DESIGN AND EVALUATION OF CONTROLLED RELEASE LAYERED MATRIX TABLETS OF PARACETAMOL AND VERAPAMIL HCl

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by

SHAIKH RAHAMATHULLAH

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Shaikh Rahamathullah

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LIST OF ABBREVIATION & SYMBOLS

<	=	Less than
>	=	Greater than
%	=	Percent
ºC	=	Degree centigrade
ANOVA	=	Analysis of variance
ADP	=	Adenosine diphosphate
AUC	=	Area under curve
BCS	=	Biopharmaceutical Classification System
BP	=	British Pharmacopoeia
cm	=	Centimetre
C_{max}		The peak plasma concentration
C_{std}	=	Concentration of standard solution
COX 1	=	Cyclooxygenase 1
CV	=	Coefficient of variation
EC	=	Ethyl cellulose
FDA	=	Food and Drug Administration
GC	=	Gas chromatography
GC-MS	=	Gas chromatography-mass spectrometry
GRDS	=	Gastroretentive drug delivery system
HPLC	=	High performance liquid chromatography
HPMC	=	Hydroxypropyl methylcellulose
HPMCAS	=	Hdroxypropylmethyl cellulose acetate succinate
k	=	Release rate constant
K_e	=	Elimination rate constant
LLE	=	Liquid-liquid extraction
LOD	=	Limit of detection
LOQ	=	Limit of quantification
MDT	=	Mean dissolution time
ml/min	=	Millilitre/minute
mg	=	Milligram
PEO	=	Polyethylene oxide
pK_a	=	Ionization constant

mm	=	Millimeter
MW	=	Molecular weight
NaCMC	=	Sodiumcarboxymethyl cellulose
r	=	Correlation coefficient
RE	=	Relative error
RP-HPLC	=	Reversed-phase high performance liquid chromatography
RPM	=	Rotation per minute
RSD	=	Relative standard deviation
SAS	=	Statistical Analysis System
SD	=	Standard deviation
SEM	=	Standard error of mean
SPSS	=	Statistical procedures for social science
SPE	=	Solid phase extraction
T_{max}	=	The time to reach peak plasma concentration
$T_{50\%}$	=	Time for 50% of drug release
$t_{1/2}$	=	Half life
USP	=	United States Pharmacopoeia
UV	=	Ultra violet
µg/ml	=	Microgram per milliliter
µl	=	Microliter

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2 ***Shaikh Rahamathullah,*** *Yusrida Darwis, Nurzalina Abdul karim Khan* (2007) The Influence of Concentration of Polymer in Different Layers of Matrix Tablets (Geomatrix®) For Constant Rate Delivery of Verapamil HCl. **USM-UNAIR** first collaborative conference, jointly organized by Universiti Sains Malaysia and University Airlangga, June 2007, Penang, Malaysia.

3 ***Shaikh Rahamathullah,*** *Yusrida Darwis, Nurzalina Abdul karim Khan* (2008) Design and *In Vitro* Evaluation of pH-Independent Controlled Release Layered Matrix Tablets of Verapamil Hydrochloride. **Asian Scientific Conference in Pharmaceutical Technology 2008**: Current Trend in Pharmaceutical Technology, June 2008, Penang, Malaysia.

4 ***Shaikh Rahamathullah,*** *Yusrida Darwis, Nurzalina Abdul karim Khan* (2008) Design and Evaluation of Controlled Release Layered Matrix Tablets of Paracetamol and Verapamil HCl. **Universiti Sains Malaysia**, Penang, Malaysia.

REKABENTUK DAN PENILAIAN TABLET MATRIKS BERLAPIS PELEPASAN TERKAWAL PARASETAMOL DAN VERAPAMIL HCl

ABSTRAK

Tablet matriks berlapis pelepasan terkawal parasetamol dan verapamil HCl dibangunkan menggunakan polimer hidrofilik dan hidrofobik, dan disediakan dengan kaedah pengranulan basah. Tablet matriks parasetamol teras, dua dan tiga lapis diformulasikan menggunakan polimer hidrofilik (Metolose 60SH) dan hidrofobik (Ethocel 10cP). Tablet matriks teras mengandungi Metolose 60SH pada kepekatan yang berbeza (5, 10, 15 dan 20%) manakala lapisan terdiri daripada Metolose 60SH (10 dan 20%) atau Ethocel 10cP (5 dan 10%) atau gabungan kedua-dua polimer. Kepekatan polimer di dalam teras dan lapisan berkadar songsang dengan kadar pelepasan drug daripada tablet matriks. Jenis polimer juga mempengaruhi pelepasan drug dari pada tablet matriks berlapis. Lapisan hidrofilik memanjangkan pelepasan drug manakala lapisan hidrofobik tidak ada kesan. Walau bagaimanapun, tablet matriks tiga lapis yang mengandungi campuran Methocel 60SH (20%) dan Ethocel 10cP (10%) dalam lapisan mempunyai jangkamasa pelepasan drug yang paling tertahan dengan nilai $T_{50\%}$ 10.97 jam dan MDT 10.50 jam. Pelepasan drug daripada sediaan mengikut kinetik tertib sifar. Oleh itu, tablet matriks parasetamol tiga lapis yang mengandungi polimer hidrofilik dan hidrofobik mempunyai pelepasan drug yang paling tertahan. Tablet matriks verapamil HCl teras, dua dan tiga lapis disediakan menggunakan beberapa kepekatan polimer hidrofilik Methocel K15M dan K100M (5, 10, 15 dan 20%), dan polimer hidrofobik Ethocel 10cP (5, 10, 15, 20 dan 30%). Sebagai tambahan, beberapa kepekatan asid suksinik (5, 10, 15 dan 20%) dimasukkan ke dalam teras. Formulasi dengan asid suksinik 15% di dalam teras

didapati yang paling bagus untuk menghasilkan pelepasan drug daripada tablet matriks yang tidak bergantung kepada pH. Kepekatan polimer di dalam teras berkadar songsang dengan kadar pelepasan drug daripada tablet matriks. Pada amnya, pelepasan drug daripada teras yang mengandungi polimer hidrofilik adalah lebih perlahan daripada teras yang mengandungi polimer hidrofobik. Matriks tablet dua dan tiga lapis disediakan dengan pelbagai kepekatan polimer di dalam teras dan lapisan tetapi jumlah amaun polimer tetap malar. Formulasi mengandungi polimer hidrofilik di dalam teras dan lapisan menghasilkan pelepasan drug lebih tertahan daripada formulasi mengandungi polimer hidrofobik di dalam teras dan lapisan. Tablet matriks tiga lapis yang mengandungi Methocel K100M di dalam teras (11.25%) dan lapisan (3.75%) mempunyai jangkamasa pelepasan drug yang paling tertahan dengan $T_{50\%}$ 10.20 jam, MDT 10.49 jam dan mengikuti kinetik tertib sifar. Sebelum melakukan kajian *in vivo*, kaedah HPLC mudah dan sensitif dengan pengesanan pendarfluor disahkan untuk penetuan severapamil dan norverapamil secara serentak pada plasma arnab, menggunakan propranolol sebagai piawai internal. Sebagai tambahan, kajian *in vivo* rekabentuk saling melintang dua arah dilakukan ke atas enam ekor arnab untuk membandingkan biokeperolehan tablet matriks hidrofilik tiga lapis dengan Isoptin® SR sebagai produk rujukan. Tiada perbezaan pada nilai T_{max}, C_{max} dan AUC antara tablet matriks tiga lapis verapamil HCl dan Isoptin® SR. Oleh itu, tablet matriks verapamil HCl tiga lapis mempunyai kadar dan takat penyerapan yang sama seperti Isoptin® SR.

DESIGN AND EVALUATION OF CONTROLLED RELEASE LAYERED MATRIX TABLETS OF PARACETAMOL AND VERAPAMIL HCl

ABSTRACT

Controlled release layered matrix tablets of paracetamol and verapamil HCl were developed using hydrophilic and hydrophobic polymers by the wet granulation method. Paracetamol core, two and three layered matrix tablets were formulated using hydrophilic (Metolose 60SH) and hydrophobic (Ethocel 10cP) polymers. The core matrix tablets contained different concentrations (5, 10, 15 and 20%) of Metolose 60SH while the layers consisted of either Metolose 60SH (10 and 20%) and/or Ethocel 10cP (5 and 10%) and combinations of both polymers. Polymer concentrations in the core and layers were found to be inversely proportional with the drug release rate from the matrix tablets. Polymer types also influenced the drug release from the layered matrix tablets. Hydrophilic layers prolonged the drug release whilst hydrophobic layers had no effect. However, a three layered matrix tablet containing a mixture of Metolose 60SH (20%) and Ethocel 10cP (10%) in the layers had the most sustained duration of drug release with $T_{50\%}$ values of 10.97 hours and MDT of 10.50 hours. The drug release from the preparation followed zero order kinetics. Therefore, the paracetamol three layered matrix tablets containing mixture of hydrophilic and hydrophobic polymers had the most sustained drug release. Verapamil HCl core, two and three layered matrix tablets were prepared using several concentrations of hydrophilic polymers Methocel K15M and K100M (5, 10, 15 and 20%), and hydrophobic polymers Ethocel 10cP and 100cP (5, 10, 15, 20 and 30%). Different concentrations of succinic acid (5, 10, 15 and 20%) were additionally incorporated into the core. Formulation with succinic acid 15% in the

core was found to be the best in producing pH independent drug releases from the hydrophilic and hydrophobic matrix tablets. Polymer concentrations in the core were inversely proportional to the drug release rate from the matrix tablets. In general, drug release from core containing hydrophilic polymers was slower than core containing hydrophobic polymers. The two and three layered matrix tablets were prepared by varying the concentrations of polymers in the core and layers whilst keeping the total amount of the polymer in the tablet constant. Formulations containing hydrophilic polymers in the core and layers produced more sustained drug release than formulations containing hydrophobic polymers in the core and layers. Three layered matrix tablets containing Methocel K100M in the core (11.25%) and layers (3.75%) had the most sustained drug release profiles with $T_{50\%}$ of 10.20 hours, MDT of 10.49 hours and followed zero order kinetics. Prior to conducting the *in vivo* study, a simple and sensitive HPLC method with fluorescence detection was validated for the simultaneous determination of verapamil and norverapamil in rabbit plasma, using propranolol as an internal standard. *In vivo* study with a two-way crossover design was performed on six rabbits to compare the pharmacokinetic parameters of the hydrophilic three layered matrix tablets and Isoptin® SR as the reference product. There were no differences in T_{max}, C_{max} and AUC values between the verapamil HCl three layered matrix tablets and Isoptin® SR. Therefore, the verapamil HCl three layered matrix tablets containing the hydrophilic polymer had a similar rate and extent of absorption as Isoptin® SR.

Chapter 1

Introduction

1.1 Controlled release drug delivery system

Oral route still remains the most popular for drug administration by virtue of its convenience to the patient. A sizable portion of orally administered dosage forms, so called conventional, are designed to achieve maximal drug bioavailability by maximizing the rate and extent of absorption. Whilst such dosage forms have been useful, frequent daily administration is necessary, particularly when the drug has a short biological half life. This may result in wide fluctuation in peak and trough steady-state drug levels, which is undesirable for drugs with marginal therapeutic indices. Moreover, patient compliance is likely to be poor when patients need to take their medication three to four times daily on chronic basis. Fortunately, these shortcomings have been circumvented with the introduction of controlled release dosage forms. These dosage forms are capable of controlling the rate of drug delivery, leading to more sustained drug levels and hence therapeutic action as outlined in Fig.1.1.

During past few decades, significant advance have been made in the area of controlled release as evidenced by an increasing number of patents, publication, as well as commercial controlled release products for the delivery of variety of pharmaceutical compounds. With a controlled release formulation a predictable and reproducible release rate can be achieved, at the target site for desired duration. This results in optimum biological response, prolonged efficacy, decreased toxicity as well as reduction in required dose levels as compared to the conventional mode of delivery (Wilding *et al*., 1991).

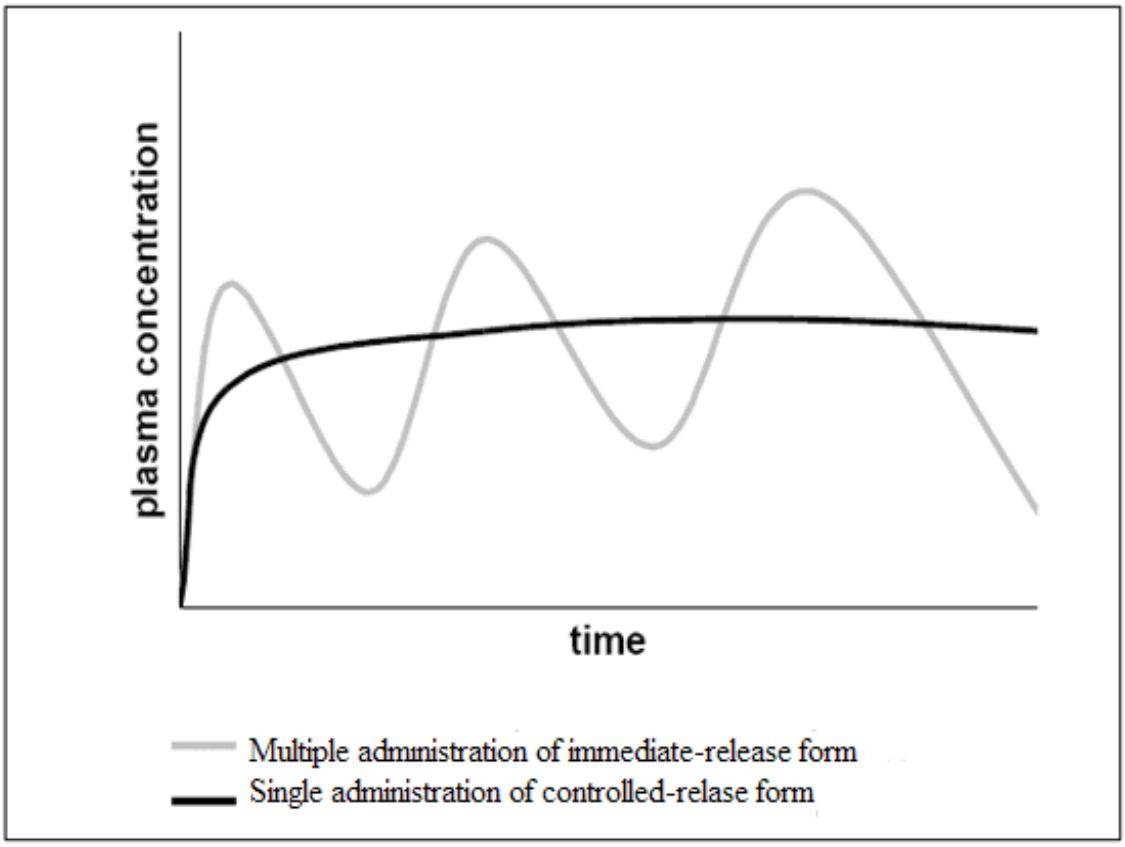

Fig.1.1: Schematic drawing of plasma concentration-versus-time profiles following administration of three immediate-release dosage forms versus one single controlled-release dosage form (Brahmankar *et al*., 2000).

The first truly effective oral drug delivery system, the “Spansule” was introduced in the 1950s. This prolonged release system was marketed by SmithKline & French Laboratories and consisted of small coated beads placed in a capsule (*US Patent* No. 2738303).

Matrix tablets which were prepared by compressing granules to form matrices appeared in 1959 (*British Patent* No. 808014). The inherent drawback of the matrix system is its first order release behavior. For most controlled dosage forms zero order release may be the “holy grail”. To overcome the inherent preponderant first order release behavior with continuously diminishing release rate from matrix systems,

geometry factors have been utilized to compensate for the increasing diffusional distance and decreasing area at the penetrating diffusion front generally encountered in matrix system. Geomatrix is a delivery device, in the form of a multi-layer tablet, proposed for constant drug release. It consists of matrix core, containing the active ingredient, and one or two impermeable or semi-permeable polymeric barriers compressed on one or both faces of the core. These barrier layers provide a modulation of the drug dissolution profile; they reduce the release rate from the tablets and are shown to be effective in obtaining zero order release (Colombo *et al*., 1989; Colombo *et al*., 1990; Colombo *et al*., 1992; Conte *et al*., 1992; Conte *et al*., 1993; Conte *et al*., 1994).

A geomatrix system has few advantages. A conventional high-speed tableting machine can be used to produce geomatrix tablets with a high degree of product consistency and uniformity. This system can be applied to a wide range of drug molecules, including some with poor water solubility and can target the site of release. The major advantage of this system being its ability to control the rate of drug diffusion throughout the release process, ensuring 100% release of the active drug. Moreover, the geomatrix technologies can improve drug efficacy and enhance patient compliance.

1.2 Advantages and disadvantages of controlled release delivery system

Controlled release technology may provide increased clinical value as well as extended product life. The advantages of an ideal controlled release dosage form over an immediate release product include improved patient compliance due to a reduced dosing frequency, a decreased incidence and/or intensity of the side effects,

greater selectivity of pharmacological activity and more prolonged therapeutic effect as well as an increase of cost effectiveness.

However, the controlled release dosage forms also possess some disadvantages. Potential disadvantages of controlled release dosage form include the possibility of dose dumping, less facile dose adjustment, increased potential for hepatic first-pass metabolism, possible delay in onset of action and possibly poor system availability.

1.3 Controlled release mechanism of drug

Mechanisms of drug release from oral controlled delivery systems can be broadly divided into following categories:

1.3.1 Dissolution controlled release

1.3.1 (a) Matrix dissolution control

1.3.1 (b) Reservoir dissolution control

1.3.2 Diffusion controlled release

1.3.2 (a) Matrix diffusion control

1.3.2 (b) Reservoir diffusion control

1.3.3 Osmotic controlled release

1.3.4 Ion exchange resins

1.3.5 Gastroretentive systems

1.3.6 Regulated systems

1.3.1 Dissolution controlled release

Dissolution controlled release can be obtained by slowing down the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer, and coating drug particles or granules with polymeric materials of varying thickness.

1.3.1 (a) Matrix dissolution control

In these systems, the drug is homogeneously dispersed throughout a rate controlling membrane. The drugs which are highly water soluble can also be formulated as controlled release products by controlling their dissolution rate using slowly soluble polymers. Waxes such as beeswax, carnauba wax and hydrogenated castor oil have been used. The wax embedded drug is generally prepared by dispersing the drug in molten wax, congealing and granulating them (Robinson, 1990; Lloyd, 1999; Varshosaz, 2006).

1.3.1 (b) Reservoir dissolution control

In reservoir dissolution controlled system the drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose derivates, polyethylene glycols, polymethacrylates, waxes etc. The resulting reservoirs (coated beads, multi-particulate system, pellets) may be filled as such in hard gelatin capsules (Spansules) or compressed into tablets (Biju *et al*., 2004). The common multi-particulate systems are microparticles (microspheres or microcapsules), nanoparticles (nanospheres or nanocapsules) and liposomes.

1.3.2 Diffusion controlled release

Diffusion of a drug molecule through a polymeric membrane forms the basis of this controlled drug delivery system. Similar to the dissolution controlled devices, these are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix.

1.3.2 (a) Matrix diffusion control

Matrix devices are very common because of ease of fabrication. Diffusion controlled involves dispersion of drug in either water-insoluble or a hydrophilic polymer (Khan and Reddy, 1997; Viega *et al*., 1997; Viega *et al*., 1998). Drug release from insoluble matrices involves penetration of fluid, followed by dissolution of the drug particles and diffusion through fluid filled pores. In case of soluble matrix containing swellable hydrophilic substances the drug becomes available as the matrix swells or dissolves and swollen matrix then undergoes surface erosion with little or no bulk erosion. The surface area of the matrix decreased with the time, with a concomitant decrease in the drug release. The diffusion depends on the solubility of the drug in the polymer. The drug may either present below its solubility limit and dissolved in the polymer or present well above its solubility limit and dispersed in the polymer (Lloyd *et al*., 1999; Robinson *et al*., 1990; Marible *et al*., 2004; Varshosaz, 2006). Bupropion hydrochloride (Zyban, GlaxoWellcome) is formulated using carnauba wax and hydroxypropylmethyl cellulose (Biju *et al*., 2004).

1.3.2 (b) Reservoir diffusion control

A core of drug is coated with the water insoluble polymer. The polymer can be applied by coating or microencapsulating technique. The drug release mechanism across the membrane involves diffusion of dissolution media through the membrane to the inside of the core, then dissolution of the drug and diffusion of the drug into the surrounding fluid. Materials used in such devices are hydroxypropyl cellulose, ethyl cellulose and polyvinyl acetate. The reservoir diffusion products are Plateau CAPS capsules (nicotinic acid), Nio-bid (nitroglycerine) and Brankadyl SR cap (theophylline) (Robinson *et al*., 1990; Sajeev *et al*., 2002; Mukerjee *et al*., 2005).

1.3.3 Osmotic controlled release

Oral osmotic pump, popularly known as ORAS® based on principle of osmotic pressure to release the drug at constant rate. The rate of drug release from the products is determined by the constant in flow of the water across semi-permeable membrane into reservoir, which contains osmotic agents. The drug is either mixed with the agent or is located in the reservoir. The dosage form contains a small hole from which the dissolved drug moves out at a rate determined by the rate of entrance of water due to osmotic pressure. The rate of release is constant and can be controlled within tight limits yielding relatively constant blood concentrations. The advantage of this type of product is that the release is unaltered by the environment of the GIT and it relies simply on the passage of the water into the dosage form. Altering the osmotic agent and the size of the hole can modify the rate of release. An example of this type of product is Adalat Oros (Nifedipine) (Prabakaran *et al*., 2003).

1.3.4 Ion exchange resins

Drugs can be bound to ion exchange resins and when ingested, the ionic environment within the GIT determines the release of the drug. The drug is released slowly by diffusion mechanism from the resins particle structure. Examples of these types of products are Duromine containing the basic drug phentermine complex onto an anionic resin and MS Contin (morphine sulphate) suspension which uses a polystyrene sulphonate resin (Lloyd *et al*., 1999; Anand *et al*., 2001).

1.3.5 Gastroretentive systems

Variability in GI transit time is a concern for oral controlled drug delivery system (Deshpande *et al*., 1996). Drugs with a narrow absorption window in the GI tract are particularly susceptible to variation in both bioavailability and times to achieve peak plasma levels. Gastroretentive controlled release formulations could offer a potential solution to the problem by offering a prolonged gastric residence time (Hwang *et al*., 1998). Gastroretentive delivery systems **(**GRDS) are beneficial for such drugs by improving their bioavailability, therapeutic efficacy and by possible reduction of dose. Apart from these advantages, these systems offer various pharmacokinetic advantages like maintenance of constant therapeutic levels over a prolonged period. This would lead to reduction in fluctuation in therapeutic levels and therefore minimizing the risk of resistance especially in case of antibiotics. Gastrointestinal retention depends on many factors such as density of the dosage form, size of the dosage form, fasting and fed condition, nature of the meal taken, sleep, posture etc. It also depends strongly on a complicated and unpredictable gastric emptying with migrating myoelectric complex motility of the stomach (Talukder and Fassihi, 2004). Various delivery systems like floating, swellable, mucoadhesive, high-density

formulations, etc., have been developed to achieve gastroretention (Baumgartner *et al*., 2000; Li *et al*., 2003).

1.3.6 Regulated systems

These devices are capable of releasing therapeutic agents by well defined kinetics and have significant improvement over conventional controlled release systems. In these devices drug output is adjusted in response to a physiological need. Regulated systems can be classified into two, one is externally regulated system and the other is self-regulatory system. Externally regulated devices can alter their drug output only in response to an intervention externally. For example, control of diabetes is achieved by delivering insulin in response to blood glucose levels. While, self regulated devices can act without external intervention. The response to changes in temperature or pH within the system leads to drug release. An example of this type of system is insulin release from pH sensitive polymers. This approach utilizes pH changes resulting from the conversion of glucose to gluconic acid by glucose oxidase. Increase in glucoronic level would reduce the pH, which lead to erosion of polymer and insulin release.

1.4 *In vitro* evaluation of controlled release formulations

1.4.1 Dissolution studies

Dissolution and drug release tests are *in vitro* tests that measure the rate and extent of dissolution or release of drug substances from products, usually in an aqueous medium under the specified conditions. Dissolution apparatus is shown in Fig. 1.2. Dissolution test is an important quality control for the drug product and is often linked to the product performance *in vivo*. *In vitro* dissolution studies are most often

used for monitoring drug product stability and manufacturing process control. Official book such as United States Pharmacopeia (USP) sets standard for dissolution of most drug products.

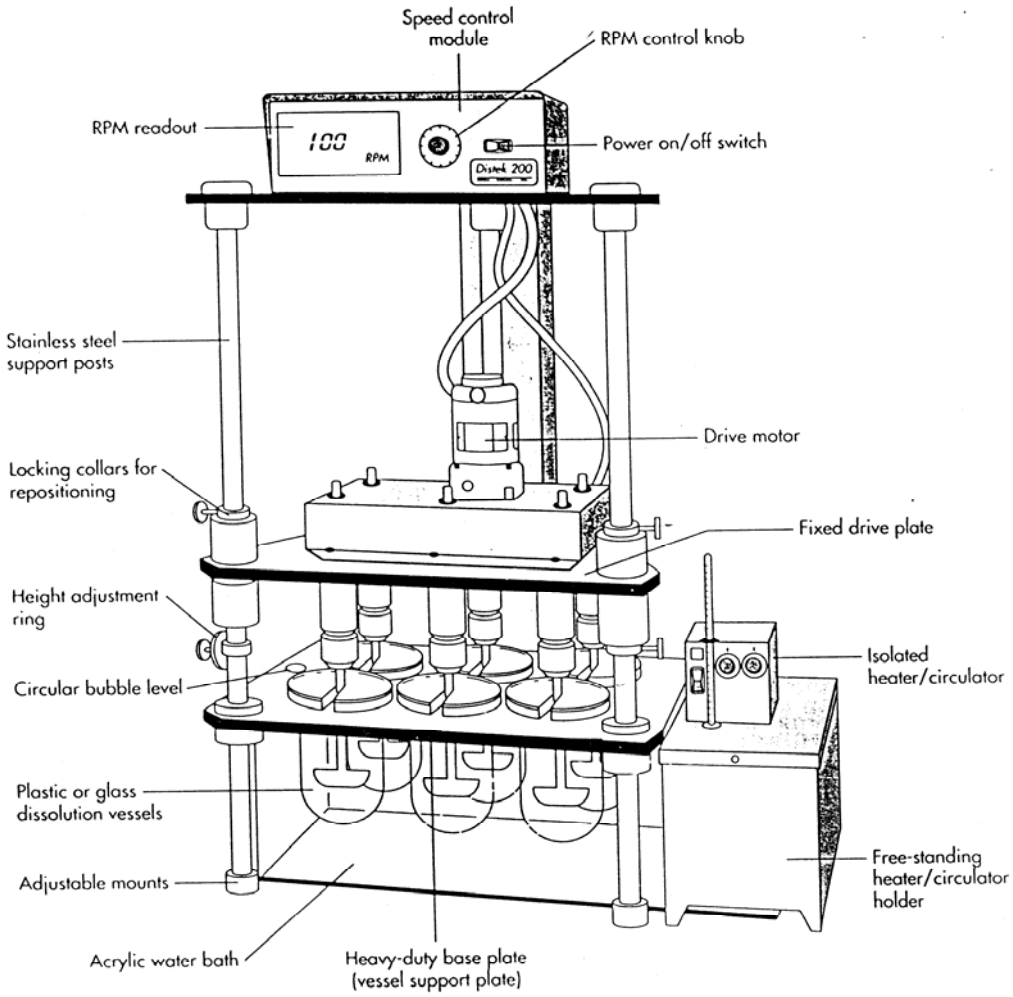

Fig.1.2: Dissolution apparatus (Distek 2000) (Leon *et al*., 2004).

1.4.2 Dissolution conditions

The development of an appropriate dissolution test requires the investigator to try different agitation rates, different media (including volume and medium) and different kind of dissolution apparatus. The rate of agitation and nature of the stirrer effect the hydrodynamic of the system (Fig. 1.3), thereby affecting the dissolution rate. Stirrings rates must be controlled and the specification differs between the drug products. The temperature of the dissolution medium must be controlled and variation in temperature must be avoided. Most of the dissolution tests were performed at 37^0C and the current USP 28 lists officially recognized dissolution apparatus. Once suitable dissolution test is obtained, acceptable dissolution criteria are developed for the drug product and its formulation. The nature of the dissolution medium will also affect the dissolution test. The solubility of the drug must be considered as well as the total amount of the drug in the dosage form. The dissolution medium should not be saturated by the drug (i.e, sink conditions are maintained). Usually, a volume of the medium larger than the amount of the solvent needed to completely dissolve the drug is used in the dissolution test.

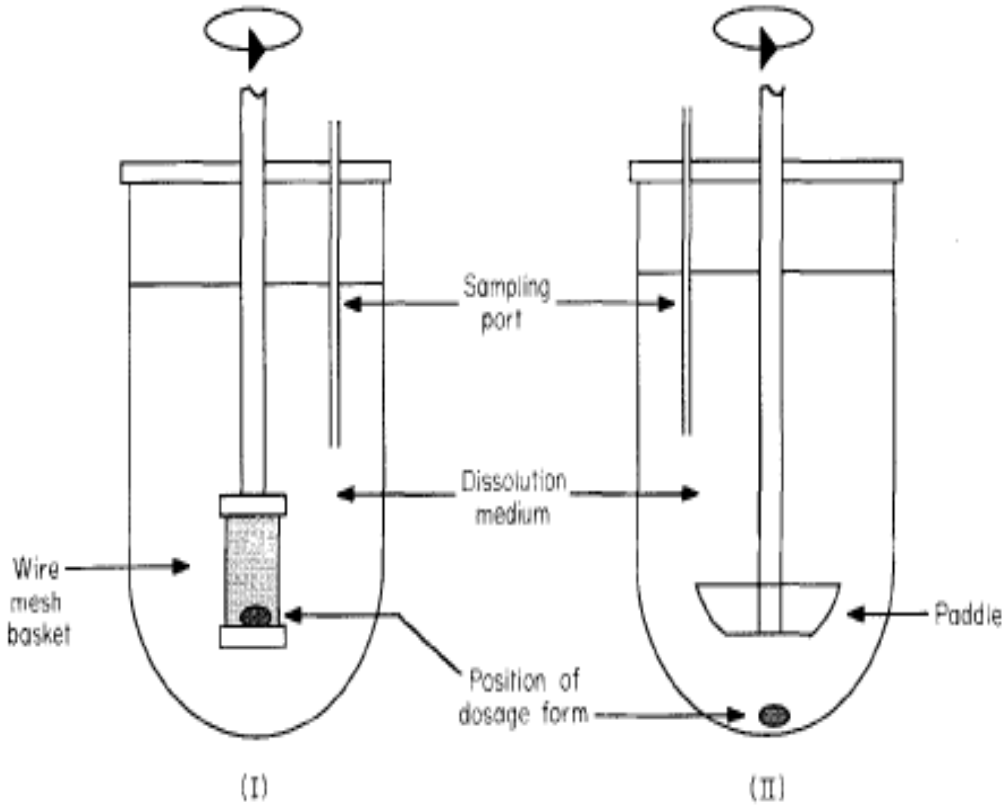

Fig. 1.3: Dissolution testing apparatus (USP 28), basket (I) and paddle (II) (Melia *et al*., 1989).

1.4.3 Compendial methods of dissolution

The USP 28 provides several official methods for carrying out dissolution tests of tablets, capsules and other special products such as transdermal preparations. Tablets are grouped into uncoated and enteric coated tablets. The selection of a particular method for a drug is usually specified in the monograph for a particular drug product. Table 1.1 lists various types of dissolution apparatus and the type of drug products that is often used in apparatus.

1.4.4 Dissolution studies for modified release dosage forms

The following factors need to be considered in selecting of dissolution conditions for evaluation of controlled release dosage forms.

1. Reproducibility of the method
2. Proper choice of medium
3. Maintenance of the sink conditions
4. Control solution hydrodynamic
5. Dissolution rate as a function of pH, ranging from pH 1 to pH 8 and including several intermediate values
6. Selection of most discriminating variable (medium, pH and rotation speed etc) as the basis for dissolution test and specification

1.4.5 Dissolution method selection

If a compendial dissolution method and specifications are not available for a drug molecule then the following criteria needs to be considered in selection of an appropriate dissolution media and to set the specification limits (Skelly and Barr, 1987).

1 The narrow limit of quantity to be dissolved at the hour time point need to be included in the dissolution specification so as to consider no dose dumping is taking place from the controlled release formulation.

2 Appropriate number of time points need to placed in a specification so as to describe the controlled release characteristics of the dosage form for whole period of study.

3 At the last time point of collection a minimum of 75 to 80% of the drug should be released from the dosage form.

4 The pH dependence/independence of the dosage form should be checked by carrying out the dissolution in water and appropriate buffers.

1.5 Paracetamol

It is widely used non-prescription, non-narcotic analgesic antipyretic (Prescott and Wright, 1973; Walson *et al*., 1989). Chemical name of paracetamol is N-Acetyl-p-aminophenol. Molecular formula $C_8H_9NO_2$ and chemical structure of paracetamol is shown in Fig.1.4.

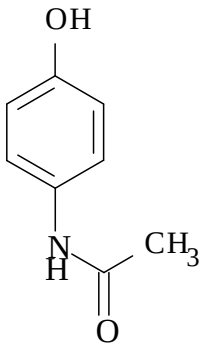

Fig.1.4: Structural formula of paracetamol

Molecular weight of paracetamol is 151.2 with melting point in the range of 169^0C and 170.5^0C. Paracetamol is a white crystalline powder, sparingly soluble in cold water but greater solubility in hot water. It is soluble in methanol, ethanol, dimethylformamide, ethylene dichloride, acetone and ethyl acetate. But it is slightly soluble in ether and insoluble in petroleum ether, pentane and benzene. According to Biopharmaceutical Classification System (BCS), it is a class I drug (high soluble and high permeable drug) (Chi-Yuan and Leslie, 2005) and it has the log P value of 0.44 (Burya *et al*., 2000).

1.5.1 Clinical pharmacology

Paracetamol also known as acetaminophen is a non-steroidal anti-inflammatory drug with potent antipyretic and analgesic actions but with very weak anti-inflammatory activity. When administered to humans, it reduces levels of prostaglandin metabolites in urine but does not reduce synthesis of prostaglandins by blood platelets or by the stomach mucosa. Paracetamol is also a weak inhibitor *in vitro* of both cyclooxygenase (COX)–1 and COX-2 (Botting, 2000).

1.5.2 Pharmacokinetics

Paracetamol is rapidly absorbed from the gastrointestinal tract and distributed throughout most body tissues. The plasma half-life is 1 to 4 hours (Qing *et al*., 2005), but may be increased by liver damage and following overdosage. Paracetamol is eliminated principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, mostly as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

1.6 Verapamil hydrochloride

Chemical name of verapamil HCl is [DL-2-(3, 4-dimethoxyphenyl)-2-isopropyl-5-(N-methyl-N-ß (3, 4- dimethoxyphenyl) ethylamino) valeronitrile] (Cole *et al*., 1981). The empirical formula is $C_{27}H_{38}N_2O_4$ and chemical structure of verapamil HCl is shown in Fig.1.5.

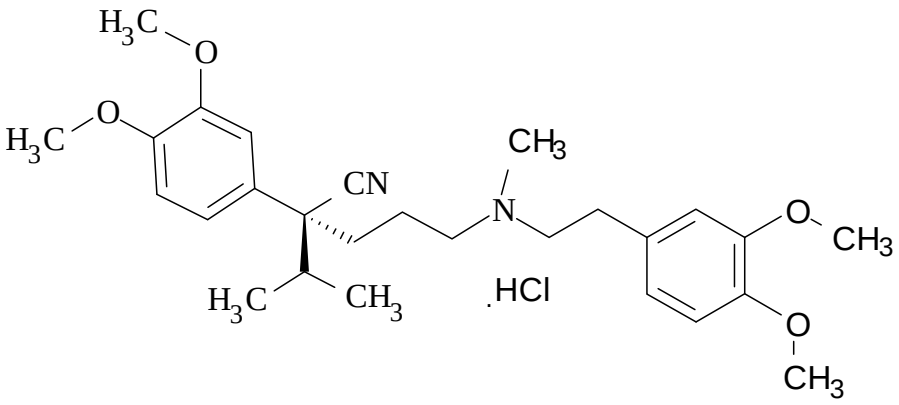

Fig.1.5: Structural formula of verapamil HCl

Molecular weight of verapamil HCl is 491.07 and melting point is in the range of 140^0C and 144^0C (USP 21). Verapamil HCl is a white crystalline powder with no described odor and has a bitter taste. Verapamil HCl is weakly basic drug with pKa 9.04 and log P value 4.6 (Christel *et al*., 2004). According to BCS, it is a class I drug (high soluble and high permeable drug) (Chi-Yuan and Leslie, 2005). Verapamil is soluble in water, methanol and chloroform. But the solubility is pH dependent and 80-90 mg/ml soluble at pH 2.3 to 6.4 where the ionize species predominates. However, the solubility decreases rapidly at high pH. The solubility of verapamil HCl at pH 6.76 is 11 mg/ml (chang, 1988).

1.6.1 Clinical pharmacology

Verapamil is a synthetic paraverin derivate, belongs to phenylalkylamine class. Verapamil is a calcium channel blocker and important therapeutic agent for treatment of angina pectoris, essential hypertension and arrhythmia (Singh *et al*., 1978; Hamann *et al*., 1983; Garcia *et al*., 1997).

1.6.1 (a) Angina

The two mechanisms of verapamil HCl as an antianginal activity are:

Relaxation and prevention of coronary artery spasm

Verapamil dilates the main coronary arteries and coronary arterioles, both in normal and ischemic regions. It is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonovine-induced. This increases myocardial oxygen delivery in patients with coronary artery spasm which responsible for the effectiveness of verapamil in vasospastic (Prinzmetal's or variant) as well as unstable angina at rest.

Reduction of oxygen utilization

Verapamil regularly reduces the total peripheral resistance (after load) against the heart works both at rest and at a given level of exercise by dilating peripheral arterioles. This unloading of the heart reduces myocardial energy consumption and oxygen requirements and probably accounts for the effectiveness of verapamil in chronic stable effort angina.

The mechanism of the antianginal effect of verapamil HCl is believed to be related to its specific cellular action of selectively inhibiting trans-membrane influx of calcium in cardiac muscle, coronary and systemic arteries and in cells of the intracardiac conduction system. Verapamil blocks the trans-membrane influx of calcium through the slow channel (calcium ion antagonism) without affecting to any significant degree the transmembrane influx of sodium through the fast channel. This results in a reduction of free calcium ions available within cells of the above tissues.

1.6.1 (b) Essential hypertension

Verapamil exerts antihypertensive effects by inducing peripheral vasodilation and reducing peripheral vascular resistance usually without reflex tachycardia. These effects are mediated by inhibition of calcium ion influx into smooth muscle cells of the arteriolar wall.

1.6.1 (c) Arrhythmia

The antiarrhythmic effects of verapamil HCl are largely due to its action on the sinoatrial (SA) and atrioventricular (AV) nodes. Verapamil HCl depresses AV nodal conduction and prolongs functional refractory periods. Verapamil HCl does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarization and conduction in depressed atrial fibers. Through this action, it interrupts re-entrant pathways and slows the ventricular rate.

1.6.2 Pharmacokinetics

More than 90% of the orally administered dose of verapamil HCl is absorbed (Jhee *et al*., 2005). Due to the rapid biotransformation of verapamil during its first pass through the portal circulation, bioavailability ranges from 20 to 35%. Verapamil HCl has non-linear pharmacokinetics because of its saturation kinetics (first pass metabolism) which leads to non-linear absorption (Eichelbaum *et al*., 1981; Hamann *et al*., 1984; Vogelgesang *et al*., 1984; Follath *et al*., 1986; Lunden, 1991). The plasma half life of verapamil ranges from 3 to 7 hours (Baselt, 1982; Barbieri *et al*., 1985; Meredith *et al*., 1985; Piotrovskii *et al*., 1986).

Verapamil undergoes extensive metabolism in the liver. Twelve metabolites have been identified in plasma (Wieslaw *et al*., 2001), out of which only norverapamil was found in significant amount whereas other metabolites were in trace amounts. Norverapamil can reach steady-state plasma concentrations approximately equal to those of verapamil itself. The cardiovascular activity of norverapamil appears to be approximately 20% that of verapamil. Approximately 70% of an administered dose is excreted as metabolites in the urine and 16% or more in the feces within 5 days. About 3 to 4% is excreted in the urine as unchanged drug.

1.7 Release retarding agents for controlled drug delivery

Polymers have gained in importance in the pharmaceutical industry as both drug encapsulants and vehicles of drug carriage either protecting an active agent during its passage through the body or in storage by preventing moisture ingress (Udeala and Aly, 1989) until its release, or controlling its release. Oral controlled release systems utilize principles such as diffusion, dissolution and permeation for achieving a constant rate of drug delivery. Polymers are research materials for the preparation of oral delivery systems. They offer a wide range of properties such as diffusivity, permeability and solubility that are important for achieving controlled delivery. They can be processed relatively easy into tablets and membrane by a variety of methods. Drugs can be dissolved in a polymer to manufacture matrix type oral dosage forms. Some of the polymers that are commonly used to develop matrix tablets are hydroxypropylmethyl cellulose, sodium carboxymethylcellulose, polyacrylic acid and polyethylene oxide (hydrophilic polymers) which are water soluble and ethyl cellulose, carbomers and waxes (hydrophobic polymers) which are water insoluble.

The properties of few hydrophilic and hydrophobic polymers used to develop a matrix tablets are given below.

1.7.1 Hydroxypropylmethyl cellulose

Hydroxypropylmethyl cellulose **(**HPMC) is white amorphous powder, with no odor and taste. The hydration rate of HPMC increases with an increase in the hydroxypropyl content. HPMC dissolves in cold water to form a viscous solution, but is not very soluble in hot water. Additionally it is soluble in mixture of water and alcohol, mixture of ethanol and dichloromethane and mixture of methanol and dichloromethane (Archer *et al*., 1992; Kumar *et al*., 1993; Budavari *et al*., 1996). Chemical name of HPMC is propylene glycol ether of methylcellulose. Chemical structure of HPMC is shown in Fig.1.6. HPMC is a methylcellulose modified with a small amount of propylene glycol ether groups attached to the anhydroglucose of the cellulose. The dry product contains 19 to 30% of methoxyl (-OCH_3) groups and 3 to 12% of hydroxypropyl (-$OCH_2CHOHCH_3$) groups.

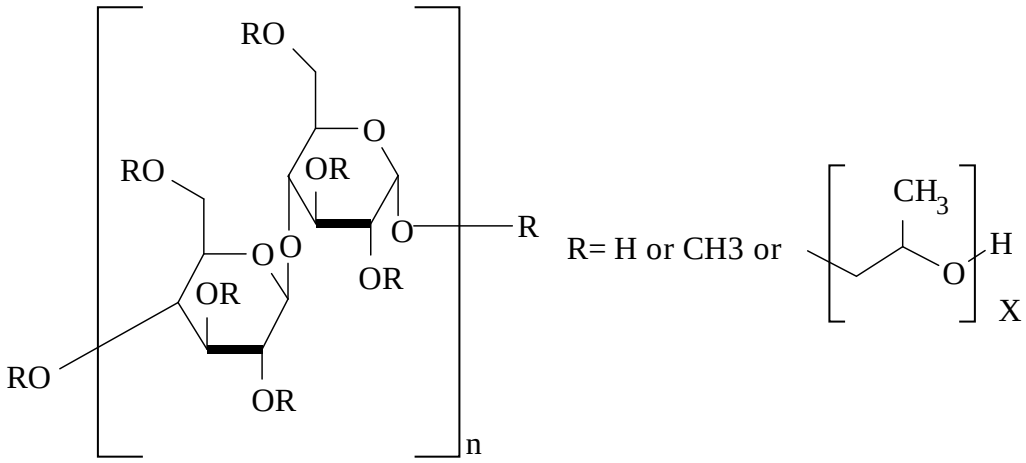

Fig.1.6: Structural formula of hydroxypropylmethyl cellulose

HPMC is an inert hydrophilic polymer with no ionic charge. HPMC is available in several grades that vary in viscosity and extent of substitution. The viscosity grade of the polymer depends on the number of substituents on the polymeric backbone and the length of the cellulose chain. The molecular weight is approximately 10,000-1,500,000 (Harwood, 2005).

HPMC is used as a rate-controlling polymer for sustained release, coating agent, film former, stabilizing agent, suspending agent, tablet binder and viscosity increasing agent. In oral products, HPMC is primarily used as a tablet binder (Chowhan, 1980), film coating agent (Okhamafe and York, 1982) and as a matrix material for extended release tablet formulation (Dahl *et al*., 1990).

1.7.2 Polymethacrylates

Polymethacrylates are synthetic cationic and anionic polymers of diethylamino ethylmethacrylates, methacrylic acid and methacrylic acid esters in varying ratios. Eudragit polymers are copolymers of acrylic and methacrylic acid or their esters. They all have the same basic structure as shown in Fig.1.7. Their specific properties are determined by different functional groups R1 to R3 and different ratios of acrylic to methacrylic acid on one hand, and free acids to esters on the other hand. Eudragit is insoluble in water but it swells, which enables the incorporated drugs to be released from the formulation by means of diffusion through the swollen matrix.

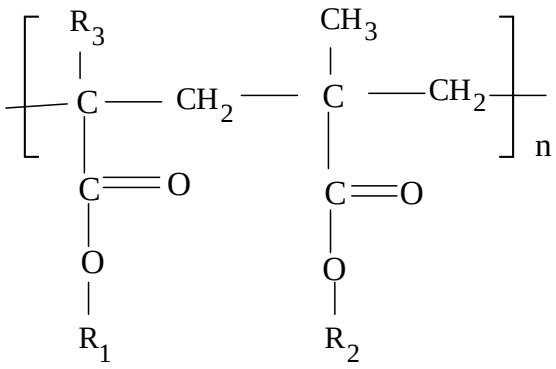

Fig.1.7: Structural formula of Eudragit

Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents (Lehmann and Dreher, 1973; Lehmann, 1973a; Lehmann, 1973b; Gurry *et al*., 1977; Dew *et al*., 1982; Lehmann, 1986; Caneron and McGinity, 1987; Okor and Obi, 1990; Beckert *et al*., 1996; Jovanovic *et al*., 1997). Depending on the type of polymer used, films of different solubility characteristics can be produced. Eudragit RL, RS and NE 30 D are used to form water insoluble film coats for sustained release products. Polymethacrylates are also used as binders in both aqueous and organic wet granulation process. Larger quantities (5-20%) of dry polymer are used to control the release of an active substance from a tablet matrix.

1.7.3 Eudragit L 100-55

Eudragit L 100-55 is an anionic copolymer of methacrylic acid and ethyl acrylate. The ratio of the free carboxyl groups to the ester groups is approximately 1:1**.** Eudragit L 100-55 structural formula is shown in Fig.1.8.

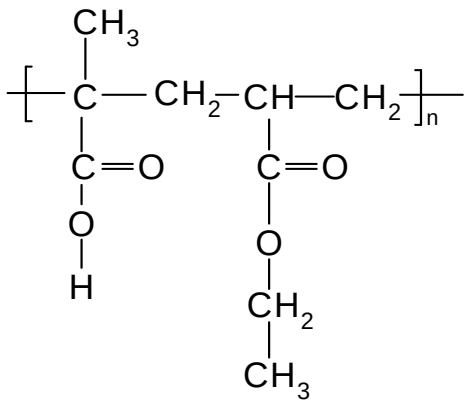

Fig.1.8: Structural formula of Eudragit L 100-55

Eudragit L 100-55 is soluble in water at pH 5.5 and above (Zahirul *et al*., 1999). Eudragit L 100-55 can be used for enteric coatings and a targeted delivery in the duodenum or jejunum. It is also used as enteric polymer for pH independent release of weakly basic drugs, because incorporation of acidic polymer in matrices would lead to lowering of the microenvironmental pH of the matrices (Aditya *et al*., 2004).

1.7.4 Eudragit S 100

Eudragit S 100 is an anionic copolymer of methacrylic acid and methyl methacrylate with free carboxyl groups in powder form. Eudragit S 100 structural formula is shown in Fig.1.9. The ratio of the free carboxyl groups to the ester groups is approximately 1:2. The polymer is soluble in water above pH 6.0 (Zahirul *et al*., 1999). But due to the lower content of free carboxyl groups, it dissolves less rapidly than Eudragit L 12.5 and Eudragit L 100-55. It can be used for a targeted delivery in the ileum or colon. The site of drug release and the release-rate of drug from the dosage form can be altered by a combination with different types of Eudragit L. These polymers provide pH independent drug release that can be used for formulating the sustained release oral dosage forms.