CHAPTER ONE

INTRODUCTION AND MOTIVATION FOR STUDY

1.1. BACKGROUND

The study of rate-modulated release of drugs and other bioactive agents from polymeric devices, facilitated by novel technologies, has become an integral part of the development of new and efficient drug delivery systems. Controlled drug delivery occurs when a polymer, whether natural or synthetic is combined with a drug or other bioactives in such a way that the active substance is released from the polymeric matrix in a predesigned manner (Colombo *et al.*, 2000, Huang and Brazel, 2001). The need for polymers with specific physical and biological properties has resulted from the ever-evolving understanding of the human body and disease states which has generated continued interest in polymeric synthesis from both academic and commercial environments (Pouton, 2001). Polymeric materials provide important avenues for explorative scientific assessments, primarily because of their ease of processing and ability of researchers to readily control their physical and chemical properties via molecular synthesis (Brannon-Peppas, 1997; Colombo *et al.*, 2000; Huang and Brazel, 2001; Vogelson, 2001).

The ultimate aim of such specialized systems is to safely tailor drug formulations in active states to individual requirements under the control of pathophysiological or *in vivo* conditions rather than *in vitro* characteristics directed towards improving patient compliance, responsiveness to therapy and care (Brannon-Peppas, 1997; Colombo *et al.*, 2000). These distinctive advances have gained importance in the pharmaceutical industry and have led to the production of drugs, which are generally more potent with reduced adverse effects and have lower solubilities resulting in prolonged release rates than drugs employed in the conventional manner (Steward, 1995; Brannon-Peppas, 1997; Sinha and Khosla, 1998; Jamzad *et al.*, 2005). In addition, targeted drug delivery to cells, tissues

and organs in a rapid or sustained manner as well as stabilization of unstable compounds such as proteins has also been accomplished in this manner (Udeal and Aly, 1989; Steward, 1995; Brannon-Peppas, 1997; Katz, 2001; Vogelson, 2001).

Some other pharmaceutical applications of polymers range from their uses as binders in tablets to viscosity and flow controlling agents in liquids, suspensions and emulsions as well as film coatings to disguise the unpleasant taste of drugs (Katz, 2001). Polymers have also been widely utilized in biomedical research such as orthopedics (joint replacement, bone cements, bone defect fillers, fracture fixations, artificial tendons and ligaments); cardiology (vascular grafts, heart valves, pacemakers, blood substitutes); ophthalmology (contact lenses, corneal implants and artificial corneas, intraocular lenses); and others such as gene therapy; dental and cochlear implants; tissue screws and tacks; artificial skin; tissue engineering and sutures (Brannon-Peppas,1997; Middleton and Tipton, 1998; Katz, 2001).

1.2. SPECIFIC APPLICATIONS AND IDEAL PROPERTIES OF POLYMERIC MATERIALS EMPLOYED IN DRUG DELIVERY

A range of polymeric drug delivery systems and carriers have being developed and employed to modify the release of drugs and other bioactives in order to facilitate controlled as well as consistent release kinetics thus achieving optimal bioavailability. Some of the numerous examples of such polymeric devices include monolithic matrix systems (Douglas *et al.*, 1987; Davis and Illum, 1988; Steward, 1995; Yang and Fassihi, 1997b; Pillay and Fassihi, 1999c; Pillay and Fassihi, 2000b; Aqil and Ali, 2002; Jamzad *et al.*, 2005); reservoir devices (Douglas *et al.*, 1987; Makino *et al.*, 1990; Gohel and Amin, 1999; Ahlin *et al.*, 2002; Shenoy and Amiji, 2005); osmotically-controlled devices

(Muhammad *et al.*, 1991; Stewards, 1995; Symn *et al.*, 1995; Liu *et al.*, 2000; Lu *et al.*, 2003); enteric films or coatings (Peeters *et al.*, 1993; Cole *et al.*, 2002; Chourasia and Jain, 2003); pendant devices (Scholsky and Fitchi, 1986; Chafi *et al.*, 1992 and 1994; Chourasia and Jain, 2003); dendrimers and buckyballs (Culotta and Koshland, 1991; Steward, 1995, Vogelson, 2001); electrically-stimulated devices (Yuk *et al.*, 1992; Murdan, 2003); hydrogels (Pedley *et al.*, 1980; Iza *et al.*, 1998; Doria-Serrano *et al.*, 2001; Vogelson, 2001; Martin *et al.*, 2002; Chen *et al.*, 2004; El-Sherbiny *et al.*, 2005); microparticles or microspheres (Davis and Illum, 1988; Steward, 1995; Batycky, 1997; Gohel and Amin, 1999; Mona, 2000); polyspheres (Pillay *et al*., 2005a); oilispheres (Sibanda *et al*., 2004, Pillay *et al*., 2005b); gelispheres (Pillay and Danckwerts, 2002); pellets (Singh *et al*., 1995; Sastry *et al*., 1996; Pillay and Fassihi, 1999a); nanoparticles (Douglas *et al*., 1987; Ahlin *et al*., 2002; La Van *et al.*, 2003; Shenoy and Amiji, 2005); and scaffolds (Peppas and Langer, 1994, Kim *et al*., 2004; Sohier *et al*., 2006).

For a polymer to be effectively utilized as a rate-controlled delivery system, it should possess properties that render it suitable for the intended application (Brannon-Peppas, 1997). These properties include: applicability to a wide range of drugs with varying pharmacokinetics; biocompatibility and non-toxicity; moderate to high modulus (i.e. physicomechanical strength); resistance to thermal deformation; chemical inertness; relative insensitivity to changing physiological conditions such as pH, fluid volumes, gastric motility, disease states, enzyme activity, metabolism as well as affordable; controllable properties to achieve the desired drug release kinetics; capability of achieving optimal drug loading; minimal burst release and accumulation in physiological fluids; simple to manufacture and administer; preferably biodegradable and if non-

biodegradable, it should be easy to remove; adaptable and readily processable; absence of leachable impurities; minimal undesired degradation; and maintenance of stability.

Polymers usually possess a few but not all, of these properties. This constitutes a major reason why researchers are incessantly conducting studies to modify and improve the properties of existing polymers that are suitable for biomedical and pharmaceutical applications (Ramchandani and Robinson, 1998; Frohoff-Hulsmann *et al.*, 1999; Gohel and Amin, 1999; Colombo *et al.*, 2000; Pillay and Fassihi, 2000a and 2000b; Sibanda *et al.*, 2004; Jamzad *et al.*, 2005; Shenoy and Amiji, 2005; Zajc *et al.*, 2005).

1.3. THE SYNTHETIC ALIPHATIC POLYAMIDES: PHYSICAL PROPERTIES, CHEMISTRY AND SYNTHESIS

1.3.1. Definition of the Synthetic Aliphatic Polyamides

The synthetic aliphatic polyamides are polymeric compounds frequently referred to as Nylons which form an important group of polycondensation polymers. They are linear molecules (i.e. aliphatic) that are semi-crystalline and thermoplastic in nature (Kiely *et al.*, 1994; Gaymans and Sikkema, 1999; Hopf, 2001). A typical polyamide chain consists of amide groups separated by alkane segments and the number of carbon atoms separating the nitrogen atoms which defines the particular polyamide type. Aliphatic polyamides have been subdivided into six categories namely even-even, odd-odd, odd-even, even-odd, even and odd (Jones *et al*., 1997; Cui *et al*., 2004).

1.3.2. The Physical Properties and Chemistry of the Aliphatic Polyamides

The aliphatic polyamides are very useful and versatile material that are valuable because of their superior physicochemical and physicomechanical properties such as abrasion

resistance, chemical inertness, relatively high modulus, minimal degradation, ease of processing, thermoplasticity, higher melting points and heat resistance than many other semi-crystalline polymers such as polyethylene (Makino *et al.*, 1990; Kiely *et al.*, 1994; Chattaraj *et al.*, 1995; Jones *et al.*, 1997; Gaymans and Sikkema, 1999; Murthy, 1999; Ostad and Gard, 2000; Hopf, 2001; Li *et al.*, 2001; Sikorski *et al.*, 2001; Ostad *et al.,* 2002; Fornes *et al.*, 2003; Cui and Yan, 2005). The aforementioned physical properties as well as the extensive clinical use of the synthetic aliphatic polyamides as surgical sutures (Van, 1996; Lundborg *et al*., 1997; Dolorico *et al*., 2003; Lee *et al*., 2003; Seitz *et al*., 2003; Lai, 2004) demonstrates their biocompatibility and non-toxicity and make them attractive for use in the design and development of drug delivery systems.

Most of these beneficial characteristics of aliphatic polyamides stem mainly from their potential to form intramolecular hydrogen bond structures between the amide (— NH —) and carbonyl (— CO —) functional groups, also known as the *carbonamide* (—CONH—) functional moiety, within the linear, polymeric chains of methylene groups, (—CH_2—) in the crystal lattice structure. A typical representation of intramolecular hydrogen bonding structure within a polyamide 6,10 chain is illustrated in Figure 1.1. The hydrogen bonds are able to retain the ordered configuration of the linear chains even after the alkane segments have melted. The length and strength of the hydrogen bonds formed are also dependent on the polyamide type and the method of synthesis, leaving each with variable properties (Gaymans and Sikkema, 1999; Hopf, 2001; Cui *et al.*, 2004).

The main limitations of the aliphatic polyamides are their hydrophilic tendencies (Gaymans and Sikkema, 1999; Hopf, 2001; Cui *et al*., 2004) and slow biodegradation rate (Huang, 1999) which may contribute to their efficiency as drug delivery systems. The

hydrophilicity of the aliphatic polyamides is due to of their moderate to high affinity for water, which results in their ability to form intermolecular hydrogen bonds with water molecules (Gaymans and Sikkema, 1999; Hopf, 2001). The hydrophilic nature of the aliphatic polyamides aids the process of polymeric wetting, disentangling and dissolution, all of which facilitate the process of drug release. Furthermore, they have been reported to be capable of undergoing gradual hydrolysis due to the presence of intermittent carbonamide groups (—CONH—) within the polymeric structure which leads to the loss of mechanical strength and molecular mass (Lai and Becker, 2004). This process may aid the formation of polar, ionic molecular portions of the linear chains, which can facilitate bioerosion, metabolism, and excretion of the polymer via the human renal system (Correia, 2000; Ives, 2000). The composition of the respective polyamide structural backbone and the method of chemical synthesis provide significant influence on the intensity of their physicochemical and physicomechanical properties (Gaymans and Sikkema, 1999; Huang, 1999 and 2003; Hopf, 2001).

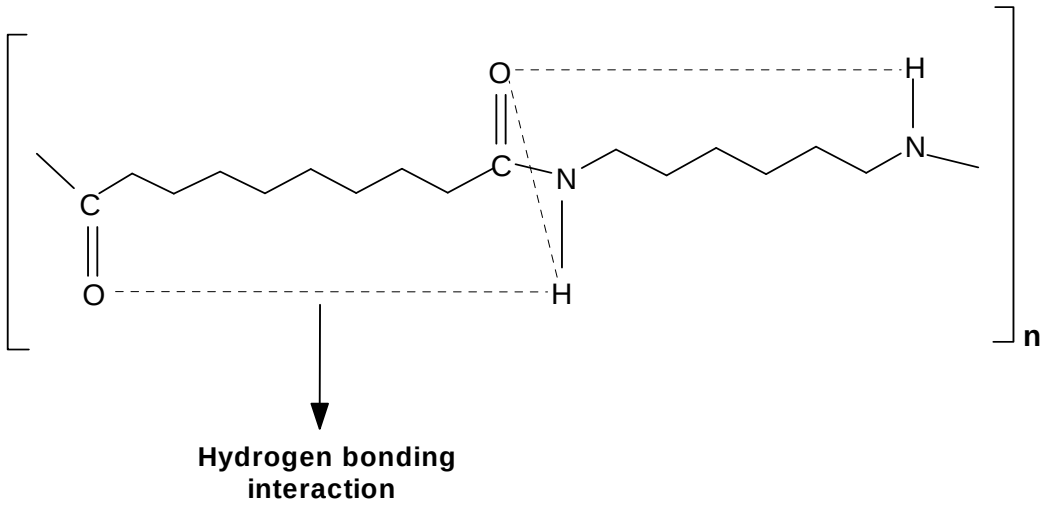

Figure 1.1: Typical intramolecular hydrogen bond structure of polyamide 6,10.

1.3.3. The Synthesis of the Aliphatic Polyamides

The aliphatic polyamides can be synthesized by various methods. The choice of method affects the inherent physicochemical and physicomechanical properties of the corresponding polyamide. The most frequently used approaches of chemical synthesis include the diacid-diamine reaction (e.g. polyamide 6,6), self-reaction of difunctional monomer units from cyclic amides (lactams) (e.g. polyamide 6 and polyamide 12)**,** a polycondensation reaction with amino acids (e.g. polyamide 11) and interfacial polymerization between acid chlorides and diamines (e.g. polyamide 6,6 and polyamide 6,10) (Gaymans and Sikkema, 1999; Hopf, 2001).

This research focused on employing interfacial polymerization as the method of choice for synthesizing polyamide 6,10. Interfacial polymerization is an established method of synthesizing polycondensation polymers (e.g. aliphatic polyamides). Interfacial polymerization was selected because it has been reported to produce synthetic aliphatic polyamide variants with lower molecular masses, densities and crystallinity, however still maintaining satisfactory stability, physicomechanical strength and reduced levels of hydrophilicity (Madan and Chareonboonsit, 1989; Phares *et al*., 1995; Gaymans and Sikkema, 1999). Theoretically, these physicochemical and physicomechanical properties provide the synthesized polyamide variants with an improved biodegradation rate which is essential when polymeric materials are utilized to formulate drug delivery systems. Also, this method of choice remains very attractive because of its simplicity and flexibility compared to the other methods of synthesizing aliphatic polyamides (i.e. diacid-diamine reaction, self-reaction of difunctional monomer units from cyclic amides and the polycondensation reaction with amino acids) (McGinity and Co, 1985; Madan and Chareonboonsit, 1989; Makino *et al.*, 1990; Phares *et al*., 1995; Jones *et al*., 1997;

Franco *et al.*, 1998a and 1998b; Ostad *et al*., 1998; Gaymans and Sikkema, 1999; Ostad and Gard, 2000; Vyas *et al*., 2000 and Ostad *et al*., 2002; Konishi and Ito, 2004).

Interfacial polymerization is based on a polycondensation reaction between two monomers dissolved separately in two immiscible solvents. The respective monomers are a diacid chloride which is an activated acid and a diamine (Gaymans and Sikkema, 1999; Song *et al*. 2005). The reaction occurs at an interface between the two immiscible liquid phases each containing a different reactant (i.e. the monomers). The dissolved monomers diffuse to the liquid-liquid interface where they undergo a co-polymerization reaction (i.e. polycondensation). The resulting polymer forms as a film at the interface that is immiscible with the liquid (solvent) phases. As the reaction proceeds, the polymeric film increases in size. Hydrochloric acid (HCl) is generated as a by-product of this chemical reaction. The solubility ratios of the diacid chloride and the diamine in the polar and non-polar liquid immiscible phases are the controlling parameters for these diffusion processes (Gaymans and Sikkema, 1999; Kang *et al*., 2006). A general representation of the chemical reaction between the monomers (dispersed in their respective solvent phases) occuring during the interfacial polymerization reaction is shown with the schematic in Figure 1.2.

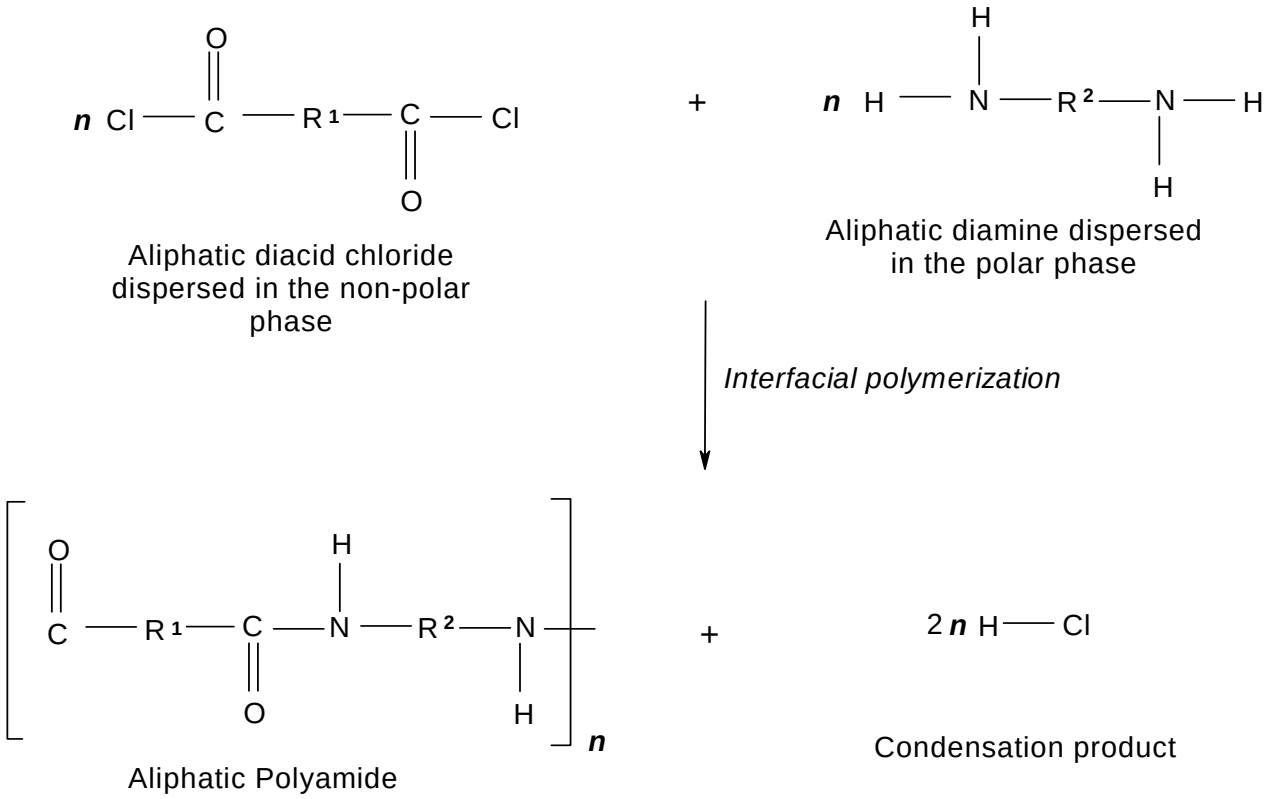

Figure 1.2: Chemical reaction between monomers of a typical aliphatic polyamide synthesized by interfacial polymerization.

1.4. THE ROLE OF SYNTHETIC ALIPHATIC POLYAMIDES IN DRUG DELIVERY

The ability of aliphatic polyamides to be employed in drug delivery has been explored to some extent by different groups of researchers over the years. In view of this, the current section presents a summary of published literature findings, indicating the approaches that have being explored to formulate drug delivery systems using synthetic aliphatic polyamides.

1.4.1. Microcapsules

Madan and Chareonboonsit (1989) synthesized novel aliphatic polyamide microcapsules by the process of interfacial polymerization and investigated the effect of selected

variables on the release characteristics of theophylline from the constructed delivery device. This system showed the potential to liberate the incorporated model drug effectively by the process of diffusion through the polyamide microcapsule membrane. The release characteristics of the drug were significantly influenced by the chosen experimental process variables.

Makino and co-workers (1990) developed a self-regulating reservoir system prepared with hydrophilic, aliphatic polyamide microcapsules containing succinyl-amidophenyl-glucopyranoside insulin (SAPG-insulin) and crosslinked concanavalin A (Con A) enclosed in a pouch polymeric membrane. The *in vitro* data demonstrated rapid diffusion of both glucose and SAPG-insulin across the microcapsule membrane with a short lag time for exchange. SAPG-insulin was released from the reservoir with a quick response to changes in glucose concentrations to control its *in vitro* levels.

In addition, Torres and colleagues (1990) produced microcapsules of a synthetic polyamide containing ion-exchange resins employing the interfacial polymerization procedure, using sodium fluoresceinate as a model resinate. In other words, the polyamide functioned as a cover for the synthesized bioactive complex. *In vitro* release studies revealed that the degree of reticulation of the resins and the presence of the polymeric coat of the polyamide delayed drug release.

Recently, Chu *et al*. (2004) successfully prepared a glucose-sensitive polyamide microcapsule synthesized by interfacial polymerization which had a porous membrane and composed of linear-grafted polyacrylic acid chains and covalently bound to glucose oxidase enzymes in the membrane pores acting as functional gates. The release rates of

model drug solutes from the fabricated microcapsules were significantly sensitive to the existence of glucose in the environmental solution. They showed a reversible glucose-sensitive release characteristic that made them an attractive new mode for injection-type, self-regulating drug delivery system which may be attractive for diabetes therapy.

1.4.2. Hollow Fibers

Ostad and co-workers (1998) carried out an investigation to characterize the release pattern of norethisterone and levonorgestrel from hollow synthetic polyamide fibers. The results showed that the two drugs were efficiently released through the hollow fibers. On the contrary, the fibers were discovered to be of potential use for the delivery of norethisterone to the uterus but were inappropriate for the delivery of levonorgestrel because of the toxic effects it elicited on the endometrial cells.

In addition, Ostad and Gard (2000) conducted an *in vivo* study on the capability of the hollow polyamide fibers to release chlorhexidine diacetate into the uterus for the treatment of pelvic infections caused by inserted intra-uterine devices. The overall findings suggested that the chlorhexidine-releasing polyamide device delivered the medicament with a relatively high level of chlorhexidine distribution *in vivo* showing that the device may be a safe means of reducing infections related to intra-uterine devices.

Ostad and co-workers (2002) also explored the efficiency of the hollow polyamide fibers in releasing glycerin trinitrate in order to reduce blood pressure with minimal dermal toxicity. The results showed that the quantity of glycerin trinitrate released per minute within the polyamide hollow fibers was sufficient to reduce blood pressure significantly while it did not show considerable dermal toxicity.

1.4.3. Other Systems

García-Encina and co-workers (1993) conducted a study on polyamide-coated ion exchange resins containing sodium diclofenac. The *in vitro* release rate of sodium diclofenac from the coated resins showed that drug release from this formulation was slower and more controlled than from a commercial sustained-release formulation of diclofenac sodium (Dolotrén Retard®).

Kumar and Münstedt (2004) prepared antimicrobial composites from silver ion and an aliphatic polyamide. The versatile antimicrobial (i.e. silver ion) was released at concentration levels capable of rendering an antimicrobial efficacy in a steady and prolonged manner from the silver-filled polyamide composite system. The polyamide system demonstrated the capability to function as an efficient delivery device for silver ion.

Vyas and colleagues (2000) prepared theophylline-loaded gelospheres coated with an aliphatic polyamide synthesized by interfacial polymerization. The polyamide outer coating was found to reduce and control the rate of drug release in a pseudo zero-order manner.

1.5. RATIONALE AND MOTIVATION FOR THIS STUDY

Based on the benefits provided by polymeric drug delivery systems, researchers from multiple disciplines are constantly seeking alternative biomaterials (both synthetic and natural), methods of biomaterial synthesis and approaches of fabricating various delivery devices which are safe, versatile, easy to administer, efficacious, economical and that would rapidly meet approval by the United States Food and Drug Administration (US

FDA) (Mona, 2000; Vogelson, 2001; Chourasia and Jain, 2003; LaVan *et al*., 2003; Mehuys *et al*., 2004). The present study contributes to this end by extensively evaluating the feasibility of polyamide 6,10; a synthetic aliphatic polyamide with the chemical name *polyhexamethylene sebacamide*, as a novel monolithic matrix system for rate-controlled drug delivery.

To the best of our knowledge, no research has reported the use of synthetic aliphatic polyamides in the development of a monolithic matrix system. The above-described studies employed aliphatic polyamides for the development of multiple-unit systems, hollow fibers and exchange resins. These drug delivery approaches may present with complexities with regard to fabricating them as versatile systems which would support easy administration and patient compliance. The technology and know-how involved in the manufacture of the above-described systems are relatively complex and may increase the overhead cost on large scale production hence limiting patient affordability. The monolithic matrix drug delivery system on the other hand counteracts these limitations, as it is more flexible and easier to fabricate with existing technology. The production sequence is simple which reduces the cost thereby enhancing patient affordability.

1.6. TECHNOLOGY APPLIED IN THIS STUDY

The technology applied in this study (i.e. formulation of a polyamide 6,10 monolithic system) can be divided into two main phases, namely the chemical synthesis and pharmaceutical formulation.

Polyamide 6,10 was synthesized using two monomers namely; sebacoyl chloride (the acid chloride) and hexamethylenediamine (the diamine) dispersed in hexane and deionized water respectively by the process of interfacial polymerization. This process was modified by simultaneously combining changes in the reaction stoichiometry (i.e. the quantitative relationships among reactants and products), volume ratio of the solvents and finally the inclusion of solvent phase modifiers namely sodium hydroxide (NaOH) and cyclohexane which influenced pH and polarity of the solvent phases respectively. This process modification strategy was employed to alter the three-dimensional network of polyamide 6,10 by influencing its physicochemical and physicomechanical properties without changing its basic chemical backbone structure. This was undertaken in the aim of producing novel polyamide 6,10 monolithic matrix systems with superior physicochemical and physicomechanical properties which can make it suitable for rate-modulated drug delivery. The whole process was guided through statistically robust experimental designs.

The polyamide 6,10 variant synthesized using the abovementioned modification strategy was thereafter formulated into a monolithic matrix system comprising specific quantities of drug/polymer blends that were directly compressed.

1.7. AIM AND OBJECTIVES OF THE STUDY

The overall aim of this research was to develop monolithic matrix systems produced using polyamide 6,10, synthesized using a modified interfacial polymerization, to achieve rate-controlled release for low and highly soluble drugs.

In order to accomplish this aim, the following objectives are specified:

(i) To initialize the synthesis of modified polyamide 6,10 variants by interfacial polymerization (partial modification) using appropriate stoichiometric combinations of the monomers namely; hexamethylenediamine, sebacoyl chloride as well as varying the volume ratios of the two immiscible solvent phases namely deionized water (polar) and hexane (non-polar) guided through a Plackett-Burman screening design. The screening process included assessing the influence of this partial modification strategy on the physicochemical and physicomechanical properties of the synthesized polyamide 6,10 variants.

(ii) To complete the synthesis of the modified polyamide 6,10 variants by simultaneously combining the inclusion of solvent phase modifiers (i.e. sodium hydroxide and cyclohexane) with the changes in reaction stoichiometry and solvent volume ratio using the higher performance Box-Behnken experimental design approach. The solvent phase modifiers influence pH and polarity of the two solvent phases namely deionized water and hexane respectively to improve on the physicochemical and physicomechanical properties of polyamide 6,10 to suit its application as a rate-modulated monolithic matrix system for drug delivery.

(iii) To incorporate model low and high water soluble drugs into the fully modified polyamide 6,10 monolithic matrix systems and investigate their *in vitro* dissolution (drug release behaviour) and matrix erosion behaviour as well as other physicochemical and physicomechanical properties.

(iv) To optimize the physicochemical and physicomechanical properties of the fully modified polyamide 6,10 variants to achieve desirable rate-controlled drug release characteristics and to assess the reliability of the statistical design using three-dimensional surface plots and the associated analysis of variance.

(v) To determine the effects of formulation variables such as compression force, pH, polymer particle size, drug solubility and excipients (such as inorganic electrolytes or salts e.g. aluminium sulphate ($Al_2(SO_4)_2$) as well as existing US FDA-approved hydrophilic and hydrophobic polymers (e.g. hydroxypropylmethylcellulose (HPMC) and Poly (lactides-co-glycolide) (PLGA) respectively) on the drug release characteristics of the optimized polyamide 6,10 monolithic matrix systems.

(vi) To develop mathematical models that best describes the drug release kinetics from the optimized polyamide 6,10 monolithic matrix systems.

(vii) To elucidate the physicochemical and physicomechanical characteristics of the optimized polyamide 6,10 variants.

1.8. OVERVIEW OF THIS DISSERTATION

Chapter one provides a summary to the dissertation. It comprises of a brief overview of the basic concepts and advancements in polymeric drug delivery, chemistry and synthesis of aliphatic polyamides and their role in drug delivery, rationale and motivation of the study, technology applied as well as the aim and objectives of this research.

In Chapter two, a partial modification process which deals with the influences of stoichiometric and volumetric ratio variations on the physicochemical and physicomechanical properties of polyamide 6,10 guided through a screening design is presented. Also, the selections of the significant factor variables to be fixed or included in the higher performance Box-Behnken design template for the full modification and optimization process of the polyamide 6,10 are explained.

Chapter three focuses on the application of a higher performance Box-Behnken design to the synthesis (full modification) as well as the optimization of the novel modified polyamide 6,10 monolithic matrix devices for rate-controlled drug delivery. In this Chapter, the three stages of the process modification (full modification) namely changes in stoichiometry, volume ratio and inclusion of solvent phase modifiers were simultaneously utilized to improve on purity and physicochemical and physicomechanical qualities of polyamide 6,10.

The influence of various formulation variables on the release characteristics of the optimized polyamide monolithic matrix system and mathematical modeling of the drug release kinetics from the monolithic matrix system is presented in **Chapter four**.

The physicochemical and physicomechanical behaviour of the optimized polyamide 6,10 matrices is extensively characterized and compared in **Chapter five**.

The conclusions of the study and recommendations for future work are presented in **Chapter six** and lastly, a list of references used in this research is documented.