1. **INTRODUCTION**

Scientific advancement and technological sophistication have made possible for alteration and modulation of drug release characteristics so as to suit the need of a patient. The oral route remains the preferred route despite tremendous advancements in drug delivery, for the administration of therapeutic agents because of ease of administration and the cost of therapy lead to high level of patient compliance.\(^1\)\(^2\)

Many of the drug delivery systems, available in the market are oral drug delivery type systems. Oral drug delivery systems have developed from site-specific delivery to immediate release over a period of time. Two main properties that are single dose and less frequent dosing for the whole duration of treatment is desired by every patient who would like to have an ideal drug delivery system. Also the dosage form must release active drug straight at the site of action.

Thus the objective of the pharmacist is to develop systems that can be as ideal system as possible. Controlled or sustained release drug delivery systems have been focused to develop a single-dose therapy for the whole duration of treatment.

Because of the ease of the administration via the oral route as well as the economy and ease of manufacture of oral dosage forms, attention has been focused particularly on orally administered sustained drug delivery systems. Sustained release describes the delivery of drug from the dosage forms over an extended period of time. It also implies sustained duration of therapeutic effect and late therapeutic action. Sustained release means not only extended duration of drug delivery and extended release, but also implies predictability and reproducibility of drug release kinetics. As it is based on different modes of operation, number of different oral sustained drug distribution systems have been variously named, for example, as diffusion controlled systems, dissolution controlled systems, ion-exchange resins, osmotically controlled systems, erodible matrix systems, pH-independent formulations, swelling controlled systems, and the like.

The drug should have decent absorption throughout the gastrointestinal tract is an important requisite for the successful performance of oral controlled release drug delivery system and that to ensure constant absorption of the released drug. However,
the development process is precluded by several physiological problems, such as first pass metabolism, limited absorption in lower part of GIT, an incapability to restrain and localize the delivery system within desired regions of the GIT, the size of the system and the highly variable nature of gastric emptying process. Depending upon the physiological state of the subject, it can be foreseen that, the emptying process can last from a few minutes to 14 hours. Since the majority of drugs are especially absorbed in the upper part of the small intestine. This variability, in turn, may lead to irregular bioavailability and times to achieve peak plasma levels.\(^4\)

Furthermore, the relatively brief gastric emptying time (GET) in humans, which normally averages 2-3 hours through the major absorption zone (stomach or upper part of the intestine), can result in incomplete drug release from the delivery system, although slight variation exist among various dosage form

Figure 1.1- oral drug delivery formulations and Technologies necessary to overcome the limitations imposed by GI physiology\(^1\)

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\(^1\) Suresh Gyan Vihar University, Mahal, Jagatpura, Jaipur (Rajasthan) 2
Table 1.1: Across the segments of the GIT transit time of various dosage forms.

<table>
<thead>
<tr>
<th>Dosage forms</th>
<th>Stomach</th>
<th>Small intestine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets</td>
<td>2.7±1.5</td>
<td>3.1±0.4</td>
<td>5.8</td>
</tr>
<tr>
<td>Pellets</td>
<td>1.2±1.3</td>
<td>3.4±1.0</td>
<td>4.6</td>
</tr>
<tr>
<td>Capsules</td>
<td>0.8±1.2</td>
<td>3.2±0.8</td>
<td>4.0</td>
</tr>
<tr>
<td>Solutions</td>
<td>0.3±0.07</td>
<td>4.1±0.5</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Although for extended periods of time such a system can control surely and precisely the drug release rate, even over a number of days, they do not always achieve satisfactory if they pass through the drug absorption site, e.g., the small intestine, before the release of loaded drug is complete and also the therapeutic window of many drugs is limited by their small circulating half-life and absorption via a defined section of the intestine. To improve the delivery of drugs to the systemic circulation, a number of oral controlled release systems have been developed. To attain the required therapeutic outcome, such pharmacokinetic limitations lead to regular dosing of these medications. This results in decreased patient compliance and “pill burden”. Thus to prolong the residence time of the system, consideration must be given to achieve comprehensive drug release in the stomach, GIT, or small intestine, as well as in order to get an ideal oral controlled release system, modulate the drug release rate as forecast by the system.
1.2 BASIC PHYSIOLOGY OF THE GASTROINTESTINAL TRACT

1.2.1 Anatomical and physiological considerations

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**I. External view**

**II. Internal view**

*Figure 1.2: Anatomy of stomach (External and Internal view)*

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### Table 1.2: Anatomical and physiological features of GIT\(^8\).

<table>
<thead>
<tr>
<th>Section</th>
<th>Average length(cm)</th>
<th>Diameter (cm)</th>
<th>Absorption mechanism</th>
<th>pH</th>
<th>Major constituents</th>
<th>Transit time(h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>15-20</td>
<td>10</td>
<td>Passive diffusion</td>
<td>5.2-6.8</td>
<td>Amylase, maltase, mucin</td>
<td>Short</td>
</tr>
<tr>
<td>Stomach</td>
<td>20</td>
<td>15</td>
<td>Passive diffusion</td>
<td>1.2-3.5</td>
<td>Hydrochloric acid, pepsin, rennin, lipase, intrinsic factor</td>
<td>0.25-3.0</td>
</tr>
<tr>
<td>Duodenum</td>
<td>25</td>
<td>5</td>
<td>Passive diffusion, active transport, facilitated transport, ion pair, pinocytosis</td>
<td>4.6-6.0</td>
<td>Bile, trypsin, chymotrypsin, amylase, maltase, lipase, nuclease, CYP3A5</td>
<td>1-2</td>
</tr>
<tr>
<td>Jejunum</td>
<td>300</td>
<td>5</td>
<td>Passive diffusion, active transport, facilitated transport</td>
<td>6.3-7.3</td>
<td>Amylase, maltase, lactase, sucrase, CYP3A5</td>
<td>-</td>
</tr>
<tr>
<td>Ileum</td>
<td>300</td>
<td>2.5-5.0</td>
<td>Passive diffusion, active transport, facilitated transport, ion pair, pinocytosis</td>
<td>7.6</td>
<td>Lipase, nuclease, nucleotidase</td>
<td>1-10</td>
</tr>
<tr>
<td>Cecum</td>
<td>10-30</td>
<td>7</td>
<td>Passive diffusion, active transport, pinocytosis</td>
<td>7.5-8.0</td>
<td>-</td>
<td>Short</td>
</tr>
<tr>
<td>Colon</td>
<td>150</td>
<td>5</td>
<td>Passive diffusion</td>
<td>7.9-8.0</td>
<td>-</td>
<td>4-20</td>
</tr>
<tr>
<td>Rectum</td>
<td>15-19</td>
<td>2.5</td>
<td>Passive diffusion, pinocytosis</td>
<td>7.5-8.0</td>
<td>-</td>
<td>Variable</td>
</tr>
</tbody>
</table>
Anatomy and physiology of the gastrointestinal tract must be fully understood, to understand the considerations taken in the design of gastro retentive dosage form and to estimate their performance. In the left upper part of the abdominal cavity the stomach is located closely under the diaphragm. Its size varies according to the amount of distention: up to 1500ml following a meal; after food has emptied, a collapsed state is gained with a resting volume of only 25-50ml. Fundus, above the opening of the esophagus; body; the central part; and antrum are the three parts anatomically the stomach is separated into. The pylorus is an anatomical sphincter situated between the most terminal antrum and the duodenum. The proximal part, made of fundus and body, acts as a reservoir for undigested material temporarily, secretes digestive juices and propulse chyme, a milky mixture of food with gastric juices, to the antrum. The antrum is the main site for triturating food particles, mixing, grinds and act as a pump for gastric emptying by propelling actions and regulates the secretion of hydrochloric acid as well as. The pyloric sphincter has a diameter of 12.8±7 mm in humans and acts as a sieve as well as a mechanical structure to the passage of large particles.

Duodenum, jejunum and ileum are comprised by small intestine and for the absorption of digestive products it is the principal site from the gastrointestinal tract. Extending from the stomach to the cecum of the large intestine, it is about 2.5-5.0 cm in diameter and approximately 6.0 meters in length. The first 25 cm of the small intestine is the duodenum, the main function of which is to neutralize gastric acid and pepsin and to initiate further digestive processes. Jejunum the next segment of the small intestine, is the major part for food absorption. In addition to the great length of the small intestine, the available surface area is further enhanced by

- Circularly arranged folds of the mucosa and submucosa, called plica circulars, or valves of kerckring (the plica are particularly numerous in the jejunum)
- Finger like projection, or villi, in the mucosa;
- Extensive microvilli (brush-border) on the surface of each intestinal lining cell;
- Invaginations of the mucosa between the bases of the villi into crypts, called the crypts of lieberkuhn.

These features boost the total surface area of the small intestine in humans approximately 463 m$^2$ which is comparable to the area of a basket ball court. This is the main reason it is the primary absorption site of water, ions, vitamins and nutrients.
such as amino acids, fats and sugars. The ileum links the jejunum to the large intestine via the ileocaecal junction.

The large intestine (colon) is approximately 5cm. in diameter and 150cm. in length and extends from ileum of the small intestine to the anus. The large intestine has two main functions:

- To absorb water and electrolytes.
- To store and eliminate fecal matter.

Important role in drug liberation and absorption are shown by the factors such as nature and volume of secretions, pH, residence time, enzymes and effective absorbing surface.

1.2.2 Gastric pH.

In selecting a drug substance, gastric pH is a significant consideration also excipients, and drug carriers for designing intragastric delivery systems also plays the same role. For effectively measuring the gastrointestinal pH in human radiotelemetry, a noninvasive device is used. The gastric pH is not constant rather it is subjective by various factors like disease, diet, presence of gases, fatty acids, and other fermentation products. This variation in pH may significantly influence the performance of orally administered drugs. It has been reported that mean value of gastric pH in fasted healthy subjects is 1.1±0.15. However, in fed state in healthy subjects are 3.6 ± 0.4, and the pH returns to basal level in about 2 to 4 hours.

Pathological situations such as AIDS may significantly decrease gastric acid secretion leads to elevated gastric pH. Gastric acid secretion is significantly reduced by proton pump inhibitors and drugs like H₂ receptor antagonists

1.2.3 Gastrointestinal motility patterns

Two distinct patterns of GI motility and secretions have been identified which is based on fasted and fed state of the stomach. As a result, depending on the state of feeding the bioavailability of orally administered drugs will vary. The fasted state is associated with migrating myoelectric complex various cyclic contractile events, which regulates GI motility patterns. The migrating myoelectric complex is organized into alternating cycles of activity and quiescence and can be subdivided into four consecutive phases.
Phase I (basal phase): It is a quiescent period, lasts from 30 to 60 minutes with lack of secretory, electrical, and contractile activity.

Phase II (preburst phase): It exhibits intermittent contractions, lasts from 20 to 40 minutes that gradually increase in intensity as the phase progresses. Gastric mucus release occurs during the latter part of phase II and throughout phase III and bile arrives the duodenum during this phase, whereas.

Phase III also known as “housekeeper waves”, It is characterized by intense distal and proximal gastric contractions, lasts from 10 to 20 minutes, as it sweep all the undigested material out of the stomach down to the small intestine.

Phase IV: It is a short transitory period, last from 0 to 5 minutes between phase III and I.

The different phases initiating in the foregut continue to the ileum in a cycle in about 2 hours. Therefore, when one phase III reaches the ileum, another initiates in the stomach and duodenum.

1.2.4 Problems associated with gastric emptying

It is well recognized that for Sustained release dosage forms the stomach may be used as a depot, stomach is anatomically divided in to three parts, both in human and veterinary applications i.e Fundus, body and pylorus

Figure 1.3: Motility patterns of the GIT².
Distal region (antrum) is the major site for the mixing motion, acting as a pump to accomplish gastric emptying while the proximal stomach made up of the fundus and body region serves as a reservoir for ingested materials. The process of the gastric emptying occurs both during fasting and fed stages, study involving measurement of gastric emptying rates (Scintigraphy) in healthy human subject have revealed that an orally administered controlled release dosage form is mainly subjected to two physiological adversities,  

a) The short Gastric Residence Time  
b) Variable Gastric Emptying Time  

To reduce systematic availability of a large number of a drug first pass effect encountered through the oral route is yet another major adversity. These problems can be exacerbated by alteration in the gastric emptying that occur due to factors such as race, age, sex and disease states, as they may seriously affect the release of a drug from DDS, it is therefore desirable to have a controlled release product that exhibits an extended, GI residence and a drug release profile independent of patients' related variables-  

1.2.5 Gastric Retention and Factors associated with it  

Density:  
Gastric emptying rate is also distressed by the density of a dosage form. A floating dosage form, having a density of less than that of the gastric fluids, floats. A density of less than one g/ml has been reported in the literature. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. However, for describing its buoyant capabilities the floating force kinetics of such dosage forms has shown that the bulk density of a dosage form is not the best appropriate factor. By resultant weight measurements and swelling experiments, the buoyant capabilities are well represented and monitored.
Size and shape

Compared to those with a diameter of 9.9 mm dosage form unit with a diameter of more than 7.4 mm are stated to have an increased GRT. Related with other shapes, the dosage form with a ring shape devices and a tetrahedron shape and with a flexural modulus of 48 and 22.5 kilopond per square inch (KSI) are stated to have better retention at 24 hrs.

Unfed or fed state

Under fasting situations, the GI motility is described by the migrating myoelectric complexes or the periods of strong motor activity that happens every 1.5 to 2 hrs, The migrating myoelectric complexes sweeps undigested material from the stomach and if the scheduling of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very less. However, in the fed state, MMC is delayed and GRT is considerably longer

Caloric content

GRT can be increased between 4 to 10 hrs with a meal that is high in proteins and fats-

Nature of the meal

Nourishing of indigestible polymers of fatty acid salts can alter the motility pattern of the stomach to a fed state, thus declining the gastric emptying rate and prolonging the drug release 14

Age

Elderly people, especially those over 70 years have a significantly longer GRT23

Gender

Mean ambulatory GRT in meals (3.4 ± 0.4 hrs) is less compared with their age and race-matched female counterparts (4.6± 1.2 hrs), regardless of the weight, height and body surface,
Posture:
GRT can vary between supine and upright states of the patient. Practical’s were conducted in no fasting human volunteers either in upright or in supine posture, who currently were given one optimized floating and one non-floating hydrophilic matrix capsules of the altered sizes. In upright subjects, all the floating forms stayed continuously above the gastric contents regardless of their size, whereas the non-floating units sank quickly after ingestion and never rose back to the surface thereafter. Consequently, the floating forms showed prolonged and more reproducible GRTs compared to the non-floating forms. The significance and extent of prolongation were gradually lessened as the dosage form size increased, in case of non-floating forms. Moreover, in supine subjects, a size effect influenced the GRT of the floating and non-floating forms.26, 27, 28

Caloric content and frequency of intake of food: concomitant ingestion of food and its nature
The GI motility is characterized by periods of strong motor activity or MMC. Under fasting condition, 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 can be expected to be very short. However, in the fed state, GRT is considerably longer and MMC is delayed. Gastric residence time is elevated by feeding of indigestible polymers or fatty acid salts. Gastric residence time is increased by acidity and caloric. Furthermore, Gastric residence time can be increased when successive meals are given compared with a single meal due to the low frequency of MMC.20, 21, 22

1.3 PHARMACOKINETIC AND PHARMACODYNAMIC ASPECTS OF GRDDS
These aspects are delineated in order to suggest rational selection of drugs for which controlled release gastroretentive dosage forms (CR-GRDF) would be a beneficial strategy (Hoffman A. et al 2004).
1.3.1 PHARMACOKINETIC ASPECTS

Absorption window validation: Drugs molecules having poor colonic absorption but are better absorbed through the upper part of the GIT are most suitable category of the drugs for CR-GRDF. Such drugs are said to have an absorption window.

Enhanced bioavailability: Once the drug has been validated as narrow absorption window, the possibility of improvement in bioavailability by continuous release of the drug to the specific site should be tested. For example, the bioavailability of riboflavin and levodopa CR-GRDF is significantly enhanced in comparison to non-GRDF CR polymeric formulations.\textsuperscript{30}

Reduced frequency of dosing: The drug which having short biological half-life, sustained and slow delivery from CR-GRDF may result in a flip-flop pharmacokinetics and can reduce the frequency of dosing.

Targeted therapy for local ailments in upper GIT: The sustained and prolonged release from the GRDF to the stomach may be advantageous for local therapy in upper GIT. By this mode of administration, therapeutic drug concentration may be attained locally while the systemic concentration, following drug absorption and distribution, are minimal.

1.3.2 PHARMACODYNAMIC ASPECTS

Reduced fluctuation of drug concentration: Slow and continuous release from CR-GRDF maintains blood drug concentration within a narrow range. Thus, peak and valley plasma concentration-time profile can be minimized as occurs in case of conventional dosage form.

Extended time over effective concentration: For some drugs such as beta- lactam antibiotics, a minimum effective concentration should be maintained at all times as the clinical response is not linked with peak concentration, but with the duration of time of effective concentration.

Minimized adverse activity in other body sites: Retention of the drugs in the GRDF at the stomach reduces the amount of drug that reaches the colon. Thus, adverse
effects of the drugs in colon may be prohibited. For example, beta-lactam antibiotics are absorbed only from small intestine, and whose release in colon leads to microorganism’s resistance.

**Improved selectivity in receptor activation:** Minimization of variation in the drug concentration enables certain selectivity in the elicited pharmacodynamic effects of drugs that trigger different types of receptors at various concentrations.

**Reduced counter-activity of the body:** Many of the pharmacodynamic response provoke a rebound activity of the body that minimizes drug action, causes tolerance. Slow input of the drug e.g. furosemide, from a GRDF has been shown to minimize the counter activity.

### 1.4 POTENTIAL DRUG CANDIDATES FOR STOMACH SPECIFIC DRUG DELIVERY SYSTEMS

- Drugs those are locally active in the stomach e.g, misoprostol, antacids etc.
- Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g., l-dopa, paraaminobenzoic acid, furosemide, riboflavin etc.
- Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
- Drugs that disturb normal colonic microbes e.g, antibiotics against Helicobacter pylori.
- Drugs that exhibit low solubility at high pH values e.g, diazepam, chlordiazepoxide, verapamil HCl.

### 1.5 DRUGS THOSE ARE UNSUITABLE FOR STOMACH SPECIFIC DRUG DELIVERY SYSTEMS

1. Drug those are locally active in the stomach i.e misoprostol, antacids.
2. Drugs that have very limited acid solubility e.g. phenytoin.
3. Drugs that suffer instability in the gastric environment e.g. erythromycin.
4. Drugs intended for selective release in the colon e.g. 5, amino salicylic acid and corticosteroids etc.

In order for a hydrodynamically balanced dosage forms to float in the stomach. The density of the dosage forms should be less than the gastric contents. However, the floating force kinetics of such dosage form has shown that the bulk density of a
dosage form is not the most appropriate parameter for describing its buoyant capabilities. The prolongation of the gastric residence time by food is expected to maximize during drug absorption from the dosage form due to increased dissolution of the drug and longer residence at the most favourable sites of absorption. Though, literature data on the connection between device size and gastric residence time are contradictory.  

4.5 APPROACHES TO GASTRIC RETENTION/ STOMACH SPECIFIC DELIVERY  
Various approaches have been paused to rise the duration of oral dosage form in the stomach. The system releases the key agent to be absorbed or released from the stomach to be absorbed in the upper parts of the small intestine. GRDDS is a device, which resides in the confines of the stomach over a prolonged period of time (prolonging the residence time of the drug delivery system) for the purpose of providing a platform for controlled release of biologically active agents. This may result in improved bioavailability of the active agent with reduced side effects. In actual it allows for less frequent dosing of the active agent than with instant release formulations or sustained released formulations that are not gastric retentive dosage forms. In other applications the frequency of dosing may be the similar, but the gastric retention dosage forms will beneficially modify the absorption profile of the active agent from that available with immediate release formulations. Over the last three decades, a various approaches have been pursued to prolong the residence time of a an oral dosage forms in the stomach, these methods include  

- High density (sinking) system  
- Bioadhesive systems  
- Swelling and expanding systems  
- Super porous hydrogel systems  
- Magnetic systems  
- Ion exchange rasins  
- Raft system  
- Floating systems  

1.6.1 High density (sinking) system  
These preparations are organized by coating drug on a heavy core or mixed with inert
materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc. This method involves formulation of dosage forms with the density that must surpass density of normal stomach content (1.004 gm/cm$^3$). A density close to 2.75 gm/cm$^3$ seems necessary for significant continuation of gastric residence time but efficiency of this system in human beings was not observed and no system has been marketed. The materials increase density by up to 2.0-2.4 gm/cm$^3$.

1.6.2 Bioadhesive or mucoadhesive drug delivery systems

In a site-specific manner, bioadhesive drug delivery systems are used as a delivery device within the human to improve drug absorption. In this approach, they can stick to the epithelial surface in the stomach in which bio adhesive polymers are used. Thus, they increase the elongation of gastric retention. By diverse mechanism the basis of adhesion, in that a dosage form can stick to the mucosal surface. These mechanisms are:

- The electron theory, which suggests attractive electrostatic forces between the glycoprotein mucin complex. Even though some of these polymers are active at producing bioadhesive, it is very problematic to maintain it effectively because of the quick turnover of mucus in the gastrointestinal tract and the bio adhesive material-Materials commonly used for bioadhesion are poly acrylic acid, chitosan, cholestyramine, sodium alginate, sucralfate, tragacanth, dextrin, polyethylene glycol and polylactic acids etc.

- The diffusion theory: which recommends physical mess of mucin strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.

- The absorption theory: advises that bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.

- The wetting theory: to spread and develop close contact with the mucous layers. to spread and develop close contact with the mucous layers.

- which is based on the ability of bioadhesive polymers

1.6.3 Swellable systems, Expandable and unfoldable:

If it bigger than pyloric sphincter a dosage form in the stomach will endure
gastric transit. However, the dosage form must not cause gastric obstacle either singly or by accumulation and must be minor enough to be swallowed. Thus, for prolong gastric retention time, their formations are required to develop an expandable system:

1. A small configuration for oral intake,
2. An expanded gastroretentive form, and
3. A final small form enabling evacuation following drug release from the device.

Thus, by the combination of substantial dimension with high rigidity of dosage form, gastroretentivity is improved to withstand peristalsis and mechanical contractility of the stomach - it has been recently tried to develop an effective gastroretentive drug delivery by Unfoldable and swellable systems that have been investigated. The swelling is usually outcomes from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid (Figure 1.4). Unfoldable systems are made of biodegradable polymers. Like tetrahedron, ring or planner membrane of bioerodible polymer compressed within a capsule. Some shortcomings are associated with expandable systems like problematical storage of much easily hydrolysable, biodegradable polymers relatively and not cost effective. They are accessible in different geometric arrangements which outspreads in the stomach. Due to their mechanical properties swellable systems are also retained in the gastrointestinal tract. Again, permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion and gastropathy.

1.6.4 Super porous hydrogel systems

![Figure 1.4: Drug release from Swellable systems](image)
In this approach to improve gastric retention time super porous hydrogels of mediocre pore size >100 micro miter, swell to equilibrium size within a minute due to quick water uptake by capillary wetting through plentiful interconnected open pores. These swellable systems differ adequately from the conventional types to warrant separate classification. They are intended to have adequate mechanical strength, they swell to a big size and to withstand pressure by gastric contraction. This is advised by co formulation of hydrophilic particulate material.

1.6.5 Magnetic systems
These dosage form contains a small internal magnet this is the simple standard method on which it is grounded, to enhance the gastric retention time. Magnet is placed on the abdomen over the position of the stomach. Even though magnetic system seems to work, patient compliance, Is the key factor which must be kept in mind in the positioning of outer magnet with a degree of correctness that might compromise.

1.6.6 Ion exchange resins
Negatively charged drug and ion exchange resins are laden with bicarbonate, and is bound to the resin, semi-permeable membrane encapsulated the resultant beads to overcome the rapid loss of carbon dioxide. An exchange of chloride and bicarbonate ions takes place upon onset in the acidic environment of the stomach, carbon dioxide is released and protected in the membrane thereby carrying beads towards the top of the gastric contents and this is the consequence of the result of this reaction, and producing a floating layer of resin beads - in contrast to uncoated beads, which sink quickly.

1.6.7 Raft systems
Sodium alginate solution containing carbonates or bicarbonates comprises the raft systems which incorporate alginate gel solution. A viscous cohesive get is comprises upon reaction with gastric fluid and form comprising entrapped CO2 bubbles. This enabled floatation of the drug delivery system. They are often used for gastroesophageal reflux treatment, as with Liquid Gavisn Because raft-forming systems (Figure 1.5) produce a coating on the top of the
gastric fluids,

![Image](image.png)

**Fig 1.5 Raft forming system created barrier**

### 1.6.8 Floating drug delivery systems

Davis in 1968 first describes floating systems; it is buoyant in stomach for an extended period as it has bulk density lower than that of the gastric fluid, this results in a better control of fluctuations in the plasma drug concentrations and rise in the gastric residence time. Floating system can be effervescent or Non effervescent in nature-

1. **Effervescent systems**
   - Volatile liquid system
     - Intragastric floating drug delivery system
     - Inflatable gastrointestinal delivery system
     - Intragastric osmotically CDDS
   - Gas generating system
     - Hydrodynamically balanced system
     - Intragastric bilayer floating tablet
     - Multiple unit type floating pills

2. **Volatile liquid containing systems**

By incorporating an inflatable chamber, the gastric residence time of a drug delivery system can be sustained which contains a liquid e.g, ether, cyclopentene, to cause the infatuation of the chamber in the stomach these gasifies at
body temperature. Such as polyethylene these devices contain of a bioerodible plug that slowly dissolves causing the inflatable chamber to release gas. And to permit the spontaneous ejection of the inflatable systems from the stomach, it breaks down after a predetermined time.

- **Gas generating systems**
To liberate CO₂, these buoyant delivery systems utilize effervescent reactions between bicarbonate /carbonate salts and tartaric /citric acid. This decreasing its specific gravity and making it to float over which gets entrapped in the gellified hydrocolloid layer of the systems thus. How the dosage form float is shown in the following figure (Figure 1.6).

![Fig: 1.6 The mechanism of floating system](image)

2. **Non-effervescent systems**
This type of system stops their exit from the stomach, after swallowing, via imbibition of gastric fluid to an optimized level. These type of formulation is incorporated by mingling of the drug with a gel, which after oral administration swells, in contact with gastric fluid and keeps a relative integrity of shape and a bulk density of less than one. Buoyancy to these dosage forms is confers by the air trapped by the swollen polymer. Polyvinyl acetate, Carbopol, agar, sodium alginate are the excipients used most commonly in these systems others are hydroxypropyl methyl cellulose polyacrylate polymers, calcium chloride, polyethylene oxide and polycarbonates.

They are further divided into 4 other types

*(i) Gel barrier colloidal system*
In this technique drug with gel-forming hydrocolloids are used to stay buoyant on the stomach content. This maximizes the amount of drug that reaches its absorption sites and delays gastro-retentive time in the solution form for ready absorption. Hydroxypropyl cellulose, hydoxyethyl cellulose, hydroxypropyl methyl cellulose, polysaccharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene are examples of high level of gel forming hydrocolloid which is integrated by this system. Nearby its surface the hydrocolloid in the system hydrates and forms a colloid gel barrier, coming in touch with gastric fluid

(ii) Alginate beads
By dropping sodium alginate solution into aqueous solution of calcium chloride Spherical beads of diameter 2.0 mm approximately can be formulated. From freeze-dried calcium alginate a multi-unit floating dosage forms have been desined, creating the precipitation of calcium alginate. Formation of pores system is initiated by frozen in liquid nitrogen, and freeze-dried at -45°C for more than 20 hours, the beads are then separated, which can be maintain to float for over 12 hours. An extended residence time of more than 5.6 hours can be attained by these floating beads.

(iii) Microporous compartment system
This technology based on the ground that a microporous compartment incapsulates the drug reservoir inside, with openings along its lower and upper walls. To prevent any direct contact of gastric surface with the undissolved drug, the exterior walls of the drug laden compartment are completely closed. For system to float over the gastric content, in the stomach, the floatation chamber comprising entangled air causes the delivery. Dissolved drug are carried through aperture via gastric fluid, and carries the for continuous transport through the intestine for absorption.

(iv) Hollow microspheres / Microballons
By novel emulsion solvent diffusion technique an outer polymer shelf were prepared by hollow microspheres laden with drug. By the evaporation of dichloromethane formed and with internal cavity in the microsphere of the polymer, the gas phase is generated in the dispersed polymer droplet. Drug and an enteric acrylic polymer was meted out into an agitated solution of Poly Vinyl Alcohol which is ethanol/dichloromethane solution. And it was thermally controlled at 40°C. Over the
surface of an acidic dissolution media, the microballoon floated continuously containing surfactant for more than 14 h.

![Image](image.png)

**Fig. 1.7:** floating unit having intragastric residence positions of

1.6.9 Design Floating Dosage Forms and its approaches.

For the design of floating dosage forms of single and multiple-unit systems, the subsequent approaches have been used.

**Single-Unit Dosage Forms:**

For a drug for its organized release a Low-density approach the globular shells seemingly having lower density than that of gastric fluid can be used as a carrier. Fluid-filled system that lifts in the stomach is another approach for buoyant dosage form. In coated shells popcorn, poprice, and polystyrol have been exploited as drug carriers. To undercoat these shells, a sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used. Which were further coated with a drug-polymer mixture. Over a continued duration while releasing the drug slowly the product floats on the gastric fluid Finally\(^\text{36}\). Either ethyl cellulose or hydroxypropyl cellulose are the polymer of excellent can be depending on the type of release wanted.

Fluid- filled floating chamber type of dosage forms includes incorporation of a gasfilled floatation chamber into a microporous component that houses a drug reservoir. Along the top and bottom walls apertures or openings are existing and through which the gastrointestinal tract fluid enters which makes the drug to dissolve.
Pertaining to the un-dissolved drug remains therein, the other two walls in contact with the fluid are closed. The fluid existing could be air, under partial vacuum or any other proper gas, an appropriate specific gravity and inert actions. The device remains afloat within the stomach for an extended time and is of swallowable size, and after the complete release the shell passes off to the intestine and disintegrates. Various types of tablets have been shown to have floatable characteristics. Few of the polymers used are hydroxypropyl cellulose, hydroxypropylmethylcellulose, crosspovidone, sodium carboxymethyl cellulose, and ethyl cellulose. Shown in Fig no.1.8

![Diagram of bilayered systems](image)

**Fig.1.8.** Schematic presentation of working of bilayered systems.

To control drug release a disproportionate 3-layer matrix technology which is self-correcting floatable asymmetric configuration drug delivery system employs. The 3-layer principle has been established by development of an unequal configuration drug delivery system in order to modify the release extent and attain zero-order release kinetics by initially keeping a constant area at the diffusing front with succeeding dissolution/erosion toward the completion of the release process.

Drugs that have pH-dependent solubility this particular characteristic are valid for, a thin window of absorption, and are absorbed by active transport from either the distal or proximal portion of the small intestine. To prolong gastric residence time, the system was designed in such a manner with full absorptive
capacity that it glided in vivo, causing greater bioavailability and consequently in elongated total transit time inside the gastrointestinal tract environment.

By incorporating a gas-generating layer, the floatation was accomplished involving of sodium bicarbonate: calcium carbonate along with the polymers $^{39,38}$ In *Helicobacter pylori*, floating ability in a swellable asymmetric triple-layer tablet with to elongate the gastric residence time of threefold drug regimen (metronidazole, tetracycline and clarithromycin). Associated peptic ulcers using the rate-controlling polymeric membrane excipients. On the swellable asymmetric triplelayer tablet approach, the design of the delivery system was based. Into the core layer of the triple-layer matrix, two drugs were amalgamated for controlled delivery, and for the outer layers for immediate release, third drug was involved. As shown in Fig no.1.9

![Fig 1.9. Triple-layer system and its schematic presentation of working](image)

A: Initial configuration of a triple-layer tablet.
B: after contacting with dissolution medium.
C: Tablet erodes after swelling.
D & E: Completely erodible tablet.

sticking together or being obstructed in the gastrointestinal tract are the problems associated with single-unit formulations such as, which may have a potential danger of producing irritation.

**Multiple-Unit Dosage Forms.**

To develop a trustworthy formulation that has all the advantages of a single-unit form is the basic purpose of designing multiple-unit dosage form and also it is lacking of any of the above mentioned disadvantages of single-unit formulations. Many multiple-unit floatable dosage forms have been designed in search of this effort.
**Introduction**

Alginates are nontoxic, biodegradable alginates have received much attention in the development of multiple unit systems. These are linear copolymers composed of Lglucuronic acid residues. From freeze dried calcium alginate multiple unit floating dosage forms have been developed. Spherical beads of approximately diameter 2.0 mm producing precipitate of calcium alginate can be constituted by dropping a sodium alginate solution in to aqueous solutions of CaCl2 solution. The beads are then frozen in liquid nitrogen, separated freeze dried at -45°C for more than 20 hours.

Many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate to produce microspheres which have great stocking capacity. Micro balloons are referred to as spherical polymeric microsponges, have been furnished. Microspheres have show an excellent in vitro floatability as it contain a typical internal hollow structure. In Carbon dioxide generating multiple unit oral formulations several strategies created in the devices after administration have been described in the recent patent literature. If a diameter of ~13 to 17 mm in their expanded state is exceeded, these dosage forms are excluded from the passage of the pyloric sphincter.

A new numerous type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. To avoid direct contact between the agents the internal layer of effervescent agents containing tartaric acid and sodium bicarbonate was separated into 2 sub layers. Polyvinyl acetate and purified shellac is two swellable polymer which comprises the membrane. Into the effervescent layer the solution infused through the outer swell able membrane and when this system was submerged in the buffer at 37ºC. By the neutralization reaction between the 2 effervescent agents CO2 was made, producing inflated pills with a density less than 1.0 g/ml. independent of pH and viscosity it was found that the system had respectable floating ability and the drug released in a continuous manner.
1.7 FORMULATION OF FLOATING DOSAGE FORMS

Addition to the drug subsequent types of the ingredients can be assimilated into HBS dosage forms in.\textsuperscript{53, 54}

- Hydrocolloids
- Inert fatty materials
- Release rate accelerants
- Release rate retardant
- Buoyancy increasing agents
- Miscellaneous

i. Hydrocolloids:

Suitable hydrocolloids are anionic or nonionic, synthetics, like hydrophilic gums, improved cellulose derivatives. E.g. agar, acasia, pectin, gelatin alginates, bentonite, veegum, casein, MC, HEC, HPC and Na CMC can be used. We must hydrate the hydrocolloids in acidic medium i.e. gastric fluid having pH 1.5. Though the bulk density of the formulation may primarily be more than 1, but for promise buoyancy, (when gastric fluid is enter in the system) it should be hydrodynamically balanced to have a bulk density of less than one.

ii. Accelerating the release rate.

Excipients like microcrystalline cellulose, lactose and mannitol can modify the release rate of the medicament from the preparation. These may be present from about 6-65% by weight.
iii. **Inert fatty materials**

To reduce the hydrophilic property of formulation, pharmaceutical inert fatty edible material, having a specific gravity less than 1 can be added to the formulation and hence raises the buoyancy. Ex. Purified grades of fatty acids, beeswax, glycerides, long chain alcohols, and mineral oils can be castoff. Such materials may exist from about 6-76 % by weight.

iv. **Release rate retardant**

Insoluble substances such as talc, dicalcium phosphate, and magnesium stearate decreased the release of medicaments and the solubility hence retard. Such materials may be present about 4-61 % by weight.

v. **Buoyancy increasing agents**

For enhancing the buoyancy of the formulation Materials like ethyl cellulose, which has bulk density less than 1, can be used. It may be added up to 80 % by weight.

vi. **Miscellaneous**

As per the requirements pharmaceutically acceptable adjuvant like stabilizers, preservatives, and lubricants can be incorporates in the dosage forms. The hydrodynamic balance of the systems are not adversely affected.

### 1.8 TYPES OF FLOATING DOSAGE FORMS

- New floating bilayer compressed matrices
- New multiple unit oral floating dosage form
- Sustained release intragastric floating granules
- Floatable asymmetric configuration drug delivery system
- Floating non compressed sustained release tablets
- Microballoons

- **New floating bilayer compressed matrices:**

  The carbon dioxide being caught in the gasified hydrocolloid as liberated by the action of the gastric medium creates the upward motion of the tablet. Carbon dioxide generating blend as well as hydrodynamic polymer is contained in one of the tablet layers and preserves its buoyancy. The dug which is release in the
prolong and controlled way are contained in the outer layer of hydrophilic matrix.

Advantages

• with regard to erosion double layer matrix tablet shows an extra homogenous conduct and is less sensitive to the GI peristaltism and this allows the separate regulation of the floating abilities and the drug release kinetics by the preparation of the matrix dosage form with two discrete layers

  • for carrying drugs which are sufficiently stable and soluble in acidic media this type of sustained release matrix could be favorably used and for enhanced reabsorbed in the proximal or middle portion of the GI tract, demanding a sustained release period to increase the bioavalability of poorly soluble products in non acid media or targeting to produce a local and definite effect in the stomach,

• **New multiple unit oral floating dosage forms**

The Gastric Emptying Time in the humans is in fed state from 1-6 hrs has been reported- sufficient bioavalability and prolongation of the effective plasma level occasionally could not be obtained when a sustained release dosage form was administered orally, particularly for drug having a narrow absorption site in the intestinal tract. Freshly some studies such as the bioadhesive systems and floating dosage systems have been reported prolongation of Gastric Emptying Time of certain preparations, it was possible that a single unit type might be transited in to the small intestine , as most of the floating dosage systems were single unit preparations in a short time, regardless floating ability.In order to prolong the Gastric Emptying Time of the preparation multiple type of oral floating dosage systems has been equipped The system was composed of the double layer surrounding the pills and continual release pills containing the drug. Outer layer was sellable membrane while inner layer was an effervescent layer containing both sodium bicarbonate. Outer layer was separated in to two sub layers to avoid direct contact between tartaric acid and sodium bicarbonate in the outer one.

**Advantages**

• Conservative sustained release pills, such as matrix type or barrier membrane type, can be used as the central seeds of the system,
• The system has higher density related with other floating systems so the floating dosage system is compressed before dipping in water, and is easy to handle.

• **Sustained release floating granules**
  Drug granules, which remain in the stomach, comprise core- pharmaceutically effective ingredients coated with expansive films. Drug used was Dextromethorphan HCl (20%). Granules are developed based on chitosan of different buoyancy, The release rate of indomethacine from chitosan granules was compared with that of conventional commercial indomethacine capsules. Furthermore, enhancing the mixing ratio of drug and chitosan can control the release rate. In case of conventional capsule, the plasma concentration reach the maximum level one-hour after administration, while in case of granules with a 1:2 mixing of drug and chitosan, the chitosan produced a sustained plateau level of the drug.

• **New self-correcting floatable asymmetric configuration drug delivery system**
  Apart from faced problems in pulsatile delivery system design, for total drug release, for controlled drug delivery, design of the methods that would provide zero order kinetics with no lag time or burst effect over a extend period is the greatest challenging in the last two decades amongst pharmaceutical scientists has been, its various features are:
  • These preperations floats, thus being likely to extend gastric residence time, the method is design in such a way that results in longer total transit time within the GIT environment with maximum absorptive capacity and consequently greater bioavalability.
  • Drugs, which have pH dependent solubilities following particular characteristics would be applicable to also a thin window of absorption and are absorbed by active transport from either the proximal or distal part of the small intestine.
  • As direct compression technology is involved so ease of manufacturing.
Advantages

• By adjusting the amount or composition of each layer the period of the drug release and the release pattern could be easily custom-made, and this provide a to formulation scientists a greater degree of flexibility.

• The absenteeism of the actual burst effect which is habitually seen with matrix type delivery system is highly noteworthy-

• Changes in pH of the GIT and in-vivo situation are not effected by rug release from these systems.

• Low density and the ease with which the system can be easily trapped are the feature of these swelling hydrophilic matrices adding to floating behavior after exposure to dissolution medium delay gastric emptying of stomach-

• We can achieve zero order kinetic

• In a controlled manner drug is totally released.

• **Floating noncompressed sustained release tablet**

Continued release noncompressed tablets having a network of multitude air holes and passage there in a density of less than one and capable of floating on gastric juice *in-vivo* comprises a matrix containing

• Gelling agents (0.5-0.4%)

• Inert oil (10-20%)

• Therapeutic agent (50-75%)

• Water up to 100%

• **Micro balloons**

By this system a widely distributed multiple units floating system through out the GIT, and it provide a possibility of achieving a longer lasting and more trustworthy release of drugs.

To attain this goal as a modification of the emulsion solvent diffusion method having novel method to prepare floating microspheres loaded with drug was established for the preparation of the polymeric microsponge for a controlled drug delivery system, due to its characteristic internal hollow structure these microsphere was named as "microballoons" havin excellent *in-vitro* floatability.
Introduction

Advantages

• More predictive drug release kinetic

• Less chances of Localized mucosal damage

• Larger margin of safety against dosage form failure. e.g. air compartment multiple unit system for gastric retention

1.9 EVALUATION OF FLOATING SYSTEMS

Floating duration, s dissolution profiles, specific gravity, hardness, content uniformity, and friability in case of solid dosage forms are the numerous parameters\(^9\) that need to be estimated in gastro-retentive formulations. Particle size analysis, differential scanning calorimetry (DSC), flow properties, surface morphology, and mechanical properties are also performed in the case of multi-particulate drug delivery systems.

Floating time

Kept at 37°C The check for buoyancy is usually accomplished in simulated gastric and intestinal fluid. By using USP dissolution apparatus containing 900 ml of 0.1 N HCl the floating time is resolute as the testing medium maintained at 37°C. The time for which the dosage form floats is designated as the floating or floatation time\(^{48}\).

Swelling index

At room temperature the swelling index of tablets was resolute in 0.1 N HCl (pH 1.2). At predefined time intervals the swollen weight of the tablets was determined. The swelling index was calculated by the subsequent equation:

\[
Swelling\ index = \frac{W_t - W_0}{W_t}
\]

Where, \(W_0\) is the initial weight of tablet, and \(W_t\) is the weight of the tablet at time \(t\).

In vivo study\(^{16}\)

By X-ray diffraction studies, gamma scintigraphy, or roentgenography \(In vivo\) gastrointestinal residence time of a floating dosage form is detected. The study is carried out by administering the gastroretentive tablets to human volunteer. In X-ray method the formulation is modified to include Barium Sulphate as X-ray opaque substance. The tablet was administered in the fasting state. With 250 ml of water the
X Ray opaque formulation is administered. The subjects are permitted to remain in sitting or up right position. After 2 hour of administration of the tablet a nimble meal is given to volunteer to assess effect of food of gastroretentive property. X-Ray photographs taken at desired intervals to monitor tablet position in human gastrointestinal tract The position of tablet is monitored by X-Ray screening technique.

In-vitro dissolution study

Using USP dissolution apparatus dissolution tests are executed - intermittently from the dissolution medium samples are withdrawn; with the same volume reloaded it with fresh medium at sampling time points. New methodology as described in the USP XXIII states "the dosage unit is permitted to sink to the bottom of the vessel before revolution of the blade is started, A few turns of a loose piece of wire helix small, which is nonreactive material may be attached to the dosage units that would else float" However, normal dissolution methods based on the USP or British Pharmacopoeia (BP) have been shown to be poor predictors of in-vitro performance for floating dosage forms. Pillay detected that the procedure tends to hinder drug release from the formulation as the three-dimensional swelling process of the dosage form, was suppressed- Based on their explanations, the researchers proposed an alternative method in which the floatable delivery system was fully immersed under a ring/mesh assembly, The results showed a significant rise in drug release (20%) In addition, the projected method was found to provide reproducible hydrodynamic conditions and consistent release profiles
1.10 ADVANTAGES OF FLOATING DOSAGE FORMS\textsuperscript{29,30}

- To get appreciable therapist activity all those molecules with substantially short half-life can be administered in this fashion. This is a principal manner especially all those drugs which get metabolized in upper GIT in which the bioavailability of a therapeutic agent can be improved.\textsuperscript{69}

- The Principle of hydrodynamic system may not restricted to any specific medicament or class of medicament.

- Hydrodynamic system preparation may be beneficial for the administration of aspirin and other similar drugs as acidic substances like aspirin cause irritation on the stomach wall when come in to interaction with it.

- The hydrodynamic system formulations are not limited to medicaments, which are absorbed from stomach, since it has been found that these are similarly effective with medicament, which absorbed from the intestine.

- For drugs meant for local action in the stomach the hydrodynamic system are advantageous. E.g. Antacids.

- For drugs absorbed through the stomach the hydrodynamic system are beneficial. E.g. Ferrous salts, antacids.

- Using the sustained release principle of hydrodynamic system formulation, the efficacy of the medicaments administered has been found to be autonomous of the site of specific medicaments.

- It may be advantageous to keep the drug in floating situation in stomach to get a relatively superior response, when there is vigorous intestinal movement and a shorted transit time as might occur in certain type of diarrhea, deprived absorption is expected. Under such conditions.

- It is therefore predictable that a drug will be fully absorbed from the floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

- The active entity is delivered to the site of action those minimizing the side effects.

1.11 LIMITATIONS/DISADVANTAGES:

- These systems require a high level of fluids in the stomach for drug delivery, to float and work efficiently.
The dosage form should be administered with a full glass of water (200-250 ml).

Not appropriate for drugs that have solubility or stability problem in GIT.

Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.

Drugs which are irritant to Gastric mucosa is also not appropriate or suitable.

The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.

1.12 DRUGS EXPLORED IN GASTRORETENTIVE DOSAGE FORMS:

Table 1.3: Drugs explored in gastroretentive dosage forms

<table>
<thead>
<tr>
<th>Types of dosage forms</th>
<th>Drugs explored in Gastoretentive dosage forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microspheres</td>
<td>Aspirin, Griseofulvin, P-nitro aniline, Ibuprofen, Terfenadine, Tranilast</td>
</tr>
<tr>
<td>Granules</td>
<td>Diclofenac Sodium, Indomethacin, Prednisolone</td>
</tr>
<tr>
<td>Films</td>
<td>Cinnarizine</td>
</tr>
<tr>
<td>Powders</td>
<td>Several Basic Drugs</td>
</tr>
<tr>
<td>Capsules</td>
<td>Chlordiazepoxide HCl, Diazepam, Furocemide, L-Dopa and Benserazide, Misoprostol, Propranolol HCl, Ursodeoxycholic acid</td>
</tr>
<tr>
<td>Tablets/Pills</td>
<td>Acetaminophen, Aspirin, Amoxycillin trihydrate, Ampicillin, Atenolol, Chlorpheniramine maleate, Cinnarizine, 5-Fluorouracil, Isosorbide mononitrate, Diltiazem, Isosorbide dinitrate, Para amino benzoic acid, Piretenide, Quinidine, Varapamil HCl, Riboflavin, Sotalol, Theophyllin</td>
</tr>
</tbody>
</table>

1.13 COMMERCIAL GASTRO RETENTIVE FLOATING FORMULATIONS:

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Table 1.4: Commercial gastro retentive floating formulations

<table>
<thead>
<tr>
<th>Name</th>
<th>Type and Drug</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>MadoparHBS(^{\circledast}) (PropalHBS)</td>
<td>Floating capsule, Levodopa and benserazide</td>
<td>Floating CR capsules</td>
</tr>
<tr>
<td>Valrelease(^{\circledast})</td>
<td>Floating capsule, Diazepam</td>
<td>Floating Capsules</td>
</tr>
<tr>
<td>Amalgate Float Coat(^{\circledast})</td>
<td>Floating antacid, Floating gel</td>
<td>Floating dosage form</td>
</tr>
<tr>
<td>Conviron</td>
<td>Ferrous sulphate</td>
<td>Colloidal gel forming FDDS</td>
</tr>
<tr>
<td>Cytotech(^{\circledast})</td>
<td>Misoprostol (100 mcg/200 mcg)</td>
<td>Bilayer floating capsule</td>
</tr>
<tr>
<td>Liquid Gaviscon(^{\circledast})</td>
<td>Mixture of alginate</td>
<td>Suppress gastro esophageal reflux and alleviate the heart burn</td>
</tr>
<tr>
<td>Topalkan(^{\circledast})</td>
<td>Floating Antacid, aluminum and magnesium mixture</td>
<td>Effervescent floating liquid alginate preparation</td>
</tr>
<tr>
<td>Cifran OD(^{\circledast})</td>
<td>Ciprofloxacin (1 gm)</td>
<td>Gas generating floating form</td>
</tr>
</tbody>
</table>

1.14 APPLICATION OF FLOATING DRUG DELIVERY SYSTEMS\(^{90}\)

- Recent study showed as compared to normal tablets in controlling the Blood pressure of hypertensive patients, administration of Diltiazem floating tablets two times a day might be extra effective.
- It is used to eradicate \textit{H. pylori} as it provides high concentration of drug within gastric mucosa, (a causative organism for chronic gastritis and peptic ulcers).
- Modapar\(^{\circledast}\) HBS containing L-Dopa and Benserazide, here the drug was absorbed over a period of 6-8 hours and retained substantial plasma concentration for Parkinsonian patients. Cytotech\(^{\circledast}\)- containing Misoprostol, a synthetic prostaglandin –EL analogue, for prevention of gastric ulcer caused by non-steroidal anti-inflammatory drugs (NSAIDS).
In the patients with stomach neoplasm, 5-fluorouracil has been successfully evaluated. Developing HBS dosage forms provide better delivery systems and reduced its GI side effects.

Treatment of gastric and duodenal ulcer.

### 1.15 FUTURE POTENTIAL OF FLOATING DRUG DELIVERY SYSTEM

- Floating dosage form offers various futures potential as evident from several recent publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying.
- We can deliver the drugs efficiently that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract thereby maximizing their absorption and improving their absolute bioavailability.
- for the treatment of gastric and duodenal cancers, buoyant delivery system considered as a beneficial strategy.
- In various anti-reflux formulations, the floating concept can be utilized.
- Developing a controlled release system for the drugs, which are potential to treat the Parkinson’s disease.
- By using the narrow spectrum antibodies, to explore the eradication of Helicobacter pylori

### 1.16. PEPTIC ULCER: CAUSES AND CONSEQUENCES

Stomach produces HCl and pepsin, which collectively start the digestion of food. In theory, these two substances could digest the lining of the stomach or duodenum. Ulcer is a crater like lesion in a membrane; ulcers that develop in area of gastrointestinal tract exposed to acidic gastric juices and pepsin are called peptic ulcers. Ulcers mainly occur in either duodenum or in stomach (98-99%) in ratio of 4:1. Ulceration of GIT mucosa is caused by disruption of normal balance of corrosive effect of gastric juice and the shielding effect of mucus on gastric epithelial cells. Acid neutralization was recognized as effective treatment for more than 12 centuries ago.
Gastric secretion is a complex continuous process controlled by multiple central and peripheral factors. Parietal cells secrete $H^+$ ions. There are two pathways, which activate the process of gastric secretion viz., AMP dependent pathway and calcium dependent pathway. The $H^+K^+$-ATPase pump (proton pump), which secretes $H^+$ ions in parietal cells, can be activated by histamine, Ach and gastrin via these two pathways. Ulcers may be associated with Helicobacter pylori infection of stomach. This infection may lead to impaired production of somatostatins by D cell and in time inhibition of gastrin with the resulting higher acid production as well as duodenal bicarbonate production.

**Classification of peptic ulcer**
Peptic ulcers are classified as acute (stress) ulcers and chronic ulcers. Chronic ulcers are further subdivided as per anatomical location
(a) Gastric ulcers
(b) Duodenal ulcers
In the area of the gastrointestinal tract the formation of ulcer development takes place which is exposed to acidic gastric juice. Mostly if they occur in the pyloric sphincter or first part of duodenum, they are called duodenal ulcers and if ulcers occur on the lesser curvature of stomach, where they are called gastric ulcers. Duodenal ulcers are most common. Duodenal ulcers are about 10 times more frequent than gastric ulcers. Indeed ulcers can happen not only in the stomach but also in the lower part of the oesophagus and in the duodenum. Due to decrease in PEG release ulcer formation takes place as ulcer formation involves breaking the mucosal barrier and exposing the underlying tissue to the corrosive action of acid and pepsin.

Management
The treatment of ulcer should be aimed at
1. Reduction of stomach acid
2. Protection of stomach lining
3. Eradication of Helicobacter pylori

Figure 1.12: Mechanism of drugs causing inhibition of gastric HCl

Causes of peptic ulcer
Factors suspected of playing a role in the development of peptic ulcers include:
1. Helicobacter pylori
Research shows that most ulcers develop as a result of infection with bacterium called Helicobacter pylori (H. pylori). H. pylori's corkscrew shape enables it to
penetrate the mucous layer of the stomach or duodenum so that it can attach itself to the lining. It survives its highly acidic environment by producing urease, an enzyme that generates ammonia and neutralizes the acid. The bacterium produces substances that weaken the stomach's protective mucus and make it more susceptible to the damaging effects of acid and pepsin, as well as produce more acid. Both the acid and the bacteria irritate the lining and cause a sore, or ulcer. This mechanism allows *H. pylori* to make its way to the "safe" area—the protective mucous lining.

2. Smoking

cigarette smoking as an important risk factor for peptic ulcer disease and this is identified by several studies. Smoking decreases mucosal prostaglandin and bicarbonate discharge this decreases mucosal blood flow, and increases duodenogastric reflux.

3. Diet and Caffeine

Symptoms of peptic ulcer disease are exaggerated by caffeine holding beverages and certain foods with spicy diet.. Milk, which was once prescribed for ulcer because of its ability to buffer stomach acid and rapidly relieves pain, encourages the secretion of more acid. However, no specific dietary items have been shown to cause ulcers. long-term use of milk is probably detrimental for patients with ulcers.

4. Stress

people with ulcers often report that emotional stress rises ulcer pain. Many physiological stresses such as spinal cord injury, burns, head injury, multiple trauma or sepsis may induce superficial mucosal erosions or gastro duodenal ulcerations. Diminished blood flow to the gastric mucosa, decreased cell renewal, diminished prostaglandin production and occasionally acid hyper secretion are involved in causing stress ulceration.

5. Pepsin and acid

Main contributing factor for ulcer formation is the stomach's incapability to defend itself against the hydrochloric acid , powerful digestive fluids and pepsin. The stomach can protect itself from these fluids in several ways in ideal situations as following.
Lubricant which is produced by the stomach -like mucus that coats the stomach and shields stomach tissues.

Chemical called bicarbonate which is produced by the stomach can neutralizes digestive fluids and breaks them down into less harmful substances.

Stomach is protected by blood circulation in the lining of the stomach, as well as cell renewal and repair.

6. Non steroidal anti-inflammatory drugs (NSAIDs)\textsuperscript{110,111}

The stomach susceptible to the harmful effects of acid and pepsin from the drugs such as ibuprofen, aspirin, and naproxen sodium. They are present in many non-prescription medications used to treat fever, headaches, and minor aches and pains. The rate of NSAID-caused ulcers is increasing as the long-term use of NSAIDs is the second most common cause of ulcers and. The most common NSAIDs are aspirin, diclofenac, ibuprofen, and naproxen.

Following table give the ulcer risk for different NSAIDS. Patients should discontinue taking drugs who have an ulcer caused by NSAIDs. NSAIDs definitely increase the risk for ulcers and gastrointestinal (GI) bleeding. For temporary pain relief if we take short courses of NSAIDs should not cause major problems because the stomach has time to recover damage and repair it that has occurred.

**Table 1.5. Specific NSAIDS causing Ulcer**

<table>
<thead>
<tr>
<th>Lowermost Risk</th>
<th>Mediocre Risk</th>
<th>Uppermost Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nabumetone, Sulindac, Salsalate, Etodolac</td>
<td>Aspirin, Naproxen, Diclofenac, Ibuprofen.</td>
<td>Flurbiprofen, Piroxicam Fenoprofen, Indomethacin, Meclofenamate, Ketoprofen</td>
</tr>
</tbody>
</table>

7. Over production of histamine and gastrin

The secretion of acid into the stomach lumen through cAMP/protein kinase A/proton pump pathway is triggered by gastric parietal cells especially, $H_2R$. 

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SURESH GYAN VIHAR UNIVERSITY, MAHAL, JAGATPURA, JAIPUR (RAJASTHAN) 39
Zollinger-Ellison syndrome is the least common major cause of peptic ulcer disease.

Gastrin, a hormone that stimulates gastric acid formation is produced in excess amount by gastrinomas (tumors in the pancreas and the duodenum). Proper and quick management of the disease is needed as these tumors are usually malignant. These malignant tumors must be removed and acid production suppressed to relieve the recurrence of the ulcers. Systemic mastocytosis is a disease related with diffuse infiltration of the skin, GI tract, bone marrow, spleen, and liver with mastocytes. Gastric acid hyper-secretion occurs in response to histamine production by mastocytes.

8. Diminished mucosal resistance

Due to discrepancy between mucosal protective resistance and damaging luminal factors, ulcer rises, permitting the latter to predominate. Prostaglandins (PGs) are known to protect the gastric mucosa against injury caused by a variety of necrotizing agents. Defects of mucosal protective mechanisms modulated by prostaglandins have been found in different forms of ulcer disease. The principal injurious elements are acid and peptic activity. Bile reflux, drugs, and gastroduodenal stasis may change the luminal milieu and act collectively with acid-peptic activity to produce injury, weaken mucosal resistance, or both. Such defects include impaired duodenal bicarbonate secretion, deficient secretion or faster degradation of mucus, and reduced mucosal cell proliferation.

1.17 OBJECTIVE

- Gastroretentive systems spread considerably the time period over which the drugs may be released. Thus not only increase patient compliance but also extend dosing interval beyond the level of existing controlled release dosage forms.

- Mankind has lived with peptic ulcers since ancient times. Ulcer is one of the most common disease, which is most prevalent mainly in the developed countries, but now this problem has crossed its limits and threaten to overwhelm developing countries such as India. Antiulcer agents mainly H$_2$ antihistamines and proton pump inhibitors are used to treat those patients.
These drugs suffer from low bioavailability problems, short half-life, and duration of action; this makes discomfort to patients. Recent development in novel drug delivery system, a new approach “gastric retention” is solution to these problems of antiulcer agents by keeping the dosage form at the target site for extended period of time.

- The model drug is Famotidine, used in the treatment of several gastric disorders particularly gastric and duodenal ulcers, gastritis, gastroesophageal reflux disease and zollinger-ellison syndrome. The oral bioavailability of Famotidine is 40-45%, it reaches maximum plasma concentration within 1-3 hours and has shorter half-life (2.5-3.5 hours) so dosing frequency is high.

- The objective of present research investigation was to fabricate and evaluate a gastro retentive multiparticulate floating drug delivery system of famotidine using different polymers such as sodium alginate, HPMC, Pectin. The development of such a dosage form was justifiable from various aspects as follows:
  - Famotidine has a short biological half-life (2.5-3.5 hours), which required frequent dosing to maintain the drug level within the therapeutic blood levels for longer period of times. So by reducing the frequency of administration the patient compliance can be increased.
  - Famotidine is highly soluble in acidic medium and remain in unionized form at stomach pH, making stomach as an absorption site. Hence, by formulating the floating drug delivery system of Famotidine, it is possible to increase its bioavailability and also the patient compliance.
  - 70% of I.V dose is excreted in urine unchanged proving to be good for oral route.
  - Famotidine undergoes minimum first pass metabolism. So there will be no significant effect in retaining the drug in stomach.
  - Improving physiological and pharmacological response.
  - Avoiding the fluctuation of plasma drug level.
  - Extend the duration of action of drug.
  - Extend the drug release.
  - Minimize undesirable side effects.
  - Reduce the dosing frequency and dose.
Introduction

- Improve the patient compliance.
- Provide new drug delivery system for the treatment of disease.
- Provide flexibility in dosage form design and development

The prime objectives of present research investigations is:

1. To formulate and evaluate oil entrapped stomach specific beads prepared by ionotropic gelation method.
2. To evaluate the physico-chemical characteristics like weight uniformity, size uniformity, drug content uniformity, floating time etc.
3. To evaluate in vitro dissolution studies of SRDDS in simulated gastric environment.
4. To evaluate the accelerated stability studies of optimized batch as per the ICH guidelines.
5. Optimization of beads on the basis of polymer concentration
6. Optimization of beads on the basis of height of syringe dropping the beads.
7. Optimization of beads on the basis of different needle size used.
8. Optimization of beads on the basis of different rate of dropping.
10. Optimization of beads on the basis of different concentration of curing agent.
11. Optimization of beads on the basis of different curing time.
12. Preparation and evaluation of beads having different oils of different concentration
13. Preparation and evaluation of beads having different curing agent.