REVIEW ON: GASTRORETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT

Conventional oral dosage forms pose low bioavailability problems due to their rapid gastric transition from stomach, especially in case of drugs which are less soluble at alkaline pH of intestine. Similarly, drugs which produce their local action in stomach get rapidly emptied and do not get enough residence time in stomach. So, frequency of dose administration in such cases is increased. To avoid this problem, various efforts have been made to prolong the retention time of drug delivery system. In this review, we will discuss about the various approaches to produce gastro retention of drug delivery system.
1. INTRODUCTION:
The oral delivery route is the most common of all drug administration routes and accounts for about half of all drug administration. This is partly due to the fact that the gastrointestinal tract offers a wide range of flexibility in dosage form design than other routes. Also, it is a convenient route of administration for easy access to the systemic circulation. However, drug absorption via this route can be unsatisfactory and variable even following promising in vitro release profiles. This makes it difficult to predict the in vivo performance of a drug delivery system (DDS), even though the in vitro data are reproducible. There are several physiological factors that could work against achieving successful delivery of drugs via the oral route and such factors include unpredictable gastric emptying times, shorter gastrointestinal transit time of the dosage form, partial drug release from the dosage form and the absorption site of the particular drug. The average residence time of formulations in the stomach depends on the type of dosage form. Tablets, pellets, capsules and solutions have an average residence time of 2.7 ± 1.5 hours, 1.2 ± 1.3 hours, 0.8 ± 1.2 hours and 0.3 ± 0.07 hours respectively in the fed state. The effective duration of release from non-retentive controlled release delivery systems such as oral matrix or osmotic systems can not extend beyond normal gastrointestinal (GI) transit time, and so is unpredictable and limited to around 12 hours maximum [1].

1.1. Gastroretentive Drug Delivery System:
Gastroretentive system ensures that whole drug delivery system remains within the gastric region for longer duration of time. This improves gastric retention time for such drug in comparison to conventional dosage form and further minimum effective concentration of drug remains maintained in systemic circulation for longer duration. This also improves the solubility of drugs which are less soluble at alkaline pH of intestine and wastage of drug during the absorption process is reduced remarkably.

Gastro retentive drug delivery systems prolong the dosing intervals and thus improve patient compliance. Presence of drug in solution form is the most essential requisite for a drug to get absorbed. But, if the solubility of drug is poor then the time required for drug to get dissolve within stomach would be high and transit time becomes most stringent factor, which would in turn affect the absorption of drug. So, dose of administration for such drugs should be kept at more frequent intervals in a single day. Gastro retentive drug delivery systems provide a support to reduce the frequent dosing of such drug by producing a controlled delivery within stomach for longer duration. Though, other formulations or novel dosage forms like nanoparticle, microspheres, liposome etc. can also be used for controlled release effect, but gastro retentive system are considered much better alternative for improved absorption through stomach [2].

1.2. Anatomy and Physiology of The Stomach [3]
The stomach, the most distensible part of the GI tract is located in the upper left abdominal quadrant, immediately below the diaphragm. Typically J-shaped when empty, the stomach is continuous with the esophagus superiorly and empties into the duodenal portion of the small intestine inferiorly. In the stomach, which serves as a “holding organ” for ingested food, the food is mechanically churned with gastric secretions to form a pasty material called chyme. Once formed, chyme is moved from the stomach to the small intestine.
The stomach is divided into four regions: the cardia, fundus, body, and pylorus (Figure 1.1). The **cardia** is the narrow upper region immediately below the lower esophageal sphincter. The **fundus** is the dome-shaped portion to the left of and in direct contact with the diaphragm. The **body** is the large central portion, and the **pylorus** is the funnel-shaped terminal portion. The **pyloric sphincter** is the modified circular muscle at the end of the pylorus, where it joins the small intestine. *Pylorus* is a Greek word meaning “gatekeeper,” and this junction is just that, regulating the movement of chyme into the small intestine and prohibiting backflow. The GI tract is essentially a tube about nine metres long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), oesophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum). The wall of the GI tract has the same general structure throughout most of its length from the oesophagus to the anus, with some local 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 (pH1–3) 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: interdigestive 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 [3].

**Table 1.1 Salient features of upper gastrointestinal tract**

<table>
<thead>
<tr>
<th>Section</th>
<th>Length (m)</th>
<th>Transit time (h)</th>
<th>pH</th>
<th>Microbial count</th>
<th>Absorbing surface area (m²)</th>
<th>Absorption pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>0.2</td>
<td>Variable</td>
<td>1-4</td>
<td>&lt;10³</td>
<td>0.1</td>
<td>P,C,A</td>
</tr>
<tr>
<td>Small intestine</td>
<td>6-10</td>
<td>3±1</td>
<td>5-7.5</td>
<td>10³-10¹⁰</td>
<td>120-200</td>
<td>P,C,A,F,I,E,CM</td>
</tr>
</tbody>
</table>
1.3 BASIC GASTROINTESTINAL TRACT PHYSIOLOGY [4]

Stomach has mainly 4 main regions: The cardia, fundus, body and pylorus. The cardia surrounds the superior opening of the stomach.

Pylorus has 2 main parts:- pyloric antrum which connects body of the stomach and the pyloric canal leads to duodenum.

Body is the large central portion of the stomach which is inferior to the fundus.

Body acts as reservoir for undigested material, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. The fasted state is associated with some cyclic contractile events commonly known as migrating myoelectric complex (MMC) which cycle both through stomach and intestine every 2 to 3 hours. Apparently there are four consecutive phases of activity in the MMC.
Phase-I (basal phase): It is a quiescent period lasting from 30 to 60min with no contractions.

Phase-II (preburst phase): It consists of intermittent contractions that gradually increase in intensity as the phase progresses, and lasts about 20-40min. Gastric discharge of fluid and very small particles begins later in this phase.

Phase-III (burst phase): This is a short period of intense distal and proximal gastric contractions (4-5 contractions per minute) lasting about 10-20minutes. These contractions also known as “house keeper waves” sweep gastric contents down the small intestine.

Phase-IV: This is a short transitory period of about 0-5minutes, and the contractions dissipate between the last part of phase-III and phase-I.

The different phases originating in the foregut continue to the terminal ileum, another begins in the stomach and duodenum.

Liquid components easily pass through the partially constricted sphincter. On the contrary, the large undigested materials are retained by an “antral-seieving” process and are retropulsed into the body of stomach and remain in the fed state [5].

1.4 DRUGS REQUIRE GASTRIC RETENTION [6]

- Drugs acting locally in the stomach E.g. Antacids and drugs for H. Pylori viz., Misoprostol
- Drugs that are primarily absorbed in the stomach E.g. Amoxicillin
- Drugs that is poorly soluble at alkaline pH E.g. Furosemide, Diazepam, Verapamil, etc.
- Drugs with a narrow window of absorption E.g. Cyclosporin, Methotrexate, Levodopa, etc.
- Drugs which are absorbed rapidly from the GI tract. E.g. Metonidazole, tetracycline.
- Drugs that degrade in the colon. E.g. Ranitidine, Metformin HCl.

1.5 Advantages Of Floating Drug Delivery [6]

1. Enhanced bioavailability: The bioavailability of some drugs (e.g. riboflavin and levodopa) CR-GRDF is significantly enhanced in comparison to administration of non-GRDF CR polymeric formulations.

2. Enhanced first-pass biotransformation: When the drug is presented to the metabolic enzymes (cytochrome P-450, in particular CYP-3A4) in a sustained manner, the presystemic metabolism of the tested compound may be considerably increased rather than by a bolus input.

3. Sustained drug delivery/reduced frequency of dosing: The drugs having short biological half life, a sustained and slow input from FDDS may result in a flip-flop pharmacokinetics and it reduces the dose frequency. This feature is associated with improved patient compliance and thus improves the therapy.

4. Targeted therapy for local ailments in the upper GIT: The prolonged and sustained administration of the drug from FDDS to the stomach may be useful for local therapy in the stomach.

5. Reduced fluctuations of drug concentration: The fluctuations in plasma drug concentration are minimized, and concentration-dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.
6. **Improved receptor activation selectivity**: FDDS reduces the drug concentration fluctuation that makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

7. **Reduced counter-activity of the body**: Slow release of the drug into the body minimizes the counter activity leading to higher drug efficiency.

8. **Extended time over critical (effective) concentration**: The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

9. **Minimized adverse activity at the colon**: Retention of the drug in GRDF at stomach minimizes the amount of drugs that reaches the colon and hence prevents the degradation of drug that degraded in the colon.

10. **Site specific drug delivery**: A floating dosage form is a widely accepted approach especially for drugs which have limited absorption sites in upper small intestine.

1.6 **Factors Affecting Gastric Retention [6]**

**Density**: GRT is a function of dosage form buoyancy that is dependent on the density. A buoyant dosage form having a density less than that of the gastric fluids floats, since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. A density of less than 1.004g/mL i.e. less than that of gastric contents has been reported.

**Size**: 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.

**Shape of dosage form**: Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.

**Single or multiple unit formulation**: Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

**Fed or unfed state**: Under fasting conditions, GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach. However, in the fed state, MMC is delayed and GRT is considerably longer.

**Nature of meal**: Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

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

**Frequency of feed**: The GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.

**Gender**: Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
Age: Low gastric emptying time is observed in elderly than do in younger subjects. Intra subject and inter subject variations also are observed in gastric and intestinal transit time. Elderly people, especially those over 70 years have a significantly longer GRT.

Posture: GRT can vary between supine and upright ambulatory states of the patient. An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size. In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of floating forms appear to remain buoyant anywhere between the lesser and greater curvature of the stomach. On moving distally, these units may be swept away by the peristaltic movements that propel the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects.

Concomitant intake of drugs: Drugs such as Metoclopramide, Cisapride, Codeine, Atropine and Propantheline may affect the performance of FDDS. The co-administration of GI motility decreasing drugs can increase gastric emptying time.

1.7 Approaches Of Gastroretentive Drug Delivery System:

1. Low density approach:
   A. Effervescent system:
      a. Gas generating system: Single layer floating tablet, Bilayer floating tablet, Multiparticulate system.

2. High density approach.
3. Mucoadhesive approach
4. Expansion by swelling approach and 5. Raft forming system.

**1. Floating Systems:** It is a low density approach which has a bulk density lower than gastric fluids and hence remains buoyant in the stomach, releasing the drug slowly without affecting the gastric emptying rate for a prolonged period of time. After the drug is released from the stomach, the delivery system is expelled based on the buoyancy mechanism [6]. These systems are designed to prolong the stay of the dosage forms in the gastric intestinal tract and aid in enhancing the absorption. Drugs having a better solubility in acidic environment and also having specific site of absorption in the upper part of small intestine is achieved by these HBS systems. To retain in stomach for a prolonged period of time the dosage form must have bulk density of less than ‘1’ and has to maintain its structural integrity and release drug constantly from the dosage form. Among all the advantages single-unit formulations are associated with some limitations/problems such as sticking together or being obstructed in the GIT which may lead to potential danger of producing irritation [7]. Floating dosage forms may provide gastric retention by floating on gastric contents and thereby avoiding the pylorus. It would appear that such concepts as hydro-dynamically balanced systems (HBS), For floating systems to operate, there needs to be gastric contents to float on. Because liquids empty rapidly, this means that the subject must take the dosage form on a fed stomach and may need to take multiple meals. However, most dosage forms larger than a few millimeters in diameter are retained while the stomach is in the fed state (Figure 1) such that one must demonstrate that providing a buoyant dosage form provides an additional benefit. In addition, because whether the person is upright or lying down could affect the dosage form performance, studies need to adjust for this parameter. Such restrictions as specific feeding schedules and maintaining an upright stance hinder patient compliance and would limit the usefulness of the technology [8].

The object floats better if RW is on the higher positive side (see Figure 1b). This apparatus helps in optimising FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

\[ RW = \text{total vertical force, } D_f = \text{fluid density, } D_s = \text{object density, } V = \text{volume and } g = \text{acceleration due to gravity} \]

The FDDS can be divided into effervescent and non-effervescent systems.

**EFFERVESCENT SYSTEM**

**Gas-generating systems**

Floatability can also be achieved by generation of gas bubbles. 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 optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. An alternative is to incorporate a matrix with entrapped of liquid, which forms a gas at body temperature. 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 CO2 bubbles are trapped in the swollen matrix(a). In vitro, the lag time before the unit floats is <1 min and the buoyancy is prolonged for 8 to 10 h. In vivo experiments in fasted dogs showed a mean gastric residence time increased up to 4 h.
Bilayer or multilayer systems have also been designed. Drug and excipients can be formulated independently and the gas generating unit can be incorporated into any of the layers (b). Further refinements involve coating the matrix with a polymer which is permeable to water, but not to CO₂ (c). The main difficulty of such formulation is to find a good compromise between elasticity, plasticity and permeability of the polymer. As mentioned previously, multiple unit systems avoid the “all or nothing” emptying process. However, it is essential that the units remain dispersed and suspended individually in the gastric fluid and not agglomerate into a mass floating at the top of the stomach [10].

**Figure 3: Gas-generating systems. Schematic monolayer drug delivery system (a).**

**Bilayer gas-generating systems, with (c) or without (b) semipermeable membrane.**

**Volatile liquid containing systems:**

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of PVA, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

**Non-Effervescent Systems**

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass [11].
a. Colloidalgel barrier systems
Hydrodynamically balance system (HBSTM) was first design by Sheth and Tossounian in 1975. Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids e.g. HEC, HPMC, NaCMC, Polysaccharides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to these dosage forms.

![Figure 4 Hydrodynamically balanced system](image)
b. Microporous Compartment System: This technology is based on the encapsulation of drug reservoir inside a Microporous compartment with aperture along its top and bottom wall. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolve drug for continuous transport across the intestine for absorption.

c. Alginate beads
Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at -40°C for 24 hours, leading to the formation of porous system, which can maintain a floating fource over 12 hours.

d. Hollow microspheres
Hollow microspheres (micro-ballons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol : dichloromethane solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The micro-ballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hours in vitro [12].

2. HIGH DENSITY SYSTEMS :
Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm-3) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets27. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5-2.4g/cm-3.
3. BIOADHESIVE DRUG DELIVERY SYSTEM

Bioadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as the potential means of extending the GRT of DDS in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. The concept is based on self-protecting mechanism of GIT. Mucus secreted continuously by the specialized goblet cells located throughout the GIT plays a cytoprotective role. The mucoadhesive systems are intended to extend the GRT by adhering them to the gastric mucous membrane. Bioadhesion on soft tissues of certain natural or synthetic polymers has been exploited to control as well as to prolong the gastric retention of the delivery systems. The adhesion of the polymers with the mucous membrane may be mediated by hydration, bonding, or receptor mediated. In hydration mediated adhesion, the hydrophilic polymers become sticky and mucoadhesive upon hydration. Bonding mediated adhesion may involve mechanical or chemical bonding. Chemical bonds may involve covalent or ionic bonds or Van der Waals forces between the polymer molecules and the mucous membrane. Receptor mediated adhesion takes place between certain polymers and specific receptors expressed on gastric cells. The polymers could be anionic or cationic or neutral [13].

4. EXPANDING DRUG DELIVERY SYSTEM [14]

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, thereby enabling evacuation.

The expansion can be achieved by swelling or by unfolding in the stomach. Swelling usually occurs because of osmosis. Unfolding takes place due to mechanical shape memory i.e. the GRDF is fabricated in a large size and is folded into a pharmaceutical carrier e.g. a gelatin capsule, for convenient intake. In the stomach, the carrier is dissolved and the GRDF unfolds or opens out, to achieve extended configuration. The unfolding occurs when polymeric matrices, known or designed to have suitable mechanical properties, are used with some emphasis on appropriate storage conditions of the GRDF. The storage should maintain unfoldable properties for extended time spans. As apparent from this review much artwork regarding expandable GRDFs, and this is true also for GRDFs based on other approaches has only been described in patents.

The expansion can be achieved by i) Swelling system ii) Unfolding system

i) Swelling systems

Swelling system are generally matrix system containing hydrocolloids which by action of hydration and osmosis get swelled. Swelling index means how much fold it can increase in volume and swelling time are the important factor for such systems.

In every swellable hydrogel, **there are mainly 3 layers**: 1st swelling, 2nd diffusion and 3rd erosion layer. So along with swelling, erosion process also started.
To develop dosage form having good strength to maintain integrity, it should have more cross linking of polymer chain. But higher cross linking is associated with poor swelling property and slower dissolution/diffusion of drug from hydrogel. So, there should be optimum amount of cross linking is require to maintain balance between swelling and dissolution of hydrogel.

a) Polymeric envelope
This system comprise of drug reservoir (A) in center surrounded by swellable material (B) are placed in elastic polymeric envelope type system (C). The polymeric envelope is permeable to drug and fluids. This system gets swollen in gastric fluid and integrity is retained by elastic polymeric envelope and drug is released in controlled manner.

b) Tiny pills in the matrix
Urquhart and Theeuwes developed a dosage form with a very high swelling ratio, exhibiting a 2-50 fold volume increase. In this system tiny pills containing drug are incorporated into hydrogel matrix and coated with wax to give strength to wall. Mechanism is not only by plug in pylorus sphincter, but it also keeps the stomach in fed state and thus delays house keeper waves which comes in fasted state. i) The dosage from side-view. ii) The cross-sectional view which comprises of A) Waxy wall, B) Hydrogel Matrix, C) Tiny pills. After administration, system achieves high volume and tiny pills are released slowly out from matrix and gives GR to drug.

ii) Unfolding systems
Unfolding systems are systems which are actually of larger size but they are folded to decrease size and kept in capsules. In stomach these systems comes out of capsules and unfolds to larger size. The important factor for unfolding system is shape memory. They should have sufficient shape memory such that they retain their unfolded (expanded) shape in stomach against gastric motility and not get folded again and escape out till the desired time interval.

a) Obstructing means: The 1st unfolding system developed for veterinary purpose and termed as “obstructing means” as they create obstruction in passage of food by plugging sphincter. It is capsule (A) containing 2 reservoirs (C) attached together with hydrophilic/hydrophobic strips (B). The flexible strips get enlarge and get sufficient strength and becomes rigid to achieve gastro retention.
b) Multi-layer polymeric sheets: This system has one erodible polymeric film containing drug (A) is adhere on another non-erodible carrier polymeric film (B). This bilayer sheet is folded and gelatin bands/strips (C) are used to maintain folded and system is placed in capsule. So in stomach capsule and gelatin band dissolves to give unfolded system.

![Prior to folding](image)

![Folded, administration form](image)

Figure 8: Multi-layer polymeric sheets

c) Geometrical configurations: Various geometric configurations tried are stick, ring, tetrahedron, planar disc, planar multilobe and string. These devices had various properties like, sufficient resistance to forces applied by the stomach, thus preventing rapid passage through the pylorus; allowance of free passage of food while in residence in the stomach; and desired in vivo circumference larger than 5 cm, to ensure gastro-retentivity.

![Unfolding modified dosage form](image)

Figure 9: Unfolding modified dosage form.

Although various configurations tried, only tetrahedron shape gives good positive results and however other failed with some negative results in vivo. Then after other configurations tried, made by configurations with at least three coplanar limbs extending from a center, e.g. cylindrical-shape, cross- shape or Y-shape. They contains central shape memory material (A) assuring unfolding for prolonged time and outer erodible part containing drug reservoir (B).

c) Receptacle means: This unfolding system is spiral or coil configuration. It is designed as a ‘receptacle means’ (A) that holds a drug reservoir formed as a tablet (B) or capsule, and one or more retention arms (C) attached to it. The retention arms, in the form of fibers or ribbons, are characterized by unfolding or uncoiling in the stomach to reach a circumference of more than 3 cm and gives gastro retention.
5. Raft Forming Systems

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO2 to make the system less dense and float on the gastric fluids[7] Jørgen et al. described an antacid raft forming floating system. The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus. A patent assigned to Reckitt and Colman Products Ltd., describes a raft forming formulation for the treatment of helicobacter pylori (H. Pylori) infections in the GIT. The composition contained drug, alginic acid, sodium bicarbonate, calcium carbonate, mannitol and a sweetener. These ingredients were granulated, and citric acid was added to the granules. The formulation produces effervescence and aerates the raft formed, making it float [15].

Evaluation Of Floating System

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

2. Floating Time: Test for buoyancy is usually performed in SGF-Simulated Gastric Fluid maintained at 37°C. The time for which the dosage form continuously floats on the dissolution medium is termed as floating time.

3. Resultant Weight: Now we know that bulk density and floating time are the main parameters for describing buoyancy. But only single determination of density is not sufficient to describe the buoyancy because density changes with change in resultant weight as a function of time. For example a matrix tablet with bicarbonate and matrixing polymer floats initially by gas generation and entrapment but after some time, some drug is released and simultaneously some outer part of matrixing polymer may erode out leading to change in resultant weight of dosage form.
Where, $F =$ resultant weight of object, $D_f = $ Density of Fluid, $D_S = $ Density of Solid object, $g = $ Gravitational force, $M = $ Mass of dosage form, $V = $ Volume of dosage form
So when $D_s$, density of dosage form is lower, $F$ force is positive gives buoyancy and when it is $D_s$ is higher, $F$ will negative shows sinking. Plot of $F$ vs. Time is drawn and floating time is time when $F$ approaches to zero from positive values.

4. IN-VITRO DISSOLUTION TESTS

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

![Figure 11: Dissolution methods](image)

Floating unit can be made fully submerged, by attaching some small, loose, non-reacting material, such as few turns of wire helix, around dosage form. However this method can inhibit three dimensional swelling of some dosage form and also affects drug release. Other modification is to make floating unit fully submerged under ring or mesh assembly and paddle is just over ring that gives better force for movement of unit. Other method suggests placing dosage form between 2 ring/meshes.
In previous methods unit have very small area, which can inhibit 3D swelling of swellable units, another method suggest the change in dissolution vessel that is indented at some above place from bottom and mesh is place on indented protrusions, this gives more area for dosage form. Inspite of the various modifications done to get the reproducible results, none of them showed co-relation with the in-vivo conditions. So a novel dissolution test apparatus with modification of Rossett-Rice test Apparatus was proposed.

![Rossett-Rice apparatus](image)

**Figure 12: Rossett-rice apparatus**

Rossett-Rice test is used for predicting in-vitro evaluation of directly acting antacid (action by chemical neutralization of acid), where HCl is added gradually to mimic the secretion rate of acid from the stomach. In this modified apparatus as shown in figure, it has side arm from bottom of beaker such that it maintains volume of 70ml in beaker and fresh SGF is added from burette at 2 ml/min rate. Thus sink condition is maintained along with easy sampling. Stirring is done by magnetic stirrer at 70-75 RPM. Thus this apparatus mimics in-vivo condition for GRDDS.

**REFERENCES**