FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING MATRIX TABLETS OF PERINDOPRIL ERBUMINE

Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI

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CERTIFICATE

This is to certify that the Dissertation entitled **"FORMULATION AND EVALUATION OF GASTRO RETENTIVE FLOATING MATRIX TABLETS OF PERINDOPRIL ERBUMINE"** submitted by **Ms. P.SHANMUGA PRIYA** in partial fulfillment of the requirement for the degree of **Master of Pharmacy** in **Pharmaceutics** is a bonafide work carried out by her, under my guidance and supervision during the academic year 2010 – 2011 in the Department of Pharmaceutics, Madurai Medical College, Madurai-20.

I wish her success in all his endeavors.

Place: Madurai

Date: **(Prof. A.Abdul Hasan Sathali)**

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I wish her success in all his endeavors.

Place: Madurai
Date: (**Mrs.R.Tharabai**)

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CHAPTER – I

INTRODUCTION

ORAL CONTROLLED DRUG DELIVERY SYSTEMS

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals.[18] Drug delivery technologies are the formulation technologies that modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance.[3]

Routes of administration [3]

- Enteral.
- Topical.
- Parenteral.

Enteral drug delivery:

It includes peroral i.e,

- Gastro-intestinal
- Sub-lingual
- Rectal

Topical drug delivery:

It includes skin, eyes or other membranes.

- Intranasal
- Inhalational

- Intravaginal
- Transdermal

Parenteral drug delivery:

It includes all routes of administration through or under one or more layers of skin.

- Intramuscular
- Subcutaneous
- Intravenous

The most **preferred route** of drug administration for systemic delivery of drugs is **orally.**[2] More than 50% of drug delivery systems available in the market are oral drug delivery systems. These systems have the obvious advantages of case of administration and patient acceptance. Several oral drug delivery technologies have come and gone, and new systems still emerge even today.

One would always like to have ideal drug delivery systems that will possess two main properties,[35]

1. It will be a single dose for the whole duration of treatment,
2. It will deliver the active drug directly at the site of action.

It offers advantages like, [48]

- Ease of administration
- Patient compliance
- Flexibility in formulation

THE CHALLENGE:

Most of the marketed products currently available are immediate release products. To achieve and maintain the concentration of an administered drug within therapeutically effective range, it is often necessary to take drug dosage several times and this result in a **fluctuating drug level in plasma.**[1,2,3]

THE CONTROLLED RELEASE:[2,3]

- Controlled drug delivery is one which delivers the drug at a predetermined rate, for locally or systemically, for a specified period of time.
- Continuous oral delivery of drugs at predictable & reproducible kinetics for predetermined period throughout the course of GIT.

There are many benefits offered by controlled drug delivery systems. For example, sustained release technologies allow prolonged delivery of a therapeutic dose, thus reducing the number of times that a patient needs to take their medication while maintaining a steady state of drug in the bloodstream, and time-delayed release introduces a lag time before dose release, providing pulsatile delivery of drug to specific sites, such as the colon, or at a specific time. Temporal control of drug release has particular advantages in the treatment of disorders that demonstrate a circadian pattern, such as cardiovascular disorders, asthma, anxiety and hypercholesterolemia. In such cases, the development of controlled-release formulations that deliver the payload at an optimal time can greatly enhance the therapeutic effects of the drug and reduce the dose required.

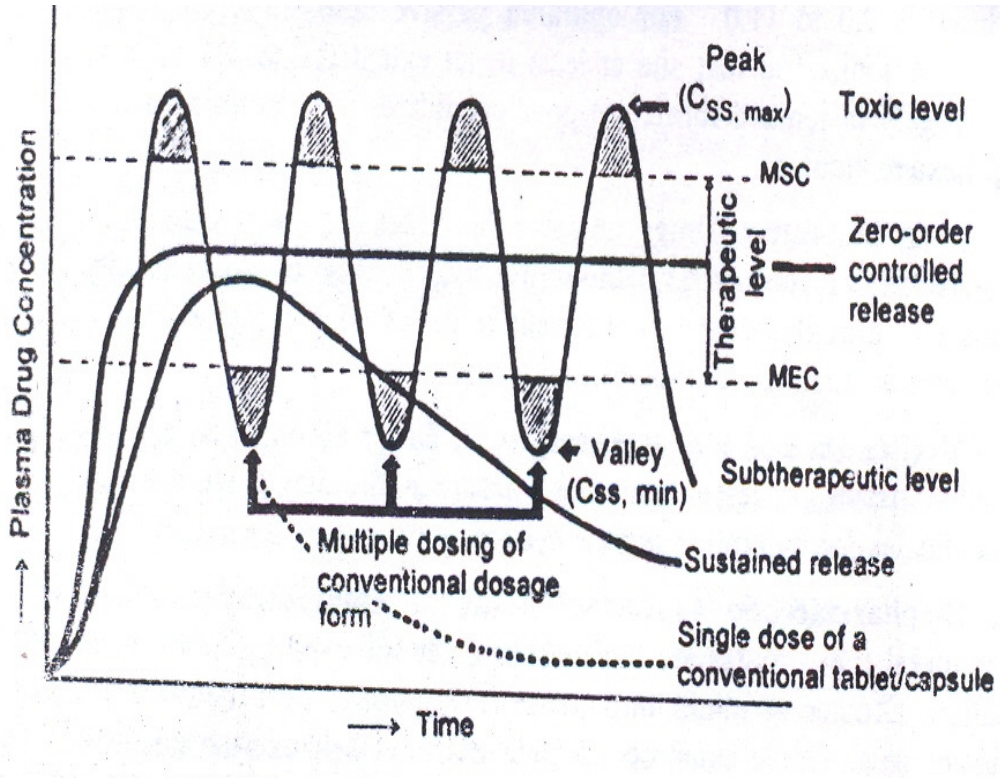


Fig: 1

ORAL CONTROLLED RELEASE FORMULATIONS[1]:

Oral route has been the commonly selected and most convenient for the drug delivery. Oral route of administration has more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than routes drug delivery.

Most of the oral controlled drug delivery systems rely on diffusion, dissolution or combination of both mechanisms, to release the drug in a controlled manner to the Gastrointestinal Tract (GIT).

Novel oral drug delivery systems are broadly classified in to two categories as they may controlled release dosage forms as well as targeting dosage forms. General controlled manner in the GIT for systemic uptake and no particular area of GIT specified. In contrast,

targeted preparations are releasing the drug in a specified area or tissue of the GIT (e.g. colon specific drug delivery systems).

Targeting systems are either releasing drug in controlled manner or in one burst at the specific area.[4] The goal of a targeted oral drug delivery system (TODDS) is to achieve better therapeutics success compared to conventional dosage form. This can be achieved by improving the pharmacokinetic profile, patient convenience and compliance in therapy, some of the advantages of TODDS are:

- ✓ Reduced dosing frequency
- ✓ Better patient convenience and compliance
- ✓ Reduced GI side effects and other toxic effects.
- ✓ Less fluctuating plasma drug level
- ✓ More uniform drug effect
- ✓ Less total dose
- ✓ Better stability of the drug.

On the other hand TODDS suffer from a number of potential disadvantages:

- o Higher cost
- o Relatively poor in vitro-in vivo correlation
- o Possible dose dumping
- o Reduced potential for dose change or withdrawal in the event of toxicity

Targeting of drugs through oral route involves control of time of release or location of release. On the basis of environmental, anatomical and physiological factors these drug delivery system can be classified with respect to target site as follows:

- ➢ **Systems targeted to stomach/duodenum**

- Systems targeted to small intestine
- Systems targeted to large intestine/colon
- Systems targeted to lymphatic.

ORAL DIFFUSION-CONTROLLED SYSTEMS[5]:

The basic concepts of oral controlled release dosage forms can be defined based on release-profile characteristic or the underlying release- controlling mechanism. Two distinct drug release profiles, extended and delayed release, are achievable, and they can be used in various combinations to provide the desired release rate. Three delivery systems dominate today's market of oral CR products:

- Matrix systems.
- reservoir systems and
- osmotic systems.

Release mechanisms from these dosage forms, diffusion plays a key role in both matrix and reservoir systems, whereas osmotic pressure is the predominant mechanism of drug release from osmotic systems and could also play a role in a reservoir system.

Matrix systems

A matrix system consists of active and inactive ingredients that are homogeneously mixed in the dosage form. Matrix systems divide into two categories, based on rate-controlling materials.

- ✓ **Hydrophobic matrix systems**
- ✓ **Hydrophilic matrix systems**

Hydrophobic matrix systems:

This is the only system where use of a polymer is not essential to provide controlled drug release, although insoluble polymers have been used. As the term suggests, the primary rate-controlling components of a hydrophobic matrix are water insoluble in nature. These ingredients include waxes, glycerides, fatty acids, and polymeric materials such as ethyl cellulose and methacrylate copolymers. To modulate drug release, it is necessary to incorporate soluble ingredients such as lactose into the formulation.

The presence of insoluble ingredients in the formulations helps to maintain the physical dimension of a hydrophobic matrix during drug release. Diffusion of the active form from the system is the release mechanism. Very often, pores form within a hydrophobic matrix as a result of the release of the active ingredient. Hydrophobic matrix systems generally are not suitable for insoluble drugs because the concentration gradient is too low to render drug release.

Hydrophilic matrix systems:[5]

The primary rate-controlling ingredients of a hydrophilic matrix are polymers that would swell on contact with the aqueous solution and form a gel layer on the surface of the system.

Drugs release from hydrophilic matrices is by polymer dissolution (erosion) and diffusion of drug molecules across the gel layer have been identified as the rate-controlling mechanisms.

The model semi empirical "exponent equation" has been used widely to differentiate the contributions of both mechanisms:

$$\mathbf{Q_t = kt^n}$$

Where Q_t is amount Q in time t, *n* is a diffusion exponent, and *k* is a kinetic constant. If diffusion dominates polymer erosion, the value of *n* would approach 0.5. On the other hand,

for erosion-controlled formulations, *n* would approach the value of unity. Under an "anomalous" condition, the value of *n* falls in between 0.5 and 1 when both diffusion and erosion play roles.

More recently, a "spaghetti" model (**fig.2**) for a swollen matrix was developed to provide mechanistic understanding of the complex release process. This model treats polymer erosion as diffusion of polymer across a "diffusion layer" adjacent to the gel layer. Thus two competitive diffusion processes contribute to overall drug release: diffusion of polymer across the diffusion layer and diffusion of drug across the gel layer.

"Spaghetti" model for a swollen matrix.

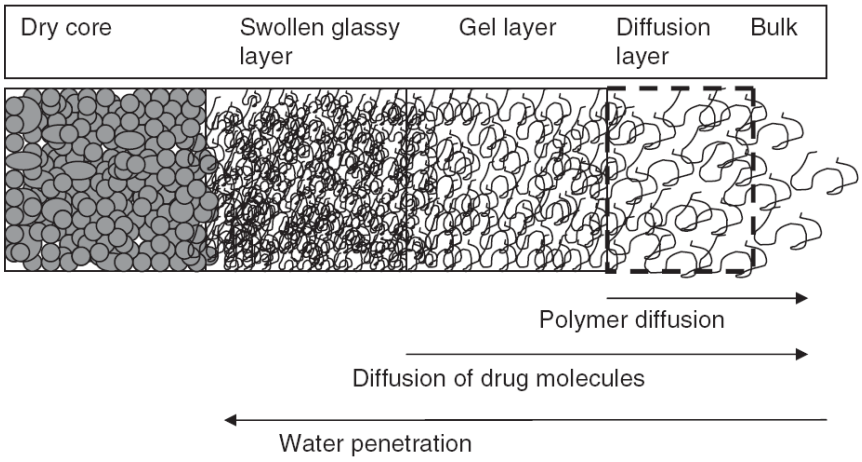


Fig: 2

For very soluble compounds, diffusion of drug molecules is the dominant mechanism of release, and the role of polymer erosion is limited in modulating drug release. Thus, developing a hydrophilic matrix for highly soluble drugs that requires prolonged release (e.g., >12 h) can be challenging. On the other hand, release of less soluble drugs from hydrophilic matrices is expected to be slow because both polymer dissolution and drug diffusion play key roles.

Classification of oral controlled drug delivery system

1. **Continuous release system**
    1. Dissolution controlled release system
    2. Diffusion controlled release system
    3. Diffusion and dissolution controlled release system.
    4. ion exchange resin drug complexes
    5. slow dissolving salt and complexes
    6. pH independent formulations.
    7. Osmotic pressure controlled systems
    8. Hydrodynamic pressure controlled systems.

2. **Delayed transit and continuous release systems**
    1. Altered density system.
    2. Mucoadhesive system.
    3. Size based systems.

3. **Delayed Release system**
    1. Intestinal release system.
    2. Colonic release system.

Factors influencing the design and performance of controlled drug delivery system [1, 4 ,5]

1. **Biopharmaceutic characteristic of the drug**
    1. Molecular weight of the drug
    2. Aqueous solubility of the drug

3. Apparent partition coefficient
4. Drug Pka and ionization physiological PH
5. Drug stability
6. Mechanism and site of absorption
7. Route of administration.

2. Pharmacokinetic characteristic of the drug

1. Absorption rate
2. Elimination half life
3. Rate of metabolism
4. Dosage form index

3. Pharmacodynamic characteristic of the drug

1. Therapeutic range
2. Therapeutic index
3. Plasma–concentration–response relationship

Advantages of controlled drug delivery systems:

1. Improved patient convenience and compliance
2. Reduction in fluctuation in steady state levels.
3. Increased safety margin of high potency drugs.
4. Reduction in dose.
5. Reduction in health care cost.
6. Total dose is low.
7. Reduced GI side effects.
8. Reduced dosing frequency.
9. Better patient acceptance and compliance.

10. Less fluctuation at plasma drug levels.
11. More uniform drug effect
12. Improved efficacy/safety ratio.
13. Dose dumping.
14. Reduced potential for accurate dose adjustment.
15. Need of additional patient education.

Disadvantages of controlled drug delivery systems

1. Decreased systemic availability.
2. Poor *invitro-invivo* correlations.
3. Chances of dose dumping.
4. Dose withdrawal is not possible.
5. Higher cost of formulation.

CHAPTER - II

GASTRO RETENTIVE DRUG DELIVERY SYSTEM

Gastro retentive Drug Delivery System [27, 28]

One of the "holy grails" in oral drug delivery is to develop gastric retention platforms for long-term (ranging from 6 to 24 hours) delivery of drugs by oral administration. Gastroretentive dosage forms are drug delivery systems which **remain in the stomach** for an extended period of time and allow both spatial and time control of drug liberation. Basically gastroretentive systems swells following ingestion and is retained in the stomach for a number of hours, while it continuously releases the incorporated drug at a controlled rate to preferred **absorption sites** in the upper intestinal tract. Their application can be advantageous in the case of drugs absorbed mainly from the upper part of GIT or are unstable in the medium of distal intestine.

Gastrointestinal Tract

Anatomy of the gastrointestinal tract:

The gastrointestinal tract is divided into three main regions namely:

- Stomach.
- Small intestine (Duodenum, Jejunum and Ileum).
- Large intestine.

The GIT is a muscular tube, from the mouth to the anus, which functions to take in nutrients and eliminate waste by secretion, motility, digestion, absorption and excretion,

which are known as physiological processes. The stomach is a J-shaped enlargement of the GIT which is divided into 4 anatomical regions:

- cardia
- fundus
- body
- antrum[3] (Fig.1).

The main function of the stomach is to store and mix food with gastric secretions before emptying its load (chyme) through the pyloric sphincter and into the small intestine at a controlled rate suitable for digestion and absorption. During empty state, the stomach occupies a volume of about 50 ml, but this may increase to as much as 1 litre when full. The walls of the GIT, from stomach to large intestine, have the same basic arrangement of tissues, the different layers, from outside to inside, comprising serosa, intermuscular plane, longitudinal muscle, submucosa, circular muscle, lamina propria, muscularis mucosae, and epithelium. In addition to longitudinal and circular muscle, the stomach has a third muscle layer known as the "oblique muscle layer", which is situated in the proximal stomach, branching over the fundus and higher regions of the gastric body. The different smooth muscle layers are responsible for performing the motor functions of the GIT, i.e. gastric emptying and intestinal transit.

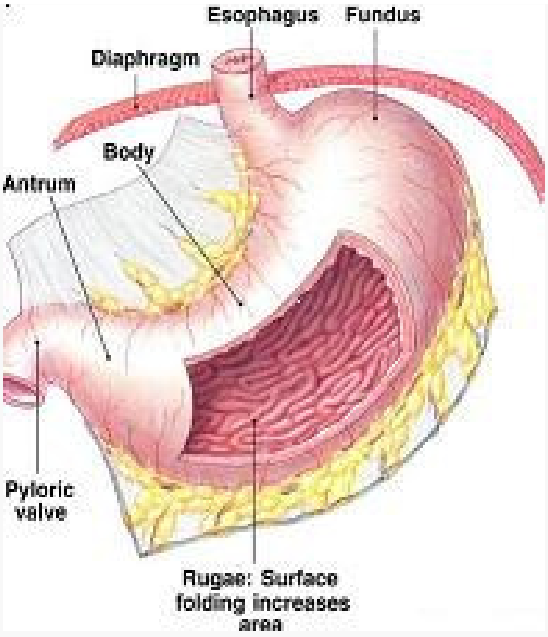


Fig: 3 Anatomy of the gastrointestinal tract

Basic gastrointestinal tract physiology

The stomach is divided into 3 regions anatomically: fundus, body, and antrum pylorus. The proximal part is the fundus and the body acts as a reservoir for undigested material, where as the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states but the pattern of motility is distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle through both stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is divided into following 4 phases[3] (Fig.2).

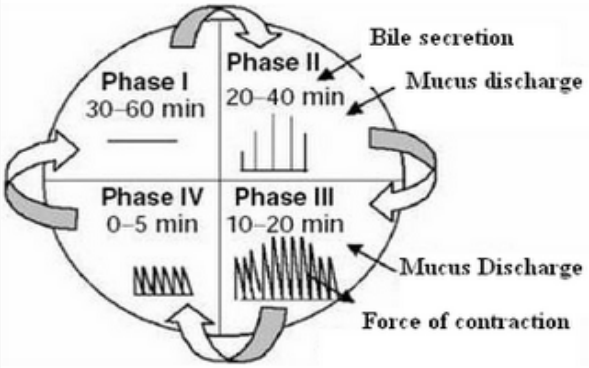


Fig: 4 Schematic representation of Interdigestive Motility

- **Phase I:** This period lasts about 30 to 60 minutes with no contractions.
- **Phase II:** This period consists of intermittent contractions that increase gradually in intensity as the phase progresses, and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begins later in this phase.
- **Phase III:** This is a short period of intense distal and proximal gastric contractions (4-5 contractions per minute) lasting about 10 to 20 minutes these contractions, also known as ‘‘**house-keeper wave**,’’ sweep gastric contents down the small Intestine.
- **Phase IV:** This is a short transitory period of about 0 to 5 minutes, and the contractions dissipate between the last part of phase III and quiescence of phase

Need for gastroretention [3, 25]

- Drugs that are absorbed from the **proximal part** of the gastrointestinal tract (GIT).
- Drugs that are **less soluble** or that degrade at the alkaline pH.
- Drugs that are absorbed due to **variable** gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal small intestine to **treat** certain conditions.
- Treatment of **peptic ulcers** caused by H.Pylori infections [63].

Formulation considerations for GRDDS[4]

- It must be **effective retention** in the stomach to suit for the clinical demand.
- It must be convenient for intake to facilitate patient compliance.
- It must have sufficient drug loading capacity and control drug release profile.
- It must have full degradation and evacuation of the system once the drug release is over.
- It should not have effect on gastric motility including emptying pattern.
- It should not have other local adverse effects.

Certain types of drugs can benefit from using gastro retentive devices[5]

- Drugs with a **narrow absorption** window [68].
- Drugs acting **locally** in the stomach.
- Drugs those are primarily absorbed in the stomach.
- Drugs those are **poorly soluble** at an alkaline P^H.
- Drugs absorbed rapidly from the GI tract.
- Drugs those **degrade** in the **colon**.

Drugs those are unsuitable for gastro retentive drug delivery systems[6]

- Drugs that have very **limited acid solubility** e.g. Phenytoin etc.
- Drugs that suffer instability in the gastric environment e.g. Erythromycin etc.
- Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

Factors affecting gastric retention[5]

Various factors that affect the bioavailability of dosage form and efficacy of the gastro retentive system are:

- **Density:** Gastric retention time (GRT) is a function of buoyancy of dosage form that is dependent on the density.
- **Size:** Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.
- **Shape:** Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.
- **Single or Multiple unit formulation:** Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
- **Fed or unfed state:** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2hrs. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

- **Nature of meal:** Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
- **Caloric content:** GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.
- **Frequency of feed:** The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender:** Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface).
- **Age:** Elderly people, especially those over 70, have a significantly longer GRT.
- **Posture:** GRT can vary between supine and upright ambulatory states of the patient.
- **Concomitant drug administration:** Anticholinergics like atropine, propantheline, opiates like codeine and prokinetic agents like Metoclopramide and Cisapride, can affect floating time.
- **Biological factors:** Diabetes and Crohn's disease etc.

Approaches to Gastric retention [59]

Various approaches for gastro retentive drug delivery systems are:

(A) Floating drug delivery [47]

Floating Drug Delivery Systems (FDDS) have a bulk **density lower** than gastric fluids and thus remain **buoyant** in the stomach, [5] (Fig.3), for a prolonged period of time, without affecting the gastric emptying rate and the drug is released slowly at a desired rate from the system, results in an increase in the gastric residence time and a better control of

fluctuations in the plasma drug concentrations and after complete release of the drug, the residual system is emptied from the stomach.

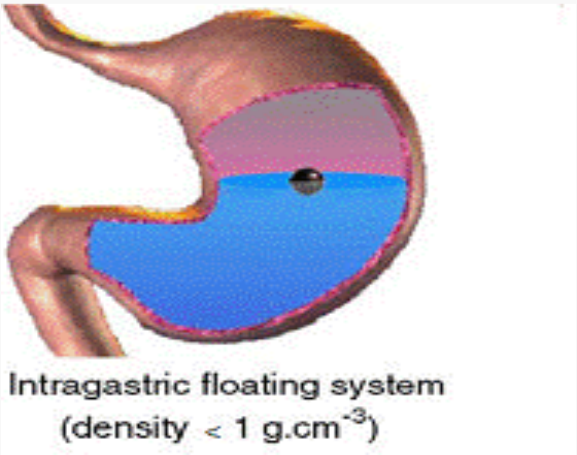


Fig: 5 Graphic of the buoyant tablet which is less dense than the stomach fluid and therefore remains in the fundus.

(B) Bio/Muco-adhesive systems

Bio/muco-adhesive systems, [5] bind to the gastric epithelial cell surface or mucin, which extends the GRT of drug delivery system in the stomach. The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio/muco-adhesive polymers. The ability to provide **adhesion** of a **drug** delivery system to the **gastrointestinal wall** provides longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect. Binding of polymers to the mucin/epithelial surface can be divided into three categories:

1. Hydration-mediated adhesion:

Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bio adhesive properties.

2. Bonding-mediated adhesion:

The adhesion of polymers to a mucus/epithelial cell surface involves various bonding mechanisms, including physical-mechanical bonding and **chemical bonding**. Physical-mechanical bonds can result from the insertion of the adhesive material into the folds or crevices of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions (i.e., Vander Waals interactions) and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups.

3. Receptor-mediated adhesion:

Certain polymers bind to **specific receptor sites** on the cell surfaces, thereby enhancing the gastric retention of dosage forms.

Various investigators have proposed different mucin-polymer interactions, [4] such as:

- Wetting and swelling of the polymer to permit intimate contact with the biological tissue.
- Interpenetration of bio adhesive polymer chains and entanglement of polymer and mucin chains.
- Formation of weak chemical bonds.
- Sufficient polymer mobility to allow spreading.
- Water transport followed by mucosal dehydration (Lehr, 1992; Mortazavi, 1993).

The bioadhesive coated system when comes in contact with the mucus layer, various non-specific (Vander Waals, hydrogen bonding and/or hydrophobic interactions) or specific **interactions** occurs between the complimentary structures and these interactions last only until the turnover process of mucin and the drug delivery system should release its drug contents during this limited adhesion time, in order for a bio adhesive system to be successful.

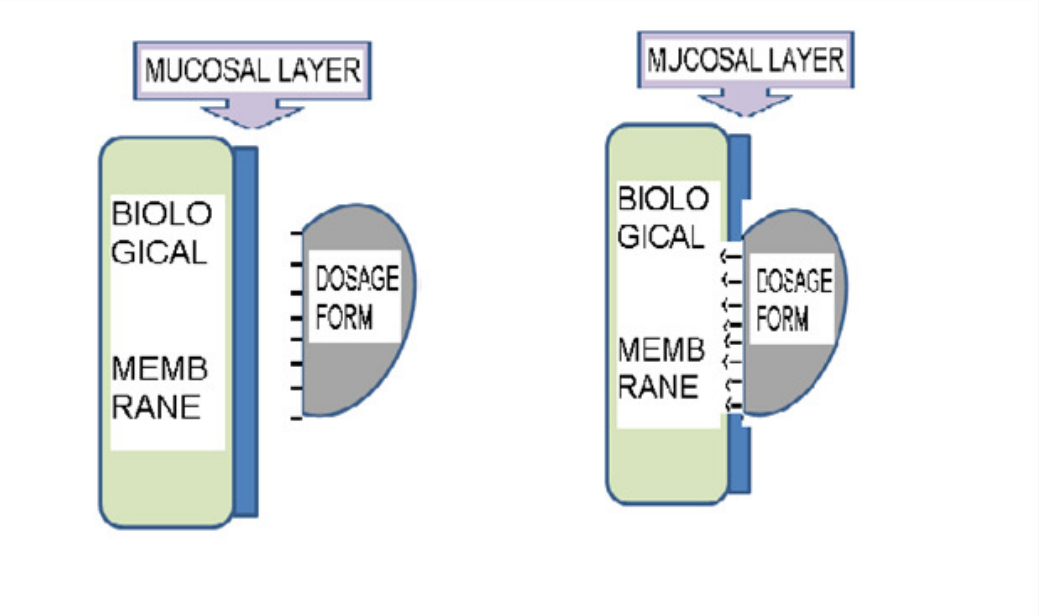


Fig: 6 Bioadhesive systems

(C) Raft-forming systems: [61]

These systems, [9] contain gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates), which on contact with the gastric contents, swells and forms a **viscous cohesive gel** containing **entrapped CO_2** bubbles, releases drug slowly in stomach by forming the raft layer on the top of gastric fluid (Fig.4). These formulations contain antacids such as calcium carbonate or aluminium hydroxide to reduce gastric acidity.

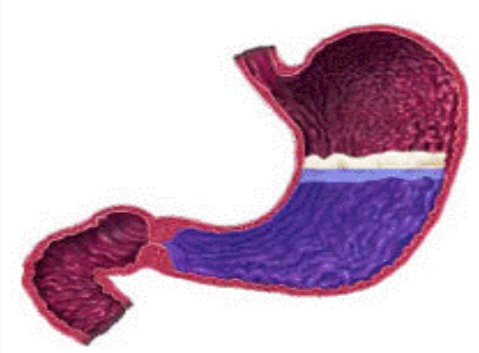


Fig: 7 Barrier formed by a raft-forming system

(D) Swelling and expanding systems: [60]

A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter, also the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations are required to develop an expandable system in order to prolong the gastric retention time (GRT), [9]:

1) A small configuration for oral intake.

2) An expanded gastroretentive form.

3) A final small form enabling evacuation following drug release from the device. Swellable systems, [9] (Fig.7), are also retained in the gastro intestinal tract (GIT) due to their mechanical properties. The swelling is usually results from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid.

- Expandable systems, [9] have some drawbacks like problematical storage of much easily hydrolysable, biodegradable polymers relatively short-lived mechanical shape

memory for the unfolding system most difficult to industrialize and not cost effective. Again, permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion and gastropathy.

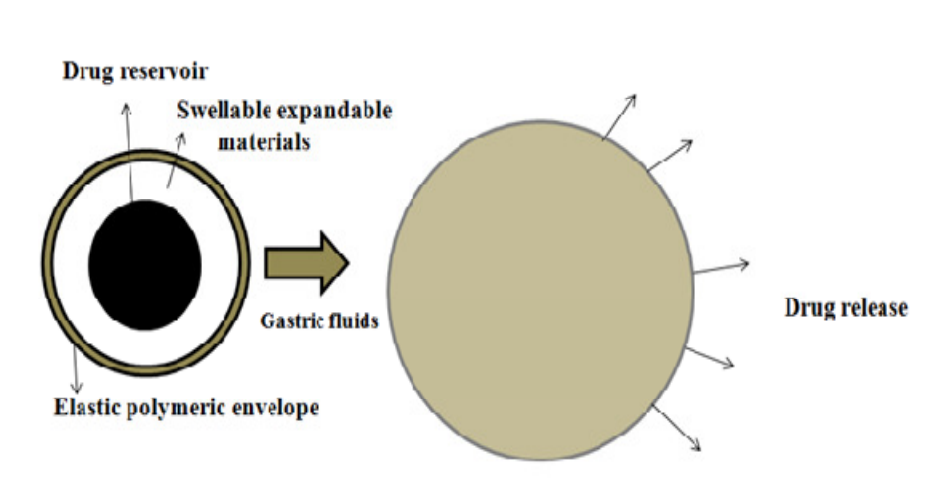


Fig: 8 Drug release from swellable systems

Thus, gastro retentivity is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Unfoldable and swellable systems have been investigated and recently tried to develop an effective gastro retentive drug delivery.

Unfoldable and swellable systems have been investigated and recently tried to develop an effective gastro retentive drug delivery.

Unfoldable systems, [9] are made of biodegradable polymers. They are available in different **geometric forms** (Fig.6), like tetrahedron, ring or planner membrane (4 - label disc or 4 - limbed cross form) of bioerodible polymer compressed within a capsule which extends in the stomach.

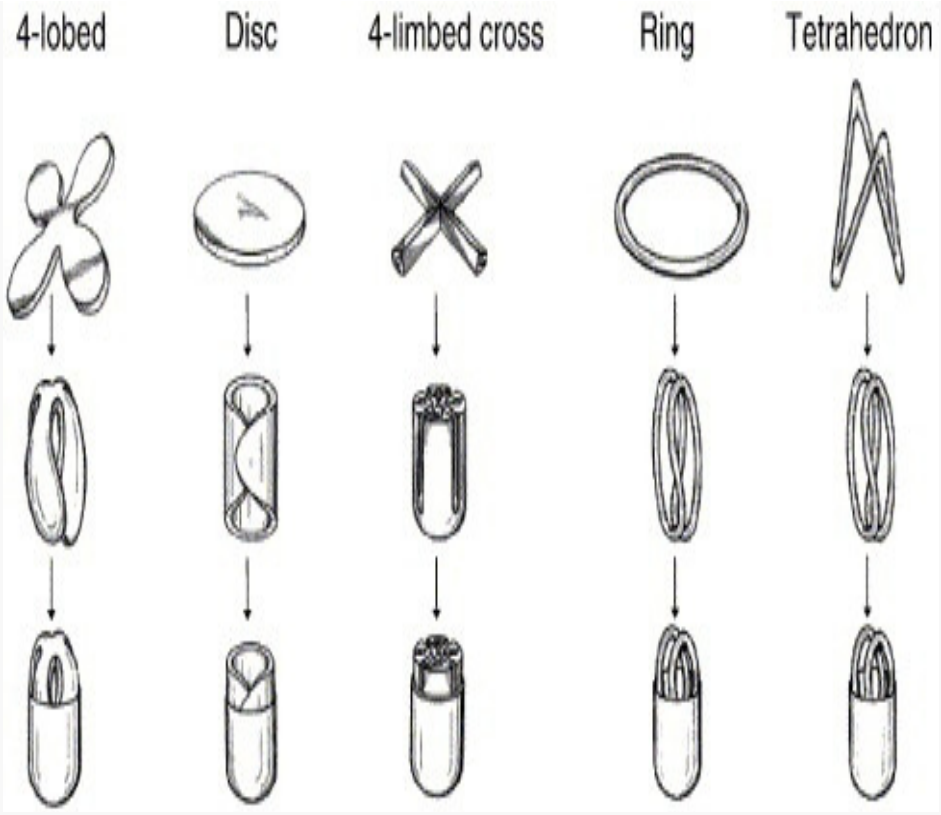


Fig : 9 Different geometric forms of unfoldable systems.

(E) Superporous Hydrogels:

Conventional hydrogels, with pore size ranging between **10 nm and 10 µm** has very slow process of water absorption and require several hours to reach an equilibrium state during which premature evacuation of the dosage form may occur while the superporous hydrogel (Fig.8), having average pore size (>100 µm), swell to equilibrium size within a minute, due to **rapid water uptake by capillary wetting** through numerous interconnected open pores. Moreover they swell to a large size (swelling ratio 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contractions. This is achieved by a co- formulation of a hydrophilic particulate material, Ac-Di-Sol (crosscarmellose sodium). [4]

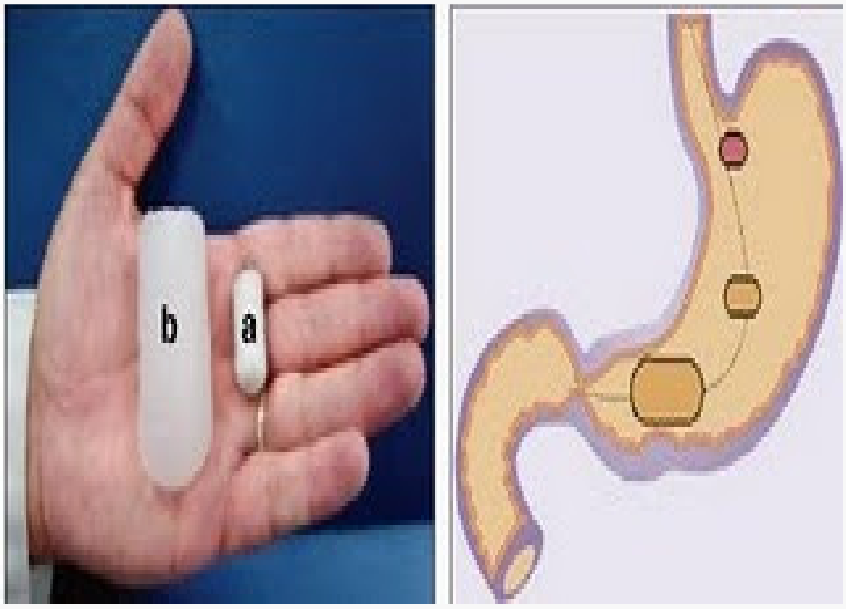


Fig:10 On the left, Superporous Hydrogels in its dry (a) and water-swollen (b) state. On the right, schematic illustration of the transit of Superporous Hydrogel.

(F) Magnetic systems:

This approach is based on the simple principle that the dosage form contains a small **internal magnet**, and a magnet placed on the abdomen over the position of the stomach to enhance the gastric retention time (GRT). [4] The external magnet must be positioned with a degree of high precision that might compromise patient compliance.

(G) Self-unfolding systems:

The self-unfolding systems are capable of mechanically increasing in size relative to the initial dimensions. This increase prevents the system from passing through the pylorus

and retains for a prolonged period of time in the stomach. A drug can be either contained in a polymeric composition of the gastro retentive system or included as a separate component. Several methods,[4] were suggested to provide for the self-unfolding effect

- The use of hydrogels swelling in contact with the gastric juice.
- **Osmotic systems**, comprising an osmotic medium in a semi-permeable membrane
- Systems based on low-boiling liquids converting into a gas at the body temperature

(H) High density systems:

These systems with a density of about 3 g/cm^3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of **2.6-2.8 g/cm^3** acts as a threshold value after which such systems can be retained in the lower part of the stomach. High density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. They are retained in the antrum of stomach, [5] (Fig.9).

Fig: 11 Graphic of heavy tablet which is denser than the stomach fluid and therefore sinks to the antrum

Floating drug delivery systems: [56, 64, 53]

A floating dosage form is useful for drugs acting locally in the proximal gastrointestinal tract. These systems are also useful for drugs that are poorly soluble (or) unstable in intestinal fluids. The floating properties of these systems help to retain in the stomach for a long time. Various attempts have been made to develop floating systems, which float on the gastric contents and release drug molecules for the desired time period. After the release of a drug, the remnants of the system are emptied from the stomach.

Based on the mechanism of buoyancy, two different technologies have been used in development of floating drug delivery systems. These include:

a) Effervescent system.

b) Non- Effervescent system.

a) Effervescent Systems

Effervescent systems, [5] include use of gas generating agents, carbonates (e.g. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to **produce carbon dioxide (CO_2)** gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature

.

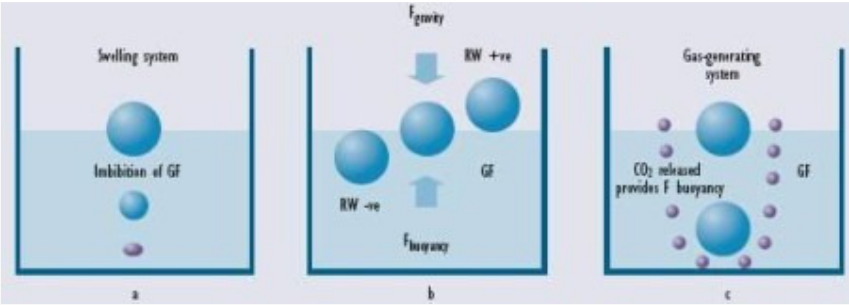


Fig: 12 Gas generating systems

These effervescent systems further classified into two types:

1) Gas generating systems.
2) Volatile liquid or vacuum containing systems.

1) Gas generating systems

A) Tablets: [29]

1. Intragastric single layer floating tablets or Hydrodynamically Balanced System (HBS)

These formulations have bulk density lower than gastric fluids and thus float in the stomach that increases the gastric emptying rate for a prolonged period, [5] (Fig.10). These are formulated by intimately mixing the gas (CO_2) generating agents and the drug within the matrix tablet. The drug is released slowly at a desired rate from the floating system and the residual system is emptied from the stomach after the complete release of the drug. This leads to an increase in the gastric residence time (GRT) and a better control over fluctuations in plasma drug concentration.

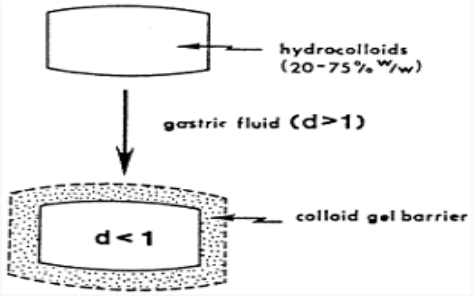


Fig 13: Intragastric single layer floating tablet

2. Intragastric bilayer floating tablets

These are also compressed tablets, [5] containing two layers (Fig.11):

- Immediate release layer
- Sustained release layer.

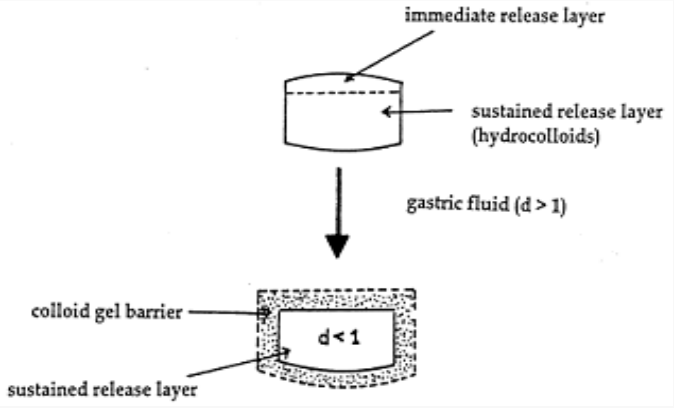


Fig 14: Intragastric bilayer floating tablet

B) Floating capsules

These floating capsules, [4] are formulated by filling with a mixture of sodium alginate and sodium bicarbonate. The systems float as a result of the generation of CO_2 that was trapped in the hydrating gel network on exposure to an acidic environment.

C) Multiple unit type floating pills

These multiple unit type floating pills, [5] are sustained release pills, known as 'seeds', which are surrounded by two layers (Fig.12). The outer layer is of swellable membrane layer while the inner layer consists of effervescent agents. This system sinks at once and then it forms swollen pills like balloons which float as they have lower density, when it is immersed in the dissolution medium at body temperature. The lower density is due to generation and entrapment of CO_2 within the system.

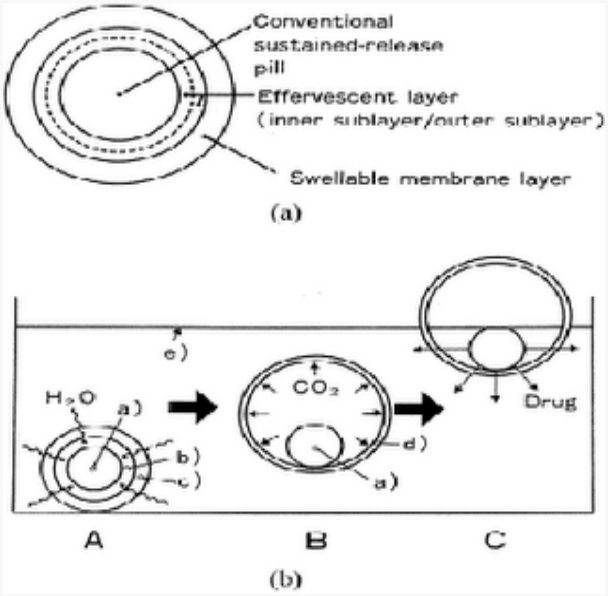


Fig: 15 (a) A multiple-unit oral floating dosage system. (b) Stages of floating mechanism: (A) penetration of water; (B) generation of CO_2 and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37^0C).

D) Floating system with Ion-Exchange resins

Floating system using bicarbonate loaded ion exchange resin was made by mixing the beads with **1M sodium bicarbonate** solution, and then the semi-permeable membrane is used to surround the loaded beads to avoid sudden loss of CO_2. On contact with gastric contents an exchange of bicarbonate and chloride ions takes place that results in generation of CO_2 that carries beads towards the top of gastric contents and producing a floating layer of resin beads. [4]

2) Volatile liquid or vacuum containing systems

(a) Intragastric floating gastrointestinal drug delivery system

This system floats in the stomach because of floatation chamber, which is **vacuum** or filled with a harmless gas or air, while the drug reservoir is **encapsulated** by a microporous compartment, [5] (Fig.13).

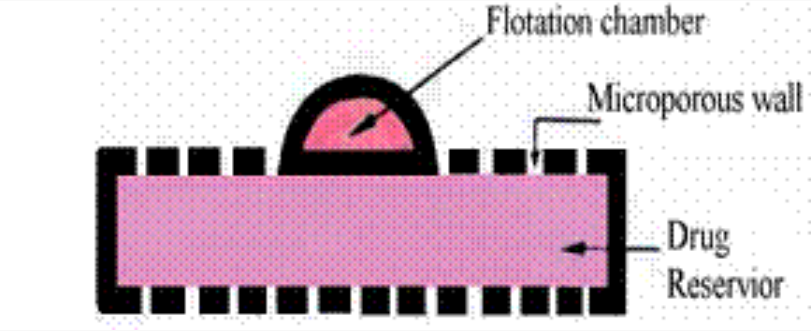


Fig: 16 Intragastric floating gastrointestinal drug delivery device

(b) Inflatable gastrointestinal delivery systems

These systems are incorporated with an inflatable chamber, which contains liquid ether that **gasifies at body temperature** to inflate the chamber in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug,

impregnated polymeric matrix, then encapsulated in a gelatin capsule, [5] (Fig.14). After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug is released continuously from the reservoir into gastric fluid.

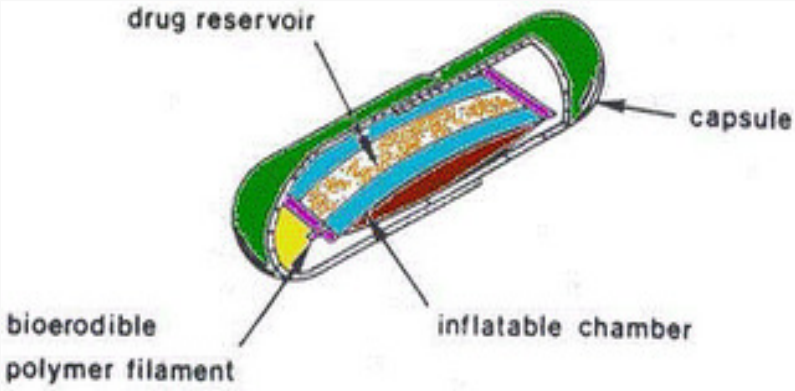


Fig: 17 Inflatable gastrointestinal delivery system

c) Intragastric osmotically controlled drug delivery system

This system is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule, [5] (Fig.15). On contact with the gastric contents in the stomach, the capsule disintegrates quickly to release the intragastirc osmotically controlled drug delivery device. The inflatable support inside forms a hollow polymeric bag which contains a liquid that gasifies at body temperature to inflate the bag and it is deformable. The osmotic pressure controlled drug delivery device consists of two components, **osmotically active** compartment and a drug reservoir compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to liquid and vapor and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi-permeable

housing. In the stomach, the osmotically active salt present in the osmotically active compartment is dissolved by absorbing the water continuously present in the GI fluid through the semi-permeable membrane. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice. The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.

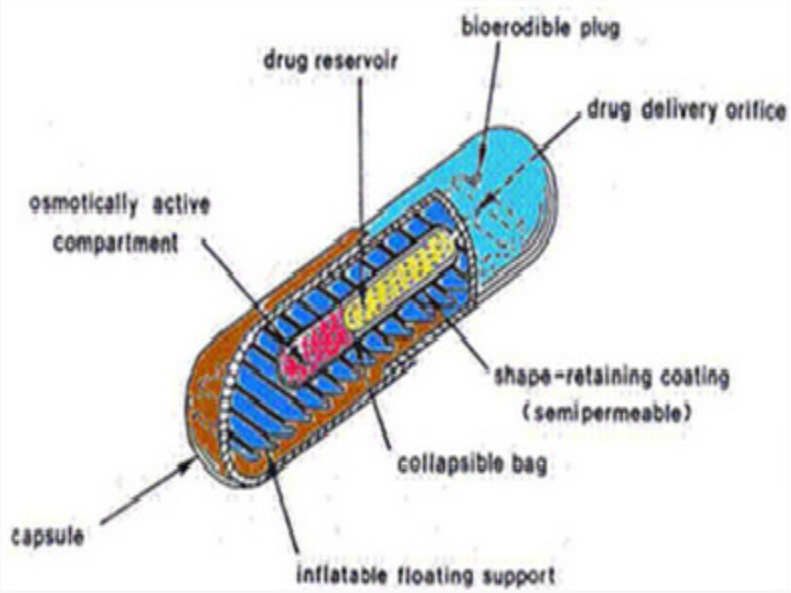


Fig: 18 Intragastric osmotically controlled drug delivery system

b) Non-Effervescent systems

The Non-Effervescent floating drug delivery systems are based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The various types of this system are:

1) Single layer floating tablets:

These are formulated by intimate mixing of drug with a gel forming hydrocolloid, that swells on contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the **swollen polymer** confers buoyancy to these dosage forms. [5]

2) Bilayer floating tablets

A bilayer tablet contain **two layer** one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach. [5]

3) Alginate beads

Multi unit floating dosage forms were developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of $CaCl_2$, causing precipitation of calcium alginate leading to formation of **porous** system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence, time of 1 hr, and these floating beads gave a prolonged residence time of more than 5.5 hours. [5]

4) **Hollow microspheres**

Hollow microspheres (microballons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method (Fig.16). The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40^0C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an

internal cavity in **microsphere of polymer with drug.** The microballons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro*. [5]

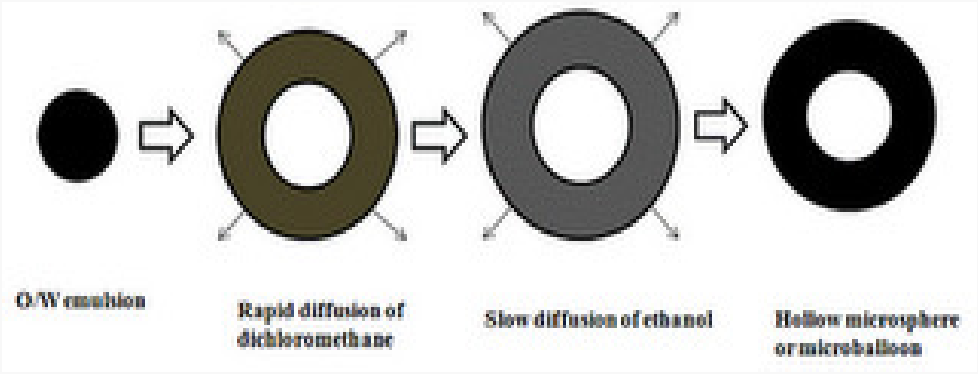


Fig: 19 Formulation of floating hollow microsphere or microballoon

v) EVALUATION OF FLOATING SYSTEMS

I.PRELIMINARY EVALUATION:

a) Buoyancy Lag Time

It is determined in order to assess the **time taken** by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

b) Floating Time

Test for buoyancy is usually performed in SGF-Simulated Gastric Fluid maintained at 370C. The time for which the dosage form **continuously floats** on the dissolution media is termed as floating time.

c) Specific Gravity / Density

Density can be determined by the displacement method using **Benzene** as medium.

II:IN-VITRO DISSOLUTION TESTS34.39

A. In vitro dissolution test is generally done by using USP apparatus with paddle and GRDDS is placed normally as for other conventional tablets. But sometimes as the vessel is large and paddles are at bottom, there is much lesser paddle force acts on floating dosage form which generally floats on surface. As floating dosage form not rotates may not give proper result and also not reproducible results. Similar problem occur with swellable dosage form, as they are hydrogel may stick to surface of vessel or paddle and gives irreproducible results. In order to prevent such problems, various types of modification in dissolution assembly made are as follows.

B. To prevent sticking at vessel or paddle and to improve movement of dosage form, method suggested is to keep paddle at surface and not too deep inside dissolution medium.

C. Floating unit can be made fully submerged, by attaching some small, loose, non reacting material, such as few turns of wire helix, around dosage form. However this method can inhibit three dimensional swelling of some dosage forms and also affects drug release.

D. Other modification is to make floating unit fully submerged under ring or mesh assembly and paddle is just over ring that gives better force for movement of unit.

E. Other method suggests placing dosage form between 2 ring/meshes.

F. In previous methods unit have very small area, which can inhibit 3D swelling of swellable units, another method suggest the change in dissolution vessel that is indented at some above place from bottom and mesh is place on indented protrusions, this gives more area for dosage form.

G. Inspite of the various modifications done to get the reproducible results, none of them showed co-relation with the in-vivo conditions. So a novel dissolution test apparatus with modification of Rossett-Rice test Apparatus was proposed.

III) IN-VIVO EVALUATION

a) Radiology

X-ray is widely used for examination of internal body systems. Barium Sulphate is widely used Radio Opaque Marker. So, $BaSO_4$ is incorporated inside dosage form and X-ray images are taken at various intervals to view GR.

b) Scintigraphy

Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is 99Tc.

c) Gastroscopy

Gastroscopy is peroral endoscopy used with fibre optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of GRDDS.

d) Magnetic Marker Monitoring

In this technique, dosage form is magnetically marked with incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment. Advantage of this method is that it is radiation less and so not hazardous.

e) Ultrasonography

Used sometimes, not used generally because it is not traceable at intestine.

f) 13C Octanoic Acid Breath Test

13C Octanoic acid is incorporated into GRDDS. In stomach due to chemical reaction, octanoic acid liberates CO_2 gas which comes out in breath. The important Carbon atom which will come in CO_2 is replaced with 13C isotope. So time up to which $13CO_2$ gas is observed.

Advantages of floating drug delivery system[5]

- The principle of Hydrodynamically Balanced System (HBS) can be used for any particular medicament or class of medicament. The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach, since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine. e.g. Chlorpheniramine maleate.

- The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.

- The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments.

- Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolved drug is available for absorption in the small intestine, therefore it is expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline p^H of the intestine.
- Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system

designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine.

- When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, poor absorption is expected under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
- Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.

Limitations of floating drug delivery system[11]

- The floating system requires, sufficiently high level of fluid in the stomach for the system to float, this can be overcome by administering dosage form with a glass full of water (200-250 ml) or coating the dosage form with bioadhesive polymer which adhere to gastric mucosa.
- Aspirin and non steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.
- Drugs, such as Isosorbide dinitrate, that are absorbed equally throughout the GI tract, drugs undergoing first pass metabolism will not benefit from incorporation into a gastric retention system.
- Floating dosage form should not be given to the patients just before going to the bed as gastric emptying occurs rapidly when the subject remains in supine posture.
- Drugs that have stability or solubility problem in gastrointestinal fluid or that irritate gastric mucosa are not suitable.

- Drugs that have multiple absorption sites or which undergo first pass metabolism were not desirable.
- The single unit floating dosage form is associated with "all or none concept". This problem can be overcome by formulating multiple unit system like floating microballons or microspheres.

Applications of floating drug delivery system[11]

Sustained drug delivery:

Hydrodynamically Balanced System (HBS) type are dosage forms which have bulk density less than one, relatively large in size and did not easily pass through pylorus, releases the drug over a **prolonged period of time** by retaining in the stomach for several hours and by increasing the gastric residence time.

Site specific drug delivery:

Floating drug delivery systems are particularly useful for drugs having **specific absorption** from stomach or proximal part of the small intestine e.g. riboflavin, furosemide etc. The absorption of captopril has been found to be site specific, stomach being the major site followed by duodenum.

Absorption enhancement:

Drugs that have **poor bioavailability**, because of their absorption is restricted to upper GIT are potential candidates to be formulated as floating drug delivery systems, thereby improving their absolute bioavailability.

Minimized adverse activity at the colon

Retention of the drug at the stomach (HBS system), minimizes the amount of drug that reaches the colon, that **prevents the undesirable** activities of the drug in colon. This Pharmacodynamic aspect provides the rationale for GRDF formulation for betalactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

Reduction in plasma fluctuations:

Patients with advanced Parkinson's disease, experienced pronounced fluctuations in symptoms while treatment with standard L-dopa. A HBS dosage form provided a better control of motor fluctuations although its bioavailability was reduced by 50-60% of the standard formulation.

Peptic ulcer treatment:

H. Pylori, causative bacterium for peptic ulcers and chronic gastritis. Patients require high concentration of drug, to be maintained at the site of infection that is within the gastric mucosa. The floating dosage form due to its floating ability was retained in stomach and maintained high concentration of drug in the stomach. A sustained liquid preparation of Ampicillin, using sodium alginate was developed that spreads out and **adheres to gastric mucosal** surfaces and releases the drug continuously.

Suitable for poorly absorbed drugs.

Floating drug delivery systems are particularly useful for drugs which are poorly soluble or unstable in intestinal fluids and acid stable drugs and for those which undergo abrupt changes in their pH-dependent solubility due to pathophysiological conditions of GIT,

food and age, e.g. floating system for furosemide lead to potential treatment of Parkinson's disease. Approximate 30% drug was absorbed after oral administration.

CHAPTER – 3

LITERATURE REVIEW

1. **Rajashree Masareddy et al.,** developed and evaluated Floating matrix tablets of Riboflavin using METHOCEL K4M and Carbopol 971 P. The release studies showed that Carbopol showed better controlled release when compared to METHOCEL K4M.

2. **Enas M.Elmowafy et al.,** done a project on Release mechanisms Behind Polysaccharides-Based Controlled Release Matrix Tablets of Famotidine for the treatment of Hypertension. The work concluded that the matrix integrity, swelling, drug release and kinetics depended on the type and composition of polysaccharides.

3. **Praneeth kumar et al .,** formulated and characterized floating matrix tablets of Metoprolol succinate using Gelucire by melt solidification technique. The results indicated Gelucire was an appropriate carrier for floating DDS due to its hydrophobicity and low density.

4. **P.Patel et al.,** developed a sustained release non-effervescent floating tablets of captopril to avoid intestinal degradation and to prolong drug release. Incorporation of hydrophobic EC along with hydrophilic polymers yielded good results compared to hydrophilic polymers alone.

5. Sustained release floating tablets of Acyclovir was formulated and evaluated by **Sachin Kumar et al.,** using HPMC K4M, HPMC K100M and sodium alginate**.** Combinations of HPMC grades and sodium alginate yielded controlled release of drugs.

6. The study of Captopril floating tablets using various grades of HPMC by **Shwetha Sharma et al.,** suggested that 12 hour gastric residence and prevention of instability in intestine could be achieved for the drug by floating DDS.

7. **J.A.Raval et al.,** investigated the effects of formulation parameters on a floating controlled DDS of drug by diluents, hardness and low density foam powder. The results revealead that HPMC K100 M provided controlled release and 15% foam powder was sufficient to achieve desired floating behaviour.

8. **Sumit R.Rathi et al.,** developed a single unit gastro retentive DDS of Famotidine due to its shorter half life. The results indicated sodium alginate could be successfully used to modify release rates in hydrophilic matrix tablets.

9. **V.D.Havaldar et al.,** studied the influence of different polymers on gastric residence time and release rate of Atenolol. The results suggested that the formulations with higher swelling indices retarded drug release more than those with lower swelling indices.

10. **Gottimukkala jayapal reddy et al.,** developed and optimized a controlled release DDS of Nizatidine to increase its gastric retention time. It was concluded that HPMC K4M resulted better controlled release properties compared to SCMC.

11. **Baljit singh et al.,** made an attempt to synthesize gastro-retentive floating drug delivery system by simultaneous ionotropic gelation of alginate and sterculia gum by using $CaCl_2$ as cross linker. The beads thus formed have been characterized by scanning electron micrographs (SEMs), electron dispersion X-ray analysis (EDAX), Fourier transform infrared spectroscopy (FTIR) analysis. The swelling of beads has been carried out as a function of various reaction parameters and pH of the swelling media. In addition, in vitro release dynamics of anti-ulcer model drug pantoprazole from drug loaded beads in different release media has been carried out for the evaluation of the drug release mechanism and diffusion coefficients. Release of drug from beads occurred through Fickian type diffusion mechanism.

12. **Nagalakshmi S. et al.,** formulated and evaluated floating matrix tablets of Pioglitazone HCL by non-effervescent and effervescent techniques. The best formulation was identified as that containing HPMC K100 M which exhibited good floating behaviour and good controlled release properties.

13. **Sivabalan M. et al.,** formulated and evaluated Hydrodynamically balanced controlled DDS of Glipizide. The methodology of factorial design helped in determining the relationships between the factors acting on the system and the response of the system. The principle of HBS offered a suitable approach to obtain controlled release of Glipizide with enhanced bioavailability and reduced dosing frequency**.**

14. **Inez Jimenez-Martinez et al.,** carried out a work on the invitro sustained release of captopril from Metolose SH and sodium bicarbonate floating tablets varying the proportions of Metolose SH and sodium bicarbonate at two different compaction pressures. The increase of the matrix polymer proportion increased the maximum hydration volume.

15. **Rajesh Kumar Ranga et al.,** developed and characterized novel gastro retentive floating bioadhesive tablets of Glipizide which possess unique combination of floatation and bioadhesion properties. The results concluded that floating and bioadhesive tablets of glipizide were potential dosage forms due to its prolonged release in stomach as compared to conventional dosage forms.

16. **Prajapathi S.T. et al.,** developed floating matrix tablets of Domperidone to prolong the gastric residence of drug using **HPMC K4M and carbopol 934.** From the results it was observed that carbopol showed negative effect on floating properties but yielded controlled release profiles.

17. **Ramesh bomma et al.,** developed floating tablets of norfloxacin to prolong the gastric residence time of the drug. The invivo studies revealed that the tablets remained in the stomach for 6 hours in fasting human volunteers and indicated that gastric retention was increased by floating mechanism and would be a promising approach for delivery of anti ulcer drugs.

18. **Padmavathi j. et al.,** outlined a systemic approach for designing and developing ofloxacin floating tablets to prolong gastric residence time. Various grades of HPMC (K4M, K15, and K100M) were used to formulate floating tablets. The results indicated HPMC K4M yielded good results comparing to other formulations.

19. **Anil kumar J. Shinde et at.,** formulated and evaluated oral floating tablets of Cephalexin using hydrophilic polymer HPMC, sodium bicarbonate and citric acid. The results of factorial design indicated that high level of HPMC K100M and citric acid favoured preparation of controlled release floating tablets of Cephalexin.
20. **Hitesh P. Dalvadi et al.,** investigated the development and evaluation of gastro retentive tablets of Atenolol using various grades of HPMC. The results indicated that the formulations containing HPMC K100 M exhibited better retardation of drug release due to its swelling properties.

21. **Vishnu m.patel et al.,** developed a controlled release Gastroretentive dosage form of verapamil hydrochloride using hydrocolloid polymer like carbopol, HPMC (K4M,K15M, E15) and Xanthan gum by direct compression technique. Sodium bicarbonate was used as gas generating agent. The results showed that tablets containing Xanthan gum showed controlled release for 24 hours hence it was the suitable polymer for formulation of matrix tablets.

22. **Liandong hu et al.,** prepared floating matrix dosage form for dextromethorphan hydrobromide based on gas formation technique. The combination of sodium bicarbonate

(18mg) and hexadecanol (18mg) with HPMC K4M was found to achieve optimum invitro release and floatability. The tablets maintained controlled release upto 24 hours.

23. **Arunachalam A. et al., developed** a floatable drug delivery system of levofloxacin hemihydrates for sustained drug delivery and Gastroretentive property with special emphasis on optimization of formulations. It was found that effervescent floating drug delivery was a promising approach to achieve buoyancy and the addition of gel forming polymer controlled the drug release.

24. **Londhe S. et al.,** developed and evaluated floating DDS with Biphasic release of Verapamil hydrochloride. The floating behaviour of drug was studied in rabbit which showed gastric residence of 7 hour.

25. **Ferdous khan MD. et al.,** prepared and evaluated Gastroretentive floating tablets of theophylline using hydrophilic polymers. Sodium bicarbonate and citric acid were used as the gas generating agents. It was found that the release rate, extent and mechanisms were dependent on the concentration of the polymers and the gas generating agent. The results suggested a proper balance of a hydrophilic polymer and the soluble component could produce a drug release profile comparable to the theoretical release profile.

CHAPTER - 4

AIM OF THE WORK

Oral drug administration still remains the preferred route of choice for delivery of drugs into systemic circulation. Some drugs have ideal characteristics for good absorption throughout the g.i.t while the others present **difficulties due to narrow absorption window** in stomach and proximal gut, stability problems in intestinal fluids, poor solubility in intestine or requirement of local action in the stomach. Rapid and unpredictable gastro intestinal transit could result in incomplete drug absorption from the tablet leading to diminished efficacy of the administered dose.

Perindopril erbumine {2-Methylpropan-2-amine (2*S*, 3aS, 7aS)-1-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl) butyl] amino] propanoyl]octahydro - 1 *H*-indole-2-carboxylate}, a newer ACE inhibitor is used in the treatment of stable coronary artery disease and hypertension. Since the **drug is preferentially absorbed in the proximal small intestine** (narrow absorption window), the drug displays oral bioavailability problems in conventional dosage forms.

An elegant and simple way to improve drug absorption and for releasing the drug in a controlled manner is to hold a DDS above the absorption window. Because most absorption windows are thought to be located in proximal small intestine, the obvious strategy is to **hold the formulation in the stomach (i.e., gastro retention).** Gastro retention can be achieved via intra-gastric floating systems, sedimentation or high density systems, swelling or expandable systems, geometry or modified shaped systems and super porous hydro gels.

CHAPTER - 4

AIM OF THE WORK

High density systems have a technical difficulty in formulating a dosage form having a density of 2.4-2.8 kg/cm^2, bio-adhesive systems may be dislodged from its site of adhesion, expandable systems may expand in oesophagus or intestines or failed to reduce in size after drug absorption to permit its transit through intestine for excretion.

The attractive principle of **floating drug delivery system** is exploited by the use of **gel forming polymers** such as semi-synthetic derivatives of cellulose along with polysaccharides which swells in gastric fluids with a bulk density less than 1. It remains buoyant and floats on g.i fluids prolonging GRT. This floating dosage forms are well known as hydro-dynamically balanced systems.

The present investigation aims to develop floating dosage forms of perindopril erbumine by **non-effervescent technique** using polymers Hydroxy propyl methyl cellulose(HPMC) K100M, Methylcellulose(MC), Hydroxy propyl methyl cellulose(HPMC) E15 and polysaccharide Xanthan gum(XG) and to evaluate the formulations for *invitro* and i*nvivo* studies.

CHAPTER - 5

PLAN OF WORK

STEP-I

PREFORMULATION STUDIES:

1. Determination of λmax of Perindopril erbumine in 0.1M HCL.
2. Calibration curve for the Perindopril erbumine at λmax in 0.1M HCL.

STEP-II

FORMULATION OF FLOATING TABLETS:

1. Precompression Evaluation.
2. Preparation of Floating matrix tablets of Perindopril erbumine using different concentrations of hydrophilic swellable gel forming polymers (HPMC K100M, HPMC E15, MC, XG) by using non effervescent technique.

STEP-III

EVALUATION OF FLOATING TABLETS:

1. Determination of Floating behaviour.
2. Determination of Swelling Index.
3. In –vitro release Studies.
4. Kinetic Analysis of release data.

STEP-IV

Selection of best formulation.

STEP-V

EVALUATION OF BEST FORMULATION:

1. Comparison with marketed formulation
2. Effect of diluents
3. Stability studies
4. *Invivo* studies

STEP-VI

INTERACTION STUDIES:

1. Differential scanning calorimetric (DSC) studies

2. Fourier Transform Infra Red Spectroscopic (FT-IR) studies

CHAPTER – 6

MATERIALS AND EQUIPMENTS

MATERIALS:

Perindopril Erbumine	Gift sample from Orchid Pharma chennai
HPMC (different grades)	Gift samples from Orchid Pharma
Methyl Cellulose	Gift sample from Orchid Pharma
Xanthan Gum	Universal Scientific Appliances
Lactose	Universal Scientific Appliances
Dicalcium Phosphate	Universal Scientific Appliances
Talc	Universal Scientific Appliances
Magnesium Stearate	Universal Scientific Appliances
Hydrochloric acid	Universal Scientific Appliances

All other chemicals were of Analytical Grade.

EQUIPMENTS:

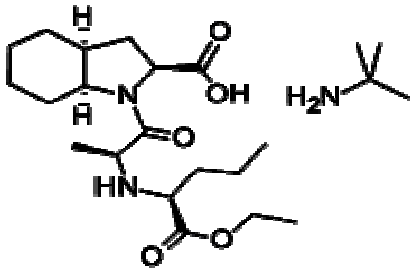
Electronic Weighing Balance	A & D Company HR 200 Japan
Single Punch Tablet Compression	Cadmach
UV Visible Spectrophotometer	Shimadzhu
Digital Tablet Dissolution Test Apparatus	Disso 2000, Lab India
Friability Test Apparatus	Indian Equipment Corporation
Incubator	Tempo Industrial Corporation
Hot air oven	Sico
Tablets hardness tester (Monsanto)	Secor India
Vernier Caliper	Linker
X-ray machine	Stallion 20, Elpro International Ltd.
Differential Scanning Calorimeter	DSC 60 Shimadzu

CHAPTER-VI

DRUG PROFILE [8, 11, 12, 18, 6, 9, 7]

PERINDOPRIL ERBUMINE

Structure:



Chemical name:

(2S, 3αS, 7αS)-1-[(S)-N-[(S)-1-Carboxy-butyl] alanyl] hexahydro-2-indolinecarboxylic acid, 1-ethyl ester, compound with tert-butylamine (1:1).

Empirical Formula: [17]

$C_{19}H_{32}N_2O_5C_4H_{11}N$.

Description:

Nature	:	white crystalline powder
Solubility	:	Freely soluble in water, alcohol and chloroform
Log P (Octanol/water)	:	2.6
Melting point	:	126 -128°C
Molecular weight	:	441.61

Identification:

208 nm in UV spectrophotometer

Pharmacodynamic properties:

Perindopril an angiotensin-converting enzyme inhibitor, Perindopril is a prodrug which is converted to active metabolite perindoprilat in liver. Perindoprilat the active metabolite competes with angiotensin converting enzyme blocking the conversion of angiotensin I to angiotensin II. It is a vasoconstrictor and a negative feedback mediator for renin activity. Lower concentrations result in decrease in blood pressure and an increase in plasma renin. Perindoprilat may also act on kininase II, an enzyme identical to ACE that degrades vasodilator bradykinin.

Pharmacokinetic properties: [52]

Absorption

- Rapid absorption after oral administration.
- T max is 1 hour for parent compound, 3 to 7 hour for active metabolite.
- Oral Bioavailability : 75% (Perindopril)
  25% (Perindoprilat)

Metabolism

- 30 – 60 % perindopril is converted to active metabolite perindoprilat in liver by the enzyme

Excretion

- Total Body Clearance: 219 - 362 ml/min.
- Mean Renal Clearance: 23.3 - 28.6 ml/min

Therapeutic indications

- Hypertension
- Stable coronary artery disease

Dose

- 4 mg and 8 mg. Maximum dose is 16 mg/day

Adverse Effects

- Postural Hypotension
- Hyperkalemia
- Cough
- Angio edema
- Neutropenia
- Agranulocytosis
- Anaphylactoid reactions
- Nausea
- Vomiting
- Dizziness

Drug Interactions: [67]

Diuretics:

Patients on diuretics and especially those started recently, may occasionally experience an excessive reduction of blood pressure after initiation of perindopril erbumine

therapy. The rate and extent of perindopril absorption and elimination are not affected by concomitant diuretics. The bioavailability of perindoprilat was reduced by diuretics, however, and this was associated with a decrease in plasma ACE inhibition.

Potassium Supplements and Potassium-Sparing Diuretics:

Perindopril erbumine may increase serum potassium because of its potential to decrease aldosterone production. Use of potassium-sparing diuretics (spironolactone, amiloride, triamterene and others), potassium supplements or other drugs capable of increasing serum potassium (indomethacin, heparin, cyclosporine and others) can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution and the patient's serum potassium should be monitored frequently.

Lithium:

Increased serum lithium and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be co administered with caution and frequent monitoring of serum lithium concentration is recommended. Use of a diuretic may further increase the risk of lithium toxicity.

Digoxin:

A controlled pharmacokinetic study has shown no effect on plasma digoxin concentrations when co administered with perindopril erbumine, but an effect of digoxin on the plasma concentration of perindopril/perindoprilat has not been excluded.

Over dose & Treatment:

Symptoms associated with over dosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. The recommended treatment of over dosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamine may also be considered. Perindopril may be removed from the general circulation by haemodialysis. Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

Prescription:

Yes

Generic Available:

Immediate-release tablets.

Preparations:

Immediate release tablets – 4mg and 8mg. Maximum dose is 16 mg/day

Storage:

It should be stored in a cool, dark and dry place.

Special Precautions

- Don't take potassium supplements without seeking medical advice

- Don't take during pregnancy.

Contra-indications

- Hypersensitivity to Perindopril
- History of angio edema.
- During Pregnancy.
- Hypotension.

Brand names:

- ACEON
- COVERSYL PLUS
- POVINACE
- APOPERINDOPRIL

CHAPTER - 8

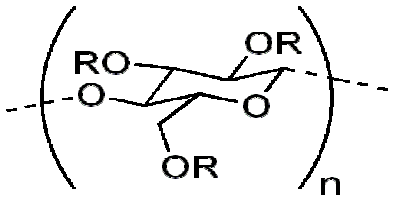
POLYMERS AND EXCIPIENTS PROFILE [9,19]

HYDROXY PROPYL METHYL CELLULOSE:

Synonym:

- Hypromellose.
- Methocel

Structure:



R = H or CH_3 or $CH_2CH(OH)CH_3$

Empirical formula:

- It ispartly O-methylated and O-(2-hydroxy propylated)cellulose. (PhEur 2005). It is available in several grades depending upon the viscosity and extent of substitution.

Molecular weight:

- 10 000 – 1 500 000

Description:

- **Colour:** White or creamy-white fibrous or granular powder.
- **Odour:** Odorless
- **Taste:** Tasteless

Solubility:

- Soluble in cold water, forming a viscous colloidal solution,
- Practically insoluble in chloroform, ethanol (95 %) and ether,
- Soluble inmixtures of ethanol and dichloromethane,
- Soluble in mixtures of water andalcohol.

Functional Category:

- Coating agent.
- Film- former.
- Stabilizing agent.
- Tablet binder.
- Viscosity increasing agent.

Typical Viscosity values for 2 % (w/v) aqueous solutions of different viscosity grades of HPMC at 20°C

Methocel K100 PremiumLVEP	:	100
Methocel K4M Premium	:	4000
Methocel K15M Premium	:	15000
Methocel K100M Premium	:	100 000
Methocel E4M Premium	:	4000
Methocel F50 Premium	:	50
Methocel E10M Premium CR	:	10 000
Methocel E3 Premium LV	:	3

Methocel E5 Premium LV	:	5
Methocel E6 Premium LV	:	6
Methocel E15 Premium LV	:	15
Methocel E50 Premium LV	:	50
Metolose 60SH	:	50, 4000, 10 000
Metolose 65SH	:	50, 400, 1500, 4000
Metolose 90SH	:	100, 400, 4000, 15 000

Storage Conditions:

- It should be stored in a well-closed container, in a cool, dry place.

Handling Precautions:

- Hypromellose dust may be irritant to the eyes and eye protection is recommended
- Excessive dust generation should be avoided to minimize the risks of explosion.
- Hypromellose is combustible.

REGULATORY STATUS:

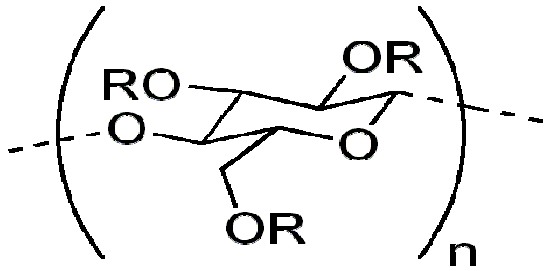
Included in the FDA inactive ingredients.Recognized by GRAS status.

METHYL CELLULOSE:

Synonym:

- Benecel,
- Metolose

Structure:



$R = H \text{ or } CH_3$

Empirical formula:

- Long-chain substituted cellulose containing approximately 27 – 32 % of the hydroxyl group in the form of methyl ether.

Molecular weight:

- 10 000 – 220 000 Dalton.

Description:

- **Colour:**White, fibrous powder or granules.
- **Odour:** Practically odorless and
- **Taste:** Tasteless.

Melting Point:

- 190–200°C.

Solubility:

- Practically insoluble in acetone, methanol, chloroform, ethanol (95 %), ether, saturated salt solutions, toluene and hot water.
- In cold water, it swells and disperses slowly to form a clear to opalescent, viscous, colloidal dispersion.

Functional Category:

- Bulk laxative (5.0 – 30.0 %).
- Emulsifying agent (1.0– 5.0 %),
- Tablet binder (1.0 – 5.0 %).
- Tablet Coating (0.5 -5.0 %).
- Tablet and capsuledisintegrant (2.0 – 10.0 %).

Storage Conditions

- It should be stored in an airtightcontainer in a cool, dry place.

Handling Precautions

- Irritant to theeyes & eye protection should be worn.
- Methylcellulose is combustible.
- Spills of the dry powder orsolution should be cleaned up immediately, as the slippery filmthat forms can be dangerous.

REGULATORY STATUS:

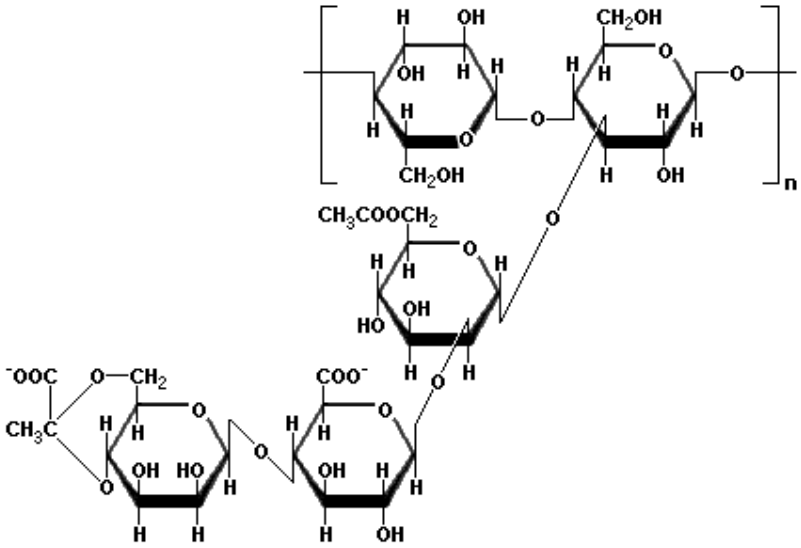
Included in the FDA inactive ingredients.Recognized by GRAS status.

XANTHAN GUM:[51]

Synonyms:

- Corn sugar gum.
- Keltrol.
- Rhodigel.
- Vanzan NF.
- Xantural.

Structure:



Empirical formula:

- $(C_{35}H_{49}O_{29})$ n

Molecular weight:

- 2×10^6

Description:

- **Colour:** White free flowing fine powder.
- **Odour:**Oduorless.
- **Taste:** Tasteless.

Melting point:

- Chars at 270°C.

Solubility:

- Practically insoluble in ethanol and ether;
- Soluble in cold or warm water.

Functional Category:

- Stabilizing agent.
- Suspending agent.
- Viscosity-increasing agent

Storage Conditions:

- It should be stored in a well-closed container.

Handling Precautions:

- Observe normal precautions appropriate to the circumstancesand quantity of material handled.
- Eye protection and gloves are recommended.

REGULATORY STATUS:

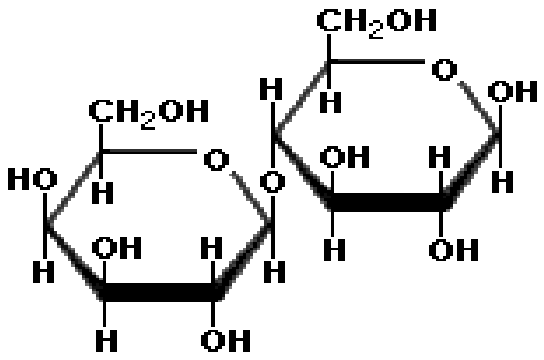
Included in the FDA inactive ingredients.Recognized by GRAS status.

LACTOSE:

Synonym:

- Lactopress Anhydrous.
- Lactosum.
- Milk sugar.

Structure:



Description:

- White to off-white crystalline particles or powder.

Empirical formula:

- $C_{12}H_{22}O_{11}$

Molecular weight:

- 342.30

Solubility:

- Soluble in water,
- Sparingly soluble in ethanol (95 %) and ether.

Functional Category:

- Binding agent.
- Directly compressible excipient.
- Lyopholization aid.
- Tablet and capsule filler.

REGULATORY STATUS:

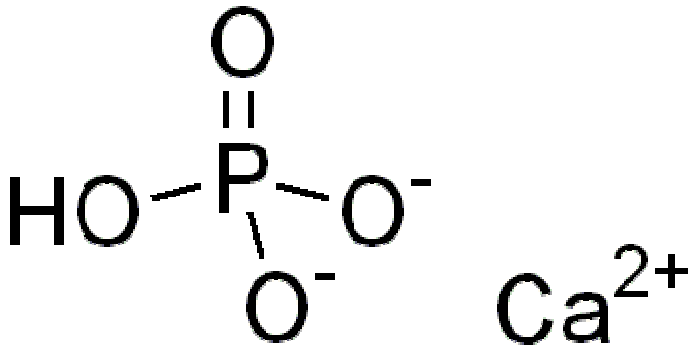
Included in the FDA inactive ingredients.Recognized by GRAS status.

DIBASIC CALCIUM PHOSPHATE:

Synonym:

- Calcium orthophosphate.
- Dicalcium orthophosphate.
- Phosphoric acid calciumsalt (1: 1).
- Secondary calcium phosphate.

Structure:



Description:

- **Colour:**White crystalline solid.
- **Odour:**Oduorless.
- **Taste:** Tasteless.

Empirical formula:

- CaHPO4

Molecular weight:

- 136.06

Melting point:

- It does not melt.
- It decomposes at 425°C to formcalcium pyrophosphate.

Solubility:

- Practically insoluble in ether, ethanol, and water;
- Soluble in dilute acids.

Handling Precautions:

- The fine-milled grades cangenerate nuisance dusts and the use of a respirator or dust maskmay be necessary.

Storage Conditions:

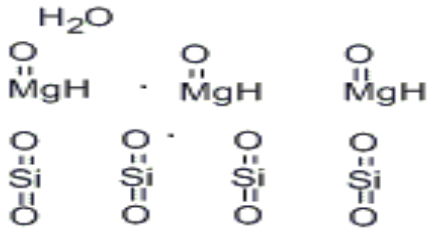
- It should be stored in a well-closed container in a dry place.

TALC:

Synonyms:

- Powdered talc.
- Purified French chalk.
- Soapstone.

Structure:



Empirical formula:

- $Mg_6(Si_2O_5)_4(OH)_4$

Description:

- **Appearance:**Very fine, unctuous, crystalline powder.
- **Colour:**White to grayish-white.
- **Odour:**Odorless, impalpable.

Solubility:

- Practically insoluble in dilute acids and alkalis,organic solvents, and water.

Storage Conditions:

- It should be stored in a tightly closed container in a cool and dry place.

Functional Category:

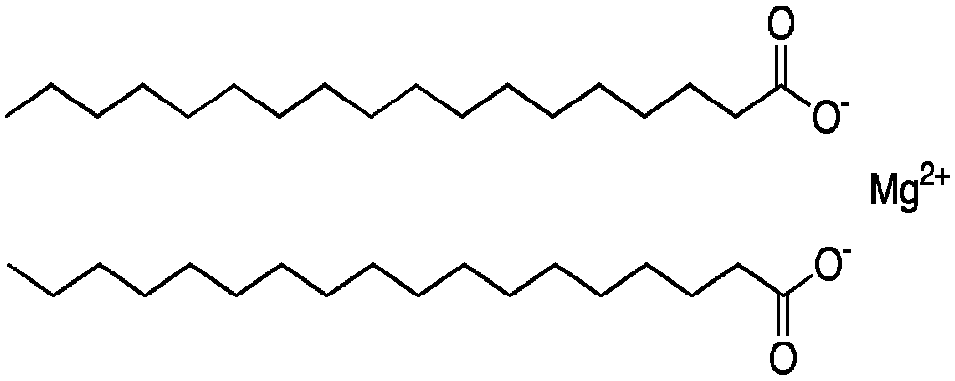
- Anti caking agent.
- Glidant.
- Lubricant.

MAGNESIUM STEARATE:

Synonyms:

- Magnesium octadecanoate.
- Octadecanoic acid.
- Magnesium salt.

Structure:



Chemical Name:

- Octadecanoic acid magnesium salt

Empirical formula:

- $C_{36}H_{70}MgO_4$

Molecular Weight:

- 591.34

Description:

- It is a very fine powder.

Solubility:

- Insoluble in ethanol, ether and water.
- Slightly soluble in warm benzene and warm ethanol95%.

Stability and Storage Conditions:

- It is stable and should be stored in a well closed container, in a cool, dry place.

Functional Category:

- Tablet and capsule lubricant.

CHAPTER – 9

EXPERIMENTAL DETAILS

PREPARATION OF DISSOLUTION MEDIUM: [51]

0.1 M HCL:

8.5 ml of hydrochloric acid was dissolved in distilled water and the volume is made up to 1L.

PREPARATION OF CALIBRATION CURVE FOR PERINDOPRIL ERBUMINE:

To the powder containing 8mg of Perindopril erbumine, 10 ml of distilled water was added and the volume was made up to 100 ml with 0.1M HCL. Dilutions were made to get the concentration of 5 to 50 µg/ ml. 10µg/ml solution was scanned in (UV) spectrophotometer to find out the λ max and absorbance of the solution was measured at the obtained λ max (208 nm) [17].

The calibration graph was plotted by taking the concentration on X axis and respective absorbance in Y axis, to get a straight line as per like Beers law. The regression value was determined.

PREPARATION OF FLOATING TABLETS:

The floating tablets of perindopril erbumine were prepared by direct compression technique. Accurately weighed quantities of drug, polymer and lactose were manually mixed homogenously. The powder blend was passed through sieve no.22 and lubricated with talc

and magnesium stearate.150mg of powder blend was weighed and compressed into 8mm biconvex tablets. The formulations were prepared according to the table **2**.

PREFORMULATION STUDIES FOR POWDER BLEND:

BULK DENSITY: (g/ml) [11, 16]

Bulk density is the ratio between a given mass of powder and its bulk volume. Apparent bulk density was determined by pouring the weighed granules into a graduated cylinder via funnel and measuring the volume. Density was calculated using the formula,

$$\text{Bulk Density} = \frac{\text{Mass of the powder}}{\text{Bulk volume of the powder}} = \frac{W}{V_0}$$

TAPPED DENSITY: (g/ml) [15]

Tapped density is the ratio between a given mass of powder and the constant or final volume of powder after tapping. It was determined by tapping a graduated cylinder containing a known mass of granules for a fix number of taps until the powder volume has reached a constant value. The tapped density was computed using the formula,

$$\text{Tapped Density} = \frac{\text{Mass of the powder}}{\text{Minimum (tapped) volume of the powder}} = \frac{M}{V_f}$$

COMPRESSIBILITY INDEX: (I) [15, 14]

Compressibility is an important measure that can be obtained from the bulk and tapped densities. The flow ability of the granules was measured by the application of compressibility index given by the equation,

$$\mathbf{I = [1-V_f / V_0] \times 100}$$

Where, V_f = volume of the sample after tapping

V_0 = volume before tapping

Values of I:

- Below 15 % indicates to excellent flow characteristics
- Between 15% - 25% indicates good flow characteristics
- Above 25 % indicates poor flow ability

ANGLE OF REPOSE: [15,13]

Angle of Repose is defined as the maximum angle possible between the surface of the pile of powder and horizontal plane. The flow property of the powder blend was assessed by determining the angle of repose which was measured by allowing the granules to fall over a paper placed on a horizontal surface through a funnel kept at a suitable height (of about 6 cm from the paper). The angle of repose 'θ' is given by the formula:

$$\mathbf{\theta = \tan^{-1} (h / r)}$$

Where h = height of the heap

r = radius of the base of the heap

Angle of Repose	Type of flow
< 20°	Excellent
20°- 30°	Good
30°- 35°	Moderate
35°- 40°	Poor
> 40°	Very Poor

DRUG CONTENT OF POWDER BLEND: [15]

10mg drug equivalent of powder blend was dissolved in 10 ml of distilled water and the volume was made up to 100 ml with 0.1M HCL. The solution was filtered and 10ml of filtrate was diluted to 100ml with 0.1M HCL. The absorbance of the resulting solution was measured at λ max (208 nm) using UV spectrophotometer and the drug content was estimated.

POST COMPRESSION EVALUATION:

GENERAL APPEARANCE:

The formulated tablets were evaluated for general appearance viz colour, shape, odour, appearance etc.

HARDNESS:[23]

Hardness of the tablet was determined using **Monsanto** hardness tester. The hardness was measured in terms of kg/cm^2. 3 tablets were randomly picked from each batch and the hardness of the tablets was determined. The mean and standard deviation values were calculated for each batch.

FRIABILITY: [23 ,34]

Friability was determined using **Roche** friabilator. 20 tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through the distance of 6 inches with each revolution. After 4 min the tablets were reweighed and the percentage loss in tablet weight was determined.

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

THICKNESS & DIAMETER: [23]

Thickness of the tablet mainly depends upon the filling, physical properties of material to be compressed and compression force. **Vernier caliper** was used to measure tablet thickness and diameter. 3 tablets were randomly picked from each batch and the thickness and diameter of the tablets was determined.

WEIGHT VARIATION: [23, 22, 63]

20 tablets from each formulation were selected randomly, weighed individually and the average weight was calculated as per I.P method. Not more than two

tablets should deviate from the percentage as given in IP and none should deviate by more than twice that percentage.

ESTIMATION OF DRUG CONTENT FOR TABLETS: [23,]

10 mg drug equivalent of the powdered formulation was dissolved in sufficient amount of distilled water, made up to 100ml with 0.1M HCL and filtered. 10ml of the filtrate was made up to 100ml with 0.1M HCL. 10µg/ml solution was prepared from the above solution and analyzed for drug content.

IN VITRO BUOYANCY STUDIES: [24]

The tablets were placed in a beaker containing 250 ml of 0.1M HCL maintained at 37°C. The time required for the tablet to rise to the surface was determined as **floating lag time** and the time period up to which the tablet remained floating was determined as **total floating time**.

SWELLING STUDIES: [43, 45, 54, 26]

Swelling is a vital factor to ensure buoyancy and dissolution of floating matrix tablet. The swelling of polymers can be measured by their ability to absorb water and swell. Swelling studies were carried out in USP type II paddle apparatus containing 900ml of 0.1M HCL rotated at 50 rpm kept at 37°C. The tablets were placed in the medium withdrawn at an interval of 2, 4, 8, 12 hrs, blotted with filter Paper to remove excess water and weighed.

Swelling index = Final weight – Initial weight / Initial weight x 100

MATRIX INTEGRITY STUDIES: [32]

The relative matrix integrity of the floating tablets was inspected **visually**.

IN VITRO RELEASE STUDIES: [33, 42, 10, 40]

In vitro release studies were performed in USP type II paddle apparatus for 12 hours. The tablets were placed in the dissolution medium of 900 ml 0.1M HCL in the dissolution apparatus. The paddle was rotated at 50 rpm maintained at 37°C. 5 ml samples were withdrawn every 15 min for the first hour and every 30 min up to 12 hours. Sink conditions were maintained after each sampling. Samples were analyzed at 208 nm using UV spectrophotometer. The studies were done in triplicate. The results were shown in table **6.**

USP Dissolution Test Apparatus

KINETIC ANALYSIS: [55, 46]

The *In vitro* release profiles obtained from the floating tablets were fitted to zero order, first order, Higuchi, Hixson Crowell, Korsemeyer & Peppas model kinetics, to find out the mechanism of drug release.

Zero Order	:	$Q_t = Q_0 + K_0.t$
First Order	:	$In\ Q_t = In\ Q_0 + K_0.t$
Hixson-Crowell	:	$Q_0^{1/3} - Q_t^{1/3} + K.t$
Higuchi	:	$Q = KH.\ t^{1/2}$
Korsmeyer - Peppas	:	$M_t / M_0 = a.tn$

Fitness of release profiles to linear equations is assessed by comparing the coefficients of determination (r) values.

For cylinder type of systems, [58, 62]

n < 0.45	**:**	Classical Fickian diffusion
n=0.45 to 0.89	**:**	Anomalous Non Fickian transport i.e. coupled drug diffusion in the hydrated matrix and polymer relaxation (Indicators of both phenomenon)
n=0.89	**:**	Case II relaxational release transport - Zero order release (Polymer relaxation or swelling controlled systems)
n> 0.89	**:**	Super Case II tranpsort **.**

FT-IR STUDIES: [33, 21, 36, 37, 39]

The possibility of drug-excipient interactions are further investigated by FT-IR. The FT-IR graph of pure drug and combination of drug with excipient are recorded .The analysis is performed by using **Shimadzu** FT-IR Spectrometer. The scanning range is 450-4000 cm^{-1} and the resolution is $4cm^{-1}$. Samples are prepared in KBr pellets.

DIFFERENTIAL SCANNING CALORIMETRIC (DSC) STUDIES: [32]

DSC was performed using **Perkin Elmer STA 6000** Thermal Analyzer. The instrument was calibrated with indium standard. Accurately weighed (it varies from 3mg-25mg) samples were placed in an open type ceramic sample pans. Thermo grams were obtained by heating the sample at a constant heating rate of 8c/minute. A dry purge of Argon gas (60ml/min) was used for all runs. Samples were heated from 37-400°C.

SELECTION OF BEST FORMULATION:

The best formulation was selected depending on the results obtained from floating behaviour, swelling index, invitro release studies and kinetic analysis.

COMPARISON WITH MARKETED FORMULATION:

The release of the best formulation was compared with the marketed formulation and the results are shown in the figure.

EFFECT OF DILUENTS ON THE RELEASE OF BEST FORMULATION:

The release profile was determined for the best formulation replacing lactose with dicalcium phosphate and the results are shown in the figure.

In vivo X – RAY STUDIES: [58, 66, 49]

The *invivo* studies approved by Institutional Animal Ethical Committee reference No. 06444/ E1/4 / 2011 and were performed on healthy male albino rabbit weighing 2-3 kg. The animal was fasted overnight but allowed to take water ad libitum. Then 60 ml of 5 % dextrose solution was given immediately before administering the tablets (2 tablets – optional) by using stomach tube (No. 12 French catheter) and 20 ml syringes.

The tablets were made opaque by incorporating $BaSO_4$ instead of drug. The rabbit was exposed to X-ray imaging in the abdominal region, and photographs were taken at 0, 2, 4, 8, 12 hrs after administration of tablet. At hourly intervals 60 ml of 5 % dextrose solution was given to maintain optimum fluid level in the stomach. The gastric residence time was observed.

STABILITY STUDIES: [65, 20, 57]

To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines. The best formulation was kept in a stability chamber maintained at 27°C and 75 % RH for 3 months. Samples were analyzed for the drug content, floating behavior and other physiochemical parameters periodically.

CHAPTER – 10

RESULTS AND DISCUSSION

CALIBRATION OF PERINDOPRIL ERBUMINE:

The λ max of perindopril erbumine was determined by scanning the 10 μg/ml solution of the drug using UV spectrophotometer and was found to be **208** nm[6] (Fig. 21). The absorbance of the solutions (5 – 50 µg/ml) was measured in UV spectrophotometer at 208 nm. The correlation coefficient was found to be **γ = 0.99945**. The results are given in table and the calibration graph of perindopril erbumine is shown in Fig:22

FORMULATION OF NON-EFFERVESCENT FLOATING TABLETS:

From the trial studies, the formula was optimized depending on the floating behaviour of the tablets and the optimized formula is shown in the table 2. It was found that the tablets showed good floating behaviour at the concentration of 20-75 % of the hydrophilic polymers.[53] HPMC grades showed better buoyancy at **50% - 80%** concentration, while Methyl Cellulose (MC) showed good floating behavior at concentrations of **40% - 70%** [19]**.**

The floating lag time was inversely related to the concentration of hydrophilic polymers and the formula was optimized accordingly. Xanthan gum **(XG)** was combined with HPMC E15M to **over counter the eroding effect** of HPMC E15M.

PRECOMPRESSION STUDIES FOR POWDER BLEND:

The powder blend of all the formulations was evaluated for the pre-compression parameters such as Bulk Density, Tapped Density, Compressibility Index, Angle of Repose,

and Percentage Drug Content. The results are tabulated in table 3.

The Powder blend of all the formulations were found to possess **good flow property** which was indicated by angle of repose 24 - 29^0, bulk density 0.38 - 0.42, tapped density 0.50 - 0.53 and percentage compressibility index 18 – 24 as shown in the Table 3.

POST COMPRESSION EVALUATION: (12, 16)

PHYSIOCHEMICAL PROPERTIES:

The floating matrix tablets were evaluated for various parameters such as General Appearance, Hardness, Thickness, Diameter, Friability and Weight variation.

The formulated tablets were white colour, biconvex, and round shaped. All the tablets were elegant in appearance. Hardness of all the formulations were found to be in the range of 3.5 – 4 Kg/cm^2, thickness 2.8 – 3 mm, diameter 8 mm, friability less than 1% and weight variation within the acceptable limits as per I.P. The results are shown in the table 4

DRUG CONTENT:

The percentage drug content of all the formulations was found to be within the limits of 99 % - 101 % as per E.P.

IN VITRO BUOYANCY STUDIES:

The time required for the tablet to rise to the surface (floating lag time) and the time period up to which the tablet remained floating (total floating time) was determined visually.

Among the four formulations containing HPMC K100M, **F1 & F2 floated immediately** while F3 & F4 showed a lag time of 2 - 3 min. Formulations F5 – F8

(containing HPMC E15M alone) had a lag time of 3-4 min, while F13 – F16 (containing HPMC E15M & XG) had 7 – 9 min. This may be due to the denser matrix formed by incorporating XG [32]. Thus XG had a negative effect on floating properties. Formulations F9 – F13 (containing MC) had a floating time of 6 – 8 min.

Formulations containing HPMC K100M and MC floated more than 12 hours, but in the case of HPMC E15 (alone or along with XG) the formulations floated for 8 – 10 hours followed by erosion.

Floating lag time was found to decrease with increasing concentration of polymers. The results were shown in the table 5 and fig.23

SWELLING STUDIES: [26, 43, 45, 54]

The results of the swelling studies (table 5) indicated that the swelling index was directly proportional to the concentration of polymers (Fig.24) The hydrophilic polymers formed a gel layer around the tablet when they contacted water. This is due to the **penetration of solvent into the free spaces between macromolecular chains of the polymer and so the dimension of the polymer molecule was increased (swelling) due to polymer relaxation caused by stress of the penetrated solvent**.

Swelling index was found to increase in the following order,

HPMC K100M > MC > HPMC E15M&XG > HPMC E15M.

HPMC K100M and MC showed less swelling index in the beginning but highest swelling index was observed (more than 200%) at the end of 12 hours. HPMC E15 containing tablets showed rapid swelling in the initial hours up to a maximum of 77% but could not retain the integrity after 7 hours because of erosion. Formulation **F1** showed the maximum swelling index of **381.5 % (fig.25)**

MATRIX INTEGRITY: [32]

Regarding the matrix integrity studies **HPMC K100M and MC** containing tablets maintained their matrix integrity for more than **24 hours. HPMC E15** containing tablets were able to retain the integrity up to **8–10 hours**.

The results of swelling and matrix integrity studies may be attributed to the fact that larger concentration of high viscosity polymer induces the formation of strong viscous gel layer that slowed down the rate of hydration of tablet matrix; the process is repeated towards new exposed surfaces thus maintaining the matrix integrity. On the contrary, low concentration or low viscosity polymer allows **rapid hydration**, rapid swelling and rapid erosion thus **low matrix integrity**.

It was also found that reaching maximum swelling would have stretched the gel structure so that the bonds responsible for gel structure were broken thus initiating polymer erosion[32.]

IN-VITRO DISSOLUTION STUDIES:

The *invitro* release studies showed that the release profiles of different formulations varied according to the **type and concentration of polymers.**

Controlled release profiles were observed in the following order of 80% > 70% > 60% > 50% > 40% concentrations irrespective of the type of polymer. This may be due to the **increasing tortuosity and length of the diffusional path** through the matrix as the polymer content increases [29].

Tablets containing HPMC E 15M alone released their whole perindopril content in

6 – 8 hours (F5 – F8) and along with XG (F13 – F16) could be able to control the release up to 9 hours. Formulations containing MC showed controlled release up to 10.5 hours (F9) while HPMC K100M containing tablets showed controlled release **99.99%** up to **11** hours (F1) and remained stable.(Table 6A, 6B, 6C, 6D). The results are shown in Fig.26,27,28,29&30.

Results suggested the existence of an inverse correlation between swelling index and drug release. **The release of the matrix was largely dependent on the polymer swelling, drug diffusion and matrix erosion**. Among all the formulations F1 (high concentration & high viscosity polymer) had the better retardant effect (99.99% in 11 hours) because of the formation of **strong viscous gel layer that slowed down the rate of diffusion of medium into the tablet**.

KINETICS OF DRUG RELEASE: [30, 31, 38]

The kinetic studies of all the formulations showed that zero order plots were fairly linear as indicated by their high regression values (Table 7). Therefore it was ascertained that the drug release from all the formulations followed **zero order** kinetics. Further F1 showed the closest linearity to unity (r = 0.99) as shown in Fig.31.

Fitness of the data to **korsemeyer peppas** (Fig.32) plots resulted a linear graph with regression values close to 1, thus showed that the release of the drug from the matrix followed diffusion mechanism.

In order to find out the exact mechanism of drug release the diffusion exponent

(n value) of korsemeyer peppas model was determined. Formulations F1, F5 and F9 corresponding to higher concentration (80%) of HPMC K100 M, HPMC E15, MC exhibited Super Case II transport (n = 1.05, 0.9, 1.04 respectively), a special case of non-Fickian diffusion.

It was found that the mechanism for all the other formulations was anomalous non Fickian diffusion (the release from initially dry, hydrophilic glassy polymers after swelling became rubbery).

Thus it was evident that as **the concentration of polymer was increased the mechanism of drug release was shifted from anomalous non Fickian diffusion to Super Case II transport because higher polymer content would lead to zero order kinetics.**[42]

DIFFERENTIAL SCANNING CALORIMETRY: [32]

The DSC thermo grams of pure drug and the different polymers were shown in the Fig. An endothermic peak corresponding to the melting point of pure drug was prominent in all the drug polymer mixture, which suggested clearly that there was **no interaction** between the drug and the polymers and the drug was existed in its unchanged form.

FT-IR STUDIES: [39]

FT-IR spectrum of the drug and polymers are shown in the fig. The spectrum of the drug had characteristic peaks of C-H stretching (VF 2929, 2848, 2750), C=O stretching (VF 2640&1739 cm^{-1}), hydrogen bonded acids (VF 2551.61 cm^{-1}), C-H bending (VF 1392 cm^{-1}), OH bending (VF 1315, 1292, 1205 cm^{-1}), aromatic rings (VF 1566 cm^{-1}),

C-H rocking (939, 750, 703, 475 cm^{-1}) thus indicating the identity and purity of the drug.

All those characteristic peaks were also found in the spectrum of drug and polymer combinations and there was no change in the existing peaks.. This clearly indicated that there was **no interaction** between the drug and the polymer and the drug was present in its unchanged form.

SELECTION OF BEST FORMULATION:

From the above results of characterization F1 was selected the best formulation because,

- Invitro release profile : 99.99% in 11 hours
- Release kinetics : closest linearity to zero order kinetics(fig:
- Swelling Index : 381.5%
- Floating lag time : 0 seconds

The selected best formulation F1 was subjected to,

- Comparison with marketed formulation
- Effect of diluents
- Stability studies
- *Invivo* studies

COMPARISON WITH MARKETED FORMULATION:

The release of the best formulation was found to be 99.99% in 11 hours when

compared to the marketed formulation whose release was 99.98% within 1 hour. Thus the formulation F1 showed **controlled release** profile than the marketed conventional tablet. The results are shown in the fig.33

EFFECT OF DILUENTS ON THE RELEASE OF BEST FORMULATION:

The tablets were prepared by replacing lactose with dicalcium phosphate (of the best formulation). The tablets were elegant in appearance and floated immediately. The in vitro release studies showed that the drug release was prolonged up to 12 hours (99.97%) in the presence of DCP, while lactose containing formulation showed controlled release of 99.99% in 11 hours. The results revealed that **insoluble diluents** such as **DCP** could **retard** the drug release when compared to the soluble diluents such as lactose. The results are shown in the fig.34.

STABILITY STUDIES:

Optimized formulation F1 was subjected to stability studies at 40°C at 75% RH. The results showed no significant change in the physical appearance, and in vitro release studies during storage. Thus it was found that the gastro retentive floating tablets of perindopril erbumine were stable under these storage conditions. The results are shown in the table 8.

IN-VIVO X-RAY STUDIES:

The Barium sulphate containing floating tablets floated immediately showed hardness of 4 kg/cm^3 and thickness 3mm. The in-vivo floating behavior of the tablet was assessed by X-ray image studies in rabbits. Gastric radiography was done in the abdominal region at periodic time intervals using the X-ray machine.

Both the tablets were clearly seen in the GIT at different positions on the upper part

of the stomach confirmed its **in-vivo floating behavior**. Also the swelling of the tablet can be visualized from the increase in the size of tablets in the images taken at 2nd hour, 4th hour and 8th hour. Both the tablets retained the matrix integrity up to 12 hours. Gastric residence time was found to be more than 12 hours. Thus it was evident that the formulation could be retained in the gastric region to ensure complete release of drug.

The X-Ray photo graphs are shown in Fig.35.

CHAPTER - 11

SUMMARY AND CONCLUSION

- ✓ The present investigation was to develop floating dosage forms of perindopril erbumine by **non-effervescent technique** using different concentrations of gel forming hydrophilic polymers.
- ✓ Formulations containing **HPMC K100M** and MC floated **more than 12 hours**, but in the case of HPMC E15 (alone or along with XG) the formulations floated for 8 - 10 hours followed by erosion.
- ✓ Swelling index was found to increase in the following order,

  HPMC K100M > MC > HPMC E15M & XG > HPMC E15M.

- ✓ **Larger concentration of high viscosity polymer** induces the formation of strong viscous gel layer that **slowed** down the rate of hydration of tablet matrix while low concentration or low viscosity polymer allows **rapid hydration**, rapid swelling and rapid erosion thus **low matrix integrity.**
- ✓ The release of the matrix was largely dependent on the polymer swelling, drug diffusion and matrix erosion. Among all the formulations **F1** (high concentration & high viscosity polymer) had the better retardant effect **(99.99% in 11 hours**)
- ✓ Fitness of the data to **korsemeyer peppas** plots resulted a linear graph with regression values close to 1, thus showed that the release of the drug from the matrix followed diffusion mechanism.
- ✓ It was evident that as the concentration of polymer was **increased** the mechanism of drug release was shifted from anomalous non Fickian diffusion to **Super Case II transport.**

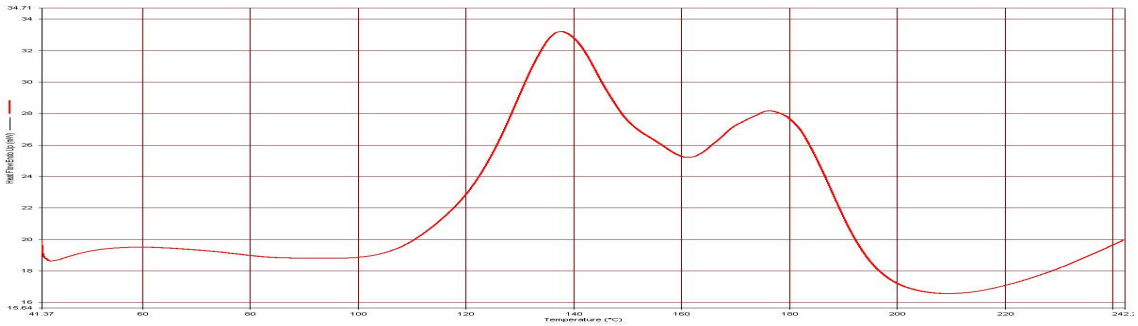
- ✓ The selected formulation F1 was found to be stable under the storage conditions and it exhibited gastric residence of more than **12 hours** in *invivo* studies.
- ✓ The results showed that insoluble diluents such as **DCP** could **retard** the drug release when compared to the soluble diluents such as Lactose.
- ✓ The *invivo* x-ray studies showed that the best formulation had gastric residence time of more than 12 hours.
- ✓ The selected formulation was stable under the conditions of 40°C at 75% RH.
- ✓ The FT-IR and DSC studies revealed that there was **no interaction** between the drug and the polymers.

CONCLUSION:

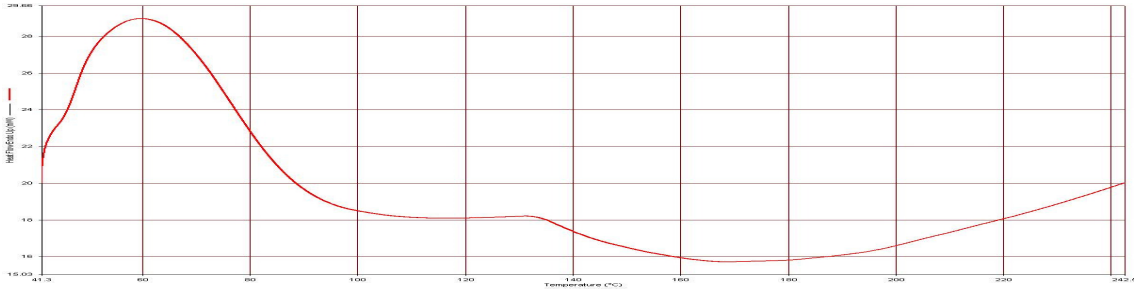
It was concluded that an inverse correlation existed between swelling index and the drug release i.e. the formulation having maximum swelling index showed better controlled release. The formulations containing HPMC K100M showed satisfactory results for floating and swelling behaviour as well as controlled release properties. In the best formulation (F1) swelling was strong enough to avoid premature disintegration as well as the burst effect and retarded drug release in a controlled manner for a longer period of time (11 hours) and 12 hour gastric residence was confirmed by invivo studies. Thus floating drug delivery system using high viscosity gel forming polymers would be a promising and feasible approach to achieve controlled release above the absorption zone especially for narrow absorption window drugs like Perindopril erbumine. It is the role of the future scientists to utilize the effectiveness of this delivery system clinically for hypertensive patients.

DSC THERMOGRAMS OF DRUG AND POLYMERS

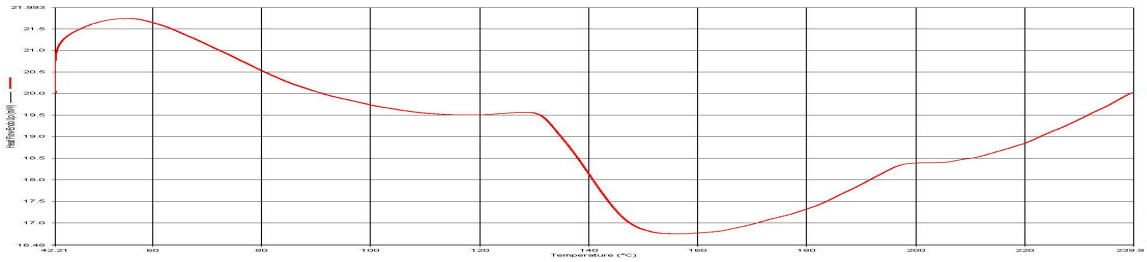
A



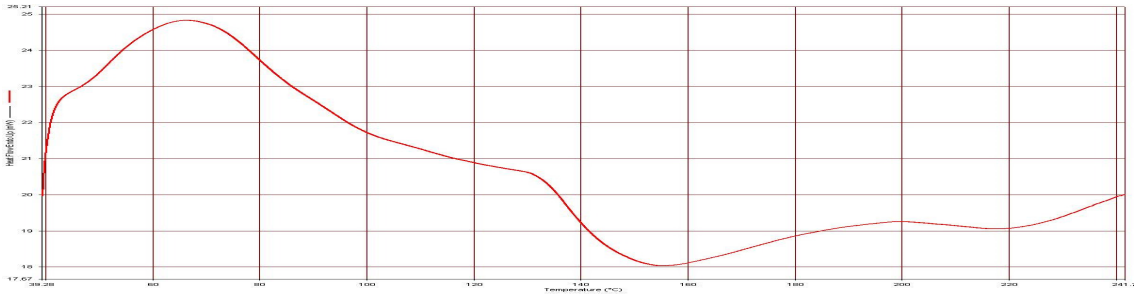
B



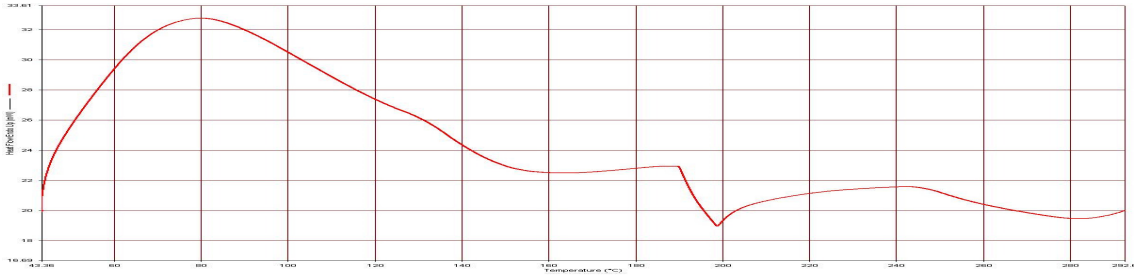
C



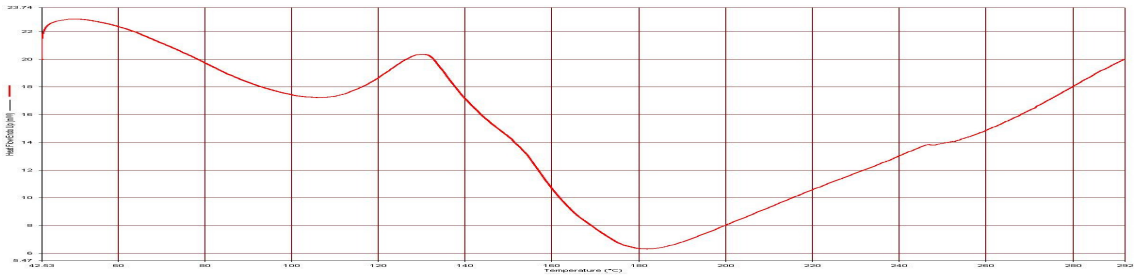
D



E



F



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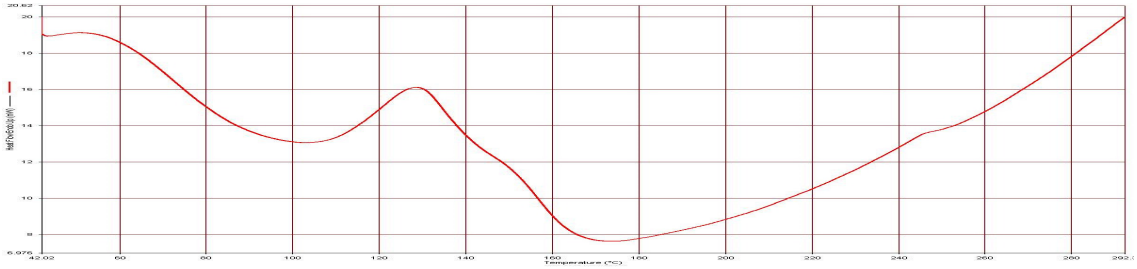
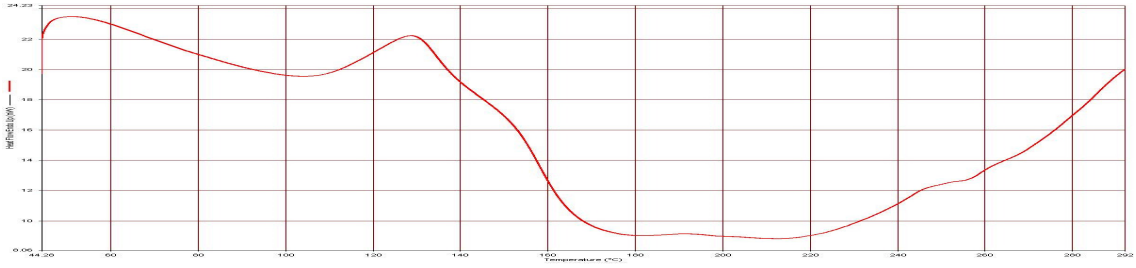


H



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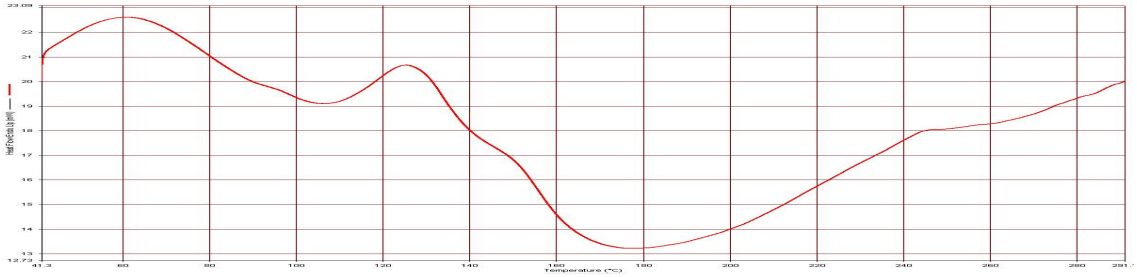

A) DRUG B)HPMC K100M C)HPMC E15 D)MC E)XG
F)DRUG+HPMC K100M G) DRUG+HPMC E15 H)DRUG+MC
I)DRUG+XG+XG

Table 1
Calibration of Perindopril erbumine

Medium : 0.1M HCL
λ max : 208 nm

S. No.	CONCENTRATION (µg/ml)	ABSORBANCE *	STANDARD DEVIATION * (± S.D)
1	5	0.115	0.0001
2	10	0.230	0.0008
3	15	0.346	0.0004
4	20	0.459	0.0023
5	25	0.573	0.0003
6	30	0.689	0.0022
7	35	0.804	0.0008
8	40	0.919	0.0010
9	45	1.033	0.0005
10	50	1.151	0.0025

* Average of three trials

Table 2
Formulation of Non-Effervescent Floating Tablets

Ingredients	Quantity (mg) for 1 tablet (total weight 150mg)							
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**
Perindopril erbumine	8	8	8	8	8	8	8	8
Hydro colloid Polymer	120	105	90	75	120	105	90	75
Lactose	19	34	49	64	19	34	49	64
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Ingredients	Quantity (mg) for 1 tablet							
	F-9	**F-10**	**F-11**	**F-12**	**F-13**	**F-14**	**F-15**	**F-16**
Perindopril erbumine	8	8	8	8	8	8	8	8
Hydro colloid Polymer	105	90	75	60	105	90	90	75
Xanthan Gum	-	-	-	-	15	30	15	30
Lactose	34	49	64	79	19	19	34	34
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Table 3
Preformulation Studies for the Granules of Non-Effervescent Tablets

Code No.	Bulk Density g / cc *	Tapped Density g / cc *	Compressibility Index (%) *	Angle of Repose (θ) *	% Yield of granules
F1	0.41	0.52	21	26.56	96.47
F2	0.39	0.51	23.5	27.15	99.21
F3	0.42	0.52	19	26.81	96.82
F4	0.38	0.53	24	27.67	98.21
F5	0.41	0.50	18	27.02	97.25
F6	0.42	0.51	18	26.56	96.86
F7	0.39	0.51	23.5	25.78	99.21
F8	0.42	0.51	18	24.56	96.82
F9	0.40	0.52	23	27.29	99.21
F10	0.38	0.51	22.4	28.32	99.23
F11	0.41	0.52	21.1	29.20	97.64
F12	0.39	0.51	23.4	26.40	98.82
F13	0.42	0.52	19.2	26.22	99.21
F14	0.41	0.51	19.6	25.12	98.82
F15	0.40	0.51	21.5	25.27	99.61
F16	0.41	0.51	19.6	24.81	98.82

Table 4
Post Compression Evaluation of Non-effervescent Floating Tablets

Code No.	Hardness (kg/cm^3)*	Thickness (mm)*	Diameter (mm)*	% Friability *	Average Weight (mg ±7.5 %)	% Drug Content
F1	3.5 – 4	3	8	0.53	149.6	99.21
F2	3.5 – 4	3	8	0.43	150.4	100.7
F3	3.5 – 4	2.8	8	0.61	151.6	98.64
F4	3.5 – 4	2.9	8	0.59	151.8	98.28
F5	3.5 – 4	3	8	0.9	150.3	98.64
F6	3.5 – 4	2.9	8	0.8	147.1	98.43
F7	3.5 – 4	3	8	0.71	147.5	99.21
F8	3.5 – 4	2.8	8	0.51	155.5	98.96
F9	3.5 – 4	2.8	8	0.2	152.7	99.6
F10	3.5 – 4	3	8	0.39	151.5	98.43
F11	3.5 – 4	2.9	8	0.72	150.3	98.82
F12	3.5 – 4	3	8	0.61	151.2	99.21
F13	3.5 – 4	2.8	8	0.1	157.7	99.6
F14	3.5 – 4	2.9	8	0.6	150.6	99.26
F15	3.5 – 4	3	8	0.7	153.4	99.21
F16	3.5 – 4	3	8	0.6	155.6	99.21

Table 5
Evaluation of Non-effervescent Floating Tablets

Formulation	Buoyancy lag time *	Total Floating Time (hrs)*	Swelling Index
F1	Float immediately	> 24 hrs	381.5
F2	Float immediately	> 24 hrs	362.7
F3	2 minutes 25 seconds	> 24 hrs	342.3
F4	3 minutes 50 seconds	> 24 hrs	335.1
F5	3 minutes 20 seconds	> 8 hrs	76.5
F6	3 minutes 50 seconds	> 8 hrs	61.2
F7	4 minutes 10 seconds	> 8 hrs	59.8
F8	4 minutes 25 seconds	> 8 hrs	57.4
F9	6 minutes 5 seconds	> 24 hrs	274.3
F10	7 minutes 10 seconds	> 24 hrs	256.4
F11	8 minutes 5 seconds	> 24 hrs	238.6
F12	8 minutes 8 seconds	> 24 hrs	225.4
F13	7 minutes 10 seconds	> 10 hrs	62.7
F14	8 minutes 30 seconds	> 10 hrs	68.8
F15	8 minutes 45 seconds	> 10 hrs	62.7
F16	8 minutes 50 seconds	> 10 hrs	77.2

In-Vitro Release Data of Non-Effervescent Floating Tablets

Table: 6 A

S. No.	Time (hrs)	Cumulative Percentage of Drug Release *			
		F-1	F-2	F-3	F-4
		K100M-80%	K100M-70%	K100M-60%	K100M-50%
1.	0.15	0.13 ± 0.08	3.23 ± 0.13	5.74 ± 0.63	8.52 ± 0.60
2.	0.30	3.25 ± 0.22	7.77 ± 0.29	7.11 ± 0.24	17.10 ± 0.24
3.	0.45	7.34 ± 0.17	10.67 ± 0.45	17.40 ± 0.42	21.35 ± 0.29
4.	1.00	9.34 ± 0.04	14.10 ± 0.70	21.50 ± 0.09	24.75 ± 0.15
5.	1.30	14.10 ± 0.46	17.62 ± 2.05	25.87 ± 0.17	28.06 ± 0.42
6.	2.00	22.84 ± 0.18	25.23 ± 3.09	29.40 ± 0.17	31.28 ± 0.33
7.	2.30	24.87 ± 0.44	27.31 ± 1.75	34.77 ± 0.17	38.60 ± 0.22
8.	3.00	28.89 ± 0.18	32.38 ± 0.43	41.50 ± 0.17	45.70 ± 0.13
9.	3.30	34.56 ± 0.35	36.17 ± 0.45	52.90 ± 2.74	59.60 ± 0.37
10.	4.00	38.65 ± 1.01	41.20 ± 3.24	65.40 ± 0.58	68.80 ± 0.21
11.	4.30	44.60 ± 0.27	47.60 ± 2.58	69.80 ± 0.82	73.70 ± 0.24
12.	5.00	49.45 ± 0.29	52.90 ± 0.73	74.70 ± 0.25	79.80 ± 0.58
13.	5.30	53.50 ± 0.17	57.70 ± 0.78	83.50 ± 0.78	87.80 ± 0.17
14.	6.00	59.61 ± 0.22	63.80 ± 0.45	88.60 ± 5.58	90.70 ± 3.45
15.	6.30	63.15 ± 0.25	67.90 ± 0.99	92.60 ± 0.21	96.20 ± 3.44
16.	7.00	66.95 ± 0.27	73.80 ± 0.59	94.60 ± 0.39	98.10 ± 0.93
17.	7.30	70.57 ± 1.21	76.70 ± 1.04	97.50 ± 0.24	100.00 ± 0.27
18.	8.00	71.76 ± 1.47	79.80 ± 0.39	100.20 ± 0.45	98.68 ± 0.17
19.	8.30	75.48 ± 1.82	84.60 ± 1.00	99.36 ± 0.62	98.15 ± 0.50
20.	9.00	80.10 ± 0.25	88.90 ± 0.86	98.82 ± 0.38	98.02 ± 0.70
21.	9.30	84.10 ± 0.04	96.80 ± 0.93	96.22 ± 2.89	98.01 ± 1.30
22.	10.00	90.98 ± 0.22	100.31 ± 0.21	95.62 ± 2.23	97.92 ± 0.87
23.	10.30	97.39 ± 0.61	99.81 ± 0.34	94.88 ± 1.75	97.66 ± 0.83
24.	11.00	99.99 ± 0.94	97.04 ± 3.23	94.53 ± 1.10	97.18 ± 1.50
25.	12.00	97.87 ± 3.77	96.79 ± 3.47	93.98 ± 1.39	97.07 ± 1.60

Table: 6 B

S. No.	Time (hrs)	Cumulative Percentage of Drug Release *			
		F-5	F-6	F-7	F-8
		HPMC E15 80%	HPMC E15 70%	HPMC E15 60%	HPMC E15 50%
1.	0.15	1.6 ± 0.14	3.4 ± 0.30	2.21 ± 0.41	4.6 ± 1.40
2.	0.30	7.7 ± 0.15	8.8 ± 0.40	10.06 ± 0.20	13.5 ± 0.30
3.	0.45	12.9 ± 0.24	15.7 ± 0.70	15.1 ± 0.90	18.9 ± 0.14
4.	1.00	22.5 ± 0.43	25.6 ± 0.40	22.3 ± 0.34	26.7 ± 0.58
5.	1.30	25.9 ± 0.16	29.1 ± 1.30	35.2 ± 0.51	38.9 ± 0.40
6.	2.00	31.8 ± 0.47	35.6 ± 0.40	38.33 ± 0.15	42.8 ± 2.21
7.	2.30	33.2 ± 0.46	38.1 ± 0.30	45.3 ± 0.13	49.8 ± 0.40
8.	3.00	39.3 ± 0.54	45.1 ± 0.30	50.1 ± 0.29	59.4 ± 2.45
9.	3.30	45.1 ± 0.33	48.9 ± 0.40	52.3 ± 0.77	62.8 ± 3.16
10.	4.00	49.9 ± 0.25	53.6 ± 0.40	60.6 ± 0.30	68.4 ± 0.82
11.	4.30	53.7 ± 0.19	59.5 ± 0.20	68.7 ± 0.20	78.7 ± 4.10
12.	5.00	57.9 ± 0.34	65.7 ± 0.30	78.7 ± 0.40	85.6 ± 4.50
13.	5.30	63.8 ± 2.70	71.1 ± 3.10	90.8 ± 0.22	93.6 ± 3.50
14.	6.00	68.5 ± 1.10	76.3 ± 3.50	96.3 ± 0.14	100.1 ± 2.50
15.	6.30	75.8 ± 3.30	78.4 ± 2.70	100 ± 0.60	98.3 ± 0.50
16.	7.00	80.2 ± 0.50	85.7 ± 1.70	96.9 ± 0.60	98.23 ± 0.60
17.	7.30	89.2 ± 0.30	95.7 ± 0.30	96.6 ± 0.50	98.12 ± 0.70
18.	8.00	96.5 ± 0.20	100.3 ± 0.80	95.99 ± 0.40	98.05 ± 0.95
19.	8.30	100.6 ± 0.20	99.1 ± 0.60	94.78 ± 0.30	97.96 ± 0.30
20.	9.00	98.68 ± 0.22	98.1 ± 0.70	94.3 ± 0.30	97.89 ± 0.45
21.	9.30	98.5 ± 0.64	97.7 ± 0.40	94 ± 0.20	97.88 ± 0.70
22.	10.00	98.4 ± 0.76	96.9 ± 0.60	93.04 ± 0.60	97.7 ± 0.60
23.	10.30	98.4 ± 0.88	95.8 ± 0.60	90.65 ± 3.35	97.2 ± 0.03
24.	11.00	97.6 ± 0.14	94.6 ± 0.70	89.88 ± 3.10	97.15 ± 0.73
25.	12.00	97.4 ± 0.48	93.8 ± 0.70	89.76 ± 3.42	97.01 ± 0.60

* Average of three trials

Table: 6 C

S. No.	Time (hrs)	Cumulative Percentage of Drug Release *			
		F-9	F-10	F-11	F-12
		MC 70%	MC 60%	MC 50%	MC 40%
1.	0.15	1.21 ± 0.40	3.30 ± 0.50	3.15 ± 0.50	3.15 ± 0.14
2.	0.30	3.6 ± 0.17	6.50 ± 0.40	10.63 ± 4.50	16.68 ± 0.28
3.	0.45	7.5 ± 0.19	9.43 ± 0.20	16.84 ± 4.90	26.11 ± 2.56
4.	1.00	10.43 ± 0.17	14.12 ± 1.60	23.43 ± 4.80	29.78 ± 0.40
5.	1.30	16.1 ± 0.33	20.13 ± 0.18	31.8 ± 0.40	34.11 ± 0.33
6.	2.00	22.66 ± 0.19	24.80 ± 0.10	35.5 ± 0.20	37.31 ± 0.38
7.	2.30	25.75 ± 0.01	31.70 ± 0.13	38.4 ± 0.22	41.71 ± 0.38
8.	3.00	27.72 ± 0.94	37.73 ± 0.25	40.6 ± 1.16	42.93 ± 0.20
9.	3.30	29.48 ± 0.47	41.00 ± 0.47	44.3 ± 1.25	47.28 ± 3.10
10.	4.00	32.22 ± 0.19	44.44 ± 0.17	48.8 ± 0.58	52.46 ± 2.70
11.	4.30	37.67 ± 0.17	45.7 ± 0.33	55.7 ± 1.39	57.92 ± 0.30
12.	5.00	44.65 ± 0.19	49.4 ± 0.50	59.6 ± 0.40	63.03 ± 4.80
13.	5.30	47.7 ± 0.17	54.7 ± 0.30	65.32 ± 4.40	69.91 ± 0.41
14.	6.00	56.76 ± 0.90	60.94 ± 1.30	69.18 ± 3.30	76.6 ± 0.19
15.	6.30	61.68 ± 0.54	66.82 ± 0.50	74.46 ± 0.41	93.8 ± 0.41
16.	7.00	67.58 ± 0.85	73.5 ± 0.33	88.54 ± 0.26	97.3 ± 0.37
17.	7.30	72.84 ± 0.19	79.1 ± 0.17	89.98 ± 0.49	99.99 ± 0.19
18.	8.00	76.39 ± 3.10	85.73 ± 0.24	95.96 ± 0.17	99.3 ± 0.14
19.	8.30	76.45 ± 0.90	90.23 ± 0.73	100.35 ± 2.70	98.8 ± 0.29
20.	9.00	85.73 ± 0.60	98.94 ± 1.70	99.66 ± 0.51	98.7 ± 0.30
21.	9.30	90.03 ± 0.90	100.39 ± 0.24	98.45 ± 1.20	98.3 ± 0.50
22.	10.00	100.62 ± 0.15	99.59 ± 0.33	97.58 ± 1.40	97.7 ± 0.40
23.	10.30	100.07 ± 0.17	98.85 ± 0.45	96.94 ± 1.20	95.9 ± 0.20
24.	11.00	99.44 ± 0.18	98.12 ± 0.25	96.1 ± 0.70	95.8 ± 0.20
25.	12.00	98.21 ± 0.80	97.61 ± 0.00	94.91 ± 0.50	95.5 ± 0.20

* Average of three trials

Table: 6 D

S. No.	Time (hrs)	Cumulative Percentage of Drug Release *			
		F-13	F-14	F-15	F-16
		E15 70% & XG 10%	E15 60% & XG20%	E1560% & XG10%	E15 50% & XG20%
1.	0.15	1.2 ± 0.00	3.2 ± 0.50	4.6 ± 0.10	6.4 ± 0.28
2.	0.30	5.9 ± 0.30	7.3 ± 0.40	8.6 ± 0.20	10.4 ± 0.40
3.	0.45	10.5 ± 0.40	12.4 ± 1.50	12.4 ± 0.30	13.4 ± 0.40
4.	1.00	15.2 ± 0.40	15.5 ± 0.50	16.4 ± 0.70	17.7 ± 0.30
5.	1.30	18.9 ± 0.50	22.5 ± 1.50	24.5 ± 0.40	25.6 ± 0.30
6.	2.00	25.3 ± 0.40	26.6 ± 0.30	28.5 ± 0.50	34.02 ± 0.33
7.	2.30	35.2 ± 0.50	36.5 ± 1.90	37.6 ± 0.20	39.5 ± 0.30
8.	3.00	38.5 ± 0.00	41.3 ± 0.50	42.5 ± 0.30	44.3 ± 0.20
9.	3.30	41.1 ± 0.30	43.6 ± 2.30	45.9 ± 0.01	47.6 ± 0.20
10.	4.00	44.7 ± 0.30	46.2 ± 1.90	49.5 ± 0.20	55.6 ± 0.20
11.	4.30	45.9 ± 0.30	49.9 ± 0.50	54.7 ± 1.20	58.7 ± 0.90
12.	5.00	51.2 ± 0.40	55.4 ± 0.70	62.7 ± 1.70	65.4 ± 0.30
13.	5.30	56.1 ± 0.80	61.9 ± 0.30	68.7 ± 0.90	72.9 ± 1.90
14.	6.00	62.2 ± 0.40	71.3 ±0.80	75.8 ± 0.40	77.9 ± 3.00
15.	6.30	68.9 ± 0.30	74.6 ± 0.20	81.9 ± 0.10	83.1 ± 3.70
16.	7.00	76.9 ± 1.90	79.7 ± 0.60	86.4 ± 0.04	88.6 ± 4.10
17.	7.30	79.9 ± 0.90	82.9 ± 0.10	91.6 ± 0.40	95.6 ± 0.30
18.	8.00	87.7 ± 0.90	88.5 ± 0.20	98.9 ± 1.10	100.5 ± 0.50
19.	8.30	91.7 ± 1.80	93.8 ± 1.60	100.2 ± 0.30	100.1 ± 0.20
20.	9.00	97.6 ± 0.50	100.7 ± 1.10	100.1 ± 0.50	99.6 ± 1.00
21.	9.30	100.4 ± 0.30	99.3 ± 1.60	98.8 ± 0.60	98.6 ± 0.20
22.	10.00	98.2 ± 0.30	99.2 ± 1.10	98.3 ± 0.40	98.1 ± 0.30
23.	10.30	97.4 ± 0.50	98.7 ± 0.90	98.1 ± 0.50	98.1 ± 0.10
24.	11.00	95.9 ± 0.50	97.9 ± 1.30	95.9 ± 0.04	96.4 ± 0.10
25.	12.00	95.1 ± 0.20	96.7 ± 1.80	94.5 ± 1.40	95.9 ± 0.30

* Average of three trials

Table 7

RELEASE KINETICS OF ALL THE FORMULATIONS

Formulations	Zero order kinetics		First order kinetics		Higuchi model		Korsemeyer peppas model		Hixon Crovel model	
	r^2	k	r^2	k	r^2	k	r^2	k	r^2	k
F1	0.99	8.82	0.72	0.11	0.93	32.8	0.98	1.05	0.86	0.29
F2	0.98	9.03	0.72	0.11	0.92	33.2	0.98	0.85	0.87	0.33
F3	0.85	8.82	0.61	0.11	0.93	35.4	0.99	0.78	0.82	0.34
F4	0.85	8.59	0.73	0.07	0.93	34.7	0.99	0.65	0.81	0.34
F5	0.94	9.08	0.66	0.09	0.94	35.1	0.95	0.96	0.88	0.35
F6	0.91	8.67	0.68	0.08	0.95	34.3	0.98	0.79	0.78	0.33
F7	0.79	8.18	0.56	0.08	0.91	33.9	0.95	0.83	0.67	0.27
F8	0.79	8.25	0.59	0.07	0.94	34.5	0.98	0.73	0.78	0.33
F9	0.98	8.56	0.74	0.13	0.98	34.5	0.98	1.04	0.84	0.35
F10	0.98	9.21	0.72	0.11	0.92	34.7	0.93	0.87	0.88	0.36
F11	0.93	8.74	0.62	0.11	0.95	34.1	0.97	0.74	0.82	0.34
F12	0.89	8.51	0.55	0.09	0.94	33.7	0.95	0.72	0.85	0.33
F13	0.92	8.97	0.68	0.10	0.94	35.2	0.98	0.76	0.83	0.36
F14	0.92	9.11	0.75	0.089	0.94	35.48	0.99	0.81	0.82	0.36
F15	0.96	9.12	0.75	0.09	0.94	34.93	0.98	0.85	0.89	0.34
F16	0.96	9.11	0.70	0.10	0.93	34.58	0.95	0.98	0.86	0.33

Table: 8

STABILITY STUDIES REPORT

F1 (HPMC 80 %)

Temperature: $40^0C \pm 2^0C$ and RH of 75 % ± 2 %

Intervals of Testing	Appearance	Hardness (4-4.5 kg / cm^2)	Floating Lag Time (< 1 min)	Drug Content (90- 110 %)
0 day	White colour, circular, biconvex tablets	4 kg / cm^2	Float immediately	100.5
15 days	White colour, circular, biconvex tablets	4 kg / cm^2	Float immediately	99.61
30 days	White colour, circular, biconvex tablets	4 kg / cm^2	Float immediately	101.87
45 days	White colour, circular, biconvex tablets	4 kg / cm^2	Float immediately	100.93
60 days	White colour, circular, biconvex tablets	4 kg / cm^2	Float immediately	100.86

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