INTRODUCTION

Oral delivery of drugs is by far the most preferred route of drug delivery due to ease of administration, patient compliance and flexibility in formulation\(^1\). Conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery\(^2\). These systems achieve as well as maintain drug concentration within therapeutically effective range needed for treatment only when taken several times a day. This results in significant fluctuation in drug levels\(^3\).

Now-a-days most of the pharmaceutical scientists are involved in developing an ideal drug delivery system (DDS). An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period\(^4\).

Controlled release drug delivery systems:

Controlled release drug delivery system (CRDDS) provide drug release at a predetermined, predictable rate and optimizes the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dosing. In general controlled delivery attempts to\(^5\):

a) Sustain drug action at a predetermined rate by maintaining a relatively constant and effective drug level in the body with concomitant minimization of undesirable side effects associated with a saw tooth kinetic pattern.

b) Localize drug action by spatial placement of controlled release system (usually rate controlled) adjacent to or in the diseased tissue or organ.

c) Target drug action by using carriers or chemical derivatization to deliver drugs to a particular target cell type.

The most conventional method to achieve a constant plasma level is the use of intravenous infusion. However, this would be inconvenient for most therapeutic situations so that other non-invasive route such as the oral or transdermal route is preferred.

For conventional drug delivery systems, rate-limiting step in drug availability is usually absorption of drugs across a biological membrane such as the gastrointestinal wall. However in a sustained /controlled release product one aims for
release of drug from the dosage form as the rate limiting step. Thus drug availability is controlled by the kinetics of drug release rather than absorption.

**Advantages of controlled release dosage forms**: Some of the advantages of controlled release (CR) dosage forms (DFs) include reduction in dosing frequency, reduced fluctuation in circulating drug levels, increased patient compliance, avoidance of night time dosing, more uniform effect, and reduction in gastrointestinal (GI) irritation and other dose-related side effects.

**Disadvantages of controlled release dosage forms**: Controlled release dosage forms (CR-DFs) have several potential disadvantages. They include cost, unpredictable and often poor in vitro – in vivo correlation, dose dumping, reduced potential for dosage adjustment, and increased potential for first pass clearance leading to poor systemic availability. In general effective drug release period is influenced and limited by GI residence time.

A major constraint in oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the gastrointestinal tract (GIT). Some drugs are absorbed only in a particular portion of GIT or are absorbed to a different extent in various segments of the GIT. An absorption window exists because of physiological, physicochemical or biochemical factors. The pH dependent solubility and stability level of a drug plays an important role in its absorption. Because most drugs are absorbed by passive diffusion of the unionized form, the extent of ionization at various pH levels can lead to non-uniform absorption or an absorption window. The presence of certain enzymes in a particular region of the GIT also can lead to regional variability in absorption of drugs that are substrates of those enzymes.

Drugs having site-specific absorption are difficult to design as oral CRDDS, because the drug released in the region preceding and in close vicinity to the absorption window is only available for absorption. After crossing the absorption window the released drug goes to waste with negligible or no absorption. This drastically decreases the time available for drug absorption after its release and jeopardizes the success of the delivery system.
The design of oral controlled drug delivery systems (DDS) is primarily aimed to achieve more predictable and increased bioavailability. However these systems have several physiological difficulties, such as inability to restrain and localize the DDS within desired regions of the GI tract and highly variable nature of gastric emptying process. Gastric emptying time in humans, which is normally 2-3 hours through the main absorption area (stomach or upper part of intestine), can result in incomplete drug release from DDS leading to diminished efficacy of administered dose. The intimate contact of the DDS with absorbing membrane has the potential to maximize drug absorption and may also influence rate of drug absorption. These considerations have led to the development of oral controlled gastroretentive dosage forms possessing gastric retention capabilities.

GASTRORETENTIVE DRUG DELIVERY SYSTEMS:

Dosage forms that can be retained in stomach are called gastroretentive drug delivery systems (GRDDS). GRDDS can improve controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site, thus ensuring its optimal bioavailability.

Drugs having narrow absorption window are mostly associated with improved absorption at jejunum and ileum due to their enhanced absorption properties e.g. large surface area, or because of enhanced solubility in stomach as opposed to the more distal parts of the GIT.

Drug absorption in case of (a) conventional dosage forms and (b) gastroretentive drug delivery systems.
Certain types of drugs that benefit from using gastric retentive devices includes:

- Drugs acting locally in stomach e.g. Antacids
- Drugs that are primarily absorbed in stomach e.g. Albuterol
- Drugs that are poorly soluble at an alkaline pH
- Drugs with a narrow window of absorption i.e. drugs that are absorbed mainly from the proximal small intestine e.g. Riboflavin, Levodopa
- Drugs absorbed rapidly from GI tract e.g. Amoxycillin
- Drugs that degrade in colon e.g. Metoprolol.

Longer residence time in stomach could be advantageous for local action in the upper part of small intestine, for example treatment of peptic ulcer disease.

**Ideal drug candidates for compounding into GRDFs:**

i) Drugs stable in gastric milieu.

ii) Drugs having narrow absorption window.

iii) Drugs to be used for gastro-duodenal local therapy.

**Drugs incorporated into GRDFs:**

The following are the list of drugs that have been incorporated into GRDF’s as microspheres, granules, capsules, tablets or pills.

- Acyclovir
- Atenolol
- Cinnarizine
- Cisapride
- Glipizide
- Levodopa
- Nicardipine
- Tetracycline
- Diltiazem HCl
- Alendronate
- Captopril
- Ciprofloxacin
- Furosemide
- Ketoprofen
- Misoprostol
- Riboflavin
- Verapamil
APPROACHES TO GASTRIC RETENTION:

A number of approaches have been used to increase gastric retention time (GRT) of a dosage form in stomach by employing a variety of concepts. These include:

a) Floating Systems:

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on gastric contents, drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in GRT and a better control of fluctuations in plasma drug concentrations. Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems.

b) Bio/Muco-adhesive Systems:

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending GRT of drug delivery system in stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. Binding of polymers to mucin/epithelial surface can be divided into three broad categories:

- Hydration-mediated adhesion.
- Bonding-mediated adhesion.
- Receptor-mediated adhesion.
c) Swelling and Expanding Systems:

These are dosage forms, which after swallowing, swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in stomach for a long period of time. These systems may be named as “plug type system”, since they exhibit tendency to remain logged at the pyloric sphincter.

d) High Density Systems:-

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

e) Incorporation of Passage Delaying Food Agents\(^9\):-

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C\(_{10}\)-C\(_{14}\).

f) Ion Exchange Resins\(^{10}\):

Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads are then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide is released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

g) Raft systems:

It incorporates alginate gels that have a carbonate component and upon reaction with gastric acid, bubbles form in the gel enabling floating.
TYPES OF FLOATING DRUG DELIVERY SYSTEMS (FDDS) \(^{11,12}\)

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:

A. Effervescent System and
B. Non-Effervescent System.

A. Effervescent Systems:

These buoyant delivery systems are prepared with swellable polymers such as Methocel or polysaccharides e.g., chitosan and effervescent components, e.g. sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature.

The matrices are fabricated so that upon contact with gastric fluid, carbon dioxide is liberated by the acidity of gastric contents and is entrapped in the gelyfiedhydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy.

The effervescent systems are classified into two types.

I. Gas generating systems
II. Volatile liquid/Vacuum containing Systems.

I. Gas generating Systems:

1. Intragastric single layer floating tablets or Hydrodynamically Balanced System (HBS)
2. Intragastric bilayer floating tablets
3. Multiple unit type floating pills

II. Volatile liquid / vacuum containing systems:

1. Intragastric floating Gastrointestinal Drug Delivery System
2. Inflatable Gastrointestinal Delivery Systems
3. Intragastric Osmotically Controlled Drug Delivery System:

B. Non-effervescent systems:

Commonly used excipients, here are gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as
polycarbonate, polyacrylate, polymethacrylate and polystyrene. One of the approaches to the formulation of such floating dosage forms involves intimate mixing of drug with a gel forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier.

The air entrapped by the swollen polymer confers buoyancy to these dosage forms. The gel structure acts as a reservoir for sustained drug release as the drug is slowly released by controlled diffusion through the gelatinous barrier.

Non-effervescent systems include the following:

1. Single layer floating tablets
2. Bilayer floating tablets
3. Alginate Beads
4. Hollow Microspheres

Advantages of FDDS: 13

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.
4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
5. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
6. Simple and conventional equipment for manufacture.
7. Ease of administration and better patient compliance.
8. Site specific drug delivery.

Limitations of FDDS: 14

GRDF have great potential in improving the bioavailability of drugs that exhibit an absorption window, but with certain limitations. One of the major disadvantages of floating systems is the requirement of high level of fluid in the
stomach for the delivery system to float and work efficiently. These systems also require the presence of food to delay their gastric emptying. In addition, there are limitations to the applicability of floating system for drugs that have solubility or stability problem in the highly acidic gastric environment or that are irritants to the gastric mucosa. Drugs such as nifedipine as well as isosorbide dinitrate, which are well absorbed along the entire GI tract and which undergoes significant first pass metabolism may not be desirable candidate for GRDF since the slow gastric emptying may lead to reduced systemic bioavailability.

**Marketed Products of GRDFs:**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Brand name</th>
<th>Drug (dose)</th>
<th>Company, country</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Madopar®</td>
<td>Levodopa (100 mg), Benserazide (25 mg)</td>
<td>Roche Products, USA</td>
<td>Floating CR capsule</td>
</tr>
<tr>
<td>2.</td>
<td>Valrelease®</td>
<td>Diazepam (15 mg)</td>
<td>Hoffmann-LaRoche, USA</td>
<td>Floating capsule</td>
</tr>
<tr>
<td>3.</td>
<td>Liquid Gaviscon®</td>
<td>Al hydroxide (95 mg), Mg carbonate (358 mg)</td>
<td>Glaxo Smith Kline, India</td>
<td>Effervescent floating liquid alginate preparation</td>
</tr>
<tr>
<td>4.</td>
<td>Topalkan®</td>
<td>Al-Mg antacid</td>
<td>Pierre Fabre Drug, France</td>
<td>Floating liquid alginate preparation</td>
</tr>
<tr>
<td>5.</td>
<td>Conviron</td>
<td>Ferrous sulphate</td>
<td>Ranbaxy, India</td>
<td>Colloidal gel forming FDDS</td>
</tr>
<tr>
<td>6.</td>
<td>Cifran OD®</td>
<td>Ciprofloxacin (1 gm)</td>
<td>Ranbaxy, India</td>
<td>Gas-generating floating tablet</td>
</tr>
<tr>
<td>7.</td>
<td>Cytotec®</td>
<td>Misoprostol (100 mcg/200 mcg)</td>
<td>Pharmacia, USA</td>
<td>Bilayer floating capsule</td>
</tr>
<tr>
<td>8.</td>
<td>Oflin OD®</td>
<td>Ofloxacin (400mg)</td>
<td>Ranbaxy, India</td>
<td>Gas generating floating tablet</td>
</tr>
</tbody>
</table>

**STOMACH: AN OVERVIEW**\(^{15,16,17}\)

The stomach is a j-shaped organ located in the upper left hand portion of the abdomen just below the diaphragm. It occupies a portion of the epigastric and left hydrochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small
surface area very little absorption takes place from the stomach. It provides barrier to the delivery of drugs to the small intestine.

Structure:-

The stomach has four main regions as shown in Fig

1. Cardia
2. Fundus
3. Body and
4. Pylorus

![Anatomy of stomach.](image)

The main function of the fundus and body is storage, whereas that of cardia is mixing or grinding. The fundus adjusts the increased volume during eating by relaxation of the fundus muscle fibers. The fundus also exerts a steady pressure on the gastric contents pressing them towards the distal region. To pass through the pyloric sphincture into the small intestine, particle size should be of order of 1-2 mm. The antrum does this grinding.

Histology of stomach:

The stomach wall is composed of the four basic layers. Simple columnar epithelial cells line the entire mucosal surface of the stomach. Epithelial cells extend down into the lamina propria, where they form columns of secretory cells called
gastric glands. The gastric glands contain three types of exocrine gland cells that secrete their products into the stomach lumen.

1. Mucous neck cells.
2. Chief cell.
3. Parietal cells.

The chief cells secrete pepsinogen and gastric lipase. Parietal cells produce hydrochloric acid and intrinsic factor. Both mucosal surface cells and mucous neck cells secrete mucus and bicarbonate. They protect the stomach from adverse effects of hydrochloric acid as mucosa has a lubricating effect, it allow chyme to move freely through the digestive system.

Functions of stomach:-

The stomach carried out three major functions. It stores food, digest food and delivers food to the small intestine at a rate that the small intestine can handle it. It mixes saliva, food and gastric juice to form chyme.

1. It acts as a reservoir for holding food before release into small intestine.
2. Secrete gastric juice, which contains hydrochloric acid, pepsin, intrinsic factor and gastric lipase.
3. Secrete gastrin into the blood.

Regulation of gastric secretion and motility:

Both neural and hormonal mechanism controls the secretion of gastric juice and the contraction of smooth muscle in the stomach wall. Events in gastric secretion occur in three overlapping phases; cephalic phase, gastric phase and intestinal phase.

1. Cephalic phase:

The cephalic phase refers to the influence of the brain on secretion. Even before food enters the stomach, the sight, taste or thought of food initiate this phase, the secretion is brought about through simulation of the nerve. This leads to presence of acid and pepsin in the stomach even before food enters the stomach.

2. Gastric phase:

The gastric phase of secretion is brought about by the presence of food in stomach. It is controlled by the hormone gastrin which is produced in the mucosa of
the pyloric region of the stomach. Gastrin is released in response to stretching of the antrum caused by the presence of food in this region or in response to specific substances in the food; particularly proteins, alcohol and coffee are also potent stimulants of gastrin release. Once released, the gastrin is transported through the blood to stomach, where it stimulates the secretion of hydrochloric acid and pepsinogen.

3. Intestinal phase:

The intestinal phase of acid secretion refers to the influence of the small intestine on gastric secretion. If the material present in the duodenum of the small intestine is too acidic, a hormone is release by the intestinal mucosa. This hormone is carried out by the blood to the body of the stomach where it inhibits further acid secretion. This serve as a protective device for the small intestine which is not as well protected against acid as the stomach. The total volume of gastric secretion in response to all the stimuli mentioned above is approximately 2-3 liters per day.

Gastric emptying:

The process of gastric emptying occurs both during fasting and fed states; however, the pattern of motility differ markedly in the two states. In the fasted state, it is characterized by an interdigestive cycle both through the stomach and small intestine every 2-3 hours. This activity is called the interdigestive myoelectric cycle or migrating myoelectric complex (MMC). It is compose of four phases: Phase 1 lasts 45-60 minute, is quiescent, with rare low amplitude contractions; Phase 2 with a length of 30-45 minute, has intermediate amplitude contractions and involves the bile secretions; Phase 3 is also termed ‘housekeeper waves’ and extends for 5-15 minutes. It is initiated in the stomach in most cases or in the duodenum, very high amplitude contractions, with a frequency of 4-5 per minute and maximal pyloric opening, characterizing this phase, which enables efficient evacuation of the stomach contents; Phase 4 has a length of less than 5 minutes and connects between the maximal amplitude contractions to the basal phase. In the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. In other words, feeding results in a lag time prior to the onset of gastric emptying.
SELECTION CRITERIA OF DRUG CANDIDATE FOR STUDY:

Floating dosage forms would remain in the stomach and upper part of the GI tract for a prolonged period of time, so the drug candidate which would get benefits should have any of the following characteristics:

- Narrow absorption window in GI tract
- Primarily absorbed form stomach
- Poorly soluble at higher pH
- Act locally in stomach
- Degrade in colon

Pithvala\textsuperscript{18} et al. reported that the bioavailability of Ranitidine hydrochloride was markedly lower from the human colon compared to the upper part of the GI tract.

Kusumdevi and Vijayalakshmi\textsuperscript{19} suggested that Ranitidine if taken along with iron-containing food, absorption of the drug may be increased as alkaline pH decreases absorption of Ranitidine.

It was also reported that relative bioavailability of Ranitidine solution from the cecum was about 15\% of that following gastric or jejunal administration.

Basit\textsuperscript{20} et al. reported that mean absolute bioavailability of Ranitidine from the immediate release, small intestinal release and colonic release formulations were 50.6, 46.0 and 5.50\% respectively.

Basit and Lacey\textsuperscript{21} reported that Ranitidine is metabolised by colonic microorganism and suggested that this is one of the reasons behind lower bioavailability of the drug.

Sood and Panchagnula\textsuperscript{22} suggested that if the drug exhibits reduced or no absorption in the colon then a gastroretentive or mucoadhesive dosage form would be required to ensure drug delivery for complete duration of $T_{del}$ (time of drug delivery) within drug absorbable intestinal regions.