ABSTRACT

This review explains the recent advances in gastro-retentive drug delivery systems with special focus on floating drug delivery systems. Oral controlled release (CR) dosage forms (DF) have been extensively used to improve therapy of many important medications. However, in the case of narrow absorption window drugs, this pharmaceutical approach cannot be utilized, as it requires sufficient colonic absorption of the drug (which contradicts the definition of narrow absorption window agents). On the other hand, incorporation of the drug into a CR delivery system, which releases its payload in the stomach over a prolonged time period, can lead to significant therapeutic advantages owing to various pharmacokinetic (PK) and pharmacodynamic aspects. Gastro-retentive dosage forms (GRDFs) are a drug delivery formulation that are designed to be retained in the stomach for a prolonged time and release there their active materials and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract. This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and/or their therapeutic outcome. This article reviews some of the latest developments in GRDF technology from a pharmaceutical point of view.

Keywords: Floating drug delivery systems, Gastric Empting Time, Short Residence Time, Controlled release.
INTRODUCTION
Historically, oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. From a pharmacokinetic point of view, the ideal sustained and controlled release dosage form should be comparable with an intravenous infusion, which supplies continuously the amount of drug needed to maintain constant plasma levels once the steady state is reached. [1]

Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the gastrointestinal (GI) tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, raft systems, expanding systems, swelling systems, bio-adhesive systems and low-density systems. 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 the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease. Furthermore, 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. [2]

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of muco-adhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents, that delay gastric emptying. [3-4]

Physiology of the Stomach
The Gastro-intestinal 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 ceacum, appendix, colon and rectum). The wall of the gastrointestinal 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 (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 organised in cycles of activity and quiescence\textsuperscript{5} which is further divided into following 4 phases as described by Wilson and Washington\textsuperscript{6}–

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

![Diagram of human stomach](image)

**Figure 1: Diagram of human stomach**

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension
form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate. \[7\]

**Requirements for Gastric Retention**
Physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.

**Need for Gastro-Retentive Dosage Forms**
The need for gastro-retentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems. These efforts resulted in gastro-retentive dosage forms that were designed, in large part, based on the following approaches:-

- Low density form of the dosage form that causes buoyancy in gastric fluid.
- High density dosage form that is retained in the bottom of the stomach.
- Bio-adhesion to stomach mucosa. \[8\]
- Slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients. \[9\]
- Expansion by swelling or unfolding to a large size which limits emptying of the dosage form through the pyloric sphincter. \[10\]

The current review deals with the Gastro-retentive approaches that have recently become leading methodologies in the field of controlled and site specific drug delivery system.

**Advantages of Gastro-retentive Drug Delivery Systems**

- **Enhanced bioavailability**
  The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption. \[11\]
• **Enhanced first pass biotransformation**
  In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P₄₅₀, in particular CYP3A4) in a sustained manner, rather than by a bolus input.

• **Sustained drug delivery/reduced frequency of dosing**
  For drugs with relatively short biological half life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

• **Targeted therapy for local ailments in the upper g.i.t**
  The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while systemic concentrations, following drug absorption and distribution, are minimal.

• **Reduced fluctuations of drug concentrations**
  Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects 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. [12]

• **Improved selectivity in receptor activation**
  Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different type of receptors at different concentrations.

• **Reduced counter-activity of the body**
  In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

• **Extended time over critical (effective) concentration**
  For certain drugs that have non-concentration dependent pharmacodynamics, such as beta-lactam antibiotics, the clinical response is not associated with peak concentration,
but rather with the duration of time over a critical therapeutic concentration. The sustained mode of administration enhances the pharmacological effects and improves the clinical outcomes.

- **Minimized adverse activity at colon**
  Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism’s resistance.

- **Site specific drug delivery**
  A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.

**Limitations**

- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- Not suitable for drugs that have solubility or stability problem in GIT.
- Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
- Drugs which are irritant to gastric mucosa are also not suitable.
- The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
- The dosage form should be administered with a full glass of water (200-250 ml).
- These systems are not advantageous over the conventional dosage forms for those drugs, which are absorbed throughout the gastrointestinal tract.

**Factors affecting gastric retention of dosage forms**

The gastric retention time (GRT) of dosage forms is controlled by several factors such as density and size of the dosage form, food intake, nature of the food, posture, age, sex, sleep
and disease state of the individual (e.g., gastrointestinal diseases and diabetes) and administration of drugs such as prokinetic agents (cisapride and metoclopramide).

a. **pH of the stomach:** To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach doesn’t get time to produce sufficient acid when the liquid empties the stomach; hence generally basic drugs have a better chance of dissolving in fed state than in a fasting state.\[16\]

b. **Gastric Emptying:** The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals. Nutritive density of meals helps determine gastric emptying time. However, increase in acidity and caloric value slows down gastric emptying time. In the case of elderly persons, gastric emptying is slowed down. Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down. The resting volume of the stomach is 25 to 50 ml. Studies have revealed that gastric emptying of a dosage form in the fed state can also be influenced by its size. Small-size tablets leave the stomach during the digestive phase while the large-size tablets are emptied during the housekeeping waves. Studies have shown that the gastric residence time (GRT) can be significantly increased under the fed conditions since the MMC is delayed. As the units of multiparticulate systems are distributed freely throughout the gastrointestinal tract, their transport is affected to a lesser extent by the transit time of food compared with single unit formulation.\[17\]

c. **Density:** Dosage forms having a density lower than that of gastric fluid experience floating behaviour and hence gastric retention. A density of <1.0 gm/cm$^3$ is required to exhibit floating property.

d. **Size and shape of dosage unit:** The size of the dosage form is another factor that influences gastric retention. In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeeping waves. In most cases, the larger the size of the dosage form, the greater will be the gastric retention time because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine.\[18\]
e. **Food Fed and Unfed State:** Food intake, the nature of the food, caloric content, and frequency of feeding has a profound effect on the gastric retention of dosage forms. The presence or absence of food in the stomach influences the GRT of the dosage form. Usually, the presence of food increases the GRT of the dosage form and increases drug absorption by allowing it to stay at the absorption site for a longer time.

f. **Gender:** Mean ambulatory GRT in meals (3.4±0.4 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.

g. **Age:** Elderly people, especially those over 70 years have a significantly longer GRT.

h. **Miscellaneous:** Biological factors such as age, body mass index (BMI), gender, posture, and diseased states (diabetes, Chron’s disease) influence gastric emptying the effect of buoyancy, posture, and nature of meals on the gastric emptying process in vivo using gamma scintigraphy also affects the gastric emptying rate.\[^{19}\]

### Techniques Of Gastric Retention

Various techniques were used to encourage gastric retention of an oral dosage form. Floating systems have low bulk density, so that they can float on the gastric juice in the stomach.\[^{2–4}\] The problem arises when the stomach is completely emptied of gastric fluid. In such a situation, there is nothing to float on. Different techniques used for gastric retention mentioned below:

- Floating drug delivery.
- Bioadhesive.
- High density.
- Swelling and expanding system.

### Floating Drug Delivery

The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as ‘hydro-dynamically balanced systems’ (‘HBS’) since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3- 4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their
bulk density is lower than that of the gastric contents. Many results have demonstrated validity of the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drugs and improved clinical situations. These results also demonstrate that the presence of gastric content is needed to allow the proper achievement of the buoyancy retention principle. [20-21]

Classification of Floating Drug Delivery Systems
A. Single Unit Floating Dosage Systems
1. Non-effervescent Systems (balanced systems)
2. Effervescent Systems (Gas-generating Systems)

B. Multiple Unit Floating Dosage Systems
1. Non-effervescent Systems (balanced systems)
2. Effervescent Systems (Gas-generating Systems)
3. Hollow Microspheres

C. Raft Forming Systems

A. Single Unit Floating Dosage
Non-effervescent Systems (balanced systems)
These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. Hydroxy propyl methyl cellulose (HPMC) is the most commonly used excipient, although hydroxy ethyl cellulose (HEC), hydroxyl propyl cellulose (HPC), sodium carboxymethyl agar, carrageen or alginic acid is 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 floating mass. [22-23] 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. [24] Incorporation of fatty excipients gives low density formulations and reduced penetration of water, reducing the erosion. Effective drug delivery depends on the balance of drug loading and the effect of polymer on its release profile. [25]

Gas-generating systems
Floatability can also be achieved by generation of gas bubbles. 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.\textsuperscript{[26-28]} The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. Gastric floating drug delivery system (GFDDS) offers numerous advantages over other gastric retention systems.\textsuperscript{[29-30]} These systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.\textsuperscript{[31]} While the system is floating on the gastric contents, the drug is released slowly at desired rate from the stomach.\textsuperscript{[32-33]}

B. Multi–Unit Dosage Forms

The purpose for designing multiple-unit dosage form is to develop a formulation which has all the advantages of a single-unit form and also devoid the above mentioned disadvantages of single-unit formulations. In pursuit of this endeavor many multiple-unit floatable dosage forms have been designed.\textsuperscript{[34]} Microspheres with high loading capacity can be formulated using various polymers such as albumin, gelatine, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate. Spherical polymeric microsponges, are referred as “microballoons,” have been prepared.\textsuperscript{[35]} Microspheres have a characteristic internal hollow structure and show an excellent in vitro float ability. The dosage forms are excluded from the passage of the pyloric sphincter if a diameter of \~12 to 18 mm in their expanded state is exceeded.\textsuperscript{[36]}

C. 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 CO\textsubscript{2}. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO\textsubscript{2} to make the system less dense and float on the gastric fluids an antacid raft forming floating system.\textsuperscript{[27]} The system contains a gel forming agent (e.g. alginic bicarbonate, calcium arbonate, mannitol and a sweetener. 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.\textsuperscript{[37]}
Table 1: Drugs Investigated In Floating Drug Delivery Systems\textsuperscript{[38]}

<table>
<thead>
<tr>
<th>S.No</th>
<th>Types of dosage form</th>
<th>Drugs Explored in floating dosage forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Microspheres</td>
<td>Aspirin, Griseofulvine, p-nitro Aniline, Ibuprofen, Ketoprofen, Terfenadine, Tranilast, Verapamil</td>
</tr>
<tr>
<td>2</td>
<td>Granules</td>
<td>Diclofenac sodium, Indomethacin, Prednisolone</td>
</tr>
<tr>
<td>3</td>
<td>Films</td>
<td>Cinnarizine drug delivery device</td>
</tr>
<tr>
<td>4</td>
<td>Capsules</td>
<td>Chlordiazepoxide HCl, Diazepam, Furosimide, L-dopa, Benserazide, Misoprostal, Nicardipine, Propranolol</td>
</tr>
<tr>
<td>5</td>
<td>Tablets/Pills</td>
<td>Acetaminophen, Aspirin, Amoxycillin, Ampicillin, Atenolol, Captopril, Ciprofloxacin, Chlorpheniramines maleate, Cinnarizine, Furosimide, 5-Fluro-uracil, Diltiazem, Nimodipine, PABA, Prednisolon, Quinidine, Verapamil HCl, Riboflavin, Sotalol, Theophylline</td>
</tr>
</tbody>
</table>

Bioadhesive

This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. The original concept of bioadhesive polymers as platforms for oral controlled drug delivery was to use these polymers to control and to prolong the GI transit of oral controlled delivery systems for all kinds of drugs.

Whereas bioadhesion has found interesting applications for other routes of administration (buccal, nasal, rectal and vaginal), it now seems that the controlling approach of GI transit has been abandoned before having shown any significant clinical outcome.\textsuperscript{[39]}

High Density Systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the 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\textsuperscript{3}) trapped in fold 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 diameter of the pellets. 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\textsuperscript{3}.

Swelling and expending systems

These dosage forms are larger than the pyloric opening and so are retained in the stomach. There are some drawbacks associated with this approach. Permanent retention of rigid large-
sized single-unit forms can cause bowel obstruction, intestinal adhesion and gastroplasty. It can be referred as Plug-Type systems Polymers in the systems swell at a very faster rate and with higher degree to form a swollen matrix of which size is greater than that of the pylorus. The rate and extent of swelling are important parameters. The rate of swelling and rate of erosion are also important. The integrity of the system is also crucial to prevent the disintegration of the system and to withstand the powerful waves from the stomach.\[^{40}\]

**Formulation Techniques of Floating Dosage Form**

Following types of the ingredients can be incorporated in to HBS dosage form\[^{41}\]

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

**Hydrocolloids:** Suitable hydrocolloids are synthethics, anionic or non ionic like hydrophilic gums, modified cellulose derivatives e.g. acacia, pectin, agar, alginates, gelatin, casein, (K4M, K100M and K15M), Gellan gum(Gelrite®), Sodium Carboxy Methyl Cellulose (CMC), Methyl Cellulose (MC), Hydroxy Propyl Cellulose (HPC), and Na CMC can be used. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid is having pH 1.2.

**Inert fatty materials:** Edible, pharmaceutical inert fatty material, having a specific gravity less than one can be added to the formulation to decrease the hydrophilic property of formulation and hence increases the buoyancy. Example: Purified grades of beeswax, fatty acids, long chain alcohols, can be used.

**Release rate accelerant:** The release rate of the medicament from the formulation can be modified by including excipients like lactose and/or mannitol. These may be present from about 5-60% by weight.

**Release rate retardant:** Insoluble substances such as dicalcium phosphate, talc magnesium stearate decreased the solubility and hence retard the release of medicaments.
**Buoyancy increasing agents:** Materials like ethyl cellulose, which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. It may be adapted up to 80% by weight.

**Low density material:** Polypropylene foam powder (Accurel MP 1000®).

**Miscellaneous:** Pharmaceutically acceptable adjuvant like preservatives, stabilizers, and lubricants can be incorporated in the dosage forms as per the requirements. They do not adversely affect the hydrodynamic balance of the systems.

**Evaluation Of Gastroretentive Dosage Form**

Various parameters that need to be evaluated in gastro retentive formulations include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms. In the case of multiparticulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, and mechanical properties are also performed. In vivo evaluation is performed by X-ray, Gamma-scintigraphy, gastroscopy and ultra sonography. The evaluation of Gastro-retentive dosage forms is carried on the basis of following criteria:

1. **Buoyancy Lag Time and Duration of Buoyancy:** The buoyancy lag time and the duration of buoyancy determine in the U.S.P. dissolution test apparatus II in a acid environment. The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of the dissolution medium is taken buoyancy lag time or floating lag time and the duration of buoyancy was observed visually.

2. **Determination of Density:** The tablet density of the floating system was determined by displacement method, using benzene as a displacing medium. A plethysmometer employed to measure tablet density. Firstly, the instrument was calibrated using benzene (density 0.8723g/cc) for its volumetric capacity. Benzene filled till a mark in capillary the instrument. Subsequently, five tablets of known weight were dropped in wider mouth of plethysmometer. The system is kept undisturbed for 1 min, to let benzene displace the air in the pores of the tablets. After that, displacement in the volume of the benzene in the side capillary was noted. Knowing the weight and volume occupied by the tablets, density of five tablets is determined.

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. The magnitude and direction of force/resultant weight (up or down) is corresponding to its buoyancy force \( F_{\text{buoy}} \) and gravity force \( F_{\text{grav}} \) acting on dosage form

\[
F = F_{\text{buoy}} - F_{\text{grav}}; \quad F = D_f \cdot g \cdot V - D_s \cdot g \cdot V; \quad F = (D_f - D_s) \cdot g \cdot V; \quad F = (D_f - \frac{M}{V}) \cdot g \cdot V
\]

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.

4. **Swelling Index**: Tablets weight individually \( (W_o) \) and placed in dissolution medium. The temperature is maintained at 37º C. At regular intervals, the samples remove using a basket and swollen weight \( (W_t) \) each tablet was determined at predefined time intervals.\(^{[51]}\)

The swelling index was calculated by the following equation:

\[
\text{Percentage Swelling Index} = \left\{\frac{(W_t - W_o)}{W_o}\right\} \times 100
\]

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

5. **Hardness and Friability**: Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet, the resistance of the tablet to chipping, abrasion or breakage under condition of storage, transformation and handling before usage depends on its hardness. Hardness of tablet is measure by using Monsanto Hardness Tester. Friability of the tablets determines using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inch in each revolution. Pre-weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed.\(^{[52]}\) The friability \( (F\%) \) is given by the formula:

\[
F\% = \left(1 - \frac{W_1}{W_2}\right) \times 100
\]

Where, \( W_1 \) is the weight of tablets before the test and \( W_2 \) is weight of the tablets after test.

6. **Weight Variation**: USP provides the weight variation test by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weights
to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

7. **In-Vitro dissolution behavior:** The release of the medicament was studied by USP-II type dissolution apparatus (Paddle type). Dissolution study is performing at predetermined speed and temperature of about 37°C in an appropriate dissolution medium. 5ml of sample withdraw at a predetermined interval and the volume of dissolution medium maintain by adding same volume of dissolution medium. The absorption of withdrawn sample measure spectrophotometrically with suitable dilution and the corresponding concentration was determined from the calibration curve.\(^{[53-54]}\)

*In-vitro* dissolution test using methods using different apparatus’ are described as under:

a) 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.

b) To prevent sticking at vessel or paddle and to improve movement of dosage form, method suggested is to keep paddle at surface and not too deep inside dissolution medium.

c) 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.

d) 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.

e) Other method suggests placing dosage form between 2 ring/meshes.

f) 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.

g) In spite 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.

8. **In-vivo evaluation**

a) **Radiology:** X-ray is widely used for examination of internal body systems. Barium Sulphate is widely used Radio Opaque Marker. So, BaSO\(_4\) is incorporated inside dosage form and X-ray images are taken at various intervals to view GR.
b) **Gamma Scintigraphy:** This method helps to locate dosage form in the gastrointestinal tract by which we can predict and correlate the gastric emptying time and the passage dosage form in the GIT. The inclusion of radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a γ emitting radio nucleotide in a formulation allows indirect external observation using a γ-camera or scinti scanner. In case of γ-scintigraphy, the γ-rays emitted by the nucleotide are focused on a camera, which helps to monitor the location of the dosage form in the gastrointestinal tract.

c) **Gastroscopy:** Gastroscopy is an examination of the inside of the gullet, stomach and duodenum. It is performed by using a thin, flexible fiber-optic instrument that is passed through the mouth. Gastroscopy is peroral endoscopy used with fiber optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of GRDDS.

d) **Magnetic marker monitoring:** It is a method to monitor the passage of an orally applied drug (tablet, capsule, etc.) through the intestinal tract. The dosage form is enriched with a small amount (0.1 – 2 mg) of magnetite (Fe₃O₄), which then is magnetized by a high-energy magnetic field. After application the path of the dosage form can be monitored with special detectors, which contain Superconducting Quantum Interference Devices (SQUIDs). Due to the very low magnetic field of the iron oxide a specially shielded room is necessary in order to eliminate environmental magnetic interference. The method should be able to yield information about why tablets dissolve unequally before or after meals, which may be important for the bioavailability of drugs.

**Applications of Floating Drug Delivery Systems**

1. **Enhanced Bioavailability:** The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.\(^{[41]}\)

2. **Sustained drug delivery:** Oral CR formulations are encountered with problems such as gastric residence time in the GIT. These problems can be overcome with the HBS systems which can remain in the stomach for long periods and have a bulk density <1 as a
result of which they can float on the gastric contents. These systems are relatively larger in size and passing from the pyloric opening is prohibited.[42]

3. **Site specific drug delivery systems:** These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug.[43]

4. **Absorption enhancement:** Drugs which are having poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption.[44]

5. **Minimized adverse activity at the colon:** Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented.

6. **Reduced fluctuations of drug concentration:** Continuous input of the drug following CRGRDF administration produces blood drug concentrations journal of current pharmaceutical research 2011; 7 (1): 6-20 within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects 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.

**Recent Research on Floating Drug Delivery Systems**

A summary of recent research on floating drug delivery systems is given in Table 2.

**Table 2: Summary of Recent Research on Floating Drug Delivery Systems**

<table>
<thead>
<tr>
<th>S.N.</th>
<th>Drugs</th>
<th>Type of Dosage form</th>
<th>Excipients/Polymers Used</th>
<th>Method</th>
<th>Reason/Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Captopril</td>
<td>Core mini tablets</td>
<td>HPMCK100, Ethyl Cellulose7cps, MCC</td>
<td>Direct Compression</td>
<td>Prolonged gastric residence time and Increased bioavailability.</td>
</tr>
<tr>
<td>2</td>
<td>Acyclovir</td>
<td>Tablet</td>
<td>Psyllium husk, HPMC K4M, sodium bicarbonate</td>
<td>Wet Granulation</td>
<td>Increased gastric residence time and bioavailability</td>
</tr>
<tr>
<td>3</td>
<td>Ciprofloxacin</td>
<td>Tablet</td>
<td>HPMC 4M, K15M, K100M, Citric acid, anhydrous sodium bicarbonate</td>
<td>Direct Compression</td>
<td>Improve GI absorption and controlled release of drug</td>
</tr>
<tr>
<td>No.</td>
<td>Drug</td>
<td>Formulation Type</td>
<td>Excipients</td>
<td>Method</td>
<td>Properties</td>
</tr>
<tr>
<td>-----</td>
<td>---------------</td>
<td>------------------</td>
<td>-----------------------------------</td>
<td>---------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>4</td>
<td>Clarithromycin</td>
<td>Tablet</td>
<td>HPMC K4M, sodium bicarbonate</td>
<td>Wet Granulation</td>
<td>Improved bioavailability</td>
</tr>
<tr>
<td>5</td>
<td>Famotidine</td>
<td>Gel beads</td>
<td>Sodium alginate, HPMC K15m</td>
<td>Gelation Method</td>
<td>Prolonged gastric residence time up to 8 hr &amp; improved bioavailability</td>
</tr>
<tr>
<td>6</td>
<td>Metformin</td>
<td>Micro capsule</td>
<td>Cellulose acetate butyrate, Eudragit</td>
<td>Solvent evaporation method</td>
<td>Enhanced absorption and improved bioavailability</td>
</tr>
<tr>
<td>7</td>
<td>Propranolol HCl</td>
<td>Tablet</td>
<td>HPMC, HPC, Xanthan gum, Sodium alginate</td>
<td>Direct Compression</td>
<td>Increased gastric residence time and bioavailability</td>
</tr>
<tr>
<td>8</td>
<td>Ranitidine</td>
<td>Tablet</td>
<td>HPMC K4M, Guar gum, Xanthan Gum</td>
<td>Direct Compression</td>
<td>Increased gastric residence time and better sustained effect</td>
</tr>
<tr>
<td>9</td>
<td>Rifabutin</td>
<td>Beads</td>
<td>Deacetylated gellan gum</td>
<td>Ionotropic gelation in acidic medium</td>
<td>Sustained pharmacological action and improved bioavailability</td>
</tr>
<tr>
<td>10</td>
<td>Silymarin</td>
<td>Tablet</td>
<td>Psyllium husk, HPMC K4M, sodium bicarbonate, Crosprovidone, MCC</td>
<td>Direct Compression</td>
<td>Prolonged drug release and improved bioavailability and patient compliance</td>
</tr>
<tr>
<td>11</td>
<td>Tizanidine</td>
<td>Matrix tablet</td>
<td>HPMC, MCC PH102, Dicalcium phosphate, Lactose</td>
<td>Wet Granulation</td>
<td>Sustained release over 24 hr</td>
</tr>
<tr>
<td>12</td>
<td>Zidovudine</td>
<td>Tablet</td>
<td>HPMC K4M, Xanthan gum, carbopol 934P</td>
<td>Direct Compression</td>
<td>Improved bioavailability and control release</td>
</tr>
<tr>
<td>13</td>
<td>Ito pride</td>
<td>Matrix tablet</td>
<td>HPMC 4M, K15M, sodium bicarbonate</td>
<td>Direct Compression</td>
<td>Improved bioavailability</td>
</tr>
<tr>
<td>14</td>
<td>Hydrochlorothiazide</td>
<td>Microspheres</td>
<td>EC, Cellulose acetate, Cross linked PVP, Polyacrilamide, PEG, HPMC</td>
<td>Ionotropic gelation in acidic medium</td>
<td>Sustained and pH independent &amp; reproducible drug release</td>
</tr>
<tr>
<td>15</td>
<td>Verapamil</td>
<td>Tablet</td>
<td>MCC 102, HPMC K4M, HPMC 15M</td>
<td>Direct Compression</td>
<td>pH dependent and controlled release</td>
</tr>
<tr>
<td>16</td>
<td>Atenolol</td>
<td>Tablet</td>
<td>HPMC k4M, K100M, directly compressible lactose, xanthan gum</td>
<td>Direct Compression</td>
<td>Prolonged gastric residence time and bioavailability</td>
</tr>
<tr>
<td>17</td>
<td>Foscarnet sodium</td>
<td>Alginate beads</td>
<td>HPMC K15M, guar gum, Tamarind gum</td>
<td>Ionic gelation method</td>
<td>Prolonged gastric residence time and bioavailability</td>
</tr>
<tr>
<td>18</td>
<td>Gabapentin</td>
<td>Tablet</td>
<td>HPMC K15m, K100M, PVPK30,</td>
<td>Direct Compression</td>
<td>Increased bioavailability and prolonged drug release</td>
</tr>
<tr>
<td>No.</td>
<td>Drug</td>
<td>Formulation Type</td>
<td>Excipients</td>
<td>Method</td>
<td>Remarks</td>
</tr>
<tr>
<td>-----</td>
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<td>---------</td>
</tr>
<tr>
<td>19</td>
<td>Metoprolol tartrate</td>
<td>Core mini tablets</td>
<td>HPMC K15M, PVP K30, HCl, MCC</td>
<td>Wet Granulation</td>
<td>Increased gastric residence time</td>
</tr>
<tr>
<td>20</td>
<td>Rifabutin</td>
<td>Microspheres</td>
<td>Gellen gum</td>
<td>Ionic gelation method</td>
<td>Remained buoyant up to 18 hr and provided controlled release</td>
</tr>
<tr>
<td>21</td>
<td>Verapamil HCl</td>
<td>Gel beads</td>
<td>sodium alginate, calcium chloride</td>
<td>Emulsion gelation method</td>
<td>Prolonged drug release</td>
</tr>
<tr>
<td>22</td>
<td>Rosiglitazone maleate</td>
<td>Microspheres</td>
<td>Eudragit RS100, tributylcitrate, heavy liquid paraffin, petroleum ether</td>
<td>Emulsification solvent evaporation method</td>
<td>Control release and improved bioavailability.</td>
</tr>
<tr>
<td>23</td>
<td>Cefpodoxime Proxetil</td>
<td>Matrix tablet</td>
<td>HPMC K4M, sodium CMC, carbopol 934P</td>
<td>Direct compression</td>
<td>Prolonged gastric residence time and increased drug absorption and bioavailability</td>
</tr>
<tr>
<td>24</td>
<td>Cefuroxime HCl</td>
<td>Matrix tablet</td>
<td>HPMC K4M, sodium bicarbonate</td>
<td>Direct Compression</td>
<td>Buoyancy over 8-24hr.</td>
</tr>
<tr>
<td>25</td>
<td>Cinnarizine</td>
<td>Gelling suspension</td>
<td>sodium alginate, calcium carbonate</td>
<td>Ionic gelation method</td>
<td>98.90% release in 12 hr over instant floating</td>
</tr>
<tr>
<td>26</td>
<td>Atorvastatin calcium</td>
<td>Tablet</td>
<td>HPMC K4M, Ethyl cellulose Bees wax</td>
<td>Melt granulation</td>
<td>Drug release in a controlled manner for extended period of time</td>
</tr>
<tr>
<td>27</td>
<td>Carbamazepine</td>
<td>Matrix tablet</td>
<td>HPMC, sodium bicarbonate, and EC</td>
<td>Melt granulation</td>
<td>Improved drug absorption and bioavailability</td>
</tr>
<tr>
<td>28</td>
<td>Labetalol</td>
<td>Matrix tablet</td>
<td>HPMCK4M Carbopol 934P, Sod CMC, citric acid sodium bicarbonate</td>
<td>Simplex Centroid Design</td>
<td>Improved bioavailability and controlled over 12hr</td>
</tr>
<tr>
<td>29</td>
<td>Levofoxacin</td>
<td>Tablet</td>
<td>Citric Acid and Sodium Bicarbonate, HPMC, EC.</td>
<td>Direct Compression</td>
<td>Drug release with prolonged Period</td>
</tr>
<tr>
<td>30</td>
<td>Lornoxicam</td>
<td>Matrix tablet</td>
<td>HPMC K15M, calcium carbonate (13%).</td>
<td>Direct Compression</td>
<td>Prolonged gastric residence time and improved bioavailability.</td>
</tr>
</tbody>
</table>
CONCLUSIONS
In the field of gastric retention, we have seen that there are many obstacles that need to be overcome in order to be able to claim true gastric retention. Considering the advantages for improved delivery of drugs, some companies have undertaken the considerable task of developing these types of devices, some with success and others with failure due to the unpredictability of the human GI tract. However, we are as close as we have ever been to seeing a greater transition of gastric retention devices from developmental level to the manufacturing and commercial stage.[55]

REFERENCES


