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Design and mechanistic evaluation of novel pore-regulated polymer matrices for transmucosal drug delivery

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CHAPTER ONE

General Literature Background, Rationale And Motivation, Technology Applied And Objectives For This Study

1.1. BACKGROUND: POLYMERIC DRUG DELIVERY

The science of drug delivery can be described as the application of physicochemical, physicomechanical and/or biological principles to regulate the sequential *in vivo* access rate and spatial positioning of drug molecules for clinical or therapeutic advantages (Uchegbu, 2006). Drug delivery systems are formulation technologies that alter drug release profile, absorption, bioavailability, distribution and elimination for the benefit of improving product efficacy and safety as well as patient convenience and compliance (Uchegbu, 2006; Ravi Kumar, 2008). Commonly utilized routes of drug delivery or administration include the oral, topical, transmucosal (intranasal, buccal, vaginal, ocular, rectal, transdermal), injection (intravenous, intramuscular, subcutaneous, intrathecal, spinal) and inhalation routes (Ravi Kumar, 2008). A notable increase in interest in drug delivery technologies exists as is shown by increase in publications and patents using synthetic as well as naturally occurring polymeric materials and pharmaceutical additives (Ranade and Hollinger, 2003). 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 (Colombo *et al.*, 2000; Huang and Brazel, 2001). The need for drug delivery systems 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 the design of polymer-based delivery systems from both academic and commercial environments (Pouton, 2001).

Furthermore, a large part of pharmaceutical research is being steadily focused away from the synthesis of new compounds to the development of novel polymer-based delivery systems for existing drugs to impart optimum benefits to patients by improving compliance, responsiveness to therapy and care (Berressem, 1999; Müller *et al*., 2000; Das and Das, 2003; Liu *et al*., 2003; Berger *et al*., 2004; Lu and Chen, 2004; Sher *et al*., 2007). Overall, the rationale for fabricating such specialized devices is to safely tailor drug formulations in the active states to individual requirements under the control of pathophysiological or normal *in vivo* conditions rather than *in vitro* characteristics (Brannon-Peppas, 1997; Colombo *et al.*, 2000). These distinctive advances have gained importance in the pharmaceutical industry and have led to the manufacture of drug products that are generally more potent with reduced side effects and regulated solubility levels resulting in controlled release rates than drugs employed in the conventional manner. Overall, these unique technological

developments can impact optimum benefits to patients by improving compliance, bioavailability, pharmacotherapeutic efficacy and medical care as a whole (Steward, 1995; Brannon-Peppas, 1997; Sinha and Khosla, 1998; Jamzad *et al.*, 2005).

The usefulness of polymeric materials (either as a single entity or in combination) in fabricating highly effective novel drug delivery systems cannot be overemphasized (Uchegbu, 2006). Polymers provide unique opportunities for explorative scientific applications primarily because of their ease of processing and ability of researchers to readily control their physical and chemical properties via the synthesis of high molecular weight compounds as compared to existing lower molecular weight counterparts (Brannon-Peppas, 1997; Colombo *et al.*, 2000; Vogelson, 2001). A range of polymeric drug delivery systems and carriers have being developed and employed to modify the release of drugs and other bioactive species in order to facilitate controlled as well as consistent release kinetics thus achieving optimal bioavailability. Some of the numerous examples of such polymer-based devices include monolithic matrices, reservoir systems, osmotically-controlled devices, enteric films or coatings, pendant and conjugated devices, dendrimers, electrically stimulated devices, microspheres, nanoparticles, scaffolds, hydrogels, implants and micelles (Uchegbu, 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. Such properties include but are not limited to applicability to a wide range of drugs with varying pharmacokinetics, biocompatibility and non-toxicity, physicomechanical strength, relative insensitivity to changing physiological conditions such as pH, fluid volumes, gastric motility, disease states, enzyme activity, metabolism, flexible properties to achieve the desired drug release kinetics, capability of achieving optimal drug loading, biodegradability, maintenance of physical stability (Brannon-Peppas, 1997). However, individual polymers usually do not possess all of these properties. This constitutes a major reason why researchers are continually conducting studies to modify and improve the properties of existing polymers by either making physical or chemical co-polymeric combinations that can be more suitable for the respective drug delivery applications (Ramchandani and Robinson, 1998; Gohel and Amin, 1999; Colombo *et al.*, 2000; Pillay and Fassihi, 2000a and 2000b; Jamzad *et al.*, 2005; Shenoy and Amiji, 2005; Zajc *et al.*, 2005, Kim *et al*., 2007).

1.2. POROUS STRUCTURED DRUG DELIVERY MATRICES: DEFINITIONS AND PHYSICAL PROPERTIES

Solid materials or particles employed as single entities or combinations with either other solids or liquids and subjected to physical processes such as crushing, grinding, dry or wet mixing, compression or compaction, crystallization and lyophilization are usually found to have characteristic cracks, cavities and or hole structures which are collectively referred to as pores. In other words, a pore can be described as an opening/interstice/orifice of varying dimensions, shape and volume (in relation to the surface area of the material), located through a solid matrix and possesses the capability to contribute to the exhibited physicochemical and physicomechanical properties of such material (Webb and Orr, 1997). Typically, pores within a particular matrix exist in multiples and may also be multi-leveled composed of the same or different pore sizes due to the aggregation of the particles which the matrix is made up of. In this case, the walls of the pores are the exposed surfaces of the particles which are contained within the specific matrix. Consequently, these numerous pores can exhibit some level of interconnectivity and tortuosity. Therefore, pore interconnectors are networks that attach one pore to another (Webb and Orr, 1997).

A porous material or drug delivery matrix can be described as a stable, flexible mono- or multi-component system typified by distinctive pore/hole structures or void spaces and interconnectors which influence their overall performances (Adeleke *et al*., 2010). They have been studied over the years and they continue to attract great research interest as they possess unique properties which can find potential applications in biological tissue scaffolds, controlled drug release, biomaterials engineering, life science and other scientific spheres (Hoa *et al*., 2006; Adeleke *et al*., 2010).

Porous materials have been investigated over the years for drug delivery applications and they continue to attract great research interest because of their attractive physical features that are suitable for drug delivery purposes. Such properties include but are not limited to the presence of a stable porous network, high surface area, flexible pore sizes arranged in various distribution patterns and well defined surface properties, which are due to their unique porous structural configurations (Sher *et al*., 2007; Adeleke *et al*., 2010). These qualities provide them with the potential to adsorb/load drug molecules and release them in a reproducible and predictable manner as well as to load high drug concentrations relative to

pore volume, enhance bioadhesion and augment transmucosal permeation and systemic absorption of biomolecules (Sher *et al*., 2007, Vallet-Regí *et* al., 2007; Zhang *et al*, 2007 and Adeleke *et al*., 2010). The formation of these specialized drug delivery devices is based on their characteristic porous structure which greatly influences their function and remains an interesting and intellectually challenging subject for systematic exploration (Hoa *et al*., 2006).

Generally, porous structured matrices are classified based on their average pore sizes which are expressed either in terms of diameter (or radius) or the width (or half width). Those with pore diameters or widths and pore distances of less than 2 nanometers (nm) or 20 Angstrom units (Å) are referred to as “microporous” or “nanoporous”. Matrices with pore geometries larger than 50nm (500 Å) are referred to as “macroporous” while an inserted classification called “mesoporous” are typified by pore diameters ranging from 2nm (20 Å) to 50nm (500 Å). In addition, the volume of pores, holes, channels, fissures within a specific body of particles or matrix is described as the total pore volume (Webb and Orr, 1997).

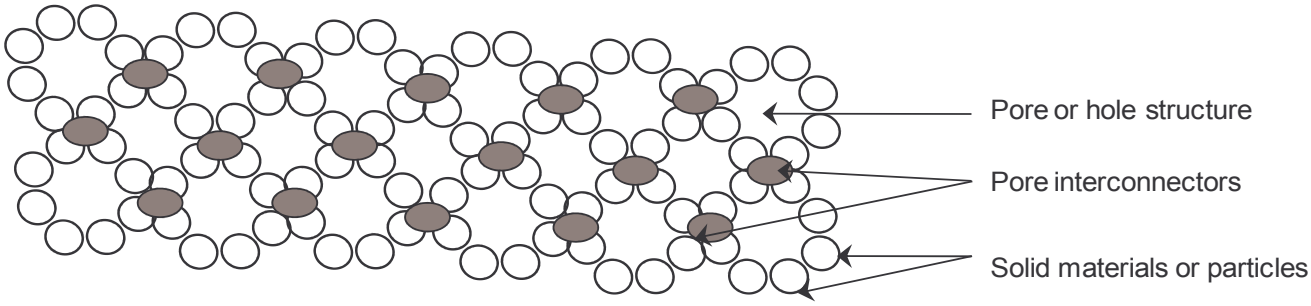


Figure 1.1: A diagrammatic representation of a typical porous matrix showing the pore structures, interconnectors and component solid particles.

1.3. DRUG DELIVERY AND BIOMEDICAL APPLICATIONS OF POROUS STRUCTURED MATRICES

Porous structured matrices have found potential biomedical and drug delivery applications which have been explored to some extent by different groups of researchers over the years. In view of this, the current section presents a summary of some published literature findings indicating typical systematic approaches that have been employed.

1.3.1. Biological tissue scaffolds

Kim and co-workers (2004) fabricated hydroxyapatite-based macroporous scaffolds using a polymeric reticulate method and coated them with hydroxyapatite-poly(ε-caprolactone) composites after being entrapped with tetracycline hydrochloride. They reported that the scaffolds displayed optimal biocompatibility and biodegradation, mechanical strength as well as effective drug loading and controlled release.

Macroporous coated scaffolds releasing protein in a controlled and independent manner was constructed by Sohier *et al*. (2006). It was reported that the scaffolds were biphasic systems with each coating controlling the release of the protein it contained and that the invented technology may be of use for tissue engineering purposes.

Recently, Kusmanto and colleagues (2008) designed a microporous, bioresorbable composite bone tissue scaffold which had a honeycomb structure with a natural architecture of interconnecting permeable pores using a salt leaching technique. The scaffold was non-cytotoxic, biocompatible and possessed optimal mechanical strength suitable for tissue engineering applications.

Furthermore, Ginty *et al*. (2008) reported the development of three microporous protein loaded scaffolds for dual controlled release kinetics intended for the delivery of growth factors in tissue engineering.

1.3.2. Implantable devices

Implantable porous wafers prepared by direct compression after freeze milling using a diblock copolymer (MPEG-PLGA) consisting of methoxypolyethyleneglycol (MPEG) and poly(*L*-lactic-co-glycolic acid) (PLGA) were investigated as potential drug carriers for implantation. Bovine serum albumin-fluorescein isothiocyanate (BSA-FITC) was employed as a model protein drug. The porous wafer generated controlled release profiles with a relevant lag time at the initial stage of drug release. Consequently, the MPEG-PLGA diblock copolymer based porous device was confirmed to be applicable as a protein delivery carrier in an implantable form (Kim *et al*., 2005).

Netz and co-workers (2001) employed hydroxyapatite ceramic in a mesoporous configuration as a drug release system. This material was processed using the gel-casting method to

produce a highly interconnected spheroidal microporous and macroporous system that showed potential for implantable drug delivery. The controlled release behaviour of cisplatin was investigated as a model.

1.3.3. Optical devices

Kundu *et al*. (2004) constructed a porous hydroxyapatite-based ocular implant containing a combination of micropores and macropores using synthesized hydroxyapatite powder. They successfully controlled the porosity and pore size of the implant to make it light weight and suitable for rapid vascularization after implantation. Also clinical, haematological and radiological investigations were conducted using dogs. These studies indicated the suitability of the implant for replacement of a lost eye in humans.

Porous networked optical devices made from mesoporous silicon with a continuous refractive index distribution for biomedical sensing applications were reported by Ilyas and Gal (2007).

1.3.4. Hydrogels

Tang and colleagues (2005) made superporous hydrogels with macropores containing poly(acrylic acid-co-acrylamide)/O-carboxymethyl chitosan interpenetrating polymer networks (SPH-IPNs). The hydrogels showed optimal mucoadhesive and mechanical strength as well as drug loading capacity. It was concluded that the hydrogels possess the potential to function as a mucoadhesive system for the peroral delivery of peptide and protein drugs.

1.3.5. Ceramics

Rodríguez-Lorenzo and Ferreira (2004) constructed macroporous ceramic bodies from thermally treated hydroxyapatite particles which were consolidated by slip casting. In addition, they investigated the effects of porosity gradients on the performance of the ceramic bodies so as to adapt them for use as tissue engineering scaffolds and drug delivery.

Miao and co-workers (2004) focused on developing a novel method of preparing calcium phosphate ceramic with high macroporosity and pore volume, pore interconnectivity and controlled pore size for biomedical applications such as bone defect fillers, tissue engineering scaffolds and drug delivery systems. This method involved the use of

polyurethane foams to produce highly porous calcium phosphate cements which were converted into sintered porous hydroxyapatite-based calcium phosphate ceramics.

Three commercially available microparticulate, micro-structured porous ceramics namely N-light N3, Starlight SLK1000 and Carbolite 16/20 were characterized using a range of techniques. Each porous ceramic were partially open cell with varying porosities and pore size distributions. They were separately loaded with diltiazem hydrochloride using a novel vacuum loading technique. It was observed that the ceramic porosity, surface pore size distribution and microparticulate surface electrostatic interactions had a significant influence on their drug loading capacity as well as drug release behaviour. Also, each ceramic displayed an initial burst followed by sustained release. The outcome of the investigation indicated that the porous ceramic microparticles may be suitable for the sustained delivery of drugs given orally and controlled release of nutrients in biological media (Byrne and Deasy, 2002).

1.3.6. Biocomposites

Wang *et al*. (2007) produced microporous biocomposite matrices by precipitation casting from solutions of poly(*e*-caprolactone) and a dispersed phase of lactose or gelatin particles with defined size ranges in acetone. The matrices comprised of an extensive system of pores sufficiently connected to permit protein diffusion with an absence of high volume, inter-pore channels. Therefore, it was concluded that the matrix surface properties can make it suitable for tissue integration making it useful as tissue engineering scaffolds while the core may be employed as a potential depot system for the controlled delivery of growth factors.

1.3.7. Sponges

A highly porous, bi-layered, mucoadhesive, flexible device referred to as a sponge was designed for buccal drug administration using the mild casting and freeze drying procedures. The device was made up of a mucoadhesive chitosan layer containing the peptide drug, insulin and an impermeable layer containing ethylcellulose. The device was designed as such to facilitate unidirectional drug release to the buccal mucosa that might be applied for the buccal administration of peptides and protein drugs (Portero *et al*., 2007).

Dziubla *et al*. (2001) synthesized mesoporous poly(2-hydroxyethyl methacrylate) (PHEMA) sponges using thermally initiated free-radical solution polymerization. These drug delivery

systems were intended for subcutaneous and intraperitoneal implantation with minimal inflammatory response and fibrous encapsulation of implant. This device was implanted over a five month period and histological evaluation showed highly vascularized tissue surrounding the implant indicating the possibility of utilizing PHEMA sponges as a tissue intermediary for long term implantation.

1.3.8. Microcapsules

Chu and colleagues (2004) prepared glucose-sensitive, polyamide-based microcapsules with macroporous membranes using interfacial polymerization. Glucose oxidase enzymes were grafted onto the pore to act as functional gates. The release rate of sodium chloride and vitamin B_{12} from the fabricated porous microcapsule were significantly sensitive to the existence of glucose in the environmental solution. In summary, the microcapsules displayed reversible glucose-sensitive release behaviour. Consequently, the porous microcapsules may provide a new mode for injection-type, self-regulated delivery system possessing the capability of modifying the release rate of drugs such as insulin in response to changes in glucose plasma levels for diabetes management.

1.3.9. Wafers

Bromberg *et al*. (2001) designed novel porous wafer drug delivery systems intended for the treatment of microbial infections associated with periodontitis. The composite wafer had porous surface layers possessing adhesive properties and a bulk layer which contained antimicrobial agents, poly(lactic-*co*-glycolic acid) and ethyl cellulose. *In vitro* analysis showed that the wafers were capable of zero-order release of the assessed antimicrobial agents (silver nitrate, benzylpenicillin and tetracycline) for over four weeks.

A dual series of porous solid wafers using low molecular weight sodium alginate and xanthan gum respectively, modified with high molecular weight methylcellulose were produced by lyophilization. These solid porous wafers were intended for use as a drug delivery system for suppurating wounds. Sodium fluorescein was employed as a model drug and the wafers demonstrated the potential to be used for the intended purpose (Matthews *et al*., 2005).

In addition, Patel *et al*. (2007) constructed a porous polymeric wafer matrix and examined its physicomechanical properties for rapid drug delivery through the oramucosal route. Lyophilization was used to produce the porous wafer matrix and this enhanced the rapid

permeation of saliva through the matrix. The wafer comprised of the polymer hydroxypropylcellulose and other additives like lactose, mannitol and glycine. Overall, the wafer proved to be a robust and flexible system that underwent quick *in vitro* disintegration in simulated saliva and its suitability for *in vivo* testing for rapid oramucosal drug delivery was established.

1.3.10. Membranes

Park and co-workers (1997) fabricated novel macroporous, biodegradable barrier membranes composed of porous poly(*L*-lactide) films cast on poly(glycolide) meshes for periodontal disease therapy using an in-air drying phase inversion technique. Flurbiprofen and tetracycline, used in periodontal therapy for their tissue regenerating effects, were incorporated in the porous membranes as model drugs. The drug release kinetics mainly depended upon the hydrophobic and hydrophilic properties of the drugs and the porosity of the membranes.

Elchidana and Deshpande (1999) designed an extended release microporous formulation which consisted of coated pellets for a non-steroidal, anti-inflammatory drug, indomethacin, indicated for the treatment of rheumatoid arthritis using the technology of extrusion/spheronization. The amount of drug released from this formulation was successfully retarded and controlled while the formulation displayed good stability.

Furthermore, porous ion exchange membranes were explored for their possible application as diffusion dependent drug delivery systems. The membranes studied were poly(acrylic acid) (PAA) grafted porous polyvinylidene fluoride membranes (Åkerman *et al*., 1998).

1.3.11. Nanoparticles

Nanoporous hollow silica nanoparticles were prepared and characterized for controlled release applications by Li *et al*. (2004). The nanoparticles were utilized as carriers to investigate the release behaviour of Brilliant blue F. It was observed that Brilliant blue F was released steadily into the surrounding bulk solution with no burst effect.

1.3.12. Tablets

Cosijns and colleagues (2007) manufactured low-dosed macroporous tablets utilizing hydroxyapatite, avicel (as a pore forming agent), corn starch and sorbitol by direct

compression followed by sintering. Model drugs explored were metoprolol tartrate and riboflavin sodium phosphate. They were added as aqueous solutions onto the surface of the tablet for absorption. Drug release from these tablets was sustained and found to be independent of drug concentration within the formulation.

1.3.13. Bio-packages

Novel hydroxyapatite-based hybrid materials with regulated porosity and optimal adhesion to silicon surfaces were designed as bio-package for Micro-Electro-Mechanical Systems (MEMS) with potential application as implants in the human body. These mesoporous bio-packaging materials were prepared using synthetic hydroxyapatite powder with polymeric agglutinants. The bio-package displayed a high wearing resistance and hydrolytic stability (Rodriguez *et al*., 2008).

1.3.14. Foams

Open-cell hydroxyapatite foams were produced by gel casting porous foams and characterized for pore size distribution, surface area, permeability, compressive strength, elastic modulus and micro-structural features. The outcome of the combination of measurements performed revealed the potential suitability of the porous hydroxyapatite foam as a non-loading biomedical device for bone repairs, carriers for controlled drug delivery and tissue engineering matrices (Sepulveda *et al*., 2000).

1.3.15. Miscellaneous

Porous hydroxyapatite with inter-connective pore structures was prepared by the burn-out method to be used as a drug carrier and promoter of bone growth in the management of periodontitis. It was discovered that the morphology of the porous device was well adapted to bone growth and drug absorption (Queiroz *et al*., 2004).

Low density porous carriers are widely used in the pharmaceutical applications. A typical low density porous carrier, microporous polypropylene (Accurel MP 1000®), was studied for drug absorption and release. The carrier showed excellent floating properties and generated release profiles that may be considered for gastroretentive drug delivery (Sher *et al*., 2007).

Vaccari and collaborators (2006) employed macroporous silicon to construct a two-layer drug carrier characterized by nanoporous coverage which was investigated for its potential to load

and release doxorubicin, an anti-cancer therapeutic agent, in a controlled manner. This system exhibited a time-dependent, regulated drug delivery behaviour which was also related to its cytotoxic effects on adenocarcinoma cancer cells exposed to it.

A mesoporous matrix based on aluminosilicate mixture was studied to assess its potential to load and release drug in a flexible but regulated manner by Cavallaro and co-investigators (2004). Model drugs employed included diflunisal, naproxen, ibuprofen and its sodium salt. Experimental outputs showed that the mesoporous matrix was capable of effectively loading the respective bioactive species and released them in a modified, well-regulated manner.

Disk-shaped mesoporous devices were developed from mesoporous silica molecular sieves (MCM-41) and loaded with ibuprofen. Drug release behaviour was assessed and profiles obtained showed flexible release kinetics based on drug levels within the device (Vallet-Regi *et al*., 2001).

1.4. TRANSMUCOSAL DRUG DELIVERY

Transmucosal drug delivery can be described as the systemic delivery of drug or other bioactive molecules across absorptive mucosal membranes in various easily accessible body sites such as the skin (dermal), oral cavity (sublingual, buccal, gingival), nose (nasal), vagina (vaginal), rectum (rectal) and eyes (ocular) (Ghilzai and Desai, 2004). Conventionally, drugs and other therapeutic agents are delivered to the body employing the predominant methods of administration which are the oral and injection routes (Tao and Desai, 2003; Ghilzai and Desai, 2004; Sudhakar *et al*., 2006).

The oral route of drug delivery offers several advantages such as being more natural thereby enhancing patient convenience during use and compliance, less invasive and pain-free during self-administered (Tao and Desai, 2003). In spite of these merits, research has shown that after oral administration, many therapeutic compounds are subject to extensive pre-systemic elimination by gastrointestinal degradation (due to the acidic condition of the stomach or the presence of enzymes), hepatic first pass metabolism and resistance exerted by the intestine that may result in low systemic bioavailability, short duration of therapeutic activity and/or formation of inactive or toxic metabolites. The use of injections (e.g. intravenous, intramuscular and intrathecal routes), on the other hand, provides rapid

physiological relief of symptoms but can be associated with a high level of pain during administration, lead to high drug concentrations being released into the systemic circulation which can be fatal, requires close medical supervision during administration and the possible need for specialized equipment (Ponchel *et al*., 1997; Ahmed *et al*., 2002; Orive *et al*., 2003; Sudhakar *et al*., 2006).

In order to circumvent some of the above-mentioned limitations associated with the oral and injection routes of drug administration, transmucosal route of drug delivery has been explored as an alternative. The transmucosal route also offers the potential for the non-invasive, regulated absorption of drugs and may serve as useful sites with good accessibility for easy application of drug delivery systems including those with bioadhesive/mucoadhesive properties (Smart, 2005; Chien, 2006; Sudhakar *et al*., 2006). The transmucosal route of administration also offers the potential for the systemic absorption of drug molecules with plasma profiles closely related to that of an injection which makes them useful especially in emergency situations. With the development of transmucosal drug delivery systems having controlled release characteristics, the mucosa is being explored as an alternative route for the sustained, systemic delivery of drugs and other therapeutic agents (Chien, 2006).

1.5. THE BUCCAL MUCOSA: THE SELECTED MODEL DELIVERY SITE FOR THIS STUDY

The buccal mucosa is the mucosal lining of the cheek area situated within the oral cavity. The primary role of the buccal mucosa is to protect underlying tissues and organs from foreign or destructive agents. Structurally, it is relatively permeable and its surface consists of the multi-stratified, non-keratinized, squamous epithelium covered with mucous (Squier and Finkelstein, 1989). The surface epithelium is separated from the underlying connective tissue layer (lamina propria and submucosa) by an undulating basement membrane (a continuous layer of extracellular material) (Rathbone and Hadgraft, 1991). The epithelium serves as a mechanical barrier while the lamina propria provides mechanical support and carries the blood vessels and nerves which supply nutrition and innervations to the epithelium respectively. Substances can be transported across the buccal mucosal epithelium by simple passive diffusion, carrier-mediated diffusion, active transport and other specialized mechanisms such as endocytosis (Squier and Wertz, 1996). The general structure of the buccal mucosa is shown in Figure 1.2.

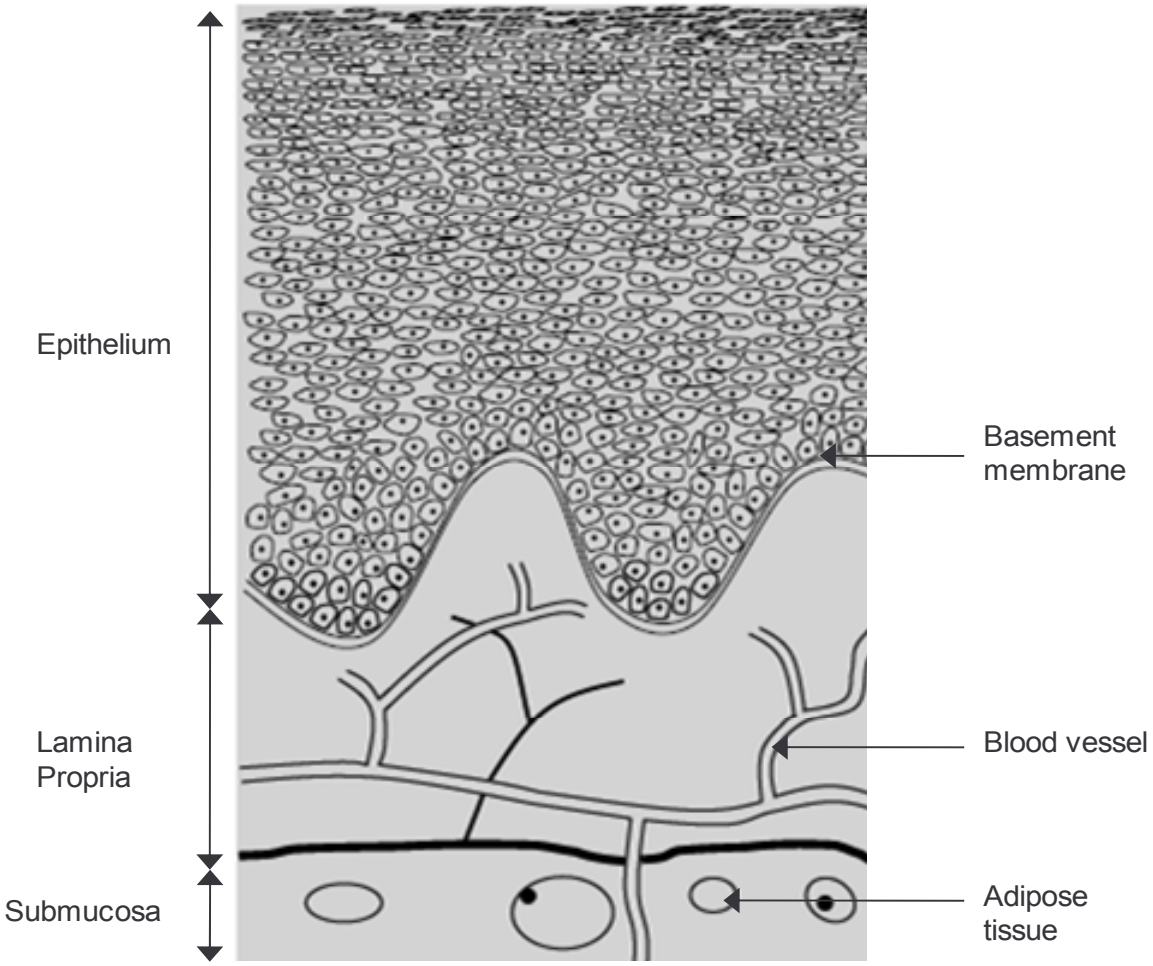


Figure 1.2: General structure of the buccal mucosa (Harris *et al*., 1992).

This study employed the buccal mucosa (i.e. the transbuccal route) as a model for transmucosal drug delivery because among the various aforementioned transmucosal sites, it is the most suitable for administration of retentive dosage forms especially those for sustained drug delivery of which the pore-regulated polymer matrix under investigation is an example. Transbuccal drug delivery involves the transport of drug molecules or other therapeutic agents from a delivery system across the buccal mucosa into the local then systemic blood circulation (Hoogstraate and Wertz, 1998; Squier and Finkelstein, 1989).

The transbuccal route has numerous advantages which makes it preferable to other transmucosal sites. This includes excellent accessibility for easy, self administration, short recovery times after stress or damage, presence of an expanse of robust, smooth muscle, rich blood supply, direct access to the systemic circulation through the internal jugular vein which allows drugs to bypass the pre-systemic metabolic processes within the

gastrointestinal tract and/or hepatic first pass effect thus leading to an increased bioavailability, relatively rapid onset of action, exhibition of little or no mucosal irritation/inflammation (Hoogstraate and Wertz, 1998; Alur, *et al*., 2001; Sudhakar *et al*., 2006). Other benefits such as painless administration, versatility and simplicity, easy dosage form withdrawal whenever desired and the ability to include pharmaceutical additives such as permeation enhancers, enzyme inhibitors, pH modifiers, bioadhesive compounds in the formulation for optimal local or systemic physiological actions. All of these advantages make the transbuccal route of drug delivery a promising option for effective pharmacotherapy (Zhang *et al*., 1994; Alur, *et al*., 2001; Attia *et al*., 2004; Sudhakar *et al*., 2006).

1.6. RATIONALE AND MOTIVATION FOR THIS STUDY

Thus far, investigations relating to drug delivery and biomedical sciences have concentrated more on the use of porous structured matrices in the fabrication of biological tissue engineering scaffolds, implantable and optical devices and oral drug delivery systems (Netz *et al*., 2001; Cavallaro *et al*., 2004; Kim *et al*., 2004; Kundu *et al*., 2004; Miao *et al*., 2004; Cosijins *et al*., 2007; Wang *et al*., 2007; Kusmanto *et al*., 2008). As far as we know, limited explorative studies exist on the design and mechanistic evaluation of such novel porous structured matrices for application as controlled release, transbuccal systems for systemic drug delivery. The few related studies focused more on localized, non-systemic oramucosal delivery of therapeutic agents for periodontal diseases and other drug delivery applications (Park *et al*., 1997; Bromberg, *et al*., 2001; Queiroz, *et al*., 2004; Patel, *et al*., 2007). In addition, researches involving transbuccal drug delivery have focused more on the use of non-porous structured formulations such as tablets, gels, hydrogels, micro-matrices, films, and pastes (Attia *et al*., 2004; Kumar *et al*., 2005; Martin *et al*., 2005; Repka *et al*., 2005; Giannola, 2007; Kim *et al*., 2007).

Porous structured formulations can be described as superior and may provide more potential benefits (in terms of their overall drug delivery performances and applications) compared to conventional non-porous structured transbuccal formulations in terms of their morphological flexibility (due to the presence of malleable pores) which can allow for easy manipulation of their drug loading efficiency, rate of drug delivery, enhanced bioadhesion to mucosal sites and permeation enhancements for systemic delivery of drug molecules (Sher *et al*., 2007; Zhang *et al*., 2007). In recent years, the demand for such sophisticated approaches for the

effective delivery of drugs and bioactive species to improve therapeutic efficacy is on the increase (Tao and Desai, 2003). Consequently, a need exists to construct and explore such novel pore-regulated drug delivery matrices for rate-modulated drug release for transbuccal applications.

Based on the morphological flexibility and complexity of porous structured matrices, this study explored and elucidated the mechanistic and/or principles guiding the entire construction and performance of the newly designed pore-regulated matrices. Besides, this research investigated the impacts of changes in pore sizes, morphology, distributions and interconnectivity on the magnitude of the various measured influential physicochemical and physicomechanical quantities. The comprehension of these salient mechanisms, which are functions of the three-dimensional pore structure and size distributions and interconnectivity, can be required for a rational-based modification of the release rates and other related physical characteristics of such porous structured matrices to suit specific clinical applications (McHugh, 2005; Conti *et al*., 2007; Pongjanyakul and Puttipipatkhachorn, 2007; Strubing *et al*., 2007).

1.6.1. The model drugs employed: rationale for selection

Phenytoin sodium and carbamazepine are model drugs selected for the execution of this study. They are employed as first-line drug in the treatment of epilepsy (Pellock *et al*., 2004). Epilepsy is a common neurological disorder typified by frequent, spontaneous seizures. It remains a major global and public health problem which affects about 1-2% of the world population. Antiepileptic drugs remain a key for treatment and the basic therapeutic goal is usually to achieve a total control of recurrent seizures without adverse medication effects (Dieter, 2002; Pellock *et al*., 2004). Unfortunately, this has been difficult to accomplish. Epilepsy is a chronic ailment with reports of patient non-compliance which is due mainly to frequency of dosing and adverse drug effects (Dieter, 2002; Pellock *et al*., 2004).

Reports have shown that currently, a sufficient lack of efficient phenytoin sodium and carbamazepine pharmaceutical preparations which can achieve systemic drug delivery (such as delivery systems capable of releasing drug molecules into the blood stream via transmucosal sites) that can enhance patient compliance exists in practice. Also, phenytoin sodium and carbamazepine have been reported to possess relatively slow rates of intestinal absorption into the systemic circulation (i.e. low bioavailability) when administered orally

(Alvarez-Núñez and Yalkowsky, 1999; Akkar and Müller, 2003; Wang and Patsalos, 2003; Pellock *et al*., 2004; Dong *et al*., 2007). Besides, research has shown that phenytoin sodium exhibits a high dissolution rate in water but under gastrointestinal acidic pH conditions, the sodium salt is rapidly converted to the practically insoluble acid form which may have some negative influence on its bioavailability (Darwish *et al*., 1996). Consequently, a need exists to design optimal drug delivery systems with potential capabilities to overcome some of the reported demerits of highly effective and commonly employed antiepileptic drugs (phenytoin sodium and carbamazepine). The chemical structures of phenytoin sodium and carbamazepine are represented in Figure 1.3.

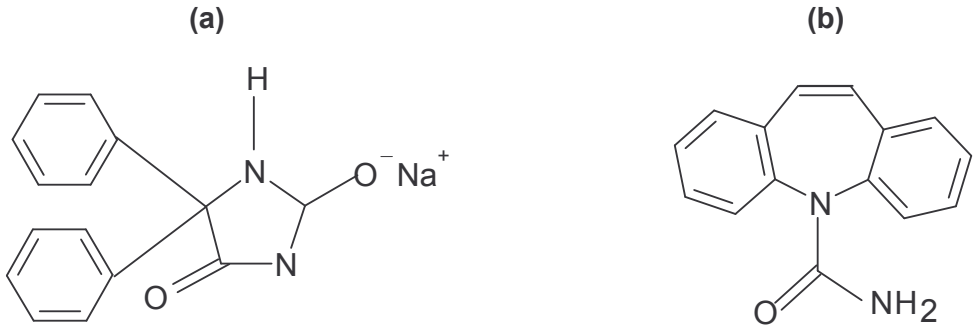


Figure 1.3: Chemical structures of (a) Phenytoin sodium and (b) Carbamazepine.

Furthermore, phenytoin sodium and carbamazepine were also both investigated as model for the purposes of developing a comparatively versatile and robust pore-regulated polymer matrix drug delivery system with the potential of modulating the release of a broad range of drug molecules and bioactives. According to the Biopharmaceutics Classification System, phenytoin sodium and carbamazepine are categorized as class I and II drugs respectively (Kasim *et al*., 2004; Dong *et al*., 2007). Consequently, phenytoin sodium, a class I drug, is described as having high aqueous solubility (100mg/mL at 25°C) and high permeability (log P = 2.14) (Darwish *et al*., 1996; Kasim *et al*., 2004) while carbamazepine which is included in the class II exhibits low aqueous solubility (practically insoluble in water) (0.01mg/mL at 25°C) and higher permeability (log P = 2.93) (Kasim *et al*., 2004; Koester *et* al., 2004; Dong *et al*., 2007).

1.7. TECHNOLOGICAL PROCESSES APPLIED IN THIS STUDY

In order to fabricate the optimized, pore-regulated matrices suitable for transbuccal drug delivery, an interphase, co-particulate, homogenization technique coupled with pre-freezing and lyophilization were employed. The choice of method of preparation was based on their simplicity and optimum efficiency in generating robust and stable porous matrix formulations. The construction of these unique pore-regulated matrices was guided through a high performance statistically and mathematically robust experimental design approach.

Each pore-regulated matrix was constructed using biocompatible and biodegradable polymeric and non-polymeric compounds and either of the hydrophobic or hydrophilic (carbamazepine or phenytoin sodium respectively) pharmaceutically active model drugs. Two polar protic solvents, water and ethanol, were employed as dispersants for the solute particles and as pore-forming agents. The hydrophilic and hydrophobic solute particles were separately dispersed in water and ethanol respectively and subsequently mixed together to form a duo-phased co-particulate suspension. In order to produce a homogenous, semi-solid, multi-component blend of the two suspensions, a surfactant (span 80) was introduced into the co-particulate suspension and subjected to homogenization. The resulting homogenous blend containing either of the model drugs was then solidified by subjecting it to freezing followed by drying by lyophilization to form the pore-regulated matrix formulation. The frozen solvent crystals formed can be referred to as the mirror images of the pores within the matrix. Therefore, during lyophilization (freeze drying) of these solidified matrix, the sublimation of the solidified solvent crystals occurred leaving behind characteristic hole structures/void spaces (pores) and the solute component (interconnectors) intact. Due to the use of vacuum during the process of lyophilization, the matrix was dried at a temperature below the melting point of the frozen solvent crystals.

Pore regulation which influenced pore diameter, distribution and interconnectivity was achieved by varying process parameters namely the quantities of solute components, solvent volumes and amount of surfactant employed in the fabrication of each pore-regulated matrix. These changes in pore characteristics significantly influenced the exhibited physicochemical and physicomechanical properties of pore-regulated matrices. This was undertaken with the aim of producing a novel, optimized pore-regulated matrix with superior physicochemical and physicomechanical qualities which could make it suitable for rate-modulated transbuccal

drug delivery. The whole process was channeled systematically using a mathematically and statistically robust Box-Behnken experimental design. The model drugs, phenytoin sodium (solubility = 100mg/mL at 25°C; log P = 2.14) and carbamazepine (solubility = 0.01mg/mL at 25°C; log P = 2.93), that were employed in this study (Section 1.6.1) were separately incorporated into the solid-liquid suspension prior to homogenization and lyophilization. A schematic illustrating the phases involved in the fabrication of the drug-loaded pore-regulated matrices is presented in Figure 1.4.

1.8. AIM AND OBJECTIVES OF THE STUDY

This research focuses on developing a novel, optimized pore-regulated drug delivery matrix for the sustained systemic release of drug molecules with low or high aqueous solubility via the transbuccal route of administration and also attempts to elucidate the mechanisms involved with the fabrication and performance of this matrix.

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

I. To prepare co-particulate, homogenous blends by using appropriate quantitative combinations of biocompatible, bioadhesive, permeation enhancing and biodegradable hydrophilic and hydrophobic polymeric compounds, non-polymeric pharmaceutical additives, as well as inorganic solvents (which served as pore generators and solute dispersants) guided through a Box-Behnken experimental design

II. To separately incorporate either of the model drugs namely carbamazepine and phenytoin sodium respectively into the prepared homogenous, co-particulate blends to prepare drug-loaded pore-regulated matrices by pre-freezing followed by lyophilization

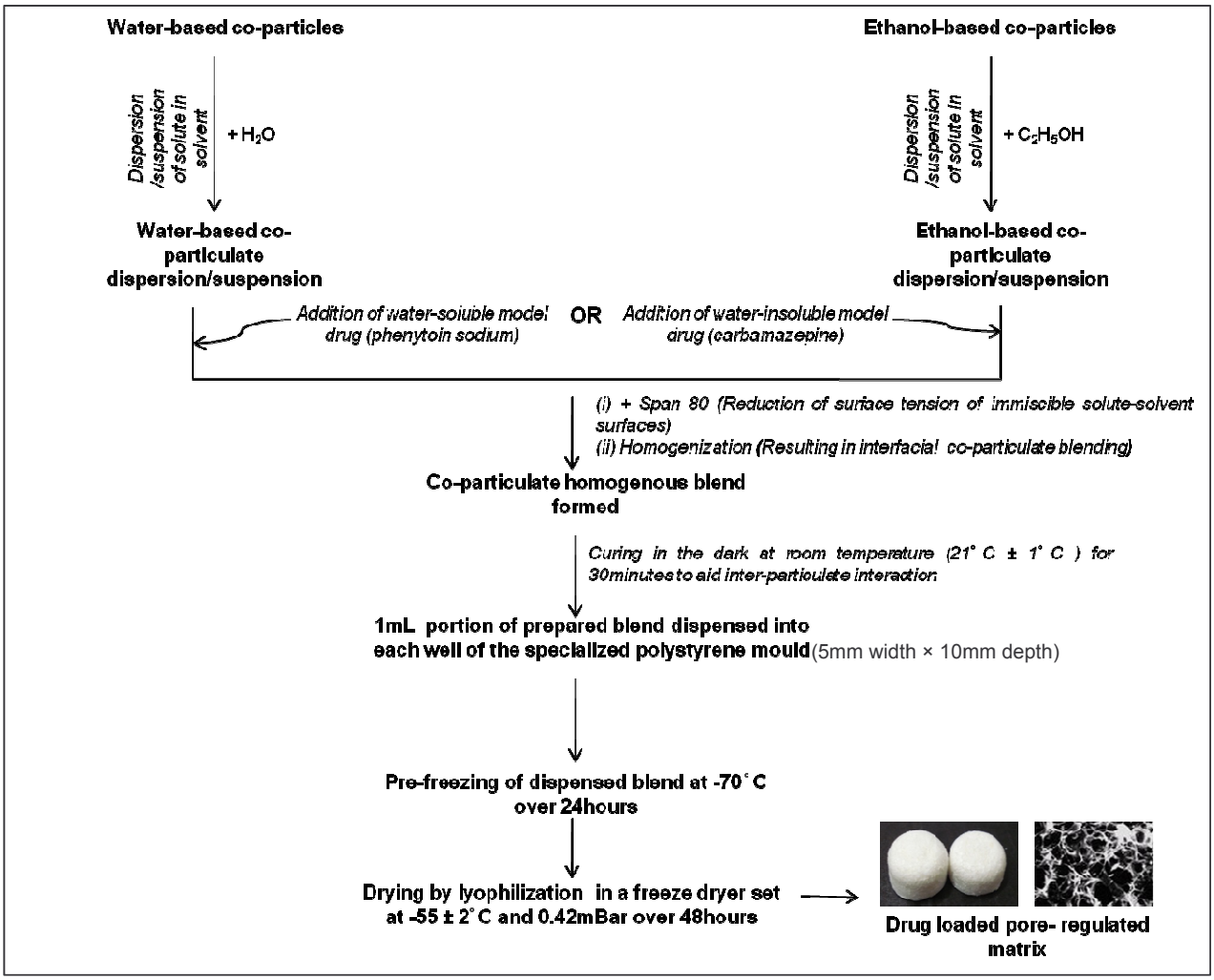


Figure 1.4: Phases involved in the fabrication of the drug loaded pore-regulated matrices.

III. To measure relevant physicochemical and physicomechanical properties (such as *ex vivo* bioadhesion and permeation, *in vitro* drug release, gravimetric weight changes, drug loading capacity, matrix porosity, matrix resilience, energy of matrix deformation and matrix rigidity) of the matrices and assess the impact of pore-regulation on these physical quantities

IV. To optimize specific physicochemical and physicomechanical properties of the pore-regulated matrices to suit the intended transbuccal drug delivery application and to evaluate the reliability of the statistical experimental design employed using the response surface methodology and associated analysis of variance respectively

V. To investigate the impact of the differences in the aqueous solubility and permeability of the model drug on the performance of the optimized pore-regulated matrix

VI. To perform *in vivo* animal studies utilizing the optimized drug loaded pore-regulated matrices using the Large White pig as a model, develop suitable solid phase extraction and Ultra Performance Liquid Chromatographic methods for the assessment and quantification of the plasma levels of the model drugs employed and to perform pharmacokinetic modeling of the generated *in vivo* data

VII. To conduct detailed cytological and histological investigations to assess the toxicity of the optimized, drug-loaded pore-regulated matrix on selected biological cell lines and the buccal mucosa of the pig animal model respectively

VIII. To elucidate and predict the possible mechanisms guiding the formation and performance of the pore-regulated matrices using both experimental and computational modeling approaches

IX. To evaluate the practicable influence of industrial scale-up processes on the overall performance of the optimized pore-regulated matrices

X. To investigate the possible impacts of environmental storage conditions (over specified durations) on the stability of the optimized pore-regulated matrices and to propose suitable storage specifications

1.9. OVERVIEW OF THIS THESIS

Chapter one presents a general idea of the basic concepts and advancements in polymeric drug delivery, definition and physical properties of porous structured matrices, their role in drug delivery and biomedicine, transmucosal drug delivery with emphasis on the transbuccal route as a model employed for this study, rationale and motivation for this research, technology applied, model drugs employed as well as the aim and objectives of the study.

In Chapter two, a high performance Box-Behnken experimental design is used to investigate the influences of varying formulation variables on the physicochemical and physicomechanical characteristics of the pore-regulated matrices. Also, the impact of pore-regulation (measured by average pore diameter and cumulative surface area of pores) on

the magnitude of selected physicochemical and physicomechanical parameters of the pore-regulated matrix variants is also evaluated employing a mathematical method. Furthermore, the optimization of the physicochemical and physicomechanical properties of these matrices in relation to the proposed transbuccal drug delivery application and assessment of the reliability of the statistical design employed using the response surface methodology is described.

Chapter three focuses on characterizing the drug loaded, optimized pore-regulating matrices as well as investigating their versatility and robustness by comparing the influences of the differences in the aqueous solubility and permeability levels of the two models drugs, phenytoin sodium and carbamazepine, on measured physicochemical and physicomechanical properties of the optimized matrices.

The *in vivo* performance of the optimized pore-regulated matrices which encompasses changes in drug plasma levels with time, the pharmacokinetic and pharmacodynamic modeling of the generated drug plasma concentration versus time profiles as well as the development of a suitable *In vitro-In vivo* correlation model are presented in Chapter four.

Chapter five presents studies on the formulation toxicity and biocompatibility employing cytological and histomorphological examinations of biological cell lines and buccal mucosal tissue specimens respectively.

Chapter six comprises of the proposed mechanisms guiding the formation and action of the optimized pore-regulated matrix utilizing the experimental and computational modeling approaches.

The probable effects of scale-up processes and relevant storage conditions, over specified periods, on the overall performance of the optimized pore-regulated matrices are evaluated in Chapter seven.

The conclusions of the study and recommendations for future work are cited in Chapter eight and lastly, a list of references utilized for this research is provided.

1.10. CONCLUDING REMARKS

This chapter has provided a concise literature background to the conceptual make-up of this research work, presented the rationale and motivation, summarized the technological processes employed in the fabrication of the matrices, specified the study aim and objectives and contains an outline for each component chapter of this thesis. The subsequent chapter will serve as an experimental foundation for this work as it will focus on the construction, measurement of physicochemical and physicomechanical quantities and optimization of the pore-regulated matrices for sustained systemic drug release through the transbuccal route of delivery. These procedures will be systematically executed with the aid of the Box-Behnken experimental design and phenytoin sodium will be employed as a model drug at this stage.