1 INTRODUCTION

1.1 Oral Drug Delivery System:

The most widely utilized and preferred route of administration amongst all the routes that have been explored till date, is the oral route for the systemic delivery of drugs. Despite tremendous advancements in drug delivery the oral route remains the preferred route because of: a) Low cost of therapy, b) Ease of administration and hence high level of patient compliance, c) And the belief that by oral administration the drug is well absorbed as the foodstuffs that are ingested daily, d) Flexibility in formulation.

All the pharmaceutical products for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained & controlled release) and the design of dosage forms (either solid, dispersion or liquid) must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

1.2 Importance of G.I. Absorption for Oral Drugs:

Oral drug administration remains the route of choice for the majority of clinical applications and conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery. Some drugs have ideal characteristics for good absorption to occur throughout the gastrointestinal tract whereas others present difficulties. The biopharmaceutical classification system introduced by Food and Drug Administration (FDA) in 1995 has categorized drugs into 4 classes in terms of their solubility and intestinal permeability.
1. Introduction

Class I compounds

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility</td>
<td>High</td>
</tr>
<tr>
<td>Intestinal permeability</td>
<td>High</td>
</tr>
<tr>
<td>Oral absorption</td>
<td>Well absorbed when given orally</td>
</tr>
</tbody>
</table>

Class II-IV compounds

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility</td>
<td>Low</td>
</tr>
<tr>
<td>Intestinal permeability</td>
<td>Low</td>
</tr>
<tr>
<td>Oral absorption</td>
<td>Present challenges to the development of products with acceptable oral bioavailability. New chemical entities display variable absorption in different regions of GI tract</td>
</tr>
</tbody>
</table>

The oral bioavailability can be affected by limited absorption site. The development of modified release product like once daily dosing becomes difficult and hence concept of absorption window has become popular.\(^4\&5\)

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

The need for gastro retentive dosage forms (GRDDF\(^5\)) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems\(^4\&6\)
Another group of drugs that could benefit from retained and controlled release in the stomach are those meant for the treatment of pathologies located in the stomach, the duodenum or the small intestine.

1.3 Gastro Esophageal Reflux Disease & Peptic Ulcer Disease (GERD & PUD):

Digestive disorders affect a very large segment of the world population. Major gastric disorders are gastro esophageal reflux disease (GERD) and peptic ulcer disease (PUD).

GERD is a chronic symptom of mucosal damage caused by stomach acid coming up from the stomach into the esophagus. A typical symptom is heartburn. GERD is usually caused by changes in the barrier between the stomach and the esophagus, including abnormal relaxation of the lower esophageal sphincter, which normally holds the top of the stomach closed, impaired expulsion of gastric reflux from the esophagus or a hiatal hernia. These changes may be permanent or temporary (transient).

Another kind of acid reflux which causes respiratory and laryngeal signs and symptoms is called laryngo-pharyngeal reflux (LPR) or extra esophageal reflux (EERD). Unlike GERD, LPR is unlikely to produce heartburn, and is sometimes called silent reflux.

1.4 Symptoms of GERD:

Most common symptoms of GERD are:

- Heartburn
- Regurgitation
- Trouble swallowing (Dysphagia)

Less common symptoms are:

- Pain with swallowing (Odynophagia)
- Increased salivation (also known as water brash)
- Nausea
- Chest pain

GERD sometimes causes injury of the esophagus like Reflux esophagitis; esophageal strictures; Barret’s esophagus; esophageal adenocarcinoma. Other atypical symptoms associated with GERD are:
1. Introduction

- Chronic cough
- Laryngitis (Hoarseness, throat clearing)
- Asthma
- Erosion of dental enamel
- Dentine hypersensitivity
- Sinusitis and damaged teeth
- Pharyngitis

1.4.1 Diagnosis:

Detailed historical knowledge is vital for our accurate diagnosis. Useful investigations may include ambulatory esophageal pH monitoring, barium swallow X-rays, esophageal manometry and esophagogastroduodenoscopy (EGD).

The current gold standard for diagnosis of GERD is esophageal pH monitoring, a most objective test to diagnose the reflux disease allowing to monitor GERD patients in response to medical or surgical treatment. One practice for diagnosis of GERD is a short term treatment with proton pump inhibitors.

In general, an EGD is done when the patient either does not respond well to treatment or has alarm symptoms including dysphagia, anemia, blood in the stool, wheezing, weight loss or voice changes.

Biopsies can be performed during gastroscopy.

1.4.2 Pathophysiology of GERD:

GERD is caused by a failure of the cardia. The “Angle of His”, the angle at which the esophagus enters the stomach creates a valve that prevents duodenal bile, enzymes and stomach acid from traveling back into the esophagus where they can cause burning and inflammation of sensitive esophageal tissue.

Factors that contribute to GERD are:

- Hiatal Hernia
- Obesity
- Zollinger Ellison syndrome
- Hypercalcemia
- Scleroderma & systemic sclerosis
• Use of medicines like prednisolone
• Visceroposis

GERD is also linked to laryngitis, chronic cough, pulmonary fibrosis, ear ache, asthma.

Factors linked not conclusively with GERD are:
Obstructive sleep apnea, Gallstones.

In 1999 a review found that on average, 40% of GERD patients had *Helicobacter pylori* infection.

1.4.3 Prevention of GERD:
GERD is largely preventable through changes in life style like

- Diet
- Sleep on left side or with your upper body raised
- Eat smaller meals
- Lose weight
- Avoid acidic rich foods

1.4.4 Treatment of GERD:
Three types of treatments exist for GERD. They include Life style modifications, Medications & surgery.

1.4.5 Medications:
A number of drugs are approved to treat GERD.

- **PROTON PUMP INHIBITORS** (Omeprazole, Esomeprazole, Pantoprazole, Lansoprazole and Rabeprazole). They reduce gastric acid secretion. They stop acid secretion at the source of acid production i.e. proton pump.
- **GASTRIC H₂ RECEPTOR BLOCKERS** (as Ranitidine, Famotidine and Cimetidine) which are antihistamines and can reduce gastric acid secretion.
- **ANTACIDS** before meals or symptomatically after symptoms begin, can reduce gastric acid.
- **ALGINIC ACID** may coat the mucosa and increase pH and decrease reflux.
- **PROKINETICS** strengthen the lower esophageal sphincter and speed up the gastric emptying. eg. Cisapride, a member of this class was withdrawn from
market for causing long QT syndrome. Another Reglan (Metoclopramide) is a prokinetic with a better side effect profile.

- SUCRALFATE (Carafate) is useful as an adjunct in helping to heal and prevent esophageal damage caused by GERD and must be taken several times daily and at least 24Hrs. apart from meals and medications.
- MOSAPRIDE CITRATE is a 5-HT4 receptor agonist used in the therapy for GERD and dyspepsia.
- BACLOFEN is an agonist of GABA\(_B\) receptor which decreases transient lower esophageal sphincter relaxations which reduces episodes of reflux.

**1.4.6 Surgery:**
The standard surgical treatment is the NISSENFUNDOPLICATION where lower esophageal sphincter is strengthened to prevent acid reflux and repair hiatal hernia and is done laparoscopically.

An obsolete treatment is VAGOTOMY, surgical removal of vagus nerve branches that innervate stomach lining and has been largely replaced by medication. Another is transoral incisionless fundoplication using Esophyx device which helps to rebuild the valve between stomach and esophagus.

**1.4.7 Epidemiology:**
Every year GERD affects approx. 4.5 per 1000 persons in U.K. and 5.4 per 1000 persons in U.S. It is possible that these figures may be larger than estimated and there is no data that support sex predominance with regard to GERD. In Western populations, the prevalence range for GERD is 10% to 20% of the population. eg. An estimated 3.4 million to 6.8 million Canadians are GERD sufferers. The prevalence rate of GERD in developed nations is also linked with age, with adults aged 60 to 70 being the most commonly affected.

The combination of longer life expectancy and aging populations in the developed world is expected to lead to an increase in GERD prevalence in the years to come.
1.4.8 Peptic Ulcer Disease:
A peptic ulcer, also known as PUD, most common ulcer of gastrointestinal tract that is usually acidic and painful, defined as mucosal erosions equal to or greater than 0.5cms. 70% to 90% of such ulcers are associated with *Helicobacter pylori* which lives in stomach. Ulcers are also caused by Aspirin, Plavix, Ibuprofen, and other NSAID\(^5\). Peptic ulcers arise in duodenum and in stomach, esophagus and Meckel’s diverticulum.

1.4.9 Signs and Symptoms of Peptic Ulcer Disease:
- Abdominal pain - 3 / 4 hours after meal intake.
- Bloating and abdominal fullness
- Water brash (rush of saliva after regurgitation to dilute acid in esophagus and more associated with gastroesophageal reflux disease.)
- Nausea and copious vomiting
- Loss of appetite and weight loss
- Hematemesis (Blood vomiting)
- Melena (tarry, foul smelling feces due to oxidized iron from haemoglobin)
- Rarely an ulcer can lead to gastric or duodenal perforation which leads to acute peritonitis.

History of heartburn, gastroesophageal reflux disease and use of certain forms of medication can raise the suspicion for peptic ulcer (drugs like NSAID\(^5\), cyclooxygenase and most glucocorticoids like dexamethasone and prednisolone)

The timing of the symptom in relation to the meal may differentiate between gastric and duodenal ulcer. Symptoms of peptic ulcers may vary with the location of ulcer and patient’s age.

Burning or gnawing feeling in stomach can last from 30mins.to 3 hours and misinterpreted as hunger, indigestion or heartburn. Pain caused by ulcer may be aggravated by stomach acid when it comes in contact with ulcerated area. Pain caused in peptic ulcer can be felt anywhere from navel to sternum and pain may be worse when stomach is empty. Pain may flare at night. Peptic ulcer symptoms may be different for every sufferer.
1.4.10 Complications of Peptic Ulcer Disease:

- Gastrointestinal bleeding.
- Perforations in the gastrointestinal wall
- Penetration is when ulcer continues into adjacent organs such as liver and pancreas
- Scarring and swelling due to ulcers causes narrowing in the duodenum and gastric outlet obstruction. Patient often presents with severe vomiting.
- Cancer is included in the differential diagnosis, Helicobacter pylori as the etiological factor making it 3 to 6 times more likely to develop stomach cancer from the ulcer.

1.4.11 Causes of Peptic Ulcer Disease:

1. A major causative factor is chronic inflammation due to *Helicobacter pylori*. The immune system is unable to clear the infection despite the appearance of antibodies. Due to active gastritis (type B gastritis) a defect in the regulation of gastrin production is formed. Gastrin stimulates the production of gastric acid by parietal cells *H. Pylori* increases gastrin which increases gastric acid which contributes to the erosion of mucosa and therefore ulcer formation.

2. Another major cause is the use of NSAID§. The gastric mucosa protects itself from gastric acid with a layer of mucus, the secretion of which is stimulated by certain prostaglandins. NSAID§ block the function of cyclooxygenase1 essential for production of these prostaglandins. Though the *H. Pylori* caused ulcers decline due to increased medical treatment, greater proportion of ulcers will be due to increasing NSAID use with pain syndrome and the growth of aging populations that develop arthritis.

3. The incidence of duodenal ulcers has dropped and incidence of gastric ulcer has shown small increase in last 30 years by use of NSAID§ and improved standards of living which has lowered *H. Pylori* infections.

4. Studies have found correlations between smoking and ulcer formation when associated with *H. Pylori*.

5. Risk factors as diet, spice consumption and blood type are of relatively minor importance in development of peptic ulcer.
6. Alcohol consumption increases risk when associated with \textit{H. Pylori}.
7. Gastrinomas a rare gastrin secreting tumors also cause multiple and difficult to heal ulcers.
8. Researchers continue to look at stress as a possible cause in the development of ulcers. Burns and head trauma can lead to physiologic stress ulcers.
9. An expert panel concluded that ulcers are not purely an infectious disease and that psychological factors do play a significant role. Stress has been demonstrated to cause production of excess stomach acid in which \textit{H. Pylori} thrives. Also a combination of chronic stress and irregular meal times is a significant risk factor in development of peptic ulcer.

\textbf{1.4.12 Diagnosis of Peptic Ulcer:}

The diagnosis is based on characteristic symptoms.

1. Stomach pain is usually the first signal of peptic ulcer.
2. Confirmation is made with tests such as endoscopies or barium contrast X-rays. The tests are done if symptoms do not resolve after a few weeks of treatment or when they appear in a person over age 45 or who has symptoms like weight loss as stomach cancer can cause similar symptoms.
3. An esophagogastroduodenoscopy (EGD, gastroscopy) is carried out on patients in whom peptic ulcer is suspected. Direct visual identification, location and severity of ulcer can be described and if no ulcer is present, EGD can provide alternative diagnosis.
4. Blood tests are not reliable for accurate peptic ulcer diagnosis due to their inability to differentiate between past exposure to the bacteria and current infection.
5. The diagnosis of \textit{Helicobacter Pylori} can be made by:
   - Urea breath test(noninvasive and does not require EGD)
   - Direct culture from an EGD biopsy specimen which is difficult to do.
   - Direct detection of urease activity in a biopsy specimen by rapid urease test.
   - Measurement of antibody levels in blood(does not require EGD)
   - Stool antigen test.
1. Introduction

- Histological examination and staining of an EGD biopsy.

The breath test uses radioactive carbon atom to detect \textit{H. Pylori}. The patient is asked to drink a tasteless liquid which contains the carbon as a part of the substance that bacteria breaks down. After an hour the patient is asked to blow into a bag that is sealed. If patient is infected with \textit{H. Pylori} the breath sample will contain radioactive carbondioxide. This test helps to monitor the response to treatment used to kill the bacteria.

If peptic ulcer perforates air will leak from inside of GIT to peritoneal cavity leading to free gas in peritoneal cavity.

Gastric ulcers are most often localized on the lesser curvature of the stomach.

1.4.13 Treatment of Peptic Ulcer Disease:

1. Younger patients are often treated with antacids or H$_2$ antagonists before EGD is undertaken. Bismuth compounds may actually reduce or even clear organisms.

2. Patients who are taking nonsteroidal anti-inflammatory drugs (NSAIDs) may also be prescribed prostaglandin analogue to help prevent peptic ulcers, a side effect of NSAID$^S$

3. When \textit{H. Pylori} infection is present, most effective treatments are combinations of 2 antibiotics (e.g. Clarithromycin, Amoxicillin, Tetracycline, Metronidazole) and 1 proton pump inhibitor (PPI), sometimes together with a bismuth compound. In absence of \textit{H. Pylori}, long term higher dose PPI$^S$ are often used.

4. Treatment of \textit{H. Pylori} usually leads to clearing of infection, relief of symptoms and eventual healing of ulcers. Wide spread use of PPI$^S$ have made the surgical procedures obsolete.

5. Perforated peptic ulcer is a surgical emergency and requires surgical repair. Most bleeding ulcers require endoscopy urgently to stop bleeding with cautery, injection or clipping.

6. Ranitidine provides relief of peptic ulcers, heartburn, indigestion and excess stomach acid and prevention of these symptoms associated with excessive consumption of food and drink.

7. Sucralfate has also been a successful treatment of peptic ulcers.
1.4.14 Epidemiology:
The lifetime risk for developing a peptic ulcer is approximately 10%. In western
countries the prevalence of *Helicobacter Pylori* infections roughly matches age (20% at
age 20, 30% at age 30 etc.). Prevalence is higher in third world countries. Transmission is
by food, contaminated ground water, and through human saliva.

1.5 Gastrotetentive Drug Delivery System:
Dosage forms that can be retained in the stomach are called Gastro retentive Drug
Delivery Systems (GRDDS). GRDDS can improve the controlled delivery of drugs by
continuously releasing the drug for a prolonged period of time before it reaches its
absorption site (by improving the bioavailability) of medications that are characterized by
a narrow absorption window. 7,11 Refer Fig 1

![Diagram of drug absorption](image)

**Figure 1: Drug absorption in case of (a) conventional dosage forms and (b) gastro
retentive drug delivery system**

Gastric retention will provide advantages such as the delivery of drugs with narrow
absorption windows in the small intestinal region. Also 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. Further improved bioavailability is expected for drugs
that are absorbed readily upon release in the GI tract. These drugs can be delivered
ideally by slow release from the stomach. Gastro retentive drug delivery systems have
been shown to have better efficacy in controlling the release rate for drugs with site
specific absorption. The gastro retentive drug delivery systems can be retained in the
stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. A controlled drug delivery system with prolonged residence time in the stomach is of particular interest for drugs that are locally active in the stomach, have an absorption window in the stomach or in the upper small intestine and are unstable in the intestinal or colonic environment or exhibit low solubility at high pH values. Thus a GRDD system can be said to be a type of CRDD system which provides drug release at a predetermined, predictable and controlled rate in stomach and duodenum.

The average time required for a dosage unit to traverse GIT is 3-4hrs and amongst various dosage forms as given in Table 1.

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Transit time in hours (hrs.)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stomach</td>
<td>Small intestine</td>
</tr>
<tr>
<td>Tablets</td>
<td>2.7 ± 1.5</td>
<td>3.1 ± 0.4</td>
</tr>
<tr>
<td>Pellets</td>
<td>1.2 ± 1.3</td>
<td>3.4 ± 1.0</td>
</tr>
<tr>
<td>Capsules</td>
<td>0.8 ± 1.2</td>
<td>3.2 ± 0.8</td>
</tr>
<tr>
<td>Solution</td>
<td>0.3 ± 0.7</td>
<td>4.1 ± 0.5</td>
</tr>
</tbody>
</table>

The absorption window exists because of physiological, physicochemical or biochemical factors. Drugs having site specific absorption are difficult to design as oral CRDDS because only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption. After crossing the absorption window the released drug goes to waste with negligible or no absorption (see Fig. 1a). This phenomenon drastically decreases the time available for drug absorption after its release and jeopardizes the success of the delivery system.
1.6 Gastric Physiology:

The GI tract is essentially a tube about 9 meters long that runs through the middle of the body from the mouth to the anus and includes throat (pharynx), esophagus, stomach, small intestine, (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of caecum, appendix, colon and rectum).

The wall of GI tract has the same general structure throughout most of its length from the esophagus to the anus with some logical variations for each region. The stomach is an organ with a capacity for storage and mixing. The antrum region is responsible for the mixing and grinding of gastric contents. Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50ml and contains a small amount of gastric fluid (pH 1-3) and air. The mucus spreads and covers the mucosal surface of the stomach as well as the rest of the GI tract. The GI tract is in a state of continuous motility consisting of two modes; inter digestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract. The inter digestive motility pattern is commonly called the “Migrating Motor Complex” (MMC) and is organized in cycles of activity and quiescence. Each cycle lasts 90-120 mins. and consists of four phases. The concentration of the hormone motilin in the blood controls the duration of the phases. In the inter digestive or fasted state, an MMC wave migrates from the stomach down the GI tract every 90-120 minutes. A full cycle consists of four phases beginning in the lower esophageal sphincter or gastric pacemaker, propagating over the whole stomach, the duodenum and jejunum and finishing at the ileum. Phase III is termed the “House Keeper Wave” as the powerful contractions in this phase tends to empty the stomach of its fasting contents and indigestible debris. The administration and subsequent ingestion of food rapidly interrupts the MMC cycle and the digestive phase is allowed to take place. The upper part of the stomach stores the ingested food initially, where it is compressed gradually by the phasic contractions. The digestive or fed state is observed in response to meal ingestion. It resembles the fasting phase II and is not cyclical, but continuous, provided that the food remains in the stomach. Large objects are retained by the stomach during the fed pattern but are allowed to pass during phase III of the inter digestive MMC. Patterns of contractions in the stomach occur such that solid food is reduced to
particles of less than 1mm. diameter that are emptied through the pylorus as a suspension. The duration of the contractions is dependent on the physico chemical characteristics of the ingested meal. Generally, a meal of ~450Kcal will interrupt the fasted state motility for about three to four hours.

1.7 Gastrointestinal Motility Patterns Affecting Dosage Form Retention:

The complex anatomy and physiology of the GIT including variations in acidity, bile salts, enzyme content and the mucosal absorptive surface, significantly influences the release, dissolution and absorption of orally administered dosage forms. Table II lists the anatomical and physiological features of the GIT.\textsuperscript{11&12}

\begin{table}
\begin{tabular}{|l|c|c|c|c|c|c|}
\hline
Section & Average Length cms & Diameter cms & Villi present & Absorption Mechanism & pH & Major Constituents & Transition of Food (HRS) \\
\hline
Oral cavity & 15-20 & 10 & Absent & Passive diffusion, convective transport & 5.2-6.8 & Amylase, Maltase, Ptyalin, mucin & Short \\
\hline
Esophagus & 25 & 2.5 & Absent & --- & 5-6 & & Very Short \\
\hline
Stomach & 20 & 15 & Absent & Passive diffusion, convective transport & 1.2-3.5 & Hydrochloric acid, pepsin, rennin, lipase, intrinsic factor & 0.25-3.0 \\
\hline
Duodenum & 25 & 5 & Scarcely Present & Passive diffusion, convective transport, active transport, facilitated transport, ion pair, pinocytosis & 4.6-6.0 & Bile, trypsin, chymotrypsin, amylase, maltase, lipase, nuclelease, CYP3A4 & 1-2 \\
\hline
Jejunum & 300 & 5 & Abundantly present & Passive diffusion, convective transport, active transport, facilitated transport & 6.3-7.3 & Lactase, amylase, maltase, sucrase, CYP3A5 & --- \\
\hline
Ileum & 300 & 2.5-5 & Abundantly present & Passive diffusion, convective transport, active transport, ion pair, facilitated transport, pinocytosis & 7.6 & Lipase, neuclease, nucleotidase, enterokinase & 1-10 \\
\hline
Cecum & 10-30 & 7 & Scarcely Present & Passive diffusion, convective transport, active transport, pinocytosis & 7.5-8.0 & --- & short \\
\hline
colon & 150 & 5 & Absent & Passive diffusion, convective transport, pinocytosis & 7.9-8.0 & --- & 4-20 \\
\hline
Rectum & 15-19 & 2.5 & Absent & Passive diffusion, convective transport, pinocytosis & 7.5-8.0 & --- & variable \\
\hline
\end{tabular}
\caption{Anatomical and physiological features of human GIT}
\end{table}
Two distinct patterns of gastrointestinal motility and secretion exists, corresponding to the fasted and fed states\[^{13}\]. As a result, the bioavailability of orally administered drugs will vary depending on the state of feeding. The fasted state is associated with various cyclic events, commonly referred to as the “Migrating Motor Complex”, (MMC), which regulates GI motility patterns. The migrating motor complex is organized into alternating cycles of activity and quiescence and can be subdivided into basal (Phase I), preburst (Phase II), and burst (Phase III), intervals. See Fig. 2.

![Figure 2: Motility patterns of GIT in fasted state](image)

Phase I, the quiescent period, lasts from 30 to 60 minutes and is characterized by a lack of secretory, electrical and contractile activity. Phase II exhibits intermittent action for 20-40 minutes, during which contractile motions increase in frequency and size. Bile enters the duodenum during this phase whereas gastric mucus discharge occurs during the latter part of Phase II and throughout Phase III. Phase III is characterized by intense, large and regular contractions termed *Housekeeper Waves* that sweep off undigested food and lasts 10-20 mins. Phase IV is the transition period of 0-5mins between Phase III and I.

This series of electrical events originates in the foregut and continues to the terminal ileum in the fasted state, repeating every 2-3 hrs\[^{14}\]. Feeding sets off a continuous pattern of spike potentials and contractions called *post prandial motility*. The particular phase during which a dosage form is administered influences the performance of per oral CRDDS and GRDDS\[^{15}\].

When CRDDS are administered in the fasted state, the MMC may be in any of its Phases, which can significantly influence the total gastric residence time (GRT) and transit time in the GIT. This assumes even more significance for drugs that have an absorption window because it will affect the amount of time the dosage form spends in the region.
preceding and around the window. The less time spent in that region, the lower the degree of absorption. Therefore, the design of GRDDS should take into consideration the resistance of the dosage form to gastric emptying during Phase III of the MMC in the fasted state and also continuous gastric emptying through the pyloric sphincter in the fed state. This means GRDDS must be functional quickly after administration and able to resist the onslaught of physiological events for the required period of time.

1.8 Need of Gastric Retention:

Gastro retentive dosage forms extend significantly the period of time over which the drugs may be released. Thus, they not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage forms. This application is especially effective in delivery of sparingly soluble and insoluble drugs. It is known that as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To address this, oral administration of sparingly soluble drugs is carried out frequently, after several times per day. As a mechanism to override this problem, erodible, gastro retentive dosage forms have been developed that provide continuous, controlled administration of these drugs at the absorption site. In addition, these dosage forms are useful for delivering drugs incorporated into vesicles such as liposomes, nanoparticles, proteoid microspheres and pharmacosomes etc. Compared with other applications the frequency of dosing may be the same, but gastro retentive dosage forms will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability. GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentrations at the gastric mucosa (eradicating Helicobacter Pylori from the sub mucosal tissue of the stomach), making it possible to treat stomach and duodenal ulcers, gastritis and esophagitis, reduces the risk of gastric carcinoma and administer non systemic, controlled release antacid formulations. GRDFs can be used as carriers for drugs with so called absorption windows.
1.9 Choice of Drug Candidates for GRDD:

Many drugs categorized as once a day delivery have been demonstrated to have suboptimal absorption due to dependence or the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine. Drugs causing gastric irritation (aspirin) and drugs that are absorbed equally well throughout the GI tract (Isosorbide dinitrate) will not benefit from incorporation into gastric retention system. Certain types of drugs which can benefit by using gastric retentive devices include:

- Drugs acting locally in stomach.
- Drugs that are primarily absorbed in the stomach.
- Drugs which are poorly soluble at alkaline pH and stable in gastric medium.
- Drugs with narrow window of absorption.
- Drugs absorbed rapidly from the GI tract.
- Drugs that degrade in the colon.
- Drugs which have short half life.
- Drugs which require good pharmacokinetic control due to narrow therapeutic index.
- Drugs which require extended local delivery to the GI tract.

After several decades of attempt to develop gastro retentive solutions, effective systems are finally emerging. Once these technologies mature and are accepted by the market, better solutions are envisioned for drugs whose efficacy is hampered by limited absorption, thus contributing to better controlling dosing, less side effects and better patient compliance. Drug classes that would benefit from gastric retention include CNS drugs, antiviral products, certain antibiotics, anti hypertension drugs, anti diabetic drugs and drugs for local treatment of GI infections. Once the technology is fully accepted, these solutions will probably increase with new pipeline drugs that need enhancement to their bioavailability.
1.10 Advantages of Gastric Retention:

1. Sustained drug delivery, achieving zero order kinetics (oral infusion)
2. Site specific drug delivery (for treatment of pathologies located in stomach, duodenum or small intestine)
3. They not only prolong dosing intervals i.e. frequency of dose administration is reduced, but also increases patient compliance beyond the level of existing controlled release dosage forms.
4. Enhancing the bioavailability of drugs.\(^{16}\)
5. Drugs having low solubility at higher pH values can be given.
6. Drugs that are unstable in the intestinal environment can be given by gastric retention.

1.11 Factors Affecting Gastric Retention:

There are several factors that can affect gastric emptying (and hence gastric retention time) of an oral dosage form. These factors include

1. Density of dosage form.
2. Size of dosage form--(dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT compared with those with a diameter of 9.9mm)
3. Shape of dosage form--Tetrahedron and ring shaped devices with flexural modulus (of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT compared with other shapes)
4. Single or multiple unit formulation--multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage form.
5. Fed or unfed state--in fasting conditions GI motility is characterized by MMC and hence GRT is very short but in fed state MMC is delayed and GRT is considerably longer.
6. Nature of meal--Feeding of indigestible polymers or fatty acid salts can change the motility pattern of stomach to a fed state thus decreasing GRT and prolonging drug release.

7. Caloric content--GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.

8. Frequency of feed--With successive meals GRT can be increased than with a single meal.

9. Gender--Mean ambulatory GRT in males (3.4 ± 0.6 hrs.) is less compared with their age and race matched female counterparts (4.6 ± 1.2 hrs.) regardless of weight, height and body surface.

10. Age--Elderly people, especially those above 70 have a significantly longer GRT.

11. Posture--GRT can vary between supine and upright ambulatory states of patient.

12. Concomitant drug administration--Intake of drugs such as anti cholinergic agents opiates and pro kinetic agents affect GRT.

13. Biological factors--such as diabetes and Crohns disease and diseases states affect GRT.

1.12 Requirements for Gastric Retention:

1. The dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and constant contractions and grinding and churning mechanisms.

2. To function as a gastric retention device, it must resist premature gastric emptying.

3. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.

4. The preparation should have no effect on gastric motility including gastric emptying pattern and no other local adverse effects.

5. The preparation should be convenient to take and have ability to load substantial amounts of drugs with different physicochemical properties and release them in controlled manner, preferably in stomach.

6. Preparation should have prolonged shelf life and inexpensive industrial manufacture.
1.13 Types of Gastroretentive Drug Delivery Systems:

1.13.1 High Density systems:

High density system sinks to the bottom of the stomach and gets entrapped in the folds of the antrum and withstands the peristaltic waves of the stomach wall. Gastric contents have a density close to water (1.004 g/cm$^3$). A density close to 2.5 g/cm$^3$ seems necessary for significant prolongation of gastric residence time and barium sulphate, zinc oxide, iron powder, titanium dioxide are used as excipients. Although encouraging results were reported in ruminants, effectiveness in human subject’s beings was not observed and no system has been marketed. Fig. 3

Figure 3: High density systems

1.13.2 Floating systems:

These have a bulk density lower than the gastric content. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug.

1.13.3 Hydro dynamically balanced systems: HBS

These are single unit dosage forms, containing one or more gel-forming hydrophilic polymers. Hydroxypropylmethylcellulose (HPMC) is the most common used excipient, although hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC),
sodium carboxymethylcellulose (Na CMC), agar, carrageenans or alginic acid are also used. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid, and hydration and swelling of the surface polymers produces a floating mass. Drug release is controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy. Effective drug delivery depends on the balance of drug loading and the effect of polymer on its release profile.

Besides minimal gastric contents needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force is also required to keep the dosage form reliably buoyant on the surface of the meal. Floating drug delivery system can be divided into gas generating and noneffervescent systems. Fig. 4

**Figure 4: Hydro dynamically Balanced System**

1.13.4 Gas generating systems:

The system is based on the gas generation mechanism which imparts floatability. Carbon dioxide (CO₂) can be generated in situ by incorporation of carbonates or bicarbonates, which react with acid, either the natural gastric acid or co-formulated as citric or tartaric acid. The approach has been used for single and multiple unit
systems. In single unit systems, such as capsules or tablets, effervescent substances are incorporated in the hydrophilic polymer, and CO$_2$ bubbles are trapped in the swollen matrix. Drug and excipients can be formulated independently and the gas generating unit can be incorporated into any of the layers. Further refinements involve coating the matrix with a polymer which is permeable to water, but not to CO$_2$.

![Figure 5: Gas Generating System](image)

**1.13.5 Raft forming systems.**

In this system, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO$_2$ bubbles on contact with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastro esophageal reflux treatment.
1.3.6 Low-density systems:

Low density systems having density less than 1g/cm\(^3\) are made up of low-density materials, entrapping oil or air. Classical example of this type of floating system is “microballoons”. They have low density core which allows flotation. Generally, techniques used to prepare hollow microspheres involves simple solvent evaporation or solvent diffusion or evaporation methods. Polycarbonate, Eudragit, cellulose acetate, calcium alginate, agar and low methoxylated pectin are commonly used as polymers. Buoyancy and drug release are dependent on quantity of polymer, the plasticizer-polymer ratio and the solvent used.\(^{20}\) Fig. 7

![Figure 6: Raft Forming System](image)

1.3.7 Expandable systems:

Expandable gastro retentive dosage forms have been designed for the past three decades. They were originally created for possible veterinary use, but later the design
was modified for enhanced drug therapy in humans. These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their gastric retention time (GRT). After drug release, their dimensions are minimized with subsequent evacuation from the stomach. Gastro retention is enhanced by the combination of substantial dimensions with high rigidity of the dosage form to withstand the peristalsis and mechanical contractility of the stomach. The expandable GRDFs are usually based on three configurations: a small (“collapsed”) configuration which enables convenient oral intake; expanded form that is achieved in the stomach and thus prevents passage through the pyloric sphincter; and finally another small form that is achieved in the stomach when retention is no longer required i.e. after the GRDF has released its active ingredient, enabling evacuation.²¹

1.13.8 Super porous Hydro gels:

Super porous hydro gels are the type of swellable systems, which swells to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores. Moreover, they swell to a large size (swelling ratio 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is achieved by co-formulation of a hydrophilic particulate material, Ac-Di-Sol (croscarmellose sodium). This swollen mass then gets blocked before the pyloric end due to larger size and thus tends to retain in the stomach. After several hours, fragmentation occurred and the composite was rapidly cleared.²² Fig.8
1.13.9 Muco adhesive or Bio adhesive Systems:

The basis of muco adhesion is that a dosage form can stick to the mucosal surface by different mechanisms. Different theories are invoked to explain these mechanisms. Firstly, the electronic theory proposes attractive electrostatic forces between the glycoprotein mucin network and the bio adhesive material. Secondly, the adsorption theory suggests that bio adhesion is due to secondary forces such as Van der Walls forces and hydrogen bonding. The wetting theory is based on the ability of bio adhesive polymers to spread and develop intimate contact with the mucus layers, and finally, the diffusion theory proposes physical entanglement of mucin strands and the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate. Materials commonly used for bio adhesion are poly(acrylic acid), chitosan, cholestyramine, tragacanth, sodium alginate, HPMC, sephadex, sucralfate, polyethylene glycol, dextran, poly(alkyl cyanoacrylate) and polylactic acid. Even though some of these polymers are effective at producing bio adhesion, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract.23

1.13.10 Magnetic systems:

Magnetic systems are based on a simple idea in which the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. In vivo human studies showed that, in the presence of an extracorporeal magnet, the plasma concentrations of acyclovir were significantly higher after 7, 8, 10
and 12hrs. Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.\(^{24}\)

1.14 Evaluation of Gastrotententive Drug Delivery System:

To ensure performance characteristics and to control batch to batch quality a drug product must be evaluated. In addition to routine tests for general appearance, hardness, friability, drug content, weight variation, uniformity of content, disintegration time, and drug release, the gastro retentive performance of GRDDS must be evaluated.

1.14.1 Floating Systems:

The floating systems are evaluated for the floating time. The test for buoyancy is usually determined in 900 ml of simulated gastric or intestinal fluids maintained at 37\(^{0}\)C using the USP dissolution apparatus. The amount of time the dosage form floats is termed the floating time. In the case of floating micro particles, the number of floating particles and the time during which they remain buoyant on the test solution can be determined. The floating process depends on the balance between the weight and volume of the dosage form. An increase in the buoyancy force caused by the increased volume causes a resultant weight increase and leads to dosage form flotation.\(^{7}\)

1.14.2 Bio/Muco Adhesion Systems:

Bio adhesive systems are evaluated for the bio adhesion strength. The bioadhesive strength of a polymer can be determined by measuring the force required to separate the polymer specimen sandwiched between the layers of either an artificial (e.g. cellophane) or biological (e.g., rabbit stomach tissue) membrane. This force can be measured by using a modified precision balance or an automated texture analyzer.

1.14.3 Swelling Systems:

Swelling systems are studied for the water uptake and subsequent swelling. The swelling behavior of a dosage unit can be measured by studying its weight gain or
WU. The study is done by immersing the dosage form in simulated gastric fluid at 37°C and determining these factors at regular intervals. The dimensional changes can be measured in terms of the increase in tablet diameter and/or thickness over time. WU is measured in terms of percent weight gain, as given by the equation,

\[ WU = \frac{(W_t - W_o) \times 100}{W_o} \]

in which \( W_t \) and \( W_o \) are the weights of the dosage form at time \( t \) and initially, respectively. Furthermore, the GRDDS should be evaluated for gastro retention and drug release behavior.\(^9\)

1.14.4 \textit{In vivo} Gastro Retention Study:

\textit{In vivo} visualization is a crucial parameter for evaluating the GI-retention characteristics of the dosage form. The inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a \( \gamma \)-emitting radionuclide in a formulation allows indirect external observation using a \( \gamma \)-camera or scintiscan. The use of X-rays involves exposing a patient to an X-ray beam, thus permitting the visualization of the GI transit of the dosage form. In the case of gamma scintigraphy, the gamma-rays emitted by the radionuclide are seen through a camera to monitor the location of the dosage form in GIT.

1.14.5 Dissolution Study:

Dissolution tests are performed using the USP dissolution apparatus. Samples are withdrawn periodically, with replacement, and analyzed for drug content after appropriate dilution. The major requirement for the dissolution test is to allow a dosage form to sink to the bottom of the vessel before the rotation of the paddle. In the case of floating systems, this can be accomplished by attaching a small, loose piece of non-reacting material, such as a few turns of wire helix, around the dosage form that would otherwise float. However, this method can inhibit the three-dimensional swelling process of the dosage form and consequently affect the drug release from the formulation. An alternative is to fully submerge the dosage form under a ring or mesh assembly. However, in case of swellable systems, drug release is highly dependent on full surface exposure, unhindered swelling, and drug solubility in water. Another modification is to position the paddle blades at the surface of the
dissolution medium. This process allows the continuous depletion of the stagnant layer around the floating dosage form and maintains constant hydrodynamic conditions.

1.15 **Helicobacter Pylori:**

*Helicobacter pylori (H. pylori)* are a spiral shaped bacterium that is found in the gastric mucous layer or adherent to the epithelial lining of the stomach. *H. pylori* cause more than 90% of duodenal ulcers and up to 80% of gastric ulcers. Before 1982, when this bacterium was discovered, spicy food, acid, stress, and lifestyle were considered the major causes of ulcers. The majority of patients were given long term medications, such as H2 blockers, and more recently, proton pump inhibitors, without a chance for permanent cure. These medications relieve ulcer related symptoms, heal gastric mucosal inflammation, and may heal the ulcer, but they do NOT treat the infection. When acid suppression is removed, the majority of ulcers, particularly those caused by *H. pylori*, recur. Since we now know that most ulcers are caused by *H. pylori*, appropriate antibiotic regimens can successfully eradicate the infection in most patients, with complete resolution of mucosal inflammation and a minimal chance for recurrence of ulcers. Approximately two thirds of the world’s population is infected with *H. pylori*. In the United States, *H. pylori* is more prevalent among older adults, African Americans, Hispanics, and lower socioeconomic groups. Most persons who are infected with *H. pylori* never suffer any symptoms related to the infection; however, *H. pylori* cause chronic active, chronic persistent and atrophic gastritis in adults and children. Infection with *H. pylori* also causes duodenal and gastric ulcers. Infected persons have a 2 to 6 fold increased risk of developing gastric cancer and mucosal associated-lymphoid-type (MALT) lymphoma compared with their uninfected counterparts.

1.15.1 **Pathophysiology:**

It is believed that *H. pylori* weaken the protective mucous coating of the stomach and duodenum by causing chronic inflammation, so that the stomach acid can cause damage. *H. pylori* are a type of bacterium, which is found in the stomach of people
with and without peptic ulcers. Although *H. pylori* is present in the stomach of 20% (1 in 5 people) of people in the USA under the age of 40 years and half of those aged over 60 years, not all these people develop peptic ulcers.\(^{25}\)

### 1.15.2 Causes:

It is not known how *H. pylori* are transmitted or why some patients become symptomatic while others do not. The bacteria are most likely spread from person to person through fecal-oral or oral-oral routes. Possible environmental reservoirs include contaminated water sources. Iatrogenic spread through contaminated endoscopes has been documented but can be prevented by proper cleaning of equipment.

### 1.15.3 Long Term Consequences of *H. pylori* Infection:

Recent studies have shown an association between long-term infection with *H. pylori* and the development of gastric cancer. Gastric cancer is the second most common cancer worldwide; it is most common in countries such as Colombia and China, where *H. pylori* infects over half the population in early childhood. In the United States, where *H. pylori* are less common in young people, gastric cancer rates have decreased since the 1930s.
1.16 References:


