FORMULATION AND EVALUATION OF
GASTRORETENTIVE FLOATING MICROSPHERES OF
ESOMEPRAZOLE MAGNESIUM TRIHYDRATE

DISSERTATION

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“With the blessings of Lord Ganesha”

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(Reg. No-26106807)
1. INTRODUCTION

1.1 MICROENCAPSULATION

Microencapsulation is a rapidly expanding technology. It is a means of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions. Microencapsulation is arbitrarily differentiated from macro coating techniques in that the former involves the coating of particles ranging dimensionally from several thousandths of a micron to 5000 microns in size.

Microencapsulation provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection, and of controlling the release characteristics or availability of coated materials.

Microencapsulation is a process whereby small discrete solid particles or small liquid droplets are surrounded or enclosed, by an intact shell. Two major classes of microencapsulation methods have evolved i.e. chemical and physical.

The first class of encapsulation method involves polymerization during the process of preparing the microcapsules. The second type involves the controlled precipitation of a polymeric solution where in physical changes usually occur.

Microencapsulation Process

Basic microencapsulation processes can be divided into chemical and mechanical.

Chemical Processes involved

- Complex coacervation
- Polymer-polymer compatibility
- Interfacial polymerization in liquid media
- In-situ polymerization
- In-liquid drying
• Thermal and ionic gelation in liquid media

**Mechanical Processes involved**

• Spray drying
• Spray coating
• Fluidized bed coating
• Electrostatic deposition
• Centrifugal extrusion
• Spinning disk or rotational suspension separation
• Polymerization at liquid-gas or solid-gas interface
• Pressure extraction or spraying into solvent extraction bath.

**Ideal Characteristics of Drug for Microencapsulation**

• The drug or the protein should not be adversely by the process
• Reproducibility of the release profile and the method
• No Stability Problem
• Particle size requirement

The lower the molecular weight, faster and complete is the absorption of the drug. The drugs having size 150-600 Daltons they can easily diffuse through the membrane.

• There should be no toxic product associated with the final product
• Therapeutic range

A candidate drug for controlled delivery system should have a therapeutic range wide enough such that variations in the release rate do not result in a concentration beyond this level.
• **Therapeutic index**

The ratio of maximum safe concentration to the minimum effective concentration of drug is called as therapeutic index. It is necessary because such drugs have toxic concentration nearer to their therapeutic range.

• **Elimination half life**

Drugs with $t_{1/2}$ in the range of 2 to 4 hours are good candidates.

Many drugs have been microencapsulated to reduce the gastric and other gastrointestinal tract irritation. The local irritation and release properties of a number of topically applied products can be altered by microencapsulation. This process is also used to mask the taste of bitter drugs.

Microencapsulation has been widely employed in the design of controlled release and sustained release dosage forms. It is the most recent addition to oral prolonged release mechanisms.

**Table No. 1**

**Microencapsulation Processes & their Applicability**

<table>
<thead>
<tr>
<th>Microencapsulation process</th>
<th>Applicable core material</th>
<th>Approximate particle size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air suspension</td>
<td>Solids</td>
<td>35-5000</td>
</tr>
<tr>
<td>Coacervation-phase separation</td>
<td>Solids &amp; liquids</td>
<td>2-5000</td>
</tr>
<tr>
<td>Multiorifice centrifugal</td>
<td>Solids &amp; liquids</td>
<td>1-5000</td>
</tr>
<tr>
<td>Pan coating</td>
<td>Solids</td>
<td>600-5000</td>
</tr>
<tr>
<td>Solvent evaporation</td>
<td>Solids &amp; liquids</td>
<td>5-5000</td>
</tr>
<tr>
<td>Spray drying and congealing</td>
<td>Solids &amp; liquids</td>
<td>600</td>
</tr>
</tbody>
</table>
1.4.1. Methods of Preparation of Floating Microspheres

Floating Microspheres can be prepared using any of the following techniques.

(a) Solvent Evaporation

It is the most extensively used method of microencapsulation, first described by (Ogawa et al.) a buffered or plain aqueous solution of the drug (may contain a viscosity building or stabilizing agent) is added to an organic phase consisting of the polymer solution in solvents like dichloromethane (or ethyl acetate or chloroform) with vigorous stirring to form the primary water containing an emulsifier like PVA or PVP to form the multiple emulsions (w/o/w). The double emulsion, so formed, is then subjected to stirring until most of the organic solvent evaporates, leaving solid microspheres. The Microspheres can then be washed, centrifuged and lyophilize to obtain the free flowing and dried microspheres.

(b) Emulsion Polymerisation

This method was first used by (Mathiowitz and Langer) to prepare microspheres of polyanhydride copolymer of poly [bis (p-carboxy phenoxy) propane anhydride] with sebacic acid. In this method, the polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 µm. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5°C above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particle solidify. The resulting microspheres are washed by decantation with petroleum ether.
(c) Solvent Removal

It is a non-aqueous method of microencapsulation, particularly suitable for water labile polymers such as the poly anhydrides. In this method, drug is dispersed or dissolved in a solution of the selected polymer in a volatile organic solvent like methylene chloride. After pouring the polymer solution into silicone oil, petroleum ether is added and stirred until solvent is extracted into the oil solution. The resulting microspheres can then be dried in vacuum \((\text{Mathiowitz and Langer})\)

(d) Spray Drying

In this process, the drug may be dissolved or dispersed in the polymer solution and spray dried. The quality of spray-dried microspheres can be improved by the addition of plasticizers, e.g. citric acid, which promote polymer coalescence on the drug particles and hence promote the formation of spherical and smooth surfaced microspheres. The size of microspheres can be controlled by the rate of spraying, the feed rate of polymer drug solution, nozzle size, and the drying temperature. This method of microencapsulation is particularly less dependent on the solubility characteristics of the drug and polymer and is simple, reproducible, and easy to scale up \((\text{Mathiowitz and Langer})\)
1.2. Classification of GRDDS

- Floating DDS (FDDS), with low density providing sufficient buoyancy to float over the gastric contents.
- Bioadhesive systems, enabling the localized retention of the system in the stomach.
- Swelling and expanding systems, preventing transit from the gastric sphincter.
- High density system, remaining in the stomach for longer period of time by sedimenting to the folds of stomach.
- Superporous hydrogels
- Modified-shaped system

1.2.1. Floating Drug Delivery Systems

The concept of FDDS was described in the literature as early as 1962. FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system. This results in an increased GRT and a better control of fluctuations in plasma drug concentration.

![Mechanism of floating system](image)

**Figure 1. Mechanism of floating system.**

Formulation of this device must comply with the following criteria

1) It must have sufficient structure to form a cohesive gel barrier.
2) It must maintain an overall specific gravity lower than that of gastric contents
   (1.004-1.010).

3) It should dissolve slowly enough to serve as a drug reservoir.

1.2.2. Types of floating drug delivery systems

   Based on the mechanism of buoyancy and two distinctly different technologies have been utilized in the development of FDDS.

1) Non-Effervescent FDDS

2) Effervescent FDDS

1) Non-Effervescent FDDS

   The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as Chitosan and carbopol.

Working Principle of Non-Effervescent Type of FDDS

   Capsule/tablet contains a mixture of drug and hydrocolloids. Upon contact with gastric fluid, the mixture swells and forms a gelatinous barrier thereby remaining buoyant in the gastric juice for an extended period of time.
The various types of this system are as:

**A. Single Layer Floating Tablets**

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity.

They are formulated by intimate mixing of drug with low-density enteric materials such as HPMC.

**B. Bi-layer Floating Tablets**

A bi-layer tablet contain two layer one immediate release layer which releases 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 (*Oth et al., 1992*).
C. 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 sodium alginate solution into aqueous solution of calcium chloride, 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 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours (Katayama et al., 1999).

D. Hollow Microspheres

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours in vitro (Kawashima, 1992).

2) Effervescent System

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO₂) 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 evaporates at body temperature.
These effervescent systems further classified into two types.

1. Gas generating systems

2. Volatile Liquid/Vacuum Containing Systems

1. Gas Generating Systems

A. Tablets

Floating bilayer tablets with controlled release for furosemide were developed by Ozdemir et al., 2000. The low solubility of the drug could be enhanced by using the kneading method, preparing a solid dispersion with β cyclodextrin mixed in a 1:1 ratio (Singh and Brahma, 2000). One layer contained the polymers HPMC K4M, HPMC K100M and CMC (for the control of the drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid. The in vitro floating studies revealed that the lesser the compression force the shorter is the time of onset of floating, i.e., when the tablets were compressed at 15 MPa, these could begin to float at 20 minutes whereas at a force of 32 MPa the time was prolonged to 45 minutes. Radiographic studies on 6 healthy male volunteers revealed that floating tablets were retained in stomach for 6 hours and further blood analysis studies showed that bioavailability of these tablets was 1.8 times that of the conventional tablets. On measuring the volume of urine the peak diuretic effect seen in the conventional tablets was decreased and prolonged in the case of floating dosage form.
Figure 3. Schematic presentation of working of a triple-layer system. (A) Initial configuration of triple-layer tablet. (B) On contact with the dissolution medium the bismuth layer rapidly dissolves and matrix starts swelling. (C) Tablet swells and erodes. (D) And (E) Tablet erodes completely.

B. Floating Capsules

Floating capsules are prepared by filling with a mixture of sodium alginate and sodium bicarbonate. The systems were shown to float during in vitro tests 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

The system consists of sustained release pills as ‘seeds’ surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO$_2$ within the system.
Figure 4. (a) A multi-unit oral floating dosage system. (b) Stages of floating mechanism: (A) penetration of water; (B) generation of CO₂ 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°C).

D. Floating System with Ion-Exchange Resins

A floating system using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1M sodium bicarbonate solution (Singh and Brahma, 2000). The loaded beads were then surrounded by a semi permeable membrane to avoid sudden loss of CO₂. Upon coming in contact with gastric contents an exchange of chloride and bicarbonate ions took place that resulted in CO₂ generation thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads. The in vivo behavior of the coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers by gamma radio scintigraphy. Studies showed that the gastric residence time was prolonged considerably (24 hours) compared with uncoated beads (1 to 3 hours).
2. Volatile Liquid / Vacuum Containing Systems

A. Intra-Gastric Floating Gastrointestinal Drug Delivery System

These systems can be made to float in the stomach because of the floatation chamber, which may be a vacuum or filled with air or a harmless gas, while the drug reservoir is encapsulated inside a micro-porous compartment.

Figure 6. Intra gastric floating gastrointestinal drug delivery device
B. Inflatable Gastrointestinal Delivery Systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, encapsulated in a gelatin capsule. 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 continuously released from the reservoir into the gastric fluid.

![Figure 7. Inflatable gastrointestinal delivery system](image)

C. Intragastric Osmotically Controlled Drug Delivery System

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intra-gastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active
salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. The osmotic pressure thus created acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate drug release 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.

![Intragastric osmotically controlled drug delivery system](image)

**Figure 8. Intragastric osmotically controlled drug delivery system**

**Bioadhesive Drug Delivery System**

**Bioadhesion/Mucoadhesion for Oral Drug Delivery**

The term bioadhesion is defined as adhesion to biological surface i.e. mucus and/or mucosal surface. In instances when the polymeric system interacts with mucus layer only, it is referred as mucoadhesion. In order to develop an ideal oral bioadhesive system, it is important to have a through understanding of mucosa, bioadhesive polymers and mucin-polymer interactions in the physiological environment.

Intestinal mucosa is composed of high molecular weight glycoproteins hydrated and covering the mucosa with a continuous adherent blanket. Mucin glycoproteins are
rich with fucose and sialic acid groups at the terminal ends which provide a net negative charge in the acidic environment. The thickness of the mucin gel layer varies in different regions of the GIT with thickness ranging between 50-500 μm in stomach to 15-150μm in the colon. Cohesion of the mucin gel is dependent upon the glycoprotein concentration. The mucus layer is created biologically to play a number of important functions of protecting the underlying tissues from various diffusing/corrosive elements such as enzymes, acid and other toxic molecules. Also being a visco-elastic gel, it helps in the passage of food over the epithelium, thereby minimizing potential erosive damages. The mucus layer, in addition to providing protection, provides a barrier to drug absorption.

Various investigators have proposed different mucin-polymer interactions, such as

- Wetting and swelling of the polymer to permit intimate contact with the biological tissue
- Interpenetration of bioadhesive 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).

As the mucus layer comes into contact with bioadhesive coated system, various non-specific (Vander Waals, hydrogen bonding and/or hydrophobic interactions) or specific interactions occur between the complimentary structures. However, these interactions last only until the turnover process of mucin and, in order for a bioadhesive system to be successful; it should release its drug contents during this limited adhesion time.
Raft-Forming Systems

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO₂ bubbles on contact with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastro esophageal reflux treatment as with liquid gaviscon.

![Schematic illustration of the barrier formed by a raft-forming system](Image)

**Figure 9. Schematic illustration of the barrier formed by a raft-forming system**

Low Density Systems

Gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density systems (<1 g/cm³) with immediate buoyancy have therefore been developed. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called “microballoons” because of the low-density core (*Sato and Kawashima, 2004*). Generally, techniques used to prepare hollow microspheres involve simple solvent evaporation or solvent diffusion methods. Polycarbonate, Eudragit S, cellulose acetate, calcium alginate, agar and low methoxylated pectin are commonly used as polymers. Buoyancy and drug release are dependent on quantity of polymer, the plasticizer–polymer ratio and the solvent used.
A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter (Caldwell et al., 1988). However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, three configurations are required, a small configuration for oral intake, an expanded gastroretentive form and a final small form enabling evacuation following drug release.

Unfoldable systems are made of biodegradable polymer; the concept is to make a carrier, such as a capsule, incorporating a compressed system, which extends in the stomach. (Caldwell et al., 1988) proposed different geometric forms (tetrahedron, ring or planar membrane (4-lobed, disc or 4-limbed cross form) of biodegradable polymer compressed within a capsule.

**Swellable System**

Swellable systems are also retained because of their mechanical properties. The swelling usually results from osmotic absorption of water. The dosage form is small enough to be swallowed, and swells in gastric liquids, the bulk enable gastric retention and maintains the stomach in a ‘fed’ state, suppressing housekeeper waves.
(Mamajek and Moyer) patented drug reservoirs, surrounded by a swellable expanding agent. (Urquhart and Theeqwes 1984) developed a system containing tiny pills, with a very high swelling ratio enabling up to 50 fold volume increase. They were coated by wax to control drug release and dispersed in a matrix of polymeric hydrogel.

Super Porous Hydrogels

Although these are swellable systems, they differ sufficiently from the conventional types to warrant separate classification (Chen and Park, 2000) with pore size ranging between 10 nm and 10 μm. Absorption of water by conventional hydrogel is very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of the dosage form may occur. Superporous hydrogel, 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) (Figure 11) 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 (cross carmellose sodium).

In vivo studies with dogs showed that under fasting conditions, the superporous hydrogel composite (i.e. containing Ac-Di-Sol) remained in the stomach for 2-3 hours. This time increased to >24 hours after feeding, even though the fed condition was
maintained only for a few hours. After several hours (30 hours), fragmentation occurred and the composite was rapidly cleared.

![Superporous hydrogel](image)

**Figure 12.** On the left, superporous hydrogel in its dry (a) and water-swollen (b) state. On the right, schematic illustration of the transit of superporous hydrogel.

**Magnetic System**

These systems appear as small gastroretentive capsules containing a magnetic material, whose elimination from the stomach is prevented by the interaction with a sufficiently strong magnet applied to the body surface in the region of the stomach. Despite numerous reports about successful tests, the real applicability of such systems is doubtful because the desired results can be achieved only provided that the magnet position is selected with very high precision. Probably, the development of new conveniently applied magnetic field sources will improve this concept.

**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 via the pylorus and provides for its prolonged stay in the stomach. A drug can be either contained in a polymeric composition of the gastroretentive system or included as a separate component. Several methods were suggested to provide for the self-unfolding effect.
(1) The use of hydrogels swelling in contact with the gastric juice.

(2) Osmotic systems, comprising an osmotic medium in a semipermeable membrane.

(3) Systems based on low-boiling liquids converting into a gas at the body temperature. This imparts to the system a desired volume and provides for the drug release.

There are several problems for these systems, the main of which is the short swelling time (within several hours) insufficient for keeping the system in the stomach.

**High Density Systems**

Gastric contents have a density close to water (1.004 g/cm$^3$). When the patient is upright small high-density pellets sink to the bottom of the stomach where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. A density close to 2.5 g/cm$^3$ seems necessary for significant prolongation of gastric residence time and barium sulphate, zinc oxide, iron powder, titanium dioxide are used as excipients.

**1.3. GASTRORETENTIVE DRUG DELIVERY SYSTEM**

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 intestinal regions. They can also be used beneficially in the local therapy of the stomach.

GRDFS can be used as carriers for drugs with so called absorption windows. These substances for example antiviral, antifungal and antibiotic agents (Cephalosporin’s, Quinolones, Penicillin’s, Sulphonamides, Aminoglycosides, Tetracycline’s etc) are taken up only from very specific sites of GIT. In addition, by
continuously supplying drug to its most efficient site of absorption, the dosage forms allow for more effective oral use of peptide and protein drugs such as Calcitonin, Erythropoietin, Vasopressin, Insulin Low molecular weight, Heparin and Protease inhibitors.

Prolonged gastric retention of the drugs may offer numerous advantages including improved bioavailability, therapeutic efficacy and possible reduction of dosage size (Sanjay Garg and Shring Sharma, 2003).

However standard controlled released dosage forms offer only limited advantages for drugs that have an absorption window in the upper small intestinal. (Eg: Levodopa, Furosemide, Riboflavin). Once emptied from the stomach, the passage through this region is rapid, thus limiting the extent of absorption at this site. In order to increase the bioavailability of this type of drugs, the residence time of the controlled-released dosage forms in the upper GIT needs to be prolonged (Alexander, 2006).

1.3.1. Drugs that would benefit from GRDDS

1) CNS drugs (for epilepsy, Alzheimer and migraine).

2) Anti-viral products (for HIV, herpes and hepatitis) and certain antibiotics.

3) Anti-hypertension drugs.

4) Anti-diabetic agents for Type 2 diabetes.

5) Drugs for local treatment of GI infections and gastric enzyme replacement (N.K. Jain).

1.3.2. Importance of GI Absorption for Oral Drugs

Oral drug administration is by far the most preferable route for taking medications. However, the therapeutic window of many drugs is limited by their short circulating half-life and absorption via a defined segment of the intestine. Such pharmacokinetic limitations lead in many cases to frequent dosing of these medications to achieve the required therapeutic effect. This results in "pill burden" and consequently, decreased patient compliance. The phenomenon of absorption via a limited part of the GI tract has
been termed the "narrow absorption window"; once the dosage form passes the absorption window, the drug will be neither bioavailability nor effective. In extreme cases, drugs that are insufficiently absorbed due to narrow absorption cannot be delivered entirely, and are either given by a parenteral route or the development of such medication, which is otherwise safe and effective, is stopped altogether. A rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamic profiles is to retain the drug reservoir above its absorption area, i.e. in the stomach and to release the drug in a controlled manner, so as to achieve a zero order kinetics (i.e. "oral infusion") for a prolonged period of time (Michel, 2005).

1.3.3. Formulation Considerations For GRDDS

1) Drug must be effective retention in the stomach to suit for the clinical demand.
2) It must be convenient for intake to facilitate patient compliance.
3) Device must have sufficient drug loading capacity.
4) It must be control the drug release profile.
5) It must have full degradation and evacuation of the system once the drug release is over.
6) It should not have effect on gastric motility including emptying pattern.
7) It should not have other local adverse effects (Davis, 2005).

1.3.4. Advantages of Gastroretentive Drug Delivery System

Gastroretentive drug delivery systems have numerous advantages listed below

1. The principle of HBS can be used for any particular medicament or class of medicament.
2. 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.
3. 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.

4. 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.

5. 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 available for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline pH of the intestine.

6. 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.

7. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.

8. Many drugs categorized as once-a-day delivery have been demonstrated to have sub optimal 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. *(Gutierrez et al., 2003).*

### 1.3.5. Disadvantages of Gastroretentive Drug Delivery System

1. There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions and slow release of such drugs in the stomach is unwanted.

2. Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.
3. Furthermore, other drugs, such as Isosorbide Dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system (Hou et al., 2003).

4. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted exactly or accurately.

5. Gastric emptying of floating forms in supine subjects may occur at random and become highly dependent on the diameter. Therefore, patients should not be dosed with floating forms just before going to bed.

6. High variability in gastric emptying time due to variations in emptying process.

7. Unpredictable bioavailability.

1.3.6. Limitations

1. The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach.

2. Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.

3. The dosage form should be administered with a minimum of glass full of water (200-250 mL).

4. The drugs, which are absorbed throughout gastro-intestinal tract, which undergo first-pass metabolism (Nifedipine, Propranolol etc.) are not desirable candidate.

5. Some drugs present in the floating system causes irritation to gastric mucosa (Chien, 1992).
1.3.7. Factors Affecting the Gastroretentive System

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include use of floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastroretentive system (Sanjay et al., 2003).

- **Density** – Gastric retention time (GRT) is a function of dosage form buoyancy 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 of dosage form** – 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 2 hours. 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. (Caldwell et al., 1998; Murthy et al., 2000).
• **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 *(Marvola et al., 1989) (Mojaverian et al., 1988).*

• **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 and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride can affect floating time.

• **Biological factors** – Diabetes and Crohn’s disease, etc.
1.4. ESOMEPROZOLE MAGNESIUM TRIHYDRATE

Esomeprazole is the S-enantiomer of omeprazole, has higher oral bioavailability. Esomeprazole belongs to the category of proton pump Inhibitors used in the treatment of peptic ulcers. Esomeprazole inhibits the final step in the gastric acid secretion.

Esomeprazole is a specific inhibitor of a proton pump (PPIs) of the parietal cells of the mucous layer of stomach. It is a form of omeprazole. It is accumulated and transformed into an active form in the secretory tubules where it inhibits secretion of hydrochloric acid, Esomeprazole is used to treat Gastro Esophageal Reflux Disease (GERD), Zollinger-Ellison syndrome, promote healing of erosive esophagitis, eradication of helicobacter pylori together with antibiotics, in the preventive therapy of ulcers.

Esomeprazole produces complete inhibition of gastric acid resulting in rapid symptom relief and more effective in promoting healing of esophageal lesions. It is the drug of choice for patients with frequent or chronic symptoms in gastric erosions.

The initial dose is 20 mg once daily. In chronic cases, the dose may range from 20-60 mg in one or two doses daily.

It has more bioavailability than omeprazole. The t_{1/2} is about 1.3 hours and has a bioavailability of 60%. Significant pharmacological action is the suppression of gastric acid secretion without H_{2} receptor blocking action. It is a powerful inhibitor of gastric acid and totally abolishes HCl secretion. It is a drug of choice for patients with frequent/chronic symptoms in Gastro Esophageal Reflux Disease (GERD).
Shah S.H. et. al., (2005) Technological attempts have been made in the research and development of rate-controlled oral drug delivery systems to overcome physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). It is known that differences in gastric physiology, such as, gastric pH, and motility exhibit both intra-as well as inter-subject variability demonstrating significant impact on gastric retention time and drug delivery behavior. This triggered the attention towards formulation of stomach specific (gastro retentive) dosage forms. This dosage forms will be very much useful to deliver ‘narrow absorption window’ drug delivery system (FDDS), swelling and expanding systems, polymeric bioadhesive system, high-density systems, modified-shape systems and other delayed gastric emptying devices.

Lodhe S. et. al., (2008) Verapamil hydrochloride bi-layer floating tablets have two layers one immediate release layer and second floating sustained release layer. Verapamil hydrochloride bi-layer floating tablet releases drug in two phases i.e immediate and sustained drug release. Direct compression method was used to formulate bi-layer floating tablets. All bi-layer formulation float more than 12 h and sustained drug release above 12 h. Kinetic release study suggests that release mechanism is quasi Fickian. The optimized formulation was selected based on in vitro characteristics and used in vivo radiographic studies in rabbits by incorporating BaSO4. This showed that, tablet significantly float in rabbit stomach for more than 7 h.

Singh Badana et. al.,(2000) Designed an experiment for present preparation of famotidine floating microspheres, evaluation of Floating Drug Delivery System (FDDS) in vitro, prediction of the release, and optimization of stirring speed and polymers ratio to match target release profile was investigated. Floating microspheres were prepared by solvent evaporation (Oil-in-water emulsion) technique using hydroxylpropyl methylcellulose (HPMC) and Ethylcellulose (EC) as the rate controlling polymers. Particle size analysis, drug entrapment efficiency,
surface topography, buoyancy percentage and release studies were performed. Results showed that the polymer ratio and stirring speed affected the size, incorporation efficiency and drug release of microspheres (> 12 h), floating time (> 12 hr) and the best result were obtained at the ratio of HPMC:EC (1:6). The mean particle size of prepared floating microspheres increased but the drug release rate from the microspheres decreased as the polymer concentration increased. The developed floating microspheres of famotidine may be used in clinic for prolonged drug release in stomach for at least 12 hrs, thereby improving the bioavailability and patient compliance.

- **Khan et. al., (2009)** Investigated preparation and *in vitro* evaluation of gastroretentive floating tablet of theophylline. Two hydrophilic cellulose derivatives, Methocel K100M and Methocel K15MCR, were evaluated for their gel forming and release controlling properties. Sodium bicarbonate and citric acid were incorporated as gas generating agents. The effects of soluble components (sodium bicarbonate and citric acid), gel forming agents and amount variation of theophylline on drug release profile and floating properties were investigated.

- **Gattani et. al., (2008)** Formulated and evaluated floating multiparticulate oral DDS of diltiazem hydrochloride, which can provide SR. The work also aims to study various parameters affecting the behavior of floating multiparticulate in oral dosage form. FM were prepared by non-aqueous emulsification solvent evaporation technique using ethyl cellulose (EC) and Eudragit RS-100 as the rate controlling polymer. The *in vitro* performance was evaluated by the usual pharmacopoeial and other tests such as drug-polymer compatibility, (%) yield, particle size analysis, drug entrapment efficiency, surface topography, *in vitro* floatability and release studies. The data obtained in this study thus suggest that a microparticulate floating dosage form of Diltiazem hydrochloride can be successfully designed to give controlled delivery and improved oral bioavailability.
➢ **Rao et. al., (2009)** Prepared and evaluated FM of rosiglitazone maleate for the prolongation of GRT. The microspheres were prepared by solvent diffusion-evaporation method using EC and HPMC. A full factorial design was applied to optimize the formulation. The results of $3^2$ full factorial design revealed that the concentration of ethylcellulose 7 cps (X1) and stirring speed (X2) significantly affected drug entrapment efficiency, percentage release after 8 hours and particle size of microspheres.

➢ **Deepaa et. al., (2009)** Developed FM of cefpodoxime proxetil in order to achieve an extended retention in the upper GIT, which may result in enhanced absorption and thereby improved bioavailability. The microspheres were prepared by non-aqueous solvent evaporation method using polymers such as HPMC K15M, EC in different ratios and Cefpodoxime Proxetil in each formulation. The best drug release profiles were seen with formulation 2 at the ratio of drug to polymer of 1:2.

➢ **Ali et. al., (2007)** Developed an HBS of Metformin as a single-unit floating capsule. Various grades of low-density polymers were used for the formulation of this system. Capsules prepared with HPMC K4M and EC gave the best *in vitro* percentage release and were taken as the optimized formulation. *In vivo* studies were carried out in rabbits to assess the buoyancy as well as the pharmacokinetic parameters of the formulation using gamma scintigraphy. The formulation remained buoyant during 5 hours of study in rabbits. The comparative pharmacokinetic study was performed by administration of the optimized HBS capsules and immediate release capsules, both with radiolabeled metformin, using gamma counter. There was an increase in AUC in optimized HBS capsules of metformin when compared with immediate release formulation.
- Jain *et al.*, (2005) Developed a CR system to increase its residence time in the stomach without contact with the mucosa. This aim was achieved through the preparation of FM by the emulsion solvent diffusion technique consisting of Calcium Silicate Florite (RE, FLR) as a porous carrier, Repaglinide, an oral hypoglycemic agent, and Eudragit as a polymer. Incorporation of FLR in the microspheres proved to be an effective method to achieve the desired release behavior and buoyancy. The designed systems, combining excellent buoyant ability and suitable drug release pattern, could possibly be advantageous in terms of increased bioavailability of Repaglinide.

- El-Kamel *et al.*, (2001) Designed an SR system for Ketoprofen to increase its residence time in the stomach without contact with mucosa through the preparation of FM by the emulsion solvent diffusion technique. The floating multi-unit system for Ketoprofen was prepared using Eudragit RS 100 (ES) alone or in a mixture with the permeable Eudragit RL (ERL). The floating microparticles of Ketoprofen prepared with a suitable ratio of ES 100 to ERL provided a convenient dosage form for achieving best performance regarding flow, release and floating properties.

- Sato *et al.*, (2004) investigated the intragastric behavior of 99mTc labeled MB and non-floating microspheres (NF) of riboflavin following oral administration in fasted and fed humans by gamma scintigraphy. Simultaneously, pharmacokinetic examination of riboflavin released from MB and NF was conducted in fasted and fed human subjects. The investigation suggests that MB are very useful for improving drug bioavailability, resulting in a more sustained pharmacological action.

- Dave *et al.*, (2004) developed a Gastroretentive DDS of ranitidine hydrochloride using guar gum, xanthan gum, and HPMC. Sodium bicarbonate was incorporated as a gas-generating agent. The effect of citric acid and stearic acid on drug release profile and floating properties was investigated. A $3^2$ full factorial design was
applied to systemically optimize the drug release profile and the results showed that a low amount of citric acid and a high amount of stearic acid favored SR of ranitidine hydrochloride from a gastroretentive formulation.

- **Sato et al., (2004)** prepared MB of riboflavin by the emulsion solvent diffusion method. The objective of the investigation was to assess the usefulness of intragastric buoyant properties in terms of sustained pharmacological action in humans. NF were prepared in order to effect comparison with MB; moreover, *in vivo* evaluation of MB and NF in humans was conducted. Pharmacokinetics was examined via analysis of urinary excretion of riboflavin adopted as a model drug following oral administration of MB.

- **Streubel et al., (2003)** developed a single-unit FDDS of Diltiazem, Theophylline and Verapamil, which was based on low-density foam power and matrix-forming polymer(s). The drug release patterns can effectively be adjusted by varying simple formulation parameters such as the "matrix-forming polymer/foam power" ratio, initial drug loading, tablet height and diameter, type of matrix-forming polymer, addition of water-soluble and water-insoluble fillers and the use of polymer blends. Thus, desired release profiles adapted to the pharmacokinetic/pharmacodynamic properties of the incorporated drug can easily be provided.

- **EL-Gibaly et al., (2002)** prepared floating microcapsules containing melatonin by the ionic interaction of Cs and a negatively charged surfactant, sodium Dioctyl sulfosuccinate (DOS). The effect of various factors (cross-linking time, DOS and Cs concentration, as well as drug/polymer ratio) on microcapsule properties was evaluated. Cs concentration and drug/polymer ratio had a remarkable effect on drug entrapment in DOS/Cs microcapsules.
Patil et al., (2009) prepared FM of Metformin hydrochloride by non-aqueous emulsification solvent evaporation technique using EC as the rate-controlling polymer. The experimental design supported product development and optimization procedure yielded the desired microspheres with drug release equivalent to those of the marketed single-unit dosage forms with the added advantage of floatability in gastric juice for prolonged slow release.

Choi et al.,(2002) prepared alginate beads of riboflavin for FDDS. The effects of gas-forming agents CaCO$_3$/NaHCO$_3$ on beads' size, floating ability, pore structure, morphology, release rate and mechanical strength of floating beads were investigated. In general, CaCO$_3$ formed smaller and stronger floating beads than NaHCO$_3$. Although CaCO$_3$ is a less effective gas-forming agent than NaHCO$_3$, it produced superior floating beads with enhanced control of drug release rates.

Srivastava et al.,(2005) prepared FM of Cimetidine by the solvent evaporation method using the polymers HPMC and EC. In vitro data obtained for FM showed excellent floatability, good buoyancy and prolonged drug release. Microspheres of different sizes and drug content could be obtained by varying the formulation variables.

Krogel et al., (1999) developed and evaluated floating and pulsatile DDS of Chlorpheniramine Maleate based on a reservoir system consisting of a drug-containing effervescent core and a polymeric coating. Ideally, the expansion of the core could result in

1. A floating dosage form with a prolonged residence time and extended drug release or
2. A pulsatile dosage form, in which the drug is released rapidly in a time-controlled fashion after rupturing of the coating.
AIM AND OBJECTIVE

To design, formulate & carry out the in-vitro evaluation studies on Gastroretentive floating microspheres of Esomoprazole Magnesium Trihydrate.

The main objective of the study was to formulate and evaluate Gastroretentive Floating microspheres of Esomeprazole Magnesium Trihydrate which is expected to deliver the drug in controlled manner with reduced frequency of drug administration, improve patient compliance & bioavailability of Esomeprazole Magnesium Trihydrate.

Presently in India Esomeprazole is available as 20-40 mg tablets in which dose quantity is optimum, bioavailability is less due to rapid systemic metabolism in the acidic pH.

The half-life of Esomeprazole is less than 3 hours. So a controlled-release formulation of Esomeprazole would increase the length of time release in which Esomeprazole achieves an effective concentration in the GIT.

This study mainly deals in the design of a formulation which produces time controlled prolonged drug release and to enhance the bioavailability of the drug to about 90% and also to reduce the dosing interval of the drug.
PLAN OF WORK

Present work was carried out to design and evaluate the Floating microspheres of Esomeprazole Magnesium Trihydrate.

1) Selection of drug
2) Literature survey
3) Preformulation studies
   a) Identification of drug
      • Physical appearance
      • Melting point
      • FT-IR spectra
   b) Solubility studies
   c) Drug-excipients interaction
   d) FTIR study for drug excipient interaction
   e) Quantitative estimation of drug
   f) Determination of absorption maxima (λmax)
4) Preparation of standard curve in Phosphate buffer pH 7.0
5) Preparation of Floating microspheres
6) Characterization of prepared Floating microspheres
   a) Determination of drug content
   b) Entrapment efficiency
   c) Determination of particle size
   d) Surface morphology by SEM
7) **Evaluation of the prepared floating microspheres of Esomeprazole magnesium trihydrate**

   a) Angle of repose
   b) Bulk density
   c) *In vitro* dissolution studies in phosphate buffer 7.4 pH buffer
   d) Interpretation of drug release mechanism by kinetic models
      - Zero-order
      - First order
      - Higuchi model
      - Korsmeyer-Peppas model
MATERIALS AND METHODS

The following materials were used as supplied by the manufacturers.

5.1. Materials Used

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Chemicals</th>
<th>Supplied by</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Esomeprazole Magnesium Trihydrate</td>
<td>Microlabs, Bangalore</td>
</tr>
<tr>
<td>2</td>
<td>HPMC</td>
<td>Oxford Laboratories, Mumbai</td>
</tr>
<tr>
<td>3</td>
<td>Chitosan</td>
<td>Central Institute of Fisheries, Kerala</td>
</tr>
<tr>
<td>4</td>
<td>Sodium Alginate</td>
<td>S.D. Fine Chem. Ltd, Mumbai</td>
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<tr>
<td>5</td>
<td>Sodium Bicarbonate</td>
<td>S.D. Fine Chem. Ltd, Mumbai</td>
</tr>
<tr>
<td>6</td>
<td>DichloroMethane</td>
<td>S.D. Fine Chem. Ltd, Mumbai</td>
</tr>
<tr>
<td>7</td>
<td>Ethanol</td>
<td>S.D. Fine Chem. Ltd, Mumbai</td>
</tr>
<tr>
<td>8</td>
<td>Petroleum Ether</td>
<td>S.D. Fine Chem. Ltd, Mumbai</td>
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<td>9</td>
<td>η-hexane</td>
<td>S.D. Fine Chem. Ltd, Mumbai</td>
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5.2. Equipments Used

<table>
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<th>S. No.</th>
<th>Equipment</th>
<th>Supplied by</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dissolution test apparatus</td>
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<tr>
<td>2</td>
<td>Remi Stirrer No. 1A323</td>
<td>Instrument and Appliances Mfg. Corporation,</td>
</tr>
<tr>
<td>3</td>
<td>UV-Visible Spectrometer Model</td>
<td>SCHIMADZU UV-Vis spectrometer</td>
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<tr>
<td>4</td>
<td>Dryer: Hot Air Oven</td>
<td>PSM Industries, Bangalore</td>
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<tr>
<td>5</td>
<td>Electro Balance</td>
<td>K. Roy &amp; Company, Varanasi</td>
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<tr>
<td>6</td>
<td>Scanning Electron microscope</td>
<td>JSM 35CF, JEOL, Japan</td>
</tr>
<tr>
<td>7</td>
<td>Sieve Shaker</td>
<td>Toshniwal, India</td>
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</tbody>
</table>
5.3 DRUG PROFILE

ESOMEPRAZOLE MAGNESIUM TRIHYDRATE

Esomeprazole is the S-enantiomer of omeprazole. Esomeprazole belongs to the category of proton pump Inhibitors used in the treatment of peptic ulcers.

**Chemical Name**: bis(5-methoxy-2-[(s)-[(4-methoxy-3,5-dimethyl-2-pyridinyl) Methyl]suliny]-1H-benzimidazole-1-yl)magnesium Trihydrate.

**Molecular Formula**: (C$_{17}$H$_{18}$N$_3$O$_3$S)$_2$ Mg x 3 H$_2$O

**Molecular weight**: 767.2

**Chemical Structure**:

![Chemical Structure Image]

**Category**: Anti Ulcer

**Appearance**: It occurs as a white amorphous powder.

**Solubility**: The drug was found to be freely soluble in the solvent system i.e., Dichloromethane + ethanol in 1:1 ratio.

**Melting Point**: The melting point was found to be 155$^\circ$C.

**Storage**: It is light sensitive and to be stored in a dark place.
Pharmacokinetics

Absorption

Following oral administration it is less absorbed and undergoes extensive first pass metabolism; systemic bioavailability is about 60%. The mean peak concentration is reached in 1.5 hrs.

Dose : 40 mg
Onset of action : 3 hrs
Volume of distribution : The volume of distribution is approximately 16 L.
Excretion : Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces
Plasma Protein binding : 97% bound to plasma proteins
Bioavailability : The systemic bioavailability is approximately 64%
Elimination half life : The plasma elimination half-life of esomeprazole approximately 1 to 1.5 hours.

Mechanism of Action

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the $\text{H}^+\text{K}^-\text{ATPase}$ in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity.
5.4 EXCIPIENT PROFILE

HYROXY PROPYL METHYL CELLULOSE

Hydroxy propyl methylcellulose is mixed alkyl hydroxyl alkyl cellulosic ether and may be regarded as the propylene glycol ether of methylcellulose.

Chemical Name: Cellulose, 2-hydroxypropyl methyl ether

Synonyms: Methyl Hydroxy Propyl cellulose, Propylene Glycol ether of methylcellulose, Culminal HPMC.

Structural Formula:

![Structural formula of hydroxy propyl methylcellulose]

Where R is H, CH₃ or CH₃-CH(OH)-CH₂

Physical and chemical properties

- Molecular weight: 10,000 - 15,000,000 Daltons
- Color: White to creamy-white
- Nature: Fibrous or granular powder
- Odour: Odourless
- Taste: Tasteless
- Density: 0.3-1.3 g/ml
- Specific gravity: 1.26
- Solubility: Soluble in cold water, practically insoluble in Chloroform, ethanol (95%) and ether but Soluble in mixture of ethanol and Dichloromethane.
- Viscosity: 3,000-5600 M Pas
- Melting point: 190-200 °C,
Functional Category

Coating agent, film-forming, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

Application

- In oral product HPMC is primarily used as tablet binder, in film coating and as an extended release tablet matrix. Concentration between 2-5% w/w may be used as a binder in either wet or dry granulation process. High viscosity grade may be used to retard the release of water-soluble drug from a matrix.
- HPMC is widely used in oral and topical pharmaceutical formulation.
- Concentration of 0.45-1% w/w may be added as a thickening agent to vehicle for eye drop and artificial tear solution.
- HPMC is used as an adhesive in plastic bandage and as a wetting agent for hard contact lenses. It is widely used in cosmetics and food products.
- In addition, HPMC is used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particle from coalescing or agglomerating thus, inhibiting the formation of sediments.

Stability and storage

It is stable although it is slightly hygroscopic. The bulk material should be stored in an airtight container in a cool and dry place. Increased in temperature reduces the viscosity of the solution.

Safety

It is generally regarded as a non-toxic and non-irritant material so it is widely used in many oral and topical pharmaceutical formulations. Excessive consumption of HPMC may have laxative effect.
SODIUM BICARBONATE

Chemical Name : Carbonic acid monosodium salt

Structural Formula : NaHCO₃

Physical and chemical properties

Molecular weight : 84.01
Color : White
Nature : Crystalline powder
Odour : Odourless
Taste : Saline/slight alkaline
Density : 0.869-2.173 g/cm³
Moisture content : less than 1%w/w
Solubility : Soluble in water, practically insoluble in ethanol (95%) and ether.
Melting point : 270 °C (with decomposition)

Functional category

Alkalizing agent, Therapeutic agent

Applications

- Used in pharmaceutical formulation as a source of carbon dioxide in effervescent tablets and granules.
- Used to produce or maintain an alkaline pH in a preparation, like solution of Erythromycin, Lidocaine, and Niacin etc.
- Used to produce a sodium salt of the active ingredient that has enhanced solubility.
- Used as a freeze-drying stabilizer and in toothpaste.
- Used as a gas forming agent in alginate raft system and in floating drug delivery system.

**Stability and Storage**

Sodium bicarbonate is stable in dry air but slowly decomposed in moist air and should therefore be stored in well-closed container in a cool dry place.

**Safety**

Orally ingested sodium bicarbonate neutralizes gastric acid with the evolution of carbon dioxide and may cause stomach cramps and flatulence *(Rowe et al., 2003)*
SODIUM ALGINATE

**Nonproprietary Names:** BP: Sodium alginate; PhEur: Natrii alginas; USPNF: Sodium alginate.

**Synonyms:** Algin, alginic acid, sodium salt, E401, Kelcosol, Keltone, Protanal, sodium polymannuronate.

**Empirical Formula**

Sodium alginate consists chiefly of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of residues of d-mannuronic acid and l-guluronic acid.

**Functional Category**

Stabilizing agent; Suspending agent; Tablet and Capsule disintegrant; Tablet binder; Viscosity-increasing agent.

**Applications in Pharmaceutical Formulation or Technology**

Sodium alginate is used in a variety of oral and topical pharmaceutical formulations. In tablet formulations, sodium alginate may be used as both a binder and disintegrant. It has been used as a diluent in capsule formulations. Sodium alginate has also been used in the preparation of sustained-release oral formulations since it can delay the dissolution of a drug from tablets, capsules and aqueous suspensions.

**Solubility**

Practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%.
CHITOSAN

Chitosan is a linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit).

**STRUCTURE**

```
\[\text{\includegraphics{chitosanStructure.png}}\]
```

**Synonyms**

2-amino-2-deoxy-(1,4)-β-D-glucopyranan; deacetylated chitin; deacetylchitin; poly-(1,4)-β-D-glucopyrosamine.

**Chemical Name**

Poly-β-(1,4)-2-amino-2-deoxy-D-glucose.

**Description**

Chitosan occurs as odorless, white or creamy white powder or flakes.

**Functional Category**

Coating agent, disintegrant, film forming agent, mucoadhesive tablet binder etc.,

**Solubility**

Sparingly soluble in water, practically insoluble in ethanol, freely soluble in acetic acid.
Applications

Used as a key component in the manufacture of mucoadhesive dosage forms and in controlled release formulations. Chitosan has been included in various pharmaceutical dosage forms such as gels, beads, microspheres, liposomes etc.,

Safety

Chitosan is found to be biocompatible to both healthy and infected skin.

Chitosan is biodegradable polymer and can be used safely.

Storage

Chitosan powder is stable at room temperature, although it is hygroscopic after drying. Chitosan should be stored in tightly closed container in a cool, dry place and should be stored at a temperature of 2-8°C.
PRE FORMULATION STUDY

Prior to the development of the dosage forms the preformulation study was carried out. Hence Infrared spectra of the physical mixture of the drug and the polymers chosen were taken. The infra-red spectra of the drug and polymers were also taken.

The application of infra-red spectroscopy lies more in the qualitative identification of substances either in pure form or in the mixture and as a tool in establishment of the structure. Since I.R. is related to covalent bonds, the spectra can provide detailed information about the structure of molecular compounds. In order to establish this point, comparisons can be made between the spectrum of the substance and the drug.

STANDARD PLOT FOR ESOMEPRAZOLE MAGNESIUM TRIHYDRATE

Standard Graph by using Phosphate Buffer (pH 7.4)

Accurately weighed 10 mg of Esomeprazole Magnesium was dissolved in 100 ml of 7.4 pH buffer solution to form 100 µg/ml stock solutions.

From this stock solution aliquots of 2.5 ml, 5 ml, 7.5 ml, 10 ml, 12.5 ml, 15 ml, 17.5ml, 20 ml, 22.5 ml, 25 ml were pipette out into a series of 50 ml in order to get a concentration ranging from 5-50µg/ml.

The absorbance of the resulting solution was then measured at 301 nm using UV spectrophotometer against respective parent solvent as a blank. The standard curve was obtained by plotting absorbance Vs. concentration µg/ml.
Table No. 4

Standard Calibration Curve of Esomeprazole Magnesium Trihydrate

<table>
<thead>
<tr>
<th>SL. No</th>
<th>CONCENTRATION(µg/ml)</th>
<th>ABSORBANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>0.057</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>0.086</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>0.115</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>0.144</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>0.173</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>0.202</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>0.231</td>
</tr>
<tr>
<td>8</td>
<td>45</td>
<td>0.261</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>0.292</td>
</tr>
</tbody>
</table>
Graph No.1

Standard Calibration Curve of Esomeprazole Magnesium Trihydrate
b) SOLUBILITY STUDIES

The solubility of Esomeprazole Magnesium was determined in solvents of different polarities. The solubility of Esomeprazole Magnesium is usually determined by the equilibrium solubility method, which employs a saturated solution of Esomeprazole Magnesium, obtained by adding an excess amount of Esomeprazole Magnesium in the solvent to promote drug precipitation, and then stirring for 2 hr until equilibrium was reached. The mixture was filtered and amount of Esomeprazole Magnesium was determined by using UV Spectrophotomer at 301 nm.

Table No.5

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Solvents</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PBS-7.4(pH)</td>
<td>Freely soluble</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>Freely soluble</td>
</tr>
<tr>
<td>3</td>
<td>Dichloro Methane</td>
<td>Freely soluble</td>
</tr>
</tbody>
</table>
c) FT-IR SPECTRA OF ESOMEPRAZOLE MAGNESIUM TRIHYDRATE

The FT-IR analysis of the Esomeprazole magnesium was carried out for qualitative compound identification. The FT-IR spectra for pure drug and with other excipients was obtained by placing the drug directly into the cavity and was determined by FT-IR spectrophotometer in the wave number region of 4000-400 cm\textsuperscript{-1}.

**Table No.6**

Comparison of I.R. Spectra of Esomeprazole Magnesium Trihydrate and in Combination with Polymers

<table>
<thead>
<tr>
<th>S. No</th>
<th>Sample</th>
<th>C=O (cm\textsuperscript{-1})</th>
<th>-CC (cm\textsuperscript{-1})</th>
<th>-CH (cm\textsuperscript{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Esomeprazole Magnesium Trihydrate</td>
<td>3182</td>
<td>1462</td>
<td>919</td>
</tr>
<tr>
<td>2</td>
<td>EMT + HPMC</td>
<td>3183</td>
<td>1458</td>
<td>915</td>
</tr>
<tr>
<td>3</td>
<td>EMT + Chitosan</td>
<td>3182</td>
<td>1462</td>
<td>919</td>
</tr>
<tr>
<td>4</td>
<td>EMT + Na\textsubscript{2}CO\textsubscript{3}</td>
<td>3182</td>
<td>1495</td>
<td>919</td>
</tr>
<tr>
<td>5</td>
<td>EMT + HPMC + Chitosan</td>
<td>3182</td>
<td>1462</td>
<td>919</td>
</tr>
</tbody>
</table>
Graph No. 2

Esomeprazole Magnesium Trihydrate Pure drug
Graph No. 3

Esomeprazole Magnesium Trihydrate + HPMC

![Graph with wave numbers and transmittance values]
Graph No. 4

Esomeprazole Magnesium Trihydrate + Chitosan

![Graph showing wave numbers and transmittance values for Esomeprazole Magnesium Trihydrate + Chitosan.](image-url)
Graph No. 5

Esomeprazole Magnesium Trihydrate + Sodium Bicarbonate
Graph No. 6

Esomeprazole Magnesium + HPMC + Chitosan
Preparation of Microspheres

In the present study, microspheres are prepared using *Emulsion-Polymerization* method. In this method, polymeric drug solution i.e., drug + polymer and solvent system (DicloroMethane + Ethanol) of 10 ml is added to 10 % solution of egg albumin. This polymeric phase is stirred continuously to form a uniform dispersion. In another beaker 86 ml of coconut oil containing 1 ml of 0.5% Sodium Lauryl Sulphate is taken which forms the organic phase. The polymeric phase is added drop wise using needle into the organic phase. It is continuously stirred for 2 hrs with a speed of 700 rpm using stirrer. After stirring 1 ml of formaldehyde is added and obtained microspheres are washed thrice with 20 ml of η–hexane and the obtained final microspheres are stored in a dessicator.
Table No. 7

Formulation Design For Floating Microspheres of Esomeprazole Magnesium Trihydrate

<table>
<thead>
<tr>
<th>Formulation No.</th>
<th>Drug (Esomeprazole Mg,3H2O) in mg</th>
<th>HPMC (mg)</th>
<th>Chitosan (mg)</th>
<th>Sodium Bicarbonate (% W/V)</th>
<th>Sodium Alginate (% W/V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F₁ (1:1)</td>
<td>50</td>
<td>50</td>
<td>-</td>
<td>1 %</td>
<td>2 %</td>
</tr>
<tr>
<td>F₂ (1:1.5)</td>
<td>50</td>
<td>75</td>
<td>-</td>
<td>1 %</td>
<td>2 %</td>
</tr>
<tr>
<td>F₃ (1:1)</td>
<td>50</td>
<td>-</td>
<td>50</td>
<td>1 %</td>
<td>2 %</td>
</tr>
<tr>
<td>F₄ (1:1.5)</td>
<td>50</td>
<td>-</td>
<td>75</td>
<td>1 %</td>
<td>2 %</td>
</tr>
</tbody>
</table>
7.1. PARTICLE SIZE DETERMINATION

The particle size of a pharmaceutical preparation is strictly maintained in order to get optimal biological activity.

Methods to estimate particle size are

a. Optical Microscopy
b. Sieving Method
c. Sedimentation Method
d. Elutriation Method
e. Centrifugal refractometry
f. Permeability Method
g. Light scattering Method

Table No. 8

Common techniques for measuring fine particles of various sizes

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Technique</th>
<th>Particle sizes in (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Optical Microscopy</td>
<td>1-100 µm</td>
</tr>
<tr>
<td>2</td>
<td>Sieving</td>
<td>&gt; 50 µm</td>
</tr>
<tr>
<td>3</td>
<td>Sedimentation</td>
<td>&gt; 1 µm</td>
</tr>
<tr>
<td>4</td>
<td>Elutriation</td>
<td>1-50 µm</td>
</tr>
<tr>
<td>5</td>
<td>Centrifugation</td>
<td>&lt; 50 µm</td>
</tr>
<tr>
<td>6</td>
<td>Permeability</td>
<td>&gt; 1 µm</td>
</tr>
<tr>
<td>7</td>
<td>Light Scattering</td>
<td>0.5-50 µm</td>
</tr>
</tbody>
</table>
7.2. SCANNING ELECTRON MICROSCOPY

Procedure

Morphology details of the specimens were determined by using a Scanning Electron Microscope (SEM), Model JSM 35CF, JEOL, Japan.

The samples were dried thoroughly in Vacuum dessicator before mounting on brass specimen studies. The samples were mounted on specimen studies using Double sided adhesive tape. The sputtering was done for nearly 3 minutes to obtain uniform coating on the sample to enable good quality SEM images. The SEM was operated at low accelerating voltage.

The condenser lens position was maintained between 4.4-5.1. The objective lens aperture has a diameter of 240 microns and the Working Distance WD is 39 mm.
Fig No.13

SEM of Prepared Microspheres Under Low Magnification
Fig No. 14

Microscopic Pictures of Esomeprazole Magnesium Trihydrate Floating Microspheres

7.3. Flow Properties

Flow property depends on particle size, shape, porosity and density of microspheres.

Angle of Repose

The flow characteristics are measured by angle of repose. Improper flow is due to frictional forces between the particles. These forces are quantified by angle surface of the pile of the powder and the horizontal plane. The flow of powder and the angle of repose is depicted in following table.
Definition

The lower the angle of repose, the better the flow property. Rough and irregular surface of particles gives higher angle of repose. Decreased in the particle size leads to a higher angle of repose.

\[ \tan \theta = \frac{h}{r} \]

\[ \theta = \tan^{-1} \left( \frac{h}{r} \right) \]

Where, \( h \) = height of pile

\( r \) = radius of the base of the pile

\( \theta \) = angle of repose

Method

A glass funnel is held in place with a clamp on a ring support over a glass plate. The glass plate is placed on a stand. Approximately 100 g of particles is transferred into funnel keeping the office of the funnel blocked by the lower thumb. As the thumb is removed, the particles are emptied from funnel, and the angle of repose is determined by above mentioned formula.
Table No.9

Relation between Angle of Repose and Flow of the Particles

<table>
<thead>
<tr>
<th>Angle of repose (º) (degrees)</th>
<th>Type of flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td>Excellent</td>
</tr>
<tr>
<td>25-30</td>
<td>Good</td>
</tr>
<tr>
<td>30-40</td>
<td>Passable</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>Very poor</td>
</tr>
</tbody>
</table>

Table No.10

Angle of Repose of Microparticles

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulation</th>
<th>Angle of repose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>25º70’</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>28º29’</td>
</tr>
<tr>
<td>3</td>
<td>F3</td>
<td>29º74’</td>
</tr>
<tr>
<td>4</td>
<td>F4</td>
<td>30º96’</td>
</tr>
</tbody>
</table>
7.4. DRUG ENTRAPMENT EFFICIENCY

Drug entrapment efficiency of Esomeprazole Magnesium was performed by accurately weighing 100 mg of microparticles and suspend in 100 ml of simulated intestinal fluid of pH 7.4±0.1 and it was kept for 12 hrs. Next day it was stirred for 15 min, and subjected for filtration. After suitable dilution, Esomeprazole magnesium content in the filtrate was analyzed Spectrophotometrically at 301 nm using Shimadzu 1201 UV-visible spectrophotometer.

The absorbance found from the UV-Spectrophotometer was plotted on the standard curve to get the concentration of the entrapped drug. Calculating this concentration with the dilution factor we get the percentage drug encapsulated in microparticles.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Absorbance at 301 nm</th>
<th>Theoretical yield (mg)</th>
<th>Practical yield (mg)</th>
<th>Drug Entrapment Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.059</td>
<td>50</td>
<td>20.34</td>
<td>79.66</td>
</tr>
<tr>
<td>F2</td>
<td>0.054</td>
<td>50</td>
<td>18.62</td>
<td>81.38</td>
</tr>
<tr>
<td>F3</td>
<td>0.032</td>
<td>50</td>
<td>11.03</td>
<td>88.97</td>
</tr>
<tr>
<td>F4</td>
<td>0.0481</td>
<td>50</td>
<td>16.58</td>
<td>83.42</td>
</tr>
</tbody>
</table>
7.5 *In-vitro* Dissolution Studies

A drug is expected to release from the solid dosage forms (granules, tablets, capsules etc) and immediately go into molecular solution. This process is called as Dissolution.

**Drug release studies**

The method specified in USP for the drug release study was followed.

**Apparatus**

USP XXIII dissolution test apparatus employing the round bottom dissolution vessel and rotating basket assembly.

**Buffer stage**

900 ml of pH 7.4 intestinal fluid (phosphate buffer) is used as dissolution media.

**Time**

At every 1 hr interval upto 12 hours.

**Procedure**

*In-vitro* release profile of the microparticles was evaluated using rotating basket dissolution apparatus. 900 ml of phosphate buffer (pH 7.4) maintained at 37±0.5°C is used as dissolution Media, and the basket was rotated at a constant speed of 75 rpm. Accurately weighed amount of microparticles were placed in the baskets.

Aliquots of samples were withdrawn at the interval of 1 hour for 9 hours in phosphate buffer pH 7.4. The samples withdrawn were filtered, diluted suitably and analyzed at 301 nm spectrophotometrically for drug release.
Table No. 12

*In-vitro* Dissolution Profile for Formulation F₁

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Absorbance</th>
<th>Concentration</th>
<th>Cumulative % Drug Released</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.08</td>
<td>0.275</td>
<td>9.931</td>
</tr>
<tr>
<td>2</td>
<td>0.12</td>
<td>0.413</td>
<td>14.89</td>
</tr>
<tr>
<td>3</td>
<td>0.18</td>
<td>0.620</td>
<td>22.34</td>
</tr>
<tr>
<td>4</td>
<td>0.22</td>
<td>0.758</td>
<td>27.31</td>
</tr>
<tr>
<td>5</td>
<td>0.25</td>
<td>0.862</td>
<td>31.03</td>
</tr>
<tr>
<td>6</td>
<td>0.29</td>
<td>1.031</td>
<td>36.01</td>
</tr>
<tr>
<td>7</td>
<td>0.35</td>
<td>1.206</td>
<td>43.44</td>
</tr>
<tr>
<td>8</td>
<td>0.43</td>
<td>1.482</td>
<td>53.37</td>
</tr>
<tr>
<td>9</td>
<td>0.57</td>
<td>1.965</td>
<td>70.75</td>
</tr>
<tr>
<td>10</td>
<td>0.65</td>
<td>2.241</td>
<td>80.68</td>
</tr>
<tr>
<td>11</td>
<td>0.71</td>
<td>2.448</td>
<td>88.13</td>
</tr>
<tr>
<td>12</td>
<td>0.75</td>
<td>2.586</td>
<td>93.10</td>
</tr>
</tbody>
</table>

Graph No 7

*Cumulative % Drug Release Vs Time*
Table No.13

*In-vitro* Dissolution Profile for Formulation F₂

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Absorbance</th>
<th>Concentration</th>
<th>Cumulative % Drug Released</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.07</td>
<td>0.214</td>
<td>8.68</td>
</tr>
<tr>
<td>2</td>
<td>0.09</td>
<td>0.310</td>
<td>11.17</td>
</tr>
<tr>
<td>3</td>
<td>0.13</td>
<td>0.448</td>
<td>16.13</td>
</tr>
<tr>
<td>4</td>
<td>0.15</td>
<td>0.517</td>
<td>18.62</td>
</tr>
<tr>
<td>5</td>
<td>0.21</td>
<td>0.724</td>
<td>26.03</td>
</tr>
<tr>
<td>6</td>
<td>0.28</td>
<td>0.965</td>
<td>34.75</td>
</tr>
<tr>
<td>7</td>
<td>0.34</td>
<td>1.172</td>
<td>42.20</td>
</tr>
<tr>
<td>8</td>
<td>0.37</td>
<td>1.275</td>
<td>45.93</td>
</tr>
<tr>
<td>9</td>
<td>0.44</td>
<td>1.517</td>
<td>54.62</td>
</tr>
<tr>
<td>10</td>
<td>0.48</td>
<td>1.655</td>
<td>59.58</td>
</tr>
<tr>
<td>11</td>
<td>0.54</td>
<td>1.862</td>
<td>67.03</td>
</tr>
<tr>
<td>12</td>
<td>0.74</td>
<td>2.551</td>
<td>91.86</td>
</tr>
</tbody>
</table>

Graph No 8

Cumulative % Drug Release Vs Time
Table No.14

*In-vitro* Dissolution Profile for Formulation F₃

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Absorbance</th>
<th>Concentration</th>
<th>Cumulative % Drug Released</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.09</td>
<td>0.31</td>
<td>11.17</td>
</tr>
<tr>
<td>2</td>
<td>0.13</td>
<td>0.044</td>
<td>16.13</td>
</tr>
<tr>
<td>3</td>
<td>0.23</td>
<td>0.724</td>
<td>26.06</td>
</tr>
<tr>
<td>4</td>
<td>0.25</td>
<td>0.852</td>
<td>31.03</td>
</tr>
<tr>
<td>5</td>
<td>0.29</td>
<td>1.068</td>
<td>38.48</td>
</tr>
<tr>
<td>6</td>
<td>0.34</td>
<td>1.172</td>
<td>42.20</td>
</tr>
<tr>
<td>7</td>
<td>0.41</td>
<td>1.413</td>
<td>50.88</td>
</tr>
<tr>
<td>8</td>
<td>0.53</td>
<td>1.827</td>
<td>65.79</td>
</tr>
<tr>
<td>9</td>
<td>0.58</td>
<td>2.006</td>
<td>72.28</td>
</tr>
<tr>
<td>10</td>
<td>0.62</td>
<td>2.137</td>
<td>76.96</td>
</tr>
<tr>
<td>11</td>
<td>0.68</td>
<td>2.379</td>
<td>85.65</td>
</tr>
<tr>
<td>12</td>
<td>0.78</td>
<td>2.689</td>
<td>96.82</td>
</tr>
</tbody>
</table>

Graph No 9

Cumulative % Drug Release Vs Time
Table No.15

*In-vitro* Dissolution Profile for Formulation F₄

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Absorbance</th>
<th>Concentration</th>
<th>Cumulative % Drug Released</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.07</td>
<td>0.241</td>
<td>8.6</td>
</tr>
<tr>
<td>2</td>
<td>0.12</td>
<td>0.413</td>
<td>14.9</td>
</tr>
<tr>
<td>3</td>
<td>0.19</td>
<td>0.655</td>
<td>23.5</td>
</tr>
<tr>
<td>4</td>
<td>0.23</td>
<td>0.793</td>
<td>28.55</td>
</tr>
<tr>
<td>5</td>
<td>0.31</td>
<td>1.068</td>
<td>38.48</td>
</tr>
<tr>
<td>6</td>
<td>0.38</td>
<td>1.310</td>
<td>47.17</td>
</tr>
<tr>
<td>7</td>
<td>0.46</td>
<td>1.586</td>
<td>57.10</td>
</tr>
<tr>
<td>8</td>
<td>0.53</td>
<td>1.827</td>
<td>65.79</td>
</tr>
<tr>
<td>9</td>
<td>0.59</td>
<td>2.034</td>
<td>73.24</td>
</tr>
<tr>
<td>10</td>
<td>0.63</td>
<td>2.172</td>
<td>78.20</td>
</tr>
<tr>
<td>11</td>
<td>0.65</td>
<td>2.241</td>
<td>80.68</td>
</tr>
<tr>
<td>12</td>
<td>0.76</td>
<td>2.620</td>
<td>94.34</td>
</tr>
</tbody>
</table>

Graph No 10

Cumulative % Drug Release Vs Time
Table No.16
Cumulative % Drug Release Vs Time

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>F₁</th>
<th>F₂</th>
<th>F₃</th>
<th>F₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.931</td>
<td>8.68</td>
<td>11.17</td>
<td>8.6</td>
</tr>
<tr>
<td>2</td>
<td>14.89</td>
<td>11.17</td>
<td>16.13</td>
<td>14.9</td>
</tr>
<tr>
<td>3</td>
<td>22.34</td>
<td>16.13</td>
<td>26.06</td>
<td>23.5</td>
</tr>
<tr>
<td>4</td>
<td>27.31</td>
<td>18.62</td>
<td>31.03</td>
<td>28.55</td>
</tr>
<tr>
<td>5</td>
<td>31.03</td>
<td>26.03</td>
<td>38.48</td>
<td>38.48</td>
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<td>93.10</td>
<td>91.86</td>
<td>96.82</td>
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</table>
Graph No.11

Percentage Cumulative Percentage Drug Release Vs Time

![Graph showing cumulative percentage drug release vs time for samples F1, F2, F3, and F4.](image-url)
Graph No 12

Zero Order Release Model Of Formulation F3

Graph No 13

First order Release Model Of Formulation F3
Graph No 14

Higuchi release model for formulation F3

\[ y = 27.839x + 1.051 \]
\[ R^2 = 0.9661 \]

Graph No 15

Korsmeyer-Peppas release model for formulation F3

\[ y = 0.6644x + 1.3824 \]
\[ R^2 = 0.9741 \]
Accelerated Stability Studies

The formulations were stored in an oven at 37±1°C and 60±1°C for a period of six weeks. The samples were analyzed for drug content every week by Spectrophotometer at 301nm.

Method

Microspheres were individually wrapped in aluminium foil and packed in amber colored screw capped bottle and put under specified condition in incubator for 3 months. After 3 months the microspheres were evaluated for In-vitro drug release.

Table No.17

Results of Assay of Formulation After Accelerated Stability Studies

<table>
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<th>Days</th>
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<tr>
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</table>
RESULTS AND DISCUSSION

Floating Microspheres of Esomeprazole were prepared by emulsion polymerization technique and various evaluation parameters were assessed, with a view to obtain oral controlled released of Esomeprazole Magnesium Trihydrate.

In the present work, total four formulations were prepared and the detailed composition is shown in Table No.5. The prepared microparticles were then subjected to granulometric study, angle of repose, scanning electron microscopy, drug entrapment efficiency, in-vitro dissolution and stability studies.

A standard calibration curve for the drug was obtained by measuring absorbance at 301 nm, and by plotting the graph of absorbance Vs concentration. Table No.4 shows the absorbance readings of Esomeprazole.

To check the compatibility of the drug with various polymers, IR spectra of drugs, polymers and combinations are shown in Graph No.2-6. The characteristics absorption peaks of Esomeprazole magnesium were obtained.

Angle of Repose

Acceptable range of angle of repose is 22º61’ to 31º60’. All the formulations showed an angle of repose within the range as shown in Table No.8.

Formulations F₁ to F₄ showed an angle of repose in the acceptable range, which indicates a good flow property.

The drug entrapment efficiency of all the formulations were in the range between 78.62% to 91.25%. The results of drug entrapment efficiency are shown in Table No.9.

The dissolution studies were conducted by using dissolution medias, a pH 7.4.
The data obtained in the in-vitro dissolution studies were grouped according to modes of data treatment as follows:

- Cumulative percent drug release Vs. Time (Zero-order).
- Cumulative percent drug retained Vs. Square root of Time (Higuchi Model).
- Log Cumulative percent drug retained Vs. Time (First-order).
- Cumulative percent drug release in (mg) Vs. Time (Korsmeyer-Peppas Model).

The results of the in-vitro dissolution studies of formulation F1 to F4 are shown in Table No 12-15. The plots of Cumulative percentage drug release Vs. Time, is drawn and represented graphically as shown in Graph No.7

Morphology of the microparticles were investigated by Scanning Electron Microscopy. The photographs of formulations taken by Scanning Electron Microscope are shown in the Figure No.13 and 14

Stability study was carried out for the formulation F3 at 40ºC ± 1ºC for a period of 45 days and the result was shown in Table No.17
SUMMARY

Systematic studies were conducted using two different polymers in different concentrations to prepare Esomeprazole Magnesium Trihydrate Floating Microspheres. All the prepared systems were evaluated for the different properties.

From the Preformulation studies for drug excipients compatibility, it was observed that no physical incompatibility existed between the drug and excipients.

All the four different formulations prepared contain drug about 97%-102%.

*In vitro* drug release profile indicated that drug release was retarded due to the presence of higher concentration of polymer.

Formulation F2 has only 68% drug release in 9 hrs due to higher ratio of the polymer.

Formulated Microspheres gave satisfactory results for various evaluation parameters like Angle of Repose, Drug Entrapment Efficiency, Scanning Electronic Microscopy and *in vitro* drug release.

Comparing the two different Polymers such as HPMC and Chitosan provided better-sustained release characteristics with excellent in-vitro drug release. From the above results also indicated that at higher viscosity grades of polymer concentrations drug release was retarded greatly.
CONCLUSION

Floating microspheres of Anti-Ulcer drug ie., Esomeprazole Magnesium Trihydrate can be formulated as an approach to increase gastric residence time and thereby improve its bioavailability. Formulation F3 gave better-controlled drug release in comparison to the other formulations. Among the polymers used to improve the gastric residence, Chitosan showed better control over drug release.

The drug release pattern from the optimized formulations was best fitted to Korsmeyer-Peppas model and zero order kinetics. Drug – excipients interaction of optimized formulations was carried out by using FTIR studies. In this analysis drug – excipients compatibility interactions were not observed.

In conclusion, very promising in vitro drug release results were observed with Floating microspheres of Esomeprazole Magnesium Trihydrate, further there is a scope to conduct the bioavailability studies in human volunteers to know the exact pharmacokinetics of the developed floating microspheres of Esomeprazole Magnesium Trihydrate.
REFERENCES

- Caldwell LJ, Gardner RC, Cargill RC. Drug delivery device which can be retained in the stomach for a controlled period of times, *US patent 4735804*, April 5, 1988.245-262.


