodium and thus this polymer combination was considered for use in an attempt to sustain the release of VRP from extemporaneously prepared products.

Formulations for batches VRP005 - VRP008 were then developed and manufactured. The release profile of VRP from tablets of batch VRP005 is depicted in Figure 4.8. Release profiles depicting VRP release from batches VRP006 – VRP008 are shown in appendix 1. It is apparent that these blends can to a certain extent sustain the release of VRP and it is clear therefore, that these blends of carbomer and HPMC are better than carbomer when used alone. The formulation composition of batches VRP005-VRP008 is able to delay the release of VRP and > 70% of drug was released in 10 hours as opposed to the > 90% released in 2 hours from batch VRP001.

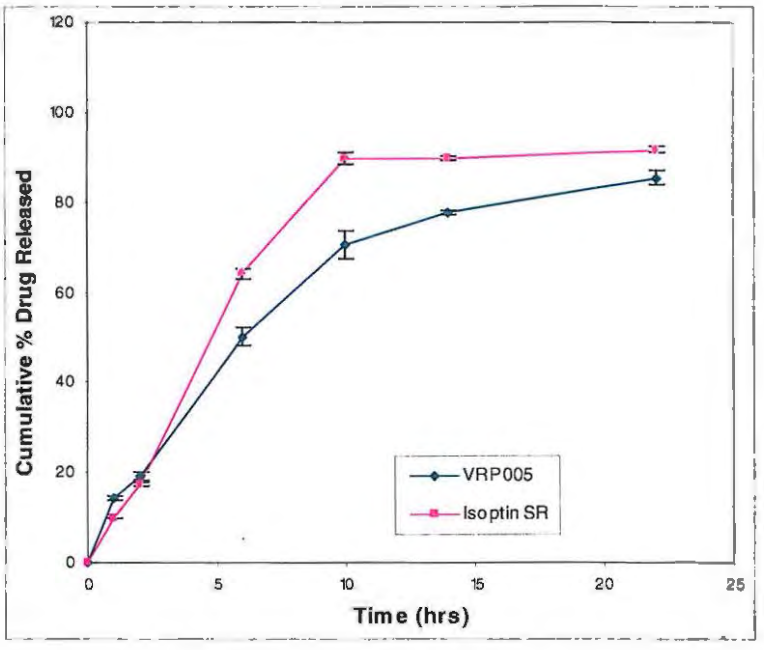


Figure 4.8. Dissolution profile of VRP release from batch VRP005 and Isoptin® SR (n = 6).

It has been shown that a combination of an anionic polymer such as carbomer with a non-ionic polymer such as HPMC can produce a synergistic increase in viscosity of a matrix [128, 155]. This effect was thought to be due to the stronger hydrogen bonding between the carboxyl groups of carbomer and the hydroxyl groups of HPMC, leading to stronger

cross-linking between the two polymers [155]. Similar results have been reported in an earlier study in which diclofenac release from matrices was evaluated [128]. It is likely therefore, that the increased viscosity of the matrix may have resulted in a greater resistance to diffusion of VRP through the polymer matrix with a subsequent decrease in the release rate from this product.

In an attempt to prolong the release of VRP further, formulations VRP009 -VRP014 were developed and manufactured. Figure 4.9 depicts the release rate data for batch VRP009. Release profiles for VRP010-VRP014 are presented in appendix 1.

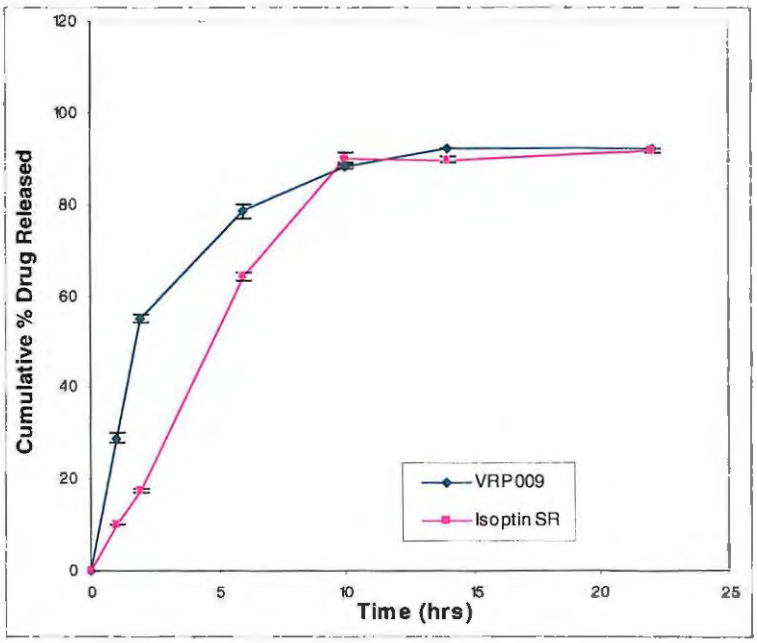


Figure 4.9. Dissolution profile of VRP release from batch VRP009 and Isoptin® SR (n = 6).

Modified-release tablet formulations may also be produced using ethylcellulose as a matrix forming material [119]. The combination of ethylcellulose (5% w/w and 10% w/w) with carbomer also failed to sustain the release of VRP from batch VRP009 as more than 50% of the drug had been released after 2 hours. In contrast, the reference product had released approximately 20% at that time, and therefore, this formulation was not deemed suitable at the concentrations of matrix forming materials used. However, when comparing the dissolution profile of batch VRP001 (Carbopol® 974P NF only) to batch VRP009, it was observed that the incorporation of ethylcellulose had an influence

on the release of VRP. Therefore, there is the probability that blends of Ethocel® with Carbopol® when used in formulation studies may retard drug release rates, synergistically.

In an attempt to prolong the release of the drug further, combinations of carbomer and Eudragit® RS/RL were also evaluated in this study and four formulations, VRP011-VRP014 were manufactured (mini-tablets). Figure 4.10 shows the release profile of batch VRP011. The profiles for VRP012-VRP014 are shown in appendix 1.

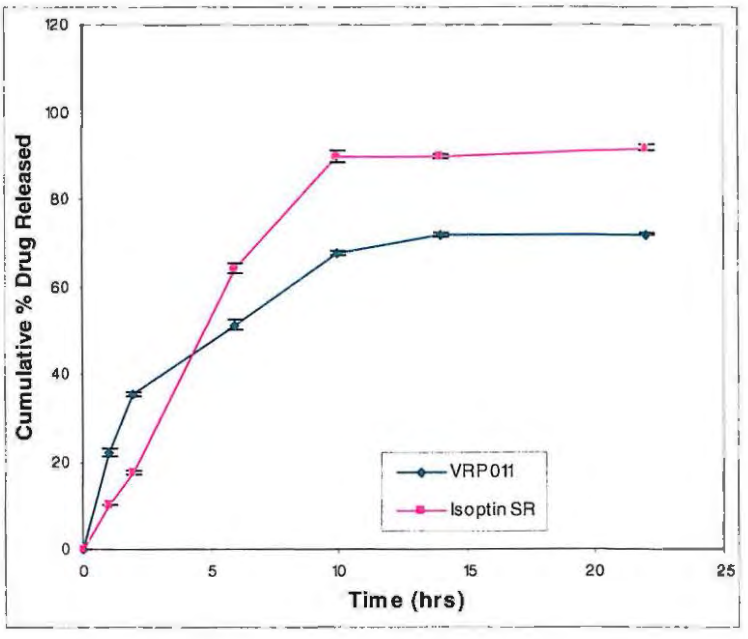


Figure 4.10. Dissolution profile of VRP release from batch VRP011 and to Isoptin® SR (n = 6).

The dissolution release profiles for batches VRP011-VRP013 were similar to that of the reference product for the early stages of the dissolution process only, but did not match the release profile for the entire 22-hour period.

Batch VRP014 in which Eudragit® RS was used as the retarding polymer alone failed to show any sustained release effect. After 2 hours, approximately 75% of the drug had been released and was in solution. In this regard, the release rate profile for this formulation was too fast and thus the formulation was not developed further. In addition the Eudragit® RS/Ethocel® combination in the concentrations tested cannot be used to sustain

VRP release and were in fact no better than the Carbopol®/Ethocel® combination that was used to prepare batch VRP009.

There was no difference in the percent drug release when Eudragit RS® and Eudragit® RL were used in batches VRP011 and VRP012, even though Eudragit® RL is more hydrophilic than Eudragit® RS [121]. Release rate studies of batch VRP015 also revealed that this composition failed to show any sustained release effect better than batch VRP014. After approximately 1 hour, 60% of the drug had been released and the dissolution profile of VRP for this batch is also shown in appendix 1.

Since formulations VRP011-VRP013 had release profiles that were similar to the reference product, these were selected as the starting point for further formulation development studies. Batches VRP016 and VRP017 were prepared with the addition of dibasic calcium phosphate (Emcompress®) or microcrystalline cellulose (Emcocel® 90M) as the diluents in these formulations instead of lactose. Batch VRP016, in which Emcompress® was used, showed almost the same release profile as batch VRP017 and therefore, either of the fillers could be used in formulation of VRP tablets for further studies. A dissolution rate profile for batch VRP016 is shown in Figure 4.11.

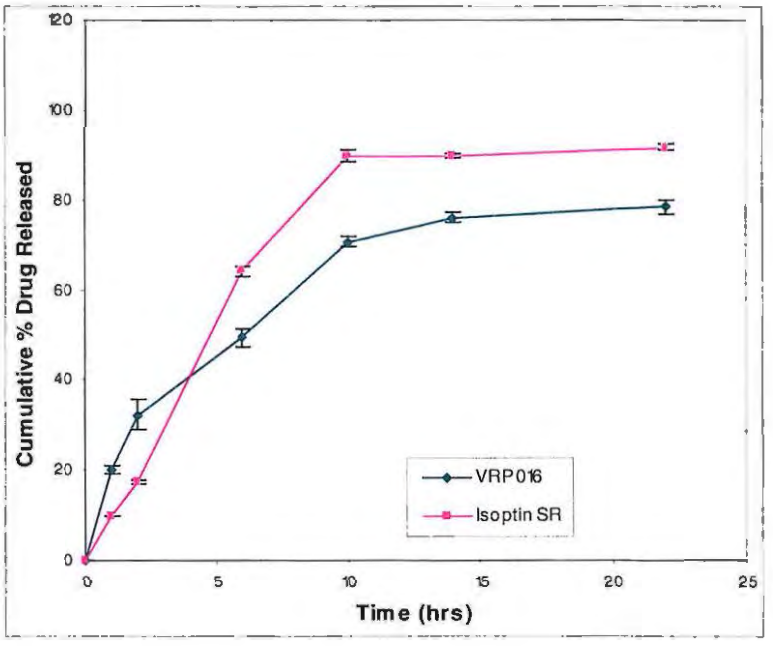


Figure 4.11. Dissolution profile of VRP release from batch VRP016 compared to Isoptin® SR (n = 6).

Batches VRP018 and VRP019 were manufactured using a combination of Eudragit® RS and ethylcellulose as the matrix forming materials at higher concentrations than used previously in the manufacture of batches VRP013-VRP014. The release patterns observed for these formulations did not show the potential to match the reference product even at high concentrations and were therefore not developed further.

Finally, a wet granulation method of manufacture was considered in order to determine whether this method of manufacture and combination of excipients might sustain the release of VRP better than from direct compression formulation. Figures 4.12 - 4.15 show the drug release patterns of batches VRP020-VRP023, respectively. These batches were manufactured using a granulating dispersion of Surelease® E-7-19010, Eudragit® RS 30D and Eudragit® NE 30D. Their release profiles were compared to that of Isoptin® SR and finally formulations VRP021 and VRP023 were adopted for intensive evaluation after satisfying the relevant pharmaco-technical specifications and similarity of release profile to Isoptin® SR.

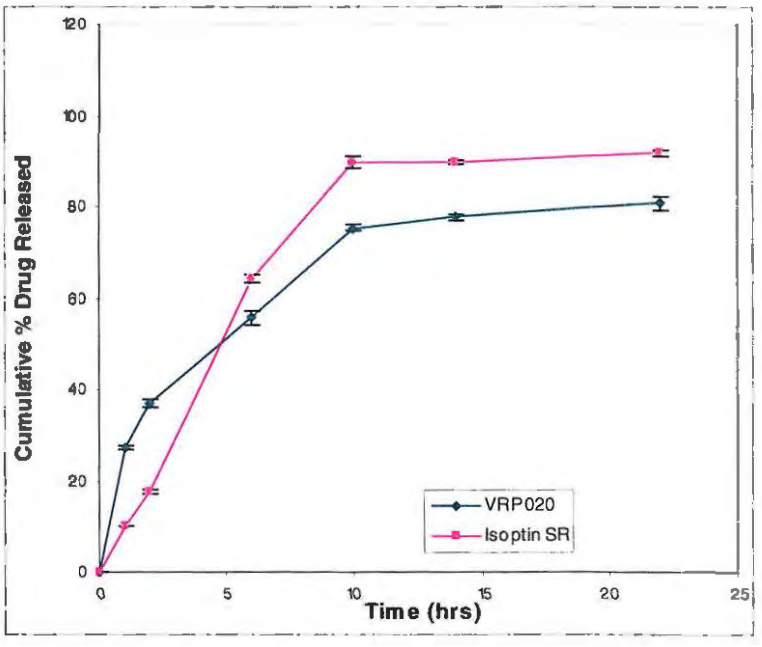


Figure 4.12. Dissolution profile of VRP release from batch VRP020 and to Isoptin® SR (n =6).

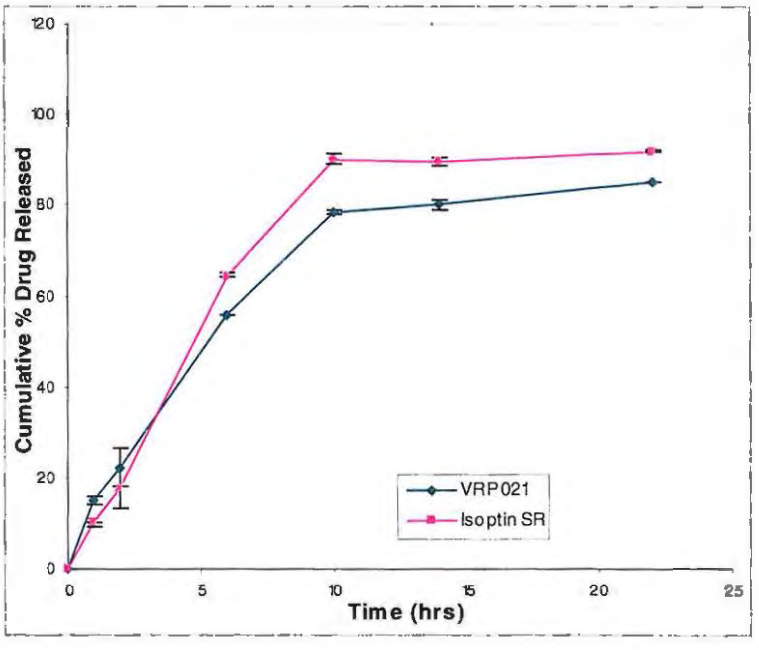


Figure 4.13. Dissolution profile of VRP release from batch VRP021 and to Isoptin® SR (n =6).

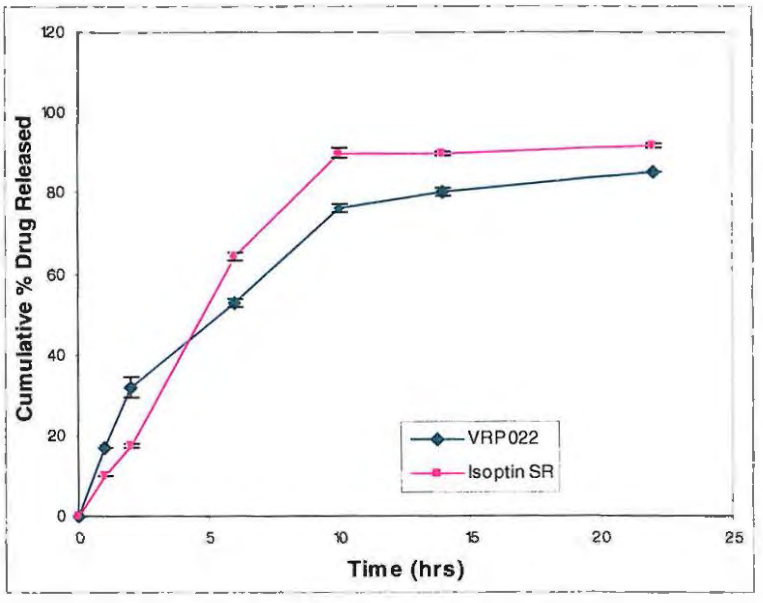


Figure 4.14. Dissolution profile of VRP release from batch VRP022 and to Isoptin® SR (n =6).

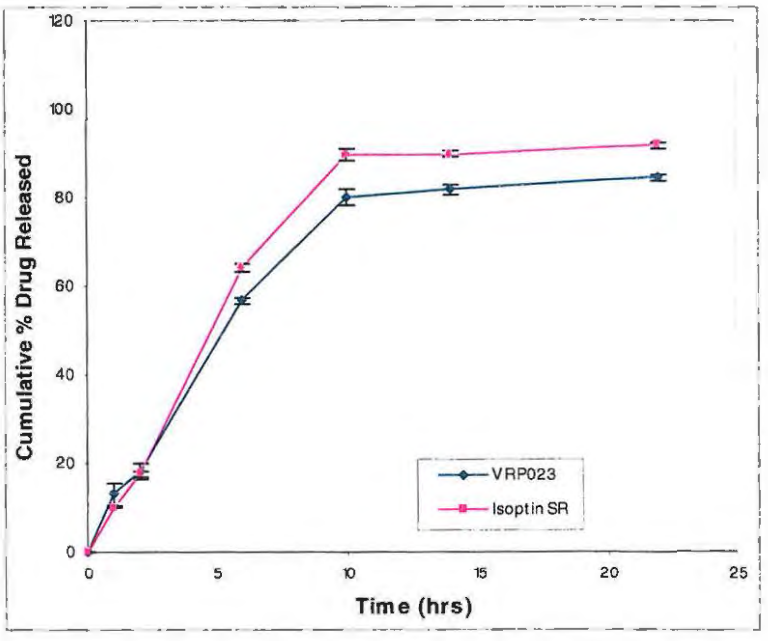


Figure 4.15. Dissolution profile of VRP release from batch VRP023 and to Isoptin® SR (n =6).

4.3.2 pH Dependence of Drug Release

Since VRP is a weakly basic compound, its solubility will vary in different parts of the gastro-intestinal tract (GIT) due to pH differences in the different regions of the GIT. Dissolution tests were conducted in two dissolution media of different pH value (1.6 and 7.4) for 22 hours using USP apparatus 1 to determine whether VRP release from batches VRP021 and VRP023 was pH dependent. The results in Figure 4.16 reveal that drug release rates are faster in dissolution media of pH 1.6 than dissolution media of pH 7.4 for both formulations tested.

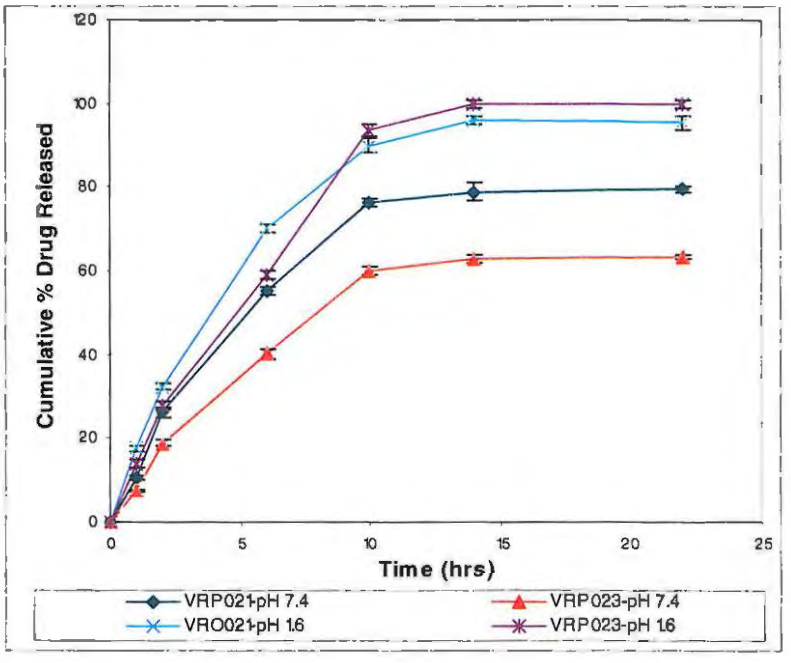


Figure 4.16. Dissolution profile of VRP release from batch VRP021 and VRP023 at different pH.

At pH 1.6, batches VRP021 and VRP023 released approximately 17% and 14% of total drug loading at the end of 1 hour. After 2hours, the formulations had released approximately 31% and 30% VRP, respectively. Following 22 hours of exposure to the dissolution media, the two batches had released approximately 95% and 100% VRP, respectively.

Dissolution testing was also conducted at pH 7.4 and tablets from batches VRP021 and VRP023 had released approximately 10% and 7% of total loading at the end of 1 hour.

After 2 hours, the formulations had released approximately 26% and 19% VRP, respectively. Following 22 hours of exposure to the dissolution media, the two batches had released approximately 78% and 63% VRP, respectively.

The results in these studies are in agreement with observations made by Streubel *et al* [123] in which it was expected that a weakly basic drug would show faster release rates at a lower pH rather than at a higher pH.

The release rates observed when carbomer is used as the primary rate retarding agent indicate that the polymer matrix may have acted as a physical barrier in slowing the rate of release. This barrier may occur due to complex macromolecular changes taking place within the polymer over time [156]. These changes in turn affect the rate of drug diffusion through the polymer and consequently the rate of release of VRP from these tablets.

The carbomer polymer would virtually be un-ionized at pH 1.6 and as a result of its low solubility, is difficult to hydrate. As the pH increases, the polymer starts to ionize and swell and the greatest degree of swelling occurs at pH 7–7.5 [157]. Consequently, during the course of the gastro-intestinal transit, a dosage form is exposed to various pH's ranging from 1.2 in the stomach to approximately 8.0 in the small and large intestines and therefore, the amount of drug that is released will depend, to a certain extent, on the degree of swelling of the carbomer. Therefore, at high pH, the diffusional path length within the dosage form is much longer and subsequently release rates tend to be slower. Release rates are also influenced by the lower solubility of VRP as the pH increases to a more alkaline state.

Dimitrov and Lambov [158] reported that the relative faster release of VRP at lower pH when compared to higher pH values is a result of more drug being available in the matrix as a salt form rather than as the base compound. After sometime, the VRP is converted to the base form as a result of hydrogen cations diffusing into the dosage form at a faster rate, due to their small size, than the VRP can diffuse out of the dosage form. The formation of the base is associated with a reduced solubility of VRP and therefore the

release process is slower and the release mechanism is complex and confounded by solubility issues.

It has been reported [159, 160] that at higher pH's, the carboxylic acid functional groups of carbomer are more likely to be dissociated and that repulsion of molecules due to negative charges, may cause expansion of the molecules to form a gel layer, which can slow drug release. Interactions between a negatively charged functional group in the polymer and a positively charged drug molecule are therefore possible and can increase at higher pH's such as 6.8 and 7.4 and drug release rates may therefore be reduced due to expansion of the molecules and the formation of a gel layer. The decrease in VRP release at higher pH values may be due to the interaction of the dissociated polymer-carboxylic groups with the basic tertiary amine of VRP [160].

A potential interaction between a cationic drug, metoclopramide hydrochloride and anionic ammonium oleate was investigated by Sadeghi *et al* [114] using dialysis studies. Formation of a precipitate when metoclopramide hydrochloride was added to the ammonium oleate solution resulted in slower drug release rates compared to those when using an anionic drug such as diclofenac. Therefore, another possible explanation that may account for the slower release of VRP from batch VRP021 is related to a possible interaction between VRP and a component of Surelease® E-7-19010. Thus due to an interaction between the cationic VRP and anionic ammonium oleate, present in Surelease® retardation of release may occur.

The manufacturing procedure for the WG products entails a 12-hour drying process. It is quite likely that during the drying cycle any ammonia present in the Surelease® used to granulate the component of batch VRP021 would evaporate. However, any residual ammonium oleate is likely to remain and thus create the potential for an interaction between VRP and ammonium oleate.

The potential for the *in situ* formation of a complex between VRP and a surfactant is an area that should be further evaluated in future formulation studies in which VRP and Surelease® are used.

4.3.3 In-Depth Investigation of Batches VRP021, VRP023 and Isoptin® SR.

In order to further characterize batches VRP021, VRP023 and Isoptin® SR additional testing was undertaken. The effect of buffer molarity on drug release rate was evaluated as were other aspects of the dissolution test method. Swelling and erosion studies were used as an attempt to facilitate an understanding of the mechanism by which VRP is released from the dosage form.

4.3.3.1 Effect of Molarity

When the molarity of the dissolution medium was decreased from 0.2M to 0.05M, the release rate of VRP decreased as shown in Figure 4.17. The effect of molarity on dissolution rates of chlorpheniramine maleate has been investigated by Neau *et al* [159]. A high molarity dissolution medium weakens the rigid/cross-linked structure of the carbomer gels by interfering with repulsive forces that exist between charged polymer molecules. This loss of the gel-like structure, results in the dosage form and drug being exposed to the hydrodynamic forces of the dissolution test medium, resulting in an increased exposed surface area with a subsequent faster drug release rate.

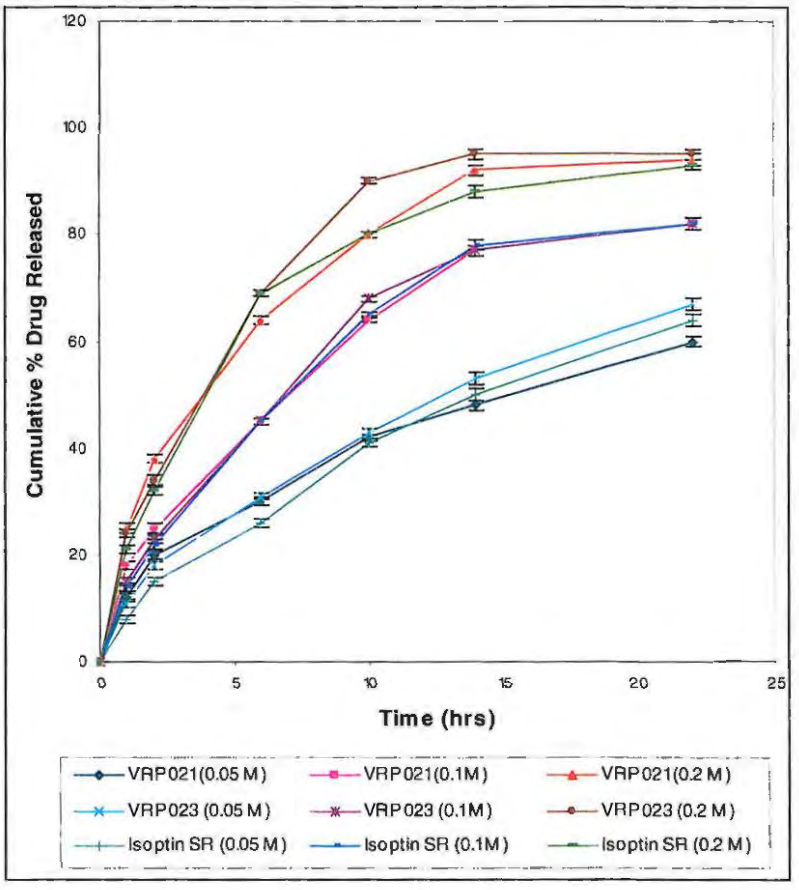


Figure 4.17. Effects of buffer molarity on verapamil release from batches VRP021, VRP023 and Isoptin® SR (n=6) release in pH 7.4 phosphate buffer using USP apparatus 1.

4.3.3.2 Swelling and Erosion

Measurements of hydration rates of the selected batches (*viz.* VRP021, VRP023 and Isoptin® SR) were carried out in an attempt to correlate the observed drug release characteristics with rate of polymer hydration. Visual observation of the mini-tablets from batches VRP021, VRP023 and the reference product confirmed that swelling was dominant in these formulations and that the polymer developed a highly viscous gel when exposed to the dissolution media. The degree of swelling increased when the dissolution medium was pH 7.4 as opposed to pH 1.6. As the hydration and swelling progressed, the mini-tablets rapidly formed a single rod-like cylinder, thus adhering to one another as shown in Figure 4.18. Thereafter, lower surface area was exposed than when the mini-tablets were separate entities to the dissolution medium.

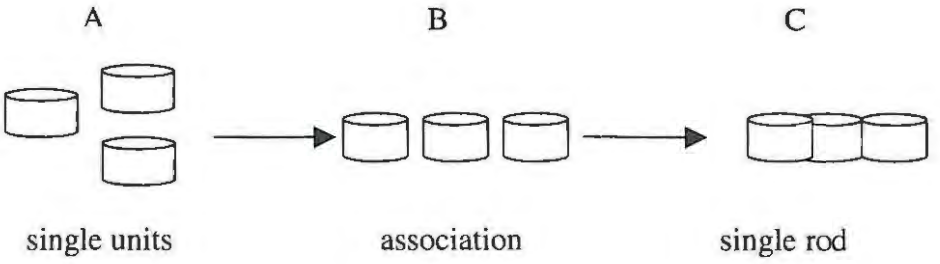


Figure 4.18. Schematic of the formation of a rod-like cylinder by 3 mini-tablets.

It has been reported [126] that swelling and erosion may determine the mechanism and kinetics of drug release. Therefore, this study was conducted to determine the mechanism of drug release in terms of liquid uptake and erosion. Swelling and liquid uptake profiles for batches VRP021, VRP023 and Isoptin® SR product are presented in Figure 4.19.

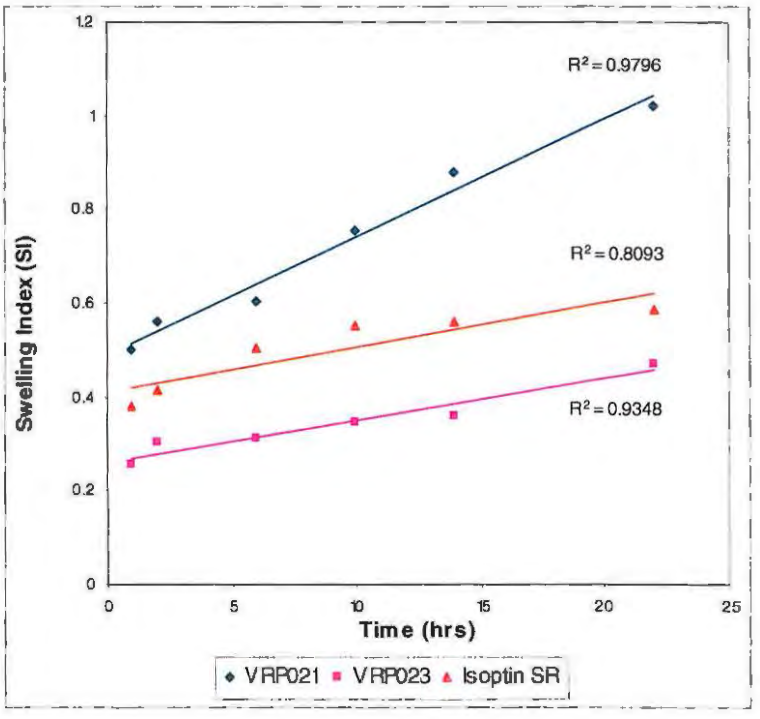


Figure 4.19. Swelling indices for batches VRP021, VRP023 and Isoptin® SR at pH 7.4 (n = 3).

The tablets from batch VRP021 showed the highest rate of swelling when compared to tablets from batch VRP023 and the reference product. A high degree of swelling results

in an increased diffusional path length within the dosage form, through which the drug must pass. The tablets from batch VRP023 had a low swelling rate. This was unexpected as the excipients used in formulation studies were similar to batch VRP023 except for the granulating fluid. The low liquid uptake by tablets from batch VRP023 is more than likely a result of the poor uptake of dissolution medium due to the presence of Eudragit® NE 30D, which has poor permeability characteristics [121].

The degree of swelling is also an indication of the rates at which preparations are able to adsorb dissolution media and for both batches swelling was observed to be proportional to liquid uptake. These results are in agreement with previously reported results [125] in that anisotropic swelling or swelling in the longitudinal direction rather than in the radial direction was observed for both formulations. Isoptin® SR showed swelling behaviour that was intermediate to both batches. In all cases the SI was proportional to the time the dosage form was exposed to the test medium. Figure 4.20 presents the degree of matrix erosion as a function of time and is reported as % erosion.

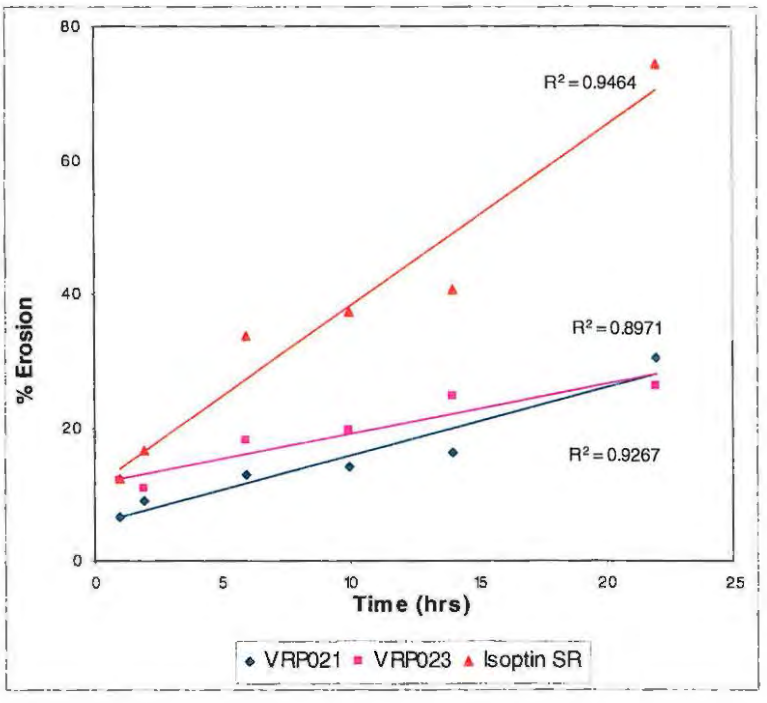


Figure 4.20. Percent erosion for batches VRP021, VRP023 and Isoptin SR (n =3).

It is evident that the tablets used in these studies undergo both swelling and erosion simultaneously. The percent erosion ranged from approximately 5% during the first hour to about 25% at the end of the run for tablets in batch VRP021, whereas the percent erosion ranged from about 10% after 1 hour to about 25% at the end of the dissolution run for batch VRP023. The reference product demonstrated a profound increase in percent erosion from approximately 15% during the first hour to about 70% at the end of the test run. It has been reported [161,162] that when both swelling and erosion occur simultaneously at the same rate, zero-order release rates can be obtained from such formulations. Different polymers used, in matrix formulations may have a different influence on the rate of tablet erosion and swelling due to variations in the disruption of polymer networks at different times and rates. Since both swelling and erosion is shown to have been occurring at the same time in these matrices, though at different rates, the drug release patterns have a tendency to follow a zero-order kinetic release model. Figure 4.21 demonstrates that there is a correlation between matrix swelling and erosion, which indicates that swelling and erosion occur simultaneously but the rate is different for each formulation.

This rate of simultaneous swelling and erosion is due to the existing balance between the increase in diffusion path length caused by swelling and the decrease in path length due to erosion. However, to verify such a phenomenon, release data need to be modelled by fitting data to mathematical models that assess drug release characteristics.

Tablets from batch VRP021 showed the highest swelling index of about 1 and a % erosion of approximately 40% at the end of a 22-hour run. This demonstrates that there was no balance between the increase in diffusional path length due to swelling with the decrease in the diffusional path length due to matrix erosion. Tablets from batch VRP023 showed the least swelling and percent erosion. The reference product showed more erosion of the tablet than swelling after 22 hours of the test, hence erosion might be predicted to be the dominant factor affecting the release of VRP from Isoptin® SR.

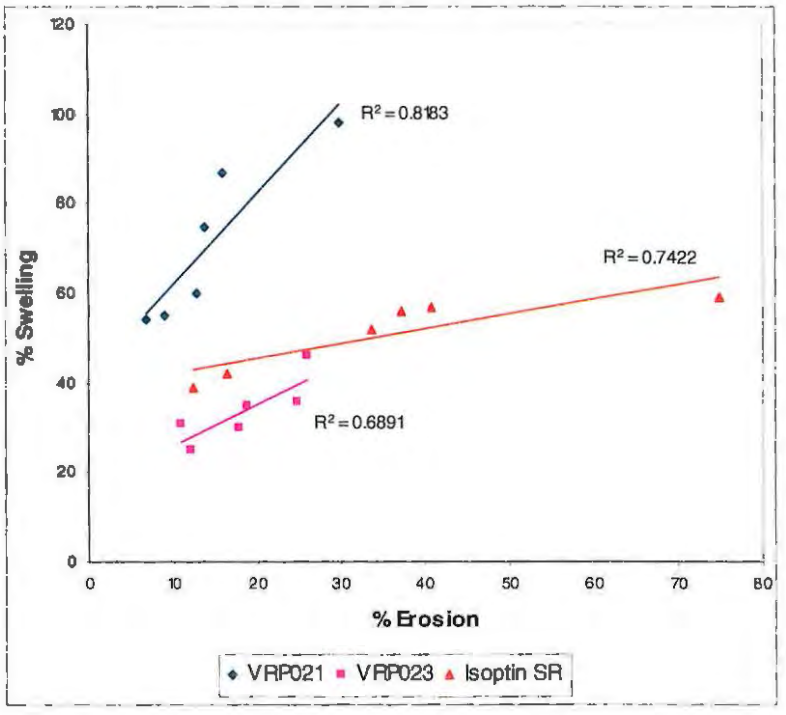


Figure 4.21. Correlation of matrix swelling and erosion for batches VRP021, VRP023 and Isoptin® SR product.

It is well known that the swelling of carbomer polymers is due to the partial dissociation of the acidic carboxyl group in aqueous solution, producing a coil-like structure [86, 119, 121, 122]. Gel formation depends on the electrostatic repulsion between these anionic carboxyl groups. When the magnitude of dissociation of the carboxyl groups is high, there is more repulsion, which in turn results in chain relaxation and a greater degree of swelling of the polymer [122]. This phenomenon was also observed in a study [163] in which the sustained-release of theophylline from matrix tablets containing Carbopol® 974 was considered to be largely dependent on the gel layer structure. It was concluded that the gel layer played a critical role in the sustained-release action.

The results of erosion depicted in Figure 4.20 show evidence that drug release from batches VRP021 and VRP023 is mainly controlled by swelling and by diffusion of the drug through the polymer matrix rather than by erosion. The high degree of crosslinking of the carbomer matrix coupled with the low solubility of VRP at high pH values and gel formation are all contributing factors in controlling drug release in these products.

4.3.3.3 Effect of Mesh / Screen Sizes

There have been reports in the literature of the effects of dissolution test conditions affecting drug release when using USP apparatus 3 [164].

A study of the effect of mesh size was therefore undertaken to determine the effect of mesh sizes on drug release rates and patterns. Polypropylene screens of a variety of mesh sizes are available for use with USP apparatus 3. The relevant sizes of mesh used in these studies are shown in Table 4.6.

Table 4.6. Mesh screen sizes used in dissolution studies in USP apparatus3.

Mesh screen size	Pore size (μm)
160	74
78	177
40	405

It was observed that if a 74 μm mesh screen is used as the top screen, all cylinders fail to drain completely and this occurred throughout the entire period of a test run. These observations are consistent with data reported in the literature [165]. In these studies [165] dissolution media were found to coat the screen, and the combination of a fine pore size and the surface tension of the dissolution media created a barrier that prevents air from penetrating the screen and displacing the media in the cylinder, thus allowing it to drain.

Replacement of the top screens with a177 μm mesh screen result in better drainage when compared to data obtained when a 74 μm screen was used because, as the mesh screen size / pore sizes are larger, air can penetrate through these openings without any difficulty and subsequently displace liquids that may be retained in these inner-tubes.

The use of a size 405 μm top screen results in the cylinders draining adequately and a student's t-test was used for comparison of the percent released when 177 μm (mesh) and 405 μm screens were used as the top screens. In all cases the bottom screen had pores of 177 μm and the results revealed a value of $p < 0.05$ ($\alpha = 0.05$), indicating that there was a

significant difference between the percent drug release when screen sizes of 177 μm and 405 μm were used as top screens in the inner-tubes.

The percent VRP released was dependent on the mesh size used for the top screens. Two sizes, 40 and 78 mesh were tested to determine their effect on VRP release at different rates of 10 and 20 dpm.

Figure 4.22 depicts the release of VRP from batches VRP021 and VRP023 when using USP apparatus 3. It can be seen that the percent release rate was higher when screen sizes were increased from 177 μm to 405 μm, as a result of the larger pore sizes.

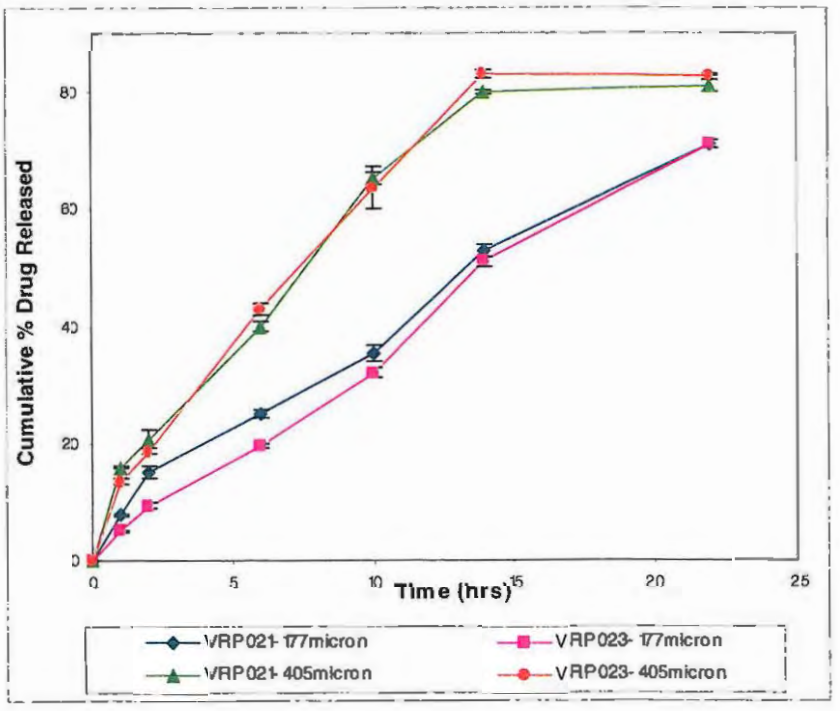


Figure 4.22. Influence of the pore size on VRP release from batches VRP021 and VRP023.

4.3.4 Characterization of Tablets

Further evaluation of the batches of tablets (Table 4.7) included determination of uniformity of thickness, diameter, weight and content. In addition, crushing strength and friability were also determined. Batches VRP021 and VRP023 satisfied all relevant pharmacopoeial specifications for such dosage forms. The tensile strength of the mini-

tablets was higher than larger tablets due to their small diameter, despite a crushing strength that was comparable to the 11 mm diameter tablets.

The % RSD for thickness, weight and content for all the tablets (large tablets and mini-tablets) was comparable and in all cases the % RSD was ≤ 5.0% and therefore, the precision of manufacture worked well. These tests were used as indications of potential areas of difficulty in the manufacturing process and it provided an indication of ultimate product quality.

Table 4.7. Physical properties of the Compressed Tablets.

Formulations	Thickness (mm)	Weight (mg)	Drug Content (%)	Crushing Strength (N)	Friability (%)	Tensile Strength (N/mm^2)
VRP001	6.67 ± 1.78	724 ± 5.54	89.89 ± 1.34	113 ± 5.21	0.460± 2.17	0.98 ± 2.45
VRP002	6.70 ± 0.13	701 ± 4.56	88.76 ± 2.02	76 ± 4.94	8.980 ± 5.26	0.66 ± 3.56
VRP003	6.50 ± 1.66	650 ± 4.67	90.10 ± 3.12	89 ± 4.91	3.500 ± 4.01	0.80 ± 3.33
VRP004	6.23 ± 2.47	690 ± 5.32	87.12 ± 5.56	112 ± 3.34	0.120 ± 10.23	1.05 ± 4.34
VRP005	6.67 ± 1.23	710 ± 4.78	95.95 ± 5.34	126 ± 4.68	0.090 ± 1.91	1.10 ± 2.54
VRP006	6.64 ± 0.89	718 ± 4.12	92.12 ± 3.56	124 ± 4.87	0.180 ± 2.45	1.09 ± 3.34
VRP007	6.54 ± 0.94	721 ± 3.23	88.44 ± 4.67	121 ± 4.91	0.180 ± 3.43	1.09 ± 1.24
VRP008	6.45 ± 1.26	733 ± 2.34	91.32 ± 5.34	137 ± 4.34	0.210 ± 4.56	1.24 ± 4.45
VRP009	6.01 ± 0.92	740 ± 3.46	93.53 ± 5.21	134 ± 3.54	0.290 ± 1.23	1.30 ± 3.34
VRP010	6.42 ± 0.78	730 ± 4.33	91.32 ± 3.46	112 ± 5.24	0.230 ± 1.78	1.02 ± 4.23
VRP011	5.39 ± 0.92	245± 4.23	87.46 ± 2.65	112 ± 2.23	0.270 ± 1.45	1.91 ± 2.68
VRP012	4.73 ± 1.25	242 ± 3.76	84.56 ± 4.59	116 ± 4.67	0.280 ± 3.34	2.25 ± 1.57
VRP013	4.63 ± 0.82	220 ± 2.56	84.78 ± 4.61	103 ± 3.67	0.260 ± 2.12	2.04 ± 1.68
VRP014	4.56 ± 0.87	248 ± 4.67	91.39 ± 4.35	107 ± 5.94	0.230 ± 1.34	2.16 ± 1.78
VRP015	4.89 ± 0.83	234 ± 1.78	96.60 ± 4.55	133 ± 6.98	0.260 ± 2.45	2.48 ± 4.78

NB: *all values are expressed as mean ± % RSD, n = 20*

Table 4.7 continued.

Formulations	Thickness (mm)	Weight (mg)	Drug Content (%)	Crushing Strength (N)	Friability (%)	Tensile Strength (N/mm^2)
VRP016	4.78 ± 0.81	246 ± 2.23	86.83 ± 4.32	131 ± 3.94	0.000 ± 0.00	2.51 ± 4.56
VRP017	4.97± 0.70	236 ± 2.33	92.43 ± 3.67	112 ± 4.45	0.060 ± 0.34	2.07 ± 2.34
VRP018	4.68 ± 1.21	243 ± 2.26	87.88 ± 5.34	116 ± 3.21	0.010 ± 0.56	2.27 ± 2.12
VRP019	4.82 ± 0.84	237 ± 3.32	91.34 ± 3.33	117 ± 5.77	0.010 ± 1.56	2.19 ± 3.23
VRP020	5.01 ± 0.78	251 ± 1.34	87.56 ± 2.67	142 ± 2.23	0.000 ± 0.00	2.58 ± 3.12
VRP021	**5.05 ± 0.91**	**244 ± 4.67**	**91.04 ± 3.65**	**138 ± 3.34**	**0.039 ± 1.45**	**2.50 ± 1.67**
VRP022	4.98 ± 0.87	237 ± 3.46	88.76 ± 3.56	144 ± 4.37	0.020 ± 1.23	2.63 ± 2.45
VRP023	**5.40 ± 0.69**	**233 ± 3.33**	**90.60 ± 1.46**	**142 ± 4.67**	**0.060 ± 1.34**	**2.39 ± 1.01**

NB: *all values are expressed as mean ± % RSD, n =20*

4.3.5 Effect of Reciprocation Rate

The effect of the agitation or dip rate on the dissolution rate of VRP from tablets prepared in the laboratory is shown in Figure 4.23. As expected, the dissolution rate increased with the increasing agitation rate.

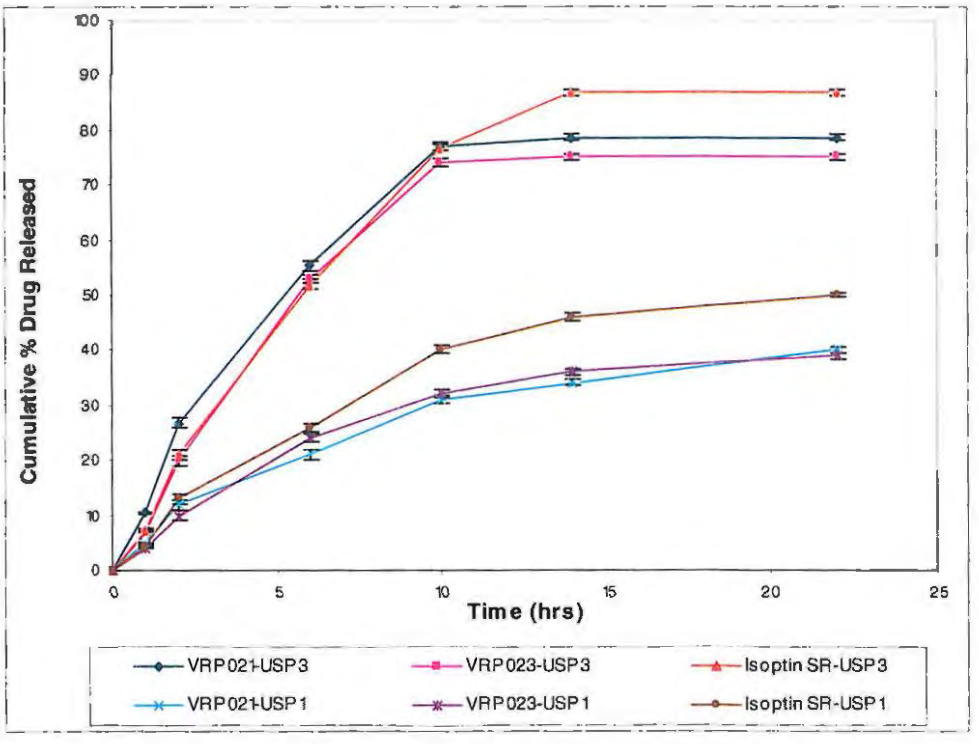


Figure 4.23. Effects of basket rotation speed and reciprocation rate on drug release for batches VRP021, VRP023 and Isoptin® SR (n = 6).

It is vitally important that dissolution test methods are optimized and that appropriate dissolution media are used when testing particular dosage forms. It has been shown that USP apparatus 1 method is not convenient when a change of dissolution media is needed [165]. The reciprocating cylinder (USP apparatus 3) eliminates the manual work required when changing dissolution media, thus providing an advantage for dissolution testing as it may mimic the pH gradient encountered in the gastro-intestinal tract. Figure 4.23 presents a comparison of VRP release profiles between the basket (USP apparatus 1) and the reciprocating cylinder (USP apparatus 3) at pH 7.4. It was observed that the amount released at 20dpm was about twice that of the dosage form tested using USP 1 at 100rpm.

These results are consistent with work previously published in which a comparison of dipping rates with USP apparatus 3 and rotation speed using USP apparatus 1 revealed that a dipping rate of 10 dpm (USP apparatus 3) was equivalent to 100 rpm (USP apparatus 1) [165]. It is obvious that dissolution test parameters have an influence on drug release rates and these must be optimized prior to performing experimental studies, in order to maximize the benefit from undertaking these studies.

The rationale behind conducting dissolution testing is that if a drug is to be absorbed from the gastrointestinal tract, it usually has to dissolve. Dissolution testing has been used as a quality control tool, but its success in predicting biological availability has not yet been fully realized, as there are limited examples of successful dissolution tests reflecting product bioavailability characteristics while there are number of unsuccessful correlations of dissolution characteristics to bioavailability reported in the literature [166].

Dissolution testing, along with other quality control tests such as assay and content uniformity provide sufficient assurance of the consistency of batch to batch quality of products and for a dissolution test to be useful as a quality control tool, it must be sensitive enough to reflect the influence of manufacturing process changes, as has been observed in this study.

4.4 CONCLUSION

The objective of this study was to develop and evaluate sustained-release tablets formulations of VRP and to develop a suitable method of manufacture for ensuring reproducible sustained-release products are produced. A direct compression method was used to develop sustained-release tablets but the tablets produced did not satisfy pharmacopoeial specifications and VRP release was faster and complete drug release was observed after about 6 hours. Surelease®-E-7-19010 and Eudragit® NE 30D were used as granulating solutions in wet granulation process. Initially, different blends of formulations were prepared by direct and wet granulation technology. The former technique involved the compression of a dry blend of powders that comprise the drug. Although simple in terms of the processes involved, this process was found to be influenced by powder characteristics, and hence it was important to first determine the powder flowability and compressibilities. The influence of polymer content, polymeric swelling behaviour, molarity, agitation rate and the pH changes on the release rate of VRP were investigated.

The VRP release from the prepared formulations was found to be pH dependent and was markedly reduced at high pH. The resultant release rates may be attributed to the poor solubility of VRP, the thickness of the gel layer and the interaction between the cationic drug VRP and carbomer or component of Surelease®-E-7-19010. It is not clear why Isoptin® SR did not show 100% drug release. The probable reason is more than likely the poor solubility of the active in the dissolution media and/or interaction with other excipients, even though the composition (excipients) of Isoptin® SR was not known in advance.

This study demonstrates that the desired drug release pattern can be obtained by adopting a systematic approach in designing an optimum formulation. It has also addressed the effects of instrumental factors such as mesh/screen sizes on drug release profiles on addition to the effect of reciprocating speed and or agitation rate.

In conclusion, sustained release formulations of VRP with satisfactory pharmacotechnical parameters, *viz.* crushing strength, friability, weight variation, thickness and diameter that were within the pharmacopoeia limits were prepared and a wet granulation technique has been proven to be an appropriate method to produce VRP mini-tablets. This work has also presented some evidence confirming that carbomer containing matrices predominantly result in swelling as opposed to erosion and drug release mechanisms can be predicted based on these phenomena.

Future studies must focus on fully understanding the complex relationship between drug-polymer and other drug-excipient interaction studies, as well as defining the necessary process parameters to ensure that a predictable, constant drug release pattern is achieved.

CHAPTER FIVE
CHARACTERIZATION OF DRUG RELEASE BY MATHEMATICAL MODELLING

5.1 INTRODUCTION

Mathematical modelling of drug release profiles from controlled drug delivery devices is a useful technique that may provide a scientific knowledge base relating to mass transport mechanisms, which are involved in the control of drug release from these systems [167]. Siepmann and Peppas [167] reported that when developing a new controlled release delivery system or elucidating drug release mechanisms, the choice of an appropriate mathematical model is dependent on the type of drug, excipients and the composition of the device into which the drug is loaded.

Further reports [156, 168] suggest that there are various mechanisms that control drug release and that diffusion, water triggered transport or swelling, coupled with chain relaxation and slow erosion of polymer, are the most important mechanisms [156, 167, 168] by which drug release may be controlled.

The occurrence of multi-component transport processes, different types of matrices, composition, device geometries, drug loading, saturation solubility in the matrix, diffusion, swelling, polymer dissolution and erosion may complicate the analysis of drug release from controlled-release delivery systems [169].

It has been reported [167] that mathematical approaches covering all possible chemical and physical processes are not yet available; hence in order to describe drug release there is a need to identify or develop an adequate mathematical theory for specific type of drug delivery systems. It is worth noting that other alternative approaches have been reported recently in the literature recently and these should also be considered and used in combination with conventional methods of analysis that have already been established

[169]. These new techniques include the use, for example, of artificial neural network (ANN) methodology to predict drug release profiles from drug delivery systems [169].

5.2 MATHEMATICAL MODELS

There are several reports in the literature that have discussed the comparison of dissolution data to establish statistical or pharmaceutical equivalence [170]. These methods for the comparison of *in-vitro* dissolution profiles can be classified into five groups:

(i) Methods based on exploratory data analysis [171],

(ii) Model-independent methods [170,172 -174],

(iii) Methods based on analysis of variance (ANOVA) [148, 172, 173,175 -177],

(iv) Model-dependent methods [148, 172-174,175, 177, 178],

(v) Mixed-effects models [179].

5.2.1 Exploratory Data Analysis Methods

Exploratory data analysis methods, despite not having been endorsed by the FDA and other regulatory bodies, is the first step in comparing dissolution profile data in a graphical manner [171]. The data are illustrated by plotting the mean dissolution profile data for each formulation with error bars that extend to twice the standard errors, at each dissolution time point. The dissolution profiles for two formulations, for example a test (T) and reference (R) product may be compared by evaluating whether or not the error bars overlap. The dissolution profiles may be considered to differ significantly from each other if the error bars at each dissolution time point do not overlap. The rationale for this is that the error bars at each dissolution time point are considered to be equivalent to a 95% confidence interval and therefore, if the confidence intervals for the two formulations at a given time point do not overlap, then the mean dissolution profiles at that time point may be considered significantly different to each other.

5.2.2 Model-Independent Methods

Moore and Flanner [174] proposed a versatile, model-independent mathematical approach for calculating the difference (f_1) and similarity factors (f_2) for the comparison of drug release profiles. The difference factor, f_1, measures the percent error between two curves over all time points and is calculated using equation 5.1.

$$f_1 = \frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t} \text{X100} \qquad \text{Eq. 5.1}$$

where

n = sampling number,

R_t = percent dissolved of the reference product and

T_t = percent dissolved of the test product at time t.

The similarity factor, f_2, is a logarithmic transformation of the sum-squared error of differences between the TEST (T) and REFERENCE (R) products over all time points, and is calculated using equation 5.2

$$f_2 = 50 \text{ x } \log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t|R_t - T_t|^2\right]^{-0.5} \text{x}100\right\} \qquad \text{Eq. 5.2}$$

where

n = sampling number,

R_t = percent dissolved of the reference product,

T = percent dissolved of the test product at time t and

w = is an optional weight factor.

The difference and similarity factors have been included in the FDA guidance on the dissolution testing of immediate-release solid oral dosage forms [180]. The FDA [180, 181] and the Human Medicines Evaluation Unit of The European Agency for the Evaluation of Medicinal Products (EMEA) [182] have accepted that two dissolution profiles will be declared similar if the f_2 value is between 50 and 100. Whilst f_1 values are

not used by the regulatory agencies, values of f_1 between 0-15 indicate similarity or equivalence of two drug release curves [172].

The main advantages of using the f_1 and f_2 factors are that they are easy to compute and they provide a single number to describe the closeness of two dissolution profiles [148, 172].

Yuksen *et al* [172] reported that because of the sensitivity of the factors to the measurements after 85% dissolution, the number of sample points be limited to not more than one, once any of the products had released greater than 85% of its drug loading.

The f_1 and f_2 equations are based on combining the differences at all time points into one measurement, and these measurements are often estimated by substituting sample means for the actual means. However, it has been reported [183] that dissolution profiles correlated at the sample time points are estimates and are complicated in that the variation of the estimates is difficult to calculate and that the estimate itself may be biased, with statistical properties that are difficult to derive, and hence, it is not possible to know what the Type I and Type II error rates are [148, 183, 184].

A relatively new factor, the similarity factor (S_d), was developed by Gohel and Panchal [170]. The parameter determines the percentage difference between two dissolution profiles. The major advantage of this method is its simplicity and ease of interpretation. The difference in similarity, S_d is calculated using equation 5.3.

$$S_d = \frac{\sum_{t=1}^{n-1} \left| \log\left(\frac{AUC_{Rt}}{AUC_{Tt}} \right) \right|}{n-1} \qquad \text{Eq. 5.3}$$

where

n = the number of data points collected during the *in-vitro* dissolution test (time and percentage / amount of drug dissolved)

AUC_{Rt} = the area under the dissolution curve of the reference, at time t,

AUC_{Tt} = the area under the dissolution curve of the test formulation, at time t.

The description of *in-vitro* dissolution profiles using model-independent methods also includes the calculation of the mean dissolution time (MDT) from the dissolution profile, and mean residence time (MRT) from the residence profile, or area under the dissolution curve (AUC) [172]. The AUC is sometimes referred to as dissolution efficiency (DE) [185].

DE of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a specific time, t, and is expressed as a percentage of the area of a rectangle described by 100% dissolution in the same time [121, 185, 186]. The DE may be calculated using equation 5.4.

$$\text{D.E.} = \frac{\int_0^t y \cdot dt}{y_{100} \cdot t} \text{ x } 100\% \qquad \text{Eq. 5.4}$$

where,

y = the percent drug dissolved at time t.

In this study the f_1 and f_2 factors were applied to dissolution data as these have been adopted by the FDA as criteria for the assessment of the similarity between two *in-vitro* dissolution profiles [180]. In addition, the S_d factor was calculated due to its simplicity and ease of interpretation. The S_d values were compared to f_1 and f_2 factors to determine if a relationship between these factors exist.

5.2.3 Mahalanobis Distance

The Mahalanobis distance or statistical distance between respective means of a REFERENCE and the TEST product using a pooled variance-covariance matrix was determined and it has been reported that this method is a multivariate analogue of the two one-sided t-test procedure used in the assessment of average bioequivalence [171]. This method has not been a topic of discussion in any regulatory guidance document, and it was thus not considered for use in this study.

5.2.4 Analysis of Variance (ANOVA)

Statistical methods, unlike mathematical methods, go some way towards taking statistical properties such as variability and correlation structure of the dissolution profile data into account, when undertaking a comparison of test and reference drug product dissolution rate profiles [171]. This method of comparing dissolution profiles takes into account the variability at each time point of the dissolution profile, yet it ignores the correlation between the dissolution time points. It is clear that each time point is treated as if it were independent of the others, which is clearly not the case in dissolution testing [171].

Furthermore, there is an overall risk of incorrectly concluding that the mean dissolution profiles are different, that is Type I error is much larger than the nominal 5% usually used to make these decisions. This is a well- known consequence of performing multiple comparisons, such as t-tests or one-way analyses of variance [171].

Although this method of comparing dissolution profile data is straight-forward, it is also rather tedious to perform and it is worth noting that these ANOVA methods are not mentioned in any of the FDA guidance documents on dissolution testing.

ANOVA-based methods do not rely on curve fitting procedures [172], and these analyses are capable of showing differences between profiles in both level and shape. The latter characteristic is especially important with respect to learning about differences in the mechanism of dissolution. The characterization as to whether these are model-dependent or model-independent methods depend on the data that are used to perform the calculation. Model-independent methods use the dissolution data in their raw form or as a simple transform, whereas, model dependent methods depend on mathematical functions to describe the dissolution profiles.

5.2.5 Mixed-Effects Models

The evaluation of dissolution profiles using mixed effects models has been described by Adams *et al* [179,186]. This approach is considered to be superior to any other modelling techniques since it takes into account the covariance structure of the data. In addition, a

distinction can be made between linear mixed effects (LME) and non-linear mixed effects (NLME) models [179, 186]. The LME models make use of sophisticated maximum likelihood estimation. In this estimation procedure, a distinction is possible between 'maximum likelihood' (ML) and 'restricted maximum likelihood' (REML) [187].

LME models allow for the accurate analysis of dissolution data and are much more discriminatory than the f_2 factor [179]. An example of this mechanistic model applied to dissolution data was reported by Crowder [188]. However the method is reported to be complicated and difficult to implement [179, 186].

The methods based on mixed effects models are not mentioned in any FDA or other regulatory guidance documents and the extent to which these methods are used in the assessment of dissolution test results is unknown [171]. Therefore, these studies were not performed for dissolution data generated in these experiments.

5.2.6 Model-Dependent Models

Although mathematical models have been used extensively to characterize dissolution profiles [172, 175], such methods are more complicated and require greater caution in both their application and the interpretation of their outcomes [175].

5.2.6.1 Zero Order

Pharmaceutical dosage forms that release the same amount of drug per unit time in order to achieve a prolonged and sustained pharmacological action usually conform to zero-order release characteristics and rates [189]. Equation 5.5 depicts the zero-order kinetic model.

$$Q_t = Q_o + K_o t \qquad \text{Eq. 5.5}$$

where

Q_t = the amount of drug released at time t,

Q_o = is the initial concentration of drug in the solution resulting from a burst effect,

K_o = the apparent dissolution constant or zero-order release constant and

t = time.

Sood and Panchagnula [190] described zero-order systems as those in which the drug release rate is independent of its concentration when applying this model to the evaluation of the release from a controlled release system containing Diltiazem. This model has been used for the linearization of drug release data from double-layered porous films, in addition to release rate profiles from ethylcellulose, hydroxypropyl cellulose and polyethylene glycol mixtures [189].

5.2.6.2 First Order

Gibaldi and Feldman [191] proposed the use of a first-order model to evaluate drug dissolution studies, and equation 5.6 shows a mathematical expression for a first order model.

$$Ln\ Q_t = Ln\ Q_o + K_1 t \qquad \text{Eq. 5.6}$$

where

Q_t = the amount of drug released at time t,

Q_0 = the initial amount of drug in the solution,

K_1 = the first order release constant and

t = time.

Pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices, release drug in a manner that is proportional to the amount of drug remaining in its interior and thus the amount of drug released per unit of time diminishes over time. A graph of the natural logarithm of the amount of drug released versus time will be linear [191].The first-order equation describes drug release from systems in which the release rate is concentration dependent [190].

5.2.6.3 *Higuchi Model*

Higuchi developed several theoretical models to describe the release of highly and poorly water soluble drugs that had been incorporated in non-erodable semi-solid and/or solid matrices [192, 193]. It is possible to reduce the Higuchi model to the expression as depicted in equation 5.7.

$$Q_t = K_H t^{½} \qquad \text{Eq. 5.7}$$

where

Q_t = the amount of drug remaining in the pharmaceutical dosage form at time t,

K_H = the Higuchi dissolution constant and

t = time.

Higuchi described drug release as a functional process based on Fick's first law and determined that the process is square root of time dependent [127, 185].

This model has been used for the linearization of drug release data from transdermal systems [177] and from sustained release matrix tablets [194] containing water soluble drugs.

5.2.6.4 *Baker-Lonsdale Model*

Baker and Lonsdale adopted the Higuchi model to describe the controlled-release of a drug from a spherical matrix [195]. This model has also been used to fit drug release from solid dispersions and physical mixtures of zolpidem in polyethylene glycol 4000 [196]. The mathematical relationship representing this model is depicted in equation 5.8.

$$\left(\frac{3}{2}\right)\left[1-\left(1-\left(\frac{Q_t}{Q_\infty}\right)^{2/3}\right)\right]-\left(\frac{Q_t}{Q_\infty}\right)=K_B t \qquad \text{Eq. 5.8}$$

where

Q_t = the amount of drug remaining in the pharmaceutical dosage form at time t,

Q_∞ = the maximal amount of drug released in infinite time,

K_B = the Baker-Lonsdale dissolution constant and

t = time.

5.2.6.5 *Hixson-Crowell Model*

The Hixson-Crowell cube root law is used to describe the release of drug from systems in which there is a change in surface area and diameter of particles or tablets over time. When this model is used, it is assumed that the release rate is limited by the dissolution rate of the drug particles and not by diffusion of the drug that might occur through the polymeric matrix these particles are made of [197]. Equation 5.9 depicts a mathematical representation of the Hixson-Crowell model.

$$Q_o^{1/3} - Q_t^{1/3} = K_s t \qquad \text{Eq. 5.9}$$

where

Q_o = the initial amount of drug in the pharmaceutical dosage form,

Q_t = the drug amount remaining in the pharmaceutical dosage form at time t,

K_s = a constant incorporating the surface/volume relationship and

t = time.

This expression may be applied to pharmaceutical dosage forms such as tablets in which dissolution of drug occurs in planes that are parallel to the surface of the tablet and if the dimensions of the dosage form diminish proportionally [185]. This equation has been used for the linearization of diltiazem hydrochloride release from modified guar gum matrix tablets [135].

5.2.6.6 *Weibull Model*

Langenbucher [198] reported that the quantitative interpretation of dissolution rate data is facilitated by the application of a general mathematical expression that describes the entire curve in terms of meaningful parameters. The mathematical expression depicted in equation 5.10 describes the Weibull model developed by Langenbucher.

$$Log\ [-ln\ (1 - (\frac{Q_t}{Q_\infty}))] = \beta\ log\ t - log\ \alpha \qquad \text{Eq. 5.10}$$

where

Q_t = the amount of drug remaining in the pharmaceutical dosage form at time t,

Q_∞ = the maximal amount of drug that can be released at infinite time

β = the shape parameter, and is obtained from the slope of the line,

α = the scale parameter, can be replaced by the more informative dissolution time, T_d and

t = time.

T_d represents the time interval necessary for 63.2% of the drug present in a pharmaceutical dosage form to dissolve or be released from the dosage form [148, 198].

This model can be successfully applied to almost all types of dissolution curves [198-200] and this function has been used for the linearization of drug release data from commercially available tablets and capsules [173, 201]. The Weibull shape parameter, β, [148] characterizes the dissolution profile as exponential (β =1 or Case 1), sigmoid, S-shaped, with upward curvature followed by a turning point (β >1 or Case 2) or as parabolic, with a higher initial slope and after that consistent with an exponential function (β <1 or Case 3) [185,194, 198].

5.2.6.7 Hopfenberg Model

The release of drugs from surface-eroding devices with several geometries was analyzed by Hopfenberg, who developed a general mathematical equation describing drug release from slabs, spheres and infinite cylinders displaying heterogeneous erosion [185]. This relationship is depicted in equation 5.11.

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_o}{C_o r_o}\right)^n \qquad \text{Eq. 5.11}$$

where

$\frac{M_t}{M_\infty}$ = the released fraction of drug at time t,

k_1 = equal to $k_o / C_o r_o$,

k_o = the erosion rate constant,

C_o = the initial concentration of uniformly distributed drug in the matrix,

r_o = the initial radius of a sphere or cylinder or the half-thickness of a slab and

n = exponent describing the type of device.

The exponent, n, has values of 1 for a slab, 2 for a cylinder, and 3 for a sphere. The model assumes that time-dependent diffusion resistances internal or external to the eroding matrix do not influence the release kinetics from these dosage forms.

Karasulu *et al* [202] used this equation for the linearization of theophylline release from different geometrically shaped erodable tablets.

The Hopfenberg model was not applied in the study because it yields complex differential expressions and interpretation of these data is difficult.

5.2.6.8 Korsmeyer-Peppas

A comprehensive, simple, semi-empirical method suitable for analyzing drug release data from polymeric systems and sometimes referred to as the power law was developed by Korsmeyer *et al* [203]. The method has been applied to the analysis of release of drugs of variable solubility and from a variety of systems [128, 134, 158, 168, 185, 190, 204 - 208]. The mathematical expression of this model is depicted in equations 5.12 and 5.13.

$$\frac{M_t}{M_\infty} = Kt^{\,n} \quad \text{or,} \qquad \text{Eq. 5.12}$$

$$log\ (\frac{M_t}{M_\infty}) = n\ log\ t + log\ k \qquad \text{Eq. 5.13}$$

where

$\frac{M_t}{M_\infty}$ = the released fraction of drug at time t,

k = a kinetic constant incorporating structural and geometrical characteristics of the device,

n = diffusion exponent of drug release and

t = time.

The exponent n is used to give an indication of the type of release kinetics of a drug from a dosage form [158,168,185]. Table 5.1 shows the interpretation of diffusional release mechanisms from spherical and cylindrical dosage forms using different polymeric compaction.

Table 5.1. Interpretation of diffusional release mechanisms from polymers

Release exponent (n)	**Shape**	**Drug transport mechanism**
0.45	cylinder	Fickian
0.5	sphere	Fickian
0.45 < n < 0.89	cylinder	Anomalous
0.5 < n < 1.0	sphere	Anomalous
0.89	cylinder	Case-II transport
1.0	sphere	Case-II transport
> 1.0	cylinder / sphere	Super Case-II transport

When n-values are close to 0.5, drug transport occurs by Fickian diffusion only. Anomalous behaviour corresponds to both diffusion and relaxation and is represented by n-values of between 0.5 < n < 1.0 [134,158, 168, 185, 207, 208]. An n-value greater than 1.0 indicates that a drug is said to being released in a fashion termed, Case-II transport. Equation 5.12 or 5.13 generally holds true for the characterization of the initial phases of a drug release profile, usually, where Mt / M∞ < 60% [134, 185, 207].

5.2.7 Other Release Parameters

Another parameter often used to characterize drug release profiles is $t_{x\%}$, sampling time. The $t_{x\%}$ parameter corresponds to the time necessary to release a determined percentage of drug. Pharmacopoeias frequently use this parameter as an acceptance limit for a specific batch when dissolution testing is a quality control release requirement (e.g., $t_{45\ min} \geq 80\%$) [185].

5.2.8 Determination of Goodness of Fit

The co-efficient of determination (R^2), the correlation co-efficient, the adjusted co-efficient of determination ($R^2_{adjusted}$), the sum squares of residuals (SSR), the mean square error (MSE), the Akaike Information Criterion (AIC), and the F-ratio probability are commonly used as drug-release model selection criteria [185].

It has been reported [177] that when comparing models with a different number of parameters, the $R^2_{adjusted}$ is more meaningful since it takes into account the effects of the added model parameters in the model studied without over fitting. In this study, the $R^2_{adjusted}$ was adopted to determine the best fit for models used to evaluate drug dissolution or release phenomena. $R^2_{adjusted}$ values greater than 0.950 were considered acceptable for these comparisons in this study. It is simple, less complicated, and faster to use than other criteria and it gives a single value that can be used to determine the best model.

The $R^2_{adjusted}$ is defined in equation 5.14 and was used in these studies.

$$R^2_{adjusted} = 1 - \frac{(n-1)}{(n-p)}(1-R^2) \qquad \text{Eq. 5.14}$$

where,

n = number of dissolution data points,

p = number of parameters in the model and

R^2 = coefficient of determination.

5.3 RESULTS AND DISCUSSION

In order to elucidate the mechanism of drug release from tablets manufactured in our laboratory, dissolution data were fitted to different models. Initially, the Korsmeyer-Peppas model was used to provide insight into the drug release mechanism. Other mathematical models were employed to determine which model best described drug release. Statistical comparisons using the student t-test method were undertaken to determine if there were differences between the products tested in certain cases.

5.3.1 Similarity and Difference Factors

The *in-vitro* performance of VRP batches and Isoptin® SR were compared by evaluating the f_1 and f_2 factors. The fit factors f_1 and f_2 are two indices that compare the dissolution profiles of a REFERENCE formulation to that of a TEST formulation.

As previously reported by Gohel *et al* [209], the results derived from the application of f_2 are superior to those of individual time points and it is always desirable to undertake dissolution profile comparison rather than to compare percent released at a specific time. Figures 5.1 and 5.2 depict the mean *in-vitro* dissolution profiles of the tablets from batches VRP021, VRP023 and Isoptin® SR and Table 5.2 lists the calculated values for f_1 and f_2. The values of f_2 obtained for these comparisons are all greater than 50 and values of f_1 are all less than or equal to 15 for both formulations indicating that they may be considered similar to the REFERENCE product, Isoptin® SR. In all cases, the tablets from other batches failed both the f_1 and f_2 tests.

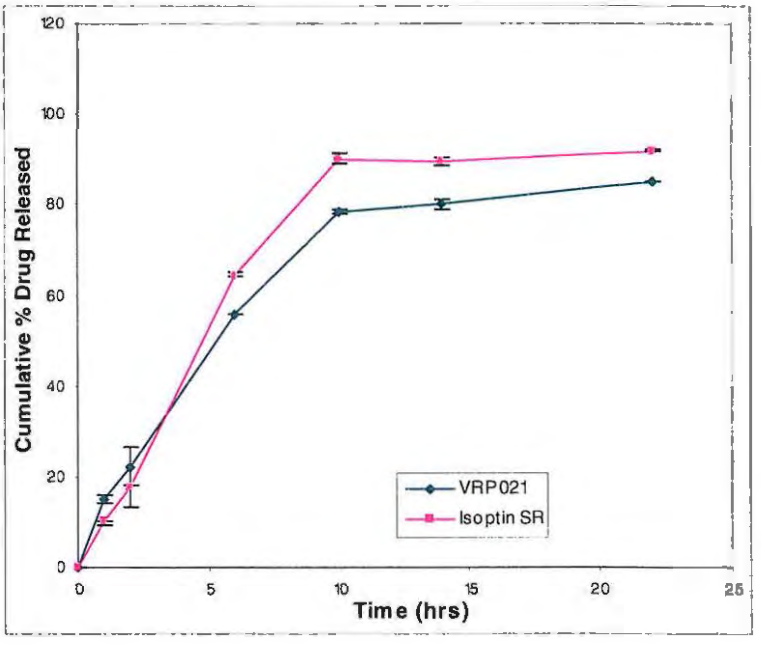


Figure 5.1. Mean *in-vitro* dissolution profiles of tablets of batch VRP021 and Isoptin® SR (n =6)

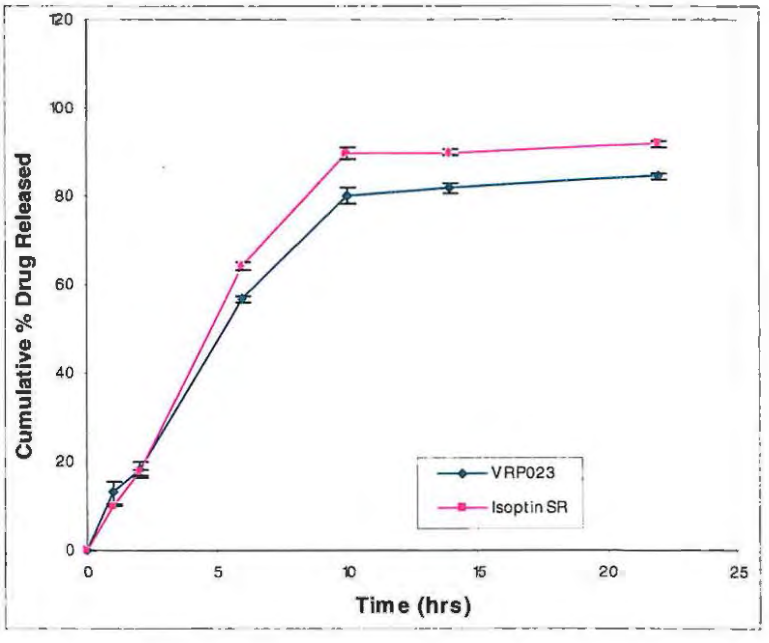


Figure 5.2. Mean *in-vitro* dissolution profiles of tablets of batch VRP023 and Isoptin® SR (n =6)

The S_d values were calculated using AUC_{Rt} and AUC_{Tt} values that had been determined by the trapezoidal rule. The standard data for S_d and percent difference between AUC_{Rt} and AUC_{Tt} (% AUC $_{(diff)}$) are listed in Table 5.2.

Table 5.2. f_1, f_2, % AUC $_{(diff)}$ and S_d values for VRP batches using Isoptin® SR as a reference.

FORMULATION	FACTORS			
	f_1	f_2	% AUC $_{(diff)}$	S_d
VRP001	521.0	7.1	84.7	1.28
VRP002	551.0	6.0	85.7	1.33
VRP003	51.5	27.2	22.5	1.03
VRP004	33.6	34.3	17.3	0.95
VRP005	34.5	34.3	21.7	0.93
VRP006	24.1	45.6	4.4	0.56
VRP007	25.6	44.7	4.1	0.56
VRP008	23.2	48.8	6.6	0.38
VRP009	39.0	32.8	25.4	0.79
VRP010	39.0	33.4	21.5	0.76
VRP011	34.7	39.6	8.6	0.49
VRP012	39.6	36.4	8.6	0.49
VRP013	39.3	37.1	8.1	0.54
VRP014	70.3	21.2	32.0	1.17
VRP015	151.6	15.1	50.0	1.25
VRP016	32.1	41.6	11.5	0.41
VRP017	34.7	40.2	7.5	0.53
VRP018	38.2	37.5	2.0	0.67
VRP019	35.4	39.5	2.7	0.61
VRP020	31.3	46.4	0.7	0.62
VRP021	**15.2**	**55.7**	**8.5**	**0.22**
VRP022	32.4	41.5	6.5	0.34
VRP023	**12.4**	**58.1**	**10.0**	**0.12**

It is evident from Table 5.2 that there seems to be a relationship between the calculated f_2 and S_d values determined in this study. Tablets from batches VRP021 and VRP023, which showed f_2 values of greater than 50 presented S_d values of less than or equal to

0.22. From a practical standpoint, the selection of a limit point to determine similarity based on this new factor may not provide convincing results, but it has been shown that when the S_d value is close to zero, the dissolution profiles show similarity and when the value approaches unity the dissolution profiles may not be similar as observed with tablets from batches VRP001-VRP005 and VRP014-VRP015.

The values for % AUC $_{(diff)}$ between TEST and REFERENCE products were also compared to determine whether or not a relationship exists between f_2 and % AUC $_{(diff)}$. Tablets from batches VRP021 and VRP023, which showed f_2 values of greater than 50, presented % AUC $_{(diff)}$ values of less than or equal to 10.0 %. A number of batches, VRP006-VRP008, VRP011-VRP013, VRP017-VRP020 and VRP022 had % AUC $_{(diff)}$ of less than 10.0%, although they were not similar based on f_2 values. Therefore, it is not possible to correlate % AUC $_{(diff)}$ and f_2 values due to the variable results obtained.

The S_d factor may be used to compare dissolution profiles and seems to be applicable and it was observed that there is a relationship that exists between the f_2 factor and S_d. The % AUC $_{(diff)}$ approach simply looks at the difference in area yet there may be differences in shape if the dissolution profiles do not overlap, resulting in small area differences. Therefore, inaccurate conclusions that dissolution profiles are similar may be drawn when in fact they are not using the % AUC $_{(diff)}$ approach.

5.3.2 Mechanism of Release

The dependence of drug release mechanism on pH of the dissolution medium was studied at constant and variable pH's using USP apparatus 1 and 3, respectively.

5.3.2.1 Effect of pH

In order to assess the impact of a constant pH dissolution medium on the kinetic rate constant, dissolution testing was performed in media of pH 1.6, 4.6, 6.8 and 7.4 individually. Data were fitted to the Korsmeyer-Peppas model and the kinetic constants calculated. A plot of kinetic constant versus pH is depicted in Figure 5.3 and the best fit model parameters are listed in Table 5.3.

At a pH of 1.6, the average values of K were high and as the pH increased to 4.6, the rate constants decreased to a minimum value between pH 5.0 and pH 6.0 after-which the release rate constants increased. However, the opposite effect was seen with the Isoptin® SR product.

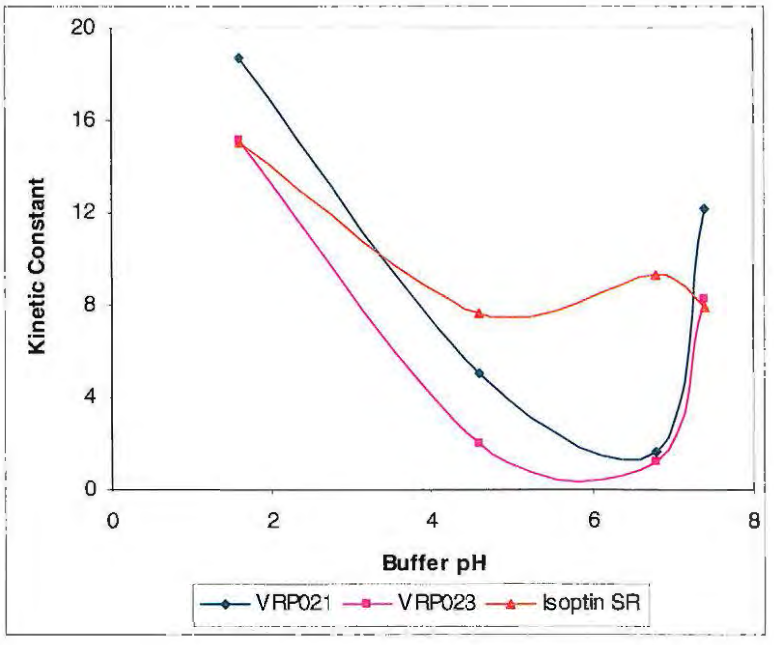


Figure 5.3. pH effect on the Kinetic constant of VRP021, VRP023 and Isoptin® SR

The lowest average kinetic constant was determined at pH 6.8 for VRP021 and VRP023. There is a direct relationship between total percent drug released and the kinetic rate constant. Therefore, the decrease in kinetic rate constants for batches VRP021 and VRP023 at higher pH values may be due to the increase in the diffusional path length for the drug to diffuse or to the decreased solubility of VRP at these pH's.

The release exponent n was found to have values of between 0.50 and 1.00 for batches VRP021, VRP023 and Isoptin® SR formulations at pH's 1.6, 4.6 and 7.4, indicating that the release mechanism from these dosage forms was non-Fickian at all pH's. The release mechanism thus involves a combination of both diffusion and chain relaxation mechanisms, thus indicating that anomalous transport kinetics are prevalent.

Table 5.3. Summary of Korsmeyer-Peppas best fit parameters for batches VRP021, VRP023 and Isoptin® SR in dissolution media of different pH using USP apparatus 1

Formulation	M_t / M_∞	Time (hrs)	pH	Kinetic constant (K)	Release exponent (n)	Coefficient of determination (R^2)
VRP021	0.32	2	1.6	17.60	0.8443	1.0000
	0.70	6		17.90	0.7644	0.9982
	0.92	10		18.34	0.7219	0.9952
	0.95	14		19.05	0.6631	0.9809
	0.95	22		20.48	0.5665	0.9281
VRP021	0.08	2	4.6	5.000	0.6781	1.0000
	0.20	6		4.869	0.7792	0.9971
	0.25	10		4.900	0.7256	0.9935
	0.28	14		5.132	0.6811	0.9864
	0.40	22		5.176	0.6713	0.9814
VRP021	0.04	2	6.8	1.500	1.4150	1.0000
	0.12	6		1.610	1.1460	0.9906
	0.18	10		1.667	1.0698	0.9896
	0.21	14		1.741	1.0001	0.9833
	0.35	22		1.768	0.9838	0.9871
VRP021	0.26	2	7.4	10.50	1.3301	1.0000
	0.55	6		11.74	0.9038	0.9640
	0.77	10		12.11	0.8389	0.9722
	0.78	14		12.76	0.7566	0.9555
	0.78	22		13.92	0.6567	0.9124

Table 5.3 continued.

Formulation	M_t / M_∞	Time (hrs)	pH	Kinetic constant (K)	Release exponent (n)	Coefficient of determination (R^2)
VRP023	0.29	2	1.6	14.00	1.0506	1.0000
	0.60	6		14.67	0.7989	0.9982
	0.93	10		14.96	0.7947	0.9952
	0.97	14		15.27	0.7408	0.9800
	0.97	22		16.72	0.6508	0.9387
VRP023	0.04	2	4.6	2.000	1.0000	1.0000
	0.15	6		1.932	1.1317	0.9977
	0.22	10		1.985	1.0730	0.9957
	0.26	14		2.062	1.0123	0.9899
	0.36	22		2.155	0.9614	0.9859
VRP023	0.04	2	6.8	1.000	1.9000	1.0000
	0.10	6		1.220	1.2441	0.9401
	0.15	10		1.290	1.1235	0.9518
	0.36	14		1.222	1.2088	0.9627
	0.42	22		1.263	1.1711	0.9698
VRP023	0.19	2	7.4	7.000	1.4632	1.0000
	0.41	6		7.985	0.9637	0.9557
	0.60	10		8.233	0.8969	0.9689
	0.63	14		8.647	0.8191	0.9594
	0.63	22		9.461	0.7159	0.9198

Table 5.3 continued.

Formulation	M_t / M_∞	Time (hrs)	pH	Kinetic constant (K)	Release exponent (n)	Coefficient of determination (R^2)
Isoptin® SR	0.25	2	1.6	14.40	0.8188	1.0000
	0.55	6		14.67	0.7483	0.9985
	0.72	10		14.96	0.7054	0.9955
	0.84	14		15.27	0.6735	0.9928
	0.95	22		15.83	0.6314	0.9840
Isoptin® SR	0.16	2	4.6	7.000	1.1926	1.0000
	0.46	6		7.282	1.0426	0.9965
	0.67	10		7.491	0.9811	0.9941
	0.72	14		7.861	0.9047	0.9817
	0.75	22		8.594	0.8024	0.9490
Isoptin® SR	0.17	2	6.8	9.000	0.9175	1.0000
	0.46	6		9.018	0.9101	1.0000
	0.70	10		9.083	0.8944	0.9997
	0.77	14		9.406	0.8391	0.9913
	0.77	22		10.20	0.7462	0.9585
Isoptin® SR	0.17	2	7.4	7.400	1.1569	1.0000
	0.47	6		7.678	1.0223	0.9970
	0.77	10		7.726	1.0054	0.9982
	0.87	14		8.000	0.9505	0.9928
	0.87	22		8.764	0.8458	0.9590

It is evident that pH has no effect on the mechanism of drug release from Isoptin® SR as can be seen in Figure 5.4. The values for n remained relatively unchanged when the ratio of drug release was in the region of approximately 60%. The mechanism of release can still be attributed to anomalous transport kinetics.

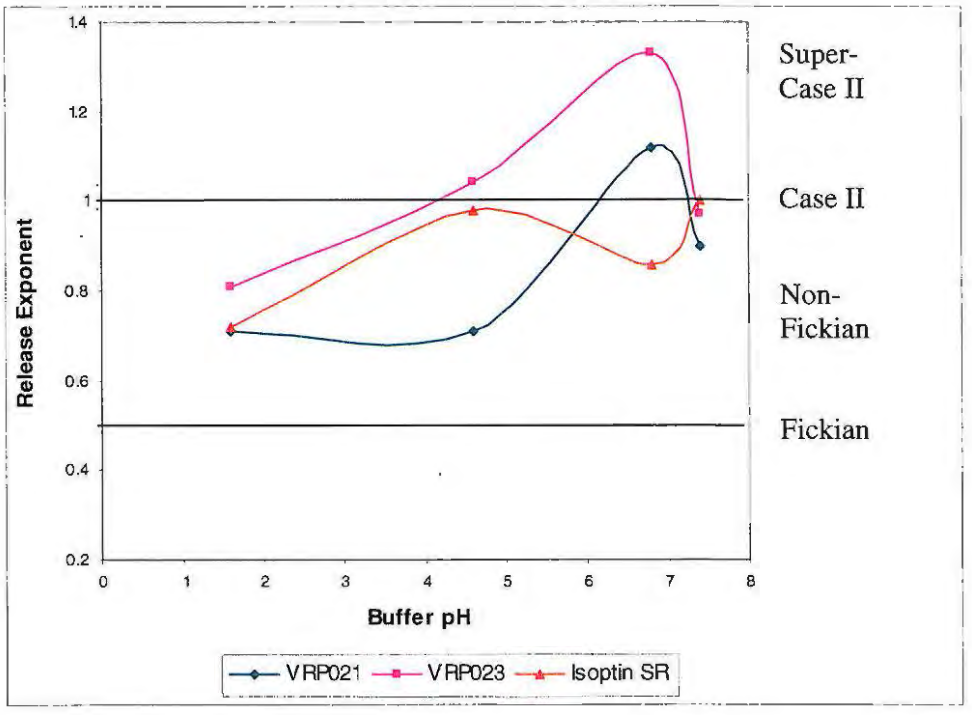


Figure 5.4. pH effect on the release exponent (n-value) for batches VRP021 and VRP023 and Isoptin® SR using USP apparatus 1.

Tablets from batch VRP023 showed an increase in n-values when the dissolution medium was increased to 4.6, and in all cases n-values of greater than 1 were obtained, indicating that Super-Case II transport was evident. The release mechanism remained relatively unchanged for tablets from batch VRP021 when the pH was increased to pH 4.6. A further increase in pH to 6.8 revealed a corresponding increase in n-value for tablets from batches VRP021 and VRP023. However, values of n for Isoptin® SR approached 1.0 at all tested pH's indicating that the mode of release was approaching zero-order and may not be controlled purely by relaxation of the polymer used in this product. Figure 5.4 also reveals that when the pH was increased to 7.4, the release can be considered Case-II transport for the tablets from batch VRP023 and Isoptin® SR. An observed shift from Super Case-II to a non-Fickian transport mechanism was observed for VRP021 at pH 7.4.

It is therefore clear that at pH's 6.8 and 7.4 Isoptin® SR seems to follow zero-order kinetic release. In this study, pH was shown to play an important role in control of the release mechanism of VRP from batches VRPP021 and VRP023, however, drug release from Isoptin® SR was not affected to any great extent. Therefore, during the course of transit of the dosage form in the gastro-intestinal tract, the release from the product may show different release mechanisms if the formulation were to reside in one place in the gastro-intestinal tract for any prolonged period of time.

The complexity of the formulations tested and the components used in sustained release products is indicative that drug release is controlled by more than one process and the effects of formulation composition and test methodology on drug release must be thoroughly investigated in formation development studies.

Dissolution was also performed using a sequence of changing pH using USP apparatus 3. The values of K, n and R^2 following linear regression of dissolution data are listed in Table 5.4. The kinetic constant, K did not show any appreciable difference between the batches VRP021 and VRP023, but values obtained for Isoptin® SR tablets were slightly lower. For all formulations, VRP021, VRP023 and Isoptin® SR, the n-values fall between 0.50 and 1.00, indicating that the release mechanism was non-Fickian, involving a combination of either diffusion and chain relaxation mechanisms or anomalous transport kinetics. It is evident from Table 5.4 that the values of n seem to remain relatively constant with increase in time, however release profiles did not show Case-II transport or that zero-order release was occurring.

It is evident that the calculated kinetic constant as depicted in Figure 5.3 was constantly changing when dissolution testing was undertaken using USP apparatus 1. However, the kinetic constant remained relatively unchanged for the duration of the dissolution testing when using USP apparatus 3 as seen in Table 5.4.

The release exponent as described showed an appreciable increase for batches VRP021 and VRP023 when the dissolution medium was increased from pH 1.6 to 6.8 indicating that both anomalous and Super Case-II transport was occuring. n-Values for Isoptin® SR

remained relatively unchanged for the duration of the dissolution testing and transport was attributed to anomalous transport. When using USP apparatus 3 the release exponent was found to have values of between 0.5 and 1.0 for all batches tested indicating that the release from these dosage forms was due to a combination of diffusion, swelling and erosion.

Table 5.4. Summary of Korsmeyer-Peppas best fit parameters for batches VRP021, VRP023 and Isoptin® SR in dissolution media of different pH using USP apparatus 3

Formulation	$\frac{M_t}{M_\infty}$	Time (hrs)	pH	Kinetic constant (K)	Release exponent (n)	coefficient of determination (R^2)
VRP021	0.23	2	1.6	15.99	0.6167	1.0000
	0.56	6	4.6	14.93	0.7420	0.9951
	0.80	10	6.8	14.52	0.7415	0.9975
	0.85	14	7.4	14.51	0.6971	0.9903
	0.85	22	7.4	15.00	0.6185	0.9563
VRP023	0.19	2	1.6	13.00	0.5475	1.0000
	0.57	6	4.6	12.06	0.8409	0.9794
	0.80	10	6.8	12.11	0.8265	0.9890
	0.84	14	7.4	12.56	0.7693	0.9809
	0.84	22	7.4	13.59	0.6790	0.9452
Isoptin® SR	0.18	2	1.6	10.00	0.8480	1.0000
	0.64	6	4.6	9.490	1.0468	0.9938
	0.92	10	6.8	9.700	0.9998	0.9949
	0.94	14	7.4	10.04	0.9138	0.9787
	0.94	22	7.4	11.32	0.7989	0.9370

5.3.3 Mathematical Models

Mathematical models have been used extensively for the parametric representation of dissolution data. In this study, a summary of the mathematical models used to evaluate dissolution data is listed in Table 5.5.

Table 5.5. Mathematical representation of models used to describe the release profiles of batches VRP021, VRP023 and Isoptin® SR

Model	Equations
Zero-order	$Q_t = Q_o + K_o t$
First-order	$Ln\ Q_t = Ln\ Q_o + K_1 t$
Higuchi	$Q_t = K_H t^{1/2}$
Hixson-Crowell	$Q_o^{1/3} - Q_t^{1/3} = K_s t$
Baker-Lonsdale	$\left(\frac{3}{2}\right)\left[1-\left(1-\left(\frac{Q_t}{Q_\infty}\right)^{2/3}\right)\right]-\left(\frac{Q_t}{Q_\infty}\right) = K_{BL} t$
Weibull	$Log\ [-ln\ (1-(\frac{Q_t}{Q_\infty}))] = \beta\ log\ t - log\ \alpha$

The most important aspect to consider when developing new pharmaceutical products or evaluating drug release mechanisms is the suitability of the predictive ability and accuracy of any model chosen to describe the release process.

The criterion used for selecting the most appropriate model was based on goodness of fit [172, 173,175, 185, 190] as it is a convenient and common metric that is used to determine the fitting of data to a model and that has been used by pharmaceutical scientists, despite limitations this parameter may have [175]. In this study, the adjusted coefficient of determination ($R^2_{adjusted}$) was used to compare models with different numbers of parameters as variable numbers of model parameters may lead to an inappropriate decision as a result of over-fitting [185].

5.3.3.1 Modelling

The results of the analysis of dissolution testing in a constant pH dissolution medium using the models depicted in Table 5.5 are shown in Table 5.6. The results of modelling were interpreted by considering the $R^2_{adjusted}$ value at constant pH's.

After fitting individual unit dissolution data at pH 1.6 to the various models, the highest $R^2_{adjusted}$ values were observed when the release data were fitted to a Weibull function for tablets from batch VRP021 and Isoptin® SR. Tablets from batch VRP023 were best fitted to the Hixson-Crowell model.

At pH 4.6, the highest $R^2_{adjusted}$ values were observed when the release data were fitted to the Weibull model for tablets from batches VRP021, VRP023 and Isoptin® SR. At pH 6.8, the highest $R^2_{adjusted}$ values were observed when the release data were fitted to the zero-order model for tablets from batch VRP023 and to the Weibull model for batch VRP021 and Isoptin® SR. At pH 7.4, the highest $R^2_{adjusted}$ values were observed when the release data were fitted to the Hixson-Crowell model for tablets from batch VRP021 and to zero-order for tablets from batch VRP023 and Isoptin® SR. These results indicate that the release pattern the different formulations may change at different pH's if using USP apparatus 1.

The Weibull model parameters describe the shape (β) of the profiles and determines the 63.2% dissolution time (T_d). Evaluation of β for batch VRP021 revealed there was no statistically significant difference between values determined at the different pH's ($p > 0.05$) when using a two side-t-test. Figure 5.5 depicts the effects of pH on the shape parameter of VRP021, VRP023 and Isoptin® SR using USP apparatus 1. It is evident that the value of β ranged from 0.700 to approximately 1.400. This is indicative of changing dissolution profiles with changes in medium pH. The shape parameter characterizes the profile of tablets from batch VRP021 as one with a steeper initial slope ($\beta < 1$) for lower pH values and that subsequently changes to an S-shaped profile with upward curvature followed by turning point ($\beta > 1$) at higher pH values. A similar S-shaped profile was observed for batch VRP023.

Table 5.6. Resultant model parameters obtained after fitting dissolution data obtained using USP apparatus 1 for batches VRP021, VRP023 and Isoptin® SR

Formulation	Time	pH	Zero-order		First-order		Higuchi		Hixson-Crowell		Baker-Lonsdale		Weibull		
	(hr)		R^2	k_o	R^2	k_1	R^2	k_H	R^2	k_{HC}	R^2	k_B	R^2	β	T_d
VRP021	1	1.6	1.0000	17.000	1.0000	2.8679	1.0000	28.7790	1.0000	0.2901	1.0000	0.2951			
	2		0.9957	15.500	0.8729	1.7266	0.9717	28.7790	0.9991	0.2760	0.9073	0.1900	1.0000	0.9723	
	6		0.9816	11.210	0.6188	0.5534	0.9623	28.7790	0.9990	0.2532	0.6751	0.0649	0.9996	1.0228	
	10		0.9660	8.7860	0.5941	0.3363	0.9799	30.3540	0.9994	0.2609	0.6184	0.0384	0.9949	1.0997	
	14		0.9066	6.8598	0.5592	0.2327	0.9764	28.1840	0.9742	0.2208	0.5681	0.0261	0.9953	1.0729	
	22		0.7537	4.3422	0.4603	0.1396	0.9222	23.4560	0.8376	0.1467	0.4608	0.0156	0.9709	0.9697	5.42
VRP021	1	4.6	1.0000	5.0000	1.0000	1.6094	1.0000	13.7240	1.0000	0.0786	1.0000	0.1536			
	2		0.9796	4.0000	0.9090	1.0397	0.9917	13.7240	0.9816	0.0636	0.9092	0.0992	1.0000	0.7365	
	6		0.9907	3.2169	0.7736	0.4194	0.9477	13.7240	0.9940	0.0539	0.8313	0.0449	0.9966	0.7343	
	10		0.9588	2.4979	0.7336	0.2660	0.9736	15.4710	0.9664	0.0424	0.7974	0.0297	0.9936	0.7747	
	14		0.9289	1.9936	0.6995	0.1916	0.9808	16.0290	0.9399	0.0345	0.7645	0.0219	0.9886	0.8274	
	22		0.9470	1.7307	0.6599	0.1305	0.9843	16.2140	0.9643	0.0315	0.7362	0.0155	0.9921	0.7010	19.21
VRP021	1	6.8	1.0000	1.5000	1.0000	0.4055	1.0000	15.1820	1.0000	0.0233	1.0000	0.0762			
	2		0.9766	2.0000	0.9457	0.6931	0.8637	15.1820	0.9786	0.0314	0.9948	0.0677	1.0000	1.0370	
	6		0.9980	2.0301	0.9362	0.4080	0.8820	15.1820	0.9979	0.0323	0.9376	0.0381	0.9919	1.0370	
	10		0.9947	1.8401	0.8946	0.2872	0.9293	18.6000	0.9964	0.0304	0.9161	0.0281	0.9916	1.0713	
	14		0.9747	1.5740	0.8461	0.2151	0.9564	20.2940	0.9793	0.0263	0.8791	0.0217	0.9862	1.0905	
	22		0.9895	1.5599	0.7995	0.1534	0.9403	19.8060	0.9911	0.0275	0.8626	0.0165	0.9903	1.0680	57.35
VRP021	1	7.4	1.0000	10.500	1.0000	2.3510	1.0000	23.1040	1.0000	0.1653	1.0000	0.2288			
	2		0.9878	13.000	0.9402	1.6370	0.8809	23.1040	0.9792	0.2254	0.9717	0.1766	1.0000	1.4663	
	6		0.9795	9.1747	0.6785	0.5464	0.9428	23.1040	0.9903	0.1804	0.7446	0.0645	0.9785	1.0807	
	10		0.9736	7.6221	0.6501	0.3388	0.9678	25.3660	0.9969	0.1780	0.7022	0.0402	0.9891	1.0780	
	14		0.9082	5.7830	0.6063	0.2351	0.9676	23.6610	0.9463	0.1410	0.6479	0.0279	0.9798	1.0026	
	22		0.7523	3.6492	0.4966	0.1412	0.9150	19.7400	0.7955	0.0902	0.5275	0.0168	0.9430	0.8846	7.74

Table 5.6 continued.

Formulation	Time	pH	Zero-order		First-order		Higuchi		Hixson-Crowell		Baker-Lonsdale		Weibull		
	(hr)		R^2	k_o	R^2	k_1	R^2	k_H	R^2	k_{HC}	R^2	k_B	R^2	β	T_d
VRP023	1	1.6	1.0000	14.000	1.0000	2.6391	1.0000	17.6000	1.0000	0.2276	1.0000	0.2644			
	2		0.9996	14.500	0.8768	1.6836	0.9365	21.4680	0.9972	0.2504	0.9393	0.1836	1.0000	1.1832	
	6		0.9737	9.6506	0.6299	0.5404	0.9615	24.8640	0.9932	0.2010	0.7029	0.0641	0.9940	0.9968	
	10		0.9882	8.9709	0.6057	0.3439	0.9608	30.3540	0.9757	0.2626	0.6666	0.0395	0.9755	1.1749	
	14		0.9422	7.2926	0.5902	0.2422	0.9719	28.1840	0.9801	0.2399	0.6173	0.0274	0.9837	1.1932	
	22		0.7939	4.7590	0.5238	0.1468	0.9391	23.4560	0.8642	0.1645	0.5036	0.0164	0.9704	1.0991	6.88
VRP023	1	4.6	1.0000	2.0000	1.0000	0.6931	1.0000	5.00000	1.0000	0.0312	1.0000	0.0905			
	2		1.0000	2.0000	1.0000	0.6931	0.9459	5.53550	1.0000	0.0314	0.9636	0.0677	1.0000	1.2646	
	6		0.9952	2.5422	0.9620	0.4309	0.8558	8.15850	0.9936	0.0416	0.9545	0.0423	0.9969	1.1897	
	10		0.9923	2.2762	0.9045	0.3007	0.9194	8.38010	0.9942	0.0382	0.9214	0.0310	0.9963	1.1786	
	14		0.9751	1.9582	0.8524	0.2250	0.9502	8.61710	0.9807	0.0334	0.8819	0.0239	0.9918	1.1152	
	22		0.9734	1.7105	0.7699	0.1528	0.9669	8.11030	0.9803	0.0279	0.8208	0.0169	0.9903	1.0089	47.00
VRP023	1	6.8	1.0000	1.0000	1.0000	0.6931	1.0000	1.00000	1.0000	0.0157	1.0000	0.0596			
	2		0.9231	2.0000	0.8500	0.6931	0.7567	2.49070	0.9216	0.0314	0.9953	0.0677	1.0000	2.0221	
	6		0.9857	1.6968	0.8102	0.3944	0.8894	4.18420	0.9869	0.0273	0.9143	0.0351	0.9431	1.2707	
	10		0.9892	1.5262	0.8035	0.2617	0.9345	4.97490	0.9914	0.0249	0.9022	0.0258	0.9555	1.1552	
	14		0.9139	2.3151	0.8776	0.2346	0.7769	9.58980	0.8913	0.0408	0.9538	0.0257	0.9600	1.2708	
	22		0.9445	2.0533	0.7987	0.1588	0.8039	8.45140	0.9410	0.0375	0.8941	0.0190	0.9701	1.2494	81.00
VRP023	1	7.4	1.0000	7.0000	1.0000	1.9459	1.0000	7.00000	1.0000	0.1109	1.0000	0.1848			
	2		0.9774	9.5000	0.9666	1.4722	0.8541	12.4190	0.9695	0.1601	0.9868	0.1540	1.0000	1.5637	
	6		0.9785	6.7590	0.7205	0.5154	0.9335	17.2590	0.9874	0.1249	0.7950	0.0609	0.9679	1.0867	
	10		0.9834	5.9360	0.7025	0.3315	0.9581	19.7560	0.9955	0.1212	0.7700	0.0400	0.9821	1.0583	
	14		0.9355	4.6817	0.6616	0.2343	0.9683	18.8960	0.9565	0.0992	0.7184	0.0284	0.9757	0.9848	
	22		0.7865	3.0118	0.5455	0.1423	0.9259	15.9710	0.8117	0.0647	0.5897	0.0173	0.9409	0.8691	11.45

Table 5.6 continued.

Formulation	Time	pH	Zero-order		First-order		Higuchi		Hixson-Crowell		Baker-Lonsdale		Weibull		
	(hr)		R^2	k_o	R^2	k_1	R^2	k_H	R^2	k_{HC}	R^2	k_B	R^2	β	T_d
Isoptin® SR	6	1.6	1.0000	14.400	1.0000	2.6672	1.0000	14.4000	1.0000	0.2344	1.0000	0.2681			
	10		0.9944	12.700	0.8768	1.6174	0.9754	17.3030	0.9976	0.2160	0.9107	0.1738	1.0000	0.9183	
	14		0.9789	8.8386	0.6299	0.5259	0.9662	22.7690	0.9950	0.1786	0.7075	0.0624	1.0000	0.9197	
	10		0.9632	7.0453	0.6057	0.3211	0.9821	23.8590	0.9924	0.1601	0.6673	0.0384	1.0000	0.9189	
	14		0.9472	5.8765	0.5902	0.2290	0.9888	23.7710	0.9925	0.1499	0.6307	0.0274	0.9998	0.9289	
	22		0.8957	4.3891	0.5238	0.1454	0.9876	22.5070	0.9970	0.1496	0.5276	0.0165	0.9892	0.9973	6.88
Isoptin® SR	6	4.6	1.0000	7.0000	1.0000	1.9459	1.0000	7.00000	1.0000	0.1109	1.0000	0.1848			
	10		0.9948	8.0000	0.9485	1.3863	0.9088	10.5170	0.9922	0.1310	0.9689	0.1410	1.0000	1.2646	
	14		0.9993	7.6988	0.7726	0.5413	0.8981	18.9250	0.9983	0.1459	0.8542	0.0639	0.9993	1.1897	
	10		0.9923	6.8052	0.7480	0.3496	0.9400	22.2130	0.9995	0.1454	0.8103	0.0421	0.9996	1.1786	
	14		0.9492	5.4598	0.7002	0.2490	0.9598	21.7360	0.9737	0.1229	0.7516	0.0301	0.9934	1.1152	
	22		0.8250	3.6503	0.5847	0.1534	0.9388	19.0120	0.8713	0.0857	0.6205	0.0185	0.9698	1.0089	11.00
Isoptin® SR	6	6.8	1.0000	9.0000	1.0000	2.1972	1.0000	9.00000	1.0000	0.1430	1.0000	0.2112			
	10		0.9988	8.5000	0.9081	1.4166	0.9602	11.4630	0.9997	0.1398	0.9354	0.1766	1.0000	1.2646	
	14		0.9982	7.5663	0.7258	0.5254	0.9214	18.8500	0.9999	0.1437	0.8155	0.0645	0.9993	1.8976	
	10		0.9962	6.6980	0.7173	0.3417	0.9439	22.7470	0.9985	0.1527	0.7885	0.0432	0.9996	1.1786	
	14		0.9611	5.7177	0.6824	0.2446	0.9640	22.5680	0.9835	0.1339	0.7367	0.0279	0.9935	1.1152	
	22		0.8184	3.7473	0.5687	0.1501	0.9374	19.5660	0.8555	0.0903	0.6071	0.0168	0.9698	1.0871	11.78
Isoptin® SR	6	7.4	1.0000	7.4000	1.0000	2.0000	1.0000	7.40000	1.0000	0.1174	1.0000	0.1904			
	10		0.9965	8.2500	0.9425	1.4017	0.9159	10.8740	0.9942	0.1354	0.9649	0.1431	1.0000	1.2501	
	14		0.9993	7.8494	0.7634	0.5407	0.9021	19.2490	0.9987	0.1488	0.8464	0.0639	0.9996	1.2484	
	10		0.9997	7.7090	0.7567	0.3599	0.9229	24.7630	0.9887	0.1776	0.8158	0.0429	0.9959	1.2501	
	14		0.9755	6.5495	0.7232	0.2610	0.9524	25.5520	0.9927	0.1697	0.7601	0.0308	0.9973	1.2484	
	22		0.8398	4.3549	0.6023	0.1609	0.9343	22.3970	0.8840	0.1184	0.6243	0.0189	0.9779	1.1409	8.41

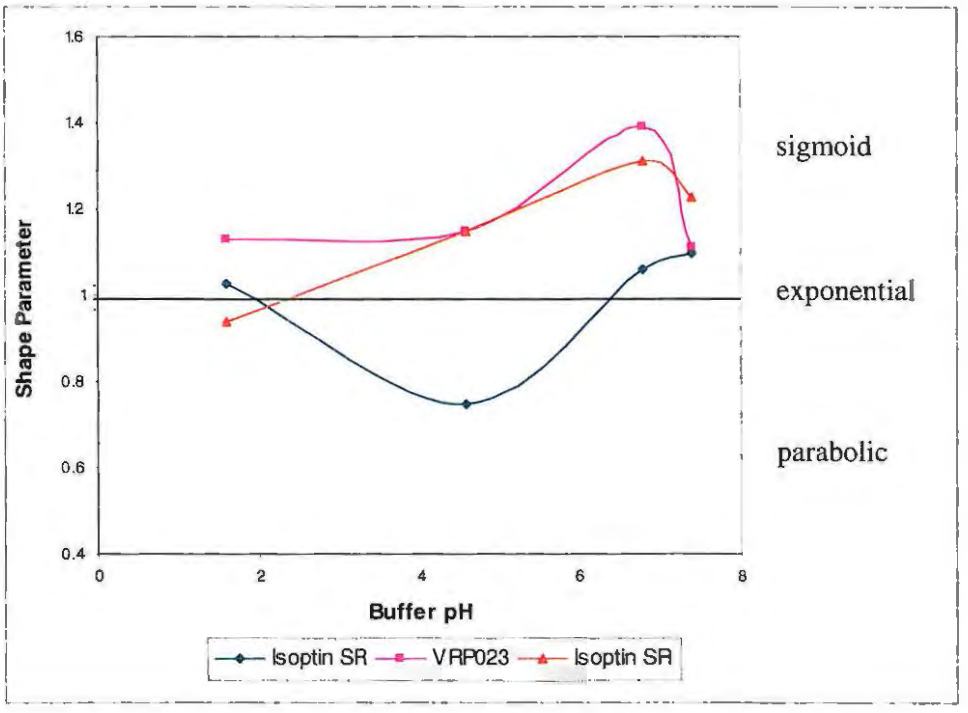


Figure 5.5. pH effect on the shape parameter for batches VRP021, VRP023 and Isoptin® SR using USP apparatus 1.

Evaluation of the T_d values of tablets from batches VRP021, VRP023 and Isoptin® SR revealed that there was a statistically significant difference between the values obtained at pH's 4.6 and 6.8 ($p < 0.05$) using USP apparatus 1. It is evident (Figure 5.6) that at pH 1.6 it takes less than 8 hours for all dosage forms to release at least 63.2% of VRP from the dosage forms. As the pH is increased to 4.6, the time taken to dissolve 63.2% of the drug had not been reached after 22 hours with only about 35-45% drug released. The predicted T_d values if dissolution testing had been allowed to continue would have been 19.21 and 47.00 hours for VRP021 and VRP023, respectively. This increase was also observed at pH 6.8 for tablets from batches VRP021 and VRP023. A pH of 7.4 is higher than the pK_a of Carbopol® and the T_d values decreased for tablets from batches VRP021 and VRP023 whereas those for Isoptin® SR remained slightly less than the values obtained at pH 6.8.

It was expected that the T_d value obtained for batch VRP021 at pH 7.4 was going to be higher as swelling studies (§ 4.3.3.2, Figure 4.19) showed a higher rate of swelling for tablets from batch VRP021 than for VRP023. A high degree of swelling will result in an increased diffusional path length through which the drug must pass, which in turn may prolong drug release. The results obtained for the REFERENCE product,

Isoptin® SR were as expected, with T_d values remaining relatively constant in all pH's tested since swelling observed for this formulation was constant at all pH levels.

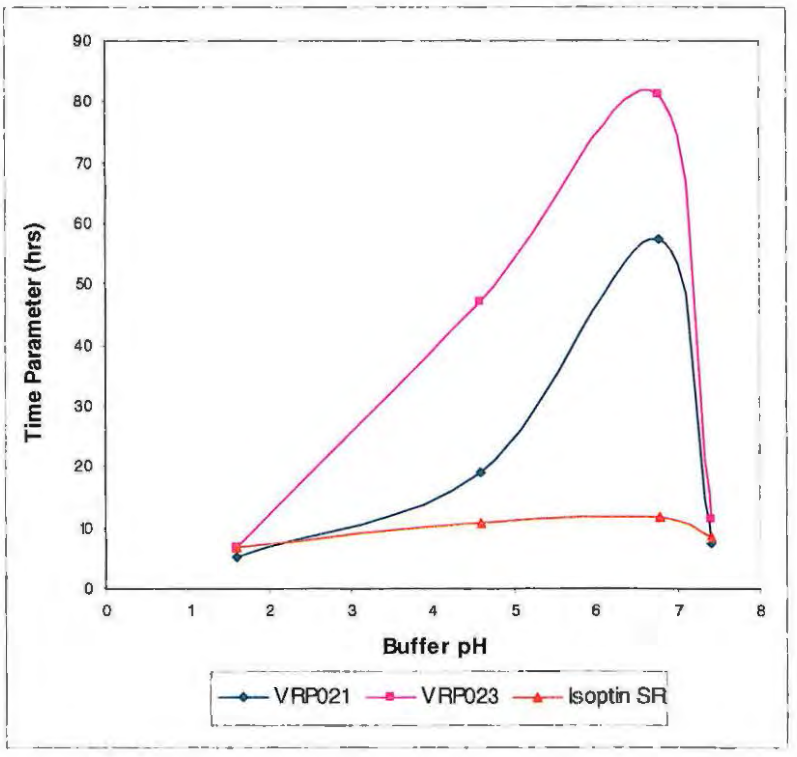


Figure 5.6. pH effect on time parameter (T_d) of batches VRP021, VRP023 and Isoptin® SR using USP apparatus 1.

Dissolution testing was also performed using a sequential increase in the pH of the dissolution media (USP apparatus 3). The results of the analysis of dissolution data using the models depicted in Table 5.5 are shown in Table 5.7. The results of modelling were interpreted by considering the $R^2_{adjusted}$ value at the different pH's a product is likely to be exposed to in the gastro-intestinal tract. The highest $R^2_{adjusted}$ values were observed when the release data were fitted to several models (zero-order, Hixson-Crowell and Weibull model).

Fitting drug release data to the zero-order model revealed K_o (rate constant) values between 4.000-15.000, 4.036-13.000 and 4.658-10.000 for batches VRP021, VRP023 and Isoptin® SR, respectively. A two-sided t-test conducted at the 95% level of significance ($\alpha = 0.05$) revealed that there was no statistically significant difference ($p > 0.05$) between the K_o values obtained for the different formulations in all cases.

A similar trend was observed when the data were fitted to the first-order, Higuchi, Hixson-Crowell and Baker-Lonsdale models. There were no statistically significant differences ($p > 0.05$) between the kinetic constant values obtained for the different formulations at a 95% level of significance for all products.

In order to assess whether β-values for VRP021, VRP023 versus Isoptin® SR obtained from the Weibull model were significantly different, a comparison of the β-values was performed using a two-sided t-test at 95% level of significance. No significant differences were observed for these assessments implying that the dissolution profiles of both VRP021 and VRP023 were similar to Isoptin® SR ($p > 0.05$) in terms of the shape parameter. The T_d values obtained were compared using a two-sided t-test and were found to be similar ($p > 0.05$) for all comparisons.

The drug release data for tablets from batches VRP021 and VRP023 were best fitted to the zero-order, Hixson-Crowell and Weibull models with average $R^2_{adjusted}$ values higher than 0.970. The drug release data from Isoptin® SR were best fitted to the zero-order model.

Table 5.7. Resultant model parameters obtained after fitting dissolution data obtained using USP apparatus 3 for batches VRP021, VRP023 and Isoptin® SR

Formulation	Time	pH	Zero-order		First-order		Higuchi		Hixson-Crowell		Baker-Lonsdale		Weibull		
	(hr)		R^2	k_o	R^2	k_1	R^2	k_H	R^2	k_{HC}	R^2	k_B	R^2	β	T_d
VRP021	1	1.6	1.0000	15.000	1.0000	0.2708	1.0000	15.0000	1.0000	0.2448	1.0000	0.2735	1.0000	0.6855	
	2	3.4	0.9700	11.500	0.8501	1.5677	0.9963	16.0300	0.9773	0.1936	0.8792	0.1665	1.0000	0.6855	
	6	4.6	0.9865	8.9393	0.6379	0.5266	0.9554	22.8120	0.9970	0.1814	0.7195	0.0625	0.9892	0.9165	
	10	6.8	0.9853	7.7878	0.6320	0.3314	0.9683	25.8920	0.9984	0.1891	0.6897	0.0392	0.9887	0.9999	
	14	7.4	0.9405	6.1897	0.6036	0.2337	0.9767	24.9740	0.9782	0.1625	0.6435	0.0274	0.9915	0.9802	6.71
	22	7.4	0.7428	3.9967	0.5013	0.1417	0.9350	21.1970	0.8450	0.1086	0.5275	0.0166	0.9692	0.8883	
VRP023	1	1.6	1.0000	13.000	1.0000	0.2565	1.0000	13.0000	1.0000	0.2105	1.0000	0.2549	1.0000	0.5975	
	2	3.4	0.9567	9.5000	0.8449	1.4722	0.9994	13.3550	0.9634	0.1574	0.8706	0.1529	1.0000	0.5975	
	6	4.6	09954	9.2892	0.6907	0.5407	0.9151	23.0950	0.9945	0.1892	0.7793	0.0643	0.9706	1.0290	
	10	6.8	0.9872	8.0058	0.6756	0.3428	0.9510	26.3530	0.9982	0.1933	0.7372	0.0408	0.9833	1.0939	
	14	7.4	0.9357	6.2862	0.6380	0.2415	0.9638	25.2580	0.9707	0.1622	0.6819	0.0286	0.9855	1.0550	8.08
	22	7.4	078494	4.0358	0.5267	0.1464	0.9230	21.3700	0.8326	0.1074	0.5565	0.0173	0.9598	0.9481	
Isoptin® SR	1	1.6	1.0000	10.000	1.0000	2.3026	1.0000	10.0000	1.0000	0.1602	1.0000	0.2232	1.0000	0.9134	
	2	3.4	0.9959	9.0000	0.8950	1.4452	0.9712	12.2440	0.9980	0.1486	1.0000	0.2232	1.0000	0.9134	
	6	4.6	0.9969	10.474	0.7630	0.5781	0.8704	26.0390	0.9870	0.2289	0.9240	0.1491	0.9856	1.2882	
	10	6.8	09909	9.4593	0.7345	0.3711	0.9280	30.7040	0.9885	0.2666	0.8445	0.0686	0.9882	1.3931	
	14	7.4	0.9300	7.3119	0.6828	0.2609	0.9459	29.1960	0.9650	0.2238	0.7759	0.0432	0.9879	1.3358	6.58
	22	7.4	0.7748	4.6576	0.5583	0.1579	0.9065	24.6030	0.8288	0.1482	0.7066	0.0301	0.9603	1.1970	

5.4 CONCLUSION

Drug delivery systems manufactured using matrix polymers have been assessed and the release characteristics were found to be affected by factors such as the degree of polymer swelling and the characteristics of the dissolution medium and test parameters.

Mathematical models were used to describe drug release from batches VRP021, VRP023 and Isoptin® SR product.

The selection of an appropriate model for the analysis of drug release provides insight to the underlying mass transport mechanism of drug release. Mini-tablets were evaluated using *in-vitro* dissolution studies in different dissolution media. The f_1 and f_2 factors were used for the selection of the most appropriate formulations. The dissolution profiles of batches VRP021 and VRP023 were found to be similar to that of Isoptin® SR using both USP apparatus 1 and 3.

An exploratory data analysis method was used in the first step to compare the dissolution profiles graphically. The preferred model selected to assess drug release was the Weibull model. Model parameters such as time and shape for the test product were compared to those of the reference product using a two-sided t-test and were found to be similar ($p > 0.05$). The exponential constant values (n) for all the models fell between 0.50 and 1.00, indicating that the release mechanism was non-Fickian (in all the formulations), at all tested pH levels, involving a combination of both diffusion and chain relaxation mechanisms or anomalous transport kinetics. However, these parameters must be viewed with caution as the power law does not account for the limited solubility of VRP at different pH's.

It is evident that there are a number of challenges associated with the formulation of solid oral dosage forms with drugs of pH dependent solubility. It is imperative therefore, that sustained release formulations should have a uniform release pattern throughout the gastro-intestinal tract to avoid any non-uniform release caused by pH dependency and subsequent associated therapeutic difficulties. In this study, pH was shown to play an

important role in controlling of the release mechanism of VRP from batches manufactured in the laboratory, but Isoptin® SR was not affected by pH to any great extent. Therefore, during the course of transit of the dosage form in the gastro-intestinal tract, the release from the product may show different release mechanisms if the formulation were to reside in one place in the gastro-intestinal tract for a prolonged period.

The similarity factor, S_d has been tested along with the existing f_2 method and was found to be applicable in comparing dissolution data. Its primary advantage is its simplicity in calculation and interpretation of results. The second advantage is that the S_d approach is similar to the f_2 method in that it characterizes the entire dissolution profile and this is better than a single-point approach such as using $t_{\%}$.

The method of comparing dissolution profiles using % AUC $_{(diff)}$ was evaluated and was found not to be usable as some of the differences were minimal in certain batches yet the curves or profiles were not similar when evaluating f_2 and S_d values.

What has emerged from this study is that considerable attention must be focused on understanding mathematical models as these provide useful guidance and insight to drug release transport from sustained-release delivery systems.

CHAPTER SIX
CONCLUSION

Oral administration of drugs has been the most convenient route employed for drug delivery systems for which the main aim is the maintenance of constant therapeutic concentrations of drug in the blood. Therapeutic level control is achieved by use of sustained or modified-release dosage forms.

An HPLC method was developed and validated according to the ICH guidelines. The method was found to be linear over the concentration range 3.0-280.0 μg/ml. The precision of the method was measured at two levels, *viz.* intra-day and inter-day precision and the % RSD values were less than or equal to 5.0%, which were within the limits set in our laboratory. The method was accurate with % RSD values obtained complying with the 2.0% tolerance, set in our laboratory, for this parameter.

Initially, USP apparatus 1 was used to determine *in-vitro* drug release rates from the TEST and REFERENCE products over a 22-hour period. However, due to the single container nature of the basket apparatus, experimental challenges such as change in solubility, were evident as seen when a change in pH of the dissolution medium was made. There was a relative faster release of VRP at lower pH compared to higher pH values, as a result of more drug being available in the matrix as a salt form rather than as the base compound. Furthermore, at higher pH values, the carboxylic acid functional groups of the carbomer are likely to be dissociated and a possible interaction between the carboxylic acid groups and the tertiary amine of VRP may also contribute to the slow drug release from these tablets. The release of VRP was significantly influenced by the pH of the dissolution media and may consequently results in complex release mechanisms being evident.

USP apparatus 3 was therefore selected as it eliminates manual changing of dissolution media and offers an advantage of mimicking, in part, the changes in the physicochemical environment experienced by products in the gastro-intestinal tract [151]. A study of the effect of inner tube mesh size was undertaken to determine the effects of the pore size on

drug release rates. When a smaller pore size was used, the cylinders failed to drain completely, as the dissolution media was found to coat the screen. The combination of a fine pore size and the surface tension of the dissolution media created a barrier that prevented air from penetrating the tube with the result that fresh dissolution media did not reach the dosage form.

The effect of buffer molarity on drug release was shown to weaken the rigid/cross-linked structure of carbomer gels. This loss of the gel structure resulted in the dosage form being exposed to greater hydrodynamic forces of the test medium thus resulting in increased exposure of the tablet to the dissolution media, with a subsequent faster drug release rate. The effect of the agitation or dip rate on the dissolution rate of VRP from tablets was also evaluated. As expected, the dissolution rate increased with the increasing agitation rate.

Sensitivity, discriminating ability and reproducibility are important characteristics of a dissolution method. The FDA dissolution guidelines identify the need for a sensitive test, as this allows for the detection of *in-vitro* differences prior to the assessment of performance of product [146]. It is vitally important that dissolution test methods are optimized and that appropriate dissolution media are used when testing particular dosage forms.

In response to the challenges of formulating sustained-release dosage forms, combinations of rate retarding polymers, Carbopol® 974 P NF, Methocel® K 100M and Eudragit® RS were used as matrices for the manufacture of VRP tablets. Since a number of pharmaceutical products are available as solid oral dosage forms, powder rheology, flowability and compactibility were two essential characteristics that were investigated to ensure successful tablet manufacture. In terms of tablet formation, the different compressibilities and flow properties of powders pose a challenge to manufacturers, which may result in formulation difficulties due to the selection of inappropriate excipients.

Large, 11 mm diameter tablets were prepared by both direct compression and wet granulation techniques, evaluated and compared to Isoptin® SR. The direct compression

method of manufacture using either Carbopol® 974 P NF or Eudragit® RS as the only polymer resulted in rapid and complete release of VRP, which was observed after approximately 2 hours. The direct compression method of manufacture produced tablets that exhibited a large degree of capping and lamination. Powder rheology studies revealed poor flow properties when using the angle of repose determination. Carr's compressibility index and the Hausner's ratio further supported the poor flow characteristics of some of the blends produced using direct compression methods. Capping and lamination often occurs as a result of excessive compression force, that may in this case, may have occurred, due to inadequate die filling as a result of poor powder flow. These formulations were thus considered inappropriate, but served as a useful starting point for identifying potential composition for further studies.

Blends of Methocel® K 100M and Carbopol® 974 P NF were then prepared. Results obtained were not suitable as VRP release was faster and complete drug release was observed after 6 hours. Whilst not ideal, this combination can sustain the release of VRP better than when either Carbopol® 974 P NF or Eudragit® RS were used as the primary release retarding polymers. Values for f_2 of between 35-40 were obtained for the comparison of test product to Isoptin® SR. After several trials with a combination of the polymers at different drug/polymer ratios, further development was undertaken by compressing the blends into mini-tablets of 7 mm diameter. The tablets were incorporated into a size 00 capsule prior to dissolution testing. The dissolution release rate profiles for test were similar to that of the reference product for the early stages of the dissolution process only, but did not match the release profile for the entire 22-hour period. Finally, it was decided that a wet granulation method of manufacture was more appropriate, than direct compression from a manufacturing perspective, for production of these products.

VRP sustained-release matrix mini-tablets were manufactured using Eudragit® NE 30D or Surelease® E-7-19010 dispersion as the granulating fluid. The tablets were characterized by determination of crushing strength, friability, thickness, weight variation and *in-vitro* release rates. The content of VRP in the tablets was quantitated using HPLC. The results satisfied the pharmacopoeial specifications for formulations VRP021 and

VRP023, which were selected for further evaluation due to their similarity to Isoptin® SR. Similarity was determined on the basis of f_2 values.

Water uptake studies including swelling and erosion behaviour of the tablets when in contact with the dissolution medium were undertaken. Swelling and erosion behaviour dictate the kinetics and mechanism of drug release from these formulations. Although one process may predominate over the other, as a result of different polymer characteristics. Both swelling and erosion often occur simultaneously, as was the case in these studies. In addition, mathematical modelling provided an insight into the mechanism of drug release from these dosage forms. It was observed that non-Fickian diffusion was the primary release controlling mechanism. Diffusion of the drug occurs within the polymer and the rate of release is determined by polymer characteristics such as relaxation of the polymer chains on contact with dissolution media. Water uptake studies provided a macroscopic picture of the overall swelling and erosion of tablets that take place yet provided little detailed information on the nature of the gel layer formed as a consequence of the uptake. Therefore, future studies using Scanning Electron Microscopy (SEM) and/or textural analysis will assist in defining the microscopic structure that exists when the polymers hydrate, which would in turn provide an understanding of how drug transport occurs at a microscopic level in these dosage forms.

The statistical parameters f_1 and f_2 suggest that the formulations VRP021 and VRP023 are similar to Isoptin® SR and values of $f_1<15$ and $f_2>50$ were obtained for both test products. Determination of similarity using the S_d factor was tested along with the existing f_2 method. The determination of S_d is based on calculation of the area under the curve by using the trapezoidal rule and was found to be applicable for comparing dissolution data in these studies.

The release data generated from *in-vitro* release studies were fitted to various kinetic models such as Zero order, First order, Higuchi, Hixson-Crowell, Baker-Lonsdale and the Weibull function. The release mechanism was determined by using the Korsmeyer-Peppas or Power-law model. The data for formulations were found to fit several different models and the drug release mechanism was ascribed to an anomalous transport process

in which diffusion and swelling or chain relaxation dictate release. However, the data were best fitted to the Weibull function for batches VRP021 and VRP023. These observations reveal that the tablets exhibited similar *in-vitro* release performance to Isoptin® SR. The release parameters, T_d, and shape parameter, β, were calculated and these were compared to the values obtained for Isoptin® SR using the two-sided student t-test. It was found that there was no significant difference between the TEST products and Isoptin® SR at a 95% level of confidence.

Despite the apparent complexity of formulations VRP021 and VRP023, this study proposes the applicability of using polymer combinations such as Carbopol® 974P NF, Surelease® E-7-19010 and Eudragit® NE 30D in sustaining the release of VRP from dosage forms prepared from these materials. It has been observed that the use of Carbopol® 974 PNF in combination with other polymers can sustain the release of VRP from tablets since carbomers can form strong matrices due to their cross-linked structure.

The formulations developed and assessed in these studies have defined a starting point for further studies in which the impact of drug-excipient and excipient-excipient interactions can be assessed. Further investigation using SEM, Differential Scanning Calorimetry, X-Ray Diffraction and Fourier Transform Infrared Analysis will provide insight into the physical and chemical characteristics of these dosage forms. Furthermore, it would be useful to determine whether an *in-vitro in-vivo* correlation exists for these dosage forms using either USP 1 or USP 3 dissolution test methods and *in-vivo* bioavailability and or bioequivalence studies.

APPENDIX ONE
BATCH SUMMARY

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP001 **Batch Size** : 300g

Blending Date :04-07-2004 **Blending Time (start)** 09:00 am

Tableting Date :04-07-2004 **(end)** 10: 30am

Formula

Material	**% (w/w)**	**Added amount (g)**	**Rhodes #**
VRP	33	99.00	RM000138
Carbopol® 974P NF	10	30.07	RM000121
Lactose monohydrate	56	168.11	RM000056
Talc	0.5	1.50	RM000300
Magnesium stearate	0.5	1.50	RM000200

Target Weight :740mg

Target Hardness :100 – 140N

Temperature :17.3°C

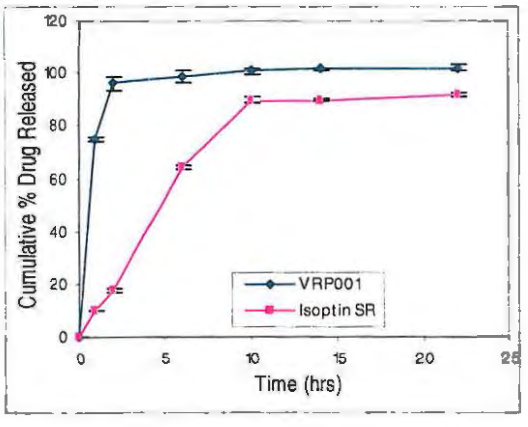
Humidity :39.0% RH

Blender Used Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control

Tablet Press :Manesty® B3B Rotary Press

Tooling :11mm concave punches

Dissolution



Comments / Observations

- no sticking , no surface abrasion during ejection
- no edge – splitting
- no capping / laminating
- good surface finish was observed in tablets
- tablet weight and hardness did not vary

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP002 **Batch Size** : 300g

Blending Date :04-07-2004 **Blending Time (start)** 12:00 noon

Tableting Date :04-07-2004 **(end)** 01:30pm

Formula

Material	% (w/w)	Added amount (g)	Rhodes #
VRP	33	99.10	RM000138
Carbopol® 974P NF	15	45.07	RM000121
Lactose monohydrate	51	153.06	RM000056
Talc	0.5	1.50	RM000300
Magnesium stearate	0.5	1.51	RM000200

Target Weight :740mg

Target Hardness :100 – 140N

Temperature :14.7°C

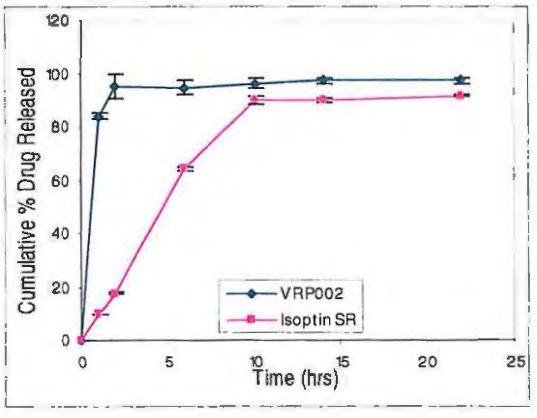
Humidity :48.0% RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control)

Tablet Press :Manesty® B3B Rotary Press

Tooling :11mm concave punches

Dissolution



Comments / Observations

- no sticking , no surface abrasion during ejection
- no edge – splitting
- capping during friability test
- good surface finish was observed in tablets
- tablet hardness was not greater than 80N

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP003 **Batch Size** : 300g

Blending Date :06-07-2004 **Blending Time** **(start)** 08:30am

Tableting Date :06-07-2004 **(end)** 10:00am

Formula

Material	**% (w/w)**	**Added amount (g)**	**Rhodes #**
VRP	33	99.00	RM000138
Carbopol® 971P NF	10	30.01	RM000121
Lactose monohydrate	56	168.00	RM000056
Talc	0.5	1.51	RM000300
Magnesium stearate	0.5	1.50	RM000200

Target Weight :740mg

Target Hardness :100 – 140N

Temperature :14.7°C

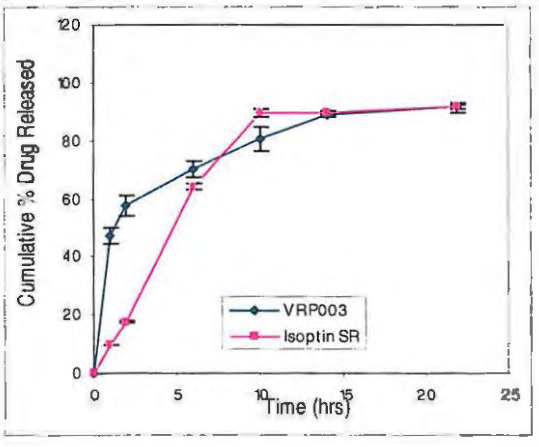
Humidity :56.0 %RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control)

Tablet Press :Manesty® B3B Rotary Press

Tooling :11mm concave punches

Dissolution



Comments / Observations

- capping of tablets near the apex and separates from the balance of tablet
- no sticking , no surface abrasion during ejection
- tablet hardness was between 50 and 100N (huge variation)
- high friability
- tablets were brittle

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP004 **Batch Size** : 300g

Blending Date :06-07-2004 **Blending Time** **(start)** 12:00 noon

Tableting Date :06-07-2004 **(end)** 1:30pm

Formula

Material	**% (w/w)**	**Added amount (g)**	**Rhodes #**
VRP	33	99.00	RM000138
Carbopol® 971P NF	15	45.01	RM000121
Lactose monohydrate	51	153.01	RM000056
Talc	0.5	1.50	RM000300
Magnesium stearate	0.5	1.50	RM000200

Target Weight :740mg

Target Hardness :100 – 140N

Temperature :14.7°C

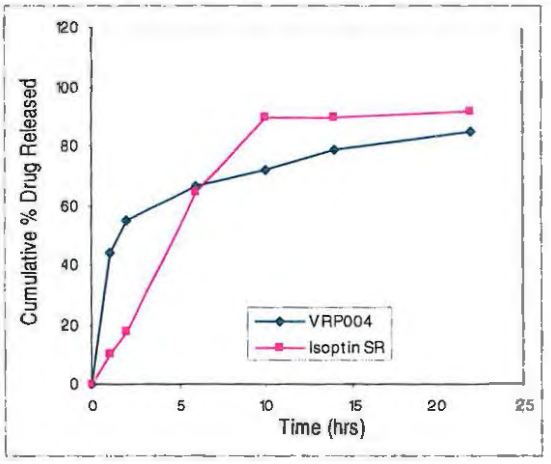
Humidity :56.0 %RH

Blender Used Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control

Tablet Press :Manesty® B3B Rotary Press

Tooling :11mm concave punches

Dissolution



Comments / Observations

- no sticking , no surface abrasion during ejection
- no edge splitting of tablets
- no capping / laminating of tablets
- good surface finish
- no variation in tablet weight
- hardness was not greater than 100N

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP005 **Batch Size** : 300g

Blending Date :06-07-2004 **Blending Time** **(start)** 3:00 pm

Tableting Date :06-07-2004 **(end)** 4:30pm

Formula

Material	**% (w/w)**	**Added amount (g)**	**Rhodes #**
VRP	33	99.00	RM000138
Carbopol® 974P NF	10	30.03	RM000121
Methocel®K 100M	10	30.01	RM000115
Lactose monohydrate	46	138.00	RM000056
Talc	0.5	1.50	RM000300
Magnesium stearate	0.5	1.50	RM000200

Target Weight :740mg

Target Hardness :100 – 140N

Temperature :13.6° C

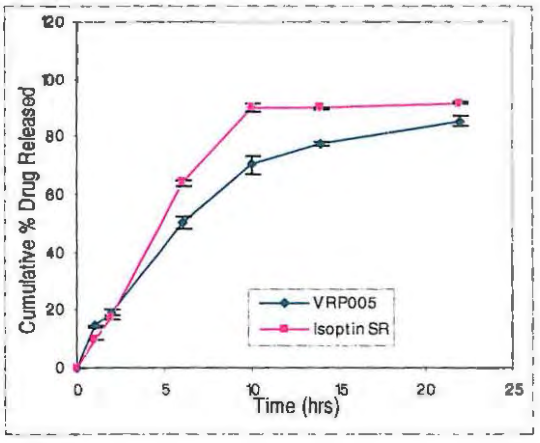
Humidity :52.0 %RH

Blender Used Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control

Tablet Press :Manesty® B3B Rotary Press

Tooling :11mm concave punches

Dissolution



Comments / Observations

- no sticking , no surface abrasion during ejection
- powder with good flowability
- no edge splitting of tablets
- good surface finish, no capping / laminating of tablets
- good surface finish

no variation in tablet weight and hardness

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP006 **Batch Size** : 300g

Blending Date :07-07-2004 **Blending Time (start)** 07:30am

Tableting Date :07-07-2004 **(end)** 09:00am

Formula

Material	% (w/w)	Added amount (g)	Rhodes #
VRP	33	99.00	RM000138
Carbopol® 974P NF	15	45.00	RM000121
Methocel®K 100M	10	30.00	RM000115
Lactose monohydrate	46	138.08	RM000056
Talc	0.5	1.51	RM000300
Magnesium stearate	0.5	1.50	RM000200

Target Weight :740mg

Target Hardness :100 – 140N

Temperature :14.4°C

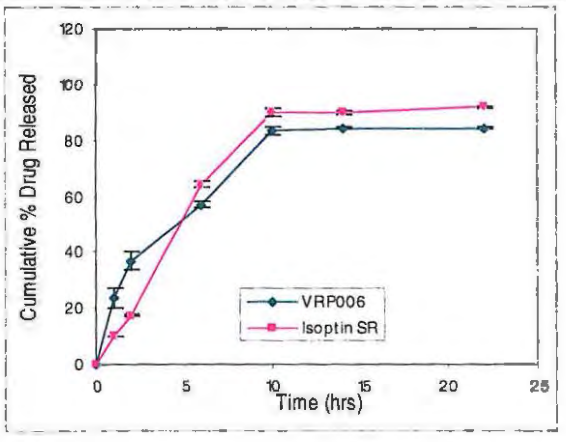
Humidity :54.0 %RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control)

Tablet Press :Manesty® B3B Rotary Press

Tooling :11mm concave punches

Dissolution



Comments / Observations

- no sticking , no surface abrasion during ejection
- powder with good flowability
- no edge splitting of tablets
- good surface finish
- no capping / laminating of tablets
- good surface finish
- no variation in tablet weight
- maximum hardness reached was 135N

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP007 **Batch Size** : 300g

Blending Date :06-07-2004 **Blending Time** **(start)** 11:00 am

Tableting Date :06-07-2004 **(end)** 12:30 pm

Formula

Material	**% (w/w)**	**Added amount (g)**	**Rhodes #**
VRP	33	99.03	RM000138
Carbopol® 971P NF	10	30.00	RM000121
Methocel®K 100M	10	30.00	RM000115
Lactose monohydrate	46	138.02	RM000056
Talc	0.5	1.50	RM000300
Magnesium stearate	0.5	1.50	RM000200

Target Weight :740mg

Target Hardness :100 – 140N

Temperature :15.8° C

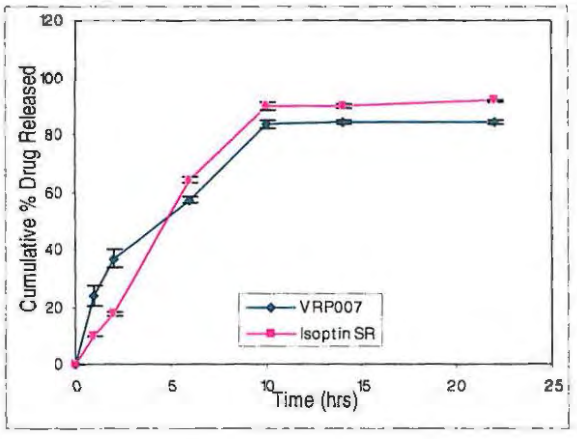
Humidity :49.0 %RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control)

Tablet Press :Manesty® B3B Rotary Press

Tooling :11mm concave punches

Dissolution



Comments / Observations

- no sticking , no surface abrasion during ejection
- powder with good flowability
- no edge splitting of tablets
- good surface finish
- no capping / laminating of tablets
- no variation in tablet weight and hardness

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP008 **Batch Size** : 300g

Blending Date :06-07-2004 **Blending Time (start)** 3:00 pm

Tableting Date :06-07-2004 **(end)** 4:30pm

Formula

Material	% (w/w)	Added amount (g)	Rhodes #
VRP	33	99.00	RM000138
Carbopol® 971P NF	15	45.01	RM000121
Methocel®K 100M	10	30.00	RM000115
Lactose monohydrate	41	123.00	RM000056
Talc	0.5	1.50	RM000300
Magnesium stearate	0.5	1.50	RM000200

Target Weight :740mg

Target Hardness :100 – 140N

Temperature :14.4°C

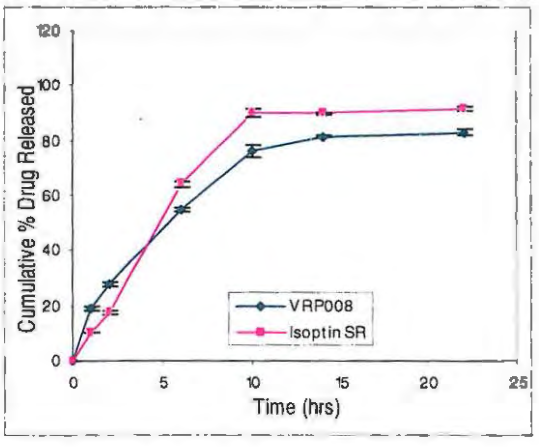
Humidity :54.0 %RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control)

Tablet Press :Manesty® B3B Rotary Press

Tooling :11mm concave punches

Dissolution



Comments / Observations :

- no sticking , no surface abrasion during ejection
- powder with good flowability
- no edge splitting of tablets
- good surface finish
- no capping / laminating of tablets
- no variation in tablet weight and hardness

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP009 **Batch Size** : 300g

Blending Date :01-08-2004 **Blending Time (start)** 08:00 am

Tableting Date :01-08-2004 **(end)** 09:30 am

Formula

Material	% (w/w)	Added amount (g)	Rhodes #
VRP	33	99.01	RM000138
Carbopol® 974P NF	10	30.00	RM000121
Ethocel®	5	15.00	RM000115
Emcompress®	24.5	73.51	RM000059
Lactose monohydrate	73.5	73.50	RM000056
Talc	0.5	1.50	RM000300
Magnesium stearate	0.5	1.50	RM000200

Target Weight :740mg

Target Hardness :100 – 140N

Temperature :15.6° C

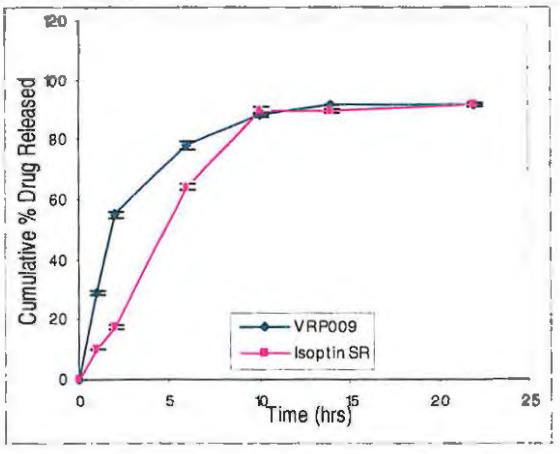
Humidity :58.0 %RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control)

Tablet Press :Manesty® B3B Rotary Press

Tooling :11mm concave punches

Dissolution



Comments / Observations

- sticking of powder particles, adhering to punch surfaces
- no edge splitting of tablets
- capping of tablets (part of tablet not bonding together).
- Tablets separate where the cup or land meets the band edge
- Poor flow properties

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP010 **Batch Size** : 300g

Blending Date :01-08-2004 **Blending Time (start)** 11:00am

Tableting Date :01-08-2004 **(end)** 12:30pm

Formula

Material	% (w/w)	Added amount (g)	Rhodes #
VRP	33	99.01	RM000138
Carbopol® 974P NF	10	30.00	RM000121
Ethocel®	5	15.00	RM000115
Lactose monohydrate	51	153.10	RM000056
Talc	0.5	1.50	RM000300
Magnesium stearate	0.5	1.51	RM000200

Target Weight :740mg

Target Hardness :100 – 140N

Temperature :14.4°C

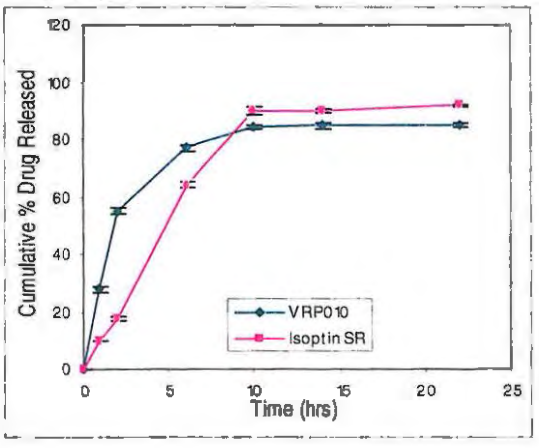
Humidity :52.0 %RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control)

Tablet Press :Manesty® B3B Rotary Press

Tooling :11mm concave punches

Dissolution



Comments / Observations

- sticking of powder particles, adhering to punch surfaces
- capping of tablets (part of tablet not bonding together.
- Tablet separates where the cup or land meets the band edge
- poor flow properties
- variation in tablet weight and hardness

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP011 **Batch Size** : 300g

Blending Date :08-11-2004 **Blending Time (start)** 07:30 am

Tableting Date :08-11-2004 **(end)** 09:00 am

Formula

Material	% (w/w)	Added amount (g)	Rhodes #
VRP	33	99.00	RM000138
Carbopol® 974P NF	10	30.00	RM000121
Eudragit ®RS	7.5	22.51	RM000023
Lactose monohydrate	48.5	145.50	RM000056
Talc	0.5	1.50	RM000300
Magnesium stearate	0.5	1.50	RM000200

Target Weight :250mg

Target Hardness :80 – 110N

Temperature :22.7°C

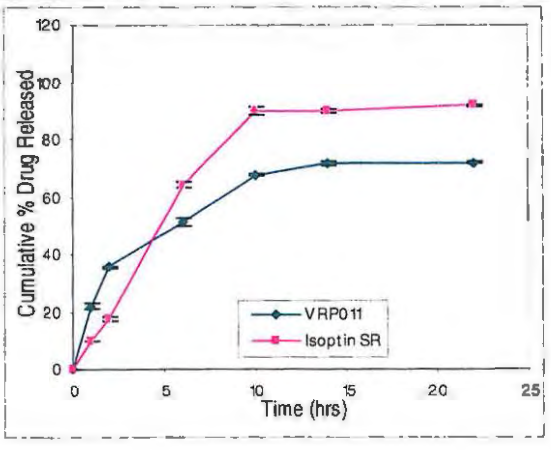
Humidity :62.0 %RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control)

Tablet Press :Manesty® F3 Single Press

Tooling :7 mm concave punches

Dissolution



Comments / Observations

- no sticking / no subsurface abrasion during ejection
- no edge splitting of tablets
- capping of tablets (part of tablet not bonding together.
- Tablet separates where the cup or land meets the band edge
- though good surface finish
- no variation in tablet weight and hardness

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP012 **Batch Size** : 300g

Blending Date :08-11-2004 **Blending Time (start)** 10:00 am

Tableting Date :08-11-2004 **(end)** 11:30am

Formula

Material	**% (w/w)**	**Added amount (g)**	**Rhodes #**
VRP	33	99.01	RM000138
Carbopol® 974P NF	10	30.00	RM000121
Eudragit ®RL	7.5	22.51	RM000022
Lactose monohydrate	48.5	145.50	RM000056
Talc	0.5	1.50	RM000300
Magnesium stearate	0.5	1.50	RM000200

Target Weight :250mg

Target Hardness :80 – 110N

Temperature :22.7°C

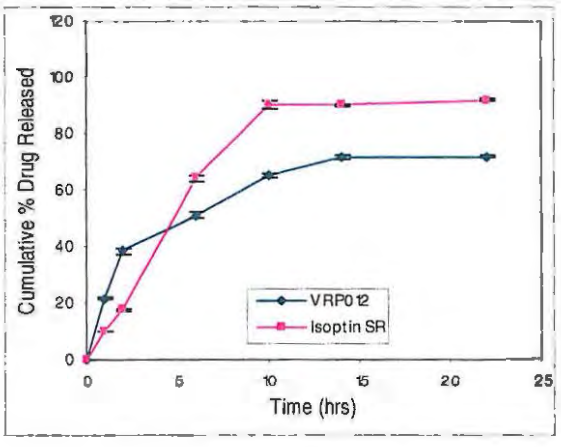
Humidity :63.0 %RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control)

Tablet Press :Manesty® F3 Single Press

Tooling :7 mm concave punches

Dissolution



Comments / Observations :

- no sticking / no surface abrasion during ejection
- no edge splitting of tablets
- no capping / laminating of tablets
- good surface finish
- no variation in tablet weight and hardness
- maximum tablet hardness was 105N

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP013 **Batch Size** : 300g

Blending Date :08-11-2004 **Blending Time (start)** 1:00 pm

Tableting Date :08-11-2004 **(end)** 2:30pm

Formula

Material	% (w/w)	Added amount (g)	Rhodes #
VRP	33	99.00	RM000138
Carbopol® 974P NF	10	30.00	RM000121
Eudragit ®RS	7.5	22.51	RM000023
Ethocel ®	7.5	22.50	RM000103
Lactose monohydrate	41	123.00	RM000056
Talc	0.5	1.51	RM000300
Magnesium stearate	0.5	1.50	RM000200

Target Weight :250mg

Target Hardness :80 – 110N

Temperature :22.8°C

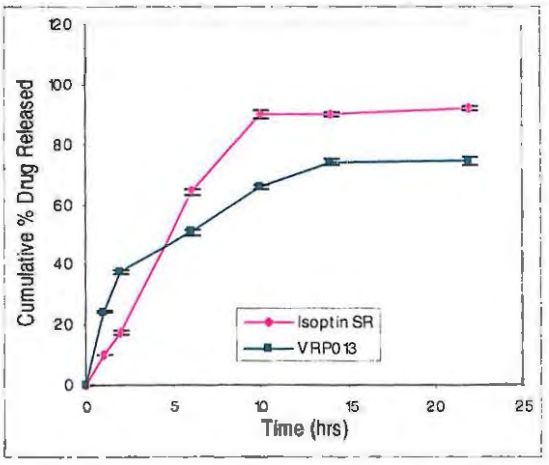
Humidity :61.0 %RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control)

Tablet Press :Manesty® F3 Single Press

Tooling :7 mm concave punches

Dissolution



Comments / Observations

- no sticking / no surface abrasion during ejection
- no edge splitting of tablets
- no capping / laminating of tablets
- good surface finish
- no variation in tablet weight and hardness
- maximum tablet hardness was 105N

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP014 **Batch Size** : 300g

Blending Date :08-11-2004 **Blending Time (start)** 4:00 pm

Tableting Date :08-11-2004 **(end)** 5:30pm

Formula

Material	% (w/w)	Added amount (g)	Rhodes #
VRP	33	99.01	RM000138
Eudragit ®RS	15	45.00	RM000023
Ethocel ®	5	15.00	RM000103
Lactose monohydrate	41	123.00	RM000056
Talc	0.5	1.50	RM000300
Magnesium stearate	0.5	1.50	RM000200

Target Weight :250mg

Target Hardness :80 – 110N

Temperature :23.0°C

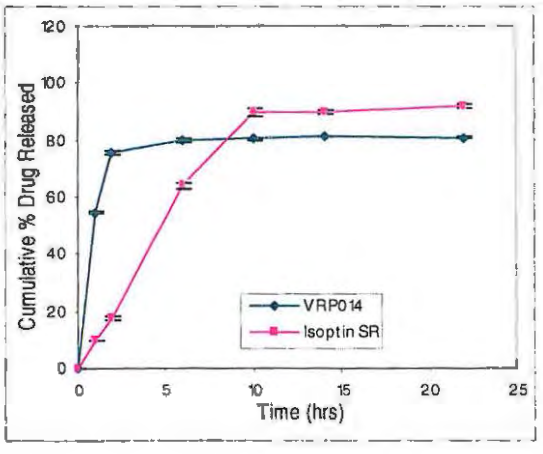
Humidity :56.0 %RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control)

Tablet Press :Manesty® F3 Single Press

Tooling :7 mm concave punches

Dissolution



Comments / Observations

- no sticking / no surface abrasion during ejection
- no edge splitting of tablets
- no capping / laminating of tablets
- good powder flow
- good surface finish
- hardness values relatively constant

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP015 **Batch Size** : 500g

Blending Date :08-11-2004 **Blending Time start)** 7:00 pm

Tableting Date :08-11-2004 **(end)** 8:30pm

Formula

Material	**% (w/w)**	**Added amount (g)**	**Rhodes #**
VRP	33	198.00	RM000138
Carbopol ®974P NF	10	60.01	RM000121
Eudragit ®RS	7.5	45.03	RM000023
Ethocel ®	7.5	45.50	RM000103
Lactose monohydrate	15	90.00	RM000056
SURELEASE E-7-19010	5ml	30ml	RM000010
A		462.50	
Eudragit ®RS	7.5	37.51	RM000023
Lactose monohydrate	15	75.00	RM000056
Magnesium stearate	0.1	0.51	RM000200

Target Weight :250mg

Target Hardness :80 – 110N

Temperature :23.0° C

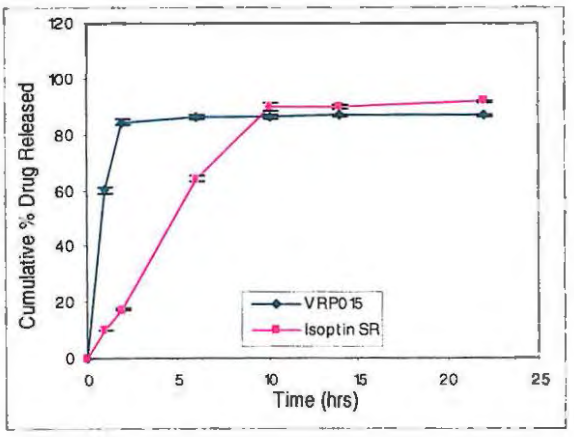
Humidity :59.0 %RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control

Tablet Press :Manesty® F3 Single Press

Tooling :7 mm concave punches

Dissolution	**Comments / Observations**



- no sticking / no surface abrasion during ejection
- no edge splitting of tablets
- no capping / laminating of tablets
- good powder flow
- good surface finish
- hardness values relatively constant

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP016 **Batch Size** : 300g

Blending Date :09-11-2004 **Blending Time** **(start)** 08:00 am

Tableting Date :09-11-2004 **(end)** 09:30 am

Formula

Material	**% (w/w)**	**Added amount (g)**	**Rhodes #**
VRP	33	99.01	RM000138
Carbopol® 974P NF	10	30.00	RM000121
Eudragit ®RS	7.5	22.51	RM000023
Ethocel ®	7.5	22.51	RM000103
Emcompress®	41	123.00	RM000059
Talc	0.5	1.50	RM000300
Magnesium stearate	0.5	1.50	RM000200

Target Weight :250mg

Target Hardness :80 – 110N

Temperature :22.6°C

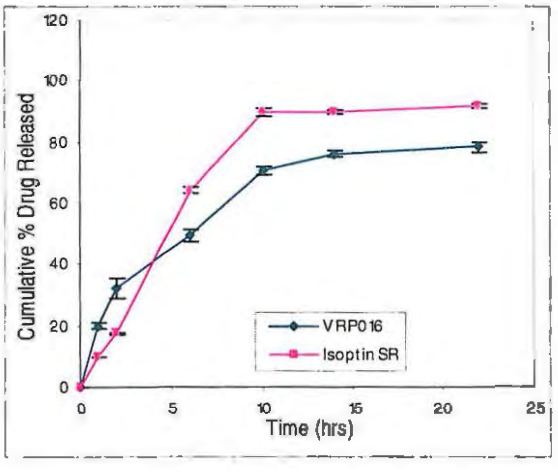
Humidity :65.0%RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control

Tablet Press :Manesty® F3 Single Press

Tooling :7 mm concave punches

Dissolution



Comments / Observations

- no sticking / no surface abrasion during ejection
- no edge splitting of tablets
- no capping / laminating of tablets
- good surface finish
- tablet weight/ hardness relatively constant throughout
- good powder flow properties

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP017 **Batch Size** : 300g

Blending Date :09-11-2004 **Blending Time (start)** 11:00 am

Tableting Date :09-11-2004 **(end)** 12:30 pm

Formula

Material	% (w/w)	Added amount (g)	Rhodes #
VRP	33	99.00	RM000138
Carbopol® 974P NF	10	30.01	RM000121
Eudragit ®RS	7.5	22.51	RM000023
Ethocel ®	7.5	22.51	RM000103
Emcocel® 90M	41	123.00	RM000059
Talc	0.5	1.50	RM000300
Magnesium stearate	0.5	1.50	RM000200

Target Weight :250mg

Target Hardness :80 – 110N

Temperature :22.1°C

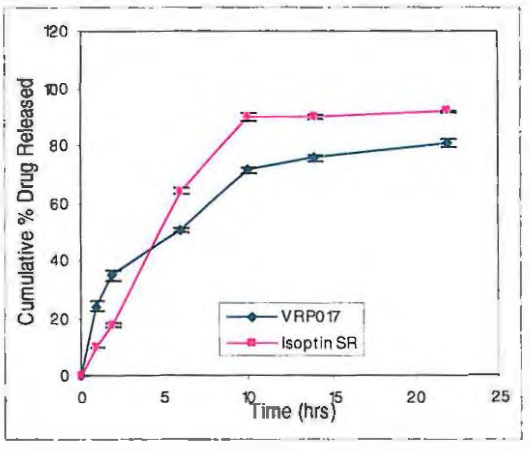
Humidity :66.0 %RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control

Tablet Press :Manesty® F3 Single Press

Tooling :7 mm concave punches

Dissolution



Comments / Observations

- no sticking / no surface abrasion during ejection
- no edge splitting of tablets
- no capping / laminating of tablets
- good surface finish
- tablet weight/ hardness relatively constant throughout
- good powder flow properties

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP018 **Batch Size** : 300g

Blending Date :09-11-2004 **Blending Time (start)** 1:00 pm

Tableting Date :09-11-2004 **(end)** 2:30 pm

Formula

Material	% (w/w)	Added amount (g)	Rhodes #
VRP	33	99.00	RM000138
Carbopol® 974P NF	7.5	22.51	RM000121
Eudragit ®RS	20	60.00	RM000023
Ethocel ®	7.5	22.51	RM000103
Lactose Monohydrate	31	93.00	RM000056
Talc	0.5	1.51	RM000300
Magnesium stearate	0.5	1.51	RM000200

Target Weight :250mg

Target Hardness :80 – 110N

Temperature :22.0°C

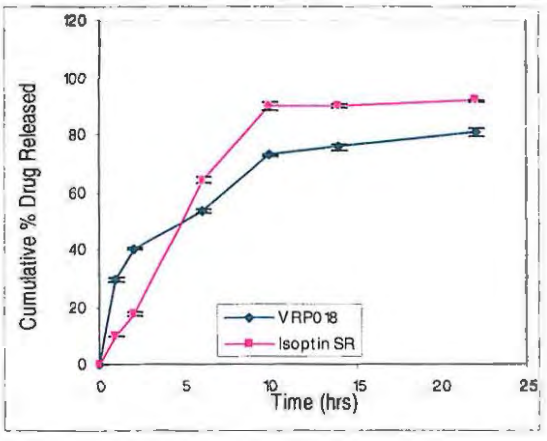
Humidity :66.0 %RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control

Tablet Press :Manesty® F3 Single Press

Tooling :7 mm concave punches

Dissolution



Comments / Observations

- no sticking / no surface abrasion during ejection
- no edge splitting of tablets
- no capping / laminating of tablets
- good surface finish
- tablet weight/ hardness relatively constant throughout
- good powder flow properties

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP019 **Batch Size** : 300g

Blending Date :09-11-2004 **Blending Time** **(start)** 4:00 pm

Tableting Date :09-11-2004 **(end)** 5:30 pm

Formula

Material	**% (w/w)**	**Added amount (g)**	**Rhodes #**
VRP	33	99.01	RM000138
Carbopol® 974P NF	7.5	22.50	RM000121
Eudragit ®RS	7.5	22.51	RM000023
Ethocel ®	20	60.00	RM000103
Lactose Monohydrate	31	93.00	RM000056
Talc	0.5	1.51	RM000300
Magnesium stearate	0.5	1.51	RM000200

Target Weight :250mg

Target Hardness :80 – 110N

Temperature :22.3°C

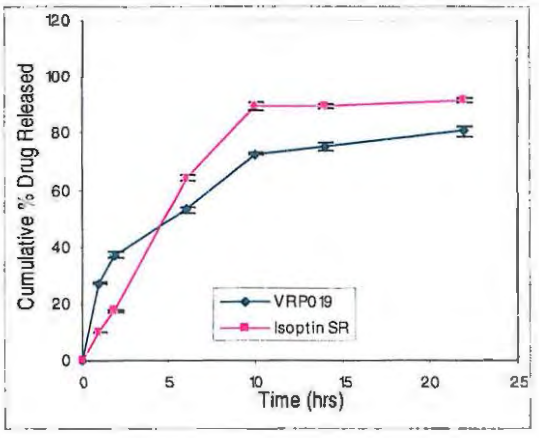
Humidity :65.0 %RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control

Tablet Press :Manesty® F3 Single Press

Tooling :7 mm concave punches

Dissolution



Comments / Observations

- no sticking / no surface abrasion during ejection
- no edge splitting of tablets
- no capping / laminating of tablets
- good surface finish
- tablet weight/ hardness relatively constant throughout
- good powder flow properties

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP020 **Batch Size** : 500g

Blending Date :10-11-2004 **Blending Time (start)** 09:00 am

Tableting Date :11-11-2004 -granules dried at 40°C for 12 hours

Formula

Material	% (w/w)	Added amount (g)	Rhodes #
VRP	33	198.00	RM000138
Carbopol ®974P NF	5	30.01	RM000121
Eudragit ®RS	7.5	45.02	RM000023
Emcocel ® 90M	10	60.00	RM000061
SURELEASE® E-7-19010	10ml	60ml	RM000010
A		292.51	
Carbopol ®974P NF	5	25.00	RM000121
Eudragit ®RS	6	30.03	RM000023
Emcocel ® 90M	10	50.00	RM000061
Emcompress ®90M	20	99.98	RM000059
Magnesium stearate	0.5	2.50	RM000200

Target Weight :250mg

Target Hardness :80 – 110N

Temperature :22.3°C

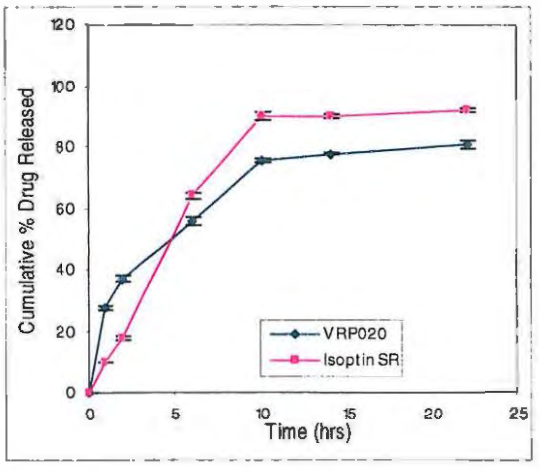
Humidity :59.0% RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control

Tablet Press :Manesty® F3 Single Press

Tooling :7 mm concave punches

Dissolution	Comments / Observations



- no sticking, but during granulation , the SURELEASE® E-7-19010 fluid was too viscous and processing was slightly difficult
- dried granules were very hard
- no surface abrasion during ejection
- no edge splitting of tablets
- no capping / laminating of tablets
- good powder flow
- good surface finish
- hardness values relatively constant

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP021 **Batch Size** : 500g

Blending Date :10-11-2004 **Blending Time (start)** 11:00 am

Tableting Date :11-11-2004 -granules dried at 40°C for 12 hours

Formula

Material	**% (w/w)**	**Added amount**	**Rhodes #**
VRP	33	198.01	RM000138
Carbopol ®974P NF	5	30.00	RM000121
Eudragit ®RS	7.5	45.00	RM000023
Emcocel ® 90M	10	60.00	RM000061
SURELEASE® E-7-19010	20ml	120ml	RM000010
A		292.50	
Carbopol ®974P NF	5	25.06	RM000121
Eudragit ®RS	6	30.00	RM000023
Emcocel ® 90M	10	50.00	RM000061
Emcompress ®90M	20	100.03	RM000059
Magnesium stearate	0.5	2.50	RM000200

Target Weight :250mg

Target Hardness :80 – 110N

Temperature :23.0°C

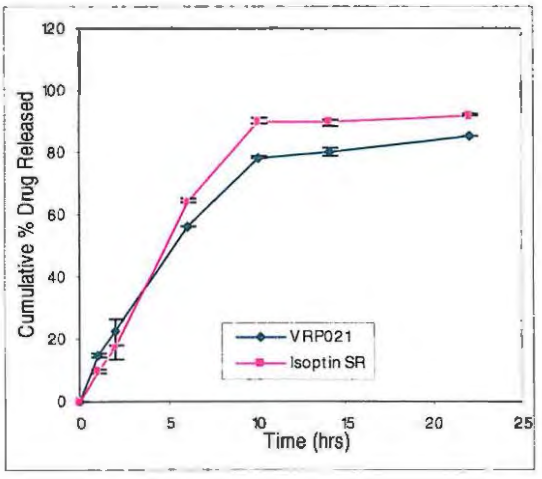
Humidity :54.0% RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control

Tablet Press :Manesty® F3 Single Press

Tooling :7 mm concave punches

Dissolution	**Comments / Observations**



- no sticking, but during granulation , the SURELEASE® E-7-19010 fluid was too viscous and processing was slightly difficult
- dried granules were very hard
- no surface abrasion during ejection
- no edge splitting of tablets and no capping / laminating of tablets
- good powder flow
- good surface finish
- hardness values relatively constant

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP022 **Batch Size** : 500g

Blending Date :10-11-2004 **Blending Time (start)** 2:00pm

Tableting Date :11-11-2004 -granules dried at 40°C for 12 hours

Formula

Material	**% (w/w)**	**Added amount (g)**	**Rhodes #**
VRP	33	198.00	RM000138
Carbopol ®974P NF	5	30.01	RM000121
Ethocel ®	10	60.03	RM000103
Eudragit ® RS 30D	10:10ml with water	120ml	RM000024
A		292.50	
Carbopol ®974P NF	5	25.00	RM000121
Ethocel ®	6	30.05	RM000103
Emcocel ® 90M	10	50.02	RM000061
Emcompress ®90M	20	100.03	RM000059
Magnesium stearate	0.5	2.50	RM000200

Target Weight :250mg

Target Hardness :80 – 110N

Temperature :23.8°C

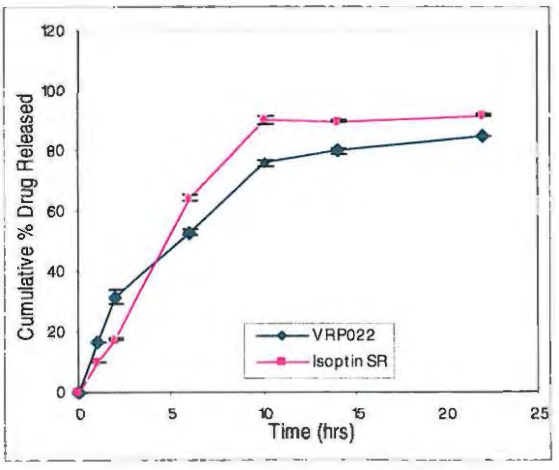
Humidity :48.0 %RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control):

Tablet Press :Manesty® F3 Single Press

Tooling :7 mm concave punches

Dissolution	**Comments / Observations**



- granulating fluid sticky
- forms a glue-like mass when put in the oven
- fluid was too viscous and processing was slightly difficult
- dried granules were very hard
- no surface abrasion during ejection
- no edge splitting of tablets and no capping / laminating of tablets
- good powder flow
- good surface finish
- tablets were spotted and hardness values relatively constant

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH SUMMARY

Formulator :Sandile Khamanga

Product :Verapamil Hydrochloride

Batch ID :VRP023 **Batch Size** : 500g

Blending Date :10-11-2004 **Blending Time (start)** 5:00pm

Tableting Date :11-11-2004 -granules dried at 40°C for 12 hours

Formula

Material	% (w/w)	Added amount (g)	Rhodes #
VRP	33	198.01	RM000138
Carbopol ®974P NF	5	30.00	RM000121
Ethocel ®	10	60.00	RM000103
Eudragit ® NE 30D	10:10ml with water	120ml	RM000124
A		292.51	
Carbopol ®974P NF	5	25.00	RM000121
Ethocel ®	6	30.00	RM000103
Emcocel ® 90M	10	50.01	RM000061
Emcompress ®90M	20	100.00	RM000059
Magnesium stearate	0.5	2.51	RM000200

Target Weight :250mg

Target Hardness :80 – 110N

Temperature :23.6°C

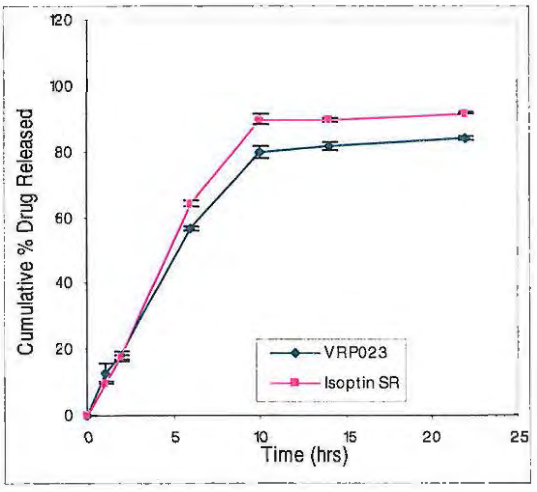
Humidity :47.0% RH

Blender Used :Kenwood Chef Classic 5-Quartz standard planetary mixer (electronic variable speed control

Tablet Press :Manesty® F3 Single Press

Tooling :7 mm concave punches

Dissolution	Comments / Observations



- granulating fluid sticky
- forms a glue-like mass when put in the oven
- dried granules were very hard
- no surface abrasion during ejection
- no edge splitting of tablets
- no capping / laminating of tablets
- good powder flow
- good surface finish but tablets were spotted
- produce very hard tablets

APPENDIX TWO

BATCH PRODUCTION RECORDS VRP001

Only one direct compression record is included for this study. The records for the other batches, VRP002 - VRP019 are available on request.

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH PRODUCTION RECORD

Product name : Verapamil Hydrochloride

Batch : VRP001

Batch size : 300g

MANUFACTURING APPROVALS

Batch record issued by : Khama **Date:** 04 - 07 - 2004

Master record issued by : / **Date:** /

Pg 1/5

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH PRODUCTION RECORD

Product name : Verapamil Hydrochloride

Batch : VRP001

Batch size : 300g

MASTER FORMULA AND BATCH FORMULA

Component	(%w/w)	RM#	Amount Dispensed (g)	Dispensed By	Checked By
VRP	33.0	RM000138	99.005	Khama	
Carbopol®974P NF	10.0	RM000121	30.07g	khama	
Lactose Monohydrate	56.0	RM000056	168.11g	Khama	
Talc	0.5	RM000300	1.50 g	Khama	
Magnesium stearate	0.5	RM000200	1.50 g	Khama	

Pg 2/5

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH PRODUCTION RECORD

Product name : Verapamil Hydrochloride

Batch : VRP001

Batch size : 300g

EQUIPMENT VERIFICATION

Description	Type	Verified By	Confirmed By
Sieves	# 20 mesh	Khama	
Scale	Mettler Model PM6000	Khama	
Blender	Kenwood mixer	Khama	

Pg 3/5

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH PRODUCTION REPORT

Product name : Verapamil Hydrochloride

Batch : VRP001

Batch size : 300g **Date:** 04 - 07 - 2004

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Done by	Checked by
1.	Screen separately the following materials through a #20 mesh screen		09:00	Khama	
	Verapamil hydrochloride		09:05	Khama	
	Carbopol®974P NF		09:10	Khama	
	Lactose Monohydrate				
2.	Place the materials in (1) in a cube blender rotating at 100rpm for 20min.		09:15	Khama	
3.	Screen separately the following materials through a #40 mesh screen				
	Talc		09:25	Khama	
	Magnesium stearate		09:35	Khama	
4.	Mix blends (1) and (3) together and blend for a further 3min				
5.	Tablet the blend on a Manesty B3B press Every 15min, sample 4 tablets to check for hardness / weight uniformity Then calculate for % yield : $\frac{275g}{300g} \times 100 = 91.67\%$		Tablet hardness / weight 09:55		113N 724mg

Pg 4/5

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH FRICA
BATCH PRODUCTION RECORD

Product name : Verapamil Hydrochloride

Batch : VRP001

Batch size : 300g

SIGNATURE AND INITIAL REFERENCE

Full Name (Print)	Signature	Initials	Date
SANDILE M. KHAMANSA	Khamansa	SK	04-07-2004
Jacyln Wright	Jrw	JW	04-07-2004

PS S/S

APPENDIX THREE

BATCH PRODUCTION RECORDS VRP021

Only one wet granulation record is included for this study. The records for the other batches, VRP020, VRP022 and VRP023 are available on request.

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH PRODUCTION RECORD

Product name : Verapamil Hydrochloride

Batch : VRP021

Batch size : 500g

MANUFACTURING APPROVALS

Batch record issued by : Khama **Date:** 10-11-2004

Master record issued by : / **Date:** /

Pg 1/6

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH PRODUCTION REPORT

Product name : Verapamil Hydrochloride

Batch : VRP021

Batch size : 500g

MASTER FORMULA AND BATCH FORMULA

Component	Quantity (%w/w)	RM#	Amount Dispensed	Dispensed By	Checked By
VRP	33.0	RM000138	198.055	Khama	
Carbopol®974P NF	5.0	RM000121	30.039	Khama	
Eudragit® RS	7.5	RM000023	45.059	Khama	
Emcocel® 90M	10.0	RM000061	60.009	Khama	
Surelease® E-7-19010	20.0ml	RM000010	120 mL	Khama	

Surelease® E-7-19010 (15 % w/v) used

Contains 24.9 % w/v Ethylcellulose solids

Pg 2/6

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH PRODUCTION REPORT

Product name : Verapamil Hydrochloride

Batch : VRP021

Batch size : 500g

EQUIPMENT VERIFICATION

Description	Type	Verified By	Confirmed By
Sieves	# 20 and 40 mesh	Khama	
Scale	Mettler Model PM6000	Khama	
Blender	Kenwood mixer	Khama	
Pump	Masterflex	Khama	
Tubing	Masterflex LS14	Khama	
Granulator	Erwerka Oscillating	Khama	
Oven	Gallenkamp	Khama	

Pg 3/6

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH PRODUCTION REPORT

Product name : Verapamil Hydrochloride

Batch : VRP021

Batch size : 500g **Date:** 10 – 11 – 2004

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Done by	Checked by
1.	Screen separately the following materials through a #20 mesh screen.				
	Verapamil hydrochloride	198.01g	11:00	Khama	
	Carbopol®974P NF	30.00	11:05	Khama	
	Eudragit® RS	45.00	11:00	Khama	
	Emcocel® 90M	60.00	11:15	Khama	
2.	Place the materials in (1) in a cube blender		11:20	Khama	
3.	Blend the materials 2 for 3min at low speed, setting speed of 1.		11:25	Khama	

Pg 4/6

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH PRODUCTION REPORT

Pg 5/6

Product name : Verapamil Hydrochloride

Batch : VRP021

Batch size : 500g **Date:** 10 -11- 2004

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Done by	Checked by
4.	Place the Surelease in a tared measuring cylinder and insert pump tubing.	121.05g	11:30	Khanya	JM
5.	With blender at speed 1, add Surelease® E-7-19010 at a rate of 7-10 for a total time of 15min. Time started : 11:35 Time completed: 11:50 Time taken : 15 minutes Blender speed : 1 Pump setting : 6 Amount of Surelease® E-7-19010 added: 120 ml = 189 Ethylcellulose			Khanya	JM
6.	Transfer granules to Erwerka granulator and screen using a #20 mesh screen and 100rpm motor speed. Speed setting: 48-52 rpm		12:00	Khanya	JM
7.	Place granules on weighing paper and dry in the oven. Time started : 12:15 Time finished : 00:30 Total drying time : 12hrs 15 min Oven temperature : 60.0°C		12:15 (10-11-2004) 00:30 (11-11-2004)	Khanya Khanya	JM JM
8.	Remove dried granules from the oven, and re-screened using the Erwerka granulator (#10mesh). Speed : 50rpm		08:00 (11-11-2004)	Khanya	JM
9.	Record the weight of granules obtained Acceptable weight : 453 g Observed weight : 410 g % yield : 410/453 x 100 = 90.51%		08:30 (11-11-2004)	Khanya	JM
10.	Granules transferred to airtight container until tableting.		09:00 (11-11-2004)	Khanya	JM

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH PRODUCTION RECORD

Product name : Verapamil Hydrochloride

Batch : VRP021

Batch size : 500g

SIGNATURE AND INITIAL REFERENCE

Full Name (Print)	Signature	Initials	Date
SANDILE KHAMANGA	[signature]	SK	11-11-2004
Jaylin Wright	[signature]	JW	11-11-2004

Pg 6/6

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH PRODUCTION REPORT

Product name : Verapamil Hydrochloride

Batch : VRP021

Batch size : 500g

MASTER FORMULA AND BATCH FORMULA

Component	(%w/w)	RM#	Amount Dispensed (g)	Dispensed By	Checked By
Verapamil hydrochloride gramules	33.0		292.50g	Km amc	
Carbopol®974P NF	5.0	RM000121	25.06g	Km amc	
Eudragit® RS	6.0	RM000023	30.00g	Km amc	
Emcocel® 90M	10.0	RM000061	50.00g	Km amc	
Emcompress®	20.0	RM000059	100.03g	Km amc	
Magnesium stearate	0.5	RM000200	2.50 g	Km amc	

Pg 1/4

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH PRODUCTION REPORT

Product name : Verapamil Hydrochloride

Batch : VRP021

Batch size : 500g

EQUIPMENT VERIFICATION

Description	Type	Verified By	Confirmed By
Sieves	# 20 mesh	Km amc	
Scale	Mettler Model PM6000	Km amc	
Blender	Kenwood mixer	Km amc	
Tablet press	Manesty B F3	Km amc	

Pg 2/4

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH PRODUCTION REPORT

Product name : Verapamil Hydrochloride

Batch : VRP021

Batch size : 500g **Date:** 11- 11- 2004

MANUFACTURING DIRECTIONS

Step	Procedure	Weight	Time	Done by	Checked by
1.	Screen the following materilas through a #20mesh screen				
	Carbopol 974P NF	25.0 g	10:30	Kh amu a	
	Eudragit® RS	30.00g	10:45	Kh amu	
	Emcocel® 90M	50.00g	10:50	Kh amu	
	Emcompress®	100.00g	10:55	Kh amu	
2.	Place verapamil hydrochloride granules and material in (1) in a cube blender.	292.5g 205.16g	11:00	Kh amu	
3.	Blend the materials in step 2				
	Time started : 11:10		11:10		
	Time completed: 11:30		11:30		
	Time taken : 20 minutes				
	Blender speed : 48 - 52 rpm			Kh amu a	
4.	Screen magnesium stearate using a #40 mesh screen	2.50s	11:40	Kh amu	
5.	Add material in (4) to blender and blend for a further 3min.				
	Time started : 11:45				
	Time completed : 11:48				
	Speed : 48 - 52 rpm			Kh amu	
6.	Record the weight and yield				
	Expected weight : 500g				
	Obtained weight : 478g				
	% yield :	478/500 x100 =	95.60g	Kh amu	
7.	Tablet the blend on tablet press according to standard operating procedures.				
	Target hardness : 80- 110N			Kh amu	
	Target weight : 250mg				
8.	Every 15min, sample 4 tablets to check hardness and weight				
	Store product in airtight containers till ready for *in-vitro* test			244mg & 138N	
9.	Record weight of acceptable tablet obtained and % yield				
	478g/0.25g x100 = 1912 tablets expected ≈ 1750 obtained ≈ 92% (yield)				

m 3/4

RHODES UNIVERSITY, Faculty of Pharmacy, Grahamstown, SOUTH AFRICA

BATCH PRODUCTION RECORD

Product name : Verapamil Hydrochloride

Batch : VRP021

Batch size : 500g

SIGNATURE AND INITIAL REFERENCE

Full Name (Print)		Signature	Initials	Date
SANDILE	KHAMANSA		SK	11-11-2004
Jaclyn	Wright		JW	11-11-2004

Pg 4/4

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