DESIGN AND EVALUATION OF PROLONGED RELEASE GLICLAZIDE MATRIX TABLETS

by

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Dedication

To my beloved mother Zainub, my father Abdelragiq and my lovely wife Julia
may Allah bless them

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LIST OF ABBREVIATION & SYMBOLS

SPSS	=	Statistical package for social science
ANOVA	=	Analysis of variance
rpm	=	Rotation per minute
min	=	Minute
SD	=	Standard deviation
UV	=	Ultra violet
°C	=	Degree centigrade
%	=	Percent
mg	=	Milligram
mg/ml	=	Milligram per milliliter
HPLC	=	High performance liquid chromatography
hr	=	Hour
kg	=	Kilogram
UK	=	United Kingdom
mm	=	Millimeter
CV	=	Coefficient of variation
µl	=	Micro liter
µg	=	Microgram
IS	=	Internal standard
Eq	=	Equation
AUC	=	Area under the time curve
K_e	=	Elimination rate constant

HPMC	=	Hydroxypropylmethylcellulose
XG	=	Xanthan gum
BP	=	British pharmacopoeia
USP	=	United states pharmacopoeia

LIST OF EQUATIONS

LISTS OF PRESENTATIONS

Fathelrahman, A., Peh, K.K. and Yvonne, T.F.T. (2005) in-vitro release of sustained release gliclazide matrix tablets prepared using Eudragit RSPO and Kollidon RS. *20th Scientific Meeting of Malaysian Society of Pharmacology and Physiology* (MSPP), 25t^{h}-27th April 2005, Penang, Malaysia. University of science Malaysia.

Fathelrahman, A., Peh, K.K. and Yvone, T.F.T (2007). *Thesis presentation*, design and evaluation of prolonged release gliclazide matrix tablets 29th june 2007, school of pharmacy, Universiti Sains Malaysia.

REKABENTUK DAN PENILAIAN TABLET PELEPASAN TERKAWAL MATRIKS GLIKLAZID

ABSTRAK

Tablet pelepasan terkawal matriks gliklazid disediakan dengan menggunakan bahan-bahan polymer, iaitu, HPMC, Kollidon SR, Carbopol dengan Xanthan gum, Eudragit RSPO dan Eudragit RLPO. HPMC, Kollidon SR dan Carbopol dengan Xanthan gum mampu merencat pelepasan gliklazid daripada tablet matriks dalam corak yang bergantung pada kepekatan, tetapi kadar perencatan adalah berbeza di antara polimer. Sebaliknya, pelepasan drug daripada tablet yang mengandungi Eudragit RSPO dan Eudragit RLPO, tidak bergantung pada kepekatan polimer yang digunakan dan tidak ada corak yang konsisten diperhatikan. Di antara pelbagai jenis polimer dan kepekatan yang dikaji, profil pelepasan tablet matriks yang mengandungi 6% HPMC (formulasi H2) didapati setara dengan tablet Diamicron MR, seperti yang ditunjukkan oleh nilai-nilai "similarity factor" dan "difference factor". Di samping itu, pelepasan drug formulasi H2, tidak dipengaruhi oleh perubahan dalam pH tetapi dipengaruhi secara drastic oleh perubahan dalam kadar pengacauan. Sebelum kajian in vivo, kaedah isokratik HPLC-UV yang mudah, sensitive dan spesifik untuk penentuan kepekatan gliklazid dalam plasma arnab telah dibangunakan dan divalidasikan. Kaedah ekstrasi cecair-cecair digunakan dalam rawatan sample. Kaedah esei ini digunakan untuk kajian farmakokinetik gliclazide, membandingkan formulasi H2 dan Diamicron MR sebagai produk rujukan. Empat arnab digunakan dalam penilaian in vivo. Tidak ada perbezaan yang signifikan secara statistic di antara formulasi F2 dan Diamicron MR dalam nilai-

niali Tmax, Cmax dan AUC. Secara kesimpulan, kadar dan jumlah gliklazid yang diserap untuk formulasi H2 adalah standing dengan Diamicron MR.

DESIGN AND EVALUATION OF PROLONGED RELEASE GLICLAZIDE MATRIX TABLETS

ABSTRACT

The prolonged release gliclazide matrix tablets were prepared using polymeric materials, namely, HPMC, Kollidon SR, Carbopol with Xanthan gum, Eudragit RSPO and Eudragit RLPO. HPMC, Kollidon SR and Carbopol with Xanthan gum were able to retard gliclazide release from matrix tablets in a concentration dependent manner, but the rate of retardation differed among the polymers. On the other hand, drug release from matrix tablets containing Eudragit RSPO and Eudragit RLPO, was independent of the amount of polymer used, and no consistent drug release pattern was observed. Among the various types of polymers and concentrations studied, the dissolution profile of matrix tablets containing 6% HPMC (formulation H2) was found to be similar to that of Diamicron MR tablets as indicated by the values of similarity factor and difference factor. In addition, the drug release of formulation H2, was not affected by changes in pH but affected drastically by changes in the stirring rate. Prior to the in vivo study, a simple, sensitive, and specific isocratic HPLC-UV method for the determination of gliclazide concentration in rabbit plasma was developed and validated. A liquid-liquid extraction method was used in the sample treatment. The assay method was used in the pharmacokinetic study of gliclazide, comparing formulation H2 and Diamicron MR as a reference product. Four rabbits were used in the in vivo evaluation. There was no statistically significant difference between formulation F2 and Diamicron MR in the values of Tmax, Cmax and AUC. In conclusion, the rate and extent of

absorptions of gliclazide for formulation H2 was comparable with Diamicron MR.

CHAPTER 1

INTRODUCTION

1.1 ORAL CONTROLLED RELEASE DOSAGE FORM

Oral drug delivery system is the most popular route, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes (Gupta and Robinson, 1992). There is a plethora of oral controlled release products in the market place. For example, in 1998, the U.S Food and Drug Administration (FDA) approved 90 oral controlled release products. From 1998 to 2003, FDA approved an additional of 29 new drug applications that used controlled release technologies and 12 of them were based on matrix systems (Liu *et at.*, 2006).

1.2 ADVANTAGES AND DISADVANTAGES OF ORAL CONTROLLED RELEASE DELIVERY SYSTEM

Development of oral controlled release dosage forms of a given drug involves optimization of the dosage form characteristics within the inherited constrains of the gastrointestinal physiology. Controlled release delivery systems have added advantages over immediate release dosage form. These include reduction of dosing frequency by administering the drug once or twice a day (Hayashi *et al*., 2005). Since the frequency of drug administration is reduced, patient compliance can be improved, and drug administration can be more convenient (Nokhodchi *et al.*, 2002) due to reduction of gastrointestinal side effects (Hosny, 1996). Also

causes less fluctuation of plasma drug level and leads to more uniform drug effect and lesser total dose.

On the other hand, controlled release dosage forms have some disadvantages which include, generally higher cost, relatively poor in vitro/in vivo correlation, unpredictable and even reduced bioavailability and subjected to increased first-pass metabolism for certain drugs. In order to exert control over the rate of the drug release, as well as movement of the dosage from through the gastrointestinal tract, a number of factors such as motility, pH, ionic strength of luminal content and differential absorption must be considered (Gupta and Robinson, 1992).

1.3 VARIOUS APPROACHES TO ACHIEVE CONTROLLED RELEASE DRUG DELIVERY

Various techniques have been used in the formulation of controlled release products. In general, controlled release formulations can be divided into different categories based on the mechanism of drug release (Venkatraman *et al*, 2000).

1.3.1 Ion exchange resins

Ion exchange resins are cross-linked water-insoluble polymers carrying ionizable functional groups. The resins have been used in various pharmaceutical applications, primarily for taste masking and controlled release systems. In tablet formulations, ion exchange resins have been used as disintegrants because of their swelling ability. It forms irreversible complex with ionizable drugs upon prolonged exposure of the drug to the resin. A resin bound-drug is removed when

appropriate ions are in contact with ion-exchanged groups. The area and length of diffusion pathway, and the amount of cross-linked polymer in the resin moiety governs the rate of drug release. Sriwongjanya and Bodmeier (1988) investigated the effect of ion exchange resins as release modifiers in matrix formulations containing oppositely charged drugs and they concluded that addition of ion exchange resins to HPMC-matrices significantly modified the release of oppositely charged drug molecules, because a complex formed between the drug and resin retarded the drug release.

1.3.2 Dissolution controlled release

This type of controlled release involves two processes, the 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. The rate of dissolution and the amount dissolved per unit of time from this system can be calculated using Noyes-Whitney equation (1897). Colo *et al*. (2002) investigated the effect of poly-ethylene oxide in the release profile of metformin hydrochloride. They found that a combination of acrylic acid polymer (mainly Eudragit) with PEO could sustain the release of metformin when administered orally.

1.3.3 Diffusion controlled release

In this type of controlled release system, the active ingredient diffuses through the polymeric material. There are mainly reservoir and matrix systems.

1.3.3 (a) Reservoir system

It consists of a core (the reservoir) and coating membrane (the diffusion barrier). The active ingredient diffuses from the reservoir through the coating membrane. For a reservoir system where the drug depot is surrounded by a polymeric hydrogel membrane, Fick's first law of diffusion can be used to describe drug release through the membrane (Lin and Metters, 2006).

1.3.3 (b) Matrix system

A matrix system consists of active and inactive ingredients, that are homogeneously dispersed and mixed in the dosage form. It is by far the most commonly used oral controlled release technology and the popularity of the matrix systems can be attributed to several factors which will be discussed in the later section. The release from matrix type formulations governed by Fick's first law of diffusion.

$$J = \frac{dQ_t}{dt} = -D\frac{dC}{dx} \qquad \text{Eq1.1}$$

J is flux, or rate of diffusion, while Q is the amount diffused per unit of time t, and D is diffusion coefficient.

1.4. ADVANTAGES OF MATRIX SYSTEM

Unlike reservoir and osmotic systems, products based on matrix design can be manufactured using conventional processes and equipments. Secondly, development cost and time associated with the matrix system generally are viewed as variables, and no additional capital investment is required. Lastly, a matrix system is capable of accommodating both low and high drug loading and active ingredients with a wide range of physical and chemical properties.

1.5 LIMITATIONS OF THE MATRIX SYSTEMS

As with any technology, matrix systems come with certain limitations. First, matrix systems lack flexibility in adjusting to constantly changing dosage levels as required by clinical study outcome. When new dosage strength is deemed necessary, more often than not a new formulation and thus additional resources are expected. Furthermore, for some products that require unique release profiles (dual release or delayed plus extended release), more complex matrix-based technologies such as layered tablets are required.

1.6 TYPES OF MATRIX SYSTEMS

The matrix system can be divided into two categories depending on the types of retarding agent or polymeric materials.

1.6. (a) Hydrophobic matrix system

This is the only system where the use of polymer is not essential to provide controlled drug release, although insoluble polymers have been used. As the term suggests, the primary rate-controlling components of hydrophobic matrix are water insoluble in nature. These ingredients include waxes (Zhou *et al*, 1998; Vergote *et al*, 2001; Hayashi *et at*, 2005), glycerides (Yu Ksel *et al*, 2003), fatty acids, and polymeric materials such as ethyl cellulose, methyl cellulose (Makhija and Vavia. 2002; Crowley *et al.*, 2004) and acrylate copolymer (Azarmi *et al.*, 2002; Krajacic and Tucker. 2003). To modulate drug release, it may be necessary to incorporate soluble ingredients such as lactose into formulation. The presence of insoluble ingredient in the formulations helps to maintain the physical dimension of hydrophobic matrix during drug release. As such, diffusion of active ingredient from the system is the release mechanism (Kincl *et al.*, 2004), and the corresponding release characteristic can be described by Higuchi equation known as square root of time release kinetic (Higuchi, 1963). The square root of time release profile is expected with a porous monolith, where the release from such system is proportional to the drug loading. In addition, hydrophobic matrix systems generally are not suitable for insoluble drug because the concentration gradient is too low to render adequate drug release. As such, depending on actual ingredient properties or formulation design, incomplete drug release within the gastrointestinal transit time is a potential risk and need to be delineated during the development. With the growing needs for optimization of therapy, matrix systems providing programmable rates of delivery become more important. Constant rate

delivery always has been one of the primary targets of controlled release system especially for drug with narrow therapeutic index (Liu *et at.,* 2006).

1.6. (b) Hydrophilic matrix system

The primary rate limiting ingredients of hydrophilic matrix are polymers that would swell on contact with aqueous solution and form a gel layer on the surface of the system. When the release medium (i.e. water) is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process, due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the encapsulated drug to diffuse more rapidly out of the matrix. On the other hand, it would take more time for drug to diffuse out of the matrix since the diffusion path is lengthened by matrix swelling. Moreover, it has been widely known that swelling and diffusion are not the only factors that determine the rate of drug release (Sujja-areevath *et al.*, 1998). For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug delivery rate. While either swelling or dissolution can be the predominant factor for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms (Tahara *et al.*, 1995). The presence of water decreases the glassy-rubbery temperature (for HPMC from 184°C to below 37°C), giving rise to transformation of glassy polymer to rubbery phase (gel layer). The enhanced motility of the polymeric chain favours the transport of dissolved drug. Polymer relaxation phenomena determine the

swelling or volume increase of the matrix. Depending on the polymer characteristics, the polymer amount in the rubbery phase, at the surface of the matrix, could reach the disentanglement concentration; the gel layer varies in thickness and the matrix dissolves or erodes. The concentration at which polymeric chains can be considered disentangled was demonstrated to correspond to an abrupt change in the rheological properties of the gel. Boniferoni *et al*. (1995) showed a relationship between rheological behaviour of HPMC gels and their erosion rate, conforming that the polymer-polymer and polymer-water interaction are responsible for the gel network structure and its sensitivity to erosion. In turn, they affect drug release rate in the case of poorly soluble drugs.

Swelling controlled release systems are based upon these principles. Due to the viscoelastic properties of the polymer which are enhanced by the presence of cross-linked network, anomalous penetrant transport can be observed. This behaviour is bound by pure Fickian diffusion and case II transport. Therefore, transport can be reduced to three driving forces. The penetrant concentration gradient, polymer concentration gradient and osmotic force behavior are observed as a result of polymer network. Appropriate polymer can counterbalance normal Fickian diffusion by hindering the release of embedded drug, leading to an extended period of drug delivery, and possibly zero-order release (Cox *et al.*, 1999).

Drug release from swellable matrix tablets can be affected by glassy-rubbery transition of polymer (as a result of water penetration into the matrix where interaction among water, polymer and drug or fillers is considered as the primary factor for release control) and the various formulation variables, such as polymer grade and type, drug to polymer ratios, drug solubility, drug and polymer particle sizes, compaction pressure and presence of additives or excipients in the final formulation. Lotfipour *et al*. (2004) investigated the effect of various polymers, fillers, and their concentration on the release rate of atenolol form polymeric matrix. They concluded that, the release rate and mechanism of atenolol releases from hydrophobic and hydrophilic matrices are mainly controlled by the drug to polymer ratio. The results also showed that an increase in the concentration of fillers resulted in an increase in the release rate of the drug from matrices and hydrophilicity or hydrophobicity of the fillers had no significant effect on the release profile. Regarding the mechanism of release, the results showed that in most cases the drug release was controlled by both diffusion and erosion depending on the polymer type and concentration. On the other hand, incorporation of water soluble fillers like polyethylene glycol, lactose and surfactant into gel forming matrices can improve phenomenon of insufficient drug release, because these excipients can enhance the penetration of the solvent or water into the inner part of matrices, resulting in drug release from the matrices (Genç, *et al.*, 1999; Nokhodchi *et al.*, 2002).

1.7. POLYMERS USED IN HYDROPHILIC MATRICES

Hydrogel polymers were much investigated in literature on basis of drug release and release mechanism from hydrophilic matrix tablets as well as pellets. HPMC polymers achieve considerable attention due to their unique properties, and they can display good compression characteristics, including when directly compressed. They are nontoxic and can accommodate high level of drug loading, and also having adequate swelling properties that allows rapid formation of an external gel layer which retards or plays a major role in controlling drug release. Furthermore, HPMC polymers are well known as pH-independent materials, this advantage enable them to withstand fluctuations of pH induce by intra and inter-subject variations of both gastric pH and gastrointestinal transit time. They have been used alone or in combination in formulation of matrix tablets, therefore the hydrophilic gel forming matrix tablets are extensively used for oral extended release dosage forms due to their simplicity, cost effectiveness and reduction of the risk of systemic toxicity which happens as a result of dose dumping (Sung *et al.*, 1996; Huang *et al.*, 2004). Soliman *et at.* (2003) investigated the release of diclofenac sodium from a mixture of HPMC, Carbopol 940, and lactose as water soluble fillers. The results showed that the combination of hydrogels retarded the drug better than single polymer.

The principal advantage of HPMC matrix formulations is the drug release rates are generally independent of processing variables such as compaction pressure, drug particle size, increasing of initial granulation liquid and incorporation of lubricants

(Lapidus and Lordi, 1968; Nochochi *et al*., 2002). The relationship between particle size, tensile strength and the viscosity grade of HPMC was complicated. At smaller particle size, an increase in the viscosity grade of HPMC resulted in a reduction in the tensile strength of its compacts. However, at the large particle size, the tensile strength of HPMC compacts decreased with an increase in viscosity grade. For HPMC K100M, there was an increase in tensile strength (Nokhodchi *et al.*, 1995). The combination of HPMC and HPC at different ratios was investigated. Increasing the HPMC-HPC ratio increased both the particle size of granules and the tablet hardness (Ebube *et al.*, 1997). The drug release of HPMC matrix tablets was slightly influenced by type and concentration of diluents, but the viscosity grade of the polymer did not affect the release mechanism (Vueba *et al.*, 2004).

Ishikawa *et at*. (2000) reported an increase in crushing strength of tablets made of Macrogol 6000 and HPMC, due to an increase in compression force during tableting stage and the dissolution of formulated tablet was significantly affected by increasing HPMC concentration.

Huang *et al*., (2004) developed once daily propranolol extended release tablets using HPMC polymer as a retarding agent. The mechanism of the drug release from HPMC matrix tablet followed non-Fickian diffusion, while the in vivo absorption and in vitro dissolution showed a linear relationship.

Other polymers used in hydrophilic matrix preparations include poly ethylene oxide (Sriwongjanya and Bodmeier., 1998; Maggia *et al.*, 2003), hydroxypropyl cellulose (Ferrero *et al.*, 1997) and hydroxyl ethyl cellulose.

Xanthan gum (XG) was widely used as a thickening agent in food industries, but recently introduced in pharmaceutical formulations (Talukdar and Kinget. 1995; Ntawukulilyayo *et al.*, 1996; Talukdar *et al.*, 1996; Tobyn *et al.*, 1996; Talukdar and Kinge. 1997; Talukdar *et al.*, 1998; Helton *et al.*, 2004; Santos *et al.*, 2004; Santos *et al.*, 2005; Veiga-Santos *et al.*, 2005). It is a high molecular weight extracellular heteropolysaccharide, produced by fermentation with the gram-negative bacterium *Xanthamonas campestris.* XG shows excellent swelling properties and the swelling of the XG polymer matrix shows a square root of time dependence whereas drug release is almost time independent (Talukdar and Kinget, 1995).

Carbopol is a derivative of polyacrylic acid. It is a synthetic, high molecular weight, crosslinked polymer. It is readily hydrates, absorbs water and swell. In addition, its hydrophilic nature and highly crossliked make it a potential candidate and has been used in controlled release drug delivery systems (Khan and Jiabi, 1998; Wong *et al.*, 1999; Juang and Storey, 2003; Ikinci *et al.*, 2004; Tapia and Villafuerte, 2004). In the case of tablets formulated with Carbopol polymer, the drug is entrapped in the glassy rubbery core in the dry state. It forms a gelatinous layer upon hydration. However, this gelatinous layer is significantly different structurally from the traditional matrix tablets. The hydrogel is not entangled chains

of polymer, but discrete microgel made up of many polymer particles in which the drug is dispersed. The crosslinked network enables the entrapment of drug in the hydrogel domains. Since these hydrogels are not water soluble they do not dissolve, and erosion in the manner of linear polymer does not occur. Rather, when the hydrogel is fully hydrated, osmotic pressure from within works to break up the structure, essentially by sloughing off discrete pieces of the hydrogel. This hydrogel remains intact, and the drug continues to diffuse through the gel layer at a uniform rate (Khan and Jiabi, 1998).

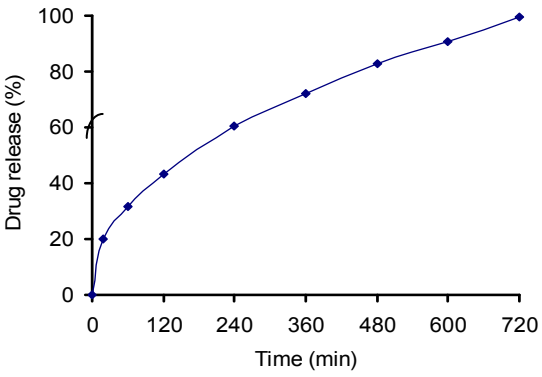
It is well recognized that key formulation variables are matrix dimension and shape, polymer level and molecular weight, as well as drug loading and solubility. Other factors such as tablet hardness, type of inactive ingredients and processing normally play secondary roles. The choice of manufacturing process such as direct blending or granulation typically des not affect product performance significantly, although exception does exist. In general, processing and scale-up associating with hydrophilic matrices are more robust than other controlled release systems.

1.8 COMPARISON OF HIGUCHI WITH ZERO-ORDER RELEASE MECHANISMS

Drug release from matrix tablets becomes progressively slower with time (Higuchi, 1963). This is in contrast to the ideal situation in which the drug is released from

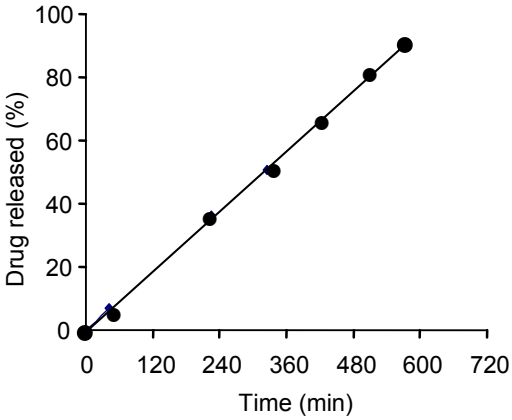
the tablets at the same rate throughout the release period. Higuchi profile is compared with the ideal release pattern (zero-order release profile) in Figure 1.1

The reason for the attenuation of the drug release rate in Higuchi profile is illustrated in Figure 1.2. When a matrix tablet is placed in the dissolution medium, the initial drug release occurs from the tablet superficial layer and, consequently, the release rate is relatively fast. As time passes, the external layers of the tablet become depleted of the drug and water molecules must travel through long, tortuous channels to reach the drug remaining in the deeper layer of the tablet. Similarly, the drug solution that is formed within the tablet must diffuse through long capillaries to reach the external dissolution medium. The primary reason for continuously decreasing rate of drug release is the more the matrix swells, the longer the diffusion pathlength required for the drug to come out. Therefore, any mechanism that lessens the time–dependent increase in the diffusion pathlength would reduce the attenuation of the dissolution (Talukdar *et al.*, 1996; Pather *et al.*, 1998).



$Q = Kt^{1/2}$

(a)

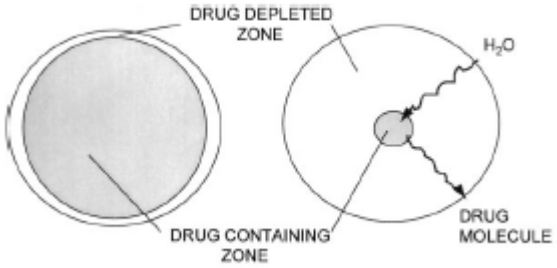


$Q = kt$

(b)

Figure 1.1 Comparison between (a) Higuchi and (b) zero-order release profiles.

(Adapted from Pather *et al*. 1998)



Initial stage Final stage

Figure 1.2 Diagrammatic representation of drug release according to Higuchi model

(Adapted from Pather *et al.,* 1998)

1.9 GLICLAZIDE

Gliclazide, 1-(4methylbenenesulphonyl) 3-(3azabicyclo [3.3.o] octyl) urea, is a second generation sulphonylurea oral hypoglycemic agent used in the treatment of non-insulin-dependant diabetes mellitus (NIDDM). It improves defective insulin secretion and may reverse insulin resistance observed in patients with NIDDM or known as type two diabetes. These actions are reflected in blood glucose level which is maintained during short and long term administrations, and is comparable with that achieved with other sulphonylurea agents (Palmer and Brogden, 1993).

Gradually accumulating evidence suggests that gliclazide may be useful in patients with diabetes retinopathy, due to its hematological actions, and that addition to insulin therapy enables insulin dosage to be reduced (Schernthaner, 2003).

Gliclazide is an effective agent for the treatment of the metabolic disorder associated with NIDDM and may have the added advantage of potentially slowing the progression of diabetic retinopathy. These actions, together with its good tolerability and low incidence of hypoglycemia, allow gliclazide to be well placed within the array of oral hypoglycemic agents available for the control of NIDDM.

1.9.1 Pharmacodynamic

Gliclazide reduces blood glucose levels in patients with NIDDM by correcting both defective insulin secretion and peripheral insulin resistance. Un-stimulated and

stimulated insulin secretions from pancreatic ß cells are increased following the administration of gliclazide, with both first and second phases of secretion being affected. This occurs via binding of gliclazide to specific receptor on pancreatic ß cells which results in a decrease in potassium efflux and causes depolarization on the cell. Subsequently, calcium channels open, leading to an increase in intracellular calcium and induction of insulin release. In addition, gliclazide increases the sensitivity of ß cells to glucose (Palmer and Brogden, 1993).

Gliclazide may have extra pancreatic effect which restores peripheral insulin sensitivity, such as decreasing hepatic glucose production, and increasing glucose clearance and skeletal muscle glycogen synthesis activity. These effects do not appear to be mediated by effect on insulin receptor number, affinity or function. There is some evidence that gliclazide improves defective hematological activity in patients with NIDDM (Riccio *et al*., 1996).

1.9.2 Pharmacokinetic properties

Oral absorption of gliclazide is similar in patients and healthy volunteers, but there is intersubject variation in time to reach peak plasma concentrations (t_{max}). Ages related differences in plasma peak concentrations (C_{max}) and t_{max}, have been observed. A single oral dose of 40 to 120 mg of gliclazide results in a C_{max} of 2.2 to 8.0 µg/ml within 2 to 8 hours. T_{max} and c_{max} are increased after repeated gliclazide administration. Steady state concentration is achieved after 2 days administration of 40 to 120 mg of gliclazide. Gliclazide has low volume of distribution (13 to 24L)

in both patients and healthy volunteers due to its high protein binding affinity (85 to 97%) (Najib *et al.,* 2002). The elimination half-life ($t_{1/2}$) is about 8.1 to 20.5 hr in healthy volunteers and patients after administration of 40 to 120 mg orally. Moreover, its plasma clearance is 0.78 L/h (13 ml/min). It is extensively metabolized to 7 metabolites and excreted in urine therefore renal insufficiency has no effect in pharmacokinetic of gliclazide.

The variability in absorption of gliclazide could be related to its early dissolution in the stomach leading to more variability in the absorption in the intestine (Delrat *et al.*, 2002). This process resulted in low bioavailability of the conventional dosage forms. The use of solubilizing agents like PEG 400 was reported to increase the bioavailability of gliclazide in its oral dosage forms (Hong *et al.*, 1998). Also gliclazide was included with α-cyclodextrin or β-cyclodextrin (Winters. *et al.*, 1997; Maria *et al.*, 1998).

1.9.3 Dosage and administration

Gliclazide is administrated for the treatment of NIDDM which know as type two in patient who failed to respond to dietary restriction. The drug is administered in doses range from 40 to 320 mg/day as tablets once to three times daily. Recently, modified release formulations containing 20 mg or 30 mg of gliclazide has been developed to obtain a better predictable release of active principle (Delrat *et al.*, 2002; Miwa *et al.*, 2004).

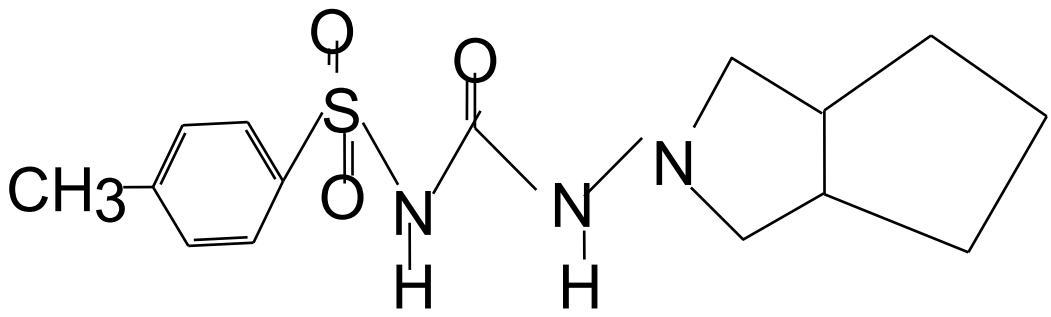


Figure 1.3 Chemical structure
of gliclazide

1.10 PROBLEM STATEMENT

At present, patients have to take one or more doses of conventional or sustained release gliclazide tablets, to maintain normal plasma glucose levels. Currently, the gliclazide tablets available in the market have not yet attained the physiological goal of providing constant plasma glucose levels over an extended period of time to meet the basal needs between meals and during the night. If there was a formulation of gliclazide that could provide adequate control of glucose level for an extended period of time without any hypoglycaemic symptoms (Crepaldi and Fioretto, 2000), patients could be relived from the necessity of taking 1-4 tablets of 80 mg of gliclazide daily. Such a formulation would be a helpful not only to improve the patients' conditions and convenience but also to reduce the risk of prevalence of other diseases associated with diabetes mellitus.

Currently, a lot of researches are carried out to prepare prolonged release gliclazide tablets with pharmacokinetic characteristics suited to the circadian glycemic profile of type two diabetes. This approach will minimize the complications associated with diabetes mellitus (Al-kassas *et al*., 2007). Diamicron MR (30 mg gliclazipe) is available but very expensive. The development of a generic version of gliclazide will reduce the price of drug and make the drug more affordable to the patients.

1.11 SCOPE OF THE PRESENT STUDY

The aims of the present study were to design and evaluate prolonged release gliclazide matrix tablets.

The study was carried out in the following stages.

1. Development and in vitro evaluation of gliclazide matrix tablets.
2. Development of HPLC-UV method for quantification of gliclazide concentration in rabbit plasma.
3. In vivo evaluation of gliclazide matrix tablets using rabbits

CHAPTER 2

PREPARATION OF PROLONGED RELEASE GLICLAZIDE MATRIX TABLETS

2.1 INTRODUCTION

Tablet is one of the most common and popular oral pharmaceutical dosage forms. Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration, least aseptic constrain and flexibility in the design of the dosage form. Normally, a tablet contains a single dose of one or more active substances with excipients (such as diluents, binders, disintegrating agents, glidents and lubricants), and is usually obtained by compressing uniform volume of particles using a tableting machine, to provide a single rigid body of defined mechanical strength. Tablets can exist in many geometrical shapes. They are usually circular solid cylinders, the end surface of which are flat or convex and the edges of which may be beveled. Most recently, there are even the development of multiparticulate dosage forms into compressed tablet to overcome the high production cost of encapsulating them into hard gelatin capsules (Marshall and Rudnick, 1990; Santos *et al.*, 2004)

It is well known that modified release dosage forms may offer one or more advantages over immediate release formulation of the same drug. The design of modified release drug product is usually intended to optimize therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval, and also to increase patient compliance (Gupta and Robinson,

1992). There are many ways to design modified release dosage form for oral administration. These include film coated pellets, tablets or capsules to more sophisticated and complicated delivery systems such as somatically driven system, system of controlled release by ion exchange mechanism, system using the three dimensional printing technology and system using electrostatic deposition technology (Abdul and Podar, 2004).

Some of the common controlled release matrix delivery systems are in the forms of tablets, pellets and granules, where the drug is uniformly dissolved or dispersed throughout the polymer matrix. Many researches have been carried out to investigate the drug release mechanisms and effects of polymer concentration on the release rate of drug from both the hydrophilic and hydrophobic matrices (Ford *et al.*, 1987; Ford *et al.*, 1991; Nokhodchi *et al.*, 1995; Tahara *et al.*, 1995; Sung *et al.*, 1996; Mosquera *et al.*, 1996). For example, the use of hydrophilic polymers, in particular cellulose derivatives in the formulation of pharmaceutical product, due to their gel-forming ability in aqueous medium (Ford *et al.*, 1991). It is reported that the hydration rate of cellulose ether polymers depends mainly on the nature of the substituent present and the degree of the substitution (Roy and Rohera, 2002). In addition, the penetration of the dissolution medium into the cellulose matrix formulation depends also on the type of fillers used (Sako *et al.*, 2002; Lotfipour *et al.*, 2004). On the other hand, the release rate from hydroxypropyl methylcellulose (HPMC) matrices is influenced by the concentration and viscosity grade of the polymer in the formulation (Campos-Aldrete *et al.*, 1997; Ebube *et al.*, 1997; Samani *et al.*, 2003). However, the major disadvantage associated with HPMC

matrices was that the release of drug did not follow a time-independent kinetics (Ford *et al.*, 1985; Rao and Devi, 1988).

Most of the above mentioned works on the fabrication of modified release dosage forms utilized wet granulation method to increase the uniformity of drug distribution in the final product, densify the material, enhance the flow rate, facilitate volumetric dispensing, reduce dust and improve the appearance of the product. In addition, other advantages of wet granulation include preventing segregation of powder mix and enhancing hydrophobic surface to be more hydrophilic. Despite of all these advantages, wet granulation has disadvantages such as loss of material during various processing stages and inactivating active constituents that are affected by moisture (Parikh, 1997).

The aim of this study was to formulate matrix tablets of gliclazide with a controlled drug release over a 12-hour period. For this purpose, HPMC, Carbopol 940, Xanthan gum, Kollidon SR, and Eudragits (RSPO and RLPO), were chosen as the matrix forming polymeric materials. The influence of polymer type and concentration on the physical properties and dissolution of the tablets were investigated. Moreover, the effects of pH of the dissolution medium and stirring rate on drug release as well as the release mechanism of a selected formulation were examined.