

**DEVELOPMENT AND ASSESSMENT OF PROPRANOLOL SUSTAINED  
RELEASE DOSAGE FORMS SEPARATELY AND IN COMBINATION WITH  
HYDROCHLOROTHIAZIDE**

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## ABSTRACT

Hypertension is a chronic illness that is often undiagnosed and untreated leading to high mortality rates in South Africa. The use of diuretics such as hydrochlorothiazide and beta blockers such as propranolol has been advocated as first line therapy for the treatment of hypertension.

The study and use of controlled release dosage forms for the treatment of various disease states has gained wide interest over the past two decades. The use of controlled release systems offers improved therapeutic efficiency over conventional immediate release dosage forms, the use of which at times have often led to poor patient adherence and decreased therapeutic efficiencies.

The current research objective was to develop a sustained release multi-source product for propranolol such that once daily dosing would be achieved. In addition, the sustained release product was developed using Inderal<sup>®</sup> LA 80mg capsules as a reference product. In addition the development of a suitable immediate release hydrochlorothiazide tablet was undertaken to produce a combination dosage form.

The use of two different technologies, namely direct compression and wet granulation were employed to develop the sustained release dosage form. The release of propranolol from these dosage forms was assessed using USP apparatus 1 with quantitation of the relevant dissolution samples using a validated high performance liquid chromatographic method.

The release profiles from the prototype and subsequent products were subjected to model independent and model dependent analyses in order to compare them to the innovator product and to elucidate the mechanisms of drug release respectively.

Dissolution test results reveal that dosage forms prepared from wet granulation showed better rate retardation and more appropriate release profiles than those prepared by direct compression techniques. The subsequent model independent and model dependent analysis show that a dosage form that is comparable to the innovator product has been developed, with drug release occurring by a diffusion type mechanism.

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## STUDY OBJECTIVES

Propranolol is a commonly used beta-blocker that is advocated for the treatment of hypertension. It can be used alone or in combination with diuretics such as hydrochlorothiazide to provide an enhanced therapeutic effect, than when either drug is used alone. These drug candidates are the first line choice of therapy for treating hypertension as indicated by the South African Essential Drugs List. Propranolol has a short half life, and is rapidly eliminated from the body, which often necessitates multiple dose regimens that may lead to patient non-compliance. The rationale for developing a once daily dosage form, with an immediate release hydrochlorothiazide component was to provide for improved patient compliance, and management of hypertension, such that the immediate release component would provide initial lowering of hypertension, with the propranolol sustained portion providing relief thereafter for the time interval.

The objectives of the current research were to

1. Develop and validate a suitable high performance liquid chromatographic method for the simultaneous determination of propranolol and hydrochlorothiazide.
2. Develop and assess a sustained release propranolol dosage form, separately and in combination with an immediate release hydrochlorothiazide component
3. Compare the release of the developed dosage forms to a commercially available product using a suitable dissolution method.
4. Evaluate the release data from dosage forms by model independent and model dependent analyses.

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## CHAPTER 1

### DRUG MONOGRAPHS

#### 1.1. Propranolol Hydrochloride

##### 1.1.1. Introduction

$\beta$ - Adrenergic blockers are one of the most frequently prescribed cardiovascular drugs [1]. Propranolol hydrochloride (PHCL) is non-selective beta-blocker with no intrinsic sympathomimetic activity (ISA) [1-3] that is widely used in the treatment of angina pectoris, cardiac arrhythmias and hypertension [1, 4]. It is available as either an immediate release or sustained release product, with a variety of both innovator and generic forms available on various National and International markets [1, 5].

##### 1.1.2. Physico-Chemical Properties

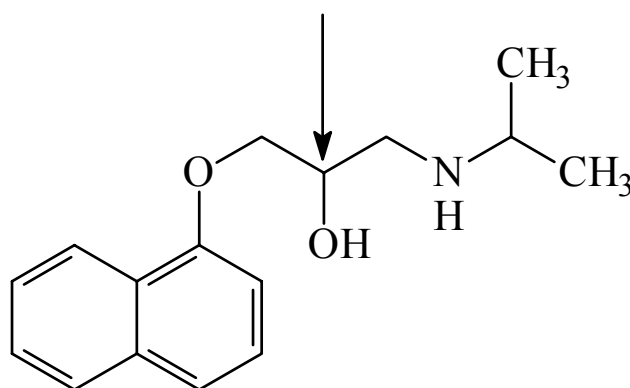
###### 1.1.2.1. Chemical Name

Propranolol hydrochloride (PHCL) is known as:

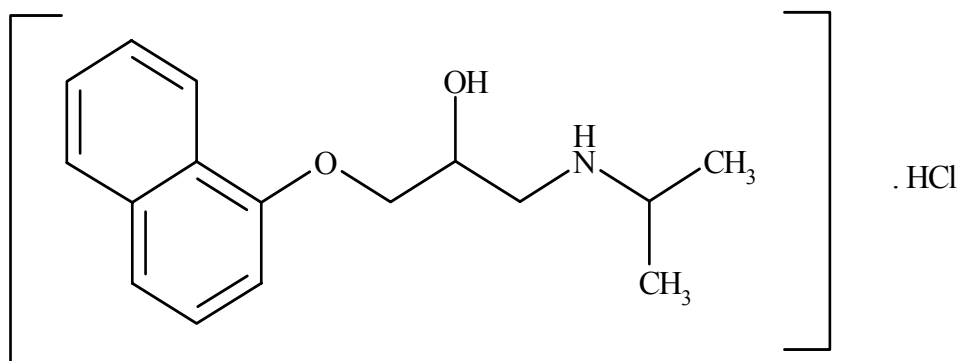
2- propranolol ,1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-,hydrochloride, ( $\pm$ )- or ( $\pm$ )-1-(Isopropyl amino)-3-(1-napthyloxy)-2-propranol hydrochloride [6].

###### 1.1.2.2. Structure

The molecular structure of PHCL is depicted in Figures 1.1 and 1.2 respectively



**Figure 1.1** Molecular structure of propranolol as the free base form [ $C_{16}H_{21}NO_2$ ] (MW 259.36)



**Figure 1.2** Molecular structure of propranolol as the hydrochloride salt (PHCL)  
 $[C_{16}H_{21}NO_2 \cdot HCL]$  (MW 295.8)

### 1.1.2.3. Chemistry

Propranolol is comprised of a naphthalenyloxy aromatic functionality with a methyl ethyl-amino side chain that possesses an asymmetric carbon atom, as indicated by the arrow in Figure 1.1. The presence of the asymmetric carbon results in the presence of two stereoisomers, *viz.*, (R)-(+)-propranolol and (S)-(-) propranolol of which the S-(-) isomer is the more potent compound [7, 8].

### 1.1.2.4. Melting Point

The melting point of a crystalline solid can be defined as the temperature at which the pure solid and liquid forms of the compound exist in equilibrium [9, 10]. The melting point of propranolol crystals that were re-crystallized from cyclohexane is 96° C and that of the hydrochloride salt ranges between 162°C and 165° C [6, 11].

### 1.1.2.5. Optical Activity

Molecules that have an asymmetric centre lack symmetry about a single plane and are thus optically active and rotate the plane of polarized light [9]. Propranolol has optical activity, which has been reported to be between -1.0° to +1.0° [6].

### 1.1.2.6. Infrared Spectrum

Infrared spectroscopy is used to study the interaction of electromagnetic radiation with vibrational or rotational resonances within a molecular structure [9, 10, 12, 13]. The principal peaks depicted in Figure 1.3 for propranolol occur at wavenumbers 1103, 1270, 772, 1580, 795 and 1240 [14, 15]. These peaks represent the stretching vibrations of the different functional groups [16] that are present in the PHCL structure. The wavenumbers 772 and 795 can be associated with the aromatic functional groups, 1240 and 1270 with the amine functional group, 1103 with the OH group and 1580 with the ketone group respectively [16].

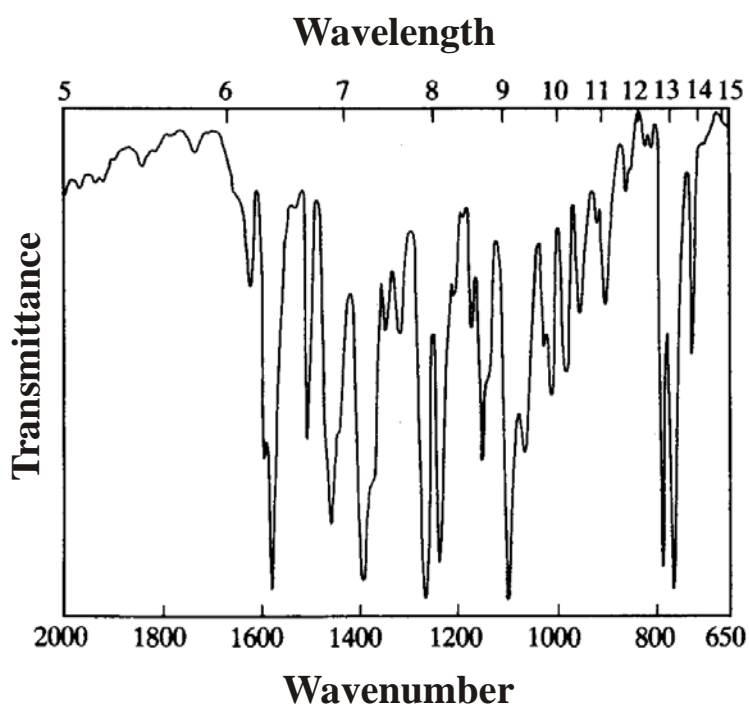
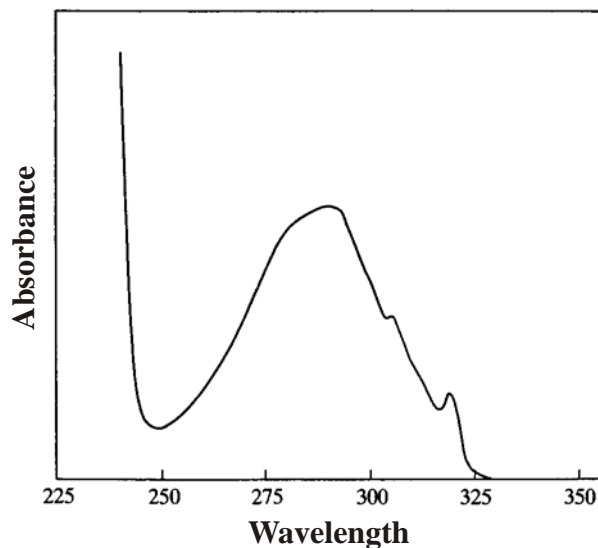


Figure 1.3 Infrared spectrum of propranolol

### 1.1.2.7. Ultraviolet Absorption Spectrum

Organic molecules that are in solutions and that are exposed to light in the visible and ultraviolet regions of the light spectrum can absorb radiation of particular wavelengths depending on the type of electronic transition that is associated with the absorption [9, 10, 12]. The electronic transitions depend on the electron bonding within the molecule. A molecule can have more than one characteristic absorption band, and the complete spectrum in the ultraviolet and visible wavelength regions can provide information for the positive identification of a compound [9, 10, 12]. The absorption maximum or lambda maximum

( $\lambda_{\max}$ ) for PHCL is 288 nm in aqueous acidic media and 290 nm in methanolic solutions [15]. The absorption spectrum of PHCL in acidic media is depicted in Figure 1.4.



**Figure 1.4** Absorption spectrum of PHCL in acidic media

#### **1.1.2.8. Solubility and Partition Co-efficient**

Solubility is defined in quantitative terms, as the concentration of solute in a saturated solution and is usually stated at a specific temperature; where a saturated solution is a solution in which the solute in solution is in equilibrium with the solvent [9]. Solubility can be qualitatively defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion [9]. PHCL has a high degree of aqueous solubility due to the presence of the hydrochloride salt moiety, whereas the base compound has limited aqueous solubility [11, 15]. The solubility of PHCL in different solvents is represented in Table 1.1 [15].

**Table 1.1 Solubility of PHCL**

Solvent	Solubility
Water	1 in 20
Ethanol	1 in 20
Ether	Slightly soluble
Chloroform	Insoluble

Knowledge of the partition co-efficient of a drug is useful as it provides an indication of how a particular drug may be distributed through the body, provide insight into the potential for absorption in addition to drug action at non-specific sites in the human body [9, 17]. The partition co-efficient of a drug is a measure of the lipophilicity of that compound [17] and is expressed as the ratio of solute distribution between a lipophilic and hydrophilic phase [10, 17]. PHCL has a relatively high oil-water partition co-efficient and shows a high degree of lipid solubility. The partition co-efficients experimentally determined for propranolol in n-octanol/buffer systems of different pH and temperature are listed in Table 1.2 [18, 19].

**Table 1.2 Partition co-efficients of propranolol between octanol and aqueous media**

Aqueous Medium	Temperature	$P^{org}/c_{aq}$
0.1 M PO <sub>4</sub> pH 7.0	20° C	5.4
0.1 M PO <sub>4</sub> pH 7.0	37° C	8.6
0.1 M PO <sub>4</sub> pH 7.4	30	3.37
0.1 M PO <sub>4</sub> pH 7.4	37° C	20.2

#### 1.1.2.9. pH of solution

A 1 % w/v solution of PHCL in water has a pH of between 5.0 and 6.0 [20]

#### 1.1.2.10. Dissociation Constant

One of the most important properties of a drug molecule is its dissociation or acidity constant ( $K_a$ ) which for many drugs can be related to the relative physiologic and pharmacological activity, solubility, rate of solution, extent of binding and rate of absorption of that specific compound [9, 21, 22]. The  $pK_a$  of a drug is the negative log concentration of the  $K_a$  and its value is equivalent to the pH at which 50 % of the drug is ionized [9, 21]. Propranolol is a

weakly basic drug and has a  $pK_a$  in the region of 9.45 - 9.5 [15, 19, 21]. This value is of importance during formulation development, as the pH at which the drug is ionized may affect its distribution in biological fluids and within or across membranes [17].

#### **1.1.2.11. Chemical Stability**

Propranolol hydrochloride (PHCL) is unstable in light and in aqueous solution [3, 20]. The isopropylamine side chain decomposes by oxidation, accompanied by a reduction in pH and subsequent discoloration of the solution [3, 20]. PHCL shows maximum stability in solution at a pH of 3.0 [3, 20].

#### **1.1.2.12. Compatibility**

Physical and chemical changes in a molecule and incompatibility effects may be induced by changes in temperature and analytical methods that can be used for characterizing these changes include thermal analytical techniques. One of the most commonly used thermal techniques used for establishing compatibility characteristics between compounds, is differential scanning calorimetry (DSC) [9, 23, 24]. Thermal analysis has proven valuable in both research and quality control as it can be used for the characterization and identification of compounds, determination of purity, detection of polymorphism, solvent and moisture content, stability and compatibility with other excipients [23-25]. The use of DSC revealed that propranolol hydrochloride may interact with a number of commonly used tablet excipients; including magnesium stearate, Emcompress<sup>®</sup>, calcium phosphate monohydrate, Primojel<sup>®</sup>, stearic acid, Avicel<sup>®</sup>, lactose as well as anionic methacrylic acid copolymers such as Eudragit<sup>®</sup> S 100<sup>®</sup> and Eudragit<sup>®</sup> L 100-55<sup>®</sup> [23, 25].

#### **1.1.3. Pharmacokinetics of PHCL**

Pharmacokinetics is the science of mathematical assessment of changes in concentration of drugs or of changes caused by drugs in the biological system [26] and is a mechanism for quantitatively assessing the disposition of a drug after it has been administered to the biological system [27]. Most commonly the term is used in a general sense to cover the areas of drug absorption, metabolism, tissue localization and excretion [26].

### **1.1.3.1. Dose**

The recommended dose for propranolol varies according to the type of pharmacological indication for which it is prescribed, and is also a function of its therapeutic and pharmacological response in specific groups of patients [3, 28]. In the treatment of hypertension, PHCL is initially given in doses of 40 mg to 80 mg twice a day and then the dose is increased if required up to a dose of between 160mg and 320mg daily as needed [3, 28]. Doses for various other disease states, such as for example angina pectoris, acute myocardial infarction, anxiety, cardiac arrhythmias and thyrotoxicosis are variable, though are usually similar to the doses used for the treatment of hypertension [3, 28]. Doses may need to be adjusted in patients with hepatic impairment, as propranolol is a highly protein bound compound that is primarily metabolized in the liver [3, 20, 29, 30].

### **1.1.3.2. Absorption and Bioavailability**

Propranolol has a relatively low oral bioavailability [5, 21, 29], with an F value of 30 [29]. Peak plasma concentrations usually occur within 1 to 2 hours following administration of an oral dose [3, 21, 29]. Propranolol is rapidly and almost completely absorbed from the gastrointestinal tract (GIT), but is highly bound to hepatic tissues and is more than 90 % bound to plasma proteins. Propranolol undergoes significant hepatic 1<sup>st</sup> pass metabolism, which may reduce its systemic bioavailability following oral administration [3, 21, 29, 31].

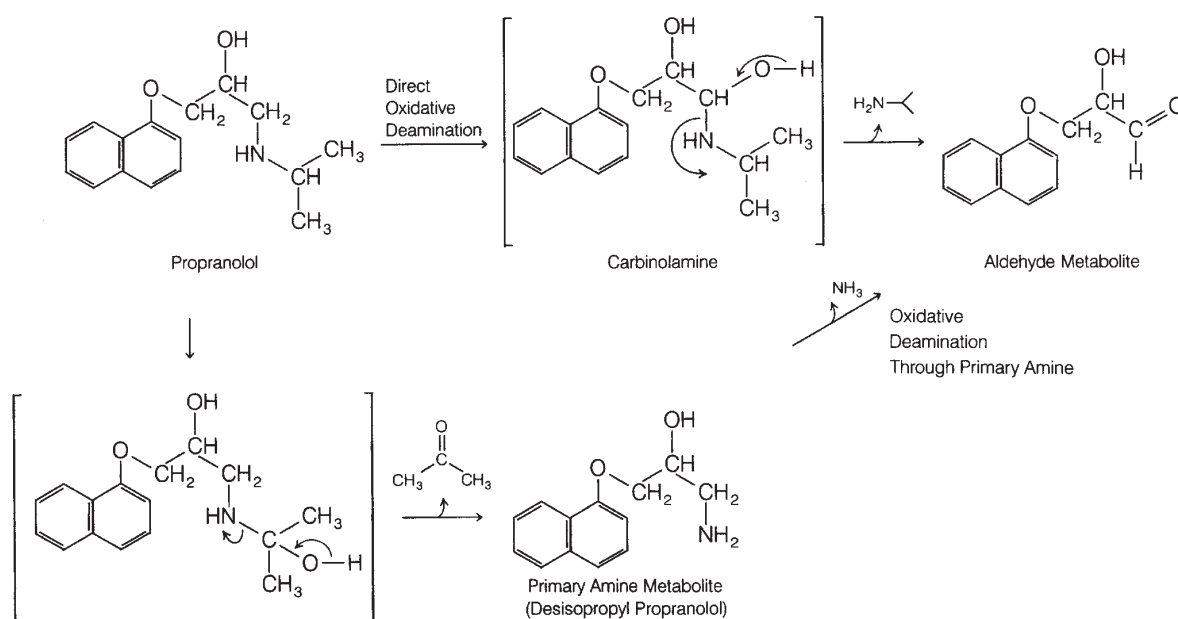
### **1.1.3.3. Distribution**

Propranolol is a lipophilic compound and is relatively easily distributed across the blood brain barrier and can be secreted in breast milk [5, 21]. The volume of distribution for propranolol has been reported to be 4 L/kg [5] and between 2.8-5.5 L/kg [21, 29]. It is highly plasma protein bound (> 90 %), but it has been reported that it is not significantly dialyzable [3, 5, 21, 29, 31].

### **1.1.3.4. Metabolism**

Propranolol is primarily metabolized in the liver by the CYP1A enzyme [30, 32] and at least one of its metabolites, *viz.*, the 4-OH propranolol is biologically active [21, 29, 32]. However, there is a dearth of information as to whether the other metabolites contribute in any way to overall activity of propranolol. Metabolic pathways for propranolol include oxidation, N-

dealkylation and deamination and these metabolic pathways are depicted in Figure 1.5 [3, 32, 33].



**Figure 1.5 Metabolic pathways for propranolol**

### 1.1.3.5. Excretion

Propranolol is a relatively short acting  $\beta$ - adrenergic blocker and has a plasma elimination half-life ( $t_{1/2}$ ) of between 3 and 6 hours [3, 5, 21, 29, 31]. It is excreted almost exclusively as metabolic products in the urine, and approximately 1-4 % of an oral dose is found in the faeces [5]. The elimination of propranolol from the body is dose dependent and follows non-linear kinetic processes [34, 35].

#### **1.1.4. Clinical Pharmacology**

##### **1.1.4.1. Mode of Action**

Propranolol is a non-cardio selective beta-blocker and does not possess intrinsic sympathomimetic activity [1-3]. The primary mode of action of propranolol is membrane stabilization and it is a competitive antagonist of catecholamine transmitters at beta-adrenergic receptors in a wide range of tissues [2, 3].

##### **1.1.4.2. Indications**

Beta-blocker drugs are used primarily for the treatment of conditions where there is over or excessive stimulation of the sympathetic nervous system. Propranolol is used in the treatment of conditions such as hypertension, angina pectoris, acute myocardial infarction, essential tremor and hyperthyroidism [3, 5].

##### **1.1.4.3. Contra-Indications**

Propranolol is contraindicated in patients with a known hypersensitivity to propranolol or other beta-blocker drugs [3, 5]. Propranolol must be avoided in patients who suffer from bronchospasm, asthma or have a history of obstructive airway disease [3]. Propranolol is also contraindicated in patients suffering from bradycardia, cardiogenic shock, metabolic acidosis, hypotension, peripheral arterial circulatory disturbances, in the presence of 2nd degree or 3rd degree heart block, sick sinus syndrome, Prinzmetal's angina, untreated pheochromocytoma and specifically in patients with uncontrolled heart failure, due to the negative inotropic effect of propranolol on cardiac tissues [3, 5, 36]

##### **1.1.4.4. Risk Groups**

Propranolol is a non-selective agent and causes blockade of all beta-receptors [1-3]. Therefore the compound should be used with extreme caution in patients who suffer from asthma or other related obstructive airway diseases [3, 5]. It may cause reduced peripheral circulation in patients with Raynaud's syndrome and should be used with caution in patients with hepatic impairment as it is almost completely metabolised in the liver [3, 5]. Propranolol is also known to affect carbohydrate and lipid metabolism due to its effects on the beta-adrenergic system, as the sympathetic nervous system is implicated in carbohydrate

metabolism. Furthermore, the adrenergic system is implicated in lipid metabolism [3]. The effects of propranolol on these metabolic processes may mask signs of hypoglycaemia and may have some effect on plasma lipid concentrations by increasing the levels of very low-density lipoproteins (VLDL) and triglycerides, whilst lowering high density lipoprotein (HDL) concentrations [3].

#### **1.1.4.5. Side Effects**

Propranolol has a number of side effects, on the cardio-vascular region such as bradycardia and postural hypotension [1, 3, 5, 36], and on the central nervous system, which may include confusion, dizziness mood changes, and other sleep disturbances [3, 5, 36].

The drug may also cause haematological effects such as pupura and thrombocytopenia in addition to gastro-intestinal disturbances such as nausea, vomiting and diarrhoea [1, 3, 5, 36].

#### **1.1.4.6. Drug Interactions**

Drug interactions can be classified as either pharmacodynamic or pharmacokinetic in nature. Pharmacodynamic interactions describe a situation where another drug enhances or antagonizes the effects of the compound of interest [3]. Pharmacodynamic interactions that have been reported for propranolol and have occurred, including the ace inhibitors and the  $Ca^{2+}$  channel blockers that may enhance the antihypertensive activity of propranolol [3, 5, 36]. Concurrent use of propranolol with agents such as digoxin may potentiate bradycardia [3, 5, 36] and may reduce the response of insulin when co-administered in insulin dependent diabetic patients [3, 5, 36]

Pharmacokinetic drug interactions are interactions where a drug may alter the absorption, disposition and/or metabolism of co-administered drugs [3]. Although pharmacokinetic drug interactions can alter the resultant plasma levels of beta-blockers, the interactions may not necessarily be clinically significant [3]. The metabolism of some beta-blockers may be increased on concomitant treatment with drugs such as rifampicin, which is a known inducer of the CYP1A2 enzyme [37], the enzyme responsible for the hepatic metabolism of propranolol [30]. The changes in microsomal enzyme activity may result in pharmacokinetic changes [3, 38] of the API under investigation. The metabolism of propranolol may be decreased when drugs such as cimetidine, erythromycin, fluvoxamine, and hydralazine are administered concomitantly. Cimetidine and hydralazine are known to decrease hepatic blood

flow and this will contribute to a decreased hepatic clearance of propranolol as a consequence of a lower hepatic clearance [3, 36].

### **1.1.5 Conclusion**

PHCL is an ideal candidate for incorporation into modified release dosage forms such that once or twice daily dosing regimens can be used to optimize therapy. Propranolol is a drug that undergoes high first pass metabolism with kinetics that are non linear. The use of controlled release dosage forms to provide a constant rate of drug release should ensure that a better therapeutic effect may be observed with this drug candidate. The physico-chemical and pharmacological properties of PHCL in addition to its relatively short half-life make it a suitable candidate for delivery from prolonged release dosage forms. A knowledge of many of the physico-chemical properties of the drug are of paramount importance, as they provide the necessary information needed for the development of analytical methods that will be discussed in Chapter 2 and in formulation development studies as described in Chapters 3 and 4 *vide infra*.

## 1.2. HYDROCHLOROTHIAZIDE (HCTZ)

### 1.2.1 Introduction

Hydrochlorothiazide is a widely used thiazide diuretic agent that can be used for the treatment of both diuretic and hypertensive clinical indications [2, 3, 5]. HCTZ is listed as the first line therapy for the treatment of hypertension in the South African Essential Drugs List and Standard Treatment Guidelines for the treatment of the condition [39] and can be used in combination with drugs such as beta-blockers in second line therapy [2, 40]

### 1.2.2. Physico-Chemical properties

#### 1.2.2.1. Chemical Name

HCTZ is known as, 6-chloro-3, 4-dihydro-7-sulfamoyl-2H-1, 2, 4-benzothiadiazine 1,1-dioxide, 6-chloro-3, 4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-7-sulfamyl-3, 4-dihydro-1, 2, 4 - benzothiadiazine 1,1-dioxide, 2H-1, 2, 4-Benzothiadiazine-7-sulfonamide, 6-chloro-3, 4-dihydro-1, 1-dioxide [3, 6, 40].

#### 1.2.2.2. Structure

The molecular structure of HCTZ is depicted in Figure 1.6.

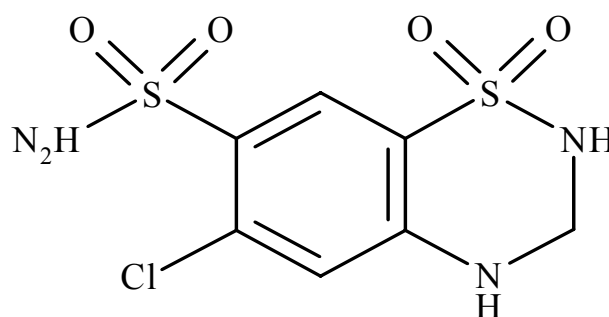


Figure 1.6 Molecular structure of HCTZ ( $C_7H_8ClN_3O_4S_2$  MW 297.72)

### 1.2.2.3 Chemistry

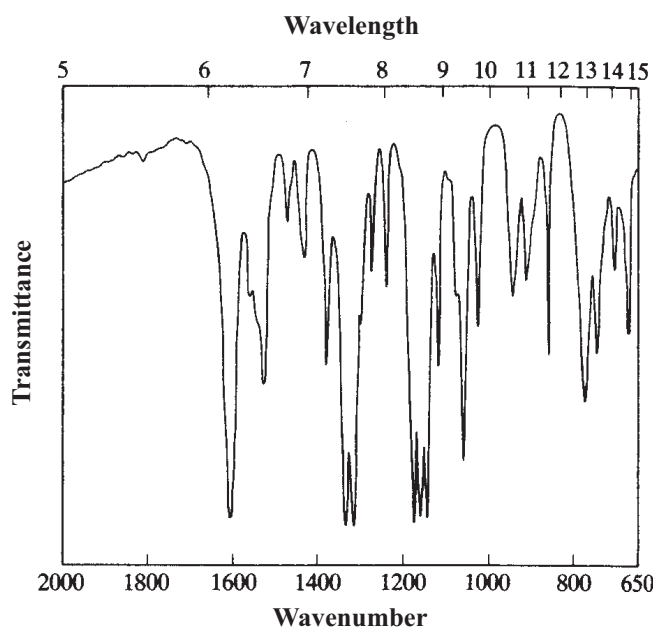
Hydrochlorothiazide (HCTZ) is a benzothiadiazine derivative with diuretic action of intermediate potency and low toxicity [40, 41]. It is comprised of a benzothiadiazine dioxide nucleus with chloride and hydrogen substituents which play a role in the determination of the diuretic activity of the drug [33].

### 1.2.2.4. Melting Point

The reported melting point of HCTZ varies, however there is consensus that the melting point occurs between 268°C and 275° C [11, 15, 40]

### 1.2.2.5. Infrared Spectrum

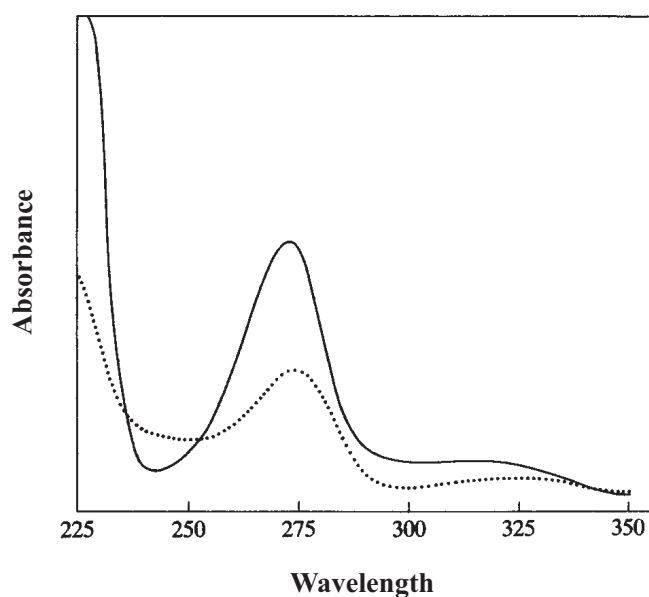
The principal peaks for the infrared spectrum of HCTZ occur at wave numbers of 1318, 1180, 1150, 1168, 1602 and 1060 [15]. The infrared spectrum of HCTZ is depicted in Figure 1.7. As previously mentioned these peaks represent the stretching vibration of various functional groups. The wave numbers 1318, 1180, 1150 and 1168 can be associated with the SO<sub>2</sub> functional group, while the wave numbers 1602 and 1060 represent stretching of the heterocyclic ring structure and S-N bond stretching respectively [40].



**Figure 1.7** Infrared spectrum of HCTZ

### 1.2.2.6. Ultraviolet Absorption Spectrum

The absorption maximum or  $\lambda_{\text{max}}$  for HCTZ occurs at 275 nm when the compound is dissolved in an aqueous acidic media [15] and occurs at 273 nm when in aqueous solution of alkalai media such as NaOH [40]. The absorption spectrum of HCTZ in acidic solution is depicted in Figure 1.8.



**Figure 1.8** Absorption spectrum of HCTZ in aqueous acid ( - - - - ) and in aqueous alkaline solution ( ——— ).

### 1.2.2.7. Solubility

HCTZ is soluble in aqueous solutions of inorganic bases such as sodium hydroxide or ammonium hydroxide and in organic bases such as n-butylamine. The solubility of HCTZ in various aqueous solutions is shown Tables 1.3 and 1.4 [40].

**Table 1.3 Solubility of HCTZ in different aqueous solutions**

Solvent	Temp °C	pH	Solubility g /100ml
Water	25	6.2	60.9 x10 <sup>-3</sup>
Water	37	7.2	108 x10 <sup>-3</sup>
0.9 % NaCL	25	6.1	59.4 x10 <sup>-3</sup>
0.1 N HCL	25	1.0	60.8 x10 <sup>-3</sup>
0.1 N acetic acid	25	2.9	63.6 x10 <sup>-3</sup>
0.1 N acetic buffer pH 4.4	25	4.5	62.3 x10 <sup>-3</sup>
0.067 M PO <sub>4</sub> buffer pH 7.4	25	7.4	61.6 x10 <sup>-3</sup>
0.05 M borate buffer pH 9.0	25	8.9	103 x10 <sup>-3</sup>
1 M ammonia	25	11.6	2.2 x10 <sup>-3</sup>
0.1 N NaOH	25	10.2	1.79 x10 <sup>-3</sup>
SGF* pH 1.1	37	1.1	108 x10 <sup>-3</sup>
SIF*pH 7.4	37	7.5	109 x10 <sup>-3</sup>

\*SGF = simulated gastric fluid [6]

\*SIF = simulated intestinal fluid [6]

**Table 1.4 Solubility of HCTZ in non-aqueous solvents**

Solvent	Temperature °C	Solubility g/ 100ml
Acetone	25	13.7
Acetic acid	25	0.15
Acetonitrile	25	2.0
Ethylacetate	25	0.59
Chloroform	23	0.1
Ethanol 96 %	23	1.3-1.4
Methanol	23	3.9-4.1
Dichloromethane	23	< 0.02

#### 1.2.2.8. Partition co-efficient

The partition coefficients of HCTZ between n-octanol and different aqueous phases at 25° C are shown in Table 1.5 [40].

**Table 1.5 Partition coefficients of HCTZ**

Media	$P^{org}/C_{aq}$
0.1N HCl (pH 1.06)	1.94
0.1 M Glycine buffer (pH 3.0)	0.866
0.067 M PO <sub>4</sub> buffer (pH 7.4)	0.855

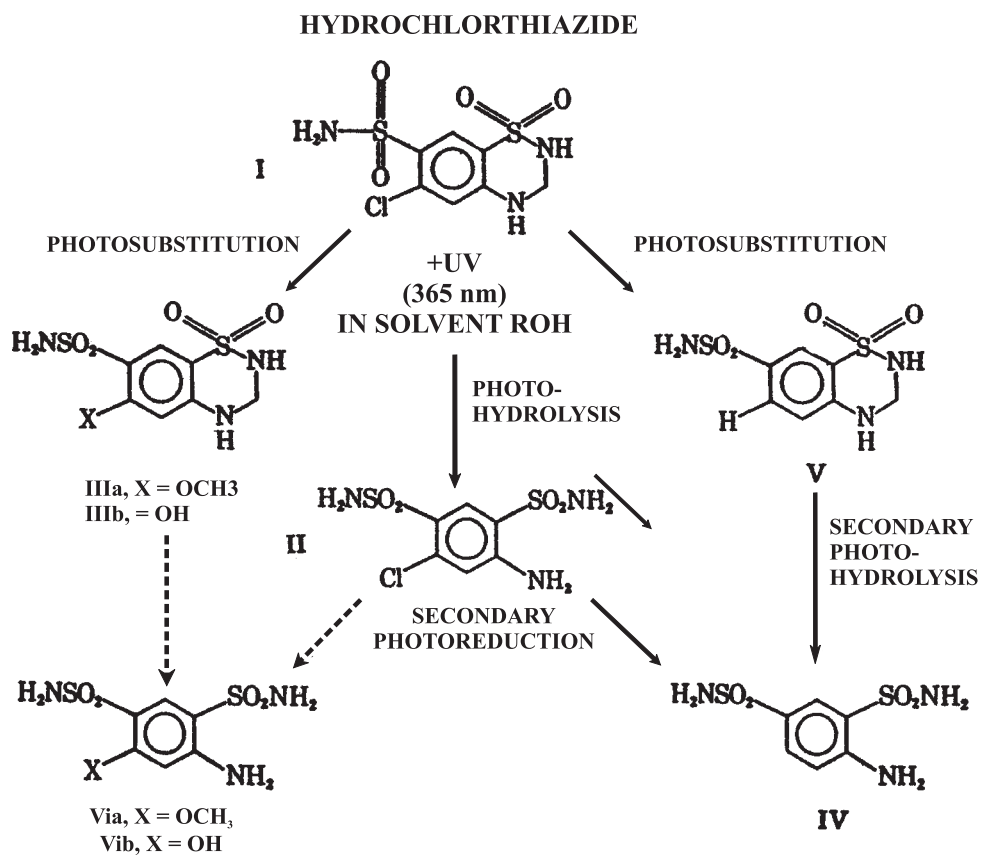
#### 1.2.2.9. Dissociation Constant ( $K_a$ )

The ionization constants that have been reported for HCTZ differ slightly, but in general the two  $pK_a$  values of 7.9 and 9.2 are consistent [11, 15, 40].

#### 1.2.2.10. Physical and Chemical Stability

HCTZ is reasonably stable at room temperature (25° C) [40] but is affected by heat in the solid state to a slight extent with a resultant slight discoloration and no other significant changes to other physical properties of the compound [40]. HCTZ has been found to be stable on exposure to normal daylight conditions; however it should not be exposed to direct intense light as it degrades through a photolytic pathway. A schematic diagram showing the photolytic degradation pathways of HCTZ is shown in Figure 1.10 [33, 42, 43]. HCTZ does however react with adjuvants containing metal compounds, when exposed to conditions of high humidity and these factors must be considered when developing formulations and packaging for HCTZ products [3].

HCTZ is unstable in aqueous solution between the pH of 2.5-11.5 [39] and can undergo degradation by hydrolysis to yield formaldehyde and 6-chloro-2, 4-disulfamoylaniline [3, 42, 43], as seen in Figure 1.9.



**Figure 1.9** Photolytic degradation pathway of HCTZ

### **1.2.3. Pharmacokinetics**

#### **1.2.3.1. Dose**

Thiazides, when used for the treatment of hypertension are usually given as a single dose of between 25 and 50 mg, either alone or in conjunction with other antihypertensive medication. However, in some cases doses of as low as 12.5 mg are usually adequate for effective diuresis and treatment of hypertension [3, 5].

#### **1.2.3.2. Absorption and Bioavailability**

HCTZ is rapidly absorbed from the GIT, primarily from the duodenum and upper jejunum [40, 41]. Peak plasma levels are reached within 3-4 hours after administration [5, 40].

The absorption of HCTZ increases when it is administered with food and this increase has been attributed to a delayed gastric emptying rate [40]. In patients with congestive heart failure the absorption varies from between 20 to 70 %, and in patients with intestinal shunts absorption is diminished to approximately 30% [41].

HCTZ, although rapidly absorbed from the GIT, has an oral bioavailability of approximately 65- 70 % [3, 5].

#### **1.2.3.3. Distribution**

HCTZ has an apparent volume of distribution of approximately 3 L/kg [15]. It is preferentially bound to red blood cells by an unknown mechanism [3, 5, 40], and has a plasma: whole blood ratio of 0.41 [15]. HCTZ has a low degree of protein binding of approximately 40 % [15, 40]. HCTZ is permeable and can cross the placental barrier and is distributed into breast milk [3, 40].

#### **1.2.3.4. Metabolism**

HCTZ undergoes minimal hepatic metabolism and is rapidly eliminated from the body unchanged via the kidney [44].

### **1.2.3.5. Excretion**

HCTZ is almost completely inactivated in humans, with more than 95% of an administered dose excreted unchanged in the urine [3, 5, 40]. The renal clearance of HCTZ was approximately 335ml/min after an oral dose of 12.5 -75mg HCTZ was administered to human subjects with normal renal function [40, 41]. The high value obtained for renal clearance is an indication that HCTZ undergoes tubular secretion and the renal clearance of HCTZ is decreased in patients with congestive heart failure and varies between 10 and 187 ml/min [41].

### **1.2.4. Clinical Pharmacology**

#### **1.2.4.1. Mode of Action**

HCTZ exerts a diuretic effect by inhibiting sodium and chloride ion reabsorption from the luminal region of the epithelial cells that are present in the distal convoluted tubule of the kidney [2, 3]. In addition, the excretion of both potassium and magnesium ions is also enhanced [3]. The combined effect of the inhibition of sodium and chloride ion reuptake and promotion of potassium and magnesium ion excretion, effectively increases the amount of water excreted; while the hypotensive effect of HCTZ is probably due to a decrease in peripheral resistance within the vasculature as a result of fluid loss [2, 3, 5].

#### **1.2.4.2. Indications**

The major therapeutic indications for the thiazide diuretics are for the treatment of hypertension, congestive heart failure, nephrolithiasis due to idiopathic hypercalciuria and nephrogenic diabetes insipidus [3, 30]. Thiazide diuretics are also indicated for use in hypertension either alone or in combination with beta-blockers or ACE inhibitors [3, 39].

#### **1.2.4.3. Contra-Indications**

HCTZ should not be used in patients with severe renal or hepatic impairment, hypokalaemia, pre-existing hypercalcaemia or hypersensitivity to thiazide type compounds or other sulphonamide derivatives [3, 5]. They should also be used with caution in the treatment of gout, diabetes and dyslipidaemia [2, 3, 5].

#### **1.2.4.4. Side Effects**

HCTZ may cause fluid and electrolyte imbalances such as hypokalaemia, hypochloaemic alkalosis, hyponatremia and hypomagnesaemia when administered at levels higher than the recommended doses of 12.5 – 100mg [2, 3, 5]. HCTZ may also cause hyperuricaemia, which may precipitate gout. HCTZ may be potentially diabetogenic due to its effects on glucose metabolism such as promoting insulin resistance, impaired glucose tolerance, precipitation of overt diabetes, with the result that diabetic control is lost. Blood lipoprotein levels may be adversely affected thus causing a resultant increase in triglyceride levels in addition to LDL levels, whereas HDL levels are reduced [3, 5]. Thiazide diuretics may cause renal failure when overused, and can cause hypovolaemia, hypertension and weakness. HCTZ and other thiazide diuretics may also produce GIT disturbances, haematological reactions, pancreatitis, photosensitivity and sulphonamide related hypersensitivity reactions [3, 5].

#### **1.2.4.5. Drug Interactions**

HCTZ is susceptible to numerous drug interactions and a number of these can be attributed to their effect on the fluid and electrolyte balance in the biological system [3, 5]. Diuretic induced hypokalaemia may cause an increase in toxicity of the digitalis glycosides and may also increase the risk of arrhythmias with drugs such as terfenadine, halofantrine, pimozide and sotalol due to prolongation of the QT interval [3, 5]. The hypokalaemic effect of these diuretics may also enhance the neuromuscular blocking effect of competitive muscle relaxants such as atracurium [3, 5]. The potassium depleting effect of thiazide diuretics may be potentiated by corticosteroids, corticotrophin, beta-2- agonists such as salbutamol, amphotericin B, reboxetine or carbenoxolone [3, 5].

Diuretics may also enhance the effect of other antihypertensive agents particularly the first dose hypotension that occurs following administration of ACE inhibitors and alpha blocking drugs [3, 5]. The concomitant use of barbiturates, alcohol and opiates yields the same hypotensive result [3, 5]. The antihypertensive actions of these diuretics are antagonized by drugs, which promote fluid retention, including the NSAID'S, corticosteroids and carboxenolone [3, 5].

Hyponatraemia may be caused by the concomitant use of thiazide diuretics with certain anti-bacterial agents, such as trimethoprim [3] and antiepileptics agents such as carbamazepine [3].

The absorption of thiazide diuretics may be affected by the presence of bile acid binding resins, such as colestipol and cholestyramine, where the latter has a more pronounced effect on hydrochlorothiazide than the former [3].

### **1.2.5 Conclusion**

HCTZ is listed as the first line drug of choice, after lifestyle modification for the treatment of hypertension. It is widely available on the South African market as a generic immediate release product. HCTZ can be used in combination with beta-blockers as previously mentioned.

The aim of this project was to produce a combination product that incorporates an immediate release component of HCTZ with a sustained release PHCL component. The rationale for this combination is based on the fact that these agents are first and second line therapies for the treatment of hypertension and the immediate release of the HCTZ component would provide hypertensive relief initially, whilst the slow release PHCL component would provide relief later in the dosing interval. Consequently attempts were made to develop a once a day combination product in which both HCTZ and PHCL were included.

## CHAPTER 2

### DEVELOPMENT AND VALIDATION OF AN HPLC METHOD FOR THE SIMULTANEOUS DETERMINATION OF PROPRANOLOL AND HYDROCHLOROTHIAZIDE IN PHARMACEUTICAL DOSAGE FORMS

#### 2.1. Introduction

Chromatography is a widely used analytical technique for the separation of compounds from a variety of different matrices [10, 45, 46]. Chromatography involves the separation of the components of a mixture, by virtue of the differences in the equilibrium distribution constant (K) of the components between the two phases of a chromatographic system, *viz.*, the stationary and the mobile phase [10, 45-47]. Separations are achieved as a result of specific interactions between molecules of interest in a sample matrix and the stationary and/or mobile phase(s) used to effect the separation [10, 45-47]. The equilibrium distribution constant (K) can be calculated using Equation 2.1, which represents the distribution of the molecules in sample matrices between stationary and mobile phase(s) of the separation system [10, 45- 47].

$$K = \frac{C_s}{C_m} \quad \text{Equation 2.1}$$

where,

$C_s$  = the concentration of a component on the stationary phase, at equilibrium

$C_m$  = the concentration of a component in the mobile phase, at equilibrium

Liquid chromatography (LC) refers to any chromatographic process in which the mobile phase used for a separation is a liquid, in contrast to gas chromatography (GC) where a gas is used as the mobile or carrier phase [10, 45- 48]. Separations in liquid chromatography can be achieved by several different mechanisms. This includes partitioning, adsorption and exclusion between the mobile and stationary phases [46, 48]. HPLC provides several

advantages over separative techniques such as GC in that separations by HPLC are not limited by the volatility or thermal stability of the compounds of interest [10, 45, 46]. Thus HPLC offers the possibility of using two chromatographic phases compared to one in GC [10, 45; 46]. Furthermore there is a greater variety of stationary phases which are readily available for HPLC and separations can be achieved at lower temperatures than those used for GC methods [10, 45, 46].

Liquid chromatography may take the form of liquid-liquid or partition chromatography (LLC) [10, 45, 46, 48], where a liquid stationary phase is used. Depending on the polarity of the mobile and stationary phases, LLC can be either normal or reversed phase separations [10, 45, 46, 48]. Normal phase chromatography refers to a system in which the stationary phase is more polar in nature than the mobile phase. The converse holds true for reversed phase chromatography, in which the mobile-phase is more polar than the stationary phase [10, 45, 46]. LLC has some specialized applications particularly, for the separation of ionic or ionisable compounds [10, 45, 46, 48]. Where additives are used to facilitate the separation of ionisable compounds, the chromatographic separation is termed ion pair chromatography [10, 45, 46, 48]. Liquid chromatography may also use liquid-solid interactions, in which case the technique is termed adsorption chromatography or LSC. In situations where ionic separations are achieved by use of preferential binding of one ion over another, the separation is said to have been achieved by ion-exchange chromatography or exchange chromatography [10, 45, 46].

PHCL is a weakly basic compound that has a  $pK_a$  of 9.5 [5, 19, 21], whereas HCTZ is a weakly acidic drug with  $pK_a$  values of 7.9 and 9.2 respectively [11, 15, 40]. The analysis of beta-blockers with high  $pK_a$  values poses a challenge for the analyst as the separation of these compounds using reversed phase HPLC is sensitive to changes in pH, which may alter retention times [49-52]. In addition, peak tailing which leads to poor separation efficiency [49, 50, 53] as a result of the affinity of the compound with residual silanols of the stationary phase is another problem [49, 50]. This poor chromatographic performance of weakly basic drugs has also been attributed to concurrent retention mechanisms with different kinetics of mass transfer which, include anion and cation exchange in addition to hydrophobic

interactions, of which include hydrogen bonding,  $\pi$ - $\pi$  interactions, ion exchange, ion pair formation and salting out effects [53].

HPLC conditions for the determination of beta- blockers such as propranolol, either alone or in combination with other drugs for both *in-vitro* and *in-vivo* studies, are abundant in the literature and a selection of the conditions that have been reported [50, 54-64] are summarized in Table 2.1. It can be seen that for all methods that are listed, detection was achieved using UV detectors and that some methods required the use of an internal standard. The varieties of the methods also utilize a C18 column to obtain suitable elution of propranolol.

A summary of the methods that have been reported for the determination of HCTZ is listed in Table 2.2. These methods utilize a C<sub>18</sub> column with phosphate buffers, with or without and internal standard to achieve resolution of hydrochlorothiazide in combination with other drugs [65-68].

The initial stages in the development of an isocratic reversed phase HPLC method for the simultaneous analysis was focused on varying the molarity, pH, and the proportion of phosphate buffer and acetonitrile in the mobile phase in order to achieve adequate resolution of the compounds of interest, *viz.*, propranolol and hydrochlorothiazide. The appropriate stationary phase was selected based on the literature where adequate resolution of propranolol was achieved using phosphate buffers [54-56].

**Table 2.1 Summary of HPLC methods used for the analysis of PHCL**

Reference Number	Stationary Phase	Mobile Phase	Detection Wavelength	Internal Standard
50	C <sub>18</sub>	0.01M PO <sub>4</sub> : Acetonitrile: Methanol (70:15:15 v/v)	254	-
54	C <sub>18</sub>	0.02 M PO <sub>4</sub> (pH 4.5) : Acetonitrile (80:20 v/v)	235	PHCL
55	C <sub>18</sub>	0.067M PO <sub>4</sub> (pH 3.0) with 0.2 % w/v Triethylamine: Acetonitrile (60:40 v/v)	294	-
56	C <sub>18</sub>	0.067M PO <sub>4</sub> (pH 3.0) with 0.2 % w/v Triethylamine: Acetonitrile (60:40 v/v)	294	-
57	Cyanopropylsilane	0.05 M PO <sub>4</sub> (pH 3.0) : Acetonitrile (85:15 v/v)	290	-
58	Non polar Octadecyltrichlorosilane	0.02 M Ammonium formate: glacial acetic acid: methanol (56.5:05:43 v/v/v)	270	Verapamil hydrochloride
59	Perphenylcarbamate β-CD	Methanol or buffer: Triethylamine: Methanol	230	-
60	C <sub>18</sub>	Acetonitrile: water: phosphoric acid triethylamine (50:50:0.15:0.06 v/v)	280, 325	4- methyl propranolol hydrochloride
61	C <sub>18</sub>	PO <sub>4</sub> Buffer (pH 3.8): Acetonitrile (gradient)	220	-
62	C <sub>8</sub>	Water (with 0.03 v/v trifluoroacetic acid) or Acetonitrile : Water (0.03 v/v TFA)	205	-
63	Octadecasilyl	Hexane: Ethanol ( 75:25 v/v)	280	-
64	C <sub>18</sub>	PO <sub>4</sub> , or sodium trifluoacetate, or sodium perchlorate(pH 3.0): Acetonitrile(70:30 v/v)	225	-

**Table 2.2 Summary of HPLC methods for the analysis of HCTZ**

<b>Reference Number</b>	<b>Stationary Phase</b>	<b>Mobile Phase</b>	<b>Detection Wavelength</b>	<b>Internal Standard</b>
65	C <sub>18</sub>	0.02 M PO <sub>4</sub> (pH 7.0) : Acetonitrile (93:7 v/v)	250	-
66	C <sub>18</sub>	0.01 M PO <sub>4</sub> (pH 6.2) : Acetonitrile ( 65:35 v/v)	251	Trimethoprim
67	C <sub>18</sub>	0.025 M PO <sub>4</sub> (pH 3.0): Acetonitrile ( 84:16 v/v)	278	-
68	C <sub>18</sub>	0.02 M PO <sub>4</sub> (pH 3.2) :Acetonitrile (55:45 v/v)	225	Trimethoprim

## **2.2. Experimental**

### **2.2.1. Materials**

All reagents used were at least of analytical reagent grade. Acetonitrile 200 far UV ROMIL-SpS™ super purity solvent and methanol 215 ROMIL-SpS™ super purity solvents were obtained from ROMIL Ltd (Waterbeach, Cambridge, UK). Ortho-phosphoric acid (85%v/v) was purchased from Merck Chemicals (PTY) Ltd (Wadeville, Johannesburg, South Africa), and sodium hydroxide pellets were purchased from Saarchem (Merck Chemicals (PTY) Ltd, Wadeville, Johannesburg, South Africa). A Millipore RiOS™ 16 and Milli-Q Academic® A10 system (Waters Corp., Milford, MA, USA) was used to prepare polished HPLC grade water. The mobile phase was vacuum filtered using a Millipore Durapore® HVLP (Waters Corp., Milford, MA, USA ) membrane filter with a 0.45 µm pore diameter prior to use.

PHCL (Batch no. PHC 204) was purchased from Kothari Phytochemicals International (Nagari, India). HCTZ USP standard (Lot no. RV24189) was obtained from MSD (PTY) Ltd (Johannesburg, RSA) and sulphadimethoxine (SDM) the internal standard was purchased from Sigma-Aldrich (St. Louis, MO, USA). All weighing was conducted on a Mettler-Toledo AG 135 analytical balance (Mettler-Toledo, Griefensee, Zurich, Switzerland).

### **2.2.2. Preparation of Buffers**

75mM phosphate buffer was prepared by accurately weighing 10.2067g potassium dihydrogen orthophosphate and quantitatively transferring it into a 1000 ml A-grade volumetric flask. The sample was made up to volume with HPLC grade water and the solution was sonicated using a Sonicor® model SC-211 TH sonicator [Sonicor Instrument Corp, Copiague, N.Y, USA] for 10 minutes in order to ensure dissolution had occurred. The pH of the buffer was adjusted to pH = 3 by the controlled addition of 85% v/v ortho-phosphoric acid. The buffer pH was monitored using Model GLP 21 Crison pH meter (Lasec, Port Elizabeth, RSA).

### **2.2.3. Preparation of Stock Solutions**

Stocks solutions of PHCL and HCTZ were prepared by accurately weighing approximately 10mg of the relevant drug candidate directly into a 100ml A-grade volumetric flask and making up to volume with 75mM phosphate buffer (pH 3). The solution was sonicated for 10 minutes to facilitate total solution of the drug. A stock solution of SDM was prepared by accurately weighing approximately 15mg SDM into a 100ml A-grade volumetric flask and making up to volume with HPLC grade methanol.

### **2.2.4. HPLC Systems**

There were two HPLC systems utilized during the course of the research work. System A described in section 2.2.4.1 was the first system used to develop and validate the analytical method. A more modern HPLC modular system, System B as described in section 2.2.4.2 became available and it was envisaged that the new system would improve the analytical precision and accuracy of the method and was investigated.

#### **2.2.4.1 System A**

The modular HPLC system used for method development was comprised of a Waters<sup>®</sup> 510 solvent delivery module (Waters, Bedford, MA, USA) a Waters<sup>®</sup> WISP 710B auto-sampler (Waters, Bedford MA, USA) and a Waters<sup>®</sup> M490 programmable multi-wavelength detector (Waters, Bedford MA, USA) coupled to a Linear Instruments model 200 chart recorder (Linear Instruments Corp, Irvine, CA). System A was used for the development and validation of the HPLC method for the quantitation of PHCL and HCTZ.

#### **2.2.4.2 System B**

A second modular HPLC system, System B, was used for all subsequent analysis of samples and consisted of a Spectra-Physics<sup>®</sup> IsoChrom LC pump (Spectra-Physics,

San Jose, CA, USA), a Waters<sup>®</sup> WISP 710B auto-sampler (Waters, Bedford, MA, USA) a Linear UVIS 200 detector (Linear Instruments Corp, Irvine, CA) coupled to a Spectra-Physics<sup>®</sup> DataJet integrator (Spectra-Physics, San Jose, CA, USA). A second validation was performed to assess the linearity, precision and accuracy of the method that had been validated using System A, to assess whether System B was suitable for the quantitation of PHCL and HCTZ.

#### **2.2.4.3 Test columns**

Two analytical columns were initially tested for their ability to effect a suitable separation for the analysis of PHCL and HCTZ. The analytical columns that were used included Supelco<sup>®</sup> Supelcosil LC-18 (15cm x 4.6mm) (Supelco Inc, Bellefonte, PA USA) and a Beckman Ultrasphere<sup>®</sup> 5 $\mu$ m C<sub>8</sub> (150m x 4.6mm) (Beckman Coulter, Fullerton, CA USA).

### **2.3. Method development**

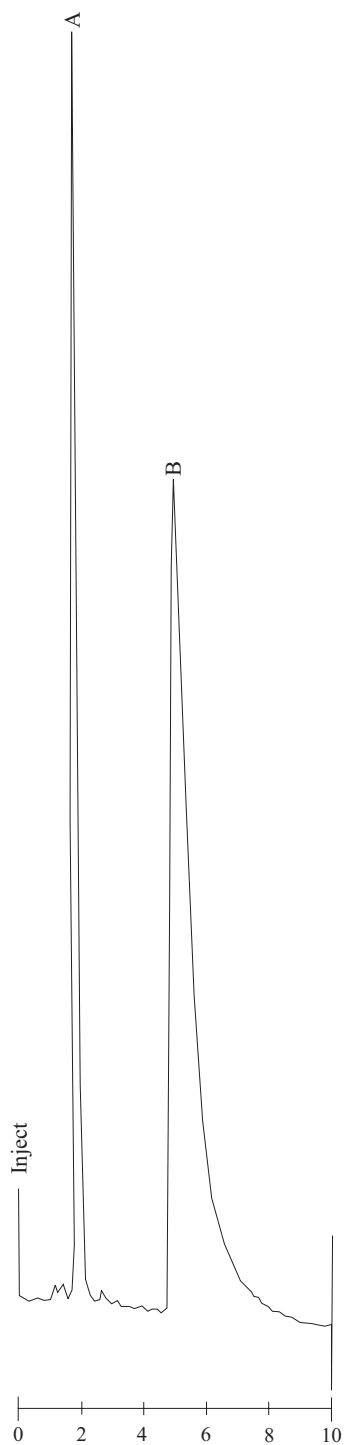
#### **2.3.1. Column selection**

The selection of a suitable stationary phase for reversed phase liquid chromatography (RP-HPLC) for a specific separation is a difficult process [69]. However, there are a number of empirical and model based test protocols that can be performed to assess the suitability of a column for a specific separation. These methods include tests for hydrophobicity, steric selectivity, efficiency and silanol activity [70, 71].

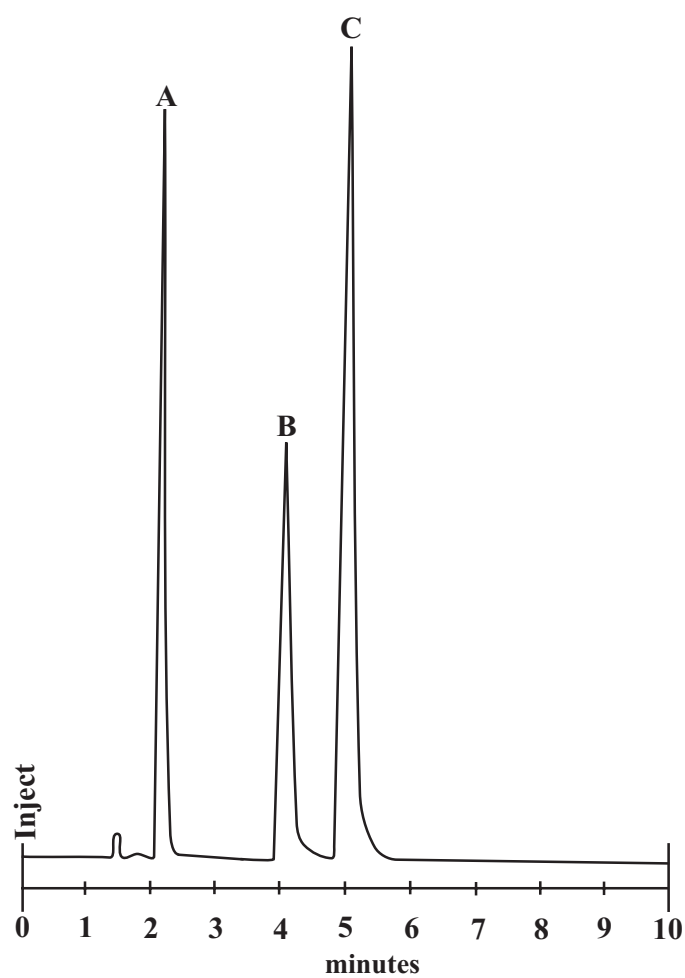
Silica particles are heterogeneous by nature [72] and are by far the most popular substrate used for the manufacture of RP-HPLC columns [69, 72]. Silica particles possess a high degree of mechanical strength, and do not shrink or expand when exposed to organic solvents [69]. Furthermore these particles can be bonded by a number of non-polar or moderately polar groups [69, 72], which enables their use in HPLC processes [69]. The size of the silica particles has an influence on the retention and separation of the analyte of interest, with columns of the smaller particle size,

such as those of 3  $\mu\text{m}$  in diameter having more theoretical plates per unit of column length [73]. This therefore permits faster elution of the analyte(s) of interest than for columns manufactured using larger silica particles of 5  $\mu\text{m}$  or 10  $\mu\text{m}$  in diameter [73].

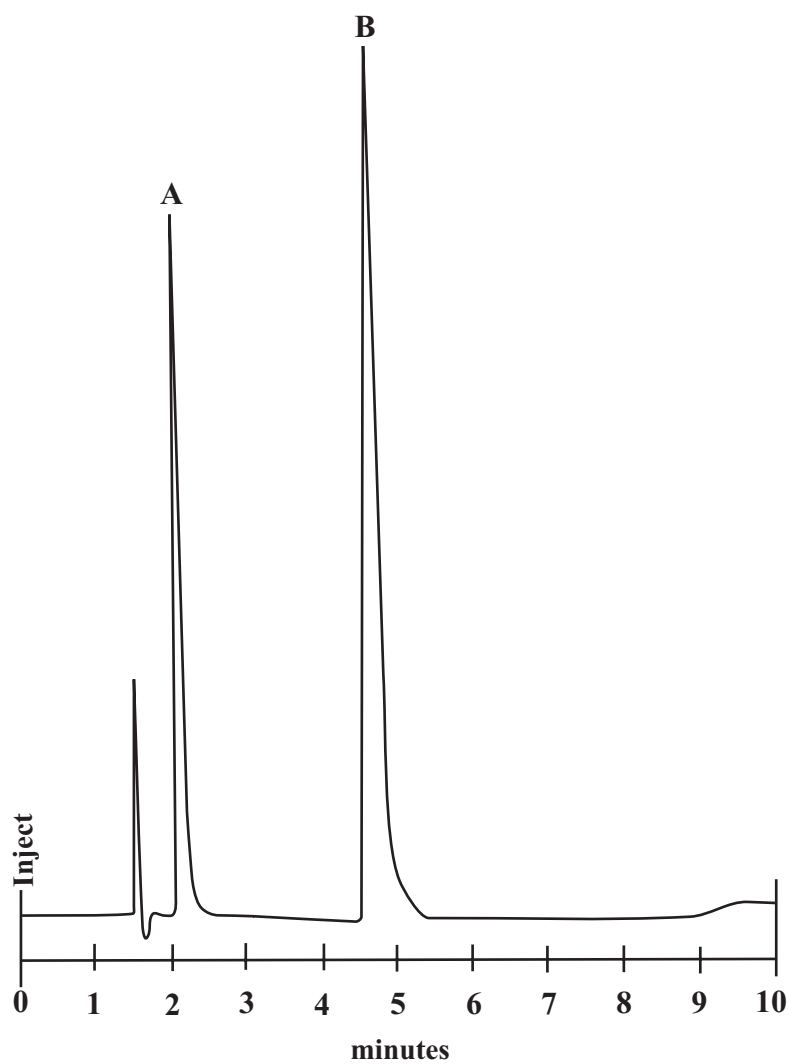
A Supelco<sup>®</sup> Supelcosil LC-18 (15cm x 4.6mm) (Supelco Inc, Bellefonte, PA USA) column was tested initially to determine whether an appropriate separation could be achieved for the analysis of PHCL and HCTZ. The resultant chromatograms revealed a large degree of peak tailing which can more likely be attributed to the relatively high  $\text{pK}_a$  and basicity of PHCL. A typical chromatogram obtained using this column is depicted in Figure 2.1. The use of a Beckman Ultrasphere<sup>®</sup> 5 $\mu\text{m}$  C<sub>8</sub> (150m x 4.6mm) (Beckman Coulter, Fullerton, CA USA) column instead of a C<sub>18</sub> column produced better peak resolution with marginal peak tailing as can be seen in Figure 2.2. The use of ion pair reagents such as 1-Heptane-Sulfonic acid (HSA) or 1-Octanesulphonic acid (OSA) (Sigma-Aldrich, St. Louis, MO, USA), at a concentration of 2 % w/v produced slightly better resolution than mobile phases without ion pair reagents. However, the retention time of the peaks of interest were affected to a slight extent as seen in Figures 2.3 and Figure 2.4 respectively, where an increase in retention time can be observed.



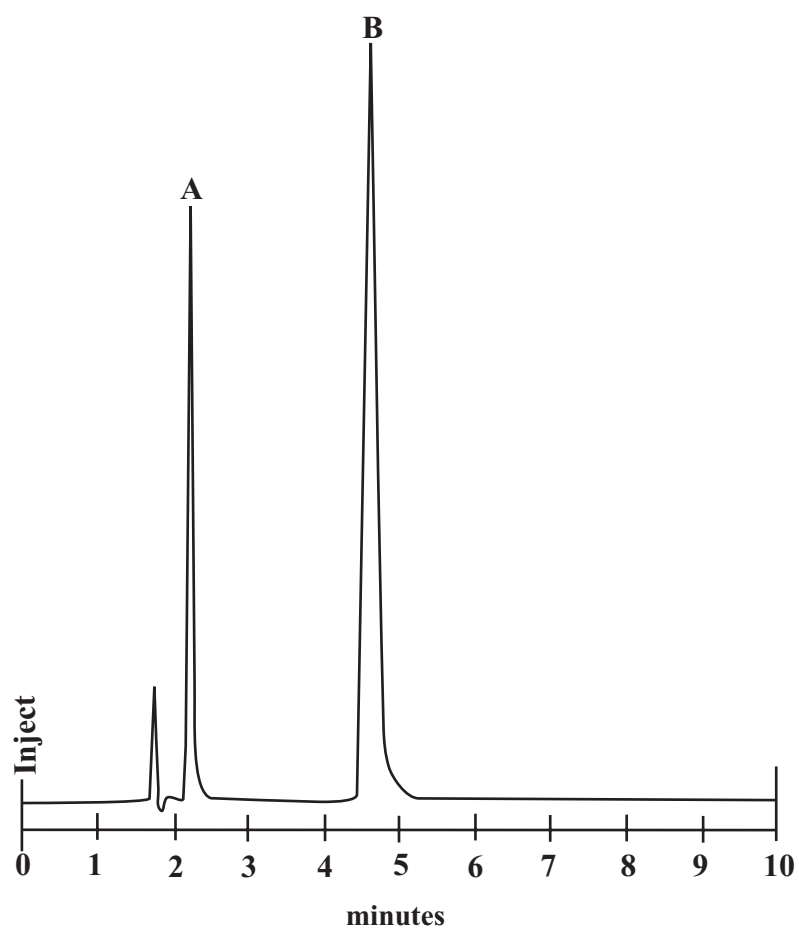
**Figure 2.1** Representative sample chromatogram of the separation of hydrochlorothiazide (A) and propranolol (B) using  $C_{18}$  column with drug loading of 30 and 60  $\mu\text{g}/\text{ml}$  respectively and mobile phase 75mm  $\text{PO}_4$  (pH 3):ACN (70:30 v/v). Retention times are A= 2.2 and B=5.7 minutes respectively.



**Figure 2.2** Representative chromatogram of the separation of hydrochlorothiazide (A), propranolol (B) and internal standard sulphadimethoxine (C) using  $C_8$  column with drug loading of 30  $\mu\text{g/ml}$  for A, B, and C with mobile phase 75mm  $\text{PO}_4$  (pH 3):ACN (70:30 v/v). Retention times are A=2.25, B=4.22 and C=5.5 minutes respectively.



**Figure 2.3** Representative chromatogram of the separation of hydrochlorothiazide (A) and propranolol (B) using C8 column with drug loading of 30 $\mu$ g/ml for A and B with mobile phase 75mM PO<sub>4</sub> (pH 3): HSA :ACN (70:2:30 v/v/v). Retention times are A=2.11 and B=4.87 minutes respectively.



**Figure 2.4** Representative chromatogram of the separation of hydrochlorothiazide (A) and propranolol (B) using C8 column with drug loading of 30 $\mu$ g/ml for A and B with mobile phase 75mm PO<sub>4</sub> (pH 3): OSA :ACN (70:2:30 v/v/v). Retention times are A=2.28 and B=4.69 minutes respectively.

### 2.3.2. Mobile Phase Selection

The mobile phase in liquid chromatography should be immiscible with the stationary phase, and should have a low viscosity to ensure high column permeability and efficiency [46]. Mobile phase selection is a vital consideration in some instances where the detection system used may limit the composition that can be used [46, 48]. There are a variety of solvents that can be used for the development of mobile phases with resultant viscosities and polarities that are different [46, 74], and the choice of the composition of the solvent systems is dependent on the nature of the elution required to effect an appropriate separation [10, 46]. Investigation into varying the mobile phase content produced unresolved peaks. Further investigation comprised of mobile phase composition of PO<sub>4</sub>: ACN (70:30 v/v), with investigations done into the effect of pH and buffer molarity.

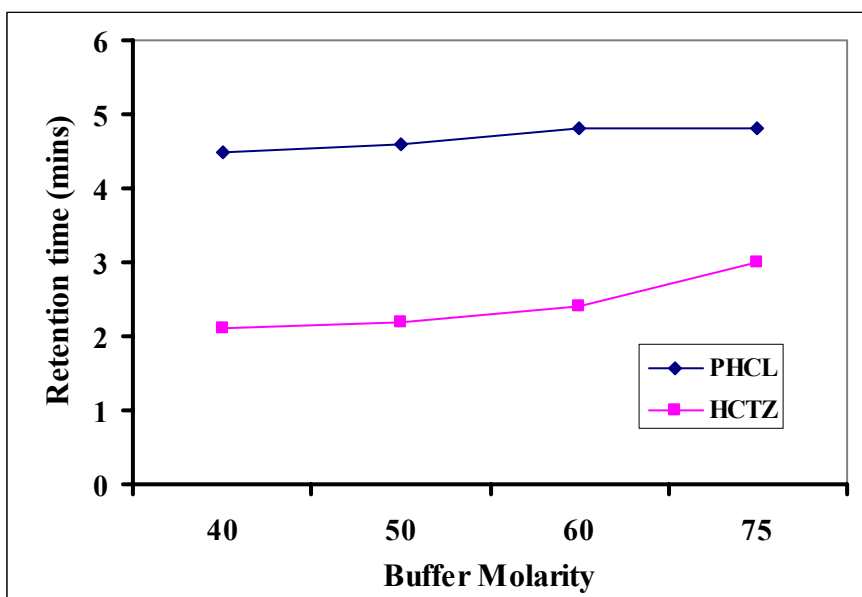
The variation of pH of a mobile phase is of vital importance as it can be used to manipulate the chromatographic retention time(s) of a specific analyte [51, 52, 75, 76]. An increase in the pH of a mobile phase would increase the retention time for weakly basic compounds [46, 48] and for weakly acidic drugs the converse would hold true [49, 51].

The use of inorganic salts and/or organic amines has been reported to improve the efficiency of analysis of basic compounds [49, 50, 64], however the addition of these agents to mobile phases may cause an increase in the retention time of the analytes of interest [50].

Numerous HPLC methods for the determination of either a single beta-blocker or a beta-blocker in combination with other drugs have been reported. The methods have either used isocratic or gradient mobile phases with either C<sub>18</sub> or C<sub>8</sub> reversed phase columns being used as the stationary phase. A summary of the relevant conditions for these methods is listed in Table 2.1. The reported methods show efficient elution of propranolol by use of mobile phases consisting of phosphate buffer in combination with acetonitrile and/or methanol [54-56, 64].

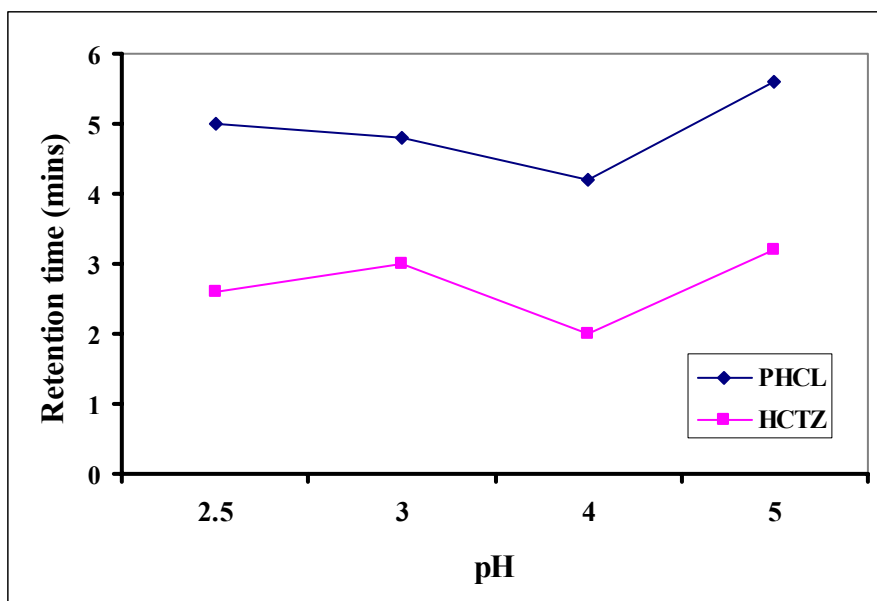
The initial mobile phase selected for testing in these studies was based on the data from literature [54-56]. The effects of buffer molarity, pH and the addition of organic modifiers used in ion pair chromatography were investigated.

The effects of buffer molarity and pH on retention time are shown in Figures 2.5 and 2.6.



**Figure 2.5** Effect of buffer molarity on retention time

As can be seen in Figure 2.5 an increase in buffer molarity had a marginal effect on the retention time of both propranolol and HCTZ. In contrast to the effects if changes in molarity on retention times, changes in pH had a resultant effect on retention times of both PHCL and HCTZ, as shown in Figure 2.6.



**Figure 2.6 Effect of pH on retention time**

It was finally decided that a mobile phase buffer of pH 3 would be appropriate as PHCL is most stable in solutions of this pH [3], with a buffer molarity of 75mM as this produced adequate resolution as shown in Figure 2.2.

The use of mobile phases of low pH will result in the majority of the residual silanol groups of an analytical column being in a neutral state and therefore will minimize the potential for silanol- weakly basic compound interactions [49, 50]. However the use of low pH mobile phases may facilitate the early elution of highly solvated protonated basic compounds [49], which was considered appropriate for these studies in order to develop a method with a rapid turnaround time for multiple sample analyses.

### **2.3.3. Method of Detection**

The selection of a specific method of detection for analysis by HPLC is to a large extent dependent on the physico-chemical properties of the compounds of interest. Both PHCL and HCTZ possess chromophores that are able to absorb light in the UV range (Sections 1.1.2.7 and 1.2.2.6). The wavelength selected for detection of PHCL and HCTZ was the  $\lambda$  maximum of PHCL (290 nm); which is above the  $\lambda$  maximum of HCTZ (274 nm). The selection of this wavelength was based on the fact that the

dosage form to be developed would contain PHCL in a sustained release system and therefore samples taken early during dissolution rate studies may require the highest sensitivity. Furthermore the HCTZ was to be included as an immediate release component and the total content dissolved within 15-30 minutes of the commencement of dissolution testing.

#### 2.3.4. Chromatographic conditions chosen

The optimal chromatographic conditions established during the method development procedure and selected for the purposes of validating the analytical method are listed in Table 2.3.

**Table 2.3 Chromatographic conditions**

<b>Column</b>	Beckman Ultrasphere <sup>®</sup> 5 $\mu$ m C <sub>8</sub> (150m x 4.6mm)
<b>Mobile phase</b>	Acetonitrile : 75mM KH <sub>2</sub> PO <sub>4</sub> Buffer (pH 3) 30:70
<b>Flow rate</b>	1.2 ml/min
<b><math>\lambda</math> max</b>	290 nm
<b>Injection volume</b>	20 $\mu$ l
<b>AUFS</b>	0.1
<b>Temperature</b>	Ambient

The parameters listed in Table 2.3 were selected after preliminary investigative studies into the factors that may have affected the analysis of PHCL and HCTZ as previously described in Sections 2.3.1 and 2.3.2. These parameters were optimized to allow for the development of an HPLC method that yields well-resolved peaks for both drug candidates at reasonable retention times. The analytical method that was developed as described in Section 2.3 was meant to achieve quantitation using the peak height ratio of drug/ internal standard method for the validation process as described *vide infra* in Section 2.4.

## **2.4. Method Validation**

### **2.4.1. Introduction**

Following the development of an analytical method and prior to its subsequent use for the quantitation of compounds of interest, a validation procedure must be followed to qualify the method for use, such that the test results generated by use of the method are both reliable and valid [77 – 82]. The initial stages of method development, the improvement of a current analytical method and thereafter validation is a requirement when analytical methods that have been reported in the literature are not suitable for the intended purpose or do not meet the specific requirements for the precise and accurate analysis of the analyte under investigation [77, 78].

The term validation refers to a process whereby a proposed analytical method is investigated to ascertain whether the purpose of a method can be achieved with acceptable levels of certainty [7-81]. The extent of validation and the choice of performance parameters for the validation, depend to a large extent on the analytical requirements of the proposed method [77-80].

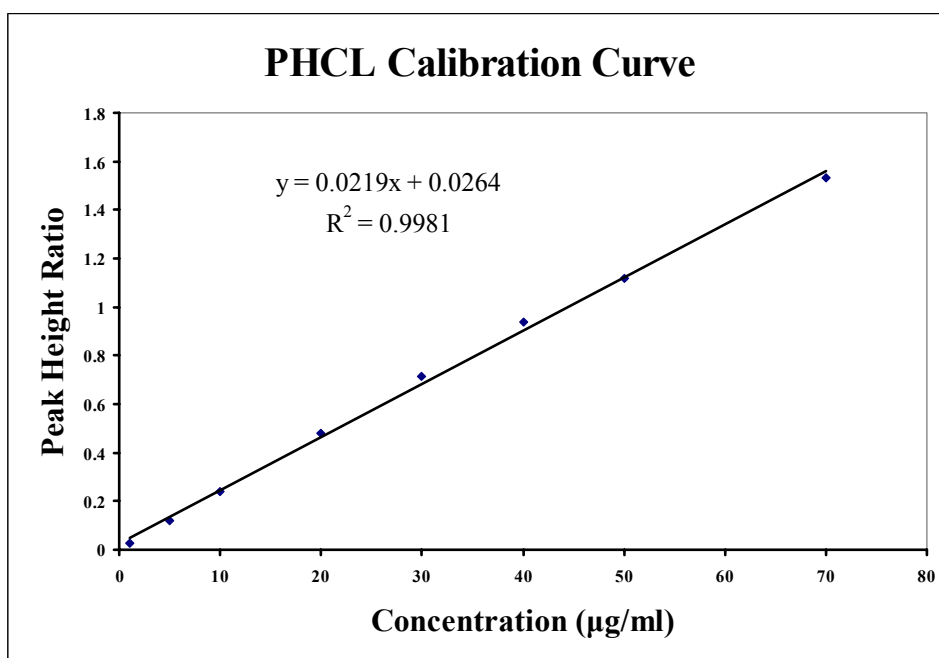
The validation parameters investigated for these studies included linearity and range, precision, accuracy, the limit of quantitation (LOQ), the limit of detection (LOD), and specificity [77 - 82].

### 2.4.2. Linearity

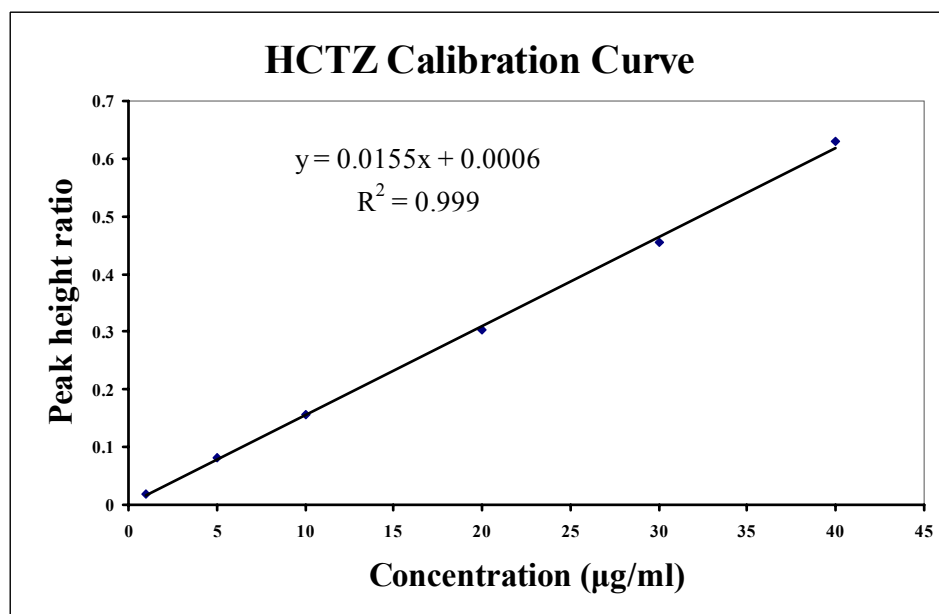
The linearity of an analytical method is the ability of an analytical method to show a directly proportional relationship of a quantitative response to a specific concentration of an analyte within a given specified range of concentrations [77-81]. The range of a method may be defined as the interval between the upper and lower limits of quantitation to which the method produces test results that are proportional to the analyte concentration or to which a linear calibration model may be applied within a known confidence interval [77 -80].

Stock solutions of PHCL and HCTZ were prepared as described in Section 2.3.3. Serial dilution of the stock solution by removal of suitable aliquots were undertaken to yield calibration curves over the concentration range of 1-70 µg/ml and 2-40 µg/ml for PHCL and HCTZ, respectively. The resultant concentrations of the standards used for the calibration curve were 1, 5, 10, 20, 30, 40, 50 and 70 µg/ml for PHCL and 1, 5, 10, 20, 30 and 40 µg/ml for HCTZ respectively. Five replicate analyses of each of the concentrations were used to establish the calibration curve for System A and three replicate analyses were performed for System B.

The results of the validation procedure for linearity using HPLC System A, reveal that the assay was linear over the concentration range studied and yielded regression coefficients of  $R^2 = 0.9981$  for PHCL and  $R^2 = 0.9990$  for HCTZ. Examples of typical calibration curves generated in these studies are depicted in Figures 2.7 and 2.8 for the determination of PHCL and HCTZ, respectively.



**Figure 2.7** Typical calibration curve obtained for the analysis of PHCL using HPLC System A



**Figure 2.8** Typical calibration curve obtained for the analysis of HCTZ using HPLC System A

The results of the validation for linearity using HPLC System B yielded similar results to that of System A with resultant regression co-efficients of  $R^2 = 0.9947$  for PHCL and  $R^2 = 0.9982$  for HCTZ respectively. The relevant equations for these are  $y = 0.0129x + 0.0283$  and  $y = 0.022x + 0.0144$  for PHCL and HCTZ on System B respectively.

The test for linearity of the proposed analytical method yielded  $R^2$  values that were greater than 0.9900 for both HPLC systems used during validation. Therefore the linearity of the method is suitable for the quantitation of PHCL and HCTZ in pharmaceutical dosage forms.

### **2.4.3. Precision**

The precision of an analytical method is defined as the closeness in agreement between independent test results obtained under stipulated conditions, and is a measure of the extent of agreement between repeated injections of a homogenous sample. The precision of a method is usually expressed as the standard deviation or as percent relative standard deviation (%RSD) [77-80]. Intra day precision was assessed by evaluating the chromatographic responses of repeated injections (n=5) for System A and (n=3) for System B of known concentrations of both PHCL and HCTZ over the concentration ranges studied. The results of intra day precision determinations for PHCL and HCTZ are listed in Tables 2.4 and 2.5 for System A and B respectively.

**Table 2.4 Intra-day precision of PHCL using Systems A (n=5) and B (n=3)**

<b>System A</b>			
<b>Concentration µg/ml</b>	<b>Mean Peak Height Ratio PHCL/SDM N=5</b>	<b>SD</b>	<b>RSD %</b>
1	0.028	0.002	5.626
5	0.121	0.004	3.044
10	0.240	0.002	0.853
20	0.478	0.003	0.680
30	0.712	0.009	1.281
40	0.938	0.000	0.047
50	1.119	0.006	0.523
70	1.532	0.007	0.468
<b>System B (n=3)</b>			
1	0.0343	0.0002	0.4785
5	0.0841	0.0005	0.5932
10	0.1444	0.0003	0.1826
20	0.2602	0.0099	3.7992
30	0.5025	0.0004	0.0743
40	0.5401	0.0013	0.2329
50	0.6627	0.0009	0.1364
70	0.9145	0.0002	0.0224

The results for the intra-day precision for reveal % RSD values < 5.626 % for all samples using System A and %RSD value of < 3.7992 % for System B for all samples respectively. This indicates that the method shows good intraday precision for both Systems A and B with System B having a greater precision than that System A.

**Table 2.5 Intra-day precision of HCTZ using Systems A (n=5) and B (n=3)**

<b>System A</b>			
<b>Concentration µg/ml</b>	<b>Mean Peak Height Ratio PHCL/SDM N=5</b>	<b>SD</b>	<b>RSD %</b>
2	0.026	0.001	5.441
5	0.081	0.004	5.130
10	0.156	0.003	1.759
20	0.302	0.002	0.548
30	0.455	0.002	0.448
40	0.629	0.002	0.342
<b>System B (n=3)</b>			
2	0.0380	0.0001	0.3411
5	0.1211	0.0003	0.2143
10	0.2115	0.0017	0.8252
20	0.4183	0.0017	0.3999
30	0.7793	0.0017	0.2118
40	0.8313	0.0079	0.9509

The intra-day precision results when analyzing samples of HCTZ reveal that System A % RSD of < 5.441 % for all samples and with System B a % RSD < 0.9509 % was obtained. This follows the trend in Table 2.4 with System B having a better intra-day precision than System A.

Intermediate precision can be determined by the variability in response to an analytical method within a laboratory arising from analyses conducted on different days, or by different analysts or where different equipment have been used to conduct the analyses [82]. The intermediate precision of the analytical method was assessed by repeating the analysis on different days. The results of intermediate precision determination are summarized in Tables 2.6, 2.7 for Systems A and B respectively.

**Table 2.6 Inter-day precision of PHCL using Systems A (n=5) and B (n=3)**

<b>System A</b>			
<b>Concentration µg/ml</b>	<b>Mean Peak Height Ratio PHCL/SDM N=5</b>	<b>SD</b>	<b>RSD %</b>
1	0.043	0.003	6.061
5	0.117	0.003	2.692
10	0.208	0.005	2.452
20	0.419	0.027	6.332
30	0.669	0.015	2.248
40	0.824	0.031	3.781
50	0.980	0.028	2.857
70	1.336	0.040	2.962
<b>System B (n=3)</b>			
1	0.036	0.001	2.287
5	0.089	0.004	4.731
10	0.167	0.008	4.642
20	0.318	0.017	5.448
30	0.476	0.027	5.714
40	0.620	0.032	5.189
50	0.779	0.043	5.572
70	1.111	0.057	5.170

The results represented in Table 2.6 reveal that System A has an inter-day precision with % RSD values < 6.061 % and with System B having % RSD values < 5.572 %. These results illustrate that the modern modular HPLC system, namely System B is not necessarily better than the older system, System A.

**Table 2.7 Inter-day precision of HCTZ using Systems A (n=5) and B (n=3)**

<b>System A</b>			
<b>Concentration µg/ml</b>	<b>Mean Peak Height Ratio PHCL/SDM N=5</b>	<b>SD</b>	<b>RSD %</b>
2	0.033	0.002	5.339
5	0.131	0.001	0.418
10	0.258	0.004	1.383
20	0.521	0.011	2.174
30	0.797	0.005	0.645
40	1.036	0.059	5.695
<b>System B (n=3)</b>			
2	0.042	0.003	5.978
5	0.164	0.008	4.724
10	0.288	0.019	6.595
20	0.561	0.036	6.415
30	0.841	0.057	6.775
40	1.083	0.055	5.036

The inter-day precision studies performed on HCTZ samples reveal that System A has a % RSD value of < 5.695 % for all samples, with System B having a % RSD value < 6.775 %. This does not follow the trend as seen in Table 2.8 where System B shows lower % RSD values. As previously mentioned the new modular system, System B is not necessarily more precise than the older system, (System A) as represented by the results shown in Tables 2.6 and 2.7.

The %RSD values used to determine the intra-day and intermediate precision of the HPLC method are all less than 6 % for System A and 7 % for System B for both drugs tested. The limit for precision set in our laboratory is 10 %, and this indicates that the proposed method is suitable for the quantitative analysis of both drug candidates by HPLC.

#### 2.4.4. Accuracy

The accuracy of an analytical method is the exactness, or the closeness of agreement between a measured value and the value that is accepted as either a conventional true value or accepted reference value [77–80]. Accuracy can be expressed in terms of the percent bias, which represents the percentage error difference between a measured value and a reference value [77-80]

Accuracy was determined by injection of solution (n=3) of known concentrations of both drugs that had been prepared from new stock solutions as described in Section 2.2.3. The measured concentrations of these samples were interpolated from a calibration curve specifically generated for the determination of the accuracy of the method. The results of accuracy studies for both HPLC Systems for PHCL and HCTZ are summarized in Tables 2.8 and 2.9 respectively.

**Table 2.8 Accuracy data for determination of PHCL in solution**

<b>System A</b>			
<b>Concentration µg/ml</b>	<b>Theoretical Concentration µg/ml</b>	<b>Experimental Concentration µg/ml</b>	<b>% Bias</b>
15	15.15	15.934	5.17
45	45.45	44.499	2.09
<b>System B</b>			
15	15.21	15.715	3.32
45	45.19	45.678	1.08

**Table 2.9 Accuracy data for determination of HCTZ in solution**

<b>System A</b>			
<b>Concentration µg/ml</b>	<b>Theoretical Concentration µg/ml</b>	<b>Experimental Concentration µg/ml</b>	<b>% Bias</b>
15	16.35	16.825	2.91
35	39.2	41.054	4.73
<b>System B</b>			
15	15.45	15.92	3.04
35	36.45	37.01	1.54

It is clearly evident from the reported % bias data, calculated for this analytical method during the validation of accuracy, that the method can be considered accurate, as the %bias was < 6 % for all determinations, which is well below the 10% limit set in our laboratory.

#### **2.4.5. Limit of Quantitation (LOQ) and Limit of Detection (LOD)**

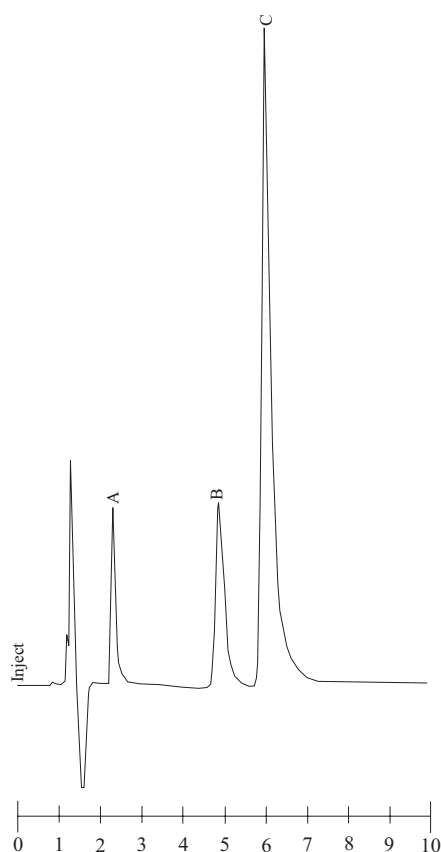
The LOQ of an analytical method is the lowest concentration or amount of analyte that can be accurately determined with an acceptable level of precision [77 - 80]. The LOD of an analytical method is the lowest concentration or amount of analyte that can be reliably distinguished from zero or that can be detected or measured with a reasonable statistical certainty [77- 81].

The signal to noise ratio of the analyte peak is often used to determine the LOQ and LOD, using the ratios of 10:1 and 3:1 for each limit, respectively. There are however analogous methods for the determination of these limits, including a method in which the lowest concentration producing a response with % RSD values lower than 5% percent after multiple injections. This may be considered the LOQ of the method. The LOD is then determined by using a value one third that of the previously determine LOQ. The latter method was used to determine the LOQ and LOD for both PHCL and HCTZ for this HPLC method with System A. The results reveal that the LOD and LOQ are 0.3 and 1µg/ml for PHCL and 0.6 and 2 µg/ml for HCTZ respectively.

## 2.4.6. Specificity

The specificity of an analytical method is the ability of an analytical method to determine accurately and specifically the analyte of interest in the presence of other components of a mixture or sample matrix under stated conditions [77-81].

The specificity of the HPLC method developed for the analysis of PHCL and HCTZ can be demonstrated from the chromatograms as shown in Figure 2.9. This was generated following the analysis of samples obtained during dissolution rate test studies where dosage forms that contained both drugs of interest were present. As is evident in Figure 2.9, with all peaks of interest, viz., PHCL, HCTZ and the internal standard are baseline resolved and free from interference from tablet excipients, the solvent front and from each other.



**Figure 2.9** Typical chromatogram obtained following analysis of matrix dosage form containing HCTZ (A) and PHCL (B) with internal standard SDM (C) from dissolution studies. Retention times are A=2.34, B=4.91 and C=6.01 minutes respectively.

## 2.5. Conclusions

An HPLC method has been developed and validated on two different modular HPLC systems. The proposed analytical method is simple, sensitive, precise, and accurate. It has the necessary selectivity for the analysis of PHCL and HCTZ and has been successfully validated according to the ICH guidelines [77, 79]. The method is therefore suitable for the quantitation of PHCL and HCTZ in pharmaceutical dosage forms. The method was successfully applied to the quantitation of HCTZ and PHCL in commercially available products and in dissolution rate studies, *vide infra*.

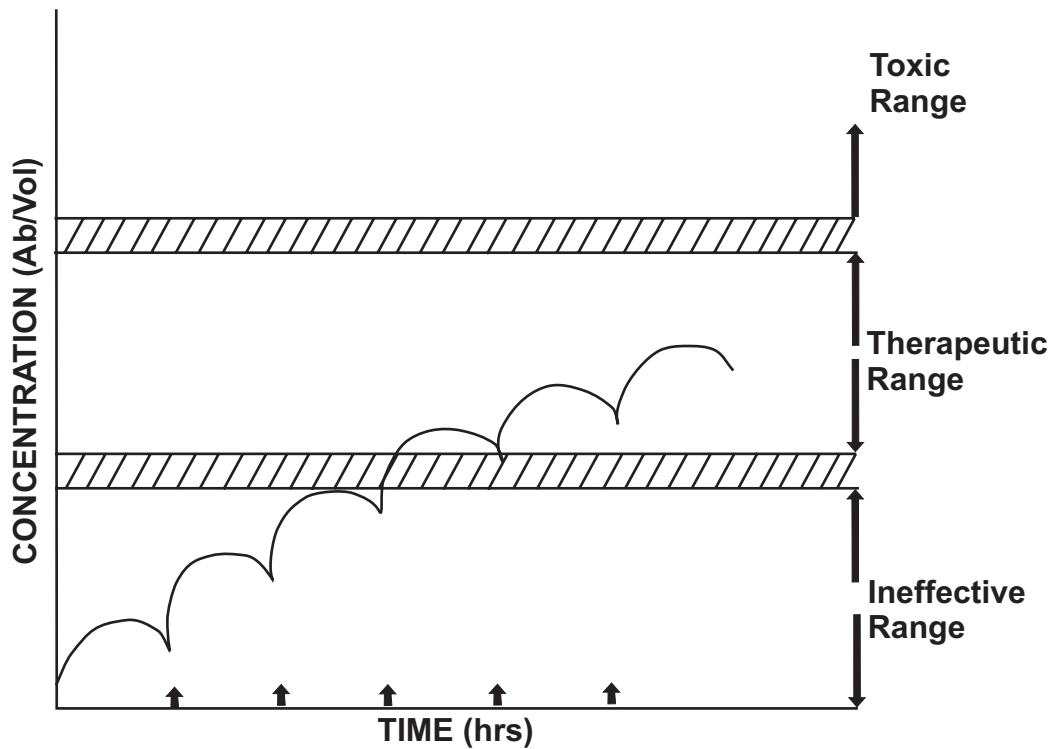
**CHAPTER 3**  
**DEVELOPMENT AND ASSESSMENT OF PROPRANOLOL**  
**HYDROCHLORIDE SUSTAINED RELEASE (PHCL SR) DOSAGE FORMS**  
**BY DIRECT COMPRESSION**

**3.1. Controlled Release Technologies**

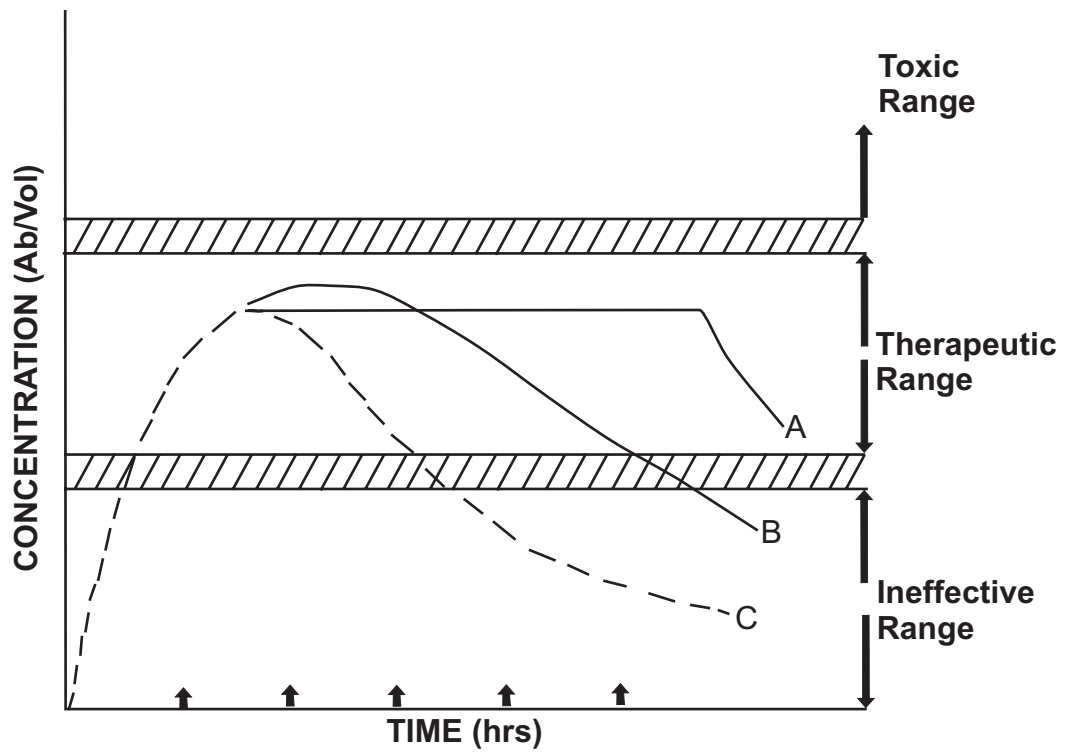
A drug substance or active pharmaceutical ingredient (API) is rarely, if ever administered alone [83] and is usually administered as a component of a drug delivery system. The delivery system is usually comprised of the API, and pharmaceutical adjuvants or excipients, which are included in the formulation to facilitate manufacturing, or perform specialized functions in the delivery system, and were different delivery systems are unique with respect to their physical and pharmaceutical characteristics [83, 84]. The goal of drug delivery systems is to deliver a specific amount of an API such that an appropriate therapeutic response is attained at the proper site in the body whilst achieving and maintaining an adequate concentration at that site of activity [84-86]. Some API's have intrinsically long half lives and are thus inherently long lasting and may only require once daily oral dosing to achieve a suitable therapeutic effect [84-87]. However the vast majorities of API's have relatively short half-lives and are thus shorter acting and require multiple daily dosing from conventional immediate release (IR) dosage forms to achieve a constant and sustained therapeutic effect [84-87].

The use of multiple dosing with IR dosage forms has several limitations, including the requirement that the patient follows a strict dosing regimen in order for optimum therapeutic benefits to be achieved [83, 85-87]. However the need to adhere rigidly to a dosing regimen often leads to non-compliance or lack of adherence by patients with the result that doses are missed thus impacting negatively on desired therapeutic outcomes [83, 85, 86]. If doses are administered too frequently minimum toxic concentrations may be reached with the result that unwanted side effects become prevalent, whereas infrequent dosing may lead to sub-therapeutic blood levels being achieved [83, 85-87]. A hypothetical blood-level-time curve obtained following the administration of a conventional IR product is depicted in Figure 3.1 [85] whereas the

blood levels that may be expected following administration of a controlled release dosage form are shown in Figure 3.2 [85]. Low patient adherence combined with the fluctuations in steady state drug concentrations following conventional IR medication administration have led to the development of sustained release dosage forms to counteract therapeutic variations [83, 85, 87].



**Figure 3.1** Hypothetical blood concentrations following multiple dosing of conventional IR dosage forms. Dosage intervals are represented by arrows.



**Figure 3.2** Hypothetical blood concentrations following administration of sustained or controlled release dosage forms. IR dosing intervals are represented by arrows for comparison. Curves A, B and C represent controlled, prolonged release and immediate release products, respectively.

The term sustained release (SR) is a broad expression that describes drug delivery in systems where the API is released in a controlled manner, at a predetermined rate, duration or location to achieve and maintain optimum therapeutic blood levels of an API [83, 85, 87, 88]. SR dosage forms include extended release (ER), delayed release (DR), repeat action (RA), controlled release (CR) and prolonged release (PR) systems [85-88].

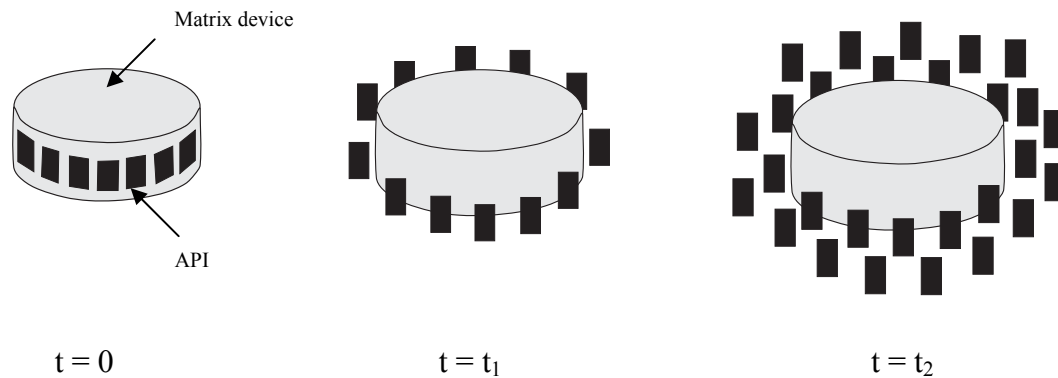
The design of SR dosage forms necessitates that several variables including the physicochemical properties of API, route of administration, type of delivery system, disease, patient and the length of the proposed therapy be considered [83, 85, 87, 89]. Drugs that are best suited for incorporation into modified release dosage forms are those that exhibit neither slow nor fast absorption or elimination rates [83, 85, 87, 89]. Potential candidates for inclusion in SR delivery systems must be uniformly absorbed along the gastro-intestinal tract and be administered in relatively small doses for chronic rather than acute conditions, and have a reasonably good margin of safety [83, 85, 87, 89].

Oral sustained release delivery systems can be separated into one of four categories *viz.*, monolithic matrix systems, reservoir or membrane-controlled systems, osmotic pump systems and ion exchange systems [83, 85-89].

### **3.1.1. Monolithic Matrix Systems**

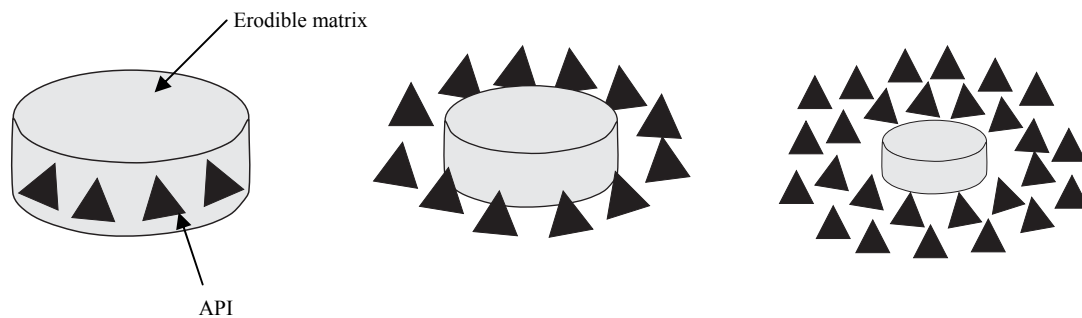
Monolithic matrix type systems can be further subdivided into two subgroups. One type of system is that in which the API is dispersed in a soluble matrix and from which the drug becomes available as the matrix swells and/or erodes following administration [83, 85-90]. The second type of system is that in which the API is dispersed in an insoluble matrix and from which the drug becomes available as solvent enters the matrix and dissolves the drug prior to its release from the device [83, 85, 87-91]. The release rates of API from these systems may be described using the Higuchi model [85-87, 89, 91-93]. The pattern of API release from these monolithic matrix systems that are not controlled by zero order release kinetics, may be clinically equivalent to a constant rate of release, for many drugs [85, 87, 89, 91,

92]. A schematic representation of drug release from these types of delivery system is depicted in Figures 3.3 and 3.4 [87].



**Figure 3.3 Drug release form conventional non-eroding SR matrix systems**

Figure 3.3 depicts drug release from a non eroding matrix dosage form. The API is initially dispersed in the matrix system, which at time  $t = 0$  has 100% drug in the dosage form. Subsequently, following administration at some time  $t = t_1$  some of the drug has been released from the matrix system and as  $t$  approaches  $t_2$  more drug has been released from the system. Drug release would continue from these systems provided there is drug present in the system.

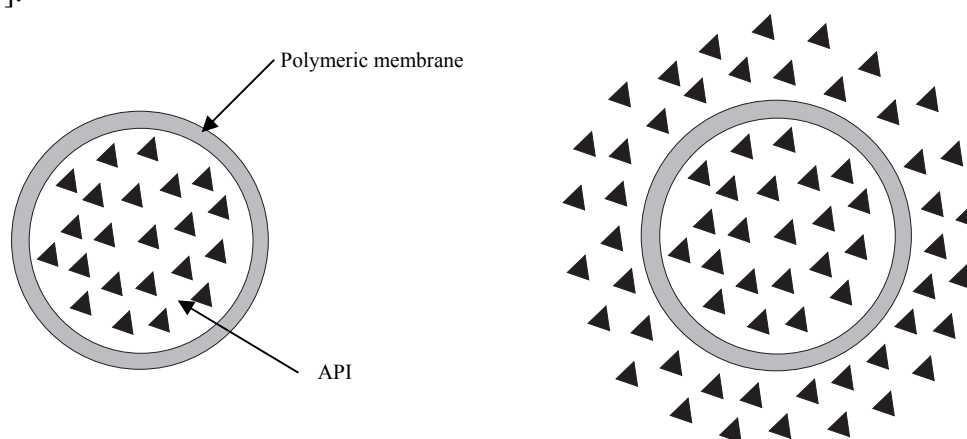


**Figure 3.4 Drug release from an eroding matrix SR matrix system**

In contrast to drug release from non-eroding systems, the release from erodible delivery systems relies on the dissolution or degradation of the polymeric material in which the drug is dispersed to achieve constant release rates as depicted in Figure 3.4.

### 3.1.2. Membrane Controlled or Reservoir Systems

Membrane-controlled or reservoir systems are manufactured with a drug reservoir in which the API is either dispersed as solid particles, or as a solution that has been encapsulated by an outer rate controlling polymeric membrane that is usually semi-permeable [85, 87, 88, 90, 94]. These systems differ slightly from matrix systems in that the membrane does not swell on hydration and does not erode with time [85, 87, 88, 94]. The rate of release of drug from these systems is primarily controlled by interfacial partitioning of the drug from the reservoir into the membrane or by matrix diffusion controlled process [85, 87, 90, 94]. A schematic representation of the drug release process from a membrane controlled delivery system is depicted in Figure 3.5 [87].

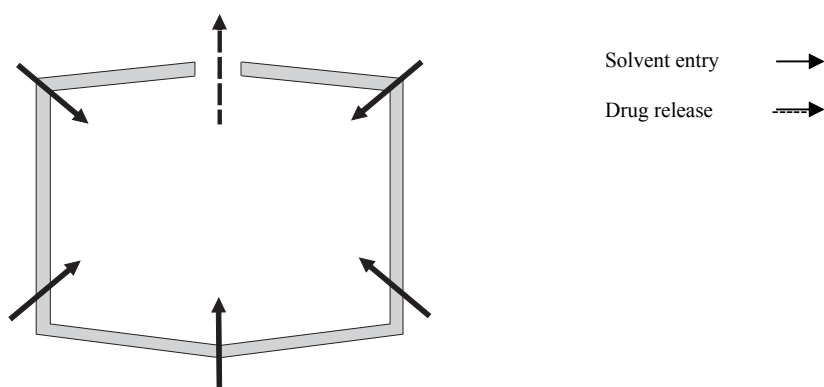


**Figure 3.5** Schematic representation of drug release from a membrane controlled sustained release delivery system.

The reservoir containing API is encapsulated with a membrane through which the drug must diffuse in order for drug release to occur. Constant rates or zero-order release from devices such as those depicted in Figure 3.5 will be achieved, provided that a constant concentration gradient is maintained across the rate controlling membrane.

### 3.1.3. Osmotic Pump Systems

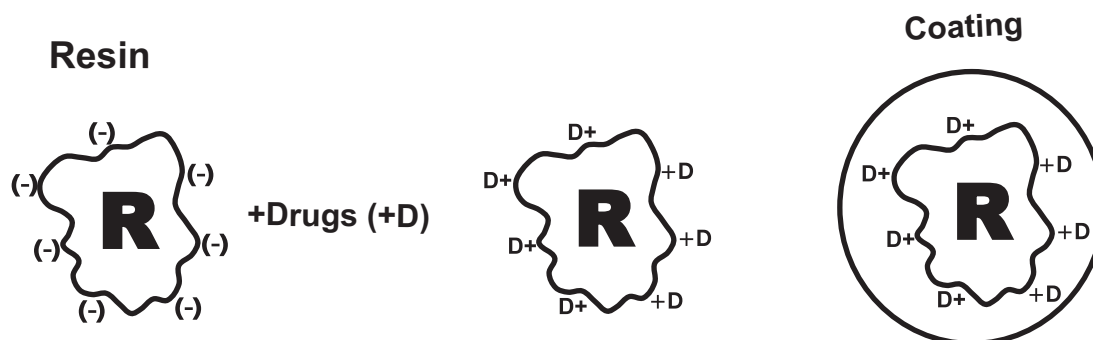
Osmotic pump systems may be considered as an alternate type of membrane-controlled systems, however the energy source that drives drug delivery from such systems is a direct result of the properties of the API or other osmotic pressure generating substance that may be included in these systems [83, 85, 87, 88, 90, 95, 96]. In osmotic pump systems the API is usually included in a water-soluble tablet core, which is subsequently coated with a semi-permeable membrane [83, 85, 87, 88, 95]. The properties of the membrane are such that only water can penetrate to the tablet core, dissolve the API or energy source and creates hydrostatic or osmotic pressure within the delivery device [83, 85, 87, 88, 90, 95, 96]. The pressure build up within the device, provides the impetus for release of API from the dosage form [83, 85, 87, 88, 90, 95, 96]. The release of drug from these systems occurs as a result of the diffusion of water into the device on the basis of an osmotic potential difference between the interior and exterior of the device and constant drug release will be achieved until the concentration of API or energy source inside the dosage form falls below saturation levels [83, 85, 87, 88, 90, 95]. A schematic representation of drug release from a simple osmotic delivery system is depicted in Figure 3.6 and shows API release through an aperture in the coating following permeation of solvent into the device [86, 87].



**Figure 3.6** Schematic representation of a simple osmotic pump SR system

### 3.1.4. Ion Exchange Sustained Release Systems

Ion exchange systems are those in which an API is bound to an ion exchange resin to form a drug-resin complex [85, 87, 88, 97, 98]. The resins that are used to form the backbone of the delivery system are water insoluble cross-linked polymers containing either cationic or anionic salt forming functional groups repeated across the polymeric chain [85, 87, 88, 97-99]. The release of an API from these dosage forms occurs by ion exchange in the gastro-intestinal tract, allowing for dissolution of drug molecules from the drug-resin complex [88, 97, 98]. The rate and extent of drug release from these systems is controlled by the cross sectional diffusional area [85, 87, 88, 97, 98], the path length for drug transport and degree of water infiltration within the resin, and the extent of cross-linking of the polymeric subunits that make up the resin [85, 87, 88, 97, 98]. A schematic of resin being applied to drug particles to form a drug resin complex is depicted in Figure 3.7 [97].



**Figure 3.7** Schematic representation of a resin applied to drug particles to form a drug resin complex.

### 3.2. Proposed Formulation Design

The objective of these studies was to design a SR delivery system for PHCL in the form of a monolithic matrix system that would permit once daily dosing in combination with an immediate release HCTZ dosage form. Furthermore, the matrix formulation was to be designed such that the *in vitro* dissolution profile for PHCL matched that of Inderal<sup>®</sup> LA 80mg capsules with a view to developing a generic multi-source medication, equivalent to the reference product. Initial formulation development studies consequently focused on the development of direct compression mini-tablets for the sustained release component of the combination product.

The rationale for the development of these dosage forms is to provide a constant or specified rate of drug delivery over a specified period of time, *e.g.* twenty four hours. Inderal<sup>®</sup> LA 80mg capsules was chosen as the reference product as it is a commonly used sustained release propranolol formulation that is widely available in South Africa.

The initial stages of this project involved the characterization of the *in-vitro* release profile of the reference product using the basket or USP Apparatus 1 and BioDis<sup>®</sup> or USP Apparatus 3 dissolution methods. Dissolution studies were conducted using a slightly modified method to that outlined in the USP for propranolol extended release products using USP Apparatus 1[6]. The experimental procedure is outline in section 3.3.

### 3.3. Experimental Procedure for Dissolution Studies

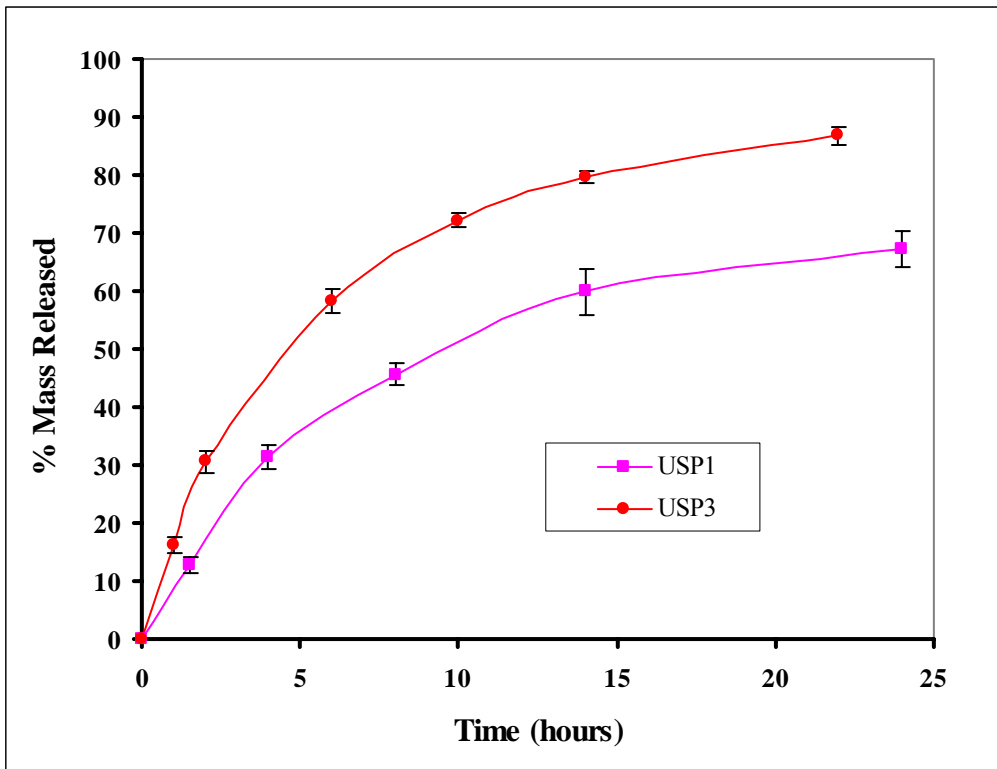
Initial dissolution test studies were performed utilizing USP 1 dissolution test apparatus (HANSON SR8PLUS equipped with AutoPlus™ Maximiser and AutoPlus™ MultitFill, Hanson Research Corp, Chatsworth, CA USA) and USP Apparatus 3 (VanKel VK Bio-Dis™ Extended Release Tester equipped with VanKel VK 750D Heater, VanKel Technology Group, Cary, NC, USA). The parameters used for the initial dissolution studies are shown in Table 3.1.

**Table 3.1**      **Dissolution test parameters**

	<b>USP1</b>	<b>USP3</b>
<b>Dissolution media</b>	0.1 M PO <sub>4</sub> buffer	0.1 M PO <sub>4</sub> buffer
<b>Media pH</b>	1.2	1.6, 3.4, 4.6, 5.4, 6.8, 7.2
<b>Media volume</b>	900 ml	150ml
<b>Speed</b>	100 rpm	20 dips/min
<b>Test length</b>	24 hours	22 hours
<b>Sampling times</b>	1.5, 4, 8, 14, 24 hours	1, 2, 6, 10, 14, 22 hours
<b>Sample volume</b>	2ml	2ml

85 % (w/v) Orthophosphoric acid (Merck Chemicals (PTY) Ltd, Wadeville, Johannesburg, South Africa), 32 % (w/v) hydrochloric acid (Merck Chemicals (PTY) Ltd, Wadeville, Johannesburg, South Africa) and sodium hydroxide pellets (Associated Chemical Enterprises, Southdale, South Africa) were used to prepare the dissolution media. Approximately 49 ml of orthophosphoric acid was added to a 5L volumetric flask and made up to volume with HPLC grade water. The pH was adjusted using either hydrochloric acid to lower the pH to 1.2 for use with USP Apparatus 1, or sodium hydroxide to increase the pH of the dissolution media for use with USP Apparatus 3.

The cumulative percentage mass release data were obtained by subjecting dissolution samples quantified using a validated HPLC method as described in chapter 2 *vide infra*. The resultant dissolution profile on Inderal® LA 80mg capsules are shown below in Figure 3.8.



**Figure 3.8** Dissolution profile for Inderal<sup>®</sup> LA 80mg capsules (n=6) using USP Apparatus 1 and 3

Following an evaluation of the resultant data, USP Apparatus 1 was chosen as the preferred dissolution test method for all future *in-vitro* release rate studies as this method is outlined in the USP [6] for testing of propranolol extended release products.

### **3.4. Materials used for the Manufacture of Direct Compression (DC) Products**

#### **3.4.1. Propranolol hydrochloride**

The PHCL (Batch no. PHC 204) that was used to formulate and manufacture SR products was purchased from Kothari Phytochemicals Inc. (Nagari, India). Preformulation, physicochemical and pharmacological information pertaining to this compound have been reported in Chapter 1.

#### **3.4.2. Hydrochlorothiazide**

Hydrochlorothiazide (Lot no. RV24189), the second drug candidate to be included in a combination product as the immediate release component of the intended combination dosage form was obtained from MSD (PTY) Ltd. (Johannesburg, South Africa). Preformulation, physicochemical and pharmacological information pertaining to this compound have been reported in Chapter 1.

#### **3.4.3. Methocel<sup>®</sup> K4M, Methocel<sup>®</sup> K100M, Methocel<sup>®</sup> K100 LV EP**

Methocel<sup>®</sup> (Colorcon Ltd, Orpington, Kent, UK) is the propriety name for the methylcellulose derivative that is also known as hypromellose or hydroxypropyl methylcellulose (HPMC). It has the chemical name cellulose, 2-hydroxypropyl methyl ether and a CAS registry number 90004-65-3. HPMC is an odourless, tasteless white or creamy-white fibrous or granular powder that is widely used in solid oral products and is primarily used as a tablet binder, as a film coating or as the release-controlling matrix of extended release dosage forms. There are different viscosity grades of HPMC available with the higher viscosity grades being used in varying concentrations of 10-80 % w/w, in order to retard drug release from tablet and capsule dosage forms. HPMC is a GRAS (Generally Regarded As Safe) listed compound that is non-toxic and non-irritant, but ingestion of large quantities may lead to a laxative effect. HPMC is stable and becomes hygroscopic on drying. Aqueous solutions of HPMC are stable at in a pH range of 3-11 and are generally enzyme-resistant, but are vulnerable to microbial spoilage. HPMC is non-ionic and therefore does not complex with ionic

organic agents or metallic salts but has been reported to be incompatible with a few oxidizing agents [100].

#### **3.4.4. Emcompress<sup>®</sup>**

Emcompress<sup>®</sup> (Penwest, Patterson NJ, USA) is the propriety name for dibasic calcium phosphate. It has the chemical name dibasic calcium phosphate dehydrate and a CAS registry number of 7789-77-7. Dibasic calcium phosphate is an odourless, white tasteless powder that is widely used in solid oral products as a diluent, or as a source of calcium in nutritional supplements. There are different particle size grades of dibasic calcium phosphate available, with the course grade normally being used for direct compression tableting. The fine grade material is preferred for inclusion in wet granulation formulations and manufacturing processes. Dibasic calcium phosphate is a GRAS listed compound that is generally regarded as non-toxic and non-irritant, but ingestion of large quantities may lead to abdominal discomfort. Dibasic calcium phosphate is a stable non-hygroscopic material and should not be used with drugs that are sensitive to alkaline pH. It is generally incompatible with drugs such as indomethacin, aspirin, aspartame, ampicillin, cephalexin and erythromycin [100].

#### **3.4.5. Emcocel<sup>®</sup> 90M**

Emcocel<sup>®</sup> (Penwest, Patterson NJ, USA) is the propriety name for microcrystalline cellulose (MCC). It has the chemical name cellulose and a CAS registry number of 9004-34-6. MCC is an odourless, tasteless crystalline white crystalline powder made up of porous particles that is primarily used as a binder or diluent in oral tablet and capsule formulations. It also possesses lubricant and disintegrant properties, which are of particular use in immediate release tablet formulations. MCC is a GRAS listed compound that is regarded as non-toxic and non-irritant, but large quantities may have a laxative effect. Microcrystalline cellulose is a stable hygroscopic material that is incompatible with strong oxidizing agents [100].

### **3.4.6. Eudragit<sup>®</sup> L100-55, Eudragit<sup>®</sup> L100, Eudragit<sup>®</sup> RS PO**

Eudragit<sup>®</sup> (Röhm Pharma, Darmstadt, Germany) is the propriety name given to a range of polymethacrylate or methacrylic acid copolymers. Eudragit<sup>®</sup> L100, Eudragit<sup>®</sup> L100-55 and Eudragit<sup>®</sup> RS PO have the chemical names of poly (methacrylic acid, methyl methacrylate) 1:1, poly (methacrylic acid, ethyl acrylate) 1:1 and poly (ethyl acrylate, methyl methacrylate, triethylaminoethyl methacrylate chloride) 1:2:0:1 with CAS registry numbers of 25806-15-1, 25212-88-8, 33434-24-1, respectively. Eudragit<sup>®</sup> L-100 is a free flowing white powder with at least 95 % w/w of dry polymer. Eudragit<sup>®</sup> L100-55 is also a fine white powder that is free flowing, and, Eudragit<sup>®</sup> RS PO is a fine white powder with an amine like odour that is comprised of 97% w/w of dry polymer. The polymethacrylates are primarily used as film coating materials, tablet binders or as tablet diluents. The type of film that is formed and subsequent properties associated with the film coat is dependent on the type of polymethacrylate polymer used for the coat. The Eudragit<sup>®</sup> polymers are listed in the FDA inactive ingredients guide [101]. They are generally regarded as non-toxic and non-irritant materials. In the dry powder form, Eudragit<sup>®</sup> polymers are stable at temperature below 30° C, however, some incompatibilities amongst the Eudragit<sup>®</sup> latex dispersions may occur, depending on the ionic properties of the polymer in the dispersion and the solvent used as the vehicle in the dispersion. Incompatibilities may be due to a pH change, the presence of soluble electrolytes or organic solvents and is manifested by clumping of certain types of polymethacrylates [100].

### **3.4.7. Ethocel<sup>®</sup> FP 10cp**

Ethocel<sup>®</sup> (Dow Chemical Company, Midland, Michigan, USA) is the propriety name for ethyl cellulose. It has the chemical name cellulose ethyl ether and a CAS registry number of 9004-57-3. Ethyl cellulose is a white to light tan coloured powder which is free flowing and tasteless. The main use of ethylcellulose in solid oral formulations is as a functional hydrophobic film coating for tablets and granules, to modify the release of a drug from the resultant dosage form. Ethyl cellulose can also be used to mask unpleasant tastes or in increase the stability of a dosage forms, for example, coating granule to minimize oxidation. Ethyl cellulose can be applied from solvent mixture to produce water-insoluble films, or in combination with plasticizers or

HPMC where the solubility of a film coat may need modification. Ethyl cellulose is a GRAS listed compound and is regarded as a non-toxic, non irritant and non-allergenic, but parenteral use may be harmful to the kidneys. Ethyl cellulose is a stable slightly hygroscopic material, which may be subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. It is incompatible with paraffin and microcrystalline wax. [100].

#### **3.4.8. Ac-di-sol<sup>®</sup>**

Ac-di-sol<sup>®</sup> (FMC, Philadelphia, Pennsylvania, USA) is the propriety name for croscarmellose sodium. It has the chemical name cellulose, carboxymethyl ether, sodium salt, crosslinked and has a CAS registry number of 74811-65-7.

Croscarmellose sodium is a white or greyish white powder that is used mainly as a disintegrant for tablet and capsule dosage forms in concentrations of between 2-5 % w/w for tablets manufactured by direct compression and between 10-25 % w/w for capsule dosage forms. Croscarmellose sodium is listed in the FDA inactive ingredients guide [101], and is generally regarded as non-toxic and non-irritant, however ingestion of large amounts may cause a laxative effect. Croscarmellose sodium is a stable hygroscopic material that is not compatible with strong acids or with soluble salts of iron and other metals which include aluminium, mercury and zinc [100].

#### **3.4.9. Talc**

Talc was obtained from Aspen Pharmacare, Port Elizabeth, SA and has a CAS registry number of 14807-96-6. Talc is an odourless fine white to grayish white impalpable crystalline powder. Talc is used in solid oral dosage forms as a lubricant and/or a diluent and it has been used as a dissolution retardant, which is of value in extended release products. Talc is included in the FDA inactive ingredients guide [101]. Talc is generally regarded as non-toxic, however, intravenous or intranasal use of talc may lead to the formation of granulomas, whilst inhalation of talc may cause respiratory distress in infants. Talc is a naturally occurring material that is stable, but may contain micro-organisms and may be incompatible with quaternary ammonium compounds [100].

### **3.4.10. Magnesium Stearate**

Magnesium stearate was obtained from Aspen Pharmacare, Port Elizabeth, SA and is the non-propriety name for the chemical compound octadecanoic acid magnesium salt that has a CAS registry number of 557-04-0. Magnesium stearate is a fine, impalpable white powder with a faint odour of stearic acid and a characteristic metallic taste.

Magnesium stearate is widely used, in tablet and capsule formulations as a lubricant at concentrations varying between 0.25 and 5.0 % w/w. Magnesium stearate is a GRAS listed compound, and is generally regarded as being non toxic, however consumption of large quantities orally, may lead to a laxative effect or mucosal irritation.

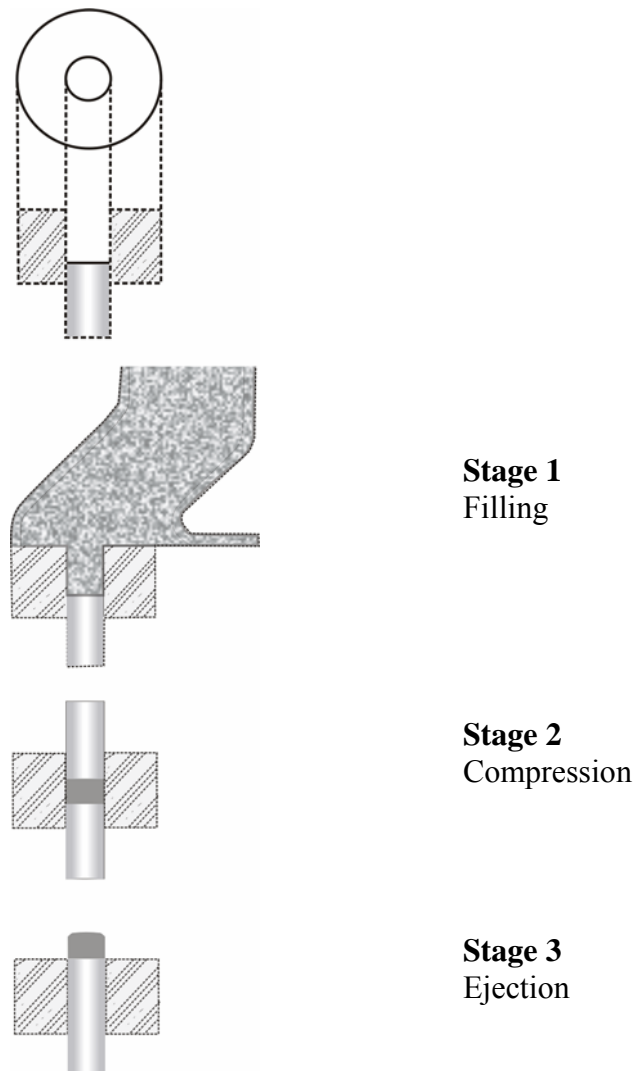
Magnesium stearate is a stable compound that is incompatible with strong acids, alkalis and iron salts. It cannot be used in products that contain aspirin, certain vitamins and a majority of alkaloidal salts [100].

### **3.5. Manufacture of SR PHCL Dosage Forms by Direct Compression**

#### **3.5.1. Introduction**

Compressed tablets are the most widely used dosage forms available and account for approximately 80 percent of all dosage forms currently available and administered to patients worldwide [102, 103]. Tablets are versatile drug delivery devices that are convenient, relatively easy to manufacture and use [83, 85, 103]. In addition, tablets possess relatively good stability properties compared to that of other pharmaceutical dosage forms such as solutions or suspensions [102]. The manufacture of tablets is often viewed as being a simple and easy process. However, this is a paradox as the design and art of tableting is an exact science that requires a wealth of expertise to turn a mass of powder or powdered particles into a low porosity dosage form, which is easy and convenient to manufacture for use by the end user [102, 103].

The process of tableting involves three basic steps, *viz.*, die filling, compression and the ejection and the process is depicted in Figure 3.9 [87, 104-106].



**Figure 3.9** A schematic representation of the powder compaction process using a single punch press

The initial stage of a tableting process involves filling of a die cavity with powder or particulate matter, that flows readily into the cavity by gravitational forces from a feed hopper [87, 103, 105, 106]. Modern tablet presses use either forced or induction feeders to ensure adequate filling of a die cavity occurs during high speed tablet manufacture. The filling stage of the process is a volumetric in nature, whereby the volume of material allowed to flow into the die cavity depends on the depth to which the lower punches are set [87, 102-104]. The filling process results in some variability in the amount of material that flows into the die cavity and is thus not completely reproducible [87, 103, 104]. Consequently it is critical that the materials to be compressed have adequate flow properties [87, 103-106] to ensure uniform tablets are produced during the compression process [87, 103-106].

The second stage of the tableting process, involves the compression of the powders in the die cavity [87, 102-106]. The upper punch descends and confines the particulate matter to the die cavity, between the upper and lower punches [87, 102-106]. The powder particles fragment or deform, whilst forcing the individual units of the blend together such that interparticulate forces dominate and aggregation of the materials occur to form a compressed tablet [87, 102, 103, 107].

The final stage of a compression process is ejection of the compressed tablet from the die cavity. The applied compaction force is removed as the upper punch is withdrawn from the die cavity [87, 102-106]. As the upper punch is withdrawn, the lower punch is raised and the compact powder or table is forced out of the die cavity [87, 102-106]. The compression cycle then is repeated in order to produce the next tablet. The fundamentals and principles of operation of a single punch press and tablet compaction as depicted in Figure 3.9 are similar to those that are used when multi-station rotary presses are used to produce tablets; however, the machinery and mechanics of operation are different.

There is a tremendous amount of friction generated during the second and third stages of a compression cycle [103, 106], and these are primarily located at the edges of tablet and the die wall of the die cavity [103, 106]. Therefore anti-frictional agents must be incorporated into a formulation to ensure proper compaction and ejection of tablets from the die cavity [103-106].

The successful manufacture of tablets is dependent on achieving an appropriate balance of brittle fracture and plastic behavior within a formulation mix [102, 102, 108, 109], which in turn are dependant on the compression characteristics of the API and the excipients that are blended together in that particular formulation to produce a uniform and acceptable dosage form [102, 103, 107-109].

There are three methods that can be used for the production of tablets, *viz.*, direct compression (DC) and compression following wet granulation (WG) or dry granulation. The initial dosage forms produced in these studies were manufactured using DC technologies and subsequently WG manufacturing procedures were used in an attempt to produce PHCL SR dosage forms with *in-vitro* release rate profiles similar to that of Inderal<sup>®</sup> LA Capsules

### **3.5.2. Direct Compression Tableting**

The term DC refers to a process whereby tablets are compressed or compacted directly from powder blends that contain the API and adjuvants which flow uniformly into a die cavity, and can be formed into a firm compact without additional manipulation [83, 87, 110, 111]. There is no granulation process as is used wet or dry granulation manufacturing methods [83, 87, 110, 111]. DC is often viewed as being easier to perform than wet or dry granulation manufacturing procedures, which may in part be true, as the technique involves fewer unit operations [83, 87, 110, 111]. However, it is the inherent simplicity of the DC process that may lead to formulation failure if the critical aspects of compressibility and flowability of the materials of a formulation are not seriously considered [83, 87, 110, 111]. As with any process DC has advantages and disadvantages of which some are listed in Table 3.2 [83, 87, 102, 110-112]. These advantages include fewer unit operations and utilization of a smaller number of excipients; however particle segregation of the powder material may occur [110-112].

**Table 3.2 Advantages and disadvantages of DC as compared to WG**

<b>Advantages</b>	<b>Disadvantages</b>
Fewer unit operations	Particle segregation
Anhydrous process	API content may be limiting
No drying procedures	Unsuitable for poor flowing API compounds
Faster dissolution rates may be achieved	when high API content
Fewer excipients may be required	Static charges on drug particles may lead to poor
Economy	mixing
	Not applicable to low bulk density materials

### **3.5.3. Formulation Development for Direct compression Tableting**

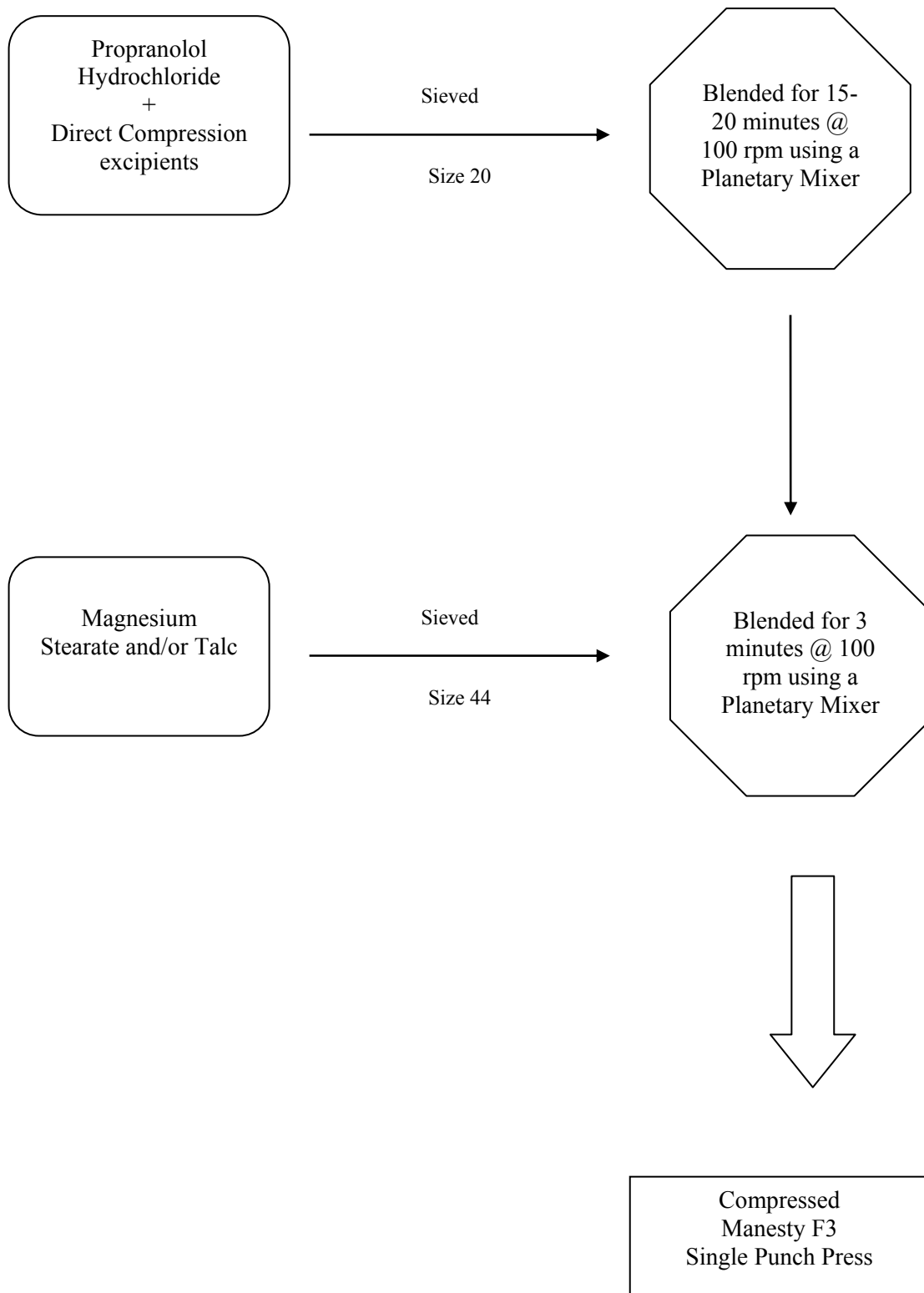
The DC method of tablet manufacture was chosen for initial formulation development studies, due to the apparent ease and simplicity of manufacturing process for the production of these dosage forms [101, 111]. The relevant formulation compositions for these products are listed in Table 3.3.

**Table 3.3 Formulation compositions of DC tablets**

<b>Materials</b>	<b>PC001</b>	<b>PC002</b>	<b>PC003</b>	<b>PC004</b>	<b>PC005</b>	<b>PC006</b>	<b>PC007</b>	<b>PC008</b>	<b>PC009</b>	<b>PC010</b>
<b>PHCL</b>	13.5	13.5	13.5	13.5	30	40	40	40	40	30
<b>Methocel<sup>®</sup> K4M</b>	6.8	4.6	11.8	9.6			30		30	
<b>Methocel<sup>®</sup> K100M</b>	14	14	14	14	40	30		30		35
<b>Eudragit<sup>®</sup> L100-55</b>						7	7			15
<b>Eudragit<sup>®</sup> RS PO</b>								7	7	
<b>Ethocel<sup>®</sup> fp 10cp</b>	2.8	5	2.8	5						
<b>Emcocel<sup>®</sup></b>	26.9	26.9	26.9	26.9	12	19	19	19	19	19
<b>Emcompress<sup>®</sup></b>	32.3	32.3	27.3	27.3	15					
<b>Ac-di-sol<sup>®</sup></b>						3	3	3	3	
<b>Talc</b>	3	3	3	3	2					
<b>Magnesium Stearate</b>	0.7	0.7	0.7	0.7	1	1	1	1	1	1

The focus of the development project was to design and develop a SR dosage form that delivers the API in a temporal or time delayed release pattern rather than as a site specific or site directed formulation.

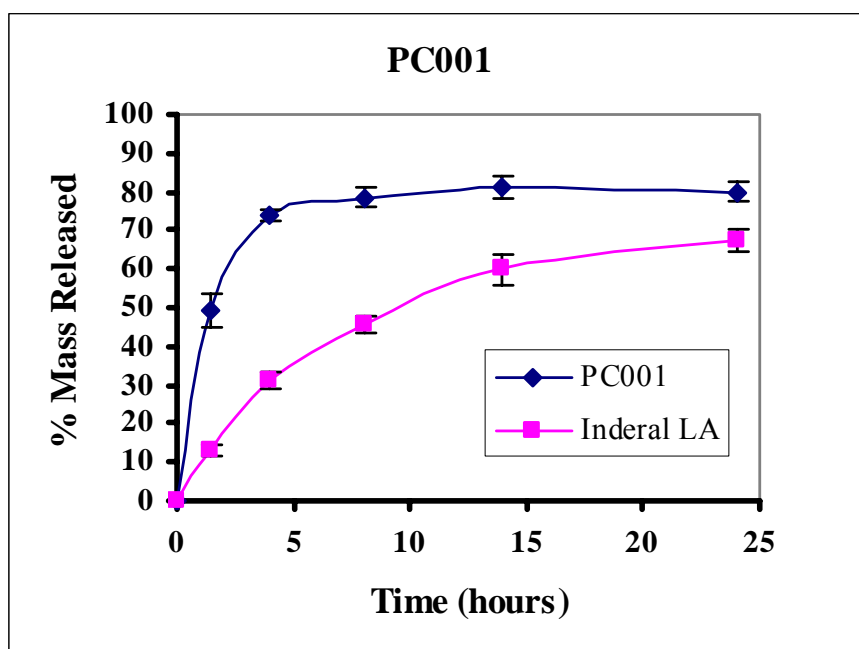
The initial formulation, batch PC001 was manufactured using DC tableting technology and was based on the formulation and production process used for the manufacture of sustained release dosage forms for five different  $\beta$ -blocking drugs, *viz.*, acebutolol, labetalol, metoprolol, oxprenolol and propranolol [113]. A schematic representation of the production process is illustrated in a flow diagram format in Figure 3.10 and the batch production record and batch production summary are included in Appendices I and II for reference.



**Figure 3.10** Flow diagram of the DC manufacturing process for batch PC001

Cellulose derivatives such as HPMC [114-117], and EC [118- 120] have been reported to be useful excipients for the manufacture of rate controlled drug delivery dosage forms for PHCL. The prototype formulation, batch PC001, contained both EC FP 10cp (Dow Chemical Company, Midland, Michigan, USA) and two different viscosity grades of HPMC, *viz.*, Methocel<sup>®</sup> K4M and Methocel<sup>®</sup> K100M (Colorcon Ltd, Orpington, Kent, UK). PHCL was included at an initial drug load of 13.5 % w/w equivalent to a 20 mg dose of the API per tablet. The resultant *in-vitro* dissolution profile obtained for these dosage forms is shown in Figure 3.11.

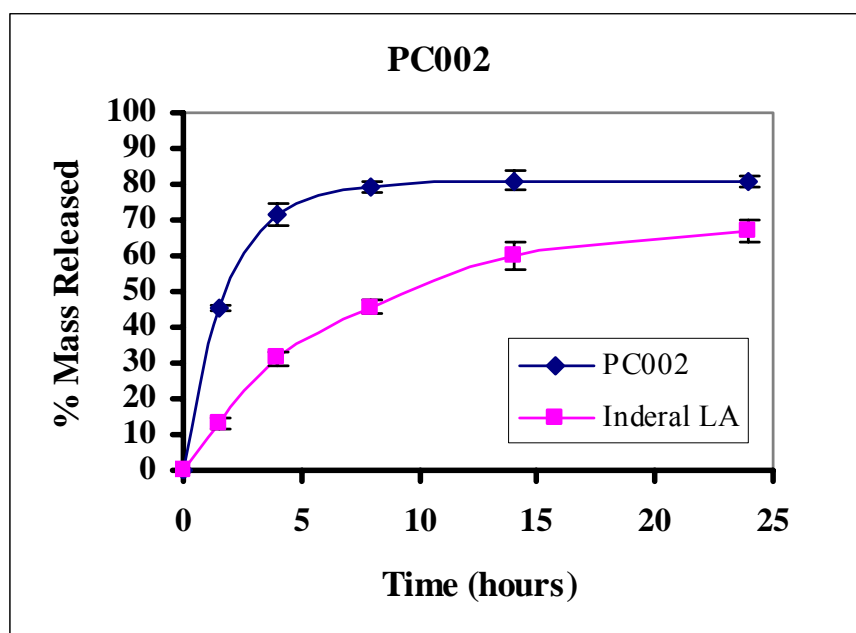
**Figure 3.11** Dissolution profile for DC tablets (batch PC001) (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1



The resultant dissolution profile of the prototype showed a slight SR effect but was not comparable to that of the innovator product, based on the  $f_1$  and  $f_2$  difference and similarity factors that were used to compare dissolution profiles over the 24-hour test period. The values for  $f_1$  and  $f_2$  were 67.15 and 25.36, respectively. The merits of using the fit factors are discussed in Chapter 5 *vide infra*. However, for two curves to be considered equivalent the values for  $f_1$  and  $f_2$  should be  $<15$  or  $> 50$  respectively. The prototype formulation required further modification in order to slow the rate of release of PHCL from these tablets. The formulation for batch PC002 that was

subsequently manufactured had a reduced quantity of talc and an increased amount of the high viscosity grade HPMC, viz., Methocel<sup>®</sup> K100M, and EC, viz., Ethocel<sup>®</sup> FP 10 cp, whilst maintaining the drug load of PHCL at a 13.5% w/w level. The resultant dissolution profile for batch PC002 is depicted in Figure 3.12.

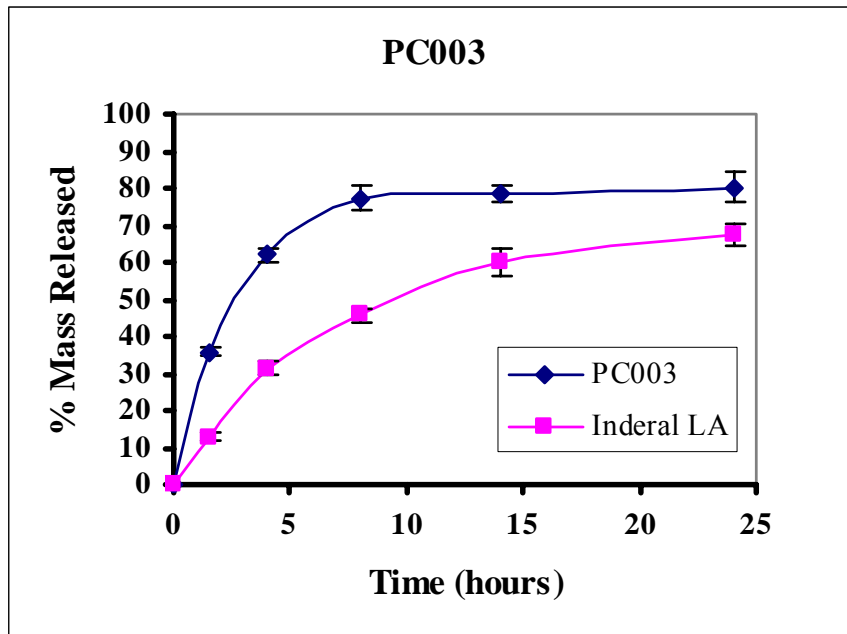
**Figure 3.12** Dissolution profiles for DC tablets (batch PC002) (n=4) and Inderal<sup>®</sup> LA capsules (n=6) using USP apparatus 1



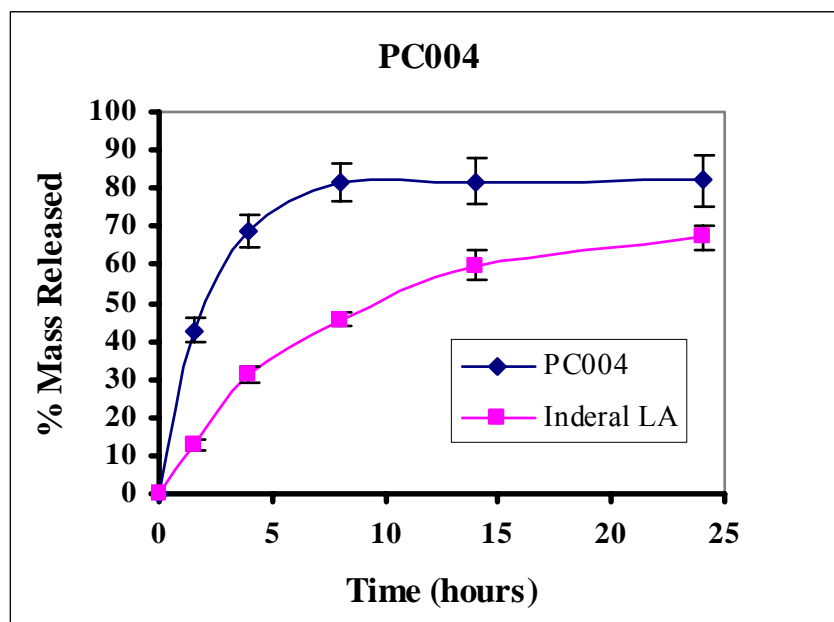
The *in-vitro* dissolution rate profile of batch PC002 revealed that despite a slightly better sustained release profile for PHCL than that obtained for batch PC001 the rate of release was significantly faster than that obtained for the reference product, and the resultant *f1* and *f2* values for the comparison were 64.78 and 26.35, respectively, indicating that the two curves were not similar. Once again, further developmental changes were necessary to achieve the desired sustained release profile. Batches PC003 and PC004 were therefore produced. The composition for these batches were modified to reduce the amount of directly compressible diluents by 5 % w/w and to increase the Methocel<sup>®</sup> K4M content to 11.8 % w/w. The Methocel<sup>®</sup> K100M content was retained at a 14 % w/w level in batches PC003 and PC004. The Ethocel<sup>®</sup> FP 10cp content was reduced to 2.8 % w/w for batch PC003 and 5 % w/w for batch PC004. The rationale for these changes was to increase the hydrophilic polymer content to further to ascertain whether further rate retardant effects are achieved. The resultant

dissolution profiles following testing using USP apparatus 1 are depicted in Figures 3.13 and 3.14 for batches PC003 and PC004, respectively.

**Figure 3.13** Dissolution profile obtained for batch PC003 (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1

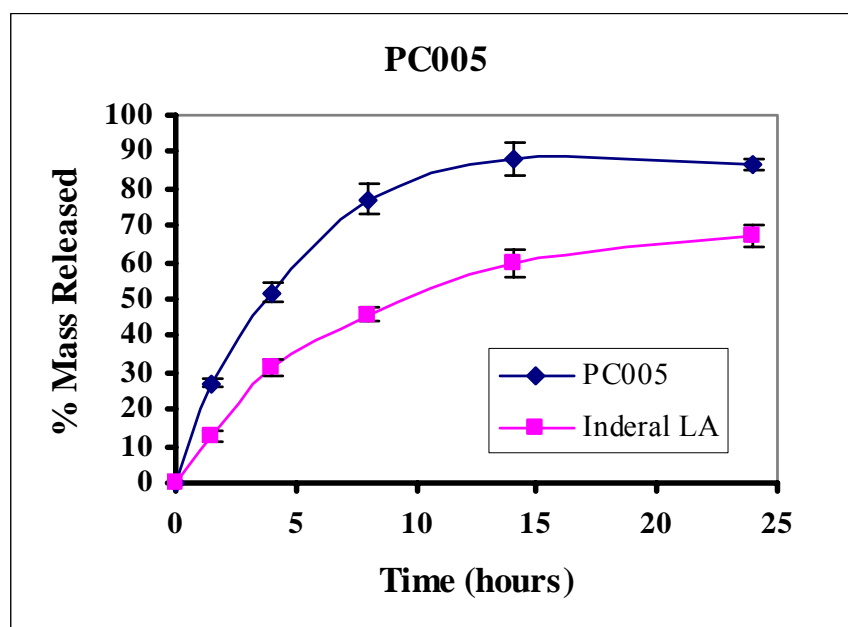


**Figure 3.14** Dissolution profile obtained for batch PC004 (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1



The dissolution profiles depicted in Figures 3.13 and 3.14 respectively reveal that the release rate of PHCL is too rapid from these prototype formulations, as compared to that obtained for the Inderal<sup>®</sup> LA capsules. Consequently, the formulation was further modified in attempt to slow the rate and extent PHCL dissolution further. The formulation was further modified such that the content of Methocel<sup>®</sup> K100M was again increased to 40 % w/w in an attempt to retard drug release even further, and with only HPMC K100M employed as the rate retarding agent in batch PC005. The dissolution rate profile generated for batch PC005 is depicted in Figure 3.15.

**Figure 3.15** Dissolution profile obtained for batch PC005 (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1



The dramatic increase in HPMC content in the formulation composition of batch PC005 appeared to slow the rate and extent of PHCL release to some degree and this effect was more than likely the result of the substantially increased content of the high viscosity grade of HPMC in the tablet formula. However, despite this improvement, the rate and extent of PHCL release was not comparable to that of the reference product and thus a different approach to the modification of the formulation was attempted in an effort to further reduce the release rate PHCL from these dosage forms.

### 3.5.4. Influence of changing the Rate Retarding Agents in DC formulations

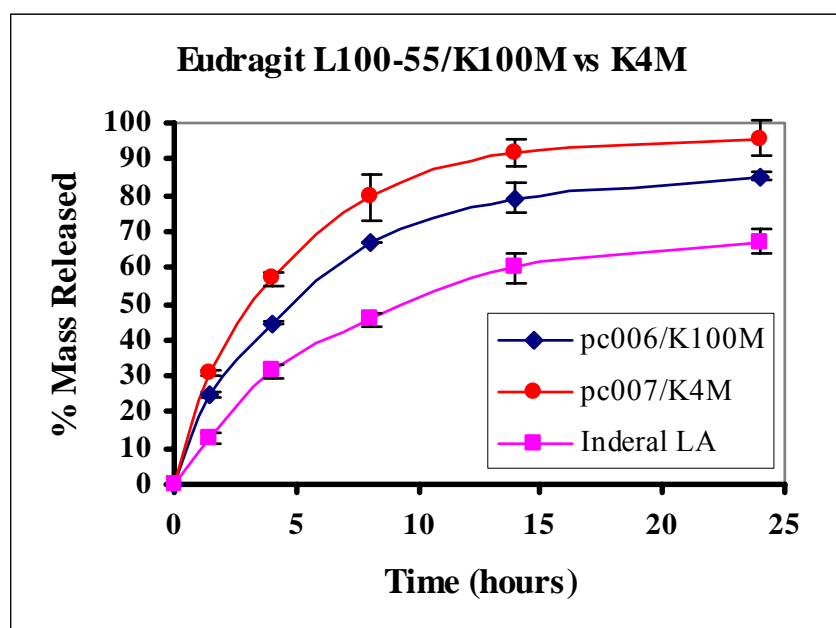
A new approach to reducing the rate of release of PHCL from DC tablet formulations was attempted and involved changing the rate retarding agent combinations used in batches PC001-PC005 and substituting alternate potential rate retarding polymers in their place. The use of HMPC and EC as a combination rate-retarding polymer was replaced with HPMC and polymethacrylate combinations. Consequently Eudragit<sup>®</sup> L100-55 and Eudragit<sup>®</sup> RS PO (Röhm Pharma, Darmstadt Germany) powders were incorporated into formulations for the manufacture of direct compression dosage forms. Formulation development experiments involved the addition of different grades of Eudragit<sup>®</sup> in combination with two different viscosity grades of HMPC, *viz.*, Methocel<sup>®</sup> K100M and K4M. Different amounts of Methocel<sup>®</sup> K4M or K100M were used in combination with either Eudragit<sup>®</sup> L100-55 or Eudragit<sup>®</sup> RS PO, respectively.

The polymethacrylates and/or methacrylic acid co-polymers are often used for the development of site-specific drug delivery systems and were used to facilitate a temporal effect rather than site specific effects on drug delivery profiles. The modifications to the formulation were made in an attempt to further retard drug release rates so as to match the release profile for PHCL that is obtained when Inderal<sup>®</sup> LA capsules were subjected to dissolution testing [121-123]. In addition croscarmellose sodium was also incorporated into the formulations in an attempt to further retard drug release, as there have been reports of cross-linking interactions between cellulose derivatives and PHCL [116, 121-124]. Furthermore the swelling capabilities of the superdisintegrant [125-128] may add to the rate retarding capabilities of the excipient combinations.

The subsequent release rate profiles for these dosage forms are depicted in Figures 3.16 – 3.19, and reveal that Methocel<sup>®</sup> K100M retards the release of PHCL better than Methocel<sup>®</sup> K4M (Figure 3.16) and that Eudragit<sup>®</sup> L100-55 is marginally better than Eudragit<sup>®</sup> RS PO when considering its rate retarding capabilities as seen in Figures 3.18 and 3.19 respectively. In addition, it was found that the best combination of HPMC and polymethacrylate for slowing the release rates of PHCL is Methocel<sup>®</sup> K100M and Eudragit<sup>®</sup> L100-55 as depicted in Figure 3.18. The relevant composite

formula for these batches are shown in Table 3.3 and the resultant  $f_1$  and  $f_2$  values for these products are shown in Table 3.4 *vide infra*.

**Figure 3.16** Dissolution profile for batch PC006 (n=4), PC007 (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1



The *in-vitro* dissolution profiles of batches PC006 and PC007 (Figure 3.16) reveal that batch PC006 demonstrates better rate retarding capabilities of PHCL when compared to batch PC007. These batches vary only in the type of HPMC polymer used where Methocel<sup>®</sup> K100M was employed for PC006 and Methocel<sup>®</sup> K4M was utilized for PC007. These products although having a SR effect cannot be favorably compared to the innovator product as demonstrated by the  $f_1$  and  $f_2$  values shown in Table 3.4. These results are moderately similar to the *in-vitro* dissolution profiles shown by batches PC008 and PC009 based on the  $f_1$  and  $f_2$  values, where the Eudragit polymer utilized was changed from Eudragit<sup>®</sup> L100-55 to Eudragit<sup>®</sup> RS PO, whilst varying the HPMC polymer, Methocel<sup>®</sup> K100M and Methocel<sup>®</sup> K4M for batches PC008 and PC009 respectively.

Figure 3.17 Dissolution profile for batch PC008 (n=4), PC009 (n=4) and Inderal® LA (n=6) using USP apparatus

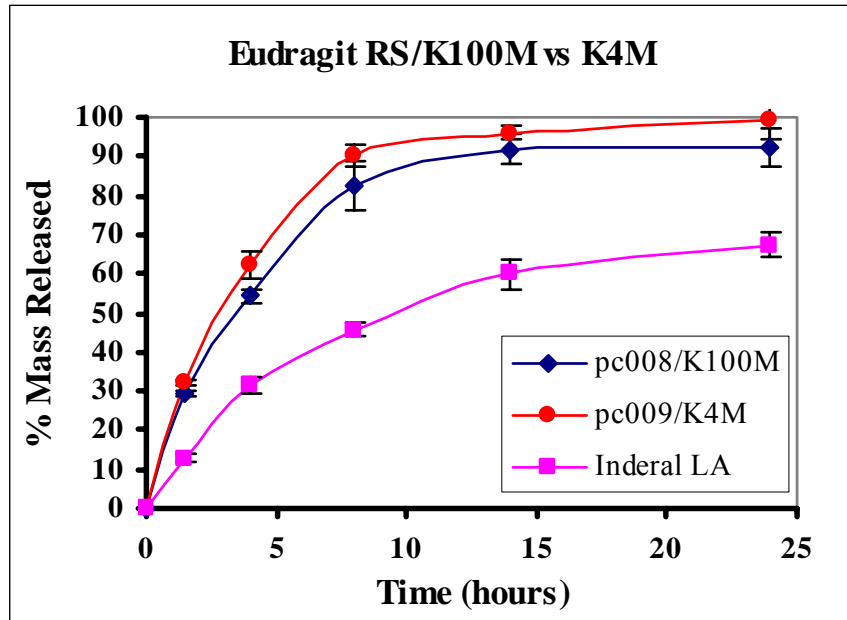
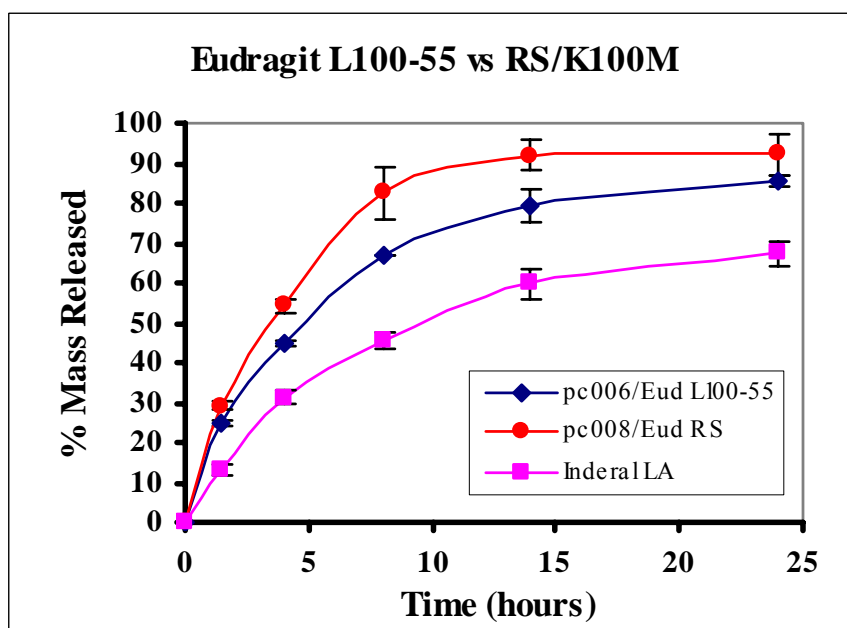
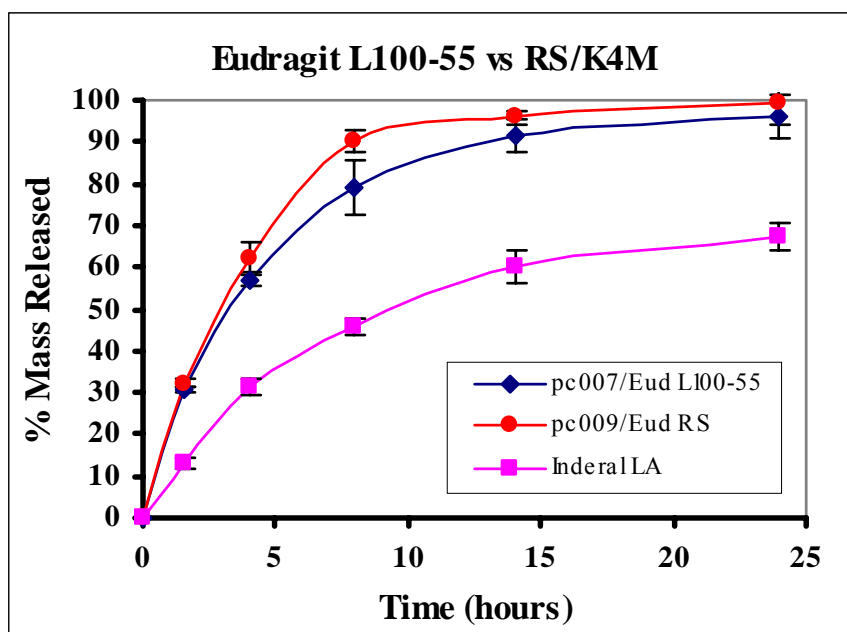


Figure 3.18 Dissolution profile for batch PC006 (n=4), PC008 (n=4) and Inderal® LA (n=6) using USP apparatus 1



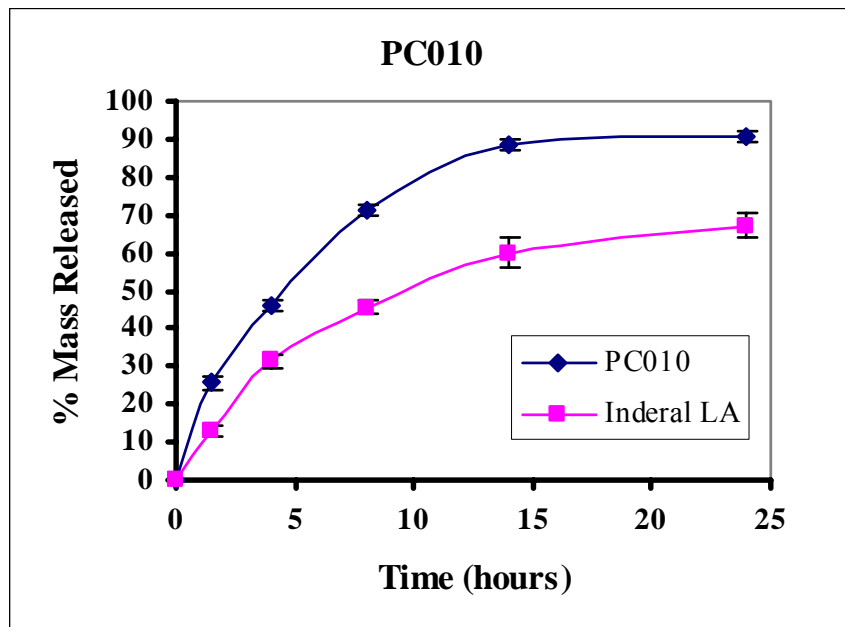
**Figure 3.19** Dissolution profile for batch PC007 (n=4), PC009 (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1



The results from these investigations as to which combination of polymers yield the best rate retardant effect were then used to manufacture batch PC010 that comprised of formulation composition as described in Table 3.3. The resultant dissolution profile is shown in Figure 3.20.

There are reports in the literature that reveal that Eudragit L100-55 is sensitive to changes in pH [122, 232], in contrast to Eudragit RS which is sensitive to type of counterion present in the dissolution media [233]. The effect of these factors on drug release rates from these dosage forms was thought to be negligible as the composition of the dissolution media and pH were kept constant for the aforementioned formulations during *in-vitro* testing.

**Figure 3.20** Dissolution profile obtained for batch PC005 (n=4) and Inderal® LA (n=6) using USP apparatus 1



The results reveal that batch PC010 whilst demonstrating a sustained release effect also showed drug release that occurs to rapidly even when using the combination of polymers. The decrease in drug load seem to have a marginal effect as demonstrated by the  $f_1$  and  $f_2$  at time 24 hours ( $t_{24}$ ), shown in Table 3.4.

**Table 3.4**  $f_1$  and  $f_2$  values for the DC matrix products

Formulation name	$f_1$	$f_2$
PC001	67.15	25.36
PC002	64.78	26.35
PC003	54.06	30.50
PC004	64.43	26.68
PC005	52.25	31.41
PC006	38.52	38.29
PC007	63.27	27.60
PC008	61.38	27.96
PC009	74.90	23.72
PC010	48.41	32.92

## **3.6. Physical Assessment of Dosage Forms**

### **3.6.1. Introduction**

Solid oral dosage forms account for more than eighty percent of the medication consumed by patients [102], and the assurance of quality, safety and efficacy of the dosage forms on the market is controlled and/or monitored by Regulatory authorities some of which, such as the Medicines Control Council in South Africa, have been established by statutes.

Guidance documents such as the FDA draft guidance for powder blends and finished dosage units [129], or the draft guidance for drug products [130] and the SUPAC-MR guidance document on modified release solid oral dosage forms [131] provide useful information and advice. Whilst these guidance documents do not guarantee that safe and effective products will be produced, they provide a reasonable assurance that should the procedures contained in these documents be followed, it is reasonable to assume that a quality product may be produced. Furthermore, it is important to note that following Guidance documents alone will not suffice and that these should be used in conjunction with current Good Manufacturing Practice procedures (cGMP).

Tablet dosage forms must satisfy several unique design compromises, as the desired properties required of these dosage forms must be counter-balanced with their manufacturability and aesthetic attributes to produce a suitable compact, resistant to mechanical attrition yet able to perform adequately *in-vivo* [110].

In order to assess whether a specific dosage form meets the desired specifications a variety of physical tests must be performed on solid oral dosage forms including but not limited to content and weight uniformity, crushing and tensile strength and friability [110].

### **3.6.2. Content Uniformity**

The uniformity of dosage units can be demonstrated by either of two methods, namely content uniformity or weight variation [6]. The test for content uniformity is based on the assay of the individual content of an API in a sample of single dosage form units to determine whether the individual content of each unit falls within specified limits, which are set with reference to the average content of a sample [6, 14].

The results of content uniformity analyses undertaken on direct compression PHCL SR dosage forms are summarized in Table 3.5. Their content uniformity is also variable with only 4 batches, *viz.* PC005, PC008, PC009 and PC010 meeting the USP [6] requirement.

### **3.6.3. Weight uniformity**

The uniformity of weight test is such that a representative sample of tablets manufactured during a compression run, are weighed to determine the average weight or mass of each unit [6, 14]. There are two stage tests listed in guidance documents [129] for routine manufacturing batch testing. For stage 1 testing, 3 dosage units from each sampling location is collected and from these one dosage unit from each location is assayed and the results are weight corrected [129]. The stage 2 test is where the remaining dosage units from stage 1 testing are assayed and the mean data from both stages 1 and 2 testing are computed [129]. The draft guidance suggests that the % RSD values for these tests should be  $\leq 5\%$  [129].

Twenty tablets from each batch were randomly selected and weighed on a Mettler model AE 163 balance (Mettler, Greifensee, Zurich, Switzerland). The average weight in milligrams (mg) and standard deviation of each tablet batch were determined and a summary of these results is shown in Table 3.5. The results reveal that there is a large inter-batch variation of the products made by DC, in both their content and weight uniformity which can be seen by their representative % RSD values as shown in Table 3.5 for both the content and weight uniformity.

### 3.6.4. Crushing Strength

The mechanical or crushing strength of a tablet is an indication of the resistance of the solid compact to withstand fracturing and/or attrition [87, 132]. The application of a load to a tablet and determination of the force required to fracture the tablet along its radial diameter allows for the determination of the crushing strength of a dosage form [87, 132].

Tablet crushing strength in Newtons (N), was determined using an Erweka model TBH 28 hardness tester (Erweka GmbH, Heusenstamm Germany). Twenty tablets were randomly selected from each batch and subjected to testing and a summary of the results are listed in Table 3.5. The results reveal that batch PC010 showed the highest crushing strength value, however these tablets follow the same trend that is seen in section 3.6.2 and 3.6.3 in that there is a high degree of inter batch variability and this are represented by the high % RSD values.

### 3.6.5. Tensile Strength

The tensile strength ( $T_s$ ) of a tablet can be determined using a relationship that was developed by Fell and Newton and which is shown in Equation 3.1 [133]. The  $T_s$  relates the crushing strength to the dimensions of a tablet in order to determine the fractional force required to generate a fracture per unit area of a tablet [133]. The  $T_s$  of the tablets were calculated using the crushing strength data reported in Table 3.5, in addition to the thickness and diameter ( $n = 20$ ) of the representative batches using Equation 4.1 [133, 134].

$$T_s = \frac{2F}{\pi DT} \quad \text{Equation 3.1}$$

where,

F = force in Newtons

D = diameter of the tablet in mm

T = thickness of the tablet in mm

$\pi$  = pi and is 3.1415

The results for tensile strength are represented in Table 3.5. As previously mentioned the dimensions of the tablet are considered with the crushing strength and this should provide a more representative measure of the strength of the compact. The results show that there is a large inter batch variation, combined with high % RSD values such as 20.86 % for batch PC007.

### **3.6.6. Friability**

Friability is evaluated under specific conditions and is used to determine whether the surface of tablets may be damaged, or whether lamination or tablet failure may occur when a dosage form is subjected to mechanical shock [6, 14]. There are official guidelines for friability testing as outlined by the USP and BP [6, 14]

Tablet friability testing was performed using an Erweka TA220 (Erweka GmbH, Heusenstamm, Germany). Twenty (20) tablets were randomly selected, dusted, weighed and then placed into a perspex drum that was then attached to the friability tester. The tablets were rotated for 100-drop cycles, removed, dusted and reweighed, to record any mass loss that may have occurred during the application of mechanical shock. Friability was determined by calculating the percent mass lost from the tablets included in the test and a summary of the results obtained is listed in Table 3.5. The data obtained from these tests reveal that all batches, except batch PC008 pass the requirements for friability.

**Table 3.5 Results of Physical Assessment of DC Tablets**

<b>Formulation</b>	<b>Content uniformity</b> Mean + S.D % (n=20)	<b>%RSD</b>	<b>Weight uniformity)</b> Mean + S.D mg (n=20)	<b>%RSD</b>	<b>Crushing strength</b> Mean + S.D N (n=20)	<b>%RSD</b>	<b>Tensile strength</b> Mean + S.D N/mm <sup>2</sup> (n=20)	<b>%RSD</b>	<b>Friability</b> % (n=20)
<b>PC001</b>	85.94 ± 1.52	1.76	152.88 ± 3.79	2.85	82.55 ± 9.38	11.37	2.01 ± 0.23	11.56	0.78
<b>PC002</b>	87.64 ± 8.57	9.78	146.39 ± 5.89	1.81	61.70 ± 2.47	4.01	1.36 ± 0.06	4.66	0.44
<b>PC003</b>	85.23 ± 4.55	5.34	144.92 ± 7.09	2.23	65.35 ± 3.22	4.92	1.44 ± 0.08	5.32	0.45
<b>PC004</b>	88.40 ± 5.25	5.94	144.94 ± 10.49	2.29	84.80 ± 5.97	7.04	1.81 ± 0.15	8.33	0.45
<b>PC005</b>	93.82 ± 6.41	6.84	136.88 ± 4.59	2.48	88.95 ± 9.52	10.70	2.63 ± 0.31	11.60	0.33
<b>PC006</b>	86.33 ± 2.34	2.71	143.85 ± 4.98	4.02	97.80 ± 10.83	11.07	2.78 ± 0.36	12.89	0.69
<b>PC007</b>	89.43 ± 1.25	1.39	186.95 ± 5.96	4.89	89.40 ± 18.16	20.32	2.62 ± 0.55	20.86	0.39
<b>PC008</b>	94.60 ± 2.02	2.14	191.64 ± 6.10	7.24	74.75 ± 10.58	14.15	1.98 ± 0.34	17.27	1.12
<b>PC009</b>	101.37 ± 8.85	8.73	185.29 ± 4.29	3.36	80.85 ± 6.48	8.02	2.46 ± 0.21	8.74	0.38
<b>PC010</b>	94.97 ± 2.23	2.35	191.84 ± 7.28	3.47	106.25 ± 7.97	7.50	3.06 ± 0.25	8.24	0.35

### 3.6.7. Discussion

The USP limits for the content of PHCL in extended release tablets or capsules are set in a range between 90 - 110 % of label [6]. The results obtained in these studies reveal that only four of the DC PHCL batches manufactured, fall within the limits in terms of the standards set by the USP [6]. There is also a large degree of inter batch variation in terms of tablet weight, crushing and tensile strength. The friability of all DC batches, except for batch PC008 fall within the limit for friability of < 1 % loss during friability testing.

The weight variation that is evident may be attributed to the fact that, in the process of tableting, tablet presses fill by volume and not by weight [120]. The flowability of the tablet blend that is intended for compaction is of vital importance [111, 135] and is influenced by the excipients that make up the heterogenous blend mix [102, 111, 135]. Studies that have been reported reveal that the resultant variability in a batch of tablets can be attributed to a number of factors including the types of tooling [136, 137], excipients in particular with respect to binders and fillers used, in addition to their compressibility, flowability and mechanical properties [138-143]. Furthermore the force of compaction used during the tableting process can also impart variability to a batch of tablets [137]. It has been reported that the use of Emcompress<sup>®</sup> in combination with microcrystalline cellulose may also introduce content and weight variation to a batch of tablets, whilst impacting the crushing strength of direct compression dosage forms [144].

The aforementioned considerations may have contributed to the variability that was observed for the batches of tablets manufactured by DC.

### 3.7. Conclusions

The dosage forms that were manufactured by direct compression demonstrated marginal SR effects, however the resultant dissolution profiles did not match the target *in-vitro* release profile of the innovator product Inderal<sup>®</sup> LA. Evaluation of the dissolution profiles, using graphical assessment and model independent analyses by the difference and similarity factors,  $f_1$  and  $f_2$  confirmed that the DC dosage forms were different to that of the reference product and these methods of analysis are described in Section 5.2.4 *vide infra*. The formulation composition and processing techniques used for DC tableting, to develop a PHCL SR dosage form produced tablets with a large degree of variability with respect to their physical characteristics as described in Section 3.6. Consequently extensive developmental work would be necessary to produce a suitable DC formulation and therefore the future development of dosage forms by DC tableting technology was considered inappropriate.

A decision to switch to a WG method of manufacture was made in an attempt to further modify the dissolution profile of PHCL from the extemporaneously manufactured dosage forms. The change to a WG manufacturing approach was thought to be appropriate, since API release from the direct compression products was too rapid, which is more than likely due to the high degree of solubility of PHCL. Furthermore, DC tablet formulations have the potential for improved drug release characteristics as no binding solution is added to facilitate granule formation as would occur if a WG method of manufacture were used. Therefore a strategic switch to a WG method of production may produce the desired retardation of PHCL release from matrix tablets. Furthermore the use of granulating agents, which were non-water soluble, may be beneficial for the retardation of PHCL release if the polymeric coated granules are incorporated into a monolithic matrix formulation.

## CHAPTER 4

### DEVELOPMENT AND ASSESSMENT OF PROPRANOLOL HYDROCHLORIDE SUSTAINED RELEASE (PHCL SR) DOSAGE FORMS MANUFACTURED BY WET GRANULATION

#### 4.1. Introduction

Wet granulation (WG) is a method of tablet production in which an API is mixed with excipients and forced to agglomerate by use of an appropriate binding solution, to form larger, multi-particulate entities called granules [87, 110, 145-148]. Granulation in tablet processing is often a necessary step as the formation of granules may prevent or minimize segregation of the components of a powder, in addition to imparting better flow properties to that blend [87, 110, 145-148]. Granules possess better compressibility and flow properties when compared to the individual powder constituents of a blend, which when used individually may impact negatively on the mixing and compaction process [87, 110, 149].

The use of WG for the manufacture of modified release delivery systems may allow for the control of release rates of an API, as a consequence of using polymeric dispersions as granulating fluids [150-152]. A wet granulation procedure using polymeric granulating fluids was developed in an attempt to produce PHCL SR tablets that had better rate retardation properties than those dosage forms that had been produced by the DC tableting methods described in Chapter 3 *vide infra*.

The formation of granules is dependent on the nature and strength of the bonds that form between constituent powder particles [87, 110, 149]. Therefore components of granules must adhere to each other to form a multi-particulate mass and the resultant bonds should have sufficient strength to prevent the total desegregation and/or deaggregation of particles during the normal processing procedures that are necessary prior to tablet compression [87, 110, 149].

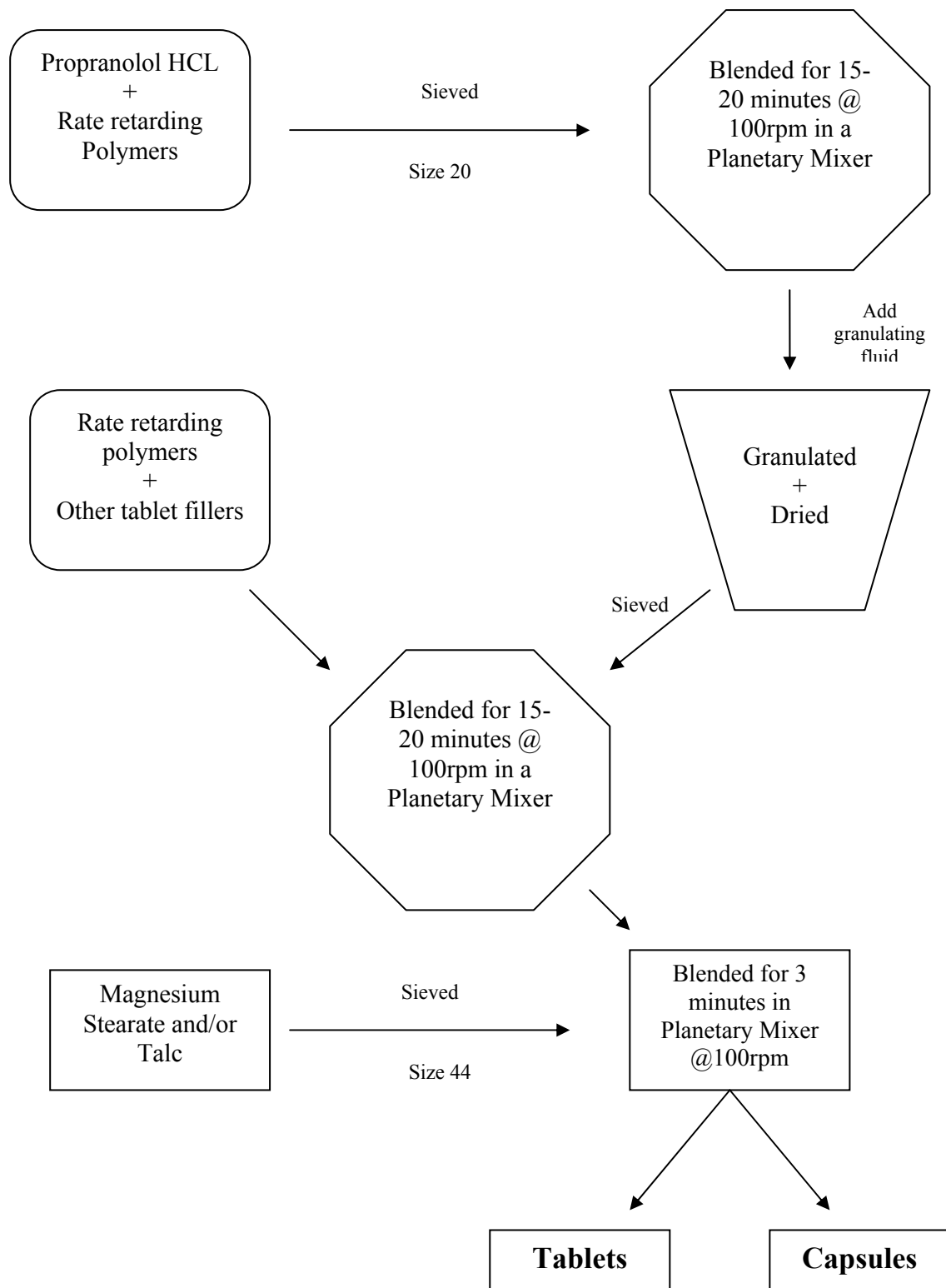
The process of granule formation can be separated into three broad categories *viz.*, wetting and nucleation, consolidation and growth followed by attrition and breakage [146, 147, 149, 153]. The wetting or nucleation stage commences when a binding agent is brought into contact with the powdered material to be granulated to form nuclei [146, 147, 149, 153]. The consolidation or growth stage occurs when collisions between granules, the granules and the feed powder or the granules and the equipment lead to powder agglomeration and therefore, granule growth [146, 147, 149, 153]. The final stage of granule formation involves attrition and occurs as a result of wet or dried granular material fracturing or crumbling due to impact, wear, or compaction during continued or subsequent powder handling throughout the manufacturing process [146, 147, 149, 153].

Despite the advantages of the WG method of tablet manufacture, there are several disadvantages that must be considered prior to embarking on the use of these methods to manufacture quality products, and these are summarized in Table 4.1 [87, 110].

**Table 4.1 Advantages and disadvantages of wet granulation**

<b>Advantages</b>	<b>Disadvantages</b>
Reduces air entrapment	Each unit process adds complications
Enhances fluidity and compactibility	Large numbers of unit processes increases the problems and possible operator error
Suitable for high dose drugs	Difficult to control and validate
Reduces cross contamination and dust	Potential adverse effects of temperature, time, rate of drying on drug stability and distribution during drying
Permits handling of powders without loss of blend quality	More costly when compared to DC
Enhances wettability of an API	
Provides for addition of a liquid phase suited to dispersion of drug to ensure content uniformity	

A schematic outline of the wet granulation process is outlined in Figure 4.1. The granulation process employed to produce the polymeric coated granules are described in Sections 4.3.1 and 4.3.2 respectively.



**Figure 4.1** Schematic representation of the manufacturing procedure used to prepare granules for compression into tablets or filling into capsules

## **4.2. Additional Excipients used for the Manufacture of Tablets by WG**

### **4.2.1. Eudragit<sup>®</sup> NE 30D/ NE 40D**

Eudragit<sup>®</sup> NE 30D and NE 40D (Röhm Pharma, Darmstadt, Germany) are the propriety names for a 30 % w/v and 40% w/v polymethacrylate dispersion with the chemical name poly(ethyl acrylate, methyl methacrylate) 2:1 and a CAS registry number of 9010-88-2. Eudragit NE 30 D is a milky white aqueous dispersion of low viscosity that is used for the formation of water insoluble coatings for sustained release products. Eudragit<sup>®</sup> is listed in the FDA inactive ingredients guide [101] and is generally regarded as non-toxic and non-irritant. The Eudragit<sup>®</sup> dispersions are sensitive to extreme temperatures and phase separation may occur at low temperatures. Incompatibilities amongst these latex dispersions may occur, depending on the ionic properties of the polymer in the dispersion, and the solvent used in the dispersion. The incompatibilities may be due to pH change, the presence of soluble electrolytes, or organic solvents, and manifest themselves as clumping of certain types of polymethacrylates [100].

### **4.2.2. Surelease<sup>®</sup> E7-19010**

Surelease<sup>®</sup> (Colorcon Ltd, Orpington, Kent, UK) is the propriety name for a 25% w/w aqueous dispersion of an ethylcellulose FP 20cp dispersion and has a CAS registry number of 9004-85-3. Surelease<sup>®</sup> is an off white turbid viscous liquid that is primarily used to coat beads, particles or tablets. In addition, the product has been used as a binding agent for modified release dosage forms manufactured by wet granulation and as a taste-masking coating. . The components of Surelease<sup>®</sup> E7-19010, *viz.*, purified water, ethylcellulose FP 20cp, ammonium hydroxide 28% w/v, medium chain triglycerides and oleic acid all meet the USP pharmacopoeial requirements [6]. Surelease<sup>®</sup> is regarded as safe and is unlikely to cause adverse health consequences or pose a toxicological hazard. There is some degradation of the medium chain triglycerides and oleic acid during the manufacture of Surelease<sup>®</sup>, and levels of these may increase over the shelf life of the product. Consequently, it is recommended that Surelease<sup>®</sup> products be stored in well sealed containers with minimal exposure to high humidity and temperature conditions [100].

#### **4.2.3. Acetyl Tri-ethyl Citrate (ATEC)**

Acetyl tri-ethyl citrate (Morflex Inc, Greensboro, NC, USA) is the non-propriety name of the chemical compound 1, 2, 3-Propanetricarboxylic acid, 2-acetyl, triethyl ester that has a CAS registry number of 77-89-4. Acetyl tri-ethyl citrate is a clear, colourless and odourless oily liquid that is used as a plasticizer for pharmaceutical coating applications for tablets, capsules, granules and beads, which require to be modified. Acetyl tri-ethyl citrate is approved in the United States for direct food contact in food films and is stable when stored under the prescribed conditions. Acetyl tri-ethyl citrate is incompatible with strong alkalai and oxidizing agents [100].

#### **4.2.4. Dibutyl Sebacate (DBS)**

Dibutyl sebacate (Morflex Inc, Greensboro, NC, USA) is the non-propriety name for the chemical compound decanedioic acid, di-*n*-butyl ester that has a CAS registry number of 109-43-3. Dibutyl sebacate is a clear colourless oily liquid that has a bland to slightly butyl odour. Dibutyl sebacate is used as a plasticizer for pharmaceutical coatings and has been used as a synthetic flavour in food products at very low concentrations. When used as a plasticizer in pharmaceutical applications for coating of tablets, beads or granules it is used at concentrations varying between 10-30 % by weight of the coating polymer. Dibutyl sebacate is included in the FDA inactive ingredients guide [101] and is generally regarded as as non-toxic and non-irritant. It is a stable in solution and is incompatible with oxidizing materials and strong alkali agents [100].

The other excipients that were used for the production of WG formulations have been listed and described in Section 3.4 of Chapter 3, *vide infra*.

### **4.3. Manufacture of PHCL SR Dosage Forms by WG**

The relevant formulation compositions for the PHCL SR dosage forms manufactured by WG are listed in Tables 4.2 and 4.3, representing the different granulating fluids employed respectively.

**Table 4.2 Formulation compositions % w/w for dosage forms using Eudragit<sup>®</sup> granulating fluids**

Formula	PC011		PC012		PC015		PC016		PC018		PC019	
	A	B	A	B	A	B	A	B	A	B	A	B
<b>PHCL</b>	46.51	29.7	46.51	28.95	46.51	27.93	46.66	27.21	45.58	25.18	44.15	23.47
<b>Eudragit<sup>®</sup> NE30D</b>	40ml		40ml		120ml		120ml		120ml			
<b>Eudragit<sup>®</sup> NE40D</b>											120ml	
<b>Water</b>	40ml		40ml									
<b>Methocel<sup>®</sup> K100M</b>	27.13	17.32	31	19.3	27.13	16.29	34.07	18.14	12.1	7.18	14.7	7.15
<b>Methocel<sup>®</sup> K100 LV EP</b>									30.23	14.37	29.39	14.31
<b>Eudragit<sup>®</sup> L100-55</b>	11.63	7.42			11.63	6.98			12.1	7.18	11.75	7.15
<b>Emcocel<sup>®</sup> 90M</b>	14.73	9.4	9.3	5.8	14.73	8.85	10.22	5.44	7.18		7.15	
<b>Emcompress<sup>®</sup></b>			11.63	7.24			12.77	6.8				
<b>Talc</b>			1.55	0.97			1.36	0.73				
<b>Magnesium Stearate</b>	1		0.97		0.93		0.9		0.9		0.9	

**A represents the % w/w composition for the the granulation step**

**B represents the % w/w composition of the the final blend mix**

**Table 4.3 Formulation compositions % w/w for dosage forms using Surelease<sup>®</sup> E7-19010 granulating fluid**

Formula	PC013		PC014		PC017		PC020A		PC020B		PC021TC	
	A	B	A	B	A	B	A	B	A	B	A	B
PHCL	46.51	29.74	46.51	29.47	46.32	23.86	44.12	22.28	44.12	21.53	44.12	19.71
Surelease <sup>®</sup> E7-19010	45ml		45ml		150ml		150ml		150ml		150ml	
ATEC							10ml					
DBS									10ml			
Water	75ml		75ml									
Methocel <sup>®</sup> K4M						6.37						
Methocel <sup>®</sup> K100M	27.13	17.35	31	19.65	27	19.11	14.7	9.59	14.7	9.39	14.71	16.5
Methocel <sup>®</sup> K100 LV EP							29.41	19.19	29.41	18.78	29.41	16.5
Eudragit <sup>®</sup> L100-55	11.63	7.54			11.75	7.96						
Eudragit <sup>®</sup> L100							11.76	7.67	11.76	7.51	11.76	6.6
Emcocel <sup>®</sup> 90M	14.72	9.42	9.3	5.89	14.91	6.37		7.67		7.51		6.6
Emcompress <sup>®</sup>			11.63	7.52								
Talc			1.55	0.98								
Magnesium stearate		1		0.98		0.9		0.96		0.94		0.82

**A represents the % w/w composition for the the granulation step**

**B represents the % w/w composition of the the final blend mix**

#### 4.3.1. Use of Eudragit<sup>®</sup> NE 30D as the Granulation Fluid

WG was used to manufacture batch PC011 using Eudragit<sup>®</sup> NE 30D, a 30 % w/w polymeric dispersion of polymethacrylate, as the granulating fluid. The initial formulation used for the preparation of granules contained 45% w/w PHCL, 27.13 % w/w Methocel<sup>®</sup> K100M and 11.63% w/w powdered Eudragit<sup>®</sup> L100-55 Emcocel<sup>®</sup> 90M was included as a diluent to improve the mixing and flow characteristics of the blend during the granulation procedure. The powders were passed through a sieve (mesh size 20) and then mixed for 15 minutes using a planetary mixer (Kenwood, Kenwood Ltd, Johannesburg, SA) set at 100 rpm. The blend was then granulated using a 50:50 % v/v mixture comprised of 40 ml of Eudragit<sup>®</sup> NE 30 D and 40ml of de-ionised water. The granulating fluid was sprayed onto the powders rotationally with a spray gun into the kenwood mixer bowl, whilst the powders were agitated in the planetary mixer at 100 rpm. The granulation fluid was added at a rate of 2 ml/min and the entire process was completed in 50 minutes for the prototype batch, PC011. The granules that had been formed were removed and dried for 6 hours at 60°C in a Memmert<sup>®</sup> TV 50 convection oven, (Memmert GmbH, Schwabach, Germany). The granules were removed after 6 hours, passed through an Erweka<sup>®</sup> model FGS (Erweka GmbH, Heussenstam, Germany) oscillating granulator fitted with a size 10 mesh, using a Kraemer Elektronik<sup>®</sup> model UPE drive unit (Kraemer Elektronik, Darmstadt, Germany). The resultant granules were combined with additional excipients as shown in Table 4.2, and outlined by Figure 4.1, and blended for 15 minutes on the planetary mixer at 100rpm. Magnesium stearate was sieved and then added and the blend mixed for a further 3 minutes using the planetary mixer. The blend was compacted on a Manesty<sup>®</sup> F3 (Ganzleben and Burns Ltd, London, England) single punch press using 7.5mm biconcave punches (Ganzleben and Burns Ltd, London, England).

An additional batch of granules, batch PC012, was produced using Eudragit<sup>®</sup> NE 30D as the granulation fluid, and in which Emcompress<sup>®</sup> and talc were added as the diluent and glidant respectively. A summary of the composition of batch PC012 can be found in Table 4.2. The resultant dissolution profiles obtained following testing of batches PC011 and PC012 are depicted in Figures 4.2 and 4.3, respectively.

All dissolution profiles generated during these studies were assessed for similarity to the innovator product, Inderal<sup>®</sup> LA capsules using model independent analysis that is described in detail in Chapter 5, *vide infra*. A summary of the *f1* and *f2* factors calculated for all comparisons undertaken for WG formulations are summarized in Table 4.5 *vide infra*.

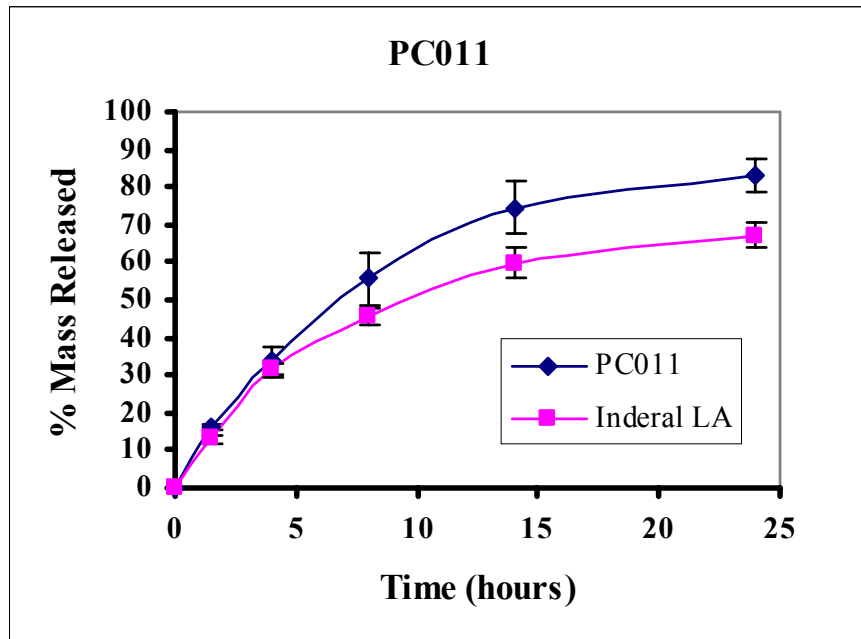


Figure 4.2 Dissolution rate profile of PHCL from batch PC011 (n=4) and Inderal<sup>®</sup> LA capsules (n=6) using USP apparatus 1

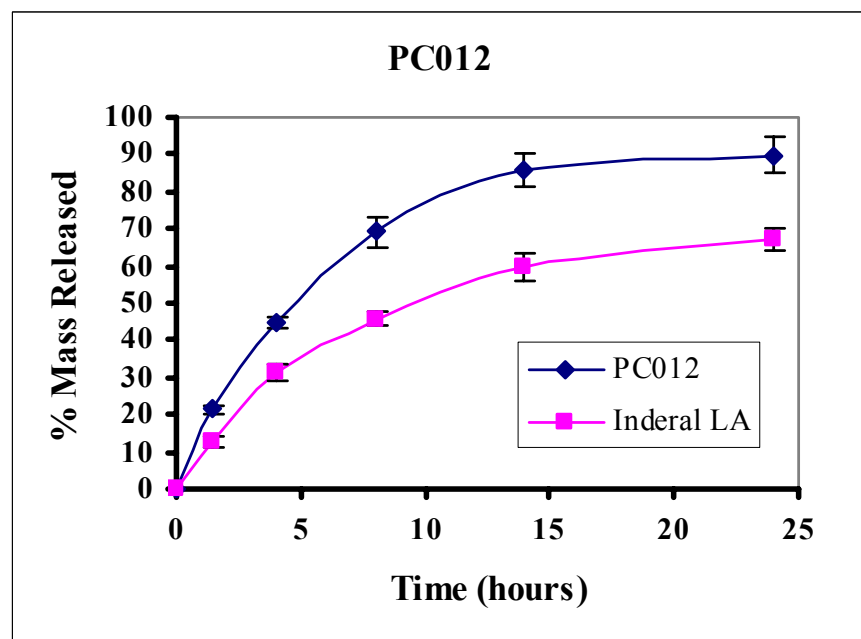
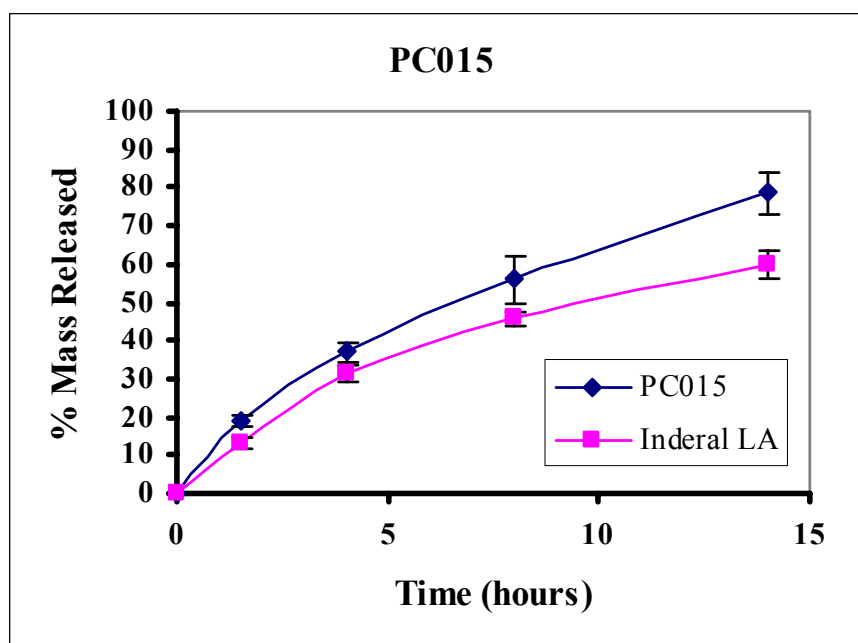


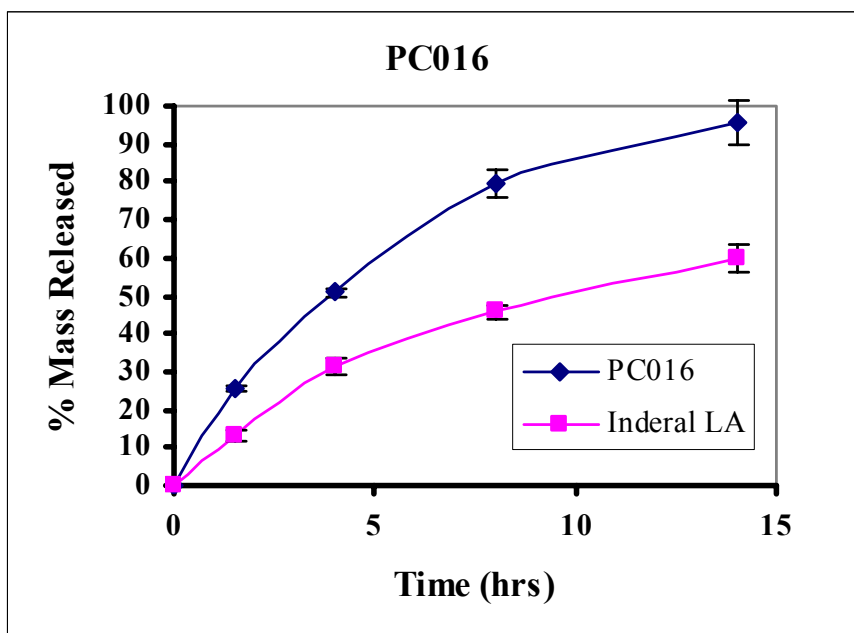
Figure 4.3 Dissolution profile obtained for batch PC012 (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1

The resultant dissolution profiles revealed that PHCL release from these initial WG developmental products were better than those batches that had been produced by DC with respect to the retardation of drug release. However, based on  $f1$  and  $f2$  difference and similarity factors of 21.58 and 47.98 for PC011, and 43.32 and 34.98 for PC012 the profiles were not comparable to that of the Inderal<sup>®</sup> LA capsules.

The formulation was further modified to produce batch PC015, however the composition of the granulating fluid was altered and 120 ml of a 50:50 blend of Eudragit<sup>®</sup> NE 30 D and Surelease<sup>®</sup> E7-19010 a was used to prepare the granules using the same manufacturing conditions as described for the manufacture of batches PC011 and PC012. An additional batch of granules, namely, PC016, was produced using the same composition of granulation fluid, and in which Emcompress<sup>®</sup> and talc were added as the diluent and glidant respectively. The resultant dissolution profiles revealed better release rate retardation in the early stages of the dissolution test as compared to previous batches and the profiles are depicted in Figures 4.4 and 4.5 respectively.



**Figure 4.4** Dissolution profile obtained for batch PC015 (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1



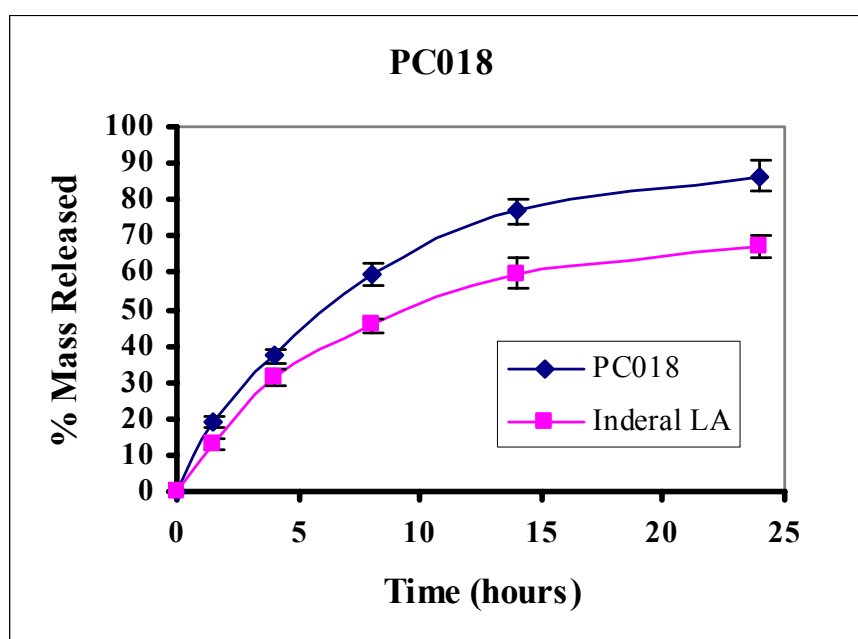
**Figure 4.5** Dissolution profile obtained for batch PC016 (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1

Despite the improved sustained release profiles generated for the release of PHCL from these batches, they were not equivalent to that of the Inderal<sup>®</sup> LA capsules, when evaluating the  $f_1$  and  $f_2$  difference and similarity factors as represented in Table 4.5.

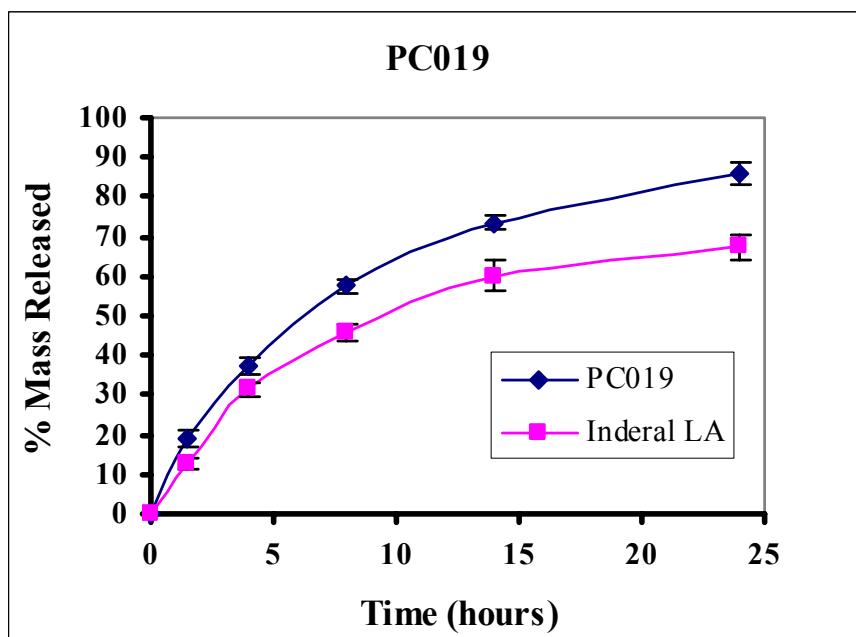
The tablet batches, namely PC012 and PC016 that have the diluent Emcompress and the glidant talc show much faster rates of drug release in comparison to their counterparts, batches PC011 and PC015 respectively, were these excipients were not utilized. It would appear that the incorporation of these two excipients in the tablet blends had a negative effect with respect to rate retardation of PHCL. The incorporation of Emcompress and talc in batches PC012 and PC016 show differences in the physical parameters, with respect to crushing strength. These batches were shown to produce harder compacts than the aforementioned batches PC011 and PC015, as represented in Table 4.8 *vide infra*.

It was evident that the formulation required substantial modification to delay the release of PHCL further, such that the release profile would match that of the reference product. Consequently the diluents used in the preparation of the powders for granulation were removed and replaced with Methocel<sup>®</sup> K100 LV EP (Colorcon

Ltd, Orpington, Kent, UK). Furthermore 120 ml of Eudragit<sup>®</sup> NE 30 D and Eudragit<sup>®</sup> NE 40D were used as the granulating fluid for batches PC018 and PC019, respectively. The resultant products varied only in the type of granulating fluid and their final tablet production mix, where the PHCL drug loading is 25.2 % w/w and 23.5 % w/w with a variance of less than 2 % for the rate retarding agents and diluents as can be seen in Table 4.2. The resultant dissolution rate profiles for batches PC 018 and PC019 are depicted in Figures 4.6 and 4.7, respectively.



**Figure 4.6** Dissolution profile obtained for batch PC018 (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1



**Figure 4.7** Dissolution profile obtained for batch PC019 (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1

The release of PHCL from batches PC018 and PC019 do not differ significantly from each other, despite the use of two different proportions of polymeric dispersion as granulating fluids, *viz.*, 30 % w/w and 40 % w/w dispersions of polymethacrylate. The dissolution profiles reveal that release of PHCL is different, in terms of model independent analysis to the Inderal<sup>®</sup> LA capsules. Further development and modifications of formulations manufactured using the Eudragit<sup>®</sup> series of dispersions as granulating fluids therefore ceased, as these experiments failed to produce a product with release characteristics similar to that of Inderal<sup>®</sup> LA capsules. Therefore, an EC dispersion, *viz.* Surelease<sup>®</sup> E7-19010 was used alone, in an attempt to determine whether a better rate retardant effect could be achieved when compared to that using the polymethacrylate copolymers as granulation fluids.

#### **4.3.2. Use of Surelease<sup>®</sup> E7-19010 as a Granulation Fluid**

The initial developmental products produced using Surelease<sup>®</sup> E7-19010 as the granulating fluid commenced using the same formulation for the granulation blend and tablet formulation as those used to manufacture batches PC011 and PC012. The Surelease<sup>®</sup> E7-19010 granulation fluid was used to produce material to manufacture batches PC013 and PC014 in which a dispersion of water: Surelease<sup>®</sup> E7-19010 in a ratio of 1:1.67 was used as the granulation fluid. The method used for granulation with Surelease<sup>®</sup> E7-19010 was the same as used for manufacture with the Eudragit<sup>®</sup> polymers described in section 4.3.1. However, drying of the granulation was increased to 10 hours at 60°C. The granules were initially dried for 4 hours prior to passing through an oscillating granulator. The resultant material was then cured for six hours at 60°C as it has been reported that an increase in curing time may decrease the rate and extent of drug release when Surelease is used as a coating material [154, 155]. It was expected that these developmental products would display similar if not better release rate profiles with respect to the degree of retardation of PHCL release rates than those observed when testing batches PC011 and PC012. Furthermore, as a polymeric dispersion of EC was used in these formulations as opposed to EC FP powder used in DC formulations, the resultant effect on PHCL release rates was expected to be more pronounced for batches PC013 and PC014 than previously observed. The resultant dissolution profiles following dissolution testing of batches PC012 and PC014 are shown in Figures 4.8 and 4.9 respectively.

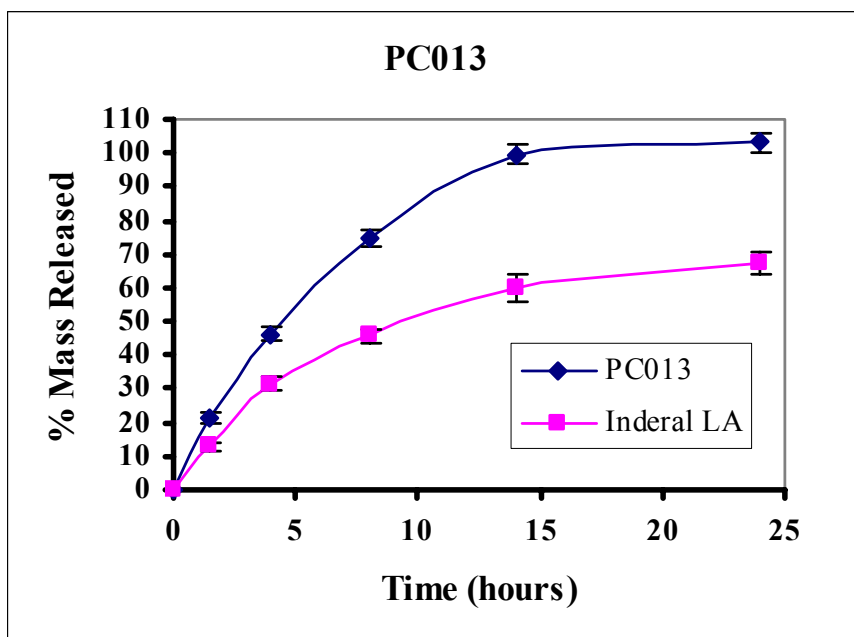


Figure 4.8 Dissolution profile obtained for batch PC013 (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1

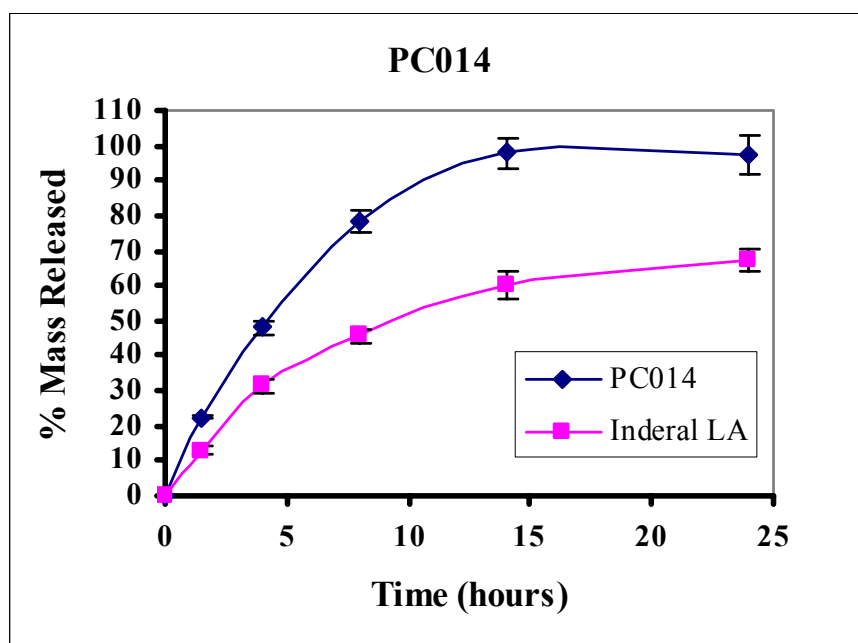
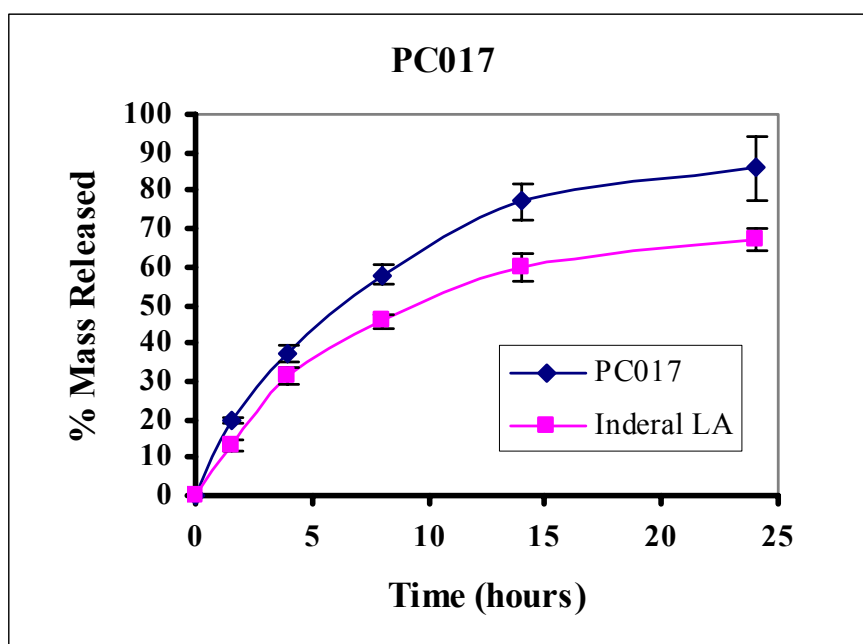


Figure 4.9 Dissolution profile obtained for batch PC014 (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1

It is clear from the  $f_1$  and  $f_2$  values, 59.08 and 27.41, and 58.58 and 27.98 respectively obtained for the comparison of batches PC013 and PC014 to the reference product that the dissolution profiles are not similar.

In addition, the resultant dissolution profiles may be similar to those generated from batches in which polymethacrylate dispersions were used as the granulation fluids, however no statistical analyses were undertaken to determine the degree of similarity. In an effort to evaluate the effect of additional granulation fluid on the release rate of PHCL from these formulations, batch PC017 was manufactured using 150 ml of Surelease<sup>®</sup> E7-19010 and the resultant dissolution profile is depicted in Figure 4.10.



**Figure 4.10** Dissolution profile obtained for batch PC017 (n=6) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1

The use of 150 ml of Surelease<sup>®</sup>, equivalent to 37.05 g of EC solids, as the granulation fluid during the manufacture of batch PC017 yielded similar results to those obtained from the previously formulated products, PC013 and PC014. The rapid rate and final percentage mass released failed to produce a product with a dissolution profile equivalent to that of the innovator product, Inderal<sup>®</sup> LA capsules.

There are possibly two significant factors that may have contributed to the failure of the products prepared by DC and WG to match the innovator product. The inclusion of fines material produced during granulation in the final tablet production blend may have significantly increased the surface area available for dissolution of PHCL. The granules were sieved using an oscillating granulator following drying, which may have resulted in the destruction of granule integrity with the resultant formation of

finer material and/or granules, in which the integrity of the EC coating was damaged. In addition, granules that had not been damaged following sieving with the oscillating granulator may have cracked during compression as there may have been insufficient plasticity of the EC following drying.

In an attempt to ascertain whether damage to granules following drying could be prevented during sieving and compression, the granulation fluid was modified to include additional plasticizers. Furthermore any finer material that were produced was not included in the final tablet blend. The removal of finer material was achieved by use of a 0.8 mm sieve.

### 4.3.3. Use of Plasticizer and Surelease<sup>®</sup> E7-19010 as a Granulation Fluid

The use of plasticizers has been reported to be of value when combined with polymeric dispersions such as Surelease<sup>®</sup> E7-19010 for the coating of tablets [156]. The use of additional plasticizer in granulation fluids may enhance the flexibility of polymeric materials that may have coated granules thus preventing fracture [156], and subsequent loss of potential rate retardant effects of the polymers, during the sieving and compression steps of tablet manufacture [156].

Two further developmental formulations, batches PC020A and PC020B were developed and manufactured using different plasticizers in the granulation fluid. Hydrophobic plasticizers were used as it was thought that their inclusion would not only impart flexibility to the EC but would also facilitate retardation of the rate of PHCL release from these products. Batches PC020A and PC020B were manufactured using acetyl triethyl citrate (ATEC) and dibutyl sebacate (DBS) as plasticizers, respectively.

The formulation composition of the granulation and the final tablet blend were modified to include an additional 5 % w/w Methocel<sup>®</sup> K100 LV EP in the final blend mix. In addition Eudragit<sup>®</sup> L100 was used instead of Eudragit<sup>®</sup> L100-55. Granulation fluids were prepared by the addition of 10 ml ATEC or DBS to 150ml of Surelease<sup>®</sup> E7-19010 (equivalent to 37.05 g of EC solids). The mixture of Surelease<sup>®</sup> and added plasticizer was shaken manually for 5 minutes in the spray gun container and then left to stand for 10 minutes prior to use. The manufacturing procedure used for the production of batches PC020A and PC020B is outlined in Figure 4.1 and described in section 4.3.2. After drying the granulations, fines material were removed by passing the material through a 0.8 mm sieve and the final tableting blend was prepared by mixing the excipients shown in Table 4.3 as previously outlined in section 4.3.2.

The resultant dissolution profiles are depicted in Figures 4.11 and 4.12 for batches PC020A and PC020B, respectively, and were found to be suitably comparable to the innovator product when using model independent analysis in which the difference and similarity factors,  $f_1$  and  $f_2$  were calculated. Batch PC020A produced a release profile for PHCL that was favorably comparable to that of the Inderal<sup>®</sup> LA capsules passing

the  $f_2$ , but not the  $f_1$  value whereas batch PC020B was not comparable as shown in Table 4.5.

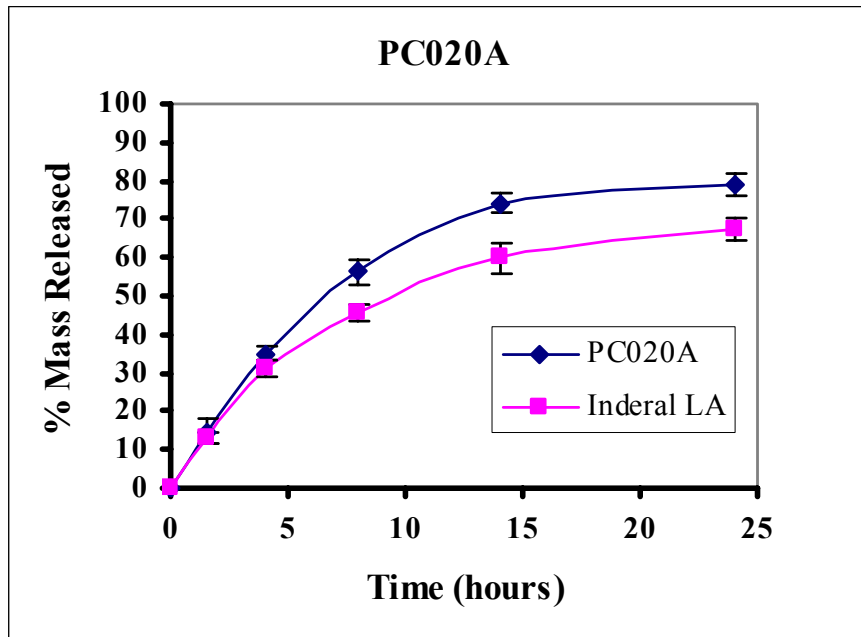


Figure 4.11 Dissolution profile obtained for batch PC020A (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1

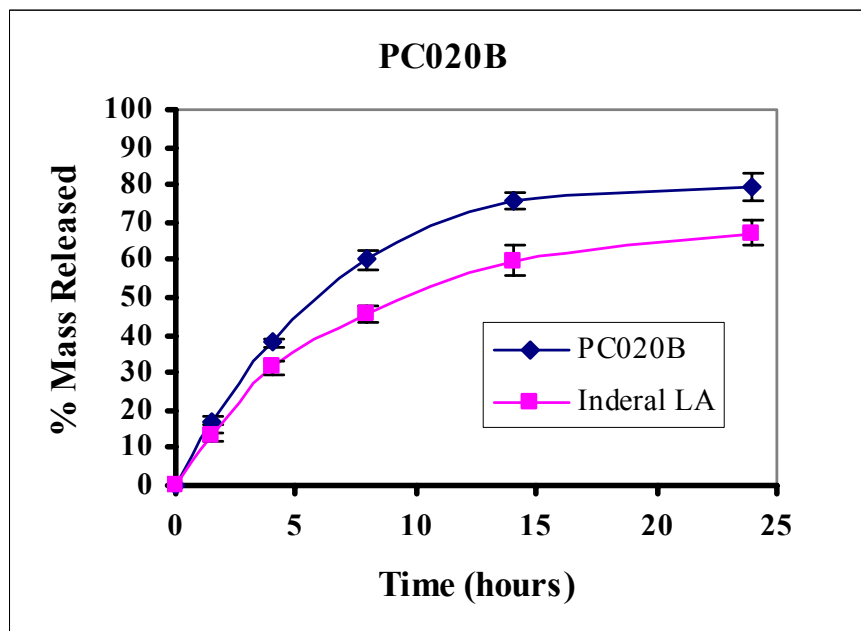


Figure 4.12 Dissolution profile obtained for batch PC020B (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1

The tablets from batch PC020A produced dissolution rate profiles that were comparable to that the reference product based on the  $f_2$  value, therefore an attempt was made to reproduce the product by manufacturing a second batch of tablets using a similar formulation composition and procedure. However, an attempt to prepare a batch that produced a dissolution profile similar to that of PC020A resulted in the production of tablets that failed the  $f_1$  and  $f_2$  as shown in Table 4.5 for batch PC021TC, and described in section 4.4. The inability to reproduce the results obtained for batch PC020A was thought to be a consequence of processing related difficulties such as incomplete and/or inefficient blending of the final tablet mix or possible damage of the granular material during sieving through the oscillating granulator and tablet compaction.

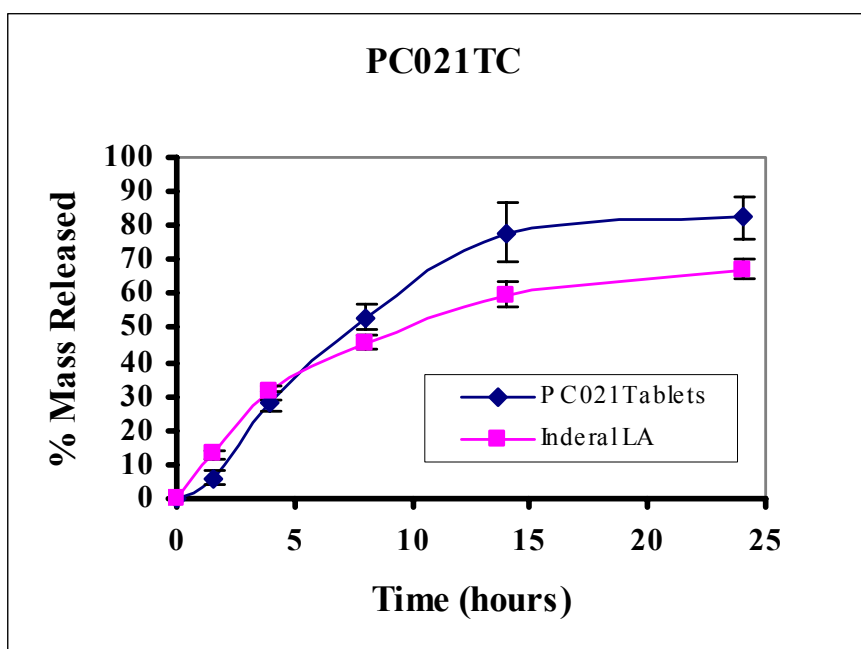
#### **4.3.4. Capsule Delivery Systems**

The use of capsules for the development of sustained release dosage forms is well known and offers an alternate means of manufacturing drug delivery systems without subjecting the powder blends to excessive compression forces that are achieved during conventional tableting procedures [157, 158]. In addition, the reference product used in these studies was Inderal<sup>®</sup> LA, which is a capsule dosage form that contains ethylcellulose coated beads and contains HPMC [36, 159].

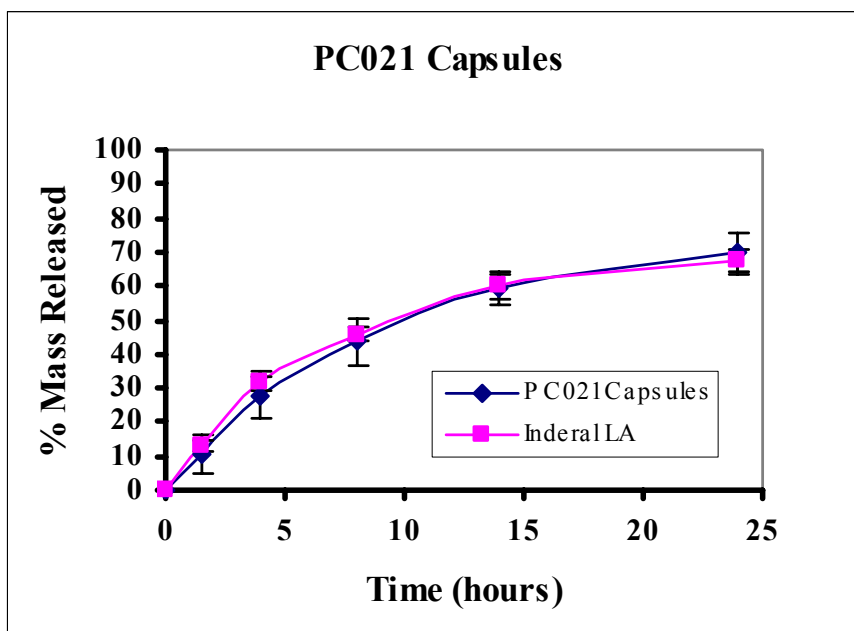
Therefore, as attempts to match the innovator product by use of DC and WG manufacturing processes had been unsuccessful, a capsule delivery system was considered as a viable alternate to tablets in an attempt to produce a delivery system from which the release rate of PHCL matched that of the innovator product, Inderal<sup>®</sup> LA.

The use of a capsule system would specifically exclude the impact of high compaction forces on the granular material and any associated damage that may impact adversely on drug release from the dosage form. Furthermore, these studies would provide insight into the reasons for product failure based on results observed for previous batches manufactured in these studies. Batch PC021 was manufactured using exactly the same blend composition as that used for the production of batch PC020A, however instead of subjecting the blend to a tableting process, an average

of 320 mg of the blend was manually filled into each of four size 0 gelatin capsules. The balance of the blend was then compressed into tablets as previously described to product batch PC021TC. Four of the resultant tablets were transferred into each of four size 0 gelatin capsules and the resultant dosage forms were subjected to dissolution testing. The resultant dissolution rate profiles generated for these studies are shown in Figures 4.13 and 4.14 for the tablets in a capsule and blend in a capsule, respectively.



**Figure 4.13** Dissolution profile obtained for batch PC021TC tablets in a capsule (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1



**Figure 4.14** Dissolution profile obtained for batch PC021 blend in a capsule (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1

Observation of the dissolution rate profiles generated following dissolution testing of batch PC021TC and PC021 capsules as shown in Figures 4.13 and 4.14 reveal that there is a distinct difference between the release profiles of the two products. The dissolution profile obtained for evaluation of PHCL release from the tablets in a capsule form exhibited faster release than that of the capsule dosage form in which the powder blend was filled into capsules. The results of evaluation of the difference and similarity factors reveal that the dosage form manufactured with tablets was not comparable to the reference product, whereas the capsule dosage form in which powder only was filled produced dissolution profiles that matched the innovator product with resultant  $f_1$  and  $f_2$  values of 5.01 and 79.23, respectively. These results confirmed that the tablet compaction process has some impact on the resultant release of PHCL from sustained release WG blends, possibly as a consequence of cracking of the polymeric granular material during compaction.

The capsule products that were tested showed potential for the production of a once-daily SR dosage form for the delivery of PHCL. However, none of the tablets that were produced generated dissolution profiles that were comparable to the innovator product, Inderal<sup>®</sup> LA 80mg capsules.

The resultant dissolution profiles depicted in Figures 4.13 and 4.14 suggest that the compaction force during tableting may damage the integrity of polymeric granule materials, causing a burst release of PHCL. Therefore it was decided that future developmental formulation powder blends would be incorporated into size 0 and 00 hard gelatin capsules for assessment for use as a potential once a day PHCL SR delivery system.

The dosage forms developed for the early capsule studies used the same formulation used to manufacture the tablets for batch PC021. The drug load and amount of rate retarding polymer were varied in order to ascertain the optimal drug load and polymer concentration to produce a product with drug release kinetics that would match the innovator product. The formulation compositions used to assess the impact of these variables on drug release rates are listed in Table 4.4.

**Table 4.4 Formulation compositions % w/w for trial capsule dosage forms**

Formula	PC022		PC022RW		PC023	
	A	B	A	B	A	B
<b>PHCL</b>	44.12	20.02	44.12	14.95	44.12	17.98
<b>Surelease<sup>®</sup> E-19010</b>	150ml		150ml		150ml	
<b>ATEC</b>	10ml		10ml		10ml	
<b>Methocel<sup>®</sup> K100M</b>	14.71	16.95	14.71	12.66	14.71	12
<b>Methocel<sup>®</sup> K100 LV EP</b>	29.41	16.95	29.41	37.97	29.41	28.69
<b>Eudragit<sup>®</sup> L100</b>	11.76	6.78	11.76	5.06	11.76	4.8
<b>Emcocel<sup>®</sup> 90 M</b>		6.78		5.06		4.8
<b>Magensium Stearate</b>		0.85		0.63		0.6

**A represents the % w/w composition for the the granulation step**

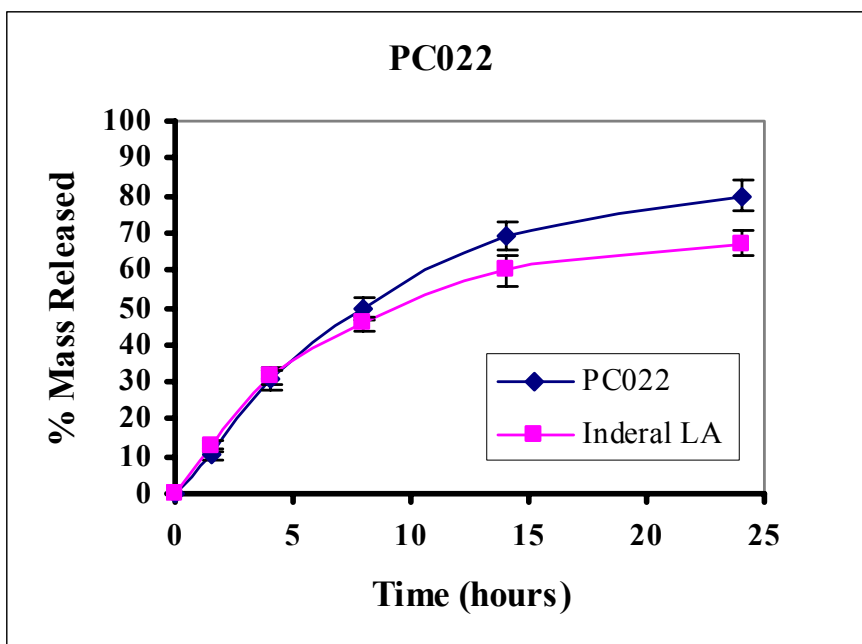
**B represents the % w/w composition of the the final blend mix**

Batch PC022 was manufactured such that PHCL and two grades of HPMC, namely Methocel<sup>®</sup> K100M and Methocel<sup>®</sup> K100 LV EP comprising of 20 % w/w PHCL and with, the two HPMC grades comprising 16.5 %w/w of the final blend respectively. Batch PC022RW was reworked blend of PC022 with a resultant drug load of 14.95 % w/w and with the Methocel<sup>®</sup> K100 LV EP content increased to 37.97 % w/w. This blend was reworked in order to ascertain the effects of the increase polymer content. Batch PC023 was manufactured using a final powder blend in which the fines material produced during the granulation process were included and the resultant drug loading in this batch was 18 % w/w with 12 % w/w Methocel<sup>®</sup> K100M and 28.69 % w/w Methocel<sup>®</sup> K100 LV EP in the final blend respectively.

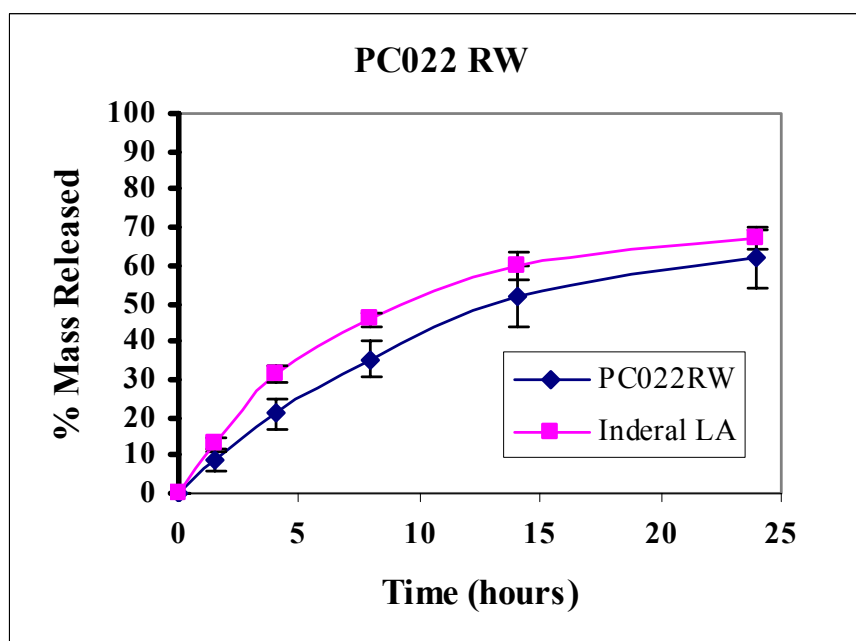
The impact of changing drug load and inclusion of additional fines material were studied to order to assess whether these parameters would have an impact on the release rate kinetics of PHCL from capsule dosage forms.

The resultant dissolution profiles are depicted in Figures 4.15, 4.16 and 4.17 for batches PC022, PC022RW and PC023 respectively. In comparison to the innovator product batch PC022 showed initial promise, but over time showed faster drug release rates. Batch PC022RW with higher polymer content showed an *in-vitro* dissolution profile that was superior to Inderal LA, however batch PC023 were fine material was incorporated showed faster drug release rates and could not match those shown by the innovator product.

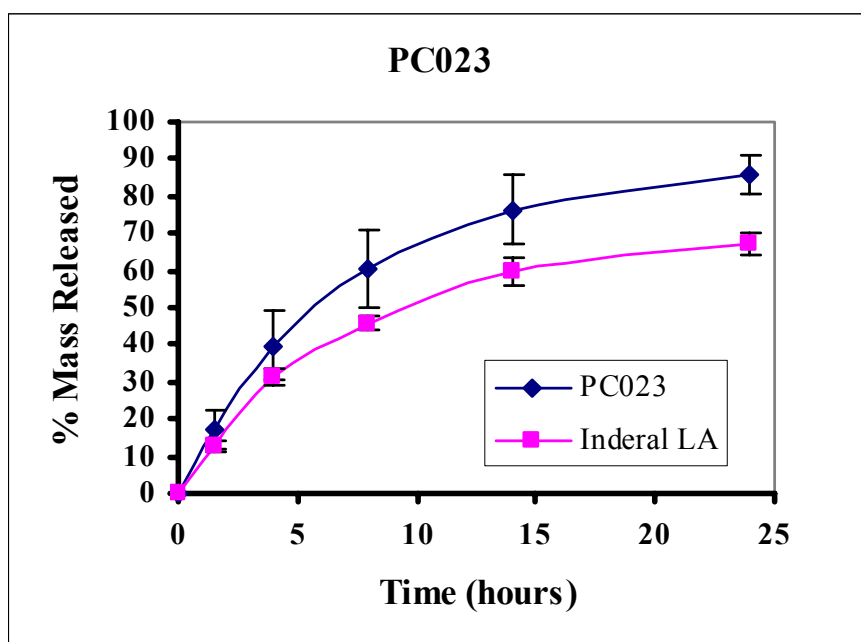
These results reveal that drug loading, polymer content and inclusion or exclusion of fines material may effect the release kinetics of PHCL from capsule dosage forms and a systematic study should be conducted in future investigations to determine the impact of these variables on dosage form performance .



**Figure 4.15** Dissolution profile obtained for batch PC022 capsules (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1

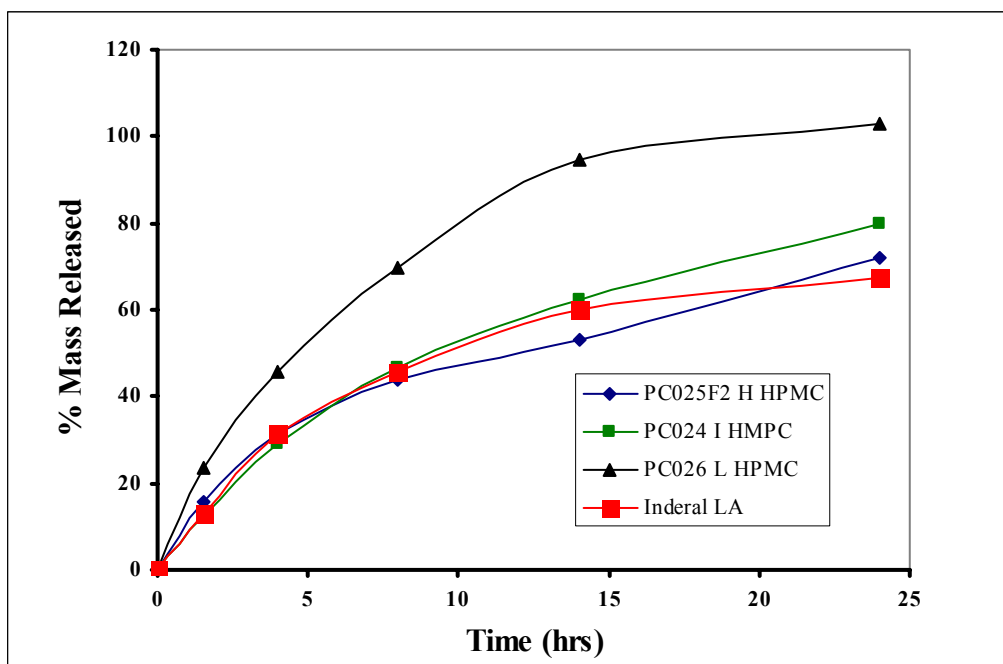


**Figure 4.16** Dissolution profile obtained for batch PC022RW capsules (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1



**Figure 4.17** Dissolution profile obtained for batch PC023 capsules (n=4) and Inderal<sup>®</sup> LA (n=6) using USP apparatus 1

The results obtained following dissolution testing the batches PC022, PC022RW and PC023 revealed that the polymer content of the final capsule fill blend was of importance in achieving control of drug release rates. Additional batches were formulated and manufactured with varying polymer content whilst maintaining the drug loads, such that only a small variation of between 1- 2 % w/w was permitted. Batches PC024, PC025F2 and PC026 were produced with intermediate (31.7 % w/w), high (40.04) and low (24.5 % w/w) HPMC polymer content in the final blend, respectively. The resultant blends were filled into size 00 capsules and the fill volumes were adjusted in order to ensure that an 80 mg PHCL dose was maintained for each batch. The capsules were filled as previously described, and the resultant dissolution profiles for these studies are depicted in Figure 4.18. Furthermore, the resultant dissolution profiles were compared to the dissolution profile of the reference product, Inderal<sup>®</sup> LA capsules.



**Figure 4.18** Dissolution rate profiles obtained for batches manufactured with intermediate (PC024), low (PC026) and high (PC025F2) HPMC content (n=4) and Inderal<sup>®</sup> LA capsules (n=6), using USP apparatus 1

The in-vitro dissolution profiles represented in Figure 4.18 above show results that were as expected, with batch PC026 with a low HPMC content showing the fastest release rates and, with the intermediate and high content of HPMC in batches PC024 and PC025F2 matching the innovator product based on  $f_1$  and  $f_2$  values. These latter products differ in terms of % w/w PHCL and polymer content which may explain why batch PC022 showed higher drug release rates over the 24 hour period. Furthermore batch PC024 was a combination product that included the IR HCTZ tablet that is described in Section 4.4.2.

**Table 4.5 Summary of  $f_1$  and  $f_2$  values for products manufactured by WG at  $t_{24}$**

<b>Formulation Batch Number</b>	<b><math>f_1</math></b>	<b><math>f_2</math></b>
PC011	21.58	47.98
PC012	43.32	34.98
PC013	59.08	27.41
PC014	58.59	27.98
PC015**	27.35	46.86
PC016**	67.66	28.33
PC017	27.97	43.87
PC018	28.62	43.23
PC019	26.05	45.49
*PC020A	19.33	50.56
PC020B	24.33	46.97
PC021TC	23.34	46.74
*PC021 Capsules	5.01	79.23
PC022RW	18.01	54.13
PC023	28.88	43.22
*PC024	8.59	61.65
*PC025F2	7.42	69.23
PC026	54.99	29.28

\*Shaded areas represent a passed  $f_1$  and/or  $f_2$  test

\*\* Represent values at  $t_{14}$

#### 4.3.5. Conclusion

The manufacture of dosage forms using a wet granulation manufacturing procedure with polymeric granulation fluid has been shown useful for the preparation of matrix materials for the production of controlled release dosage forms [150,151,152]. Three granulating fluids, namely Eudragit<sup>®</sup> NE30D, Eudragit<sup>®</sup> NE40D and Surelease<sup>®</sup> E7-19010 were used as the granulating fluids for these studies. Prototype formulations, batches PC011 (Figure 4.2) and PC013 (Figure 4.8) manufactured using these granulating fluids showed promising results in terms of the rate retardant effects when compared to DC dosage forms that were produced previously. However, the dissolution profiles for these batches were not comparable to the dissolution profile of the innovator product, Inderal<sup>®</sup> LA.

Further modifications of the formulation included the use of additional granulating fluid, in one instance and a 50:50 v/v combination of the granulating agents in another (Figures 4.4 and 4.5). The increased granulation fluid had little impact on the rate of release of the PHCL for the Eudragit<sup>®</sup> (Figures 4.6 and 4.7) and Surelease<sup>®</sup> (Figure 4.10) granulating fluids. These results were unexpected as an increase in granulating fluid resulted in an increase in the solids content of the rate retardant polymers in the matrix and should result in a lower rate and extent of drug release.

The formation of granules is often dependent on the type of binder used [146, 147], its viscosity [146, 147] and rate and method of introduction [146, 147], which may have affected its distribution throughout the powder blend [145, 147], thus resulting in a heterogenous dispersion of polymer that has little impact on controlling drug release.

The use of plasticizers added to Surelease<sup>®</sup> to optimize the processing of tablets in batches PC020A (Figure 4.11) and PC020B (Figure 4.12), revealed superior release profiles compared to earlier batches studied. However, attempts to replicate these results failed, and after consideration it was thought that the tablet compaction process may have caused damage to the granules. Further experiments were performed in order to investigate these effects and the release profiles demonstrated by batch PC021 (Figures 4.13 and 4.14) confirmed that the granular material may be subject to damage during the compaction process.

Capsule drug delivery was investigated further to ascertain whether it was a viable option for the production of a PHCL once a day delivery system. Optimal drug loads and polymer content were investigated to produce a product that that matched the dissolution profile of the innovator product. The results of these studies revealed that an intermediate to high polymer content is necessary to achieve the desired release profile in order for equivalence to the innovator product to be attained.

#### **4.4. Production of the Combination Product**

The primary aim and focus of this research project was to develop a PHCL SR dosage form, which incorporates an immediate release HCTZ component. Therefore, as powder blends that were able to sustain the release of PHCL from capsules had been produced, the development of the IR HCTZ tablet was commenced.

##### **4.4.1. Additional Excipient used for Production of IR HCTZ DC Tablets**

###### **4.4.1.1. Starch**

Starch was obtained from Aspen Pharmacare, Port Elizabeth, SA and has a CAS registry number of 9005-25-8. Starch is an odourless fine white powder. Starch is used in solid oral dosage forms as a binder, diluent and/or disintegrant. Starch is a GRAS listed compound that is considered non-toxic and non-irritant, but large quantities may cause bowel obstruction. Starch is a stable material that considered inert under normal storage conditions [100].

##### **4.4.2. Incorporation of HCTZ as an IR component**

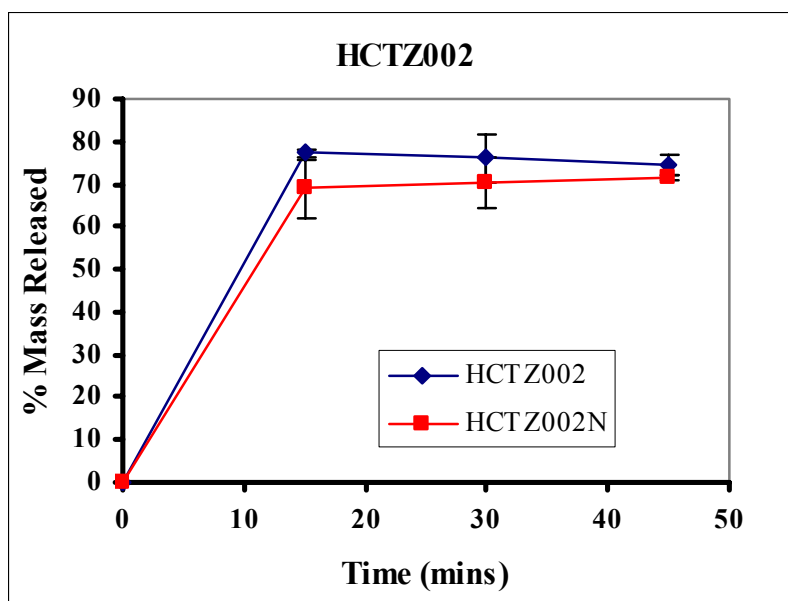
An IR HCTZ tablet was developed using DC technology using a modification of a prototype formulation developed in our laboratory for the manufacture of salicylic acid tablets [160]. The relevant composition of this formulae and the formula used to produce the DC HCTZ tablets are listed in Tables 4.6 and 4.7 respectively. The tablet was manufactured as outlined by procedure depicted in Figure 3.10 Section 3.5.3. HCTZ tablets were subjected to dissolution testing either alone or in combination with the PHCL SR capsule formulation (batch PC024) and the resultant dissolution profiles are depicted in Figure 4.19 showing HCTZ both alone and in combination with PC024. The combination product was produced by addition of the PHCL SR powder blend to a size 00 capsules and then adding a single HCTZ IR tablet to the same capsule. The combination was subjected to dissolution testing in order to ascertain whether the combination of the IR tablet and the SR mixture would impact negatively on the dissolution of HCTZ and consequently retard the release of HCTZ due to possible formation of an HMPC plug following dissolution of the capsule shell.

**Table 4.6 Formulation composition % w/w for Salicylic Acid tablets**

<b>Formula</b>	<b>% w/w</b>
<b>Salicylic Acid</b>	30
<b>Methocel<sup>®</sup> K4M</b>	6.8
<b>Emcompress<sup>®</sup></b>	23.5
<b>Emcocel<sup>®</sup> 90M</b>	35
<b>Ac-di-sol<sup>®</sup></b>	1
<b>Talc</b>	3
<b>Magnesium Stearate</b>	0.7

**Table 4.7 Formulation compositions %w/w for DC HCTZ tablets**

<b>Formula</b>	<b>HCTZ001</b>	<b>HCTZ002</b>
	<b>% w/w</b>	<b>% w/w</b>
<b>HCTZ</b>	15	15
<b>Methocel<sup>®</sup> K4M</b>		1
<b>Emcompress<sup>®</sup></b>	21	25
<b>Emcocel<sup>®</sup></b>	30	35
<b>Starch</b>	25	15
<b>Ac-di-sol<sup>®</sup></b>	5	5
<b>Talc</b>	3	3
<b>Magnesium Stearate</b>	1	1



**Figure 4.19** Dissolution rate profile for batch HCTZ002 (HCTZ tablets alone) and HCTZ002N (HCTZ tablets in a PHCL SR capsule) (n=4) using USP apparatus 1

The resultant dissolution profiles depicted in Figure 4.19 reveal that the incorporation of an IR HCTZ tablet into a capsule containing a PHCL SR formulation was successful and that dissolution of the HCTZ was only marginally affected.

Therefore these dosage forms could be used in combination, and the future bioavailability studies would be necessary to assess the performance of these products *in vivo*.

#### **4.5. Physical Assessment of Dosage Forms**

The physical testing of dosage forms manufactured by WG and the IR HCTZ tablets were performed as described in Section 3.6 *vide infra*. The results of the analyses obtained following physical testing of dosage forms are summarized in Table 4.8, and include weight and content uniformity, crushing strength, tensile strength and friability.

**Table 4.8 Results of the physical testing of PHCL tablets produced by WG and HCTZ tablets produced by DC**

Formulation	Content uniformity	%RSD	Weight uniformity)	%RSD	Crushing strength	%RSD	Tensile strength	%RSD	Friability
	Mean + S.D % (n=20)		Mean + S.D mg (n=20)		Mean + S.D N (n=20)		Mean + S.D N/mm <sup>2</sup> (n=20)		
PC011	98.57 ± 9.14	9.27	186.95 ± 3.94	3.19	58.80 ± 7.73	13.15	1.22 ± 0.17	13.86	0.27
PC012	101.61 ± 4.46	4.38	191 ± 5.91	3.18	67.45 ± 6.30	9.33	1.47 ± 0.15	10.12	0.26
PC013	92.87 ± 2.58	2.78	185 ± 5.63	2.31	56.15 ± 6.28	11.18	1.18 ± 0.14	11.70	1.50
PC014	109.62 ± 1.07	0.97	191.84 ± 6.48	3.80	54.25 ± 5.50	10.13	1.18 ± 0.12	10.23	0.52
PC015	109.91 ± 2.88	2.62	182.11 ± 6.53	2.17	55.85 ± 4.38	7.84	1.21 ± 0.10	8.57	0.83
PC016	104.51 ± 12.07	11.51	179.63 ± 5.24	3.08	60.35 ± 6.68	11.07	1.33 ± 0.15	11.15	0.26
PC017	107.46 ± 4.86	4.52	184.65 ± 4.72	3.13	44.00 ± 5.03	11.42	0.94 ± 0.11	11.84	0.56
PC018	93.08 ± 4.50	4.83	194.37 ± 3.12	3.33	46.25 ± 7.93	17.15	0.90 ± 0.17	18.45	0.26
PC019	89.90 ± 4.38	4.87	185.9 ± 5.58	3.51	45.05 ± 3.59	7.97	0.93 ± 0.08	8.27	0.55
PC020A	108.00 ± 1.78	1.65	193.21±10.23	2.71	60.40 ± 5.29	8.75	1.17 ± 0.10	8.37	0.26
PC020B	106.11 ± 4.91	4.63	184.65 ± 4.72	2.56	45.40 ± 4.50	9.91	0.90 ± 0.09	10.06	0.27
PC021	95.81 ± 3.06	3.19	193.55 ± 3.12	1.61	45.35 ± 3.72	8.20	0.86 ± 0.08	8.98	0.77
PC022*	108.68 ± 4.89	4.49	419 ± 13.6	3.25	-	-	-	-	-
PC023*	95.46 ± 10.61	11.11	414.83 ± 3.59	0.87	-	-	-	-	-
PC024*	96.62 ± 4.63	4.79	434.5 ± 5.02	1.15	-	-	-	-	-
PC025F2*	100.99 ± 18.13	18.12	389.2 ± 1.78	0.46	-	-	-	-	-
PC026*	106.71 ± 19.32	18.11	439.3 ± 3.03	0.69	-	-	-	-	-
HCTZ001	90.25 ± 6.73	7.45	218.75 ± 5.58	2.55	55.70 ± 5.05	9.06	1.24 ± 0.11	9.10	0.46
HCTZ002	81.84 ± 3.75	4.58	178.97 ± 10.22	5.71	39.20 ± 2.09	5.34	1.06 ± 0.06	5.47	0.57

\* For the capsule weight analyses only 4 capsules were tested for each batch and these were manually filled\*

#### 4.5.1. Results and Discussion

The results obtained for the physical testing of all dosage forms reveal that the products comply with the USP [6] standards for content uniformity and friability except for batches PC019 and PC013, respectively. It was thought that the particle size distribution of the granular material may have accounted for this.

The crushing strength of the various batches varied between 45 N and 67 N for the PHCL tablets, whilst the tensile strength varies, as it is dependent on the crushing strength and tablet dimensions as described in section 3.6.5 *vide infra*. There is however a large degree of inter-batch variation seen with the tablets produced in terms of their weight uniformity.

A factor that can introduce variability in WG dosage forms is the amount, type and rate of addition of binder [161-163] and the granulation procedures used [164, 165]. Therefore it is clear that the granulation process can affect the mechanical properties of a tablet, in particular to the crushing strength where studies have shown that an increase in the binder used may influence the crushing strength. However, crushing strength is also dependent on the porosity of the granule [163, 165-167] which affects the particle size of granules [145, 147] thus contributing to flow properties of granules.

Furthermore, larger granules may not fill the die cavity uniformly during an automated tablet manufacturing run, which in turn will result in non-uniform weights. Non-uniform filling of the die cavity can result in the production of tablets that have different and variable crushing strengths. Other mechanical properties such as friability can be influenced by the amount and type of binder used [168, 169], the amount and type of lubricant used and the compression force applied [169, 170]. A variance in the particle size distribution of the granulation may also contribute to the variations displayed in content uniformity, where the larger particle sizes contain more drug than the smaller particles. Large particle size difference may also result in segregation in the blender and feed hopper during manufacture thereby causing variations in content uniformity.

The variances seen in capsule fill weight are a result of the manual filling procedure used to fill the capsules and the need for different fill weights for batches PC022, PC024 and PC026, respectively. The filling of only four capsules for analyses would not provide a good statistical representation, and variability in the results and % RSD values may represent themselves when there are small sample sizes.

## **4.6. Assessment of Capsule and IR Powder Blends by Powder Rheology**

### **4.6.1. Introduction**

The term rheology relates to the science that deals with the flow and deformation properties of matter. Powder rheology therefore is the science of assessing the flowability of excipients and powders that are used in the manufacture of solid oral dosage forms.

The flowability and compactibility of powders are critical process parameters that must be investigated when a material is intended to be included in a formulation for tableting [132]. The flow properties of powders are often affected by the physico-chemical and mechanical properties of a powder in addition to operational processing conditions [132]. Furthermore, the rheological properties of a powder are functionally dependant on interparticulate attractive forces between the components of a powder [132]. It is therefore essential that accurate assessments of the flow characteristics of a material are investigated, in order to maximize the chances of success in formulation development.

There are a number of methods that have been reported in the literature for the assessment of powder flow properties, and include the Hausner ratio [6, 132, 171, 172], Carr's compressibility index [173, 174] and the Static Angle of Repose [173, 175,176].

#### 4.6.2. Hausner Ratio

The Hausner ratio can be determined using Equation 4.2, and is a measure of the propensity of a powder to be compressed [6]. The Hausner ratio is determined using bulk and tapped bulk densities of a powder [6].

The bulk density of a powder is determined by measuring the volume of a known mass of powder that has been passed through a screen into a graduated measuring cylinder or through an apparatus that can measure the volume of a powder that has been passed into a cup and is calculated using Equation 4.1 [6, 14]

$$BD = \frac{M}{V_0} \quad \text{Equation 4.1}$$

where,

$BD$  = Bulk density

$M$  = weight of the powder for which the bulk density is to be determined

$V_0$  = volume in ml of the cup or cylinder

$$HR = \frac{V_o}{V_f} \quad \text{Equation 4.2}$$

where

$V_o$  = tapped density

$V_f$  = bulk density

The tapped bulk density of a powder is measured by mechanically tapping a measuring cylinder containing a known mass of powder. The initial volume occupied by the mass of powder is recorded prior to the commencement of tapping at a specific frequency for a specified period of time, prior to recording the volume occupied by the powder that had been subjected to tapping. [6, 14]

The Hausner ratio can be used to ascertain whether a powder blend demonstrates good flow properties and a relationship between the ratio and type of flow exhibited is listed in table 4.9 [177].

**Table 4.9 Relationship between Hausner ratio and powder flow properties**

<b>Hausner Ratio</b>	<b>Flow Characteristics</b>
< 1.25	Good
> 1.5	Poor

The bulk density and tapped bulk density of powder were experimentally determined using the method described by Liu et al [173]. Approximately 30g of a powder blend was accurately weighed and transferred into a 50 ml graduated cylinder. The volume occupied by the powder was recorded and used to calculate the bulk density of the powder using Equation 4.1. The graduated measuring cylinder was then tapped manually 200 times at a rate of 30 taps per minute to determine the tapped bulk density. The Hausner ratio was then calculated using Equation 4.2 and the resultant values are listed in Table 4.10.

**Table 4.10 Hausner ratio for capsule and IR tablet blends**

<b>Formulation</b>	<b>Hausner ratio</b>
<b>PC022RW</b>	1.21
<b>PC023</b>	1.12
<b>PC024</b>	1.18
<b>PC025</b>	1.11
<b>PC026</b>	1.18
<b>HCTZ001</b>	1.21
<b>HCTZ002</b>	1.23

The Hausner ratio analysis of the capsule powder and HCTZ IR tablet blends reveal that all values are < 1.5 indicating that the blends demonstrate good flow characteristics. However, following manufacture the content and weight variation of the IR HCTZ IR tablets produced by DC reveal a large degree of variation. It was thought that inconsistency in the blending time of these dosage forms, and factors such as temperature and humidity may have induced variability seen in the physical parameters for these batches.

### 4.6.3. Carr's Compressibility Index

Carr's Compressibility Index (CI) can also be used as an index of powder flow and is based on experimental research undertaken in which interparticle cohesive properties are investigated [175]. The results of these studies revealed that the density of a powder depends on particle packing properties and that the density of a powder changes as the powder packing is consolidated [175]. The CI for blends used in these studies was calculated, using the bulk and tapped densities determined as described in Section 4.6.2, using Equation 4.3. A relationship for the CI and the type of flow properties exhibited is shown in Table 4.11 [177]. The results obtained by calculating the CI for the blends under investigation are shown in Table 4.12.

$$CI = (TD - BD) \times \frac{100}{TD} \quad \text{Equation 4.3}$$

where,

*CI* = Carr's compressibility index

*TD* = tapped density

*BD* = bulk density

**Table 4.11 Relationship between Carr's index and powder flow properties**

<b>Carr's Index</b>	<b>Flow Characteristics</b>
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair
23 – 35	Poor
33 – 38	Very poor
> 40	Bad Flow

**Table 4.12 Carr's Compressibility Index for capsule and IR tablet blends**

<b>Formulation number</b>	<b>Carr's index</b>
<b>PC022RW</b>	21.21
<b>PC023</b>	12.12
<b>PC024</b>	17.65
<b>PC025</b>	10.81
<b>PC026</b>	18.18
<b>HCTZ001</b>	20.93
<b>HCTZ002</b>	23.33

The CI index analyses of the powder blends show that all values are between 10 and 24, indicating that the tested blends show fair to good flow properties. These results are consistent to those obtained when testing the blends by the Hausner ratio and the static angle of repose respectively. As previously mentioned these results are contradictory in comparison to those obtained for the physical test parameters for the HCTZ tablets.

#### 4.6.4. Static Angle of Repose (AOR)

The AOR is another parameter used as a measure of powder flow characteristics and properties [171-173 176]. The AOR of the powder blends under investigation were determined experimentally by use of a funnel placed 2cm above a glass plate and into which the powder mass was filled. The powder was released from the funnel in such a way so as to form a cone at the tip of the funnel. The height and diameter of the cone were then measured and used to calculate the AOR with the aid of Equation 4.4 [171, 172].

$$\text{Tan}\alpha = \frac{2h}{d} \quad \text{Equation 4.4}$$

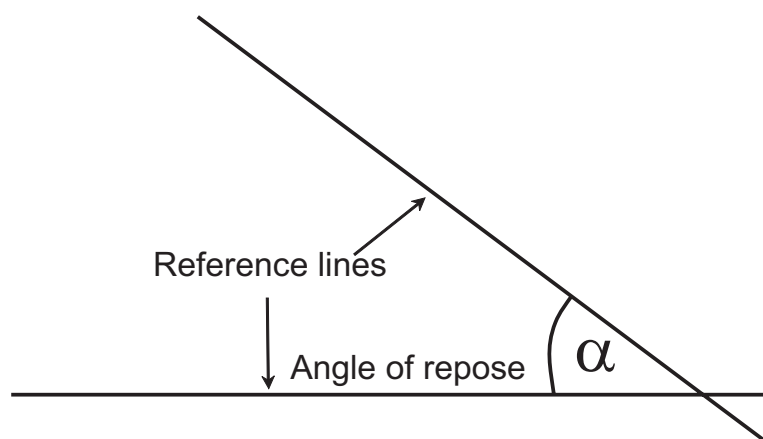
where,

$\alpha$  = angle at the base of the cone

$h$  = height of the powder cone

$d$  = diameter of the powder cone

A schematic representation of the apparatus used to determine the AOR is shown in Figure 4.20 [171]. The relationship between the AOR and powder flow properties is shown in Table 4.13 [177] and the results of AOR determinations for the powders under investigation in these studies are listed in Table 4.14. It is evident that all powders possessed passable flow properties.



**Figure 4.20** Schematic diagram for the measurement of AOR

**Table 4.13 Relationship between AOR and powder flow properties**

<b>Angle of Repose (<math>\alpha</math>)</b>	<b>Flow Characteristics</b>
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very Poor

**Table 4.14 AOR values for capsule fill and IR tablet powder blends**

<b>Formulation</b>	<b>Angle of repose (<math>\alpha</math>)</b>
<b>PC022RW</b>	30.90
<b>PC023</b>	27.60
<b>PC024</b>	30.30
<b>PC025</b>	23.80
<b>PC026</b>	29.20
<b>HCTZ001</b>	22.80
<b>HCTZ002</b>	29.10

Analyses of capsule and HCTZ IR powder blends by the AOR show that all values fall between 22 and 31. These results reveal that all the blends tested show good to excellent powder flow properties. The analyses performed by the AOR are consistent with those obtained for the Hausner ratio and the CI.

#### 4.6.5. Conclusion

The flow properties of the capsule blends and the two HCTZ IR batches were assessed by the three parameters, namely the Hausner ratio, CI and the AOR. All of the blends tested reveal values for each model that is indicative of good powder flow; however some of these results appear contradictory when evaluating the results of physical testing in particular with respect to content uniformity and weight variation. The weight variation in the capsule dosage form can be attributed to the manual filling process and the different amounts required to achieve the relevant doses in each batches as described previously in Section 4.4. Chowlan and Yang [178] reported that the incorporation of glidants and lubricants may increase the powder flowability but may adversely affect the tensile strength of the powder bed [178]. Both the HCTZ batches had the same amount of glidant and lubricant and this may have had an impact on the variance of tensile strength observed. The two HCTZ IR dosage forms manufactured by direct compression follow the trend observed when PHCL SR direct compression matrices were manufactured, in that they show poor physical parameters and poor content uniformity. As previously described in Section 3.6.7, there are various factors that may influence the tablet compaction process that may have introduced variability in the direct compression dosage forms, and these were thought to account, in part for the variability seen in the HCTZ tablet dosage forms.

#### 4.7. Conclusions

The release of PHCL, a water-soluble beta-blocker can be retarded to a certain extent, by wet granulation manufacturing processes that use aqueous polymeric dispersions as granulating fluids. The greatest effect on release rates were observed when Surelease<sup>®</sup> E7-19010 in combination with ATEC was used as a granulating fluid to produce granules that were mixed with HPMC to form a blend that was filled into hard gelatin capsules. The results reveal that an intermediate to high content of HPMC is necessary to achieve the desired drug release rates, such that the test product produced is comparable to that of the innovator product, Inderal<sup>®</sup> LA capsules. The tablet dosage forms manufactured using both the polymeric dispersions were unsatisfactory in terms of their drug release characteristics which were not equivalent to those shown by Inderal<sup>®</sup> LA based on difference and similarity factors.

The HCTZ IR component was successfully introduced into the capsule dosage form with minimal rate retardant effects. A once daily PHCL SR dosage form has been developed that has been shown to produce similar dissolution profiles in comparison to the innovator product Inderal<sup>®</sup> LA 80 mg capsules and that has the potential for use with HCTZ IR tablets as a combination product as a once a day treatment for hypertension.

## CHAPTER 5

### MODEL INDEPENDENT AND MODEL DEPENDENT ANALYSIS OF DISSOLUTION DATA

#### 5.1. Introduction

Dissolution testing was initially introduced in order to characterise the dissolution rate profiles of low solubility compounds (< 1% m/v) in aqueous media [179, 180]. The increased use of dissolution testing has been attributed to the growing demand by regulatory authorities such as the Food and Drug Administration (FDA) [181], the European Agency for Evaluation of Medicinal Products (EMA) [182], and others such as the Medicines Control Council of South Africa (MCC) [183] to provide *in-vivo* predictability of the release and absorption behaviour of drugs in relevant dosage forms by means of *in-vitro* testing. Dissolution testing is a tool that can provide guidance to a formulator with respect to the manipulation of formulation compositions during drug product and formulation development [179, 184, 185]. Dissolution testing can be used for the assessment and comparability of pharmaceutical products, and may serve as a surrogate for *in-vivo* bioequivalence studies where one can develop an appropriate *in-vitro/in-vivo* correlation [179, 184, 185].

The characterisation of drug release from a specific dosage form entails generating a dissolution profile in which drug release or dissolution rate is determined as a function of time [186]. Although dissolution testing has been successfully used for the characterisation of drug release from conventional immediate release dosage forms there has been difficulty in harmonizing test conditions and parameters for the successful monitoring of the dissolution process for modified release dosage forms [179, 185].

The comparative and quantitative analysis of data derived from dissolution testing is made simpler when mathematical models that express the results as a function of the characteristics of a dosage form are used for the purposes of such comparisons [187].

There are analyses that can be used for the comparison of dissolution profiles that are advocated for use by regulatory authorities such as the FDA, EMEA and the MCC [179-183]. Guidance documents produced by regulatory agencies provide direction for both academic and industrial researchers on the requirements that have to be met for dissolution testing and the assessment of newly developed products [179-183].

## 5.2 Model Independent Analysis

### 5.2.1. Introduction

Model independent analyses may be divided into pair wise comparison procedures and ratio tests [187]. The ratio tests determine the relationship between parameters obtained from the analysis of drug release from a reference formulation and the analysis of drug release from a test formulation at the same time point and include the determination of a simple ratio of percent drug dissolved at a specific time ( $t_x\%$ ), a ratio of area under the release curve (AUC), dissolution efficiency (DE) [187-190] or a ratio of mean dissolution times (MDT) [187, 188, 191-193].

Pair wise model independent procedures include the determination of the difference and similarity factors [185, 187, 188, 194] and the Resicigno index [184, 187, 188, 195].

Model-independent approaches make no assumptions as to the shape of the dissolution curve in comparison to model-dependent methods in which equations in which parameters that define the shape of a curve are optimised.

### 5.2.2. Dissolution Efficiency (DE)

The dissolution efficiency (DE) of a pharmaceutical dosage form can be defined as the area under the dissolution curve up to a specific time and can be expressed as a percentage of the area of a rectangle described by 100 % dissolution in the same time [187-190]. DE may be calculated using Equation 5.1.

$$DE = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\% \quad \text{Equation 5.1}$$

where,

$y$  = percent drug dissolved at time =  $t$ .

The DE can have a range of values depending on the time intervals that are selected for evaluation [190]. This model has certain advantages in that it can summarize drug release data into a single figure that enables comparison between a large number of formulations [190] and can be theoretically related to *in-vivo* data [190].

### 5.2.3. Mean Dissolution Time (MDT)

The mean dissolution time (MDT) is a model independent ratio that can be calculated using Equation 5.2 [187, 188, 191-193]. The MDT applies statistical moment analysis to the assessment of dissolution rate data and is an alternative to calculating  $c_{\max}$  and  $t_{\max}$  for evaluating the comparative *in-vivo* absorption rates of different formulations [193].

$$MDT = \frac{\sum_{j=1}^n t_j \Delta M_j}{\sum_{j=1}^n \Delta M_j} \quad \text{Equation 5.2}$$

where,

$j$  = the sample number,

$n$  = the number of dissolution sample times

$t_j$  = the time at the midpoint between time =  $t_j$  and  $t_{j-1}$

$\Delta M$  = the additional drug dissolved between time =  $t_j$  and  $t_{j-1}$

This model has some limitations in that, under certain conditions the accuracy of the MDT value tends to decrease as the multi-exponential character of the concentration time curve become more pronounced [193].

### 5.2.4. Difference and Similarity factors

The difference and similarity factors, commonly known, as  $f_1$  and  $f_2$  fit factors are model independent pair wise comparisons originally reported by Moore and Flanner [194]. These parameters are currently recommended for use in most guidance documents [181-183] published by regulatory agencies for the comparison of dissolution profiles [181-183]. The regulatory requirement as set by the FDA specifies

that a minimum of 12 dosage units from each manufactured batch should be tested with suitable sampling times [181].

The difference factor ( $f_1$ ) is calculated using Equation 5.3 and is the sum of absolute values of the vertical distances between the test and reference values at each dissolution time point, and is expressed as the percent of the sum of the mean fraction released from a reference formulation at each time point [194]. The percent error is zero if the test and reference profiles are exactly the same and increases proportionally as the two profiles become different from each other [194].

$$f_1 = \frac{\sum_{j=1}^n |R_j - T_j|}{\sum_{j=1}^n R_j} \times 100 \quad \text{Equation 5.3}$$

where,

$n$  = the sample number

$R_j$  = the percent drug dissolved from the reference product at  $t = j$

$T_j$  = the percent drug dissolved from the test product at  $t = j$ .

The similarity factor ( $f_2$ ) calculated using Equation 5.4 and is the logarithmic reciprocal square root transformation of one plus the mean squared or average sum of squared differences of percent drug dissolved, between the test and the reference products [185, 187, 194]. The similarity factor fits a result between 0 and 100, and the value for  $f_2$  is 100 when the test and reference profiles are identical [187, 194].

$$f_2 = 50 \times \log \left\{ \left[ 1 + \left( \frac{1}{n} \right) \sum_{j=1}^n w_j |R_j - T_j|^2 \right]^{-0.5} \right\} \times 100 \quad \text{Equation 5.4}$$

The fit factors are advantageous to use for dissolution curve comparison, as they are easy to compute and provide a single number for the purposes of describing two dissolution profiles. They do however have certain limitations in that they do not take into account, the variability or correlation of structure and they are sensitive to the number of dissolution time points used [185, 187]. In addition, in many cases, the

basis for determining whether two dissolution profiles are similar or different is unclear [185].

### 5.2.5. The Rescigno Index

The Rescigno index ( $\xi_i$ ) may be calculated using Equation 5.5 and is a model-independent analysis that was proposed by Rescigno [195] as a bioequivalence index to measure the dissimilarity between a reference and a test product based on the plasma concentrations as a function of time [195]. The Rescigno index may also be applied to dissolution curve analysis [195] and is equal to zero when two dissolution profiles are identical and is one when drug is not released from either the test or reference product [195].

$$\xi_i = \left\{ \frac{\int_0^{\infty} |d_R(t) - d_T(t)|^i dt}{\int_0^{\infty} |d_R(t) + d_T(t)|^i dt} \right\}^{1/i} \quad \text{Equation 5.5}$$

where,

$d_R(t)$  = the amount of drug dissolved from the reference product at each time point

$d_T(t)$  = the amount of drug dissolved from the test product at each time point

$i$  = any positive integer number

The Rescigno index has advantages and disadvantages in that it provides a single number for the comparison of dissolution profiles [195] and the indices do not change when test and reference products are changed, however, it is harder to compute than the fit factors described in Section 5.2.4 and does not take into account the variability or correlation structure of the data [185].

### 5.2.6. $S_d$

A new factor,  $S_d$ , has been proposed by Gohel and Panchal [173] for the purposes of describing dissolution profile similarity [173]. The value for  $S_d$  can be calculated using Equation 5.6 and describes a model-independent method in which the ratio of

AUC for test and reference products are used to determine the difference of the amount of drug dissolved from the products. There is no real number associated with the similarity of the curves, however the  $S_d$  expresses the difference between the test and reference products as a percentage where the closer the percentage value is to zero, the smaller the difference between the *in-vitro* dissolution profiles of the reference and test products [173]. The advantage of this model is its inherent simplicity and ease of interpretation.

$$S_d = \frac{\sum_{i=1}^{n-1} \left| \log \left( \frac{AUC_{Rt}}{AUC_{Tt}} \right) \right|}{n-1} \quad \text{Equation 5.6}$$

where,

$AUC_{Rt}$  = the area under the curve for the reference formulation  
 $AUC_{Tt}$  = the area under curve for the test formulation

### **5.2.7. Statistical Methods**

In addition to the methods previously described, conventional and other statistical test methods can be used for the comparison of dissolution profiles [185, 197, 198] including but not limited to, one- or two-way analysis of variance [185, 197, 198], mixed effects modelling or multivariate analyses [185, 197, 198] and the Chow and Ki method [199].

#### **5.2.7.1. One- and Two-way Analysis of Variance (ANOVA)**

The one-way analysis of variance procedure uses a separate statistical comparison of mean dissolution data at each sample point, and is equivalent to a t-test in the case in which dissolution profile data for two formulations are being compared [185]. This method of analysis is particularly useful as it takes into account the variability of dissolution data. However, disadvantages of this procedure include potentially large type 1 errors and the possibility of ambiguity in the interpretation of results [185].

The two-way analysis of variance method is a method whereby two variables, which may include formulation and time, are used for the analysis [185]. This model is advantageous as it uses only a single analysis as opposed to the need to conduct separate analyses as for the one-way ANOVA at each time point. However, disadvantages include the potential for a time effect to use too many degrees of freedom and therefore the assumption of independence between dissolution points may be violated [185].

ANOVA -based analyses rely on an underlying model, but are not considered as model-dependent since these procedures do not fit data to a curve generated by observed or experimental data [197, 198]. ANOVA analyses test dissolution profiles for statistical differences in level or size and shape or level [197, 198]. The results derived from the use of ANOVA tests at specific times demonstrate more statistical equivalence rather than pharmaceutical equivalence [197, 198].

### 5.2.7.2. Mixed effects models and Multivariate methods of Analysis

Mixed effects models use a mixture of fixed and random effects in the analysis of data. When comparing dissolution profiles, the fixed effect is the formulation, which has two levels if a test and reference formulation are being compared [185] and the random effects that are the dosage unit, for which each formulation has as many different levels as there are dosage units in a batch being tested [185]. This model has been used to determine whether the shapes of test and reference products are the same [185, 197, 199, 200]. These methods take into account the variability and correlation structure of the data under investigation and assume that they are compound symmetric, which in simple terms means that the correlation between two dissolution time points is the same regardless of the how far apart the timing intervals are [185].

Multivariate methods of analysis include the use of a multivariate ANOVA method such as the Hotellings  $T^2$  -test in which a coincidence hypothesis is tested or a method in which the Mahalanobis distance, which is a multivariate analogue of the two one-sided t-test procedure, is calculated [185, 197]. These models have various shortcomings and may not be very informative about the nature of differences between two mean dissolution profiles of a test and reference product [185].

### 5.2.7.3. Chow and Ki Method

Chow and Ki described a method for the comparison of dissolution profile data that can be regarded as similar to that used in the assessment of the average bioequivalence of two drug formulations [185, 199]. Test and reference formulations are bioequivalent if the ratio of the mean bioavailability parameters of AUC and  $C_{\max}$  lie between the 80-125 % limits of a 90 % confidence interval on the log transformed scale [185, 199]. The equivalence limits for similarity between test and reference products are derived from their mean dissolution rates [185, 199]. Chow and Ki use a ratio of mean dissolution rate to ascertain whether test and reference products are 'locally similar', *i.e.* when the test and reference products are within the defined equivalence limits at a given time point, and 'globally similar' if the products are similar at all specified time points [185, 199].

### **5.2.8. Conclusion**

There are a number of model independent methods of analysis that can be used to evaluate dissolution profile data that have been derived from various studies. However, there is a lack of harmonization as to which models should be used for the evaluation of dissolution rates from modified release dosage forms [185, 187].

The models that have been described are all extremely useful for the comparison and assessment of dosage forms, yet provide little or no information on the kinetics and mechanisms of drug release from a variety of modified release dosage forms [185].

The models used for the analyses of the dissolution data in these studies include the difference and similarity factors as they are advocated by regulatory authorities such as the FDA, EMEA and the MCC of South Africa for the comparison of dissolution data [181-183]. The models based on statistical methods, whilst having their place in academic research studies and are proposed by various literature sources for comparison of dissolution data, are not advocated by these regulatory agencies and hence analyses by these methods were not performed.

## 5.3. Model Dependent Analysis

### 5.3.1 Introduction

The application of mathematical modelling using defined equations is useful in the design of new controlled release dosage forms as it can provide information on mass transport release mechanisms that govern the release of a drug from a specific system. In addition, these models can be used to quantitatively predict the kinetics of drug release from specific dosage forms [201, 202].

Drug release kinetics from HPMC monolithic matrix device systems may be influenced by a variety of factors including the composition of the matrix device *i.e.*, type and amount of drug, the geometry of a system [201], the solubility of the drug in the matrix material [191, 201] and the dynamics of the gel layer in which the drug is dissolved, including thickness and viscosity, [201]. In addition, drug release may be limited by the rate of dissolution medium infiltration into the drug delivery device [191, 201].

There are simple empirical or semi-empirical models such as those defined by Higuchi [187, 188, 201-204] and Korsmeyer-Peppas, also known as the “power law” [187, 201, 205-212] that can be applied to characterise drug release profiles and elucidate the mechanisms of drug release from HPMC monolithic devices. The empirical models include those described in Sections 5.3.2- 5.3.9. In addition, more mechanistic theories that consider diffusion, swelling and dissolution processes simultaneously have also been defined [213-217].

### 5.3.2. The Zero Order Model

The dissolution of an API from dosage forms that do not disintegrate or deaggregate and release drug at a constant rate may be characterised or represented by a zero-order model [187, 218]. Dosage forms that follow a zero-order model release mechanism, release the API in a constant amount per unit time. Zero order release is an ideal target for sustained drug delivery formulation development in order to achieve a prolonged pharmacological action [187, 218], and zero order models usually take the form as represented in equation 5.7.

$$Q_t = Q_0 + K_0t \quad \text{Equation 5.7}$$

where,

$Q_t$  = the amount of drug released at time =  $t$   
 $Q_0$  = the initial amount of drug in solution at  $t = 0$   
 $K_0$  = the zero-order release rate constant  
 $t$  = time

### 5.3.3. The First Order Model

The first order kinetic model was initially proposed by Gibaldi and Feldman [219] and later by Wagner [220], where it was used to describe and characterise the absorption and/or elimination of certain drugs from biological systems [220]. The first order kinetic model can be represented by equation 5.8. This model may be applied to dissolution testing where sink conditions exist, as the percentage of drug dissolved at a certain time point may be equivalent to the percentage surface area at that time point [220].

$$\ln Q_t = \ln Q_0 + K_1t \quad \text{Equation 5.8}$$

where,

$Q_t$  = the amount of drug released at time =  $t$   
 $Q_0$  = the initial amount of drug in solution at  $t = 0$   
 $K_1$  = the first order release rate constant  
 $t$  = time

#### 5.3.4. The Higuchi Model

The Higuchi model [203, 204] describes the dissolution of drugs in suspension from a non-eroding matrix such as an ointment base. The model is applicable for the description of dissolution rates that are observed for pharmaceutical dosage forms other than ointments [187, 204]. Higuchi described drug release as a diffusion process, fundamentally based on Ficks law, but that is dependent on the square root of time. This description of drug release can be used to characterize the dissolution process from several types of modified release systems [187, 204] and a simple form of Higuchi equation is shown in Equation 5.9.

$$f_t = K_H t^{1/2} \quad \text{Equation 5.9}$$

where,

$K_H$  = Higuchi dissolution rate constant

$f_t$  = the amount of drug released at time =  $t$

$t$  = time

Higuchi also developed several other theoretical models to describe release from spherical homogenous, planar or spherical systems manufactured from heterogeneous matrices [187, 203, 204]. An advantage of the Higuchi model is its simplicity, however due to the inherent simplistic nature of the model it is difficult to make definite mechanistic conclusions about drug release when applying the model [202].

#### 5.3.5. The Hixon Crowell Model

Hixon and Crowell [221] recognised that the regular area of a particle is directly proportional to the cubic root of its volume and developed a mathematical relationship to describe this phenomenon and which is defined in Equation 5.10. [221]. This expression can be applied to pharmaceutical dosage forms, such as tablets in which, dissolution occurs in planes that are parallel to the surface of a drug, and in which the tablet dimensions diminish proportionally whilst the geometrical shape of the dosage form remains constant [187]. This model has some disadvantages as it assumes that the release rate of drugs from a dosage form is limited by the drug particle dissolution rate [187, 221].

$$W_0^{1/3} - W_t^{1/3} = K_s t \quad \text{Equation 5.10}$$

where,

$W_0$  = the initial amount of drug in a pharmaceutical dosage form  
 $W_t$  = the remaining amount of drug in a pharmaceutical dosage form  
 $K_s$  = a constant incorporating the surface volume relationship  
 $t$  = time

### 5.3.6. The Baker Lonsdale Model

The Baker-Lonsdale model [222] was developed as an extension of the Higuchi model and describes controlled drug release from a spherical matrix that is depicted by the mathematical relationship shown in Equation 5.11 [187, 222].

$$\left(\frac{3}{2}\right) \left[ 1 - \left(\frac{Q_t}{Q_\infty}\right)^{2/3} \right] - \left(\frac{Q_t}{Q_\infty}\right) = K_B t \quad \text{Equation 5.11}$$

where,

$Q_t$  = the amount of drug remaining in a pharmaceutical dosage form at time =  $t$   
 $Q_\infty$  = the maximal amount of drug released from a dosage form in infinite time  
 $K_B$  = the Baker-Lonsdale constant  
 $t$  = time

The Baker Lonsdale model assumes that there is a uniform initial drug concentration and constant diffusivities [202].

### 5.3.7. The Weibull Model

The Weibull model [223] is a general empirical equation. Langenbucher [224] used the empirical relationship proposed by Weibull [223] for the quantitation of dissolution rate data, using a linearized equation adapted from the Weibull distribution. This linearized equation is depicted in Equation 5.12 [224]. The major advantage of this model is that it can describe common types of dissolution curves satisfactorily, as it combines the advantages of first order and log-normal data presentations [224]. It is not without its disadvantages, as data may have to be manipulated in order to define the best linearization of the data [224].

$$\text{Log} \left[ -\ln \left( 1 - \left( \frac{Q_t}{Q_\infty} \right) \right) \right] = \beta \log t - \log \alpha \quad \text{Equation 5.12}$$

where,

- $Q_t$  = the amount of drug remaining in a pharmaceutical dosage form at time =  $t$
- $Q_\infty$  = the maximal amount of drug that can be released at infinite time from a pharmaceutical dosage form
- $\beta$  = shape parameter, obtained from the slope of the line
- $\alpha$  = the scale parameter
- $t$  = time

The Weibull model can be used to characterise the shape of a dissolution curve. The shape parameter,  $\beta$  can be exponential or case 1, in which  $\beta=1$ , sigmoidal or S-shaped, with an upward curvature followed by a turning point, or case 2 in which case  $\beta>1$  or parabolic, with an higher initial slope and after that, a consistent slope with an exponential or case 3, in which case  $\beta<1$  [187, 198, 224].

### 5.3.8. The “Power Law”

A simple semi-empirical model that relates drug release to elapsed time with an exponential function has been reported [205]. This relationship is referred to as the Korsmeyer-Peppas model [205] or the “Power law” and is represented mathematically using Equation 5.13.

$$\frac{M_t}{M_\infty} = Kt^n \quad \text{Equation 5.13}$$

where,

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

$k$  = a kinetic constant

$n$  = diffusion exponent for drug release

This model has been applied to various systems in which the value for  $n$  is used to describe different release mechanisms [187, 202, 205-212]. Specific values for  $n$  represent different mechanisms and/or types of release that may occur from these dosage forms and a summary of these descriptions are listed in Table 5.1. It must be emphasized that the value for  $n$  describes mechanisms of release in specific geometric shapes.

**Table 5.1 Relationship between the release exponent  $n$  and mechanism of drug transport**

Release exponent (n)	Shape	Drug Transport Mechanism	Reference
0.43	Sphere	Fickian	187, 202, 205-208, 210, 211
0.43 < n < 0.85	Sphere	Anomalous	187, 202, 205-208, 210, 211
0.85	Sphere	Case-II transport	187, 202, 206-208, 210
> 1.0	Sphere	Super Case-II transport	187, 202, 205, 207, 208
0.45	Cylinder	Fickian	202, 206
0.5 < n < 0.89	Cylinder	Anomalous	202, 206
0.89	Cylinder	Case-II transport	202

The relationships described in Table 5.1 show that the release from polymer matrices as described from Equation 5.14 may occur due to one of four types of mechanism of release, *viz.*, Fickian diffusion, anomalous diffusion, case II and super case II.

In general Fickian or non-fickian diffusion is observed depending on the state of the polymer matrix [202, 205, 207]. Fickian diffusion occurs when drug release follows the diffusion process as described by Ficks 2<sup>nd</sup> law of diffusion through thin films

[202, 205], and is generally observed when water diffusion controls the drug release process [210]. Anomalous transport occurs when drug release deviates from Ficks law [202, 205] and where drug release is both diffusion and swelling controlled [205]. Case II transport represents drug release that is zero- order [202, 205, 215] and is generally observed when macromolecular relaxations predominate and control drug release [210]. Super case II transport is where drug delivery rates increase over time [207].

### 5.3.9. The Hopfenburg Model

Hopfenburg analysed the release of drugs from self-eroding matrices with different geometries and developed a mathematical relationship to describe the resultant drug release profiles which is depicted in Equation 5.14 [225-227].

$$\frac{M_t}{M_\infty} = 1 - \left( 1 - \frac{k_0}{C_0 r_0} \right)^n \quad \text{Equation 5.14}$$

where,

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

$k_0$  = the erosion rate constant

$C_0$  = the intial concentration of uniformly distributed drug in a matrix

$r_0$  = the initial radius of a sphere or cylinder

$n$  = the exponent describing the type of device

This model proposed by Hopfenburg assumes that drug release occurs from the surface of an eroding matrix device [226, 227] and that the resultant release kinetics are not influenced by time dependent internal or external diffusional resistances [226, 227], and where the erosion of the matrix is the rate controlling step for drug release [226, 227]. The constraints of the model is an inherent disadvantage as when modelling drug release from tablets that have erosion properties, contribution of the eroding areas of the device cannot be neglected and are not accounted for in the model [226]. This model was not applied to the dissolution data due to its assumptions and constraints.

### 5.3.10. Conclusion

There are an abundance of mathematical models that can be applied to the analysis of dissolution data. The models described herein include both empirical and semi-empirical models that can be applied to the evaluation of dissolution rate data. The use of these models permits the elucidation of the mechanism and type of drug release that can be expected from certain types of modified release dosage forms that are based on matrix systems.

The coefficient of determination ( $R^2$ ) [228] value can be used as a measure of the best fit of data to a specific model, and where there are a number of comparisons to be performed by varying model parameters [228]. Besides the coefficient of determination other parameters such as the Akaike's information criterion (AIC), or the Bayesian information criterion (BIC) have been used to select the best model for data analyses performed [229].

The experimentally derived dissolution data obtained from dissolution studies for dosage forms manufactured during these studies were subjected to mathematical analyses using selected models that are listed in Table 5.2 and the coefficient of determination was used as the single criterion to ascertain which mathematical model best fitted the dissolution data generated during these studies.

**Table 5.2 Mathematical models applied to the analysis of dissolution data**

<b>Mathematical models used to describe drug dissolution curves</b>	
<b>Zero order</b>	$Q_1 = Q_0 + K_0 t$
<b>First order</b>	$\ln Q_t = \ln Q_0 + K_1 t$
<b>Higuchi</b>	$f_t = K_H t^{1/2}$
<b>Hixon-Crowell</b>	$W_0^{1/3} - W_t^{1/3} = K_s t$
<b>Baker-Lonsdale</b>	$\left(\frac{3}{2}\right) \left[ 1 - \left(\frac{Q_t}{Q_\infty}\right)^{2/3} \right] - \left(\frac{Q_t}{Q_\infty}\right) = K_B t$
<b>Weibull</b>	$\text{Log} \left[ -\ln \left( 1 - \left(\frac{Q_t}{Q_\infty}\right) \right) \right] = \beta \log t - \log \alpha$
<b>Korsmeyer-Peppas</b>	$\frac{M_t}{M_\infty} = K t^n$

## 5.4. Results

### 5.4.1. Model-Independent Analysis

The results of model independent analyses of dissolution profiles, *viz.*, the difference and similarity fit factors,  $f_1$  and  $f_2$  and the  $S_d$  value are listed in Table 5.3. The data summarize the results generated for the analysis of dissolution data for batches PC001-PC010 that were manufactured by DC and for batches PC011-PC026 that were manufactured by wet granulation. The dissolution data obtained for Inderal<sup>®</sup> LA capsules, the reference product, were used as the reference data. The results represent analysis of the dissolution profiles over a 24-hour period for all batches except for batches PC015 and PC016, which were only subjected to dissolution testing for 14 hours.

**Table 5.3 Results of model-independent analysis**

<b>Formulation Batch Number</b>	<b><math>f_1</math></b>	<b><math>f_2</math></b>	<b><math>S_d</math></b>
PC001	67.15	25.36	1.03
PC002	64.78	26.35	0.98
PC003	54.06	30.50	0.81
PC004	64.43	26.68	0.94
PC005	52.25	31.41	0.62
PC006	38.52	38.29	0.51
PC007	63.27	27.60	0.72
PC008	61.38	27.96	0.69
PC009	74.90	23.72	0.79
PC010	48.41	32.92	0.56
PC011	21.58	47.98	0.19
PC012	43.32	34.98	0.45
PC013	59.08	27.41	0.48
PC014	58.59	27.98	0.51
PC015	27.35	46.86	0.28
PC016	67.66	28.33	0.55
PC017	27.97	43.87	0.33
PC018	28.62	43.23	0.31
PC019	26.05	45.49	0.31
<b>*PC020A</b>	<b>19.33</b>	<b>50.56</b>	<b>0.14</b>
PC020B	24.33	46.97	0.25
PC021TC	23.34	46.74	0.44
<b>*PC021 Capsules</b>	<b>5.01</b>	<b>79.23</b>	<b>0.14</b>
<b>*PC022RW</b>	<b>18.01</b>	<b>54.13</b>	<b>0.37</b>
PC023	28.88	43.22	0.27
<b>*PC024</b>	<b>8.59</b>	<b>61.65</b>	<b>0.04</b>
<b>*PC025F2</b>	<b>7.42</b>	<b>69.23</b>	<b>0.11</b>
PC026	54.99	29.28	0.51

\*Shaded areas represent passed  $f_1$  and/or  $f_2$  test and the corresponding  $S_d$  value

It is clearly evident that all batches manufactured by DC failed the test for similarity when using  $f1$  and  $f2$  as indicators of similarity. The  $S_d$  values exceeded 0.5 for all DC batches indicating that there was little or no similarity between the test and reference dissolution profiles, as the smaller the  $S_d$  value the closer the dissolution profiles for test and reference products are [196].

The results of model independent analyses that are listed in bold and in shaded cells in Table 5.4 indicate that for these comparisons the test products are similar to the reference product and for which the best results were obtained for batches PC021, PC024 and PC025F2 with respect to  $f1$  and/or  $f2$  and  $S_d$  values. These values show that the test products are comparable to the innovator product, Inderal<sup>®</sup> LA capsules, based on *in-vitro* dissolution data.

The results obtained for batches PC020A and PC022RW reveal that based on  $f2$  alone the profiles may be considered similar to that of the Inderal<sup>®</sup> LA capsules. However, the  $f1$  and  $S_d$  values for these two batches suggest that the profiles are different. Regulatory agencies such as the FDA [157] recommend that  $f2$  values be used for these comparisons and on this basis the curves would be considered similar. For the purposes of these studies, both the  $f1$  and  $f2$  values must fall within the requisite specifications and therefore these batches are not equivalent to the reference product.

#### **5.4.2 Model Dependent Analysis**

Model dependent analysis was performed on the dissolution data of all batches and the results of model fitting are listed in Tables 5.4 and 5.5 for the batches manufactured by DC and WG, respectively. The resultant dissolution profiles that were subjected to analysis were modelled using *GraphPad Prism Version 4.00* for windows (GraphPad Software Inc, San Diego USA).

**Table 5.4 Results of model dependent analysis of all dosage forms manufactured by DC**

<b>Formulation Batch Number</b>	<b>Zero order R<sup>2</sup></b>	<b>First order R<sup>2</sup></b>	<b>Higuchi R<sup>2</sup></b>	<b>Hixon-Crowell R<sup>2</sup></b>	<b>Baker-Lonsdale R<sup>2</sup></b>	<b>Weibull</b>			<b>Korsmeyer-Peppas</b>		
						<b>R<sup>2</sup></b>	<b><math>\alpha</math></b>	<b><math>\beta</math></b>	<b>R<sup>2</sup></b>	<b><i>n</i></b>	<b><i>k</i></b>
<b>PC001</b>	0.42	0.41	0.71	0.49	0.26	0.83	5.11	0.78	0.75	0.17	0.23
<b>PC002</b>	0.46	0.44	0.75	0.54	0.28	0.88	3.99	0.89	0.78	0.20	0.22
<b>PC003</b>	0.55	0.50	0.82	0.64	0.32	0.93	2.25	1.03	0.84	0.29	0.19
<b>PC004</b>	0.49	0.46	0.77	0.57	0.29	0.87	3.28	1.01	0.80	0.23	0.22
<b>PC005</b>	0.68	0.59	0.90	0.76	0.38	0.93	0.93	1.61	0.90	0.44	0.15
<b>PC006</b>	0.77	0.69	0.95	0.88	0.42	0.97	0.81	1.41	0.95	0.46	0.13
<b>PC007</b>	0.72	0.64	0.93	0.89	0.36	0.95	0.47	2.40	0.93	0.42	0.17
<b>PC008</b>	0.68	0.60	0.90	0.80	0.37	0.95	0.70	2.07	0.91	0.43	0.16
<b>PC009</b>	0.66	0.57	0.89	0.88	0.34	0.94	0.20	3.59	0.89	0.41	0.18
<b>PC010</b>	0.76	0.68	0.95	0.87	0.41	0.93	0.56	1.89	0.95	0.48	0.13

**Table 5.5 Results of model dependent analyses of all dosage forms manufactured by WG and for Inderal® LA capsules**

Formulation Batch Number	Zero order	First order	Higuchi	Hixon-Crowell	Baker-Lonsdale	Weibull			Korsmeyer-Peppas		
	R <sup>2</sup>	R <sup>2</sup>	R <sup>2</sup>	R <sup>2</sup>	R <sup>2</sup>	R <sup>2</sup>	$\alpha$	$\beta$	R <sup>2</sup>	<i>n</i>	<i>k</i>
PC011	0.86	0.73	0.98	0.94	0.52	0.93	0.58	1.37	0.97	0.61	0.06
PC012	0.78	0.66	0.95	0.89	0.44	0.95	0.55	1.80	0.94	0.53	0.11
PC013	0.81	0.68	0.95	0.99	0.43	0.63	0.81	3.81	0.95	0.59	0.11
PC014	0.76	0.63	0.93	0.85	0.42	0.85	0.17	3.29	0.93	0.55	0.12
PC015	0.95	0.89	0.99	0.99	0.61	0.87	0.70	1.30	1.00	0.63	0.07
PC016	0.90	0.82	0.99	1.00	0.53	0.86	0.30	2.74	0.98	0.60	0.12
PC017	0.85	0.75	0.98	0.94	0.48	0.93	0.58	1.47	0.98	0.55	0.09
PC018	0.85	0.73	0.98	0.94	0.49	0.93	0.56	1.50	0.97	0.56	0.08
PC019	0.86	0.75	0.99	0.96	0.48	0.92	0.59	1.42	0.98	0.55	0.09
PC020A	0.82	0.67	0.96	0.89	0.52	0.96	0.67	1.24	0.95	0.62	0.05
PC020B	0.79	0.66	0.95	0.87	0.49	0.97	0.75	1.23	0.94	0.57	0.08
PC021TC	0.86	0.61	0.94	0.91	0.61	0.93	0.42	1.50	0.92	0.96	0.13
PC021Capsules	0.88	0.71	0.98	0.94	0.59	0.96	0.73	0.90	0.96	0.68	0.01
PC022RW	0.92	0.75	0.98	0.95	0.65	0.94	0.74	0.73	0.98	0.73	0.07
PC023	0.83	0.68	0.97	0.93	0.49	0.95	0.59	1.46	0.95	0.59	0.08
PC024	0.92	0.76	0.99	0.98	0.58	0.89	0.58	1.15	0.98	0.67	0.01
PC025F2	0.90	0.79	0.99	0.96	0.53	0.89	0.83	0.85	0.98	0.54	0.05
PC026	0.84	0.73	0.97	0.99	0.43	0.87	0.19	2.92	0.97	0.55	0.12
Inderal® LA	0.84	0.68	0.97	0.90	0.54	0.98	0.86	0.83	0.95	0.60	0.03

Batches PC005-PC010 produced by DC showed higher  $R^2$  values for all models tested than batches PC001-PC004, with batches PC006 and PC010 having the best coefficients of determination for all analyses. Batches PC006 and PC010 were manufactured using a high percentage of the high viscosity grade HPMC polymer and Eudragit<sup>®</sup> L100-55, whereas other dosage forms were manufactured using a low viscosity grade HPMC and the polymethacrylate, Eudragit<sup>®</sup> RS. These batches, namely PC006 and PC010 were probably best fit to these models due to the fact that these batches demonstrate slower rates of drug release compared to other batches manufactured by the DC process.

The mechanism of release from batches PC005-PC010 as determined by the Higuchi model is indicative of a diffusion-controlled process where Fickian type diffusion is predominant. As previously mentioned the Higuchi model is simplistic and it is difficult to make mechanistic conclusions. The power law however, can characterise the mechanistic type of release that may be observed from matrix type systems. The data was further analysed by evaluating the  $n$  value obtained following fitting of the data to the power law, and as all  $n$  values for batches PC005-PC010 ranged between 0.41 and 0.48, values that may be indicative of Fickian diffusion.

The products in which Eudragit<sup>®</sup> polymeric dispersion were used as the granulating fluid produced dissolution characteristics that were best fitted to both the Higuchi and Hixon-Crowell models when using  $R^2$  values for evaluating the goodness of fit. In addition, the Korsmeyer-Peppas model produced  $n$  values ranging between 0.53- 0.61 which is indicative of drug transport occurring by an anomalous diffusion process. The goodness of fit appeared to be a function of the amount of granulating fluid used as an increase in the  $R^2$  values was observed with an increase in the amount of granulation fluid, resulting in a better fit and in which the  $n$  values were indicative of drug transport occurring by a mechanism in which polymer relaxation is also a contributing factor.

The products in which Surelease<sup>®</sup> E7-19010 was used as the granulating fluid were best fitted to the Higuchi, Hixon-Crowell and the Korsmeyer-Peppas models, except for batches PC020A and PC020B for which the best  $R^2$  value were obtained following fitting of the dissolution curves to the Weibull function. These results imply that for

batches PC020A and PC020B, that there is a lag phase before the commencement of drug release. A closer look at the dissolution profiles of these products are shown in Section 4.3.3 and Appendix I reveals that there is no obvious lag phase, which is contradictory to what modelling of the data suggest. Therefore it can be concluded that the Weibull function may not be an entirely appropriate model to use for the characterization of dissolution data from these dosage forms.

The fitting to the Higuchi and Korsmeyer-Peppas models for the other batches that contained Surelease<sup>®</sup> E7-19010 implies diffusion controlled processes, whereas fitting to the Hixon-Crowell implies that drug release has a surface-volume relationship, and where the dissolution occurs in planes parallel to the drug surface.

The use of an increased amount of Surelease<sup>®</sup> E7-19010 as the granulating fluid appeared to have varying effects on model fitting and more specifically when calculating the  $n$  value as a result of fitting dissolution data to the “power law”. These varied effects may be attributed to the use of other excipients and grades thereof in the production of these dosage forms. The  $n$ -values derived from model fitting were found to range between 0.5 and 1.0, which is indicative that drug release is a consequence of anomalous mass transport processes occurring within these dosage forms. This implies that drug release from matrices is both diffusion and swelling controlled which deviates from Ficks 2<sup>nd</sup> law of diffusion.

The innovator product Inderal<sup>®</sup> LA 80 mg capsules was best fitted to the Higuchi, Weibull and Korsmeyer-Peppas models and the resultant  $n$  values revealed that drug release from these capsules is characteristic of an anomalous drug transport process. As previously mentioned data fitting to the Weibull model was considered inappropriate.

The fitting and resultant analyses by the Higuchi and Korsmeyer-Peppas model provide insight on mechanistic drug release on the innovator, which is of great value from a development perspective when attempting to formulate generic products.

## 5.5. Discussion of Model-dependent and Independent Analyses

Model independent analyses such as is achieved by calculation of  $f1$  and  $f2$  fit factors and the Gohel  $S_d$  value are important tools in formulation development and serve as a useful guide for new product development as they enables a formulation scientist to make informed decisions with respect to formulation composition. Therefore development scientists can maximise the chances of successfully developing generic products that are comparable to a reference product *in-vitro* and ultimately *in-vivo*.

The results depicted in Table 5.3 show that there is a relationship between the  $f1$  and  $f2$  difference and similarity factors and the  $S_d$  value. It is evident that those products that show similarity based on  $f1$  and  $f2$  values demonstrate a low  $S_d$  value, thus indicating that a low value for  $S_d$  is suggestive of similarity.

Consequently, only 4 dosage units from each batch were tested for the model independent analyses, and whilst these give an indication of similarity, more dosage units need to be tested in order to make more informed comparisons and conclusions.

Model dependent analyses are used to establish the type and mechanism of drug release that may occur from different types of dosage forms. There are many factors that can influence the kinetics of drug release, which include but are not limited to the types and amount of polymers utilized [156, 202], the geometry of the dosage form [191, 201], and gel layer thickness [201]. These are of importance where heterogeneous matrices which comprise more than one polymer and where HPMC is the primary rate-retarding agent are used to manufacture SR dosage forms.

PHCL, is a highly water soluble  $\beta$ -blocker and was the API selected for incorporation into a SR matrix delivery system. PHCL was combined with a variety of excipients in both DC and WG manufacturing procedures to produce bi-concave mini-tablets.

Therefore the most important factor that can be considered to play an integral part in the control and kinetics of drug release from these dosage forms is the amount and type polymeric material(s) that are used to achieve the desired SR effect.

The kinetics of drug release from HPMC matrices has been extensively described [191, 201, 202, 206, 208, 216, 217]. Combinations of enteric blends of GIT insoluble polymers such as ethylcellulose and the polymethacrylates have been used to modify drug release rates [230, 231], and the use of HPMC polymers in combination with NaCMC have produced zero-order dissolution curves, more than likely as a result of cross linking of the two polymeric materials. The viscosity grade of HPMC used in a specific formulation can and does influence the dissolution co-efficient of drug release, as polymer dissolution may occur during drug release and moving boundary layers may be formed [201, 202]. In such cases, drug delivery may become dependent on the dynamics of the gel layer thickness especially in swellable matrix tablets [201, 215, 205]. The formation of a gel layer is highly dependent on the rate of water uptake by the system [201, 202, 207, 215] and zero order release may be possible, but is dependant on the thickness of the gel layer [201, 207, 231].

The above-mentioned factors are important considerations in the design of delivery systems intended to retard drug release rates. . Mixtures of polymeric materials of varying viscosity grade and physico-chemical properties were used to modify the kinetics and characteristics of drug release in these studies. Furthermore, modifications were undertaken in order to develop dosage forms that were comparable to the innovator product Inderal<sup>®</sup> LA 80mg capsules.

## 5.6. Conclusions

Controlled release dosage forms are emerging as the dosage form of choice for optimising drug therapy, as they offer a variety of advantages over immediate release delivery systems. The vast majority of the commercially available SR dosage forms use hydrophilic and/or hydrophobic polymeric materials in various matrix type formulations to achieve the desired extended drug release patterns. SR dosage forms are able to release API at different rates by a variety of different transport mechanisms. The characterization of both the rate and extent of drug release and the underlying drug transport mechanisms are essential to understanding the ultimate performance criteria of these systems. Furthermore, the characterization of dissolution rate profiles is in many cases a regulatory requirement.

A number of attempts to manufacture a suitable sustained release PHCL dosage form that was similar to the innovator product were made. Two methods of manufacture, *viz.*, direct compression and wet granulation were used in order to achieve the objective of matching the dissolution profile of Inderal<sup>®</sup> LA capsules.

Initially, the comparison of drug release profiles was achieved by exploratory data analyses, where graphical representations of dissolution data were made and investigated.

Secondary assessments of the resultant data included the use of model-independent pair wise comparisons, *viz.*, the *f1* and *f2* fit factors, in combination with the  $S_d$  factor, using Inderal<sup>®</sup> LA as the reference product. It was found that five of the test batches, *viz.*, PC021 capsules, PC022RW, PC024 and PC025F2, manufactured by wet granulation technology and employed in capsules, passed the *f2* value and had a corresponding low  $S_d$  value, however in some cases, the *f1* values were different. These results confirm that the  $S_d$  value is a useful parameter that can be used in combination with the fit factors to assess the degree of similarity between test and reference products.

Model independent analyses are a useful measure to determine the degree of similarity of dissolution profiles of test and reference products, but provide little or no information on the underlying mass transfer kinetics of a drug from dosage forms.

In order to investigate the underlying transport mechanisms and characterize drug release patterns, model dependent analyses were applied to the dissolution data.

The empirical Higuchi model revealed that all dosage forms manufactured demonstrated drug release rates were primarily controlled by a diffusion mechanism. Further analyses using the Kormeyer-Peppas “power law” model revealed that although the release mechanisms of the dosage forms were diffusion controlled, differences existed between the products manufactured by direct compression, where drug release was indicative of Fickian diffusion, whereas those manufactured by wet granulation appeared to follow an anomalous diffusion processes. These two models best characterized most of the dissolution data from the majority of the manufactured dosage forms, based on the goodness of fit criterion, the coefficient of determination. The innovator product and two manufactured batches, PC020A and PC020B are best characterized by the Weibull distribution, although as previously mentioned this model appears inappropriate for the characterization of drug release kinetics for these dosage forms.

Model-independent and -dependent analyses are valuable tools for the assessment of test results generated during dissolution rate studies of extended or modified release dosage forms. These analyses enable researchers to ascertain the closeness of fit of test and reference dissolution profiles, in addition to establishing mechanisms by which the drugs are released from these dosage forms, where exploratory data analysis may not provide sufficient information to make informed formulation decisions.

## CHAPTER 6

### CONCLUSION

The objective of this research project was to develop and assess a sustained release PHCL dosage form that would produce *in vitro* dissolution rate profiles that were similar to that of a reference product, Inderal<sup>®</sup> LA 80mg capsules. In addition an immediate release dose of HCTZ was to be included in the sustained release PHCL dosage form to produce a combination product, which could be used for once a day dosing of the two APIs.

The initial phase of the project entailed the development and validation of a suitable HPLC method for the simultaneous determination of both drugs in solution. Investigations were undertaken to ascertain the effect of using two different columns, buffer molarity and pH. The optimal chromatographic conditions were determined, from these investigations, and the analytical method was subsequently validated. The method was shown to be linear, precise, specific and accurate, and was therefore suitable for testing of the innovator and test products.

The characterisation of the release profile of Inderal<sup>®</sup> LA was performed by dissolution testing using both USP Apparatus 1 and USP Apparatus 3 (Bio-Dis<sup>™</sup>) dissolution test equipment with phosphate buffer dissolution media, with pH 1.2 used for USP Apparatus 1 and various pH used for USP Apparatus 3. Dissolution studies using USP Apparatus 1 was undertaken as it is listed in the USP for the testing of PHCL extended release products.

Initial test dosage forms were produced by direct compression using two rate retarding formulation components were used to produce heterogeneous matrix tablets. Dissolution samples were quantitated using a validated high performance liquid chromatographic method. The initial prototypes although demonstrating some rate retardation, revealed dissolution rate profiles that were not similar to that of the innovator product. The influence of changing the rate retarding polymeric material in the formulation, such as the Eudragit<sup>®</sup> series of polymethacrylates and methacrylic acid copolymers was also investigated. In addition, the use of different viscosity

grades of HPMC at higher concentrations produced better dissolution rate profiles. However, the release characteristics of these dosage forms were not similar to that of the reference product, Inderal<sup>®</sup> LA. The majority of the matrix dosage forms manufactured by direct compression in an attempt to produce sustained release PHCL delivery systems, demonstrated poor physical and mechanical properties in terms of content uniformity, hardness and weight variation.

WG manufacturing techniques using polymeric dispersions of Eudragit<sup>®</sup> NE 30D and Surelease<sup>®</sup> E7-19010 as granulating fluids were used in an attempt to further modify and retard the release of PHCL. The resultant polymeric granular materials were dried and incorporated into a heterogeneous matrix mini-tablet formulation. Different formulation compositions were used with both types of granulating fluid, included into the formulation at both high and low concentrations.

In general, the use of these materials and the WG method of manufacture produced tablets in which better rate retardant effects were achieved, than had been observed for the DC formulations. However, the resultant dissolution profiles were not comparable to those of the innovator product. Further modifications of the formulation to include the use of two different plasticizers were made and investigated as it was considered that the use of plasticizers would improve the potential for coating of the powders during the granulation process. The dissolution profiles observed for formulations PC020A and PC020B revealed that only batch PC020A was similar to Inderal<sup>®</sup> LA. An attempt to reproduce the result with the formulation used to manufacture batch PC020A, *viz.*, batch PC021TC proved unsuccessful. Consequently using the same blend, was filled manually into four size 0 hard gelatin capsules and the results revealed that the products were similar to Inderal<sup>®</sup> LA capsules.

Therefore it was concluded that the compaction process may have had an impact on drug release from these dosage forms. Capsule drug delivery using SR powder blends was then considered as an option to produce a suitable SR dosage form for propranolol and experiments were undertaken to establish the effects of polymer content, drug loading and the inclusion of fine material from granulation processing on dissolution release rates from SR capsules. The resultant dissolution profiles reveal

that polymer content and the inclusion of fines material were important factors that affected drug release rates from these products. Additional investigations were undertaken to determine the relevant amount of fill for size 00 capsules, in order to achieve a similar dissolution profile to the Inderal<sup>®</sup> LA capsules. The results of these investigations suggest that an intermediate to high polymer content is essential to achieve drug release profiles that are comparable to that of the reference product.

The assessment of similarity against the innovator product was achieved using model independent analysis, using the  $f_1$  and  $f_2$  difference and similarity fit factors. The results of model independent analysis revealed that the capsule dosage form filled with powder passed the  $f_2$  test and the capsules containing tablets manufactured using the same powder blend had failed the test.

The final phase of these studies involved the development and incorporation of an immediate release HCTZ dose into the combination product. HCTZ tablets were manufactured by DC and then manually inserted in size 00 capsules that had been filled with the SR PHCL powder blend. The results indicate that there was a minimal effect on the release rate of HCTZ which was deemed acceptable. However, further investigations are necessary to determine the manufacturing parameters that are necessary to produce tablets that do not fail content and weight uniformity tests, as the powder blends for the HCTZ tablets exhibited good flow properties, yet they failed content and weight uniformity tests.

Mechanisms by which PHCL was released from these products were investigated by fitting drug release data from dissolution studies to different empirical mathematical models. The models found to be most appropriate for the elucidation and characterization of propranolol transport from these dosage forms were the Higuchi and Korsmeyer-Peppas models. The results of model fitting suggest that the direct compression matrices appear to control drug release by a process that is primarily controlled by Fickian diffusion type mechanisms, when compared to those manufactured by wet granulation that display release characteristics that are indicative of anomalous transport.

The use of model independent and model dependent analyses proved useful to allow for the comparison of drug release profiles and the elucidation of drug release mechanisms, respectively.

A sustained release once daily dosage form has been developed, and has been shown to produce *in-vitro* dissolution profiles similar to that of the commercially available Inderal<sup>®</sup> LA capsules, based on difference and similarity factors. In addition an immediate release HCTZ component has been successfully added to the capsule dosage form. This formulation has the potential to be adapted to commercial manufacture. The release of PHCL, a water soluble beta-blocker was best achieved using wet granulation technologies, with Surelease E7-19010 in combination with plasticizer ATEC as the granulation fluid and incorporated into a heterogeneous matrix blend that was filled into size 00 capsules.

Future studies on the test product should include stability and *in-vivo* testing. Furthermore attempts should be made to develop an *in-vitro/in-vivo* correlation. In addition, scanning electron and laser confocal microscopic studies may provide further insight into the performance of the polymeric granular material during compaction.

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## Appendix I

### Batch Production Summary Records

**Rhodes University  
Faculty of Pharmacy  
Department of Pharmaceutics  
Batch Summary Record**

**Batch Number** PC001

**Batch Size** 250g

**Date** 14/11/2004

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR DC

**Formulation Constituents**

Material	%
Propranolol Hydrochloride	13.5
Methocel <sup>®</sup> K4M	6.8
Emcompress <sup>®</sup>	32.3
Emcocel <sup>®</sup> 90 M	26.9
Ethocel <sup>®</sup> FP 10 cp	2.8
Methocel <sup>®</sup> K100 M	14
Talc	3
Magnesium Stearate	0.7

**Weight of product:** 202.3 ± 5.77 mg

**Temperature:** 23° C

**Hardness of product:** 82.55 ± 9.38 N

**Humidity:** 66 %

**Thickness:** 4.01 ± 0.04 mm

**Diameter:** 7.198 ± 0.007 mm

**Friability:** 0.78 %

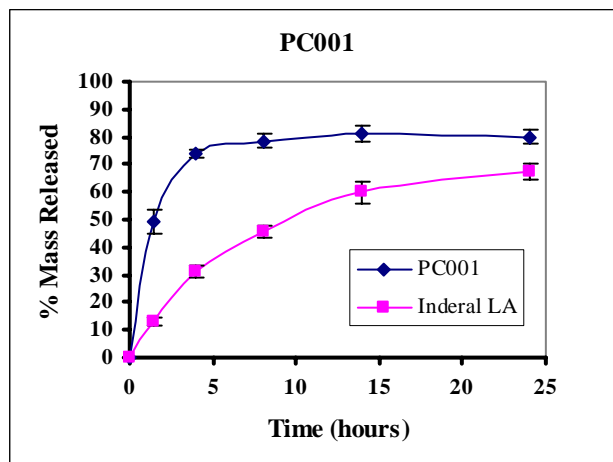
**Machine and Production Conditions:**

Machine Used

Manesty F3 Single Punch Press

Tooling

7mm Biconcave punches



**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Summary Record**

**Batch Number** PC002

**Batch Size** 250g

**Date** 23/11/2004

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR DC

**Formulation Constituents**

Material	%
Propranolol Hydrochloride	13.5
Methocel <sup>®</sup> K4M	4.6
Emcompress <sup>®</sup>	32.3
Emcocel <sup>®</sup> 90 M	26.9
Ethocel <sup>®</sup> FP 10 cp	5
Methocel <sup>®</sup> K100 M	14
Talc	3
Magnesium Stearate	0.7

**Weight of product:**  $224.16 \pm 4.05$  mg

**Temperature:** 23° C

**Hardness of product:**  $61.7 \pm 2.47$  N

**Humidity:** 66 %

**Thickness:**  $4.01 \pm 0.07$  mm

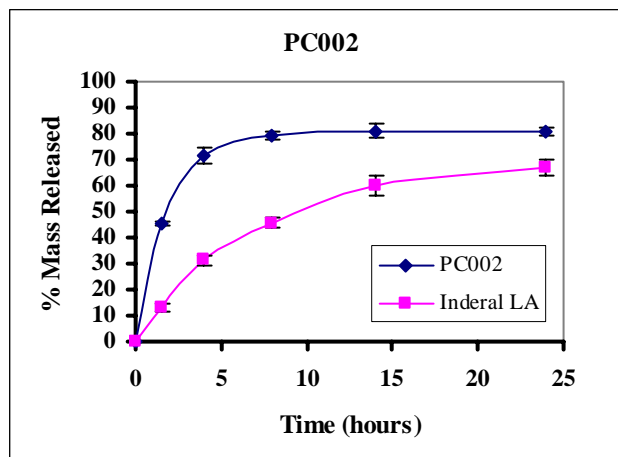
**Diameter:**  $7.216 \pm 0.006$  mm

**Friability:** 0.44 %

**Machine and Production Conditions:**

Machine Used  
Tooling

Manesty F3 Single Punch Press  
7mm Biconcave punches



**Rhodes University  
Faculty of Pharmacy  
Department of Pharmaceutics  
Batch Summary Record**

**Batch Number** PC003

**Batch Size** 250g

**Date** 20/02/2005

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR DC

**Formulation Constituents**

Material	%
Propranolol Hydrochloride	13.5
Methocel <sup>®</sup> K4M	11.8
Emcompress	27.3
Emcocel <sup>®</sup> 90 M	26.9
Ethocel <sup>®</sup> FP 10 cp	2.8
Methocel <sup>®</sup> K100 M	14
Talc	3
Magnesium Stearate	0.7

**Weight of product:** 211.56 ± 4.89 mg

**Temperature:** 22.2 ° C

**Hardness of product:** 63.35 ± 3.22 N

**Humidity:** 77 %

**Thickness:** 4.02 ± 0.1 mm

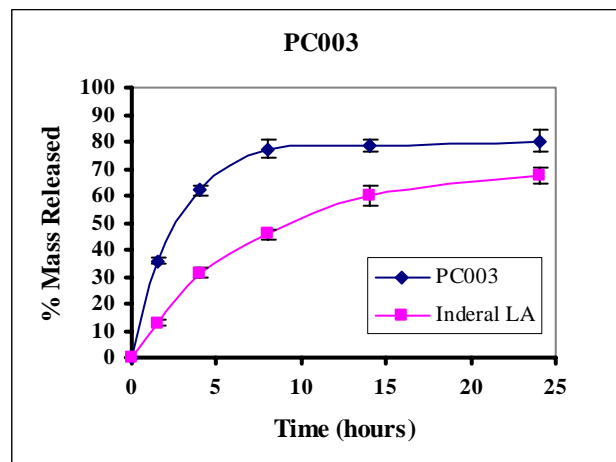
**Diameter:** 7.2 ± 0.002 mm

**Friability:** 0.45 %

**Machine and Production Conditions:**

Machine Used  
Tooling

Manesty F3 Single Punch Press  
7mm Biconcave punches



**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Summary Record**

**Batch Number** PC004

**Batch Size** 250g

**Date** 20/02/2005

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR DC

**Formulation Constituents**

Material	%
Propranolol Hydrochloride	13.5
Methocel <sup>®</sup> K4M	9.6
Emcompress <sup>®</sup>	27.3
Emcocel <sup>®</sup> 90 M	26.9
Ethocel <sup>®</sup> FP 10 cp	5
Methocel <sup>®</sup> K100 M	14
Talc	3
Magnesium Stearate	0.7

**Weight of product:** 221.085 ± 5.07 mg

**Temperature:** 22.2° C

**Hardness of product:** 84.8 ± 5.97 N

**Humidity:** 79 %

**Thickness:** 3.97 ± 0.084 mm

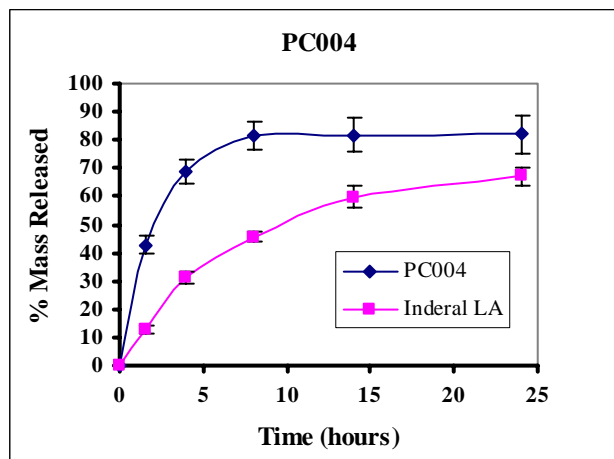
**Diameter:** 7.2 ± 0.004 mm

**Friability:** 0.45 %

**Machine and Production Conditions:**

Machine Used  
Tooling

Manesty F3 Single Punch Press  
7mm Biconcave punches



**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Summary Record**

**Batch Number** PC005

**Batch Size** 250g

**Date** 27/02/2005

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR DC

**Formulation Constituents**

Material	%
Propranolol Hydrochloride	30
Methocel <sup>®</sup> K100M	40
Emcompress <sup>®</sup>	15
Emcocel <sup>®</sup> 90 M	12
Talc	2
Magnesium Stearate	1

**Weight of product:**  $152.875 \pm 3.79$  mg

**Temperature:** 23° C

**Hardness of product:**  $88.95 \pm 9.517$  N

**Humidity:** 62 %

**Thickness:**  $3.007 \pm 0.069$  mm

**Diameter:**  $7.17 \pm 0.004$  mm

**Friability:** 0.33 %

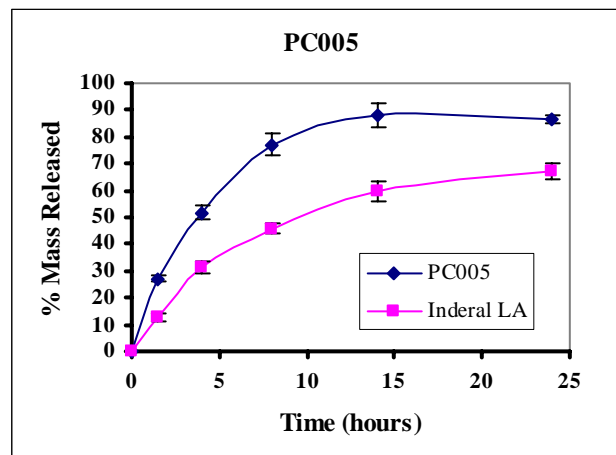
**Machine and Production Conditions:**

Machine Used

Manesty F3 Single Punch Press

Tooling

7mm Biconcave punches



**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Summary Record**

**Batch Number** PC006      **Batch Size** 250g      **Date** 31/01/2005

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR DC

**Formulation Constituents**

Material	%
Propranolol Hydrochloride	40
Methocel <sup>®</sup> K100M	30
Eudragit <sup>®</sup> L100-55	7
Emcocel <sup>®</sup> 90 M	19
Ac-di-sol <sup>®</sup>	3
Magnesium Stearate	1

**Weight of product:** 146.385 ± 5.88 mg

**Temperature:** 24.5° C

**Hardness of product:** 97.8 ± 10.82 N

**Humidity:** 66 %

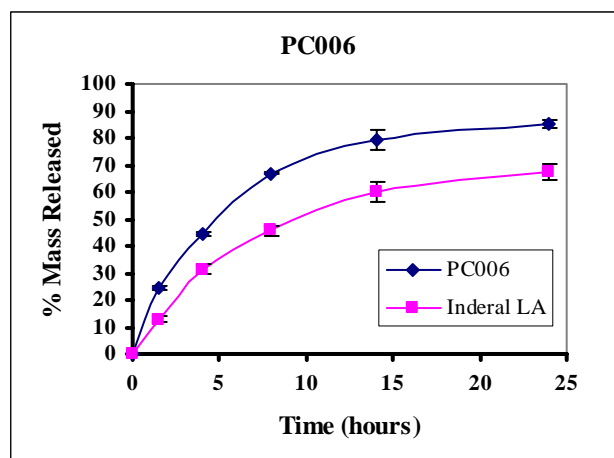
**Thickness:** 3.137 ± 0.158 mm

**Diameter:** 7.167 ± 0.004 mm

**Friability:** 0.69 %

**Machine and Production Conditions:**

Machine Used                      Manesty F3 Single Punch Press  
Tooling                                7mm Biconcave punches



**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Summary Record**

**Batch Number** PC007

**Batch Size**

250g

**Date** 31/01/2005

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR DC

**Formulation Constituents**

Material	%
Propranolol Hydrochloride	40
Methocel <sup>®</sup> K4M	30
Eudragit <sup>®</sup> L100-55	7
Emcocel <sup>®</sup> 90 M	19
Ac-di-sol <sup>®</sup>	3
Magnesium Stearate	1

**Weight of product:**  $144.92 \pm 7.087$  mg

**Temperature:** 24.5° C

**Hardness of product:**  $89.4 \pm 18.16$  N

**Humidity:** 66 %

**Thickness:**  $3.035 \pm 0.196$  mm

**Diameter:**  $7.16 \pm 0.004$  mm

**Friability:** 0.39 %

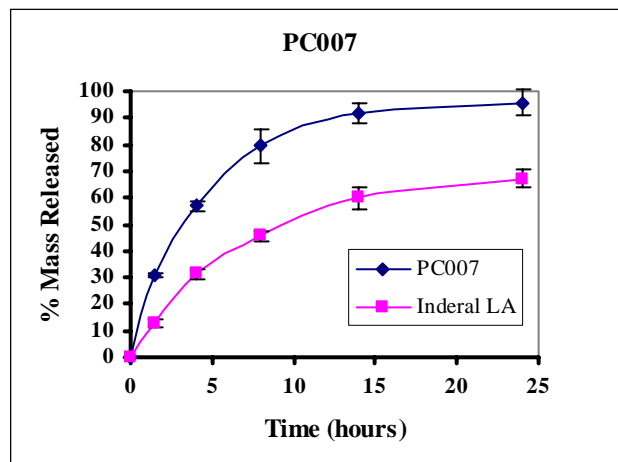
**Machine and Production Conditions:**

Machine Used

Manesty F3 Single Punch Press

Tooling

7mm Biconcave punches



**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Summary Record**

**Batch Number** PC008

**Batch Size** 250g

**Date** 09/02/2005

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR DC

**Formulation Constituents**

Material	%
Propranolol Hydrochloride	40
Methocel <sup>®</sup> K100M	30
Eudragit <sup>®</sup> RS PO	7
Emcocel <sup>®</sup> 90 M	19
Ac-di-sol <sup>®</sup>	3
Magnesium Stearate	1

**Weight of product:** 144.94 ± 10.49 mg

**Temperature:** 22.8° C

**Hardness of product:** 74.75 ± 10.57 N

**Humidity:** 66 %

**Thickness:** 3.365 ± 0.21 mm

**Diameter:** 7.168 ± 0.004 mm

**Friability:** 1.12 %

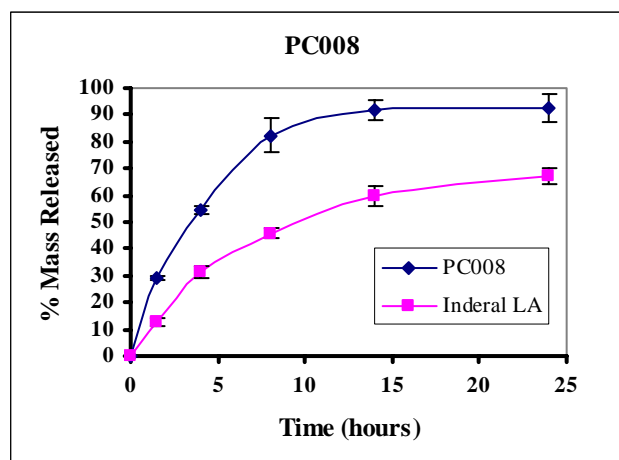
**Machine and Production Conditions:**

Machine Used

Manesty F3 Single Punch Press

Tooling

7mm Biconcave punches



**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Summary Record**

**Batch Number** PC009      **Batch Size** 250g      **Date** 10/02/2005

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR DC

**Formulation Constituents**

Material	%
Propranolol Hydrochloride	40
Methocel <sup>®</sup> K4M	30
Eudragit <sup>®</sup> RS PO	7
Emcocel <sup>®</sup> 90 M	19
Ac-di-sol <sup>®</sup>	3
Magnesium Stearate	1

**Weight of product:** 138.875 ± 4.59 mg

**Temperature:** 22.8° C

**Hardness of product:** 80.85 ± 6.48 N

**Humidity:** 66 %

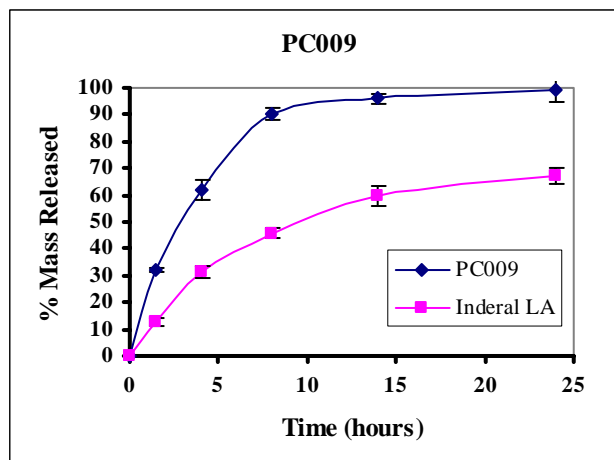
**Thickness:** 2.92 ± 0.075 mm

**Diameter:** 7.163 ± 0.004 mm

**Friability:** 0.38 %

**Machine and Production Conditions:**

Machine Used      Manesty F3 Single Punch Press  
Tooling      7mm Biconcave punches



**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Summary Record**

**Batch Number** PC010

**Batch Size** 250g

**Date** 27/02/2005

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR DC

**Formulation Constituents**

Material	%
Propranolol Hydrochloride	30
Methocel <sup>®</sup> K100M	35
Eudragit <sup>®</sup> L100-55	15
Emcocel <sup>®</sup> 90 M	19
Magnesium Stearate	1

**Weight of product:** 143.85 ± 4.98 mg

**Temperature:** 24° C

**Hardness of product:** 106.25 ± 7.97 N

**Humidity:** 73 %

**Thickness:** 3.085 ± 0.087 mm

**Diameter:** 7.16 ± 0.03 mm

**Friability:** 0.35 %

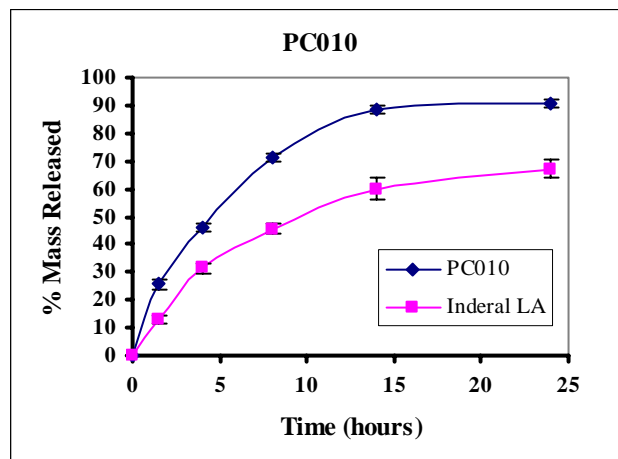
**Machine and Production Conditions:**

Machine Used

Manesty F3 Single Punch Press

Tooling

7mm Biconcave punches



**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Summary Record**

**Batch Number** PC011

**Batch Size** 253g

**Date** 7/03/05

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR WG

**Formulation Constituents**

<b>Material</b>	<b>%</b>	
	<b>A</b>	<b>B</b>
Propranolol Hydrochloride	46.51	29.7
Methocel <sup>®</sup> K100 M	27.13	17.32
Eudragit <sup>®</sup> L100-55	11.63	7.42
Emcocel <sup>®</sup> 90 M	14.73	9.4
Magnesium Stearate		1

Where

A is the percentage in the granulation step

B is the percentage in the final tablet mix

**Granulating Fluid**

Eudragit <sup>®</sup> NE 30 D	40 ml
Water	40 ml

**Weight of product:** 186.95 ± 5.96 mg

**Temperature:** 21.2° C

**Hardness of product:** 58.8 ± 7.72 N

**Humidity:** 53 %

**Thickness:** 4.27 ± 0.1 mm

**Diameter:** 7.18 ± 0.004 mm

**Friability:** 0.27 %

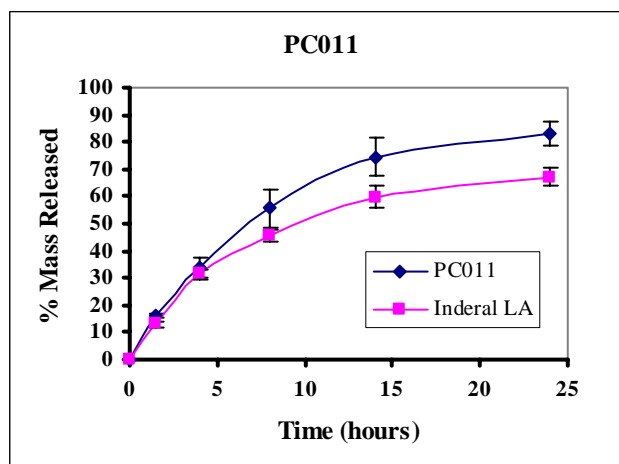
**Machine and Production Conditions:**

Machine Used

Manesty F3 Single Punch Press

Tooling

7mm Biconcave punches



**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Summary Record**

Batch Number PC012

Batch Size 259g

Date 7/03/05

Formulator: Prakash Chetty

Type of Formulation: PHCL SR WG

**Formulation Constituents**

Material	%	
	A	B
Propranolol Hydrochloride	46.51	28.95
Methocel <sup>®</sup> K100 M	31	19.3
Emcompress <sup>®</sup>	11.63	7.24
Emcocel <sup>®</sup> 90 M	14.73	9.4
Talc	1.55	0.97
Magnesium Stearate		0.97

Where

A is the percentage in the granulation step

B is the percentage in the final tablet mix

**Granulating Fluid**

Eudragit <sup>®</sup> NE 30 D	40 ml
Water	40 ml

Weight of product:  $191.64 \pm 6.1$  mg

Temperature:  $21^{\circ}$  C

Hardness of product:  $67.45 \pm 6.3$  N

Humidity: 53 %

Thickness:  $4.07 \pm 0.08$  mm

Diameter:  $7.18 \pm 0.004$  mm

Friability: 0.26 %

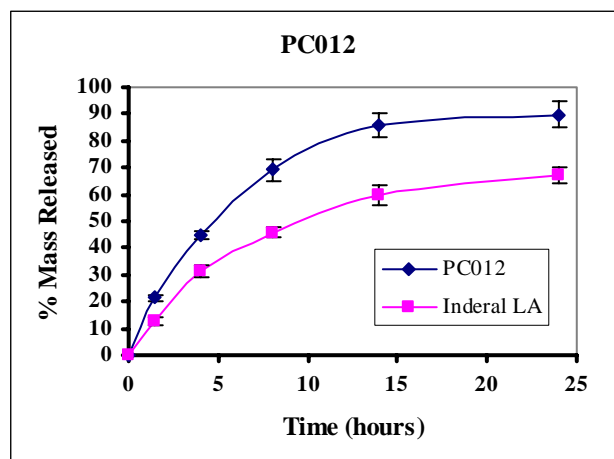
**Machine and Production Conditions:**

Machine Used

Manesty F3 Single Punch Press

Tooling

7mm Biconcave punches







**Rhodes University  
Faculty of Pharmacy  
Department of Pharmaceutics  
Batch Summary Record**

**Batch Number** PC015      **Batch Size** 269g      **Date** 28/03/05

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR WG

**Formulation Constituents**

Material	%	
	A	B
Propranolol Hydrochloride	46.51	27.93
Methocel <sup>®</sup> K100 M	27.13	16.29
Eudragit <sup>®</sup> L100-55	11.63	6.98
Emcocel <sup>®</sup> 90 M	14.73	8.85
Magnesium Stearate		0.93

Where

A is the percentage in the granulation step

B is the percentage in the final tablet mix

**Granulating Fluid**

Surelease <sup>®</sup> E7-19010	60 ml
Eudragit <sup>®</sup> NE 30 D	60 ml

**Weight of Product:** 182.11 ± 3.94 mg

**Temperature:** 21.2° C

**Hardness of product:** 55.85 ± 4.38 N

**Humidity:** 43 %

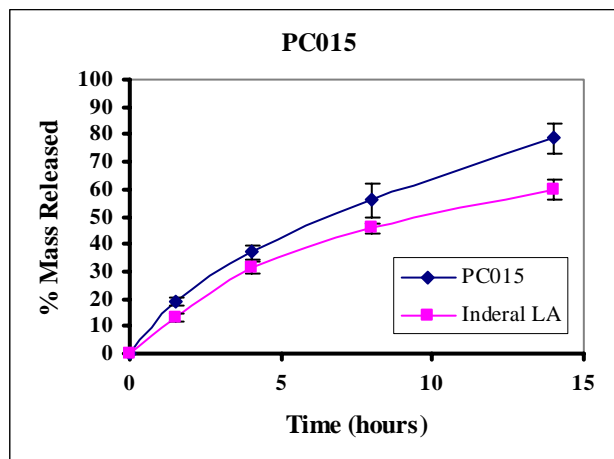
**Thickness:** 4.1 ± 0.089 mm

**Diameter:** 7.16 ± 0.004 mm

**Friability:** 0.83 %

**Machine and Production Conditions:**

Machine Used      Manesty F3 Single Punch Press  
Tooling      7mm Biconcave punches



**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Summary Record**

**Batch Number** PC016      **Batch Size** 276g      **Date** 28/03/05

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR WG

**Formulation Constituents**

Material	%	
	A	B
Propranolol Hydrochloride	46.66	27.21
Methocel <sup>®</sup> K100 M	34.07	18.14
Emcompress <sup>®</sup>	12.77	6.8
Emcocel <sup>®</sup> 90 M	10.22	5.44
Talc	1.36	0.73
Magnesium Stearate		0.9

Where

A is the percentage in the granulation step

B is the percentage in the final tablet mix

**Granulating Fluid**

Surelease<sup>®</sup> E7-19010      60 ml  
Eudragit<sup>®</sup> NE 30 D      60 ml

**Weight of Product:** 192.29 ± 5.91 mg

**Temperature:** 21.9° C

**Hardness of product:** 60.35 ± 6.68 N

**Humidity:** 41%

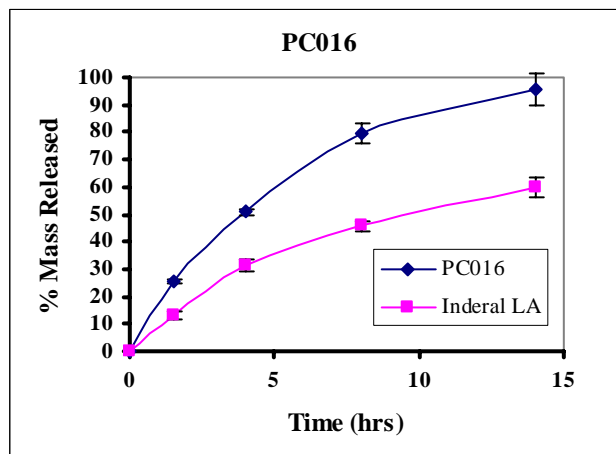
**Thickness:** 4.04 ± 0.09 mm

**Diameter:** 7.16 ± 0.005 mm

**Friability:** 0.26 %

**Machine and Production Conditions:**

Machine Used      Manesty F3 Single Punch Press  
Tooling      7mm Biconcave punches



**Rhodes University  
Faculty of Pharmacy  
Department of Pharmaceutics  
Batch Summary Record**

**Batch Number** PC017      **Batch Size** 314g      **Date** 04/04/05

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR WG

**Formulation Constituents**

Material	%	
	A	B
Propranolol Hydrochloride	46.32	23.86
Methocel <sup>®</sup> K100 M	27	19.11
Methocel <sup>®</sup> K4M		4
Eudragit <sup>®</sup> L100-55	11.75	7.96
Emcocel <sup>®</sup> 90 M	14.91	6.37
Magnesium Stearate		0.9

Where

A is the percentage in the granulation step

B is the percentage in the final tablet mix

**Granulating Fluid**

Surelease<sup>®</sup> E7-19010      150 ml

**Weight of Product:** 179.63 ± 5.63 mg

**Temperature:** 21.2° C

**Hardness of product:** 44 ± 5.02 N

**Humidity:** 54 %

**Thickness:** 4.13 ± 0.11 mm

**Diameter:** 7.18 ± 0.006 mm

**Friability:** 0.56 %

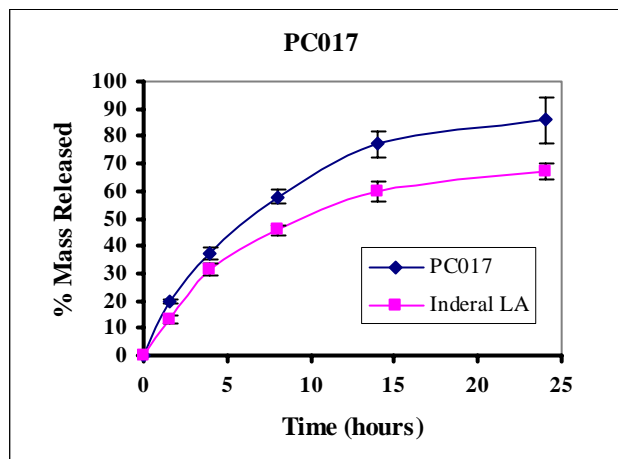
**Machine and Production Conditions:**

Machine Used

Manesty F3 Single Punch Press

Tooling

7mm Biconcave punches



**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Summary Record**

**Batch Number** PC018      **Batch Size** 278g      **Date** 09/04/05

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR WG

**Formulation Constituents**

Material	%	
	A	B
Propranolol Hydrochloride	45.58	25.18
Methocel <sup>®</sup> K100 M	12.1	7.18
Methocel <sup>®</sup> K100 LV EP	30.23	14.37
Eudragit <sup>®</sup> L100-55	12.1	7.18
Emcocel <sup>®</sup> 90 M		7.18
Magnesium Stearate		0.9

Where

A is the percentage in the granulation step

B is the percentage in the final tablet mix

**Granulating Fluid**

Eudragit<sup>®</sup> NE 30 D      120 ml

**Weight of Product:** 194.37 ± 6.48 mg

**Temperature:** 22.2° C

**Hardness of product:** 46.25 ± 7.93 N

**Humidity:** 78 %

**Thickness:** 4.56 ± 0.199 mm

**Diameter:** 7.17 ± 0.005 mm

**Friability:** 0.26 %

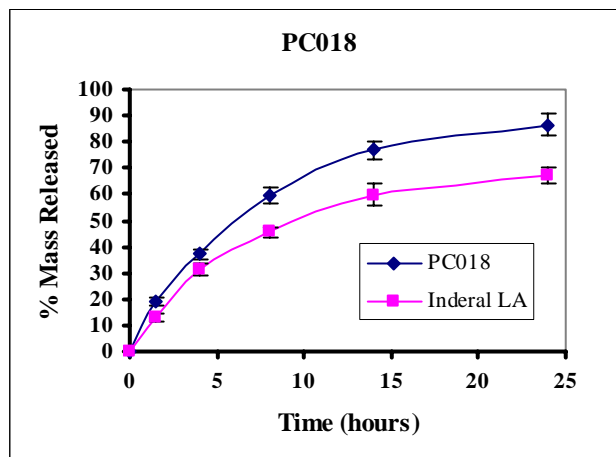
**Machine and Production Conditions:**

Machine Used

Manesty F3 Single Punch Press

Tooling

7mm Biconcave punches



**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Summary Record**

**Batch Number** PC019      **Batch Size** 279g      **Date** 10/04/05

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR WG

**Formulation Constituents**

Material	%	
	A	B
Propranolol Hydrochloride	44.15	23.47
Methocel <sup>®</sup> K100 M	14.7	7.15
Methocel <sup>®</sup> K100 LV EP	29.39	14.31
Eudragit <sup>®</sup> L100-55	11.75	7.15
Emcocel <sup>®</sup> 90 M		7.15
Magnesium Stearate		0.9

Where

A is the percentage in the granulation step

B is the percentage in the final tablet mix

**Granulating Fluid**

Eudragit<sup>®</sup> NE 40 D      120 ml

**Weight of Product:** 185.89 ± 6.52 mg

**Temperature:** 21.9° C

**Hardness of product:** 45.05 ± 3.59 N

**Humidity:** 77 %

**Thickness:** 4.32 ± .14 mm

**Diameter:** 7.17 ± 0.006 mm

**Friability:** 0.55 %

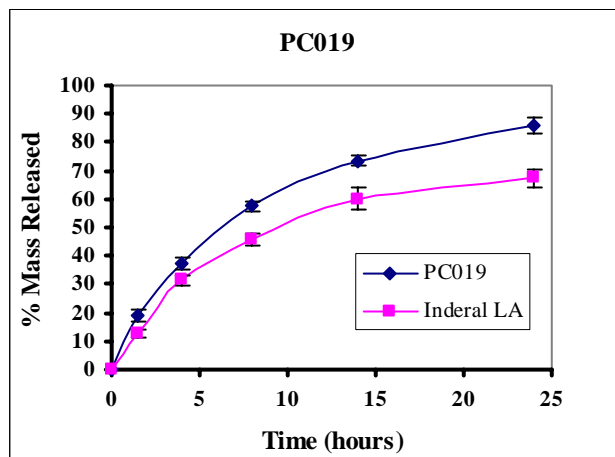
**Machine and Production Conditions:**

Machine Used

Manesty F3 Single Punch Press

Tooling

7mm Biconcave punches



**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Summary Record**

**Batch Number** PC020A      **Batch Size** 261g      **Date** 28/04/2005

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR WG

**Formulation Constituents**

Material	%	
	A	B
Propranolol Hydrochloride	44.12	22.28
Methocel <sup>®</sup> K100 M	14.7	9.59
Methocel <sup>®</sup> K100 LV EP	29.41	19.19
Eudragit <sup>®</sup> L100-55	11.76	7.67
Emcocel <sup>®</sup> 90 M		7.67
Magnesium Stearate		0.96

Where

A is the percentage in the granulation step

B is the percentage in the final tablet mix

**Granulating Fluid**

Surelease <sup>®</sup> E7-19010	150 ml
ATEC	10 ml

**Weight of Product:** 193.21 ± 5.24 mg

**Temperature:** 18.6° C

**Hardness of product:** 60.4 ± 5.29 N

**Humidity:** 53 %

**Thickness:** 4.59 ± 0.08 mm

**Diameter:** 7.18 ± 0.004 mm

**Friability:** 0.26 %

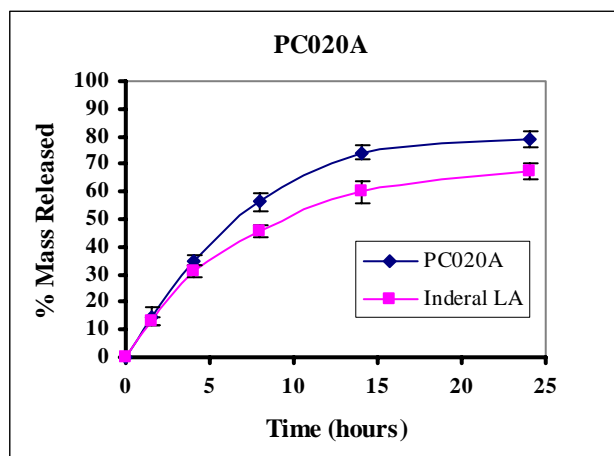
**Machine and Production Conditions:**

Machine Used

Manesty F3 Single Punch Press

Tooling

7mm Biconcave punches





**Rhodes University  
Faculty of Pharmacy  
Department of Pharmaceutics  
Batch Summary Record**

**Batch Number** PC021TC

**Batch Size** 303g

**Date** 05/05/2005

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR WG

**Formulation Constituents**

Material	%	
	A	B
Propranolol Hydrochloride	44.12	19.71
Methocel <sup>®</sup> K100 M	14.71	16.5
Methocel <sup>®</sup> K100 LV EP	29.41	16.5
Eudragit <sup>®</sup> L100	11.76	6.6
Emcocel <sup>®</sup> 90 M		6.6
Magnesium Stearate		0.82

Where

A is the percentage in the granulation step

B is the percentage in the final tablet mix

**Granulating Fluid**

Surelease<sup>®</sup> E7-19010 150 ml

ATEC 10 ml

**Weight of Product:** 193.55 ± 3.12 mg

**Temperature:** 22.3° C

**Hardness of product:** 45.35 ± 3.72 N

**Humidity:** 35 %

**Thickness:** 4.65 ± 0.1 mm

**Diameter:** 7.18 ± 0.007 mm

**Friability:** 0.77 %

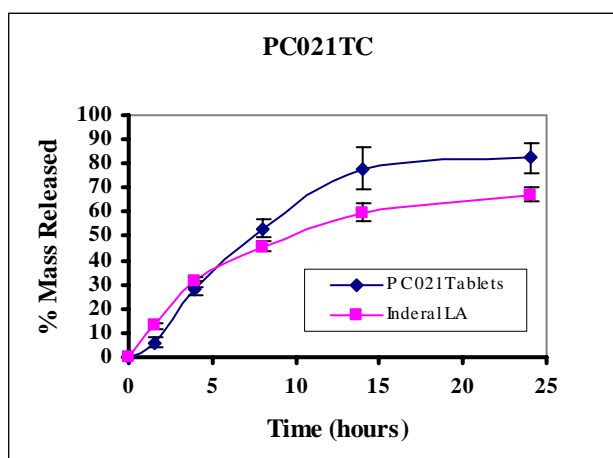
**Machine and Production Conditions:**

Machine Used

Manesty F3 Single Punch Press

Tooling

7mm Biconcave punches



**Rhodes University  
Faculty of Pharmacy  
Department of Pharmaceutics  
Batch Summary Record**

**Batch Number** PC022RW      **Batch Size** 395g      **Date** 30/05/2005

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR WG Capsule powder mix

**Formulation Constituents**

Material	%	
	A	B
Propranolol Hydrochloride	44.12	14.95
Methocel <sup>®</sup> K100 M	14.71	12.66
Methocel <sup>®</sup> K100 LV EP	29.41	37.97
Eudragit <sup>®</sup> L100	11.76	5.06
Emcocel <sup>®</sup> 90 M		5.06
Magnesium Stearate		0.63

Where

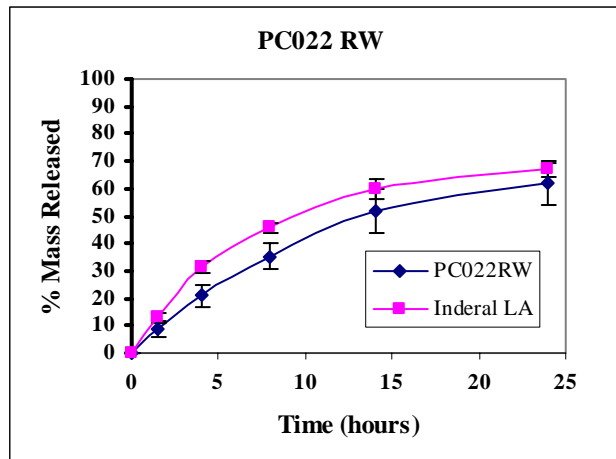
A is the percentage in the granulation step

B is the percentage in the final production mix

**Granulating Fluid**

Surelease <sup>®</sup> E7-19010	150 ml
ATEC	10 ml

Capsules were manually filled (average weight  $419.36 \pm 13.6$  mg)



**Rhodes University  
Faculty of Pharmacy  
Department of Pharmaceutics  
Batch Summary Record**

**Batch Number** PC023      **Batch Size** 417g      **Date** 06/06/2005

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR WG Capsule powder mix

**Formulation Constituents**

Material	%	
	A	B
Propranolol Hydrochloride	44.12	17.98
Methocel <sup>®</sup> K100 M	14.71	12.66
Methocel <sup>®</sup> K100 LV EP	29.41	28.69
Eudragit <sup>®</sup> L100	11.76	4.8
Emcocel <sup>®</sup> 90 M		4.8
Magnesium Stearate		0.6

Where

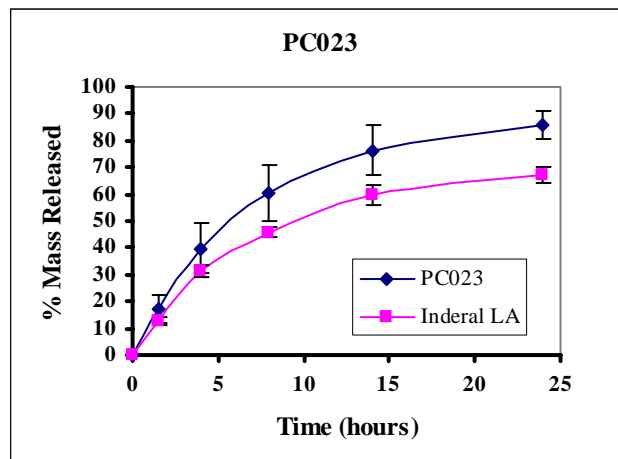
A is the percentage in the granulation step

B is the percentage in the final tablet mix

**Granulating Fluid**

Surelease <sup>®</sup> E7-19010	150 ml
ATEC	10 ml

Capsules were manually filled (average weight  $41.83 \pm 3.59$  mg)



**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Summary Record**

**Batch Number** PC024      **Batch Size** 284g      **Date** 20/08/2005

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR WG Capsule powder mix

**Formulation Constituents**

Material	%	
	A	B
Propranolol Hydrochloride	44.12	18.58
Methocel <sup>®</sup> K100 M	14.71	15.85
Methocel <sup>®</sup> K100 LV EP	29.41	15.85
Eudragit <sup>®</sup> L100	11.76	7.04
Emcocel <sup>®</sup> 90 M		7.04
Magnesium Stearate		0.88

Where

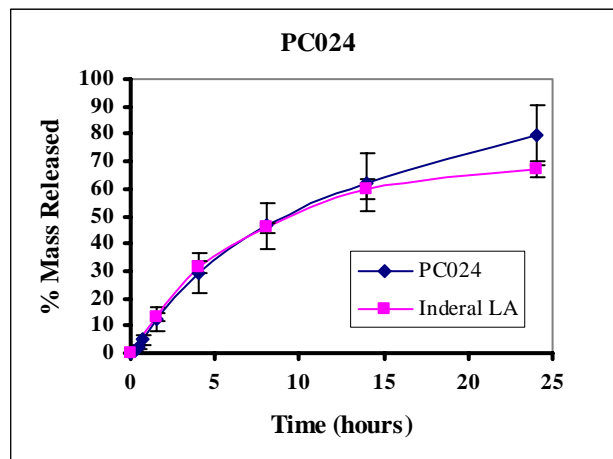
A is the percentage in the granulation step

B is the percentage in the final tablet mix

**Granulating Fluid**

Surelease <sup>®</sup> E7-19010	150 ml
ATEC	10 ml

Capsules were manually filled (average weight  $434.5 \pm 5.02$  mg)



**Rhodes University  
Faculty of Pharmacy  
Department of Pharmaceutics  
Batch Summary Record**

**Batch Number** PC025F2      **Batch Size** 333g      **Date** 02/09/2005

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR WG Capsule powder mix

**Formulation Constituents**

Material	%	
	A	B
Propranolol Hydrochloride	44.12	18.3
Methocel <sup>®</sup> K100 M	14.71	20.02
Methocel <sup>®</sup> K100 LV EP	29.41	20.02
Eudragit <sup>®</sup> L100	11.76	6.16
Emcocel <sup>®</sup> 90 M		6.16
Magnesium Stearate		0.77

Where

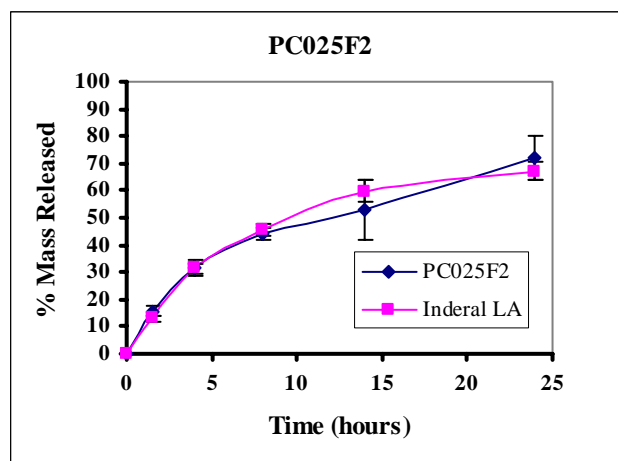
A is the percentage in the granulation step

B is the percentage in the final blend mix

**Granulating Fluid**

Surelease <sup>®</sup> E7-19010	150 ml
ATEC	10 ml

Capsules were manually filled (average weight  $389.2 \pm 1.78$  mg)



**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Summary Record**

**Batch Number** PC026      **Batch Size** 286g      **Date** 20/09/2005

**Formulator:** Prakash Chetty

**Type of Formulation:** PHCL SR WG Capsule powder mix

**Formulation Constituents**

Material	%	
	A	B
Propranolol Hydrochloride	44.12	20.6
Methocel <sup>®</sup> K100 M	14.71	12.25
Methocel <sup>®</sup> K100 LV EP	29.41	12.25
Eudragit <sup>®</sup> L100	11.76	6.99
Emcocel <sup>®</sup> 90 M		6.99
Magnesium Stearate		0.87

Where

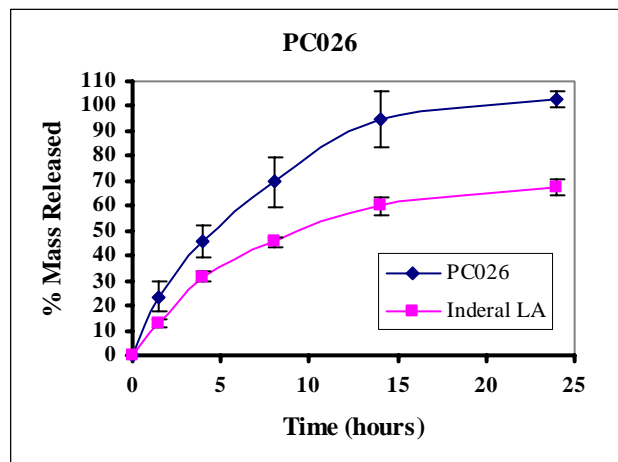
A is the percentage in the granulation step

B is the percentage in the final tablet mix

**Granulating Fluid**

Surelease<sup>®</sup> E7-19010      150 ml  
 ATEC      10 ml

Capsules were manually filled (average weight  $439.3 \pm 3.03$  mg)



**Rhodes University  
Faculty of Pharmacy  
Department of Pharmaceutics  
Batch Summary Record**

**Batch Number** HCTZ001      **Batch Size** 200g      **Date** 04/07/2005

**Formulator:** Prakash Chetty

**Type of Formulation:** HCTZ IR DC

**Formulation Constituents**

<b>Material</b>	<b>%</b>
Hydrochlorothiazide	15
Emcompress <sup>®</sup>	21
Emcocel <sup>®</sup> 90 M	30
Starch	25
Ac-di-sol <sup>®</sup>	5
Talc	3
Magnesium Stearate	1

**Weight of Product:** 218.75 ± 5.58 mg

**Temperature:** 18.6° C

**Hardness of product:** 55.7 ± 5.05 N

**Humidity:** 55 %

**Thickness:** 3.99 ± 0.06 mm

**Diameter:** 7.19 ± 0.005 mm

**Friability:** 0.46 %

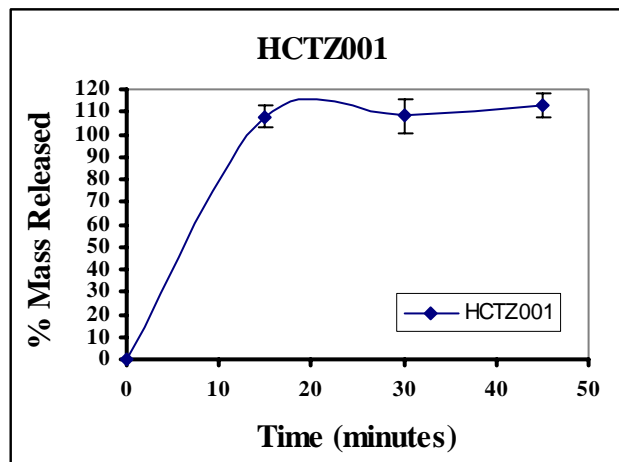
**Machine and Production Conditions:**

Machine Used

Manesty F3 Single Punch Press

Tooling

7mm Biconcave punches



**Rhodes University  
Faculty of Pharmacy  
Department of Pharmaceutics  
Batch Summary Record**

**Batch Number** HCTZ002

**Batch Size** 200g

**Date** 10/09/2005

**Formulator:** Prakash Chetty

**Type of Formulation:** HCTZ IR DC

**Formulation Constituents**

<b>Material</b>	<b>%</b>
Hydrochlorothiazide	15
Methocel <sup>®</sup> K4M	1
Emcompress <sup>®</sup>	25
Emcocel <sup>®</sup> 90 M	35
Starch	15
Ac-di-sol <sup>®</sup>	5
Talc	3
Magnesium Stearate	1

**Weight of Product:**  $178.97 \pm 10.23$  mg

**Temperature:** 17.2° C

**Hardness of product:**  $39.2 \pm 2.09$  N

**Humidity:** 58 %

**Thickness:**  $3.27 \pm 0.06$  mm

**Diameter:**  $7.21 \pm 0.002$  mm

**Friability:** 0.57 %

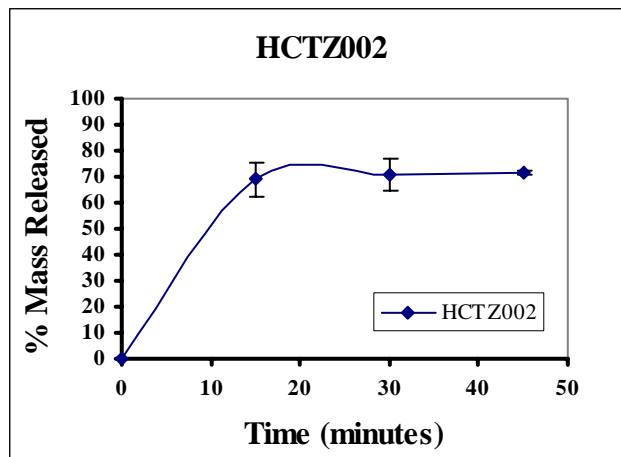
**Machine and Production Conditions:**

Machine Used

Manesty F3 Single Punch Press

Tooling

7mm Biconcave punches



## **Appendix II**

### **Batch Production Records**

Note only one batch production record for Direct Compression and one for Wet Granulation are included; other batch production records are available on request. Please note that the batch production records were filled during the manufacturing process and are available in the thesis hardcopy upon requisition.

**Rhodes University  
Faculty of Pharmacy  
Department of Pharmaceutics  
Batch Production Record**

**Product Name:** PHCL direct compression matrix tablets  
**Batch:** PC001

Page 1 of 4  
**Batch size:** 250g

**Manufacturing Approvals**

Batch record issued by: PC  
Master record issued by: PC

Date: 14/11/2004  
Date: 14/11/2004

**Rhodes University  
Faculty of Pharmacy  
Department of Pharmaceutics  
Batch Production Record**

**Product Name:** PHCL direct compression matrix tablets      **Page 2 of 4**  
**Batch:** PC001      **Batch size:** 250g

Master Formula and Batch Formula							
Quantity (w/w)	Material	RM #	Lot #	Amount/Batch	Amount Dispensed	Dispensed by	Checked by
13.5	Propranolol hydrochloride	000082	PHC 204				
6.8	Methocel® K4M	000052					
32.3	Emcomopress®	000059					
26.9	Emcocel® 90 M	000155					
2.8	Ethocel® FP 10 cp	000101					
14	Methocel® K100M	000052					
3	Talc	-					
0.7	Magnesium stearate	-					

**Rhodes University  
Faculty of Pharmacy  
Department of Pharmaceutics  
Batch Production Record**

**Product Name:** PHCL direct compression matrix tablets      **Page 3 of 4**  
**Batch:** PC001      **Batch size:** 250g

Equipment Verification			
Description	Type	Verified By	Confirmed By
Sieves	#20 mesh and #44 mesh		
Scale	Mettler PM6000		
Blender	Kenwood Major		
Tablet press	Manesty F3		

**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Production Record**

**Product Name:** PHCL direct compression matrix tablets  
**Batch:** PC001

Page 4 of 4  
**Batch size:** 250g

Manufacturing Directions						
Step	Procedure	Weight	Time	Date	Done By	Checked by
1	Separately screen following materials through a 20 mesh screen Propranolol Hydrochloride Methocel <sup>®</sup> K4M Emcompress <sup>®</sup> Emcocel <sup>®</sup> 90M Ethocel fp <sup>®</sup> 10cp					
2	Place the following materials in the Kenwood bowl Propranolol Hydrochloride Methocel <sup>®</sup> K4M Emcompress <sup>®</sup> Emcocel <sup>®</sup> 90M Ethocel <sup>®</sup> fp 10cp					
3	Blend the materials in step 2 for 15 minutes on blender Time started: Time completed: Speed setting: 1					
4	Separately screen following materials through a 44 mesh screen Talc Magnesium Stearate					
5	Add screened materials from step 4 to blender and blend for additional 3 minutes Time started: Time completed: Speed setting: 1					
6	Transfer blend to feed hopper of tablet press					
7	Tablets compressed on Manesty F3 Time started: Time completed:					
8	Machine Settings Speed : 60 rpm Target weight : 200mg Target Hardness : 50 SC					
9	Tablets stored in airtight container					
10	Testing of Physical tablet characteristics					

**Rhodes University  
Faculty of Pharmacy  
Department of Pharmaceutics  
Batch Production Record**

**Product Name:** PHCL WG Tablets/Capsules  
**Batch:** PC02TC

Page 1 of 7  
**Batch size:** 303g

**Manufacturing Approvals**

Batch record issued by: PC  
Master record issued by: PC

Date: 04/05/2005-05/05/2005  
Date: 04/05/2005-05/05/2005

**Rhodes University  
Faculty of Pharmacy  
Department of Pharmaceutics  
Batch Production Record**

**Product Name:** PHCL WG granules  
**Batch:** PC021TC

Page 2 of 7  
**Batch size:** 205 g

Master Formula and Batch Formula							
Quantity (w/w)	Material	RM #	Lot #	Amount/Batch	Amount Dispensed	Dispensed by	Checked by
44.12	Propranolol hydrochloride	000082	PHC 204				
14.71	Methocel <sup>®</sup> K100M	000052					
29.41	Methocel <sup>®</sup> K100M LV EP	000115					
11.76	Eudragit <sup>®</sup> L100	000016					
qs	Surelease <sup>®</sup> E7-19010	000010	502676				
qs	ATEC	000012					

**Rhodes University  
Faculty of Pharmacy  
Department of Pharmaceutics  
Batch Production Record**

**Product Name:** PHCL WG granules  
**Batch:** PC021TC

Page 3 of 7  
**Batch size:** 205 g

Equipment Verification			
Description	Type	Verified By	Confirmed By
Sieves	#20 mesh , #44 mesh and 0.8mm mesh		
Scale	Mettler PM6000		
Blender	Kenwood Major		
Water spray gun	Efeckto		
Oven	Memmert TV 50A		
Mechanical sieve	Erweka FPS #10 mesh		

**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Production Record**

**Product Name:** PHCL WG granules  
**Batch:** PC021TC

Page 4 of 7  
**Batch size:** 205 g

Manufacturing Directions						
Step	Procedure	Weight	Time	Date	Done By	Checked by
1	Separately screen following materials through a 20 mesh screen Propranolol Hydrochloride Methocel® K100M Methocel® K100M LV EP Eudragit® L100					
2	Place the following materials in the Kenwood bowl Propranolol Hydrochloride Methocel® K100M Methocel® K100M LV EP Eudragit® L100					
3	Blend the materials in step 2 for 15 minutes on blender Time started Time completed Speed setting: 1					
4	Prepare the granulating fluid by mixing 150ml Surelease E7-19010 and mix with 10ml ATEC by manual shaking for 5 minutes, allow to stand for 10minute Time Start: Time Completed :					
5	Granulate the material by spraying the mixture into mixing bowl at average spray rate of 2ml/min Time Start : Time Completed :					
6	Remove granules and place in oven at 60° C for 4 hours Time Start: Time Completed					
7	Remove granules and mechanically sieve with # 10 mesh (Erweka) Time Start Time Completed					
8	Granules transferred to oven for curing at 60° for another 6 hours Time Start: Time Completed:					
9	Remove fines by passing through 0.8mm sieve Time Start Time Completed					
10	Store granule material to incorporate into final blend mix.					

**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Production Record**

**Product Name:** PHCL WG Tablets/Capsules  
**Batch:** PC021TC

Page 5 of 7  
**Batch size:** 303 g

Master Formula and Batch Formula							
Quantity (w/w)	Material	RM #	Lot #	Amount/Batch	Amount Dispensed	Dispensed by	Checked by
19.71	Propranolol hydrochloride granules	000082	PHC 204				
16.5	Methocel® K100M	000052					
16.5	Methocel® K100M LV EP	000115					
6.6	Eudragit® L100	000016					
6.6	Emcocel® 90 M	000155					
0.82	Magnesium stearate						

**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Production Record**

**Product Name:** PHCL WG Tablets/Capsules  
**Batch:** PC021TC

Page 6 of 7  
**Batch size:** 303g

Equipment Verification			
Description	Type	Verified By	Confirmed By
Sieves	#20 mesh and #44 mesh		
Scale	Mettler PM6000		
Blender	Kenwood Major		
Tablet press	Manesty F3		

**Rhodes University**  
**Faculty of Pharmacy**  
**Department of Pharmaceutics**  
**Batch Production Record**

**Product Name:** PHCL WG Tablets/Capsules  
**Batch:** PC021TC

Page 7 of 7  
**Batch size:** 303g

Manufacturing Directions						
Step	Procedure	Weight	Time	Date	Done By	Checked by
1	Separately screen following materials through a 20 mesh screen Emcocel <sup>®</sup> 90 M Methocel <sup>®</sup> K100M LV EP Eudragit <sup>®</sup> L100 Methocel <sup>®</sup> K100M					
2	Place the following materials in the Kenwood bowl Propranolol hydrochloride granules Emcocel <sup>®</sup> 90 M Methocel <sup>®</sup> K100M LV EP Eudragit <sup>®</sup> L100 Methocel <sup>®</sup> K100M					
3	Blend the materials in step 2 for 15 minutes on blender Time started: Time completed: Speed setting: 1					
4	Separately screen following materials through a 44 mesh screen Magnesium Stearate					
5	Add screened materials from step 4 to blender and blend for additional 3 minutes Time started: Time completed: Speed setting: 1					
6	Four capsules manually filled					
7	Transfer rest of blend to feed hopper of tablet press					
8	Tablets compressed on Manesty F3 Time started: Time completed:					
9	Machine Settings Speed : 60 rpm Target weight : 200mg Target Hardness : 50 SC					
10	Tablets stored in airtight container					
11	Testing of Physical tablet characteristics					