CHAPTER FOUR

DRUG RELEASE FROM THE OPTIMIZED POLYAMIDE 6,10 MONOLITHIC MATRIX SYSTEMS: INFLUENCE OF FORMULATION VARIABLES AND DETERMINATION OF RELEASE KINETICS

4.1. INTRODUCTION

In Chapter three, the formulation of three optimized monolithic matrix systems demonstrating slow, intermediate and controlled drug release characteristics utilizing the modified polyamide 6,10 variants was achieved. These new diversified polymeric drug delivery systems, demonstrating flexible drug release behaviour, derived from modification of native polyamide 6,10 by changing stoichiometry, volume ratios, liquid phase pH and polarity of the interfacial polymerization method has to date not been explored by any other research group or applied in drug delivery employing the described approach. These novel drug delivery systems will be represented as formulations “SR”, “IR” and “CR” for the slow, intermediate and controlled release monolithic systems respectively throughout the subsequent sections of this dissertation.

Research has shown that drug release from monolithic matrices is mainly controlled by polymer erosion, dissolution and/or swelling front movement as well as drug dissolution and diffusion through the polymer matrix at the molecular level (Miyajima *et al.*, 1998; Jamzad *et al*., 2005). These phenomena depend upon the interaction between the dissolution media which is usually aqueous-based and polymeric matrix as well as the drug (Jamzad *et al*., 2005). The dissolution media has to penetrate the polymer matrix leading to polymer swelling, relaxation or dissolution followed by drug dissolution and diffusion out of the matrix. These processes are influenced by several formulation variables which include but are not limited to the drug concentration, drug solubility, polymer particle size (Yang and Fassihi, 1997a; Miyajima *et al.*, 1998; Velasco, 1999; Jamzad *et al*., 2005), drug to polymer ratio, polymer viscosity, polymer molecular mass (Shah *et al*., 1993; Velasco, 1999; Jamzad *et al*., 2005 and the addition of different types and levels of excipients or release modulators (Pillay and

Fassihi, 1999c; Pillay and Fassihi, 2000a and 2000b; Dürig and Fassihi, 2000; Williams III *et al*., 2002; Hite *et al*., 2005).

Mathematical modeling employed to understand the mechanisms of drug release from polymeric delivery devices is a matured art in the area of drug delivery (Peschka *et al*., 1998; Ramraj *et al*., 1999; Narasimhan, 2001; Siepmann and Göpferich, 2001; Siepmann and Peppas, 2001a and 2001b; Schliecker *et al*., 2004). Mathematical models provide appropriate understanding of the various controlling steps in the polymeric dissolution process, which is essential for drug release, and this greatly enhances the tailoring of the polymer to achieve not only desired drug release performance but also the desired release kinetics (Narasimhan, 2001). Also, mathematical models provide the practical benefits of simulating the effects of design (formulation) parameters on the generated release profiles. Therefore, the formulation variables to achieve a certain drug release profile can be predicted theoretically and the development of new pharmaceutical products can be significantly facilitated (Siepmann and Peppas, 2001a).

4.1.1. Objectives

The current Chapter focuses on investigating the diverse drug release characteristics of the optimized polyamide 6,10 monolithic matrices (i.e. formulations “SR”, “IR” and “CR”). In this study, the effects of polymer and drug concentration, drug solubility, pH of dissolution media, compression force and polymeric particle size will be evaluated using any of the optimized monolithic matrices most appropriate for the respective experimental assessments. Also, the drug release behaviour of an optimized polyamide 6,10 monolithic matrix will be modified employing formulation excipients which include hydrophilic and hydrophobic US FDA GRAS-approved polymers as well as inorganic electrolytes (salts).

In addition, appropriate mathematical models will be employed to determine the drug release mechanisms and kinetics from the three optimized monolithic matrix systems developed in Chapter three.

4.2. EXPERIMENTAL SECTION

4.2.1. Materials

The optimized polyamide 6,10 monolithic matrices (i.e. “SR”, “IR” and “CR”) developed in Chapter three were employed for this experimental phase. Amitriptyline hydrochloride (100% water soluble at 25℃; Pharmaceutical Codex, 1994) and anhydrous theophylline (0.85% water soluble at 25℃; Pharmaceutical Codex, 1994) employed as the model drugs were purchased from Sigma Chemical Company (St. Louis, USA). Poly(lactide-co-glycolide) (PLGA, Resomer 202) was obtained from Boehringer Ingelheim (Pharma KG, Ingelheim, Germany) and Hydroxypropylmethylcellulose (HPMC) K4M was purchased from Dow Chemical Company (Midland, Michigan, USA). Aluminium sulphate ($Al_2(SO_4)_2$) and magnesium sulphate ($MgSO_4$) were received from Merck Chemicals (Darmstadt, Germany) and potassium sulphate (K_2SO_4) was obtained from Rochelle Chemicals (Johannesburg, Gauteng, South Africa). All other reagents utilized were of analytical grade and used as received.

4.2.2. Formulation of the Monolithic Matrix Systems

The monolithic matrix formulations for the respective investigations were produced in triplicate by direct compression and each was composed of a mixture of 300mg of any of the powdered optimized polyamide 6,10 variants and 50mg of either model drug (i.e. amitriptyline hydrochloride or theophylline) throughout this study unless otherwise stated. All other procedural stipulations utilized for the preparation of the monolithic matrices described in Section 3.4.6.1 were adopted for this experimental phase.

4.2.3. Preparation of Calibration Curves of Amitriptyline Hydrochloride and Theophylline in USP-Prescribed Buffer Solutions

4.2.3.1. Calibration Curves of Amitriptyline hydrochloride and theophylline in PBS at pH 7.4

The calibration curve generated for amitriptyline hydrochloride in the phosphate buffer solution (PBS) at pH 7.4 described in Chapter Three (Figure 3.4) was employed in here. For theophylline, the stock solution was prepared by dissolving 20mg of theophylline in 100mL of PBS at pH 7.4. From the stock solution, a series of dilute standard solutions of the following concentrations: 0.005, 0.010, 0.015 and 0.020 and 0.025 mg/mL for were prepared. The absorbance of each standard solution was determined at the maximum wavelength (λ_{max}) 270nm. The linear calibration curve (correlation coefficient; R^2= 0.99) was constructed on the basis of this information (Figure 4.1a).

4.2.3.2. Calibration Curves of Amitriptyline Hydrochloride and Theophylline in USP-Prescribed Acidic Buffer Solution at pH 1.2

The stock solution was prepared by separately dissolving 20mg of Amitriptyline hydrochloride and theophylline in 200mL of buffer solution at pH 1.2 respectively. A series of dilute solutions of the following concentrations: 0.005, 0.010, 0.015, 0.020 and 0.025 mg/mL for amitriptyline hydrochloride and 0.005, 0.010, 0.015, 0.020, 0.025 mg/mL for theophylline were prepared using the stock solutions. The absorbance of each standard solution was determined at the maximum wavelength (λ_{max}) of 240nm as well as 270nm for amitriptyline hydrochloride and theophylline respectively. The calibration curves (correlation coefficient; R^2 = 0.98 and 0.99 for amitriptyline hydrochloride and theophylline respectively) were constructed using the generated data (Figures 4.1b and c respectively).

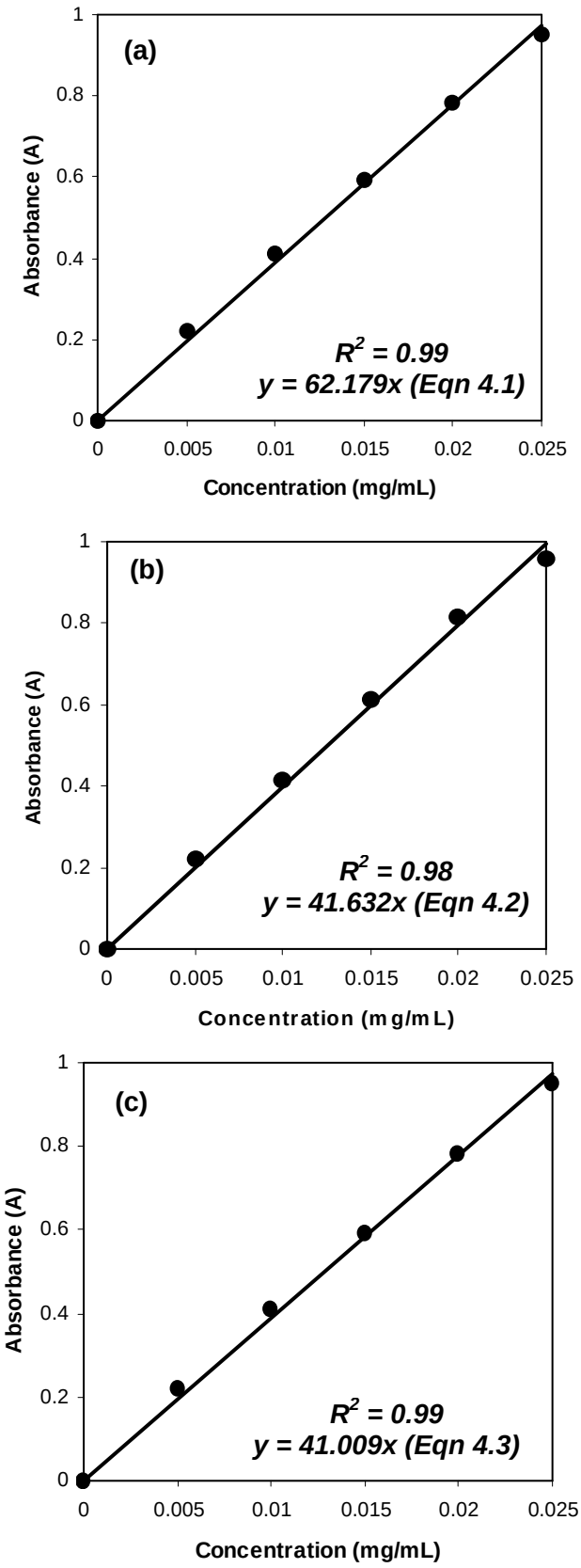


Figure 4.1: Calibration curves of: (a) Theophylline in PBS of pH 7.4 at pH 270nm (b) Amitriptyline hydrochloride and (c) Theophylline in acidic buffer of pH 1.2 at 240nm and 270nm respectively (N= 3 and standard deviation less than 0.03 in all cases).

4.2.4. Influence of Drug Solubility on Release Characteristics

The impact of drug solubility on the release behaviour of the three optimized monolithic matrices (i.e. Formulations "SR", "IR" and "CR") was assessed. Amitriptyline hydrochloride (100% water soluble at 25℃; Pharmaceutical Codex, 1994) and theophylline (0.85% water soluble at 25℃; Pharmaceutical Codex, 1994) were employed as model high and low solubility drugs respectively. Each monolithic matrix system was fabricated in triplicate (containing 300mg of each of the optimized polyamide 6,10 variant and 50mg of each model drug) using the general method already described above (Section 4.2.2). Evaluation of drug release was performed by immersing the respective monolithic matrices into a calibrated six-station dissolution test apparatus (Caleva Dissolution Apparatus, model 7ST) using a standard USP 25 rotating paddle method at 50 rpm with 500mL PBS (pH 7.4 at 37±0.5^{o}C). Experiments were conducted in accordance with the method described in Chapter Three (Section 3.4.6.2).

4.2.5. Examining the Influence of an Alternative Dissolution Approach on the Drug Release Performance of a Potential Implantable Device

Formulation "SR" was subjected to further investigation to assess its potential to release drug over a more prolonged period, as it was the matrix system that demonstrated the slowest release rate (i.e. released the lowest amount (13.9%) of drug, Figure 3.11) at the end of 24-hours. In order to achieve this objective, the shaking water bath (Stuart SBS 40, Staffordshire, UK) was employed. The monolithic matrix systems used were prepared in six replicate samples in accordance with the method described in Section 4.2.2. Each matrix system was immersed in 100mL phosphate buffer solution, pH 7.4 and placed in covered glass jars (i.e. closed system). For studies at the specified condition, six replicate samples of the matrix devices of formulation "SR" were maintained at 37 ± 0.5^{o}C and 50rpm in the shaking

water bath (Stuart SBS 40, Staffordshire, UK). The model drug for this study was Amitryptiline hydrochloride. A 5mL filtered dissolution sample was withdrawn at specific time intervals over 30-days and sink conditions maintained by replacing withdrawn volume with fresh phosphate buffer at each sampling time. The amount of drug released was determined by the Ultraviolet Spectroscopy (Specord 40, Analytik Jena, AG, Germany) at 240nm. In addition, the percentage by weight of the matrix remaining after the 30-day experiment was calculated.

4.2.6. Assessing the Effect of pH of Dissolution Media on Drug Release

The release of amitriptyline hydrochloride and theophylline from one of the optimized monolithic matrices (i.e. Formulation “CR”) were evaluated separately in buffer media at pH 1.2 and 7.4 respectively to establish the effect of media pH. The matrix systems were produced in triplicate in accordance with the method earlier described (Section 4.2.2). The procedure for the dissolution study outlined in Chapter Three (Section 3.2.6.2) was also employed for this study.

4.2.6.1. Investigating the Buoyancy and Erosion of a Potential Gastroretentive device

In addition to assessing the influence of pH of the media on drug release, the capability of the same matrix formulation “CR” to remain buoyant over the 24 hours duration of study was determined by monitoring the floating monolithic matrices over time (10 minutes, 1, 12 and 24 hours). The ability of these monolithic matrices to erode was also assessed using the mathematical expression described in Equation 3.6.

4.2.7. Examination of the Effects of Polymer and Drug Concentrations on Drug Release

To visualize the effects of varying polymer and drug concentration on the release characteristics of the optimized matrices, Formulation "SR" was employed. The monolithic matrices were produced utilizing the procedures stated earlier (Section 4.2.2). Amitriptyline hydrochloride was selected as a model drug of choice for this assessment. The composition of each formulation indicating the concentration levels of the polymer and drug are presented in Table 4.1. A control formulation composed of 50mg of amitriptyline hydrochloride and 300mg "SR" was employed all through the study to function as a reference point for comparison purposes for the set of experiments. Dissolution studies for each formulation (F1-F9) was carried out in triplicate employing the calibrated six-station dissolution test apparatus (Caleva Dissolution Apparatus, model 7ST) using the standard USP 25 rotating paddle method at 50 rpm with 500mL PBS of pH 7.4 at 37±0.5^{o}C. All other experimental procedures stated in Chapter Three (Section 3.4.6.2) were observed here (Section 3.2.6.2).

Table 4.1: Polymer and drug concentrations used in the different matrix formulations

Formulation	Composition	
	Drug (mg) [a]	"SR" (mg) [b]
SR [c]	50	200
SR [d]	50	100
SR [e]	50	50
SR [f]	50	450
SR [g]	50	600
SR [h]	100	300
SR [I]	200	300
SR [j]	300	300
SR [k]	25	300
SR [*]	50	300

[a] Amitriptyline hydrochloride; [b] optimized polyamide 6,10 demonstrating slow release; formulations SR [c] - SR [g] reflects changes in polymer concentration; SR [h] - SR [k] depicts variations in drug amounts; SR [*] control formulation containing only "SR".

4.2.8. The Effects of Varying Compression Force on Release Behaviour

Different compression forces (1.0, 2.0, 3.0 and 4.0 tonnes) were employed for the production of the monolithic matrix systems in accordance with the specifications described above (Section 4.2.2). Each matrix contained 50mg of drug and 300mg of polymer. The production of the matrix systems was done in triplicate. Formulation "IR" as well as amitrytiline hydrochloride (model drug) were employed for this purpose. Dissolution studies for each formulation was carried out in triplicate employing the method outlined in Chapter Three (Section 3.4.6.2).

4.2.9. The Effects of Polymer Particle Size on Drug Release

To evaluate the influence of changing polymer particle size on drug release, Formulation "IR" was used. Each matrix system was produced in triplicate following the procedure described earlier (Section 4.2.2) and amitriptyline was employed as a model drug. The exception was that different laboratory test sieves (Endecotts Ltd, London, UK) with varying aperture sizes were utilized. Those employed included aperture size 710µm, 1.00mm and 1.20mm indicating that particle sizes range from ≤710µm to ≤1.00mm to ≤1.20mm respectively. Dissolution studies for each formulation was carried out in triplicate using the procedure explained in Chapter Three (Section 3.4.6.2).

4.2.10. Exploring the Effects of Different Types and Concentrations of Excipients on the Release Characteristics

In order to assess the influence of formulation excipients on drug release, formulation "IR" was used. PLGA and HPMC were employed as typical hydrophobic and hydrophilic FDA-approved polymeric materials while the inorganic electrolytes utilized include aluminium sulphate ($Al_2(SO_4)_2$), magnesium sulphate ($MgSO_4$) and potassium sulphate (K_2SO_4).

Each monolithic matrix system consisting of different amounts of the FDA-approved polymers or electrolytes and an optimized polyamide 6,10 were dry-blended together with 50mg of amitriptyline hydrochloride (the model drug used for this phase) as physical mixtures. The respective monolithic matrix systems were produced in triplicate as descried in Section 4.2.2 above.

Dissolution experiments for each formulation was carried out in triplicate employing the calibrated six-station dissolution test apparatus (Caleva Dissolution Apparatus, model 7ST) using the standard USP 25 rotating paddle method at 50 rpm with 500mL PBS of pH 7.4 at 37±0.5^{o}C. All other experimental processes prescribed in Section 3.4.6.2 for the dissolution study were also employed here.

4.2.10.1. Effects of Typical FDA-approved Hydrophobic and Hydrophilic Polymers

Table 4.2 explains the make-up of each monolithic matrix system employed for this evaluation.

Table 4.2: Composition of the matrix formulations containing the hydrophobic or hydrophilic polymers

Formulations	Composition (mg)			
	"IR" (mg) [a]	PLGA (mg) [b]	HPMC (mg) [c]	Drug (mg) [d]
F1	225	75	-	50
F2	150	150	-	50
F3	75	225	-	50
F4	225	-	75	50
F5	150	-	150	50
F6	75	-	225	50
F7*	300	-	-	50
F8 *	-	300	-	50
F9 *	-	-	300	50

*[a] optimized polyamide 6,10 variant demonstrating intermediate release; [b] poly (lactide-co-glycolide); [c] hydroxypropylmethylcellulose; [d] amitriptyline hydrochloride; * control formulations containing 100% of the respective polymers.*

4.2.10.2. Effects of the Inclusion of Inorganic Electrolytes in the Formulation

The composition of the matrix formulations employed for these experiments are stated in Tables 4.3.

Table 4.3: Constituent of the matrix formulations with the inorganic electrolytes

Formulations	Constituents (mg)				
	"IR" (mg) [a]	K_2SO_4 [b]	$MgSO_4$ [c]	$Al_2(SO_4)_3$ [d]	Drug [e]
F10	300	150	-	-	50
F11	300	-	150	-	50
F12	300	-	-	150	50
F13 [*]	300	-	-	-	50

[*] *Control formulation containing 100% of "IR"; [a] optimized polyamide 6,10 variant demonstrating intermediate release behaviour; [b] potassium sulphate; [c] magnesium sulphate; [d] aluminium sulphate; [e] amitriptyline hydrochloride.*

4.2.11. Treatment of Dissolution Data

The influence of formulation variables on the release characteristics of the respective optimized polyamide 6,10 monolithic matrix systems (i.e. formulations "SR", "IR", "CR") was investigated. In order to provide concise and meaningful comparisons and explanations to the generated dissolution profiles, a model-independent analysis was employed. This approach uses fit factors or similarity indices which comprise of a difference factor (f_1) and similarity factor (f_2) (Anderson *et al.*, 1998; Pillay and Fassihi, 1998; Dürig and Fassihi, 2000; Sánchez-Lafuente *et al*., 2002; Costa *et al*., 2003). These parameters compare and establish similarities and differences between two dissolution curves obtained from experimental data through a mathematical approach (Sánchez-Lafuente *et al*., 2002). The fit factors were introduced by Moore and Flanner (Moore and Flanner, 1996; Anderson *et al.*, 1998, Pillay and Fassihi, 1998) and adopted by FDA Center for Drug Evaluation and Research (CDER) (Costa *et al*., 2003; Pillay and Fassihi, 1998). The fit factors (i.e. f_1 and f_2) are defined in equations 4.4 and 4.5 (Pillay and Fassihi, 1998).

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100\% \qquad \textit{(Equation 4.4)}$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} w_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \qquad \textit{(Equation 4.5)}$$

where R_t is the reference assay at time point t, T_t is the test assay at time point t, n is the number of pull points (or time points), w_t is an optional weight factor.

The relative difference between two dissolution profiles at each experimental time is described by f_1. It approximates the percent error between two curves. The f_1 value is zero when the test and reference profiles are identical and increases proportionally with the dissimilarity between the two profiles (Anderson *et al.*, 1998, Pillay and Fassihi, 1998). When two profiles are equal, this factor acquires a value from 0 to 15 while a f_1 value greater than 15 indicates that the two profiles are different (Sánchez-Lafuente *et al*., 2002; Costa *et al*., 2003). The f_2 value between 50 and 100 suggests that the dissolution profiles are similar while f_2 values less than 50 implies that the profiles are not similar. The f_2 value of 100 suggests that the test and reference profiles are identical and as the value becomes smaller, the dissimilarity between release profiles increases (Pillay and Fassihi, 1998; Dürig and Fassihi, 2000).

The reference and the test samples will be selected based on the theme of each experiment. The dissolution time point will be set at 24 hours for both test and reference formulations for all the variables explored throughout this investigation.

4.2.12. Determination of Drug Release Kinetics from the Optimized Monolithic Matrix Formulations

In order to establish the kinetic mechanisms and its relationship with drug release, dissolution data (Figure 3.11) obtained from the three optimized monolithic matrix formulations (i.e. “SR”, “CR” and “IR” respectively) was mathematically modeled. This analysis was accomplished using the Guassian-Newton (Levenberg-Hartley) approach for all least squares analyses on the WinNonlin Professional Edition, Version 5 (Pharsight, USA).

4.3. RESULTS AND DISCUSSION

4.3.1. Influence of Drug Solubility on Drug Release Potential of Optimized polyamide 6,10 Matrix

For the three optimized monolithic matrix systems namely formulations “SR”, “IR” and “CR” showed closely related drug release patterns in terms of the influence of drug solubility ($f_1 < 15$; *SR= 0.79, IR= 1.19, CR= 0.28*). The profiles demonstrating the release of amitriptyline hydrochloride for each optimized polyamide 6,10 monolithic matrix system was employed as the reference. This implies that the release of both amitryptiline HCl and theophylline from the optimized polyamide 6,10 monolithic matrices were similar irrespective of the differences in their solubilities (Figure 4.2a, b and c).

However, amitriptyline hydrochloride demonstrated slightly faster drug release behaviour than theophylline (Figure 4.2a, b and c). This may be attributable to the higher hydrophilic tendencies of amitriptyline hydrochloride (100% water soluble at 25℃; Pharmaceutical Codex, 1994) due to its higher solubility when compared with theophylline (0.85% water soluble at 25℃; Pharmaceutical Codex, 1994). This allows

more water to be entrapped within the matrix (relative to theophylline), which increases the rate of matrix disentanglement and drug liberation.

The similarities observed in the release characteristics (Figure 4.2a, b and c) of the three optimized monolithic matrix systems with respect to differences in drug solubility may be related to the resemblance of their basic chemical backbone structure which was confirmed with FTIR analysis (Section 5.3.5). A hypothesis that drug release from these optimized polyamide 6,10 monolithic matrix systems is independent of level of drug solubility but controlled by polymeric matrix relaxation or disentanglement may be proposed.

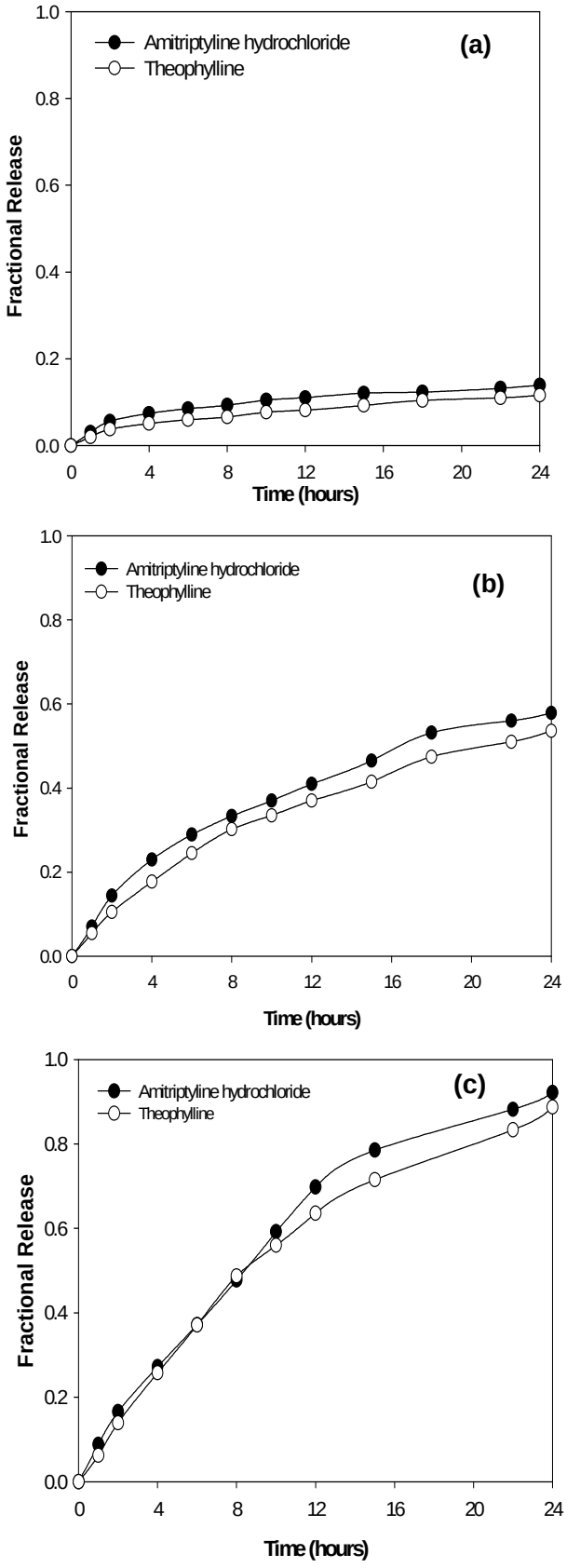


Figure 4.2: The drug release profiles of amitriptyline hydrochloride and theophylline from the optimized polyamide 6,10 monolithic matrices: (a) “SR”, (b) “IR” and (c) “CR” (N=3 and standard deviation less than 0.49 in all cases).

4.3.2. Influence of an Alternative Dissolution Approach on the Drug Release Performance of a Potential Implantable Device

Prolonged release evaluation revealed the ability of formulation "SR" produced as monolithic matrix systems to release drug constantly over an extended period. The generated profile demonstrated a consistent release pattern of about 0.09% per hour throughout the 30-days, which resembled the zero-order kinetics (Figure 4.3). A total of 14.06% of the loaded drug was liberated at the end of 30-days. Also, the optimized system showed the ability to undergo significant matrix erosion with about 78% of the matrix remaining after 30days. Typical profiles showing drug release and matrix erosion are presented in Figure 4.3.

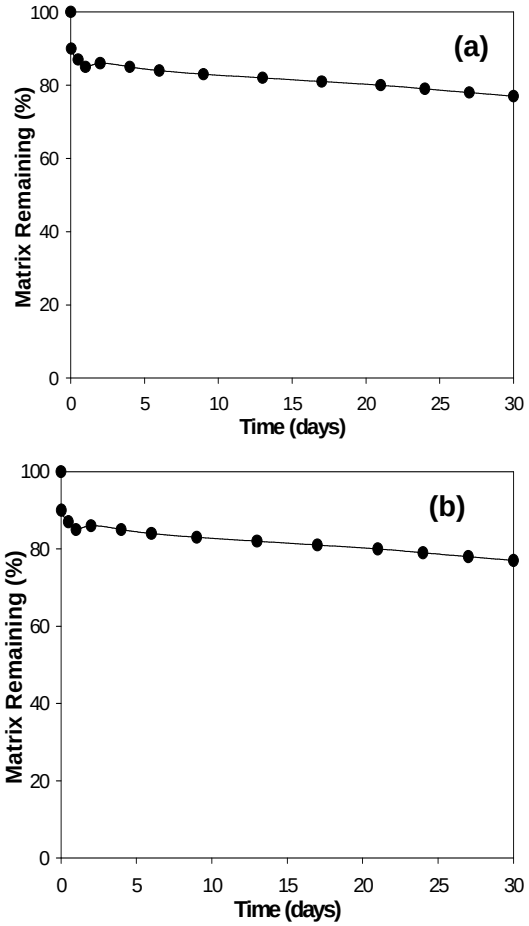


Figure 4.3: Graphical representations of the (a) drug release profiles and (b) percentage by weight of the matrix remaining at the end of the 30-day dissolution analysis (N=6 and standard deviation less than 3.52 in all cases).

4.3.3. Effect of pH of Release Media on Dissolution Profiles

The influence of pH of the dissolution medium on the release performance of formulation "CR" monolithic matrix is illustrated with Figure 4.4a. The matrices exposed to the acidic medium (pH 1.2) demonstrated a more rapid release behaviour when compared to those placed in pH 7.4 (Figure 4.4a). The dissimilarity amongst the profiles (f_2= 48.25 for amitriptyline hydrochloride and f_2= 42.22 for theophylline) were further established by computing their f_2 values. The profiles demonstrating the release of both drugs (i.e. amitriptyline hydrochloride and theophylline) at pH 7.4 (i.e. Figure 4.2a) served as the reference while the release profiles obtained at pH 1.2 were used as the test assay. The amount of drug released in the acidic media (pH 1.2) at every time-point was higher than that observed for the neutral media (pH 7.4). This suggests that the lower pH (i.e. acidic) enhances the process of matrix disentanglement and dissolution consequently increasing the amount of drug liberated. This may be associated with the hydrolytic impact of the acidic medium (pH 1.2) on the carbonamide functional moiety (— CONH—) with the linear chain of polyamide 6,10 (Sections 1.3, 2.2.2 and Figure 2.1). Hydrolysis of the moiety favours matrix cleavage, relaxation and dissolution. The above-described release behaviour was demonstrated by amitriptyline hydrochloride and theophylline (Figure 4.4(a)).

4.3.3.1. Investigation of the Buoyancy and Erosion of a Potential Gastroretentive Device

The matrix system (dealt with in section 4.3.3) showed the potential of effectively releasing both the amitriptyline hydrochloride and theophylline in a rate-controlled manner. The two drugs generated closely related release patterns showing that the drug release process is modulated by the rate of polymeric disentanglement and not drug solubility. The matrices elicited some level of burst of about 10% (at the first

hour) for each drug followed by a consistent release rate of approximately 4% per hour. Overall, close to 100% of drug was liberated in 24 hours.

The matrix device separately loaded with each model drug maintained its full buoyancy (i.e. floatability) in the acidic medium as the matrices underwent gradual dissolution and drug release throughout the test duration. Furthermore, obvious loss of matrix weight over time substantiated the outcome of the dissolution study. The profiles showing the release of amitriptyline hydrochloride and theophylline are already illustrated with Figure 4.4 (a) above. The polymeric matrix gravimetric loss with each of the model drugs is shown in Figure 4.4 (b). Photographs of the dissolution apparatus demonstrating the ability of the matrix system to remain buoyant over 24 hours is presented in Figure 4.4 (c).

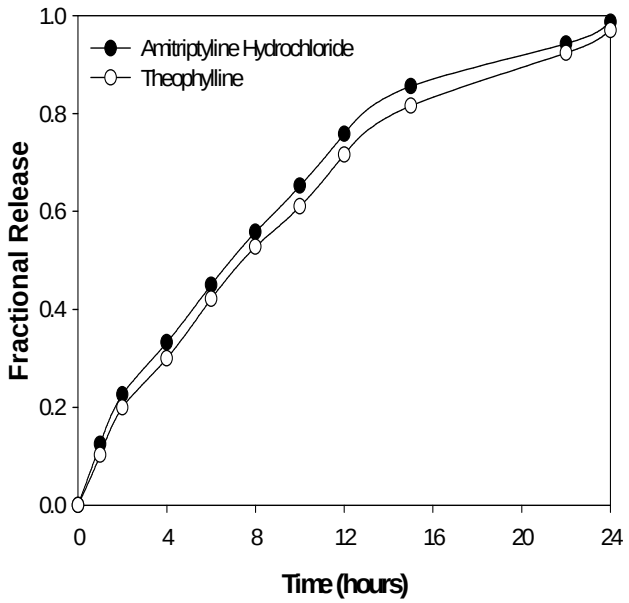


Figure 4.4 (a): Dissolution profiles showing the influence of pH on the release of model soluble and insoluble drugs from the optimized polyamide 6,10 matrix system. (N= 3 and standard deviation less than 0.04 in all cases).

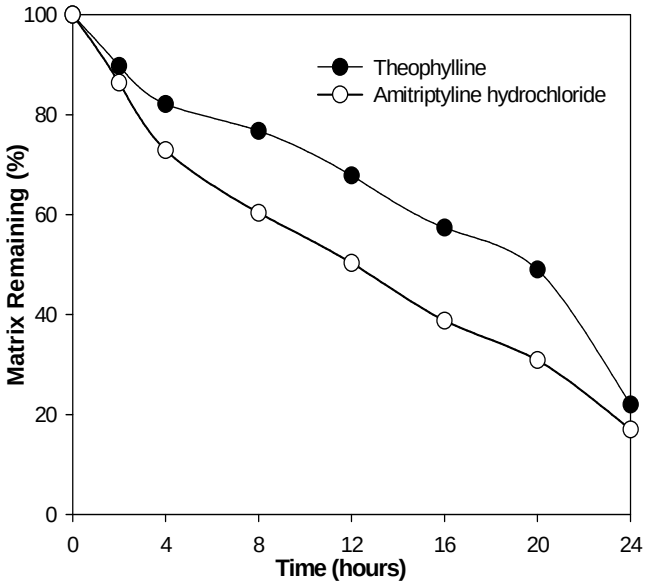


Figure 4.4 (b): Profiles showing polymeric matrix gravimetric loss with amitriptyline hydrochloride and theophylline (N=3 and standard deviation less than 3.95 in all cases).

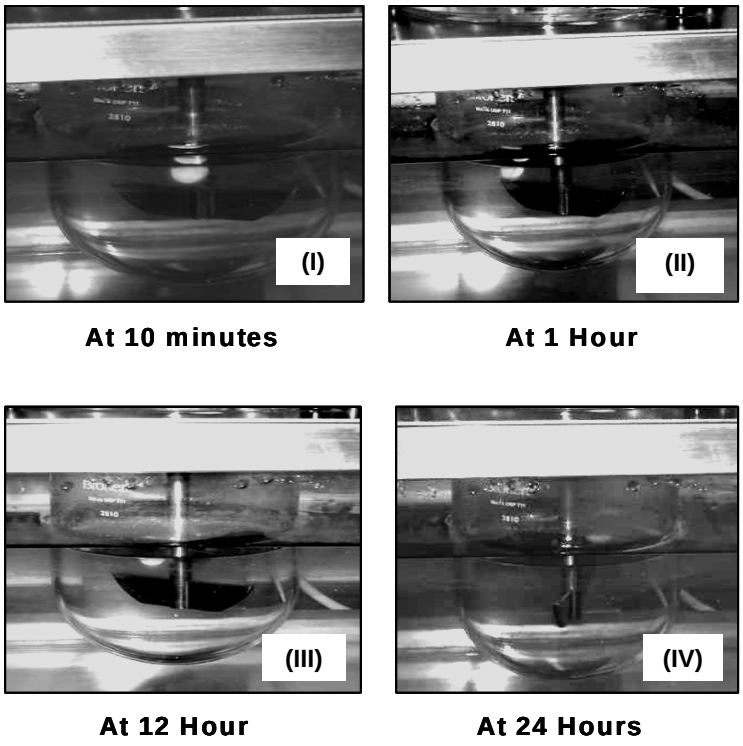


Figure 4.4 (c): Photographs of dissolution vessels showing the ability of the matrix device to remain buoyant (float) over 24 hours (i.e. vessels (I)-(IV)).

4.3.4. Influence of Polymer and Drug Concentrations on the Drug Release Performance

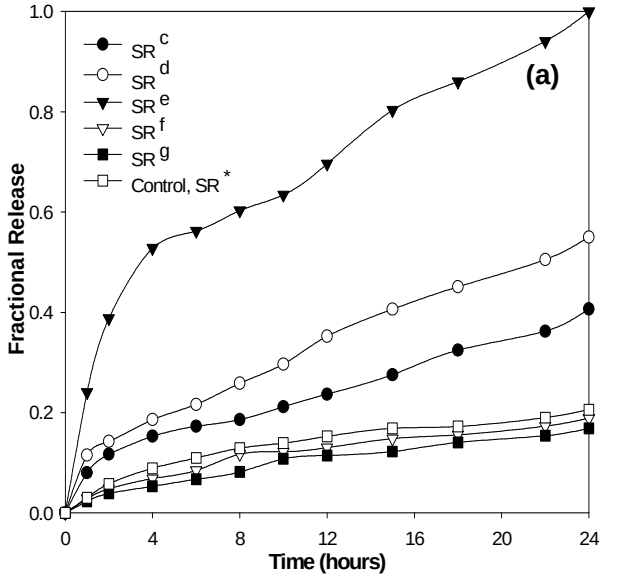
The diverse effects of changing the polymer and drug concentrations on the release characteristics of a typical optimized polyamide 6,10 matrix (i.e. formulation "SR") are illustrated in Figures 4.5 (a) and (b). The different levels of disparity in the composition of the respective matrices had significant influences on the pattern of drug liberation. The disparities in the release profiles generated are further substantiated with the difference factor ($f_2 < 50$ ranging from 16.22-49.50) values for each monolithic matrix formulation. The control formulation (i.e. SR *) was selected as the reference product while all other formulations (i.e. SR ^{c}-SR ^{d}) served as separate test products.

A decrease in polymer concentration as observed for formulations SR ^{c}–SR ^{g} (Table 4.1 and Figure 4.4a) increased the level of burst effect as well as the amount of drug released while the converse is true when the polymer concentration is increased. Formulation SR ^{e}, for instance, comprised the lowest polymer concentration (i.e. 50mg) presented with the most rapid and irregular release pattern while formulation SR ^{g} with the highest polymer concentration (i.e. 600mg) showed the slowest and most consistent release pattern (Figure 4.4a) when compared with the control formulation, SR *. The release profiles of formulations SR ^{f} and SR ^{g} were similar to that of the control matrix system and these three matrices demonstrated controlled, slow release respectively (Figure 4.4). The observed trends in the drug release may be associated with the degree of permeability of the monolithic matrices involved. In instances when polymer concentration can be referred to as low, the matrix system on hydration would be highly porous with a low degree of tortuosity leading to a low matrix mechanical strength, rapid erosion of the matrix as well as a quick diffusion of

the drug molecules from the matrix (Jamzad *et al*., 2005) while the converse is the case for matrices with higher polymer concentrations.

Furthermore, formulations SR ^{h}-SR ^{k} show the effects of drug concentration on drug release performances. This is also compared against the control formulation, SR *. An increase in drug concentration amplifies the levels of burst effect and release. Formulation SR ^{j} with the highest drug concentration (300mg) generated the most rapid release and highest level of burst effect while the contrary is observed for formulation SR ^{k} that contained the lowest amount of drug (25mg) (Table 4.1, Figure 4.5b). The may be attributed to the ability of the drug molecules to either increase or decrease water uptake within the matrix and hence intensify or reduce the rate of matrix relaxation and dissolution respectively.

Generally, the variations in the concentrations of the polymer as well as the drug integrated into the formulation of each monolithic matrix system influenced the generated release profiles but this did not drastically change the nature of the release profiles signifying the robustness and flexibility of the monolithic matrices produced utilizing an optimized polyamide 6,10 variant.



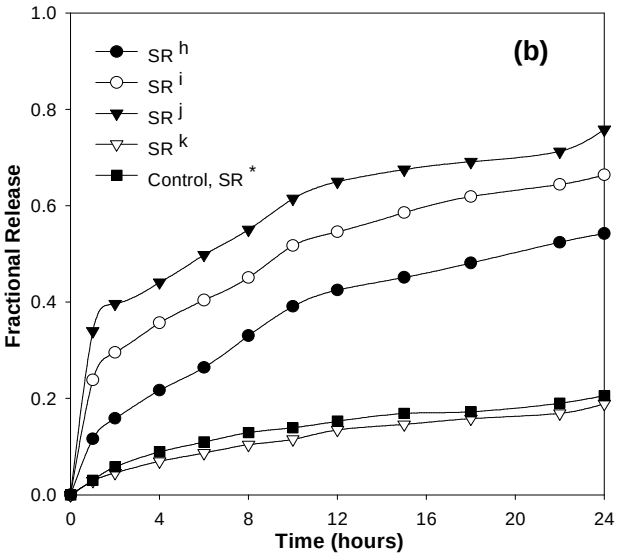


Figure 4.5: Drug release profiles showing the effects of varying (a) polymer (polyamide 6,10) concentration and (b) drug concentration. (N=3 and standard deviation less than 0.10 in all cases).

4.3.5. Effects of Varying Compression Force on Drug Release

Figure 4.6 illustrates the direct effects of changing force of compression on the drug release behaviour of the optimized polyamide 6,10. An increase in compression forces decreased the amount of drug release while the converse was observed for a decrease in compression force (Figure 4.6). This may be attributed to an increase or decrease in electrostatic forces of attraction amongst the polymer particles, the drug

molecules as well as between the polymer and the drug particles which influences the particulate packing efficiency within the matrix. For instance, an increase in particle-particle interaction based on increased compression force reduces the rate at which water molecules penetrate the matrix and this slows down the rate of matrix disentanglement, dissolution, erosion and drug release. A reverse of this pattern applies when a there is a decrease in the magnitude of the force of compression (Figure 4.6).

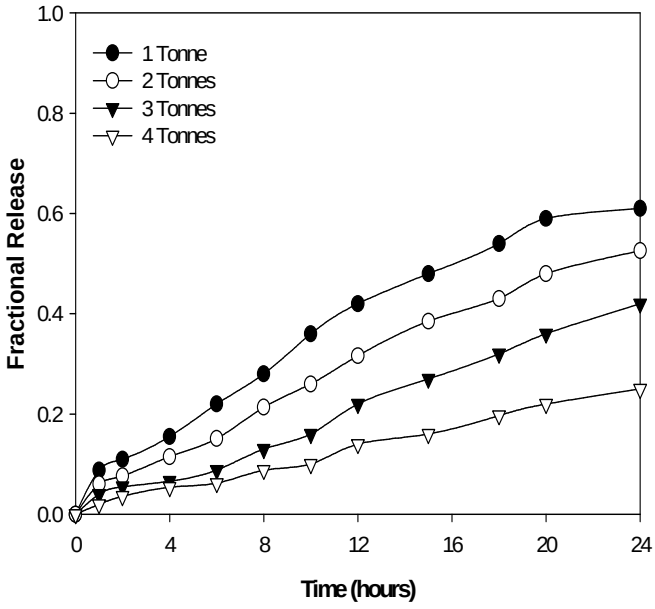


Figure 4.6: Effects of changing force of compression on the release performance of an optimized polyamide 6,10 monolithic matrix system (N=3 and standard deviation less than 0.06 in all cases).

4.3.6. Effect of Polymer Particle Size Variation on Drug Release

This study revealed the significant effect of particle size on the drug release from the optimized polyamide 6,10 matrices. An increase in particle size decreased the amount of drug released while the converse was observed for a decrease in particle size (Figure 4.7). A reduction in particle sizes increases the surface area as well as the wettability of the polymeric particles. This makes the hydrated matrix highly porous

with a low degree of tortuosity leading to rapid matrix loosening and diffusion of the drug molecules from the matrix resulting in an increase in the amount of drug released. However, with larger particle sizes (i.e. increase in particle size), the converse of the above-described trend occurs. The impact of particle size variation on the generated release profiles is illustrated with Figure 4.7 below.

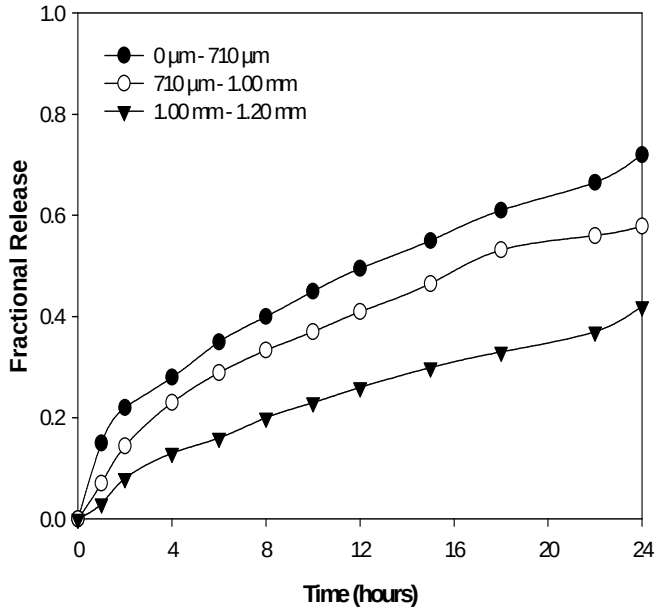


Figure 4.7: Diverse impact of particle size variation drug release from the optimized polyamide 6,10. (N= 3 and standard deviation less than 0.08 in all cases).

4.3.7. Elucidating the Impact of Formulation Excipients on Drug Release

4.3.7.1. Effects of Hydrophilic and Hydrophobic FDA-approved Polymers

Significant changes were observed for the drug release profiles generated for all combinations employed. These alterations are illustrated with Figures 4.8a and b for the hydrophilic and hydrophobic polymers respectively.

The presence of PLGA within the monolithic matrices (F1, F2 and F3) reduced the drug release compared to that of the native formulation “IR” matrix (F7) (Figure 4.8 a). Also, a specific and consistent trend of an increase in PLGA concentration decreasing

the amount of drug release was observed (Figure 4.8 a). This may be associated with the hydrophobic nature of PLGA. Therefore, the presence of PLGA within the matrix systems increases matrix stiffness as well as hydrophobicity. This minimizes the rate at which water molecules infiltrate the polymeric matrix which results in reduced rates of disentanglement and direct suppression of drug liberation. In other words, PLGA functions by minimizing the hydrophilicity of the optimized polyamide 6,10. The difference factor, f_1, ranged from 16.88-77.12 showing the inequality amongst the profiles. F7* was selected as the reference point.

A small difference was shown for the matrices containing HPMC (F4, F5, F6, F9) and that without (F7) (Table 4.2; Figure 4.8b). However, the amount of drug released at the first hour increased from 9.5% to 11.9% to 14.2% for F4, F5 and F6 respectively with an increase in the concentration of HPMC present in the particular matrix (Figure 4.8b and Table 4.2). This had minimal effect on the amount of drug release at the end of 24 hours (Figure 4.8b). The unusual trend observed may be due to: (i) the hydrophilic nature of HPMC which favours rapid infiltration of water molecules thereby enhancing matrix loosening and dissolution, (ii) the capability of HPMC to swell which influences polymeric free volume, a mechanism that it employs to modulate drug release from its matrix, and (iii) the high solubility of the drug employed may be contributing factors as well (Shah *et al*., 1993; Pillay and Fassihi, 2000b; Siepmann and Peppas, 2001b). A combination of these two polymers may not be desirable except that the intended application justifies it because no major effect is observed. In this case, the fit factors showed that the profiles were identical as the fit factor, f_1, ranged from 0.43-6.72 and F7* was also chosen as the reference point.

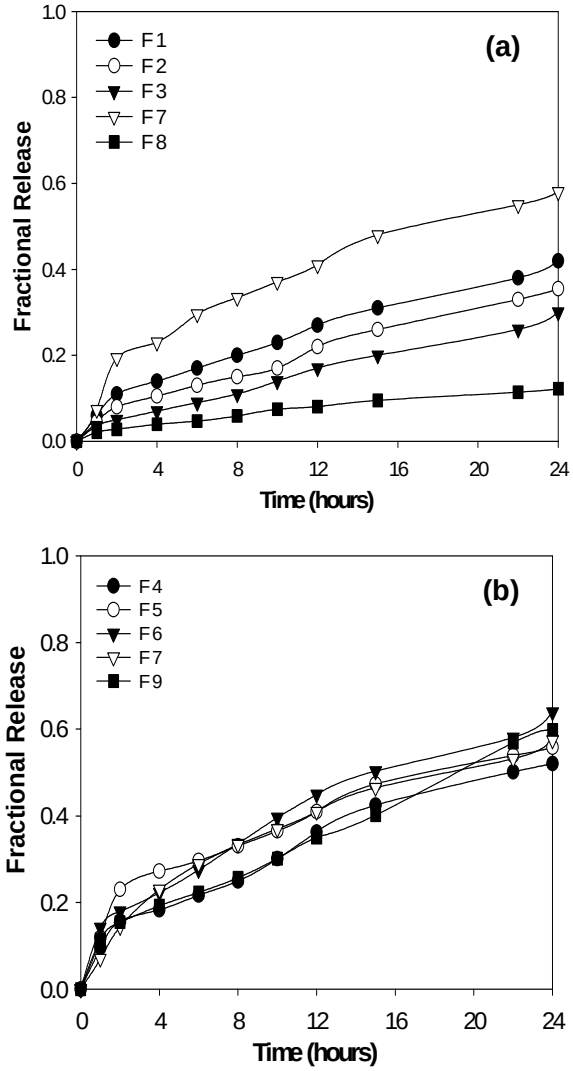


Figure 4.8: Profiles illustrating the effects of (a) Poly (lactides-co-glycolide) (b) Hydroxypropylmethylcellulose and on the drug release characteristics from the optimized polyamide 6,10 monolithic matrices. (N= 3 and standard deviation less than 0.05 in all cases).

4.3.7.2. Influence of Inorganic Electrolytes

Electrolyte inclusion played a distinct role in modulating the drug release (Figure 4.9). A relationship between the drug release and the valency of the cations (i.e. positively charged ions) of the electrolyte exists. The test formulation containing the cation with the highest valency (i.e. Al^{3+}, F12) demonstrated the slowest release while the reverse was observed for the formulation containing the cation with the lowest valency (i.e. K^{+}, F10) in comparison with the control formulation without electrolytes (i.e. F13) (Figure 4.9).

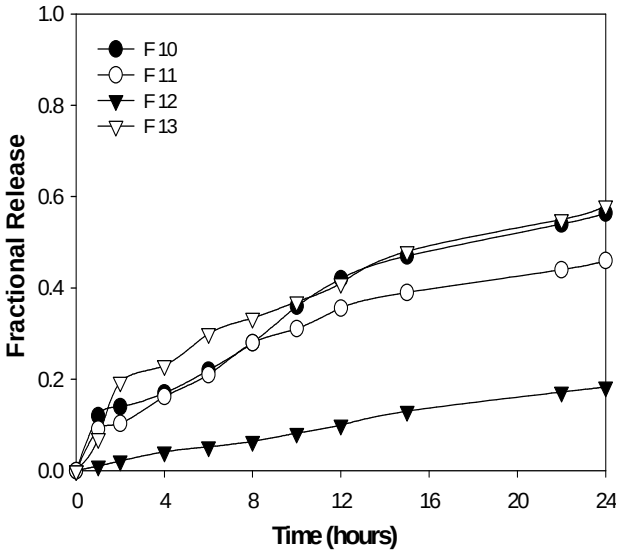


Figure 4.9: Influence of inorganic electrolytes on the drug release performance (N= 3 and standard deviation less than 2.22 in all cases).

Rate of infiltration of water molecules to facilitate matrix loosening as well as drug diffusion out of the matrix varies based on each electrolyte (Figure 4.9). Based on the phenomenon described by Pillay and Fassihi (2000b), which described that a kind of competition exists between electrolyte and water species (from the release media) within the matrix on exposure to the dissolution media. Consequently, the electrolyte species compete for water species at the outset of water influx and hence attract part of the water in order to dissociate into ions. This initial competition for water of hydration possibly dehydrates the polymer molecules leading to suppression of initial swelling as well as drug diffusion. However, once sufficient water has been attracted by the electrolyte species into the polymer matrix, the solubilized (ionized) species undergo an efflux process that creates significant porosity within the hydrated matrix for more water penetration which enhances peripheral swelling and drug diffusion (Pillay and Fassihi, 2000b).

The aforementioned theory is applicable to the scenario dealt with in this study. It has been established that the penetration of water molecules into the matrix initiates some process of competitive interaction between the electrolyte and polymer. It can be

proposed that this interaction is influenced by the valency of the ions of the electrolytes as this will determine the level of hydration as well as the amount of water molecules required by each electrolyte (Figure 4.9).

With polyamide 6,10 demonstrating some ionic tendencies (Section 3.5.5), a competition (with the electrolytes) for the water species may arise but the affinity of the electrolytes for water obviously outweighs that of the polyamide because the electrolytes are more hydrophilic. Therefore, the electrolytes determine the intensity of water infiltration into the respective matrices and this subsequently influences the rate of hydration of the polymer (polyamide 6,10). This has a direct impact on the speed of polymeric relaxation, dissolution and ultimately the drug release efficiencies.

With reference to the generated data (Figure 4.9), some hypothetical statements can be put forward to explain the observed trends: The higher the values of the ionic charges (i.e. valency) of cations (such as Al^{3+} from $Al_2(SO_4)_3$), the more the amount of water required, thereby bringing about complete hydration and ionization. This implies that there will be more competition for water molecules between the electrolyte and the polymer. Consequently, a higher level of polymeric dehydration is expected for matrices containing electrolyte species of this sort. This result in suppression of drug release, as the process of polymeric wetting, which leads to relaxation and disentanglement of the polymer chains resulting in drug release, is relatively inactivated. Once sufficient water has been attracted by the electrolyte species and they are fully hydrated, the ionized species move out of the matrix creating significant space within the matrix for water penetration which enhances matrix wetting, unfolding and drug release. For matrices containing electrolytes with lower charged cations (such as K^+ and Mg^{2+} from K_2SO_4 and $MgSO_4$ respectively), the intensity of competition with the polymer for water molecules is milder because the amount water

required for complete hydration and ionization is less (lower ionic charges). Therefore, the polymer is less dehydrated and some level of polymeric wetting, relaxation and unfolding allowing drug diffusion can occur before the completely hydrated electrolyte species begin to move out of the matrix to create more space for water penetration to further enhance drug release.

The above explains why matrices containing aluminium sulphate ($Al_2(SO_4)_3$) demonstrated the slowest release while potassium sulphate (K_2SO_4) was the quickest and magnesium sulphate ($MgSO_4$) was between the two extremes (i.e. $K^+ > Mg^{2+} > Al^{3+}$) (Figure 4.9).

4.3.8. Analysis of Kinetic Mechanisms Associated with Drug Release from the Optimized Monolithic Matrix Systems

In view of this case study, three kinetic models, namely the power law (Equation 4.6), Peppas and Sahlin (Equation 4.7) and the Hopfenberg (Equation 4.8), which fitted the respective dissolution data best were employed to identify the mechanisms involved in the release of drug molecules. The application of the models to the explaining the mechanism of drug release from the optimized systems will be focused on for this dissertation. More details on these models can be found elsewhere as they are summarized in this dissertation (Pillay and Fassihi, 2000b; Gopferich, 2001; Karatas and Baykara, 2001; Narasimhan, 2001; Siepmann and Peppas, 2001a and 2001b; Schliecker *et al*., 2004; Govender *et al*., 2005; Jamzad *et al*., 2005).

The mathematical equation representing the power law is stated below:

$$\frac{M_t}{M_\infty} = k_1 t^n \qquad \textit{(Equation 4.6)}$$

where, M_t and M_∞ are the cumulative amount of drug released at time t and the overall amount released respectively, k_1 is a release constant incorporating structural and geometrical shape of the delivery device and n is the release exponent, indicative of the mechanism of drug release. Equation 4.6 has two distinctive physically realistic meanings in the two special cases of n= 0.5 (indicative of diffusion-controlled drug release) and n= 1.0 (indicating swelling-controlled drug release where drug release is independent of time corresponding to the zero-order kinetics). Values of n between 0.5 and 1.0 can be regarded as an indicator for the superposition of both phenomena (anomalous transport) (Karatas and Baykara, 2001; Siepmann and Peppas, 2001a).

For the determination of contributions of both the Fickian diffusion (describes in many cases the dynamic swelling and diffusive drug release from glassy polymers) and matrix relaxation or dissolution on drug release, an expanded version of the power law which functions irrespective of the geometry of the drug delivery device was developed by Peppas and Sahlin (Equation 4.7).

$$\frac{M_t}{M_\infty} = k_1 t^n + k_2 t^{2n} \qquad \textit{(Equation 4.7)}$$

where, k_1 is the Fickian kinetic constant and k_2 is the relaxational or dissolution rate constant (i.e. anomalous transport), n is a kinetic constant (Pillay and Fassihi, 1999a and 2000a; Siepmann and Gopferich, 2001).

The Hopfenberg Model was proposed for the investigating drug release for systems with surface erosion and varying geometries such as slabs, cylinders or spheres showing heterogeneous erosion. It assumes that rate of drug release from these devices is proportional to their surface areas which is allowed to change with time (Pillay and Fassihi, 1999a; Pillay and Fassihi, 2000a; Siepmann and Gopferich, 2001;

Siepmann and Peppas, 2001a). The mathematical equation describing this model is stated in equation 4.8.

$$\frac{M_t}{M_\infty} = 1 - [1 - k_1 t]^n \qquad \textit{(Equation 4.8)}$$

where, k_1 is the overall erosion rate constant, n values are: n=1 for a slab, n=2 for a cylinder and n=3 for a sphere.

A summary of the essential model fitting and statistical parameters for the release kinetics of the three optimized formulations (i.e. formulations "SR", "IR" and "CR") is outlined in Table 4.4 (a), (b) and (c) respectively.

Table 4.4 (a): Release kinetics obtained from the various diffusion, relaxation and erosion models for the slow release formulation ("SR")

Model M_t/M_∞=	k_1	k_2	n	[a]AIC	[b]SBC	[c]Correlation Factor
k_1t^n	0.57	-	0.91	49.21	39.85	0.92
$k_1t^n+k_2t^{2n}$	0.14	0.59	0.95	19.21	19.85	0.99
$1-[1- k_1t]^n$	0.10	-	3	54.79	55.09	0.87

[a] *Akaike Information Criterion*
[b] *Schwartz's Bayesian Criterion*
[c] *Correlation between experimental and fitted dissolution data*

Table 4.4 (b): Release kinetics obtained from the various diffusion, relaxation and erosion models for the intermediate release formulation ("IR")

Model M_t/M_∞=	k_1	k_2	n	[a]AIC	[b]SBC	[c]Correlation Factor
k_1t^n	0.82	-	0.92	46.11	35.81	0.91
$k_1t^n+k_2t^{2n}$	0.25	0.71	0.93	17.23	29.12	0.93
$1-[1- k_1t]^n$	0.34	-	3	35.72	56.81	0.85

[a] *Akaike Information Criterion*
[b] *Schwartz's Bayesian Criterion*
[c] *Correlation between experimental and fitted dissolution data*

Table 4.4 (c): Release kinetics obtained from the various diffusion, relaxation and erosion models for the controlled release formulation ("CR")

Model M_t/M_∞=	k_1	k_2	n	[a]AIC	[b]SBC	[c]Correlation Factor
k_1t^n	0.97	-	0.94	39.22	29.84	0.93
$k_1t^n+k_2t^{2n}$	0.44	0.99	0.93	14.82	19.82	0.94
$1-[1- k_1t]^n$	0.50	-	3	44.22	45.11	0.92

[a] *Akaike Information Criterion*
[b] *Schwartz's Bayesian Criterion*
[c] *Correlation between experimental and fitted dissolution data*

Selection of the most suitable model that fits the dissolution data best by describing the mechanisms involved in the process of drug release from the optimized polyamide 6,10 monolithic matrix systems was based on the Akaike information criteria (AIC), Schwartz Bayesian criteria (SBC) and correlation factor.

The AIC is a measure of the goodness of fit of a particular model. When several models are being compared for a given set of dissolution data, the model associated with the lowest AIC value is regarded as giving the best fit out of the utilized models. In addition, the SBC and correlation values were employed as complementary pointers to confirm the accuracy of the correlation between the statistical and experimental data. Furthermore, lower SBC values and a correlation factor closest to one indicate the reliability of the mathematical model.

Utilizing the above-mentioned statistical fit parameters, the lowest AIC and SBC values for the Peppas and Sahlin model (i.e. the derivative of the power law) suggested better model suitability for the three formulation concerned (Tables 4.4 (a), (b) and (c)). In addition, the correlation factor for this model for each formulation had the closest numerical values to one (0.99, 0.93 and 0.94 respectively).

In summary, it is evident that the Peppas and Sahlin model (the power law variant) is highly stable and suitable for elucidating the drug release kinetics from the optimized polyamide 6, 10 monolithic matrices. This selection indicates that drug release from the polyamide 6,10 monolithic matrices was regulated by Fickian diffusion and matrix relaxation. Drug release from these matrices is more dependent on matrix relaxation than the Fickian diffusion based on the fact that the k_2 (relaxational rate constant) values (0.59, 0.71 and 0.99 for formulations “SR”, “IR” and “CR” respectively) are higher than the k_1 (Fickian kinetic constant) values (0.14, 0.25 and 0.44 for formulations “SR”, “IR” and “CR” respectively) and for all three formulations (Table 4.4 (a), (b) and (c)). Also, the value of n ranged between 0.5 and 1.0 (0.95, 0.93 and 0.93 for formulations “SR”, “IR” and “CR” respectively) indicating the superposition of both diffusion-controlled and swelling-controlled drug release (Equations 4.6 and 4.7, Table 4.4 (a), (b) and (c)).

In conclusion, the mechanisms involved during the process of drug release from the optimized polyamide 6,10 monolithic matrix systems developed in this study is dominantly by matrix relaxation, which is complemented by the Fickian diffusion. In addition, the n value (between 0.5 and 1.0) reveals that some matrix swelling where drug release is independent of time corresponding to the zero-order kinetics is also occurring as part of the drug release processes. The finding corresponds with the experimental data generated in terms of the dissolution and matrix erosion profiles (Figures 3.11 and 5.9) where a relatively direct relationship was observed for both matrix erosion and drug release. In addition, the outcome of the modeling approach confirms the hypothesis made earlier that drug release from the optimized polyamide 6,10 matrices is independent of level of drug solubility but controlled by polymeric matrix relaxation due to the similarity in dissolution profiles generated for both model soluble and insoluble drugs explored (Section 4.3.1). Furthermore, matrix swelling for

the three matrix systems were independent of time (Figure 5.7) which demonstrates the desired zero-order drug release kinetics. A hypothesis that drug release from these polyamide 6,10 matrices is independent of level of drug solubility but controlled by polymeric matrix relaxation may be proposed.

Furthermore, the similarity observed in the mechanisms of drug release from the three monolithic matrix systems further confirms that the modification strategy employed in this investigation only influences the physical properties (i.e. physicochemical and physicomechanical) of polyamide 6,10 and not its basic chemical backbone structure.

4.4. CONCLUDING STATEMENTS

The significant effects of some formulation variables such as drug and polymer concentration, drug solubility, pH of the release media, polymeric particle size and force of direct compression on the drug release performance of the respective optimized polyamide 6,10 monolithic matrices were investigated. In addition, the effects of formulation excipients (hydrophilic, hydrophobic and electrolytes) on the drug release behaviour of an optimized polyamide 6,10 monolithic matrix formulation was also assessed. The flexibility of the drug release characteristics of the optimized polyamide 6,10 matrix systems developed in Chapter three has been established in this Chapter. Established mathematical models were also used to explain the mechanisms of drug release from the optimized polyamide 6,10 monolithic matrix systems and a good correlation between the experimental and fitted data was observed.

The following Chapter concentrates on characterizing the three optimized polyamide 6,10 systems developed in Chapter three based on their physicochemical and physicomechanical properties.