DEVELOPMENT AND EVALUATION OF MATRIX CONTROLLED RELEASE FORMULATIONS OF KETOPROFEN

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DEVELOPMENT AND EVALUATION OF MATRIX CONTROLLED RELEASE FORMULATIONS OF KETOPROFEN

by

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This thesis is dedicated to my beloved parents, wife, sons Amiruddin Khan,

Izharuddin Khan, and my brother Nasiruddin Khan

May Allah bless them

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Jiyauddin Khan

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LIST OF ABBREVIATION & SYMBOLS

Abbreviation		Full description
ACC	=	Accuracy
ACN	=	Acetonitrile
AR	=	Analytical regent
ANOVA	=	Analysis of variance
AUC	=	Area under curve
AUC_{0-t}	=	Total area under the plasma concentration-time curve from the time zero to the last sampling time, 0-t
$AUC_{t-\infty}$	=	Total area under the plasma concentration-time curve from the last sampling time to infinity, t-∞
$AUC_{0-\infty}$	=	Total area under the plasma concentration-time curve from the time zero to infinity, 0-∞
AUFS	=	Absorbance Units Full Scale
BCS	=	Biopharmaceutics Classification System
BD	=	Below detection
BMI	=	Body Mass Index
BP	=	British Pharmacopoeia
cm	=	Centimeter
CR	=	Controlled release
CV	=	Coefficient of variation
C_{max}	=	The peak plasma concentration
°C	=	Degree centigrade
DC	=	Direct compression
DF	=	Degree of freedom
E	=	Erosion

EC	=	Ethyl cellulose
et al.,	=	Elsewhere or add others
etc.	=	Et cetera
F	=	Formulation
f_2	=	Similarity factor
Fig.	=	Figure
FDA	=	Food and Drug Administration
g	=	Gram
GIT	=	Gastro intestinal tract
HPC	=	Hydroxypropylcellulose
HEC	=	Hydroxyethylcellulose
HPMC	=	Hydroxypropylmethylcellulose
HPLC	=	High performance liquid chromatography
HSD	=	Honestly Significant Difference
hr	=	Hour
IS	=	Internal standard
IU	=	International units
K	=	Korsmeyer-Peppas kinetic release constant
K_0	=	Zero-order release rate constant
K_1	=	First-order release rate constant
K_C	=	Cube-root law release rate constant
K_e	=	Elimination rate constant
K_H	=	Higuchi rate constant
KSR	=	Kollidon® SR
kg	=	Kilogram

L	=	Liter
LOD	=	Limit of detection
LOQ	=	Limit of quantification
m	=	Meter
M	=	Molar
mg	=	Milligram
mL	=	Milliliter
mm	=	Millimeter
MOH	=	Ministry of health
MR	=	Modified release
MS	=	Mean square or, variance
MCC	=	Microcrystalline cellulose
MDT	=	Mean dissolution time
n	=	Release or, slope exponent
N	=	Newton
pKa	=	Dissociation constant
PVA	=	Polyvinyl acetate
PVP	=	Polyvinyl pyrrolidone
PS-630	=	Plasdone® S-630
Q_0	=	Amount of drug in the solution
Q_∞	=	Cumulative amount of drug remaining in the matrix in time t
Q_t	=	Cumulative amount of drug released in time t
Q_t/ Q_∞	=	Fraction of drug release at time t
r	=	Correlation coefficient
r^2	=	Regression coefficient

R	=	Reference/ reference product
RP-HPLC	=	Reversed-phase high performance liquid chromatography
RPM	=	Rotation per minute
RSD	=	Relative standard deviation
S	=	Swelling
SD	=	Standard deviation
SEM	=	Standard error of mean
Sig	=	Significance
SR	=	Sustained release
SS	=	Sum of squares
SPSS	=	Statistical procedures for social science
T	=	Test/ test formulation
$T_{50\%}$	=	Time for 50% of drug release
T_{max}	=	Time taken to reach maximum plasma concentration
$T_{1/2}$	=	Elimination half-life
UV	=	Ultra violet
UK	=	United kingdom
USA	=	United State of America
USP	=	United State Pharmacopeia
USFDA	=	United States Food and Drug Administration
v/v	=	Volume by volume
W_d	=	Dry matrix weight
W_s	=	Swollen matrix weight
w/v	=	Weight by volume
w/w	=	Weight by weight

XG	=	Xanthan gum
µg	=	Microgram
µL	=	Microliter
µm	=	Micrometer
µg/mL	=	Microgram per milliliter
%	=	Percent
<	=	Less than
>	=	Greater than

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PEMBANGUNAN DAN PENILAIAN FORMULASI-FORMULASI MATRIKS PELEPASAN TERKAWAL BAGI KETOPROFEN

ABSTRAK

Kajian ini dijalankan untuk menyiasat kesesuaian pelbagai polimer hidrofilik dan hidrofobik atau gabungan-gabungan mereka, sebagai bahan-bahan pembentuk matriks untuk pembangunan formulasi tablet pelepasan terkawal ketoprofen dengan prestasi *in vitro* dan *in vivo* yang setanding dengan sediaan tablet Apo-Keto SR® yang sudah dipasarkan. Dengan ini, pelbagai formulasi pelepasan terkawal matriks tablet ketoprofen telah dibangunkan dengan menggunakan bahan-bahan polimer hidrofilik, hidrofobik yang berbeza serta campuran-campurannya. Kesemua formulasi telah disediakan dengan menggunakan kaedah pemampatan terus. Profil pelarutan *in vitro* formulasi-formulasi telah dibandingkan dengan produk rujukan tablet Apo-Keto SR® yang boleh diperolehi secara komersial. Faktor kesamaan (f_2), nilai-nilai antara formulasi ujian dan produk rujukan juga telah dikira untuk pemilihan formulasi yang optimum. Daripada kesemua formulasi matriks yang telah dikaji, tablet-tablet yang mengandungi 20% HPC (GXF) sebagai pembentuk matriks menunjukkan profil pelarutan yang setanding dengan rujukan. Nilai f_2 antara tablet-tablet rujukan dan tablet-tablet matriks dengan 20% HPC (GXF) ialah 78.0%, dan oleh itu telah dipilih untuk siasatan lanjut. Pelepasan drug dari rujukan dan formulasi matriks dengan 20% HPC (GXF) telah dikawal oleh kedua-dua mekanisme resapan dan hakisan seperti dalam persamaan Korsmeyer-Peppas. Tambahan pula, formulasi yang telah dioptimasikan didapati stabil untuk tempoh 12 bulan dalam simpanan pada 25ºC suhu bilik untuk stabiliti jangkamosa panjang. Satu kaedah UV HPLC telah dibangunkan dan disahkan untuk pengenalpastian ketoprofen dalam plasma manusia. Satu kajian *in vivo* kemudian dikendalikan dengan 6 sukarelawan manusia

yang sihat untuk membandingkan prestasi formulasi ujian itu dengan produk rujukan komersial. Kajian dikendalikan mengikut rekabentuk kajian dos tunggal, rambang, 2-rawatan, 2-turutan, pindah silang 2-tempoh. Keputusan statistik menunjukkan bahawa tidak ada perbezaan signifikan antara parameter-parameter farmakokinetik $T_{max,}$ C_{max}, dan $AUC_{0-\infty}$ produk rujukan dan formulasi ujian. Selang keyakinan 90% nilai-nilai purata untuk nisbah ujian/rujukan ialah 96.9-107.0% untuk $AUC_{0-\infty}$ dan 99.6-104.6% untuk $C_{max,}$ masing-masing. Maka, kadar dan takat penyerapan formulasi ujian adalah setanding dengan produk rujukan. Secara kesimpulan, satu tablet pelepasan terkawal matriks ketoprofen yang stabil telah berjaya dibangunkan, yang mempamerkan profil pelarutan *in vitro* yang serupa serta prestasi *in vivo* setanding dengan tablet rujukan Apo-Keto SR® yang telah dipasarkan.

DEVELOPMENT AND EVALUATION OF MATRIX CONTROLLED RELEASE FORMULATIONS OF KETOPROFEN

ABSTRACT

The present study was conducted to investigate the suitability of various hydrophilic and hydrophobic polymers or their combination, as matrix forming materials for the development of a controlled release tablet formulation of ketoprofen with *in vitro* and in *vivo* performance comparable to that of the marketed preparation Apo-Keto SR® tablets. In this regard a number of matrix controlled release formulations of ketoprofen tablets were developed using different hydrophilic, hydrophobic and mixtures of both polymeric materials. All the formulations were prepared by direct compression method. Their *in vitro* dissolution profiles were compared to that of the commercially available reference product Apo-Keto SR® tablet. Similarity factor (f_2), values between test formulations and reference product were also calculated to select the optimum formulation. Out of all the matrix formulations studied, tablets containing 20% HPC (GXF) as matrix former showed comparable dissolution profile to that of the reference. The f_2 value between reference and matrix tablets with 20% HPC (GXF) was 78.0%, and hence it was selected for further investigation. The drug release from reference and matrix with 20% HPC (GXF) formulation was governed by both diffusion and erosion (anomalous) mechanism as per Korsmeyer-Peppas equation. Moreover, the optimized formulation was found to be stable for a period of 12 months upon storage at 25ºC of room temperature for a long term of stability. A HPLC UV method was developed and validated for the determination of ketoprofen in human plasma. An *in vivo* study was then conducted in 6 healthy human volunteers to compare the performance of the test formulation with the commercial reference product. The study was performed according to a single dose, randomized,

2-treatment, 2-sequence, 2-period crossover study design. The statistical results showed that there was no significant difference between pharmacokinetic parameters of $T_{max,}$ C_{max}, and $AUC_{0-\infty}$ of reference product and test formulation. The 90% confidence intervals of the mean values for the test/reference ratios were 96.9-107.0% for $AUC_{0-\infty}$ and 99.6-104.6% for $C_{max,}$ respectively. Hence, the rate and extent of absorption of test formulation were comparable to the reference product. In conclusion, a stable matrix controlled release tablets of ketoprofen was successfully developed, which exhibited similar *in vitro* dissolution profile as well as *in vivo* performance as that of marketed reference tablet of Apo-Keto SR®.

CHAPTER 1 INTRODUCTION

1.1 Oral controlled release dosage forms

The oral route is the most popular, convenient and traditionally preferred mode of drug administration because of its ease and convenience to the patients. Ideally, an oral dosage form should deliver the drug at a designated location, at a specified rate, for a specific period of time (Juliano, 1980; Szycher, 1991). Once the drug is administered orally, it dissolves in the gastro intestinal fluids and gets absorbed into the systemic circulation. Blood is usually the medium of transport for the absorbed drug, thus the ideal plasma concentration levels which produces optimal therapeutic activity must be obtained. However, the drug delivery targets could only be achieved in part through conventional dosage forms (Lee and Good, 1987).

Conventional dosage forms are designed to release their content without delay for absorption so that maximal rate and extent of absorption can be achieved. Hence, wide fluctuations in peak and trough steady-state drug levels are frequently obtained with these products with multiple dose administration, particularly for drugs having short biological half-lifes (Roda *et al.,* 2002). By increasing the frequency of dosing, it may be possible to reduce such undesirable fluctuations particularly with drugs of narrow therapeutic indices. However, this may lead to patient inconvenience and poor compliance. In order to overcome this problem, various sustained release formulations have been developed to improve the therapeutic performance of drugs, such as to increase pharmacological efficacy with reduced side effects (Pather *et al.,* 1998; Sanchez-Lafuente *et al*., 2002; Kramar *et al.,* 2003).

In recent years, controlled release dosage forms have made great progress in terms of improving clinical efficacy and patient compliance (Reza *et al.,* 2003). An ideal controlled release formulation should release its drug at a constant rate and provide constant drug levels in plasma with reduced fluctuation over a time period, such that the duration of its therapeutic effect is sustained.

One of the first attempts in the formulation of oral controlled release dosage forms was made by the German dermatologist, Paul G. Unna in 1884, in which the pills were coated with a thin film of keratin that would not dissolve in acidic gastric fluid but instead, dissolve in the intestine. In this way, he was among the first to introduce the enteric coating technique (Helfand and Cowen, 1982).

A commercial controlled release preparation, namely Dexedrine Spansule® capsule was among the first to be introduced to the market in 1945 by Smith, Kline and French Laboratories (SK & F). It employed a coating technique described by Blythe (1956; 1958a; 1958b). The preparation consisted of many small coated pellets, which in spite of the environment would release the therapeutic substance at controlled rates. In this method, nonpareil seeds were first coated with the drug and the obtained beads were further coated in coating pans by applying or spraying a mixture of lipid substances. The lipid substances used were glyceryl mono-, di-, and tristearate and carnauba wax dissolved in organic solvent. Finally, the coated pellets of 1 to 2 mm in diameter were mixed with non coated ones and delivered in a gelatin capsule called a spansule (Swintosky, 1963).

Saunders (1961) suggested that controlled release of ionic drugs could be obtained by binding them with ion-exchange resins. Swintosky (1963) introduced the first liquid preparation of controlled release dosage form for oral administration in 1959, which was an aqueous suspension of drug granules, 35 μm in diameter, coated by hydrogenated castor oil and ethyl cellulose.

Matrix tablets called the Duretter® which was produced by compressing granules to form plastic matrices (Fryklof *et al.,* 1959) were introduced in 1959 (British Patent No. 808014). Since then, various sustained release product have been introduced with their mechanism of release being described by such names as extended release, sustained action, prolonged action, long acting and extended action preparations (Gupta, 1999). Also, from then on, many sustained or modified release products have been introduced into the market.

The design and formulation of the early sustained release products in the 1950s were not without problems. At this time, the science of biopharmaceutics and pharmacokinetics was still in its infancy. As a result, these early products were formulated with little or no consideration of the absorption and disposition characteristics of the drug in the body. Also, the lack of appropriately sensitive analytical techniques at that time presumably made evaluation of the blood levels impossible. Thus the efficacy of these formulations could only be assessed by pharmacological methods which were often unreliable or even inapplicable to the drug under test. As the fields of biopharmaceutics and pharmacokinetics were better developed, the shortcomings of these old products became evident. Some of these old products were eventually withdrawn and improvements were made in the newer

formulations. Towards the end of 1960's, a new phrase, controlled drug delivery was introduced. This term was applied to those formulations in which the rate of dissolution of drug from the dosage forms was controlled. Such products have enhanced bioavailability, efficacy and safety (Banker, 1979; Banker and Anderson, 1986; 1987; 1991; Banakar, 1991).

Significant progress has been made in this area in the past two decades, and today, sustained release formulations have become an important product line of most major drug companies. A variety of techniques have been used in the formulation of these products but they all basically work on the same principle of slowing the rate of dissolution or release of the drug from the dosage form. In general, there are two sets of methods to achieve this objective (Lordi, 1986). The first set is based on modification of those physical and/or chemical properties of the drug that affect bioavailability. These include the use of complex formulation (example tannate complexes), ion-exchange resins to form drug adsorbates, and prodrug synthesis. The mechanism of sustained drug release is through decreased rate of dissolution of the altered drug and/or dissociation of the free drug into solution. In the case of prodrugs, a slow regeneration of the parent compound after absorption may provide an additional strategy for prolonging the drug action. A major advantage of this approach is that it operates independently from the dosage form. The resulting drug modifications can thus be formulated as liquid suspensions, capsule or tablet. However, these methods can only be applied to drug moieties containing the appropriate functional groups.

In contrast, the second sets of methods are based on modification of the drug release characteristics of the dosage form. Although products based on dosage form modification are of many designs and constructions, the mechanisms underlying the sustained release are few (Lee and Robinson, 1978). A drug with a slow dissolution rate is inherently sustained. For those drugs with rapid dissolution, embedding them within a slowly dissolving or erodible matrix provides a means of retarding the dissolution rate. Various lipid materials, waxes and other polymers have been found to be useful for this purpose. Drug release occurs through a combination of leaching of the active substance from the matrix and erosion of the matrix material. Another approach is to disperse the drug within an insoluble matrix. The most common insoluble matrix is one which is porous in nature, containing small channels and passages which are filled with drug. *In vivo*, fluids from the gastrointestinal tract penetrate and dissolve the drug, and the dissolved molecules then diffuse from these passages out of the matrix. Drug release is thus delayed as the dissolved molecules have to diffuse through a network of capillaries between the compact polymer particles forming the matrix. The kinetics of release from such matrices have been well studied by Higuchi (1963).

Thus, coating the drug particles or pellets with a barrier membrane is an effective means of controlling the drug release. The barrier coat can either be slowly soluble or insoluble in nature. In the former case, the pellets release their contents through erosion of the coat. A typical product utilizing this release mechanism may consist of a capsule containing numerous pellets coated to various thicknesses with some erodible material. Since the rate of erosion of the coat can be expected to be dependent on the coat thickness, such a product will yield a relatively continuous

drug release. The ‘Spansule’ dosage form discussed earlier was based on this design (Blythe, 1956). A variation of this method is to coat the pellets with different coating materials of different dissolution or disintegration times, or successively coating a spherical pellet, in between which, is placed the active drug (Hermelin, 1957). A second mechanism whereby coated pellets release their medicaments is by diffusion of the drug through the intact coat. Following ingestion, moisture within the gastrointestinal tract penetrates the coat to dissolve the solid drug. The dissolved drug molecules then diffuse through the intact barrier membrane. The rate of drug release can be controlled by varying the nature and/or thickness of the coat or by altering its porosity by incorporating some water soluble materials into the coat to act as channeling agents. It is interesting to note that osmosis has recently been suggested as an important mechanism for the drug release from such systems (Zentner *et al.,* 1985; Lindstedt *et al.,* 1989; Ozturk *et al.,* 1990; Lindstedt *et al.,* 1991).

Formulations in which osmosis pumping is a major release mechanism was described by Theeuwes in 1975. In this approach, the osmotically active solid, namely the drug or dispersion thereof is surrounded by a rigid rate-controlling membrane which is semipermeable with respect to water. Uptake of water through the rigid membrane at a controlled rate will cause the device to deliver, via an orifice in the membrane, a volume of saturated drug solution equal to the volume of water imbibed. The rate of drug release is constant so long as excess solid remains within the device. Because the mechanism of this system is based on osmotic pressure, the system delivers drug at a rate that is essentially independent of stirring rate and the environmental pH. A commercial therapeutic system based on the above principle has been marketed by

Alza Corporation USA, under the name 'OROS', and its applications has recently been examined with oxprenolol (Bradbrook *et al.,* 1985), metoprolol (Godbillon *et al.,* 1985a) and nifedipine (Chung *et al.,* 1987). Some clinical problems were encountered in its use with indomethacin, resulting in the withdrawal of the product, and this has been well reviewed by Bem *et al.* (1988). Davis *et al.* (1988) have also investigated the gastrointestinal transit properties of 'Oros' containing the drug oxprenolol. The rate of appearance of the drug in the systemic circulation in relation to the location of the dosage in the gut was examined.

1.2 Matrix controlled release systems

One of the most popular approaches in the design and development of oral controlled preparations is based on the matrix system because of its low cost and ease of fabrication (Lee, 1985). Matrix systems are also called monoliths, since the drug is homogeneously dispersed throughout a rate-controlling medium. Most of the oral matrix controlled release products utilize either hydrophilic or hydrophobic matrix systems where the drug is uniformly dissolved or dispersed throughout the polymer mass (Khan and Reddy, 1997; Viega *et al.*, 1997; 1998; Reza *et al*., 2003). The release mechanism of drug occurs mainly through diffusion and erosion. It is necessary to understand the material properties of the devices in order to predict the kinetics of drug release. A simple semi-empirical equation 1.1 shown below was put forward to describe the drug release behavior from a hydrophilic matrix system (Peppas, 1985; Ford *et al.,* 1991) while the release from a hydrophobic monolithic matrix system that resulted in the square-root of time release profile has been described by Higuchi, 1963 in equation 1.2 below.

$$Q_t / Q_\infty = Kt^n \qquad \text{Eq (1.1)}$$

Where, Q_t / Q_∞ is the fraction of drug releases at time t, K is the Korsmeyer-Peppas kinetic release constant which comprises the structural and geometric characteristics of the tablet, and *n,* is the release exponent, indicative of a parameter which depends on the drug release mechanism.

This equation deals with diffusion and erosion mechanism of drug release, depending on the n value in the equation. If the n value is equal to or less than 0.45 this suggests that the release from the optimized formulations follows Fickian diffusion release mechanism (Case I diffusion) of drug where the relative relaxation time of the polymer is much shorter than the characteristic diffusion time of water transport which is controlled by concentration gradient. When, the n value is between 0.45 and 0.89, it is considered to be non-Fickian type of release (Anomalous transport) which refers to a combination of both diffusion and erosion drug release mechanisms. On the other hand, when n value is equal to 0.89, the corresponds to zero-order kinetics (Case II), where polymer relaxation is the rate limiting step to the water transport and the time independent of diffusion. Finally when n value is greater than 0.89 the release is often referred to as a super case II. Generally, Case II transport refers to the dissolution of the polymeric matrix due to the relaxation of polymeric chains.

$$Q_t = K_H t^{1/2} \qquad \text{Eq (1.2)}$$

Where Q_t is the cumulative amount of drug released in time *t,* and K_H is the Higuchi rate constant which represents the diffusion rate constant. This equation describes the drug release from systems where the solid drug is dispersed in an insoluble matrix, and the rate of drug release is related to the rate of drug diffusion.

Hydrophilic matrix consists of materials that swell and form gels upon contact with water or dissolution medium. Drug release in such system is controlled by the diffusion/leaching of the active substances through the swollen and hydrated matrix, as well as due to the erosion of the gelled layer (Peppas *et al.,* 1985). Hydrogel is an important class of the hydrophilic matrix former, which is capable of swelling in water and retaining a considerable amount of water without dissolving in it (Breimer *et al.,* 1985). The drug release follows Fickian first-order diffusion under equilibrium conditions. However, during the swelling process, such equilibrium may not exist and the diffusion may be non-Fickian or anomalous diffusion.

1.3 Types of matrix systems

As mentioned previously, the matrix systems can be mainly divided into two categories depending on whether the polymeric materials used to construct the matrices are hydrophilic or hydrophobic.

1.3.1 Hydrophilic matrix systems

Hydrophilic matrix systems are constructed using water soluble polymeric materials. When the water is thermodynamically compatible with a polymer, it penetrates into the free spaces between macromolecular chains of the polymers. The polymers 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 (Rajabi-Siahboomi *et al.,* 1994a; 1994b; Rajabi-Siahboomi and Jordan, 2000). This allows the encapsulated drug to dissolve and diffuse out of the matrix. Drug release from the matrix is slowed since the diffusion path is lengthened by matrix swelling. However, polymer 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 release rate. While either swelling or dissolution can be the predominant factor for a specific type of polymer, in most cases drug release kinetic is a result of a combination of these two mechanisms (Tahara *et al*., 1995). Hydroxypropyl methylcellulose (HPMC) is one of the classical examples of water soluble matrix former. 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 favors the transport of dissolved drug and the polymer relaxation phenomenon determines the swelling or volume increase of the matrix. Depending on the polymer characteristics, the polymer amount in the rubbery phase on the surface of the matrix could reach a disentanglement concentration leading to an erosion of the matrix. 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 behaviors of HPMC gels and their erosion rate, confirming 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 Lee and Peppas (1987).

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 ratio, drug solubility, drug and polymer particle size,

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 release 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 the drug release in case of matrices where complete drug is not released or is very slowly released, because these excipients can enhance the penetration of the solvent or water into the inner part of matrices (Genc *et al.*, 1999; Nokhodchi *et al*., 2002).

Polymers used in hydrophilic matrices

Hydrophilic polymers were much investigated on the basis of drug release and release mechanism from hydrophilic matrix tablets as well as pellets (Alderman, 1984; Khan *et al.*, 1996; Khan and Jiabi, 1998; Khan and Zhu, 1998; Sen *et al.,* 2001; Huang *et al.,* 2004). HPMC and HPC polymers achieve considerable attention, due to their unique properties along with their good compression characteristics. They are nontoxic and can accommodate high level of drug loading and also have adequate swelling properties that allow rapid formation of an external gel layer which retards or plays a major role in controlling the drug release (Carstensen *et al*.,

1980; Carstensen, 1984; 1987; 1997; Mockel and Lippold, 1993; Swarbrick, 1996; Carstensen, 2000; Rani and Mishra, 2001; Mishra *et al.,* 2003; 2005). Furthermore, HPMC polymers retard the drug release independent of the pH of the media. This advantage enables them to withstand fluctuations of pH in the gastrointestinal tract. They have been used alone or in combination with other hydrophilic polymers in the formulation of matrix tablets. Hence, hydrophilic gel forming matrix tablets have been extensively used for oral extended release dosage forms due to their simplicity, cost effectiveness and reduced risk of dose dumping which can lead to drug toxicity (Sung *et al.,* 1996; Huang *et al*., 2004). Suleiman *et al*. (1989) investigated the release of diclofenac sodium from a mixture of HPMC and Carbopol 940 with lactose as the water soluble filler. The results showed that the combination of hydrogels retarded the drug better than using a single polymer.

Hydroxypropyl methylcellulose (HPMC) is a water soluble hydrophilic polymer, with the ability to swell in water to form a swollen gel phase (Harland *et al.,* 1988; Bonferoni *et al.*, 1994). It is prepared by reacting alkali treated cellulose first with methyl chloride to introduce methoxy groups and then with propylene oxide to introduce propylene glycol ether groups. The resulting products are commercially available in different viscosity grades. The erosion of the gel layer is dependent on the polymer viscosity. Increasing viscosity yields slower drug release as a stronger, more viscous gel layer is formed, providing a greater barrier to diffusion and slower attrition of the tablets (Cheong *et al.,* 1992). HPMC matrices undergo the following during dissolution test: absorption of dissolution media, swelling, gelling, erosion and complete dissolution at the end of test. The mechanism of release from hydrogel matrix systems is complex and has not been completely understood. In general, on

contact with aqueous medium, initially HPMC undergoes a relaxational process that is observed macroscopically as gelation and swelling (Vueba *et al.,* 2004). As a result of these processes, a transparent gel layer appears. Outside this layer, there is an eroding front (gel/dissolution medium interface) at which HPMC chain disentanglement and concomitant dissolution of gel occurs. Inside this layer, there is a swelling front (glassy polymer/gel interface), at which HPMC hydrates, and swells.

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 the HPMC matrix tablets 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; Maggi *et al.,* 2003), hydroxypropylcellulose (Ferrero *et al.,* 1997) and hydroxyethylcellulose.

Hydroxypropylcellulose (HPC) is non-ionic water-soluble cellulose ether, formed by reacting cellulose with propylene oxide. It provides a remarkable set of physical properties for tablet binding, sustained release and film coating (Veiga *et al.*, 1997). It is soluble both in organic solvent as well as in water. Thermoplasticity and surface activity with aqueous thickening and stabilizing properties are the other characteristics of this polymer. It has a long standing history of safe and effective use in the pharmaceutical industry. The pharmaceutical grades of HPC (Klucel®) comply with the monograph requirements of the National Formulary, the European Pharmacopoeia, and the Japanese Pharmacopoeia.

Hydroxyethylcellulose (HEC) is non-ionic water-soluble cellulose ether, formed by reacting cellulose with ethylene oxide. It is used as a sustained release tablet matrix forming material, film former, thickener, stabilizer and suspending agent for oral and topical applications when a non-ionic material is desired (Veiga *et al.*, 1998). HEC is easily dispersed in cold or hot water to give solutions of varying viscosities and desired properties. The pharmaceutical grades of HEC (Natrosol®) comply with the monograph requirements of the National Formulary and the European Pharmacopoeia.

Xanthan gum (XG) is widely used as a thickening agent in food industries but recently introduced in pharmaceutical formulations (Talukdar and Kinget, 1995; Ntawaukulilyayo *et al.,* 1996; Talukdar *et al.,* 1996; Tobyn *et al.,* 1996; Talukdar and Kinget, 1997; Talukdar *et al.,* 1998; Santos *et al.,* 2004; 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 enentially linear (Talukdar and Kinget, 1995).

Carbopol is a derivative of polyacrylic acid. It is a synthetic, high molecular weight, crosslinked polymer. It readily hydrates, absorbs water and swells making it a potential candidate for controlled release drug delivery systems (Khan and Jiabi, 1998; Goskonda *et al.,* 1998; Wong *et al.,* 1999; Juang and storey, 2003; Ikinci *et al*., 2004; Tapia-Albarran and Villafuerte-Robles, 2004). In the case of tablets formulated with Carbopol 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 erode. 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 the 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 does 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 (Upadrashta *et al.,* 1993; Velasco *et al.,* 1999; Venkatraman *et al.,* 2000; Soliman *et al.,* 2005).

1.3.2 Hydrophobic matrix systems

Hydrophobic matrix systems are constructed using water insoluble polymeric materials. The hydrophobic matrix formers include waxes (Vergote *et al.,* 2001; Hayashi *et al.,* 2005), glycerides (Yuksel *et al.,* 2003), fatty acids and polymeric

materials such as ethyl cellulose (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 the formulations. The presence of insoluble ingredient in the formulations helps to maintain the physical integrity of the hydrophobic matrix during drug release. As such, diffusion of active ingredients from the system is the release mechanism (Kincl *et al.,* 2004) and the corresponding release characteristics can be described by Higuchi equation known as square root of time release kinetics (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 general, hydrophobic matrix systems are not suitable for water insoluble drugs 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 developmental stages.

Polymers used in hydrophobic matrices

Ethylcellulose is one of the most widely used water insoluble hydrophobic polymer. It can be applied either as an organic solution or as an aqueous colloidal dispersion. Ethylcellulose is essentially tasteless, odorless, colorless, noncaloric and physiologically inert (Donbrow and Friedman, 1974; Spited and Kinget, 1980; Iyer *et al.,* 1990). Ethylcellulose contains 44 to 51% of ethoxy groups manufactured by reacting ethyl chloride or ethyl sulfate with cellulose dissolved in hydroxide. Depending on the degree of ethoxy substitution, different viscosity grades are obtained and available. This material is completely insoluble in water and

gastrointestinal fluids, and thus cannot be used alone for tablet coating. It is usually combined with water soluble additives, such as hydroxypropyl methylcellulose, to prepare films with reduced water solubility properties (Lachman *et al.,* 1986; Sadeghi *et al.,* 2000).

Kollidon® SR is a newly developed sustained release matrix excipient based on a mixture of polyvinyl acetate and povidone. Due to its excellent flow and compression properties, it is highly suitable for tablets made by direct compression (Draganoiu *et al*., 2001). Polyvinyl acetate is a very plastic material that produces a coherent matrix even under low compression forces. When the tablets are introduced into dissolution media, the water soluble povidone is leached out to form pores through which the active ingredient slowly diffuses outwards.

1.4 Advantages and disadvantages of oral controlled release dosage forms

1.4.1 Advantages

Oral controlled release dosage forms offer great advantages due to better therapeutic success than with conventional dosage forms of the same drug (Reza *et al.,* 2003). The advantages include (1) remarkable decrease in dosing frequency and improved patient compliance, (2) minimized *in vivo* fluctuation of drug concentrations and maintenance of drug concentrations within a desired range (Urquhart, 1982), (3) reduced side effects, and (4) reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction in personnel time to dispense, administer and monitor patients.

This is of great importance, especially for drugs used in long term treatment of chronic diseases. Moreover, controlled release dosage forms are useful for delivering drugs with narrow therapeutic indices since they can reduce the peak trough fluctuations in blood concentration, being characteristic of multiple dosing using conventional immediate release dosage forms (George *et al.,* 1978; Longer and Robinson, 1990). A better efficacy and toxicity ratio of drug during the complete dosing interval could be obtained. Large fluctuations in the blood levels may produce high peak drug levels associated with toxicity while low trough levels result in the loss of efficacy. Hence, a better disease management and reliable therapy can be achieved with the controlled release dosage forms (Chaffman and Brogden, 1985).

1.4.2 Disadvantages

Oral controlled release dosage forms also suffer from a number of potential disadvantages which generally include (1) higher cost, (2) reduced bioavailability, (3) possible dose dumping, (4) reduced potential for dose change or withdrawal in the event of toxicity, allergy or poisoning, and (5) increased first pass metabolism for certain drugs. Unpredictable and poor *in vitro/in vivo* correlations and bioavailability are often observed with such formulations, especially when the drug release rate is very low or drug absorption from the colon is involved. Dose dumping is a phenomenon where a large amount of the drug is released from a controlled release formulation in a short period of time, resulting in undesired high plasma drug levels and potential toxicity. Basically, this can occur due to a breakdown of the rate controlling mechanism, such as rapid disintegration of the matrix tablet.

1.5 Tableting

Tablets are solid pharmaceutical unit dosage forms containing medicinal substances with or without suitable diluents and prepared either by molding or by compression methods. They vary greatly in shape, size and weight which depend upon the amount of medicinal substances and the mode of administration.

Most commonly, tablets are disk shaped with convex surfaces but they are also available in special shapes like round, oval, oblong, cylindrical, square, triangular etc. they can also vary greatly in weight. Tablets are the most widely used solid dosage form of medicament because they offer a number of advantages to the patient, prescriber, manufacturer and the manufacturing pharmacist (Chien, 1978; Chien, 1983; Patel and Amiji, 1996; Streubel *et al*., 2000; 2006).

Tableted drug delivery systems can range from relatively simple immediate release formulations to complex extended or modified release dosage forms. The role of an oral drug delivery system is to deliver the drug in sufficient amount and at appropriate rate at the site of absorption. However, it must also meet a number of other essential criteria. These include physical and chemical stability, ability to economically mass produce and patient acceptability (Augsburger and Zellhofer, 2002).

Tablets are prepared by compressing a powder mixture in a die at high compression force. Generally, the powder mixture contains diluents, binders, disintegrants, lubricants and glidants, apart from the active ingredient. In large scale production of high quality tablets, a tablet mixture with excellent homogeneity, flowability and

compatibility properties is required. Granulation imparts good compactibility, and flowability, which is most commonly used in production of high quality tablets. The two methods used in granulation process are dry granulation and wet granulation.

In dry granulation, 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. Dry granulation is a valuable technique in situations where the effective dose of drug is too high for direct compression and the drug is sensitive to heat, moisture or both, which precludes wet granulation (Banaker, 1979; 1991).

With wet granulation, extra process steps are necessary to produce a tablet mass with sufficient tableting properties. After dry blending the tablet mixture to uniformity, a binder solution is added to the mixture to moisten the particles. Introduction of the binder solution improves binding between the particles and therefore can produce stronger tablets. Mixing is continued until granules with a specific diameter are produced. This wet mass is then screened to remove large lumps, and dried in oven to remove granulation fluid. Finally, the granules are sieved to remove the agglomerates that are formed during drying followed by lubrication of the granules.

The other technique for tablet production is direct compression. In direct compression, the powder mixture is blended to form a uniform mixture and is directly compressed into tablets without any modification of its physical nature. Lubrication step may be necessary to prevent the mixture from adhesing to the die

and punches during compression. Tablet mixtures having good flow and binding properties during compaction are suitable for direct compression (Kristensen *et al*., 1993).

1.6 Influence of physiological conditions on performance of oral controlled release dosage forms

The human gastrointestinal tract can be divided into following major sections, namely, the stomach, the small intestine, and the colon. These sections differ in both anatomical and physiological characteristics.

The stomach is mainly responsible for storage and mixing. Its fundus and body are capable of large expansion to accommodate food without much increase in the intragastric pressure, whilst the antrum, is responsible for mixing and grinding of gastric contents. At resting/fasting state, the pH of stomach is acidic with a value of 1 to 3 (Youngberg *et al*., 1987). Gastric absorption of most drugs is insignificant due to its limited surface area of 0.1 to 0.2 m^2 (Chien, 1992). The stomach is always in a state of continuous motility, and there are two modes of motility patterns, namely, the digestive and the inter-digestive modes (Quigley *et al.*, 1984). The inter-digestive mode is characterized by a cyclic pattern that originates in the foregut and propagates to the terminal ileum. The cyclic pattern consists of four distinct phases known as phase I, representing an inactive period with no electrical activity and no contraction, phase II, the period of random spike activity or intermittent contractions, phase III, the period of regular spike bursts or regular contractions at the maximal frequency that migrate distally, which is also known as “housekeeper wave”, as it plays a housekeeping role in clearing all indigestible materials from the stomach, and finally, phase IV, the transition period between phase III and phase I. The average length of

one complete cycle of these four phases is known as the interdigestive migrating motor complex (MCC) and has an average duration of 90 to 120 min (McRae *et al.,* 1982; Chien, 1992).

On the other hand, the pH of the small intestine is about 4 to 7, increasing from the proximal to the distal region. Because of the presence of vast number of villi and microvillus on its mucosal surface, a huge absorptive area of between 200 to 500 m^2 (Davenport, 1977) is presented. Therefore the small intestine is the major region for drug absorption. The number of villi is most numerous in the duodenum and proximal jejunum. There is a progressive decrease in surface area from the proximal to the distal region of the small intestine and colon. As a result, the proximal region of the small intestine may be regarded as the most efficient absorption site. Hence, in order to achieve maximum systemic bioavailability, the drug should be targeted for delivery in the locality of this region.

In the case of colon, the most important function is to store indigestible food residues. The luminal content of the colon is much more viscous than in the small intestine, with a high pH of about 7.4 or can be higher up to 8. Due to its small absorptive area, as well as lack of villi there is reduced drug absorption as compared to the small intestine. In general, colonic drug absorption is incomplete and variable (Koch-Weser and Schechter, 1981). In the distal part of the colon, insignificant drug absorption is mainly attributed to the embedding of remaining drug in semisolid faecal matter (Hirtz, 1984).

The small intestinal transit time for both liquids and solids, regardless of their nature, normally takes three to four hours, and unaffected by food (Cammack *et al.*, 1982; Davis *et al*., 1984b, 1987; Devereux, 1987; Ollerenshaw *et al.,* 1987; Mundy *et al.,* 1989). In contrast, gastric emptying is highly variable and is markedly influenced by diet (Hunt and Knox, 1968; Cooke and Moulang, 1972; Christian *et al*., 1980; Davis *et al.,* 1984b; Moore *et al.,* 1981; Davis *et al.,* 1987; Devereux, 1987).

1.7 Evaluations of controlled release dosage forms

1.7.1 *In vitro* evaluation

The dissolution rate of a drug has a great influence on its absorption/bio-availability. The best method of evaluating the bioavailability of a dosage form is to perform *in vivo* study using human volunteers. However, monitoring batch to batch consistency through use of such *in vivo* test is extremely costly, tedious and time consuming. It would therefore be always desirable to substitute the *in vivo* bio-availability tests with inexpensive *in vitro* methods (Brahmankar *et al*., 2000).

In vitro dissolution study is valuable in the initial stages of development and evaluation of controlled release dosage forms. It also provides useful information regarding the factors that could affect the drug release from the controlled release preparations. The factors include processing variables, batch to batch uniformity as well as alterations in formulation and stability determinations during various stages of the development process. Furthermore, it can also be employed as a replacement for evaluation of bioequivalence under certain conditions. In view of the significance of dissolution, it is therefore essential to investigate the drug release characteristics of preparations.

1.7.1 (a) *In vitro* dissolution apparatus

A high-quality dissolution test system possesses certain attributes. Firstly, the results must be reproducible and associated with some characteristics of the *in vivo* data. Secondly, the test must be sufficiently sensitive to differentiate *in vitro* variables that yield *in vivo* differences, but without being overly sensitive in detecting *in vitro* changes that is negligible *in vivo*. Thirdly, the method should be flexible and applicable to a wide range of products and lastly, the system should be amenable to automation (Smollen and Ball, 1984).

A wide range of dissolution testing devices has been successfully developed and reviewed (Banaker, 1991). They are basically similar in principle, although the procedures involved may differ. Generally, the dissolution systems can be classified into two distinct types, the stirred vessels and the flow through column systems. The former contains relatively large volume of dissolution medium with minimal liquid exchange. Agitation is achieved either by stirring the liquid with a rotating blade or motion of the vessel itself. The second type comprises a small dissolution cell through which fresh solvent flows at a constant rate without any agitation. The USP 28 (2005) dissolution testing methods for oral dosage forms include the basket stirring element (apparatus 1), paddle stirring element (apparatus 2), reciprocating cylinders system (apparatus 3), flow through cell system (apparatus 4), paddle over disk (apparatus 5), cylinder (apparatus 6) and reciprocating holder (apparatus 7). These methods are easy to operate and amenable to automation. Other systems include the rotating bottle, stationary basket, rotating filter, Sartorius absorption and solubility and column type flow through assembly (Lordi, 1986).

It is impracticable to simulate all the variables that affect the drug dissolution in the gastro-intestinal tract in a single *in vitro* dissolution test system. However, regardless of the types of dissolution test system, certain process variables are essential to obtain meaningful results, and should be included in the dissolution test methodology (Smollen and Ball, 1984). An agitation rate capable of discriminating *in vitro* conditions that are important *in vivo* should be sought, bearing in mind that agitation in the gastrointestinal tract under normal condition is mild (Gupta and Robinson, 1992). The normal body temperature of 37º C is a desired feature in dissolution apparatuses. In this regards, an allowance of ± 0.5º C is deemed acceptable. The dissolution medium may be buffered at different pH to simulate the changes in pH along the gastrointestinal tract. This may help to determine the dependence of drug release at various sections of the gastrointestinal tract.

1.7.1 (b) Comparison of *In vitro* dissolution profiles

The United State Food and Drug Administration guidance for industry (USFDA, 2003) on dissolution testing of solid oral dosage forms, offers general recommendations for dissolution testing, approaches for site dissolution specifications related to the biopharmaceutical characteristics of the drug material, statistical methods for comparing dissolution profiles, and a process to help determine when dissolution testing is sufficient to grant a waiver for an *in vivo* bio-equivalence study.

Shah *et al.* (1987) applied a multivariate analysis of variance method to test the difference between two dissolution profiles. Tsong *et al.* (1996) proposed dissolution difference measurement and similarity testing based on multivariate distance