DEVELOPMENT AND EVALUATION OF A MATRIX CONTROLLED-RELEASE FORMULATION OF GLICLAZIDE

BY

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Dedicate to my beloved father Abdullah Zaid, beloved mother Aisha Omar. Also to Amna Eddaly (wife), Abdullah (son), Lina and Rawya (daughters) as well as all my brothers and sisters

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LIST OF SYMBOLS AND ABBREVIATIONS

Abbreviation	-	Full description
ANOVA	-	Analysis of variance
C.V.	-	Coefficient of variation
cm	-	Centimeter
C_{max}	-	Peak plasma concentration
et al.,	-	Elsewhere or add others
FDA	-	Food and Drug Administration
g	-	Gram
GIT	-	Gastro intestinal tract
HPMC	-	Hydroxypropylmethylcellulose
hr	-	Hour
IPA	-	Isopropyl alcohol
L	-	Liter
m	-	Meter
m^2	-	Square meter
MCC	-	Microcrystalline cellulose
mg	-	Milligram
min	-	Minute
mL	-	Milliliter
mm	-	Millimeter
MR	-	Modified release
N	-	Newton
NaCl	-	Sodium chloride

NIDDM	-	Non-insulin dependent diabetes mellitus
^{o}C	-	Degree centigrade
pK_a	-	Dissociation constant
PVA	-	polyvinyl acetate
PVP	-	polyvinyl pyrrolidone
r	-	Correlation coefficient
rpm	-	revolution per minute
S.D	-	Standard deviation
SR	-	Sustained release
$t_{½}$	-	Elimination of half life
$t_{50\%}$	-	Time for 50% of drug release
T_g	-	Glass transition temperature
T_{max}	-	Time to reach peak plasma concentration
USP	-	united state pharmacopeia
UV	-	Ultraviolet
v/v	-	Volume over volume
w/w	-	Weight over weight
µg/ mL	-	Micro gram per milliliter
µm	-	Micro meter

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PEMBANGUNAN DAN PENILAIAN SUATU FORMULASI MATRIKS PELEPASAN TERKAWAL BAGI GLIKLAZIDA

ABSTRAK

Dua polimer hidrofobik, Kollidon® SR dan Eudragit® RSPO serta dua polimer hidrofilik hidroksil propil metilselulosa, iaitu HPMC K100LV dan HPMC K15M, telah dikaji sebagai bahan pembentukan matriks tablet untuk mengawal pelepasan gliklazida. Pelepasan drug dapat diubahsuai mengikut suatu gaya yang boleh diramalkan dengan mengubah kandungan polimer, di mana peningkatan kandungan polimer menghasilkan kadar pelepasan yang lebih tertahan. Pada kandungan polimer yang sama, tablet yang disediakan dengan menggunakan HPMC K15M mempunyai kadar pelepasan drug yang paling tertahan, diikuti oleh Kollidon® SR, HPMC K100LV dan akhirnya Eudragit® RSPO. Perbandingan antara beberapa gred HPMC juga menunjukkan bahawa pelepasan drug yang paling tertahan dapat dicapai dengan menggunakan HPMC K100M, diikuti oleh HPMC K15M, HPMC K4M, HPMC K100LV, HPMC E4M dan HPMC E15. Amaun dan komposisi cecair granulasi serta julat saiz partikel polimer turut memberi kesan yang signifikan terhadap pelepasan drug daripada matriks yang mengandungi 30% Kollidon® SR. Peningkatan amaun cecair granulasi, peningkatan nisbah isopropil alkohol kepada air serta peningkatan nisbah Kollidon® SR yang mempunyai saiz partikel yang lebih besar boleh menyebabkan penurunan dalam kadar pelepasan drug.

Pelepasan gliklazida daripada formulasi yang mengandungi 30% Kollidon® SR bergantung kepada pH, di mana kadar pelepasan yang tertinggi diperolehi dengan pH

7.4, diikuti dengan pH 1.2 dan drug dilepaskan dengan kadar yang terendah pada pH 4.0. Akan tetapi, apabila Kollidon® SR dikaji dengan menggunakan dua drug hidrofilik yang lain, iaitu diltiazem HCl dan theophylline, kadar pelepasan kedua-dua drug tersebut adalah lebih cepat berbanding dengan gliklazida apabila dikaji pada ketiga-tiga nilai pH yang tersebut di atas. Tambahan pula, kadar pelepasan gliklazida yang rendah serta bergantung kepada pH gagal diatasi apabila maltodekstrin, kalsium fosfat dibasic atau Plasdon® S-630 digabungkan ke dalam matriks Kollidon® SR. Justeru itu, Kollidon® SR tidak sesuai dijadikan sebagai bahan pembentukan matriks.

HPMC K100LV dikaji selanjutnya untuk menilai kesesuaiannya untuk digunakan sebagai bahan matriks untuk gliklazida. Satu formulasi yang mengandungi 30% HPMC K100LV dan 30% kalsium fosfat dibasic boleh menghasilkan profil pelepasan drug yang hampir serupa atau berpadanan dengan profil sediaan rujukan, Diamicron® MR pada pelbagai pH yang berlainan apabila dinilai dengan menggunakan faktor *differential* (F_1) dan faktor *similarity* (F_2). Kaedah penyediaan tablet yang berlainan, iaitu, granulasi basah, pemampatan terus dan granulasi kering juga boleh mempengaruhi kadar pelepasan gliklazida. Profil pelepasan drug daripada tablet yang disediakan dengan granulasi basah adalah lebih setara dengan profil Diamicron® MR, dan ini menunjukkan bahawa kaedah ini lebih sesuai digunakan untuk penyediaan tablet. Tambahan pula, profil pelepasan drug untuk tablet yang dihasilkan dengan menggunakan kaedah granulasi basah didapati stabil selepas 6 bulan.

DEVELOPMENT AND EVALUATION OF A MATRIX CONTROLLED-RELEASE FORMULATION OF GLICLAZIDE

ABSTRACT

Two hydrophobic polymers, Kollidon® SR and Eudragit® RSPO as well as two hydrophilic hydroxypropyl methylcellulose polymers, namely, HPMC K100LV and HPMC K15M were evaluated as matrix tablet forming materials for sustaining the release of gliclazide. It was found that drug release could be modified in a predictable manner by varying the content of the polymers, whereby increasing the polymer content resulted in a more sustained rate of drug release. At the same polymer content, the drug release was most sustained with tablets prepared using HPMC K15M, followed by Kollidon® SR, HPMC K100LV and lastly Eudragit® RSPO. A similar comparison of several grades of HPMC showed that the drug release was more sustained with HPMC K100M, followed by HPMC K15M, HPMC K4M, HPMC K100LV, HPMC E4M and HPMC E15. The amount and the composition of granulation fluid as well as the particle size range of the polymer were also found to have a significant impact on the drug release from a 30% Kollidon® SR matrix. Increasing the amount of granulation fluid and the ratio of isopropyl alcohol to water as well as using a higher proportion of Kollidon® SR polymer with larger particle size led to a decrease in the rate of drug release.

The gliclazide release from a formulation containing 30% of Kollidon® SR was found to be pH-dependent, with the highest release rate occurring at pH 7.4, followed by at pH 1.2 and the slowest at pH 4.0. However, when Kollidon® SR was evaluated

using two other hydrophilic drugs, namely diltiazem HCl and theophylline, their release rate was found to be faster than that of gliclazide in all the three pH values. Incorporation of maltodextrin, dibasic calcium phosphate or Plasdon® S-630 into the Kollidon® SR matrix also failed to overcome the slow and pH-dependent release of gliclazide. Thus, Kollidon® SR was found not suitable to be used as matrix forming materials.

HPMC K100LV was further studied for its suitability to be used as the matrix materials for gliclazide. A formulation with 30% HPMC K100LV and 30% dibasic calcium phosphate could produce drug release profiles quite similar or matching to those of reference preparation, Diamicron® MR at the different pH conditions when evaluated using the differential (F_1) and similarity (F_2) factors. Different methods of tablet preparation, namely, wet granulation, direct compression and dry granulation were also found to affect the rate of gliclazide release. The drug release profiles of tablets prepared by wet granulation were more comparable to those of Diamicron® MR, revealing that this method was preferred for tablet preparation. Moreover, the drug release profiles of the tablets produced using the wet granulation method was found to be stable after 6 months of study.

CHAPTER 1: INTRODUCTION

1.1 GENERAL PRINCIPLE

To date, oral administration remains the most preferred mode for delivery of therapeutic agents due to its ease and convenience to the patients. Conventional dosage forms are generally designed not only to produce maximum physical and chemical stability, but also to give maximal drug bioavailability by optimizing the rate and extent of drug absorption. Whilst such dosage forms have been useful, they often give rise to big fluctuations in peak and trough plasma drug level when given repeatedly (Vergnaud, 1993). High peak drug levels may give rise to undesirable side effects while excessively low trough levels may cause loss of therapeutic levels. Thus, maintenance of steady state drug levels with minimal fluctuations has become an important issue in drug delivery, especially with drugs of relatively narrow therapeutic indices.

Another problem with conventional dosage forms, especially if the contained drug has a short biological half life, is that the drug has to be given more frequently, for example 2 or 3 or 4 times a day to obtain the desired therapeutic response (Dash & Cudworth, 1998). This will cause great inconvenience to the patient and hence may give rise to poor compliance (Vergnaud, 1993). To overcome these problems, several technical advancements have been made in the development of new drug delivery systems capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue (Chien, 1983; Patel & Amiji, 1996; Srivastava *et al.*, 2005; Streubel *et al.*, 2006).

1.2 HISTORICAL REVIEW OF THE DEVELOPMENT OF CONTROLLED-RELEASE DELIVERY SYSTEM

The concept of controlling the drug release using a coated solid dosage form to overcome the bitter taste and unpleasant odour of drugs was mentioned by Razes between the year of 850 and 923, as cited by James *et al.* (1986). Nevertheless, one of the first notions towards the production of oral controlled-release dosage forms was only initiated by the German dermatologist, Paul G. Unna in 1884, who stated that if the pills were protected by keratin, they would not dissolve until they had emptied from the stomach (Helfand & Cowen, 1982). According to the review by Saunders (1961), it was only in the year 1944 that Romansky and Rittman successfully introduced a water-soluble salt of an antibiotic formulated in peanut oil with 4% wax for intramuscular injection, in which the release of the antibiotic was extended as a result of increased viscosity.

1.3 ORAL CONTROLLED-RELEASE DOSAGE FORM

The term controlled-release delivery system refers to a system that provides continuous delivery of the contained drug for absorption in a predictable and reproducible rate (over an extended period of time) following a single-dose administration (Chien, 1992). Terminologies such as controlled-release, prolonged action, modified release and sustained release have also been used interchangeably with extended release to describe such dosage form or delivery system. A typical controlled-release delivery system is designed to provide a constant or an almost constant plasma drug level with less fluctuation via slow release of the contained drug over an extended period of time. In practical terms, an oral controlled-release

dosage form should allow a reduction in dosing frequency of the contained drug compared to the conventional dosage form (Qiu & Zhang, 2000).

The first truly effective oral controlled-release drug delivery system was marketed by Smith, Kline and French Laboratories (SK&F), applying the patented Blythe's concept (Blythe, 1956). It was spansule® Capsule, an oral controlled-release dosage form which worked via enteric coating. As reviewed by Ranade and Hollinger (2004), this first oral controlled-release preparation actually consisted of many small coated beads placed in a capsule and the beads were designed to release the drug at different rates, independent of the gastrointestinal environment. Another system using ion exchange resins in the formulation of controlled-release delivery system was reported by Saunders (1961). Later in 1959, a tablet containing plastic matrices called Duretter, was patented (Fryklof, 1959). Since then, many controlled-release products with various mechanisms of action were introduced, and given various names such as extended release, sustained release, prolonged action or long acting dosage form.

1.4 APPROACHES FOR DEVELOPMENT OF ORAL CONTROLLED-RELEASE DELIVERY SYSTEM

Several techniques have been utilized in the development of controlled-release drug delivery systems. The basic principle works on slowing the rate of drug dissolution or release from the dosage form. Generally, there are two approaches to the development of controlled-release drug delivery system (Lordi, 1986). The first approach is by modifying the physical and/or chemical properties that affect the drug

bioavailability, and this approach is suitable only for drug moieties with certain functional groups. The second approach is via modification of dosage form design.

Many methods have been utilized to control the drug release and the commonly used methods including using a drug embedded matrix, barrier coating and osmotic pressure. A popular oral controlled-release system based on the matrix method is to use slowly dissolving polymers. This can be attributed to the recent advancement in polymeric materials which has led to a big quantum leap in the progress of most controlled-release technologies (Wise, 1984). Three delivery systems have dominated today's market of oral controlled-release products, namely, matrix, reservoir and osmotic system. Release mechanisms of drug from these systems were generally regulated by diffusion, dissolution, bioerosion or degradation and generation of osmotic pressure (Ranade & Hollinger, 2004). Thus, these mechanisms have been the subject of extensive studies on controlled-release technologies (Higuchi, 1961; Higuchi, 1963; Colombo *et al.*, 2000a; Colombo *et al.*, 2000b; Siepmann & Göpferich, 2001; Grassi & Grassi, 2005).

1.5 MECHANISMS OF CONTROLLED-RELEASE

1.5.1 DIFFUSION-CONTROLLED MECHANISM

Diffusion can be defined as a process by which molecules transfer spontaneously from one region to another in order to equalize chemical potential gradient. It is a result of random molecular motion with a wide spectrum of physico-chemical properties occurring in various conditions and situations (Liu *et al.*, 2006). In diffusion controlled mechanism, the control of drug release to the environment is achieved by diffusion of drug molecules embedded within a polymeric carrier

through an inert membrane barrier as a result of concentration gradient (Higuchi, 1963). Therefore, it is very common for diffusion controlled devices to exhibit non zero-order release due to an increase in diffusional resistance and decrease in diffusion area as the release proceeds (Venkatraman *et al.*, 2000). In general, there are two types of diffusion controlled systems, namely, reservoir and matrix systems (Jantzen & Robinson, 1996).

1.5.1(a) RESERVOIR DEVICE

The reservoir type of device is generally spherical, cylindrical or disk-like in shape and consists of a compact drug core surrounded by a non-biodegradable permeable membrane through which the drug slowly diffuses (Ranade & Hollinger, 2004). The rate at which the drug is released is determined by the thickness and the permeability of the membrane (Tsai *et al.*, 1998). Several factors affect the rate of drug release from reservoir type of diffusion controlled device. They include the surface area, diffusion coefficient, partition coefficient of the drug between the drug core and the membrane, the diffusional pathlength and the concentration gradient across the membrane. The release kinetics of this type of system suggests that if the concentration of the drug within the reservoir is in constant equilibrium with the inner surface of the enclosed membrane, the driving force for diffusional release of the drug is constant, and zero-order release kinetics of the drug is obtained (Chien, 1978; Baker, 1987). If a constant drug concentration cannot be maintained then the rate of drug release would decline with a decline in the drug concentration in the reservoir. However, there is also a possibility of the reservoir membrane to accidentally rupturing, causing a sudden large amount of drug to be released following administration (known as drug dumping), resulting in toxic side effects if

plasma drug concentration exceeds maximum safety level (Dash & Cudworth, 1998; Ranade & Hollinger, 2004). Reservoir diffusional systems have several advantages over conventional dosage forms, the former can offer zero-order release kinetics of drug and the kinetics can be controlled by changing the characteristics of the polymer to suit a particular drug as well as therapy conditions. The inherent disadvantage is that, unless the polymer used is biodegradable, the system must somehow be removed from the body after the drug has been released (Fish *et al.*, 1993).

1.5.1(b) MATRIX SYSTEM

In the matrix system, also referred to as the monolithic system, the drug is dispersed homogenously throughout the polymer matrix, which can be either hydrophobic or hydrophilic (Khan & Reddy, 1997; Viega *et al.*, 1997; Veiga *et al.*, 1998; Reza *et al.*, 2003). Slow diffusion of the drug through the matrix provides sustained release of the drug from the delivery system (Danckwerts & Fassihi, 1991). Higuchi has provided the theoretical basis for defining drug release from such matrices. In this model, drug particles dispersed in the outer layer of the matrix which is exposed to the bathing solution will dissolve and then diffuse out of the matrix. This process continues with penetration of the dissolution medium into the matrix to further dissolve the contained drug, thereby, creating channels through which diffusion of the dispersed drug in the inner core can take place. It is therefore obvious that for matrix system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix (Jantzen & Robinson, 1996).

Drug release from a matrix system can be influenced by porosity and tortuosity of the matrix. The release rate is directly proportional to the concentration of the dispersed drug in the tablet matrix, the diffusion coefficient and the solubility of the drug in the release media (Higuchi, 1961). Drug particles that are physically embedded in the polymer matrix should be at concentrations high enough to create a series of interconnected pores through which the drug can subsequently diffuse (Langer & Folkman, 1976). However, the release kinetics of the drug from this matrix system will not be constant and it depends on the volume fraction of the drug within the matrix. The greater the concentration of dissolved drug within the matrix, the greater will be its release rate from the matrix system (Dash & Cudworth, 1998). As such, a first order release kinetics is obtained from such matrix systems. Thus, unlike the reservoir device, there is minimal risk of drug dumping in case of accidental rupture of the membrane (Ranade & Hollinger, 2004).

1.5.2 DISSOLUTION-CONTROLLED MECHANISM

The releases of certain drugs are inherently sustained due to their intrinsic low aqueous solubility and thus these drugs are natural sustained release products (Hui *et al.,* 1987). Thus, in principle, it would seem possible to prepare sustained release preparations for highly water soluble drugs by controlling their dissolution rate in gastrointestinal medium. Generally, either matrix or barrier membrane based controlled-release systems are applied to slow down, delay, or control the delivery and release rate of drugs. It is well comprehended that the dissolution process includes two steps that is the initial detachment of drug molecules from the surface of their solid structure to the adjacent liquid interface followed by their diffusion from the interface into the bulk liquid medium. Therefore, this process can be

manipulated to design controlled-release delivery systems with desired release rate and profile (Wang & Shemis, 2006).

In the dissolution controlled matrix system, the drug is uniformly dispersed within a tablet core consisting of a slowly dissolving polymer which forms the matrix, in which the polymer can be hydrophobic in nature (e.g. wax, polyethylene, polypropylene and ethylcellulose) or hydrophilic matrix (e.g. hydroxypropyl cellulose, hydroxypropyl methyl cellulose and sodium carboxy methyl cellulose) (Venkatraman *et al.,* 2000). The rate of drug release is controlled by the rate of penetration of the dissolution medium into the matrix. This in turn, can be controlled by the porosity of the tablet matrix, the presence of hydrophobic additives, as well as wettability of the tablet and the particle surface (Brossard *et al.*, 1983).

In the dissolution controlled barrier system, the drug particles or granules can first be coated with slowly dissolving polymeric materials and subsequently be directly compressed into tablets or put into capsules. One of the principal methods of coating a drug is through micro encapsulation. Once the polymeric membrane has dissolved, the drug contained inside the membrane is immediately available for dissolution and absorption. Thus, the drug release can be controlled by adjusting the thickness and the dissolution rate of the polymeric membrane. A more uniformed controlled-release can be obtained via application of a spectrum of different thicknesses (Harris, 1981). Drug release from the coated beads occurs in a progressive manner. Beads with the thinnest layers will provide the initial dose, while the maintenance of drug level at a later timeframe will be achieved with beads of thicker coatings. This

was the principle engaged by the Spansule® capsule as discussed in section 1.3 (Benita & Donbrow, 1982).

The coating materials can be selected from a wide variety of natural and synthetic polymers, depending on the characteristic of the drug to be coated and the desired release pattern. The commonly used coating materials include gelatin, carnauba wax, shellac, cellulose acetate phthalate and cellulose acetate butyrate. In the dissolution controlled barrier system, the rate limiting step for drug dissolution is the diffusion across an aqueous boundary layer. The solubility of the contained drug provides the source of energy for drug release, which is countered by the diffusion boundary layer of the stagnant fluid (Theeuwes *et al.*, 1991). Besides that, there are several factors affecting the rate of drug dissolution, which include the aqueous solubility of the drug, the surface area of the dissolving particles or tablet, the diffusivity of the drug and the thickness of the boundary layer.

One of the major setbacks of the dissolution controlled barrier system is the difficulty in maintaining a constant drug release. The reasons for such difficulty are the surface area changes with time, and the solubility of drugs that are weak acids or bases is affected by the variation in pH of the gastrointestinal tract. Nevertheless, a synthetic methyl vinyl ether maleic anhydride copolymer which has extraordinary sensitivity to the surrounding pH has been introduced. This polymeric system is completely soluble in the intestine but not soluble in the stomach, thus, can be used in oral controlled-release drug delivery system when absorption at a specific site of the gastrointestinal tract is desired. Also the zero-order drug release at a particular

site of the gastrointestinal tract can be obtained by maintaining the pH of the system (Heller & Trescony, 1979).

1.5.3 EROSION-CONTROLLED MECHANISM

In erosion controlled drug delivery system, the drug particles are distributed uniformly throughout the polymer matrix and the rate of drug release depends on the erosion rate of the polymer. When erosion is faster than drug diffusion, the drug release is controlled by erosion. The difference between erodible systems and non-erodible systems is that the structure/mass in a non-erodible system remains unchanged with time and the drug is released by diffusion, while the structure or mass in an erodible system decreases with time which makes zero-order release unlikely (Katzhendler, 1997). Erosion can take place through the whole matrix, referred to as bulk erosion, or be limited to the matrix surface, termed as surface erosion.

Bulk erosion is very complex because water penetration through the matrix is much faster than polymer degradation, leading to a rapid hydration of the internal core of matrix and digestion throughout the whole matrix. This results in concurrent drug diffusion and matrix erosion (Siepmann & Göpferich, 2001). Subsequently, the weight of the polymer decreases steadily and the matrix permeability increases as a function of time. However, the matrix maintains its original shape and mass until up to approximately 90% is degraded, then only matrix dissolution and mass loss starts (Sinha & Trehan, 2003). In bulk erosion release system, the kinetics of the drug is difficult to determine, especially when the matrix disintegrates before drug is completely released (Heller, 1984).

In surface erosion, degradation takes place only at the matrix boundaries and not in the core of the polymer, thus except for the matrix at the boundaries, the physical integrity of the matrix is preserved and a consistent degradation rate of the polymer is obtained (Heller, 1984). Surface erosion can be achieved when the degradation rate of the polymer at the matrix surface is much faster than the rate of water penetration into the matrix bulk (Langer, 1990). As the drug is dispersed throughout the matrix but only a minimal diffusion takes place, the drug release rate is determined by the rate of erosion of the matrix surface. Therefore, surface erosion is often preferred over bulk erosion because the former is highly reproducible, the drug release rate is proportional to the rate of polymer erosion, and can be controlled by varying system thickness and the total drug content. Also, surface erosion eliminates the possibility of dose dumping, thus improving the safe use of the delivery system.

Nevertheless, for most biodegradable drug delivery system especially for hydrophilic matrices, both erosion mechanisms occur together. The relative extent of the predominant mechanism depends on the chemical structure of the polymer (Mainardes & Silva, 2004). Polymers with reactive functional groups tend to give rise to surface erosion, whereas polymers having less reactive functional groups commonly show bulk erosion (Siepmann & Göpferich, 2001). However, there are exceptions to this general assumption. For example, bulk eroding materials can undergo surface erosion if the critical dimensions of the matrix are exceeded (Von Burkersroda *et al.,* 2002). Besides that, in formulations of nano and micro particles, the same erosion process takes place regardless of the type of polymer used (Uhrich *et al.,* 1999). A disadvantage of this type of systems is that the release kinetics is often difficult to control (Jantzen & Robinson, 1996).

1.5.4 SWELLING-CONTROLLED MECHANISM

Swelling-controlled matrices utilize a combination of both diffusion and dissolution mechanisms (Hopfenberg & Hsu, 1978). The drug is dispersed in the polymer, but instead of using an insoluble or erodible polymer, a swellable polymer is employed. When the polymer loaded with the drug comes into contact with the gastrointestinal fluids, it absorbs water and swells without being dissolved. The swelling further increases the entrance of water, causing dissolution of the contained drug, followed by diffusion of the dissolved drug out of the swollen networks to the external environment. This system usually minimizes the bursting effect as a rapid polymer swelling takes place before the drug is being released (Jantzen & Robinson, 1996). In swelling controlled delivery systems, the absorption of water causes changes in dimensions and physical properties of the matrix, therefore, the changes in the rate of drug release is correlated with the degree of swelling. The diffusion coefficient of the drug in the matrix is initially very low but increases as the gel absorbs more fluids. Thus, the gel layer formation and consequently the rate of drug release are highly dependent on the rate of liquid penetration, polymer swelling rate, drug solubility and diffusion as well as matrix erosion (Paul & Harris, 1976; Nakagami & Nada, 2000).

The swelling composition of the swellable matrices is divided into three components: The first component is the swelling front which clearly separates the rubbery region from the glassy region. The second component is the erosion front which separates the matrix from the solvent. And the last component is the diffusion front located between the swelling and erosion fronts during drug release. The position of the diffusion front in the gel phase is dependent on the drug solubility

and loading (Colombo *et al.*, 2000b). For swellable matrix delivery systems, different models have been reported to describe the diffusion, dissolution and swelling processes involved in the drug release mechanism. (Colombo *et al*,. 1992; Colombo *et al*,. 1995; Wan *et al*,. 1995; Colombo *et al*,. 1996; Peppas & Colombo, 1997; Colombo *et al*,. 1999; Siepmann *et al*,. 1999a; Siepmann *et al*,. 1999b; Siepmann *et al*,. 1999c; Siepmann *et al*,. 2000; Wu *et al.*, 2005). Nevertheless, the essential element of the drug release mechanism is the formation of gel around the matrix which assists water penetration and protects matrix disintegration.

1.5.5 OSMOTIC PUMP SYSTEM

Osmosis can be defined as the spontaneous movement of a solvent from a region of lower solute concentration to a region of higher solute concentration across an ideal semi-permeable membrane, which is permeable only to the solvent but impermeable to the solute. In recent years, this mechanism was employed for controlling the rate of drug release (Theeuwes, 1975; Theeuwes, 1983). In this approach, the unit consists of an osmotic core containing an osmotically active drug or a combination of an osmotically inactive drug with an osmotically active salt or agent such as NaCl, coated with a rigid semi-permeable membrane.

The uptake of water across the semi-permeable membrane is at a controlled rate that causes the device to deliver an equal volume of saturated drug solution out of the core through a drilled orifice on the coat. Considering a semi-permeable membrane that is permeable to water but not drug (Chien, 1992), the osmotic and hydrostatic pressure differences on either side of the semi-permeable membrane will provide the driving force to generate controlled-release of the contained drug. The classification

of various osmotic delivery systems was discussed in detail by Verma *et al.* (2000) and Conley *et al.* (2006). These systems generally appear in two different forms. The first form contains the drug in a solid core together with the electrolyte. Both the drug and the electrolyte are dissolved by the incoming water, in which the electrolyte provides a high osmotic pressure difference. The built-up hydrostatic pressure due to the imbibed water can only be relieved by pumping the drug solution out of the drilled hole. The second form contains the drug (in solution) in an impermeable membrane within the device. The electrolyte surrounding the impermeable membrane yields high osmotic pressure to draw water into the device. This in turn causes compression of the membrane and drug is pumped out of the core through a drilled hole. Both systems have either single or multiple holes bored through the membrane to allow drug release. In general, the system can assume any shape or size, depending on the dosage requirements.

The semi-permeable membrane exhibits sufficient strength and rigidity to maintain a constant volume during pump operation. Delivery rate of the drug is dependent on membrane permeability, the osmotic pressure of the core and the solubility of the drug (Chien, 1992). Since the release mechanism is based on osmotic pressure, the rate of drug release is essentially independent of agitation speed, orifice size, variation in pH and hydrodynamic conditions (Theeuwes, 1975). The elementary osmotic pump benefits from its simple functional design and it is well suited for the formulation and delivery of drugs with intermediate water solubility (Theeuwes, 1984).

Besides the typical osmotic pump delivery system described earlier, a controlled porosity osmotic pump was described by Zentner *et al.* (1985). In this system, an osmotically active core was coated with a mixture of polymers with differing degrees of water solubility. In the presence of water, the soluble components of the coating will dissolve, leaving a micro porous film. Subsequently, water can diffuse into the core creating an osmotic gradient, which controls the release of drug. The rate of drug release depends on the coating thickness, the solubility of the coating component, the solubility of drug in the tablet core and the difference in osmotic pressure between the core and dissolution medium.

1.5.6 ION EXCHANGE RESINS

Ion exchange resin delivery systems generally use water-insoluble crosslinked polymers containing groups of exchanging ions to obtain sustained release of drug for ionizable drugs. Therefore, these polymers are also known as ion exchange resin. These resins contain salt-forming functional groups in repeating positions on the resin (Jantzen & Robinson, 1996). They may contain acidic or basic-reacting groups, whereby these reacting groups can bind to drugs. Basic drugs are bound to acidic cation ion exchangers, while the acidic drugs are bound to basic anion ion exchangers. Drug molecules attached to the resins are exchanged for release by appropriately charged ions in contact with the ion-exchange groups and the released drug molecules diffuse out of the resin. Drug release from the resins depends on properties of the resin and the ionic environment, such as pH or electrolyte concentration within the gastrointestinal tract (Ranade & Hollinger, 2004).

The rate of sustained release of the drug is a result of slow diffusion of drug molecules through the resin complex. However, release rate can be controlled by the diffusion area, diffusional pathlength and chemical composition as well as rigidity of the resin. The release rate can even be further controlled by coating the drug-resin-complex with a hydrophobic polymer such as ethyl cellulose or waxes, using micro encapsulation processes described earlier in Section 1.3.2. Resin-drug complex is advantageous for drugs that are highly susceptible to hydrolysis or degradation by enzymatic process, since it offers a protective mechanism by temporarily altering the substrate. Like all other systems, this approach also has a limitation that the release rate is proportional to the concentration of the ions present in the environment, indicating that there is a maximum release rate which cannot be further increased. Also the release rate of drug can be affected by variability in diet, and water intake as well as the individual intestinal content (Eriksen, 1986).

1.6 ADVANTAGES OF ORAL CONTROLLED-RELEASE DOSAGE FORM

Oral controlled-release formulations have attained medical acceptance and gained popularity due to several therapeutic advantages. More uniform plasma levels of drug can be maintained at steady state over an extended period of time through the reduction in fluctuations between peak and trough plasma concentrations (Urquhart, 1982). Also, the need for frequent drug administration can be minimized to once or twice daily, which is particularly advantageous for drugs used in treatment of chronic diseases, leading to improved patient compliance and convenience (Tinkelman *et al.,* 1980). The reduced fluctuations in plasma drug levels can help to reduce the incidence of adverse side effects, which are common in conventional drug

administration (Theeuwes, 1983). Moreover, local irritation of the gastrointestinal tract due to exposure to high concentration of certain drugs can be minimized (Boroda *et al*,. 1973). Furthermore, oral controlled-release formulations are useful for delivering drug with narrow therapeutic index, in which fluctuation in blood level may induce supra therapeutic levels resulting in systemic toxicity, or sub-therapeutic levels characterized by loss in therapeutic efficacy (Lordi, 1986). The overall administration of oral controlled-release products enables increased reliability of therapy (Welling & Dobrinska, 1987).

1.7 DISADVANTAGES OF ORAL CONTROLLED-RELEASE DOSAGE FORM

There are also some disadvantages with controlled-release dosage forms. Prompt termination of therapy if significant adverse effects are observed is impossible after administration of the dosage form. Besides that, the physician has less flexibility in regulating dosage regimens as the dose has been fixed by the dosage form design. The high cost employed in the processes and equipment for manufacturing of controlled-release formulations results in more expensive products compared to conventional preparations. In addition, the upscale manufacturing procedure sometimes causes unpredictable release profile and often reduces the drug bioavailability due to relatively poor understanding of *in vitro* and *in vivo* correlation (Gupta & Robinson, 1992). Furthermore, there are other disadvantages such as possible dose dumping, increased first-pass metabolism of certain drugs, and the effective drug release period is limited and affected by gastrointestinal transit time.

1.8 PREPARATION OF TABLETS

Tablets are solid masses produced by compressing suitably prepared medicaments commonly in the form of granules by way of a tabletting machine called presses. The tablets can be manufactured in various shapes and sizes. However, they are typically circular discs with either flat or convex surfaces. When the tablets are properly formulated and manufactured, they ensure that the drug is suitably stable chemically and physically and also that it is delivered at an accurate dose.

1.8.1 TABLET MACHINE

Tablet machines are designed with the following basic components, a hopper for holding and feeding the material to be compressed, a feed frame for distributing the material into the dies which respectively define the size and the shape of the tablets, punches for compressing material in the dies, and lastly, cam tracks for guiding the rotation of the punches. Tablet machines are classified into single punch and multi station rotary presses. Although both types of presses accomplish the same task, their major differences are the rate of production and mechanical features designed to control the compaction process. Although the tablet compressing machinery has gone through several era of mechanical modification over the years, the compression of material in a couple of moving punches through a stationary die has remained unchanged (Banker & Anderson, 1986). The essential alteration of primitive equipment has been aimed at increasing the production output rather than creating any fundamental changes in the tableting process. Better control and simplification of the manufacturing procedure have been the main benefits as a result of these changes.

1.8.2 METHODS OF TABLET PREPARATION

Tablets are usually heterogeneous mixtures containing powders of varying physical and chemical properties. During mixing, bonds must be formed between primary powder particles, so that they adhere to each other to form larger multi-particle entities called granules. These bonds must be sufficiently strong to prevent breakdown of the final dried granules back to its powder form in the subsequent handling processes. The magnitude of these bonding forces is determined by the size of the particles, the structure of granules, the moisture content and the surface tension of the liquid. There are three general methods to prepare powder materials/granules prior to compression into tablets (Parikh, 1997), namely:

1.8.2(a) Direct compression

In this method, the powdered materials of the tablet are mixed and compressed directly without any modification of its physical nature.

1.8.2(b) Dry granulation

In this method, the dry powder particles may be brought together mechanically via compression to form slugs, or more frequently via compaction by a roller compactor. This method has been utilized when one of the constituents, either the drug or the excipients has insufficient cohesive or flow properties to be directly compressed into tablets.

1.8.2(c) Wet granulation

The wet granulation procedure is usually opted based on the assumption that the stability of the drug is not affected by moisture or elevated temperature. The wet

granulation procedure includes initial mixing of powder to be incorporated into the dosage form and thereafter, the addition of a sufficient amount of a granulating liquid to the powder mix in order to obtain granules (Bandelin, 1989). Subsequently, the damp mass is screened and then dried. The pharmaceutical granules typically have a size range of between 0.2 mm and 4 mm, depending on their intended use. The major objectives of granulation are to improve the flow properties and compression characteristics of the powder mixture and to prevent particle segregation of the constituents. The wet granulation process is preferred over the direct compression process based on at least three advantages. Firstly, the wet granulation provides the materials to be compressed with better wetting properties, particularly in the case of hydrophobic drug substances. The addition of hydrophilic excipients makes the surface of a hydrophobic drug more hydrophilic and also facilitates disintegration and dissolution. Secondly, the content uniformity of the solid dosage forms is generally improved with wet granulation. Finally, the size and shape of the particles (comprising the granules to be compressed) are optimized by the wet granulation process. The reason for this is that when a dry solid is wet granulated; the binder glues particles together so that they agglomerate to form granules which are more or less spherical.

1.8.3 GRANULATION MECHANISM

The theory of granulation can be expressed using four transitional states (Barlow, 1968), known as the pendular, funicular, capillary and droplet or suspension state. The mechanism of agglomeration can be described as a gradual change from a triphasic stage (air-liquid-solid) in which most granules are in the pendular and funicular states to a biphasic (liquid-solid) particulate assembly, in which the

granules will be in the capillary and droplet state. Meanwhile, there are five primary bonding mechanisms between particles to form granules (Rumpf, 1962; Parikh, 1997). In practice, more than one bonding mechanisms may act simultaneously (Parikh, 1997). These mechanisms are discussed below:

1.8.3(a) Adhesion and cohesion forces

The availability of liquid between individual primary powder particles to produce a very thin immobile adsorption layer can contribute to their bonding among each other, thereby effectively reducing the interparticulate space and increasing the contact between these particles. The bond strength between these particles is dependent on the Van der Waals forces of attraction which is proportional to the particle size and inversely proportional to the square of the distance between particles.

1.8.3(b) Interfacial forces

Once sufficient liquid is added, the granulation fluid transforms from an immobile surface liquid state to a mobile liquid film state to form bridges between the solid particles. The tensile strength of these bridges increases as the amount of fluid added is increased, where capillary pressure and interfacial forces create strong bonds, although reversible after drying. These bonds antecede the solid bridges formation. However, mobile liquid films are a precondition to the solid bridges produced by binders or the granulating liquid.

1.8.3(c) Solid bridges

Solid bridges are formed during drying of the wet granules or granulating solution after wet granulation. These solid bridges may be developed by fusion of particles through partial melting at points of contact where high pressure develops, particularly at high temperature. This temperature rise can result from either an external secondary source or from friction during agglomeration or energy conversion. Solid bridges can also be built up from chemical reaction, crystallization, hardening of dissolved substances and solidification of melted components (Parikh, 1997).

1.8.3(d) Attractive forces between solid particles

In the absence of solid bridges formed by binding agent or liquids, there are two types of attractive force that can exist between granules, namely the electrostatic and Van der Waals forces. The electrostatic force is important for powder cohesion and the primary formation of agglomerates, whereby, this attractive force helps to maintain contact of particles long enough for the agglomeration process (Rumpf, 1962). Meanwhile, the Van der Waals force, which is about four times greater than the electrostatic force, contributes significantly to the strength of the granules produced by dry granulation (Sherrington & Oliver, 1981). The magnitude of the Van der Waals force will increase as the distance between adjacent surfaces decreases. In slugging or roller compaction, this can be achieved through the application of pressure to force the particles together.

1.8.3(e) Closed bonds

Fibers, little platelets, or bulky particles can interlock or fold among each other to form closed bonds. Although mechanical interlocking of particles influences the strength of agglomerates, its contribution is generally considered small compared to other mechanisms.

1.9 INFLUENCE OF PHYSIOLOGICAL FACTORS ON DOSAGE FORM DESIGN AND PERFORMANCE

In designing an oral dosage form, it is useful to have a general understanding of the drug disposition within the gastrointestinal tract as well as information pertaining to its distribution, integrity or release characteristics from the dosage form since the performance of the administered dosage form may be affected by changes in the physiological conditions. One of the most important factors affecting the design of controlled-release dosage form is the residence time of the dosage form at various sites of the gastrointestinal tract which may cause differences in drug bioavailability. Furthermore, differences in food status also can have effects on the gastrointestinal residence times, as well as drug dissolution from the dosage form.

The stomach is an organ responsible for storage and mixing. At resting state, the pH is acidic with a value of 1 to 3 (Youngberg *et al.*, 1987). Factors contributing to the limited absorption of most drugs from the stomach include the limited surface area of 0.1 m^2 to 0.2 m^2, the lack of villi on the mucosal surface, the presence of a relative thick layer of mucous on the stomach lining and the short residence time in the stomach. Unlike the stomach, the small intestine on the other hand with pH varying between 4.0 and 7.4 (depending on location), has a great number of villi on its

mucosal surface, imparting a huge surface area of between 200 m^2 to 500 m^2 (Davenport, 1977), and hence rendering it to be the essential region for absorption of most drugs. There is a progressive decrease in the surface area from the proximal region to the distal region of the small intestine. Therefore, the proximal region of the small intestine is considered the most important site for drug absorption. Hence, in order to achieve good bioavailability, the drug should be targeted for absorption from this region of the small intestine.

The principal function of the colon is to store indigestible food residues. The luminal content of the colon is much more viscous than that of the small intestine; with pH above 7 or as high as 8. The colonic mucosal surface lacks villi; its exposed surface area for absorption is thus reduced. However, in the distal part of the colon, the insignificant drug absorption is attributable to the remaining drug being embedded in the semisolid foecal matter (Hirtz, 1984). In general, the colonic drug absorption is incomplete and erratic (Kock-weser & Schechter, 1981; Gruber *et al.*, 1987).

The gastric motility is one of the important factors affecting the *in vivo* performance of controlled-release dosage forms. There are two distinct patterns of gastrointestinal tract motility, namely the digestive fed mode and the inter-digestive fasted mode (Quigly *et al.*, 1984), in which the pattern and force of the motility may be different depending on the food states (Azpiroz & Malagelada, 1984). The fasting gastrointestinal motility is characterized by a cyclic pattern that originates from the foregut and propagates to the terminal ileum. The cycle can be categorized into four manifest phases. Phase I represents an inactive period with no electrical activity and no contractions. Phase II is the period of random spike activities or intermittent