Gastro retentive Drug Delivery System: A Review
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Abstract

A Controlled release dosage forms have been extensively used to improve therapy with several important drugs. However, the development processes are faced with several physiological difficulties such as the inability to restrain and localize the system within the desired region of the gastrointestinal tract and the highly variable nature of the gastric emptying process. This variability may lead to unpredictable bioavailability and times to achieve peak plasma levels. The purpose of writing this review on gastroretentive drug delivery systems was to compile the recent literature with special focus on various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. In order to understand various physiological difficulties to achieve gastric retention, we have summarized important factors controlling gastric retention. Afterwards, we have reviewed various gastroretentive approaches designed and developed until now, i.e. high density (sinking), floating, bio- or mucoadhesive, expandable, unfoldable, super porous hydrogel and magnetic systems. Finally, advantages of gastroretentive drug delivery systems were covered in detail.

Keywords: Gastroretentive, GRDDS, Oral route. Various Approaches

Objective

The present study attempts to give an insight into the gastroretentive drug delivery systems, and gastric floating tablets, in particular. These have attracted the interest of many formulators due to their advantages over the conventional drug delivery systems, recently. The study highlights these advantages with reference to the various types of gastroretentive drug delivery systems, as well as provides an overview of the recent advances that have taken place in this arena.

Introduction

Oral administration is the most convenient and preferred means of any delivery to the systemic circulation. Oral controlled release drug delivery have recently been of increasing interest in Pharmaceutical field to achieve improved therapeutic advantages such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastro intestinal tract (GIT) and have short half life are eliminated quickly from systemic circulation. Frequent dosing of these drugs is required to achieve therapeutic activity. To avoid these limitations, the development of oral sustained controlled release formulation is an attempt to release the drug slowly into the gastro intestinal tract and maintain an effective drug concentration in the systemic circulation for long time. After oral administration, such a drug delivery would be retain in the stomach and release the drug in a controlled manner so that the drug could be supplied continuously to its absorption site in gastro intestinal tract1. Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastro intestinal tract for local and systemic effect. Gastro retentive dosage form can remain in the gastric region for a longer period and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades several gastro retentive drug delivery approaches been designed and developed, including high density (sinking) system that is retained in the gastro intestinal tract2,3,4. mucoadhesive systems that causes bioadhesion to stomach mucosa, unfoldable, extendable or swellable system which limits emptying of the...
dosage forms through the pyloric sphincter of the stomach, super porous hydrogel system, magnetic system etc. The current review deals with the various gastro retentive approaches that have been recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery systems. Gastric emptying of dosage form is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which resides in the stomach for prolong period of time than conventional dosage forms. Several difficulties are faced to designing controlled delivery system for better absorption and enhance bioavailability. One of such difficulty is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from GIT is complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns and physiological and formulation variables affecting the cosmic emptying is summarized. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolongs the gastric residence time if drugs. Prolong gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in high pH environment. It has application also for local drug delivery to the stomach and proximal small intestine. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. The controlled gastric retention of solid dosage forms may be achieved by the mechanism of mucoadhesion\(^6\) floatation, sedimentation, expansion, modified shapes systems or by the simultaneous administration of pharmacological agents\(^7,8,9\) that delay gastric emptying.

Based on these approaches, classification of floating drug delivery system (FDDS) has been described in detail. *In-vivo* / *in-vitro* evaluation of FDDS has been discussed by scientist to assess the efficiency of such system. Several recent examples have been reported showing the efficiency of such systems for drugs with bioavailability problems. The need for Gastroretentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery system. Floating drug delivery system has a bulk density lower than gastric fluids and thus remain buoyant in the stomach for prolong period of time, without affecting the gastric emptying rate. While the system is floating on the gastric content, the drug is released slowly at a desired rate from the stomach. This results in an increase in the GRT and a better control of fluctuation in the plasma drug concentrations. Number of FDDS involving various technologies carrying their own advantages and the limitation were developed such as, single and multiple unit hydrodynamically balanced systems (HBS), single and multiple unit gas generating system, hollow microspheres and raft forming systems. The current review deals with the development of GRDDS, by using natural polymers that has recently become the leading methodology in this field. Natural polymers are good candidate for oral cavity drug delivery. Also because biological property such as non toxicity, biocompatibility and bio degradability. Natural polymer is promising candidate for the enhancement of absorption of drug using floating drug delivery system\(^10\).

**Basic physiology of Gastrointestinal Tract:**

Anatomically the stomach is divided into three regions: Fundus, body and antrum (pylorus). The proximal part made of fundus and body act as reservoir for undigested materials where as the antrum is the main site for mixing motions and act as pump from gastric emptying by propelling the actions. Gastric emptying occurs during fasting as well as feed state. The patent of motility is however distinct in 2 states. During fasting state an inter digestive series of electrical events takes place, which cycle both through stomach and intestine every 2 to 3 hours\(^11\). This is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington\(^12\).

1. Phase I (basal phase) lasts from 40 to 60 minutes with contractions.
2. Phase II (pre burst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progress the intensity and frequency also increases gradually.
3. Phase III (burst phase) last for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this valve 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. 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. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage form are subjected to basically two complications that of short gastric residence time and unpredictable gastric emptying rate.

Factors affecting gastric retention:
Gastric residence time of an oral dosage form is affected by several factors. 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 amount 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 better chances of dissolving in fed state than in fasting state. The rate of gastric emptying depends mainly on viscosity, volume and caloric content of meals. Nutritive density of meals helps to determine gastric emptying time. It does not make any difference whether the meal has high protein, fat or carbohydrate contents as long as the caloric content is the same. However, increase in acidity and caloric value slows down gastric emptying time. Biological factors such as age, body mass index (BMI), gender, posture and diseased states (diabetes, Chron's disease) influence gastric emptying. In the case of elderly persons, gastric emptying is slowed down. Generally females have slower gastric emptying rate than males. Stress increases rate while depression slows it down. The resting volume of the stomach is 25 to 50 mL. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids. Studies have revealed that gastric emptying of a dosage form in 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. It has been demonstrated using radiolabelled technique that there is a difference between gastric emptying times of a liquid, digestible solid and indigestible solids. It was suggested that emptying of large (91 mm) indigestible objects from stomach was dependent upon inter digestive migrating complex. When liquid and indigestible solids are present in the stomach, it contracts 3 to 4 times per minute leading to the movement of the contents through partially opened pylorus. Indigestible solids larger than the pyloric opening are propelled back and several phases of myoelectric activity take place, when the pyloric opening increases in size during the housekeeping wave and allows the sweeping of the indigestible solids. Studies have shown that the gastric residence time (GRT) can be significantly increases under the fed state since the MMC is delayed.

Several formulation parameters can affect the gastric residence time. More reliable gastric emptying patterns are observed for multiparticulate formulations as compared with single unit formulations, which suffer from“all or none concept. As the units of multiparticulate to a lesser extent by the transit time of food compared with single unit formulation. Size and shape of dosage unit also affects the gastric emptying, it is reported that tetrahedron trans ring shaped devices have better gastric residence time as compared with other shapes. The diameter of dosage unit is also equally important as a formulation parameter. Dosage form having a diameter of more than 7.5 mm shows a better gastric residence time compared with one having 9.9 mm.

The density of a dosage form also affects the gastric emptying rate. A buoyant dosage form having density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retain in the stomach for prolong period. It is been studied the effect of buoyancy, posture and the nature of meals on the gastric emptying processes in vivo using gamma scintigraphy. To perform these studies, floating and non floating capsules of three different sizes having a diameter of 4.8 mm (small units), 7.5 mm
(medium units) and 9.9 mm (large units) were formulated. On comparison of floating and non floating dosage units, it was concluded that regardless of their sizes the floating dosage units remain buoyant on the gastric contents throughout their residence in the gastrointestinal tract, while the non floating dosage unit sinks and remain in the lower part of stomach. Floating units away from the gastro duodenal junction were protected from the peristaltic waves during digestive phase while the non floating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase. It was also observed that of the floating and non floating units, the floating units were had a longer gastric residence time for small and medium units while no significant difference was seen between two types of large unit dosage forms. When subjects were kept in the supine position, it was observed that the floating form could only prolong just stay because of their size, otherwise buoyancy remains no longer and advantage for gastric retention. A comparison was made to study the affect of fed and non fed stages on gastric emptying. For these study all subjects remaining in an upright position were given a light breakfast and another similar group was fed with a succession of meals given at a normal time intervals. It was concluded that as meals were given at the time when previous digestive phase had not completed, the floating form buoyant in the stomach could retain its position for another digestive phase as it was carried by the peristaltic wave in the upper part of stomach.

Suitable drug candidates for gastroretention:
Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolong in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effect and provide their therapeutic effects without the need for repeated dosage with a low dosage frequency. Sustain release in the stomach is also useful for therapeutic agents that the stomach does not readily absorbed, since sustain release prolongs contact time of the agent in the stomach or in the upper part of small intestine, which is where absorption occur and contact time is limited under normal or average condition, Example. material passes through the small intestine in as little as 1-3 hrs. In general, appropriated candidate CRGRDF are molecules that have poor colonic absorption but are characterizes by better absorption, properties at the upper part of GIT:
- Narrow absorption window in GIT, E.g. Riboflavin and Levodopa.
- Primarily absorbed from stomach and upper part of GIT, Example: Calcium supplements, Chlordiazepoxide and Cinnarazine.
- Drugs that are locally in the stomach, Example. Antacids and Misoprostol.
- Drugs that degrade in the colon, Example. Rantidine HCl and Metronidazole.
- Drugs that disturbs normal colonic bacteria, Example. Amoxicillin trihydrate.

Table 1: Good candidates for gastroretentive drug delivery system

<table>
<thead>
<tr>
<th>S.N</th>
<th>Drug &amp; Category</th>
<th>Bioavalibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Verapamil Calcium channel blocker</td>
<td>20-35%</td>
</tr>
<tr>
<td>2</td>
<td>Nifedipine Calcium channel blocker</td>
<td>45-65%</td>
</tr>
<tr>
<td>3</td>
<td>Omeprazole Proton pump inhibitor</td>
<td>35-60%</td>
</tr>
<tr>
<td>4</td>
<td>Atenolol Antihypertesive</td>
<td>40-50%</td>
</tr>
<tr>
<td>5</td>
<td>Propranolol Antihypertensive</td>
<td>4-26%</td>
</tr>
<tr>
<td>6</td>
<td>Verapamil Antihypertensive</td>
<td>18-35%</td>
</tr>
<tr>
<td>7</td>
<td>Diltiazem Calcium channel blocker</td>
<td>40%</td>
</tr>
<tr>
<td>8</td>
<td>Lidocaine Local anaesthetic</td>
<td>35%</td>
</tr>
<tr>
<td>9</td>
<td>Clarithromycin Antibiotic</td>
<td>50%</td>
</tr>
<tr>
<td>10</td>
<td>Ramipril ACE inhibitor</td>
<td>28%</td>
</tr>
</tbody>
</table>

The need for gastro retentive dosage form (GRDFs) has led to extensive efforts in both academic and industry towards the development of such delivery systems. These efforts resulted in GRDFs that were designated, in large part, based on following approaches.
Approaches to gastric retention:
Various approaches have been pursued to increase the retention of an oral dosage form in the stomach, for example, bioadhesive approach in which the adhesive capacity of some polymer with glycoprotein is closely applied to the epithelial surface of stomach. Other approaches include: high density and low density approach. Fig. 1

1) High density approach:
For preparing such type of formulations, the density of the pellets should be higher than the stomach fluid. It would be at least 1.50 g/ml. In this type, the drug can be coated or mixed with heavy, nontoxic materials such as barium sulfate, titanium dioxide, etc.

2) Low density approach:
Floating systems come under low density approach. In this approach, the density of pellets should be less than 1 g/ml so as to float the pellets or tablets in the gastric fluid and, release the drug slowly for a longer period of time. This type is also called as Hydrodynamically Balanced System (HBS).

3) Floating Drug Delivery systems and its mechanism:
Floating drug delivery systems (FDDS) have bulk density lesser than gastric fluids, so they remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system as shown in fig. 2(a). However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side as shown in fig. 2. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations. F = F buoyancy – F gravity = (Df – Ds) g v
Where, F= total vertical force, Df = fluid density, Ds= object density, v = volume and g = acceleration due to gravity.

Classification of floating systems:
1). Single Unit Floating Dosage Systems
a) Effervescent system
b) Non-effervescent Systems
2). Multiple Unit Floating Dosage Systems
a) Effervescent Systems
b) Non-effervescent Systems
c) Hollow microspheres
3). Raft forming system

1). Single Unit Floating Dosage Systems:
a) Effervescent systems
Effervescent floating drug delivery systems generate gas (CO2), thus reduce the density of the system, and remain buoyant in the stomach for a prolonged period of time and release the drug slowly at a desired rate. The main ingredients of effervescent system include swellable polymers like chitosan, methyl cellulose and effervescent compounds such as citric acid, sodium bicarbonate, citric acid and tartaric acid. Penners et al prepared
an expandable tablet containing mixture of polyvinyl lactams and polyacrylates that swells rapidly in an aqueous environment and thus, stays in stomach over an extended period of time. In addition to this, gas-forming agents were also incorporated so as soon as the gas formed, the density of the system was reduced and thus, the system tended to float in the gastric environment\textsuperscript{18}. prepared the effervescent floating tablet of famotidine. They found that the addition of gel-forming polymers (K100 and K15M) and gas-generating agent sodium bicarbonate along with citric acid was essential to achieve in vitro buoyancy. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed\textsuperscript{19}.

\textbf{b) Non effervescent system}

Non-effervescent systems commonly use gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as 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 less than 1 g/ml. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. Iannuccelli et al prepared air compartment multiple unit system for prolonged gastric residence. These units were composed of a calcium alginate core separated by an air compartment from membrane of calcium alginate. The porous structure generated by leaching of polyvinyl alcohol (PVA), which was employed as water soluble additive in coating composition, was found to increase the membrane permeability preventing the air compartment shrinkage. The ability of floatation increases with increase in PVA, molecular Weight\textsuperscript{20}. Wu et al prepared floating sustained release tablets of nimodipine by using HPMC and PEG 6000. Prior to formulation of floating tablets, nimodipine was incorporated into poloxamer-188 solid dispersion after which it was directly compressed into floating tablets. It was observed that by increasing the HPMC and decreasing the PEG 6000 content, a decline in \textit{in vitro} release of nimodipine occurred.\textsuperscript{21} Single unit formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. The main drawback of such system is “all or none” phenomenon. In such cases, there is a danger of passing of the dosage form to intestinal part at the time of house-keeper waves. To overcome this difficulty multiple, unit dosage forms are designed.

\textbf{Fig. 3: a) Different layers b) Mechanism of floatation via CO2 liberation}
Chen et al studied the effect of formulation variables on \textit{in vitro} performance of floating sustained release of verapamil. The formulations were comprised of variables like polymers excipients, polymer content, density of capsule and amount of effervescent Agents\textsuperscript{22}.

\textbf{b) Non effervescent systems:}

Not many reports were found in the literature on non-effervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates and floats in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio\textsuperscript{23}.

\textbf{2). Multiple Unit Floating Systems:}

Multiple unit dosage forms may be an attractive alternate since they have been shown to reduce inter and intra-subject variabilities in drug absorption as well as to lower the possibility of dose dumping. Various multiple unit floating systems have been developed in
different forms, and using principles such as air compartment multiple unit system, hollow microspheres prepared by emulsion solvent diffusion method, beads prepared by emulsion gelation method. Use of effervescent and swellable polymer is another approach for preparing multiple unit FDDS.

**a) Effervescent system:**
Ichikawa *et al.* developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into two sublayers to avoid direct contact between the two agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37°C, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO2 was generated by the neutralization reaction between the two effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/ml. It was found that the system had good floating ability independent of pH and viscosity and the drug (Para-amino benzoic acid) released in a sustained manner as shown in fig.3 (a), (b) Thanoo *et al.* developed polycarbonate microspheres by solvent evaporation technique. Polycarbonate in dichloromethane was found to give hollow microspheres that floated on water and simulated biofluids, as evidenced by scanning electron microscopy (SEM). High drug loading was achieved and drug-loaded microspheres were able to float on gastric and intestinal fluids. It was found that increasing the drug to polymer ratio increased both their mean particle size and release rate of drug.\(^{24}\) Sheth *et al.* developed hydrodynamically balanced capsules containing mixture of drug and hydrocolloids containing a homogeneous mixture of drug and the hydrocolloid in a capsule, which upon contact with gastric fluid acquired and maintained a bulk density of less than 1, thereby being buoyant on the gastric contents of stomach, until all the drug was released as shown in fig.4.\(^{25}\)

![Fig. 4: Working principle of hydro dynamically balanced system](image)

**c) Hollow microspheres:**
Both natural and synthetic polymers have been used to prepare floating microspheres. Joseph *et al.* developed a floating dosage form of piroxicam based on hollow polycarbonate microspheres. The microspheres were prepared by the solvent evaporation technique. Encapsulation efficiency of ~95% was achieved. *In vivo* studies were performed in healthy male albino rabbits. Pharmacokinetic analysis was derived from plasma concentration versus time plot and revealed that the bioavailability from the piroxicam microspheres alone was 1.4 times that of the free drug and 4.8 times that of a dosage form consisting of microspheres plus the loading dose and was capable of sustained delivery of the drug over a prolonged period.\(^{26}\)

**3) Raft forming system:**
Raft forming systems have received much attention for the 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 ingredients includes 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. Jorgen *et al.* described an antacid raft forming floating system. The system contains a gel forming agent (e.g.
sodium alginate), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft), which when comes in contact with gastric fluids, the raft floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus acting as a barrier between the stomach and esophagus

Evaluation of Floating Drug delivery system

1) Evaluation of powder blend
  a) Angle of Repose
  b) Bulk Density
  c) Percentage porosity

2) Evaluation of tablets
  a) Buoyancy capabilities
  b) In vitro floating and dissolution behaviour
  c) Weight variation
  d) Hardness & friability
  e) Particle size analysis, surface characterization (for floating microspheres and beads):
  f) X-Ray/Gamma Scintigraphy
  g) Pharmacokinetic studies

1) Evaluation of powder blend

a) Angle of repose
   Angle of repose is defined as “the maximum angle possible between the surface of the pile of powder and the horizontal plane.” Lower the angle of repose, better the flow properties. The angle of repose may be calculated by measuring the height (h) of the pile and the radius of the base(r) with ruler.

\[
\tan \theta = \frac{h}{r} \ldots 1
\]

b) Bulk density
   Bulk density denotes the total density of the material. It includes the true volume of interparticle spaces and intraparticle pores. The packing of particles is mainly responsible for bulk .Bulk density is defined as:

\[
\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk volume of powder}} \ldots 2
\]

When particles are packed, it is possible that a large amount of gaps may be present between the particles. Therefore, trapping of powder allows the particles to shift and remove the voids to minimum volume. The volume occupied by the powder in this condition represents the bulk volume. Substituting this volume for a given weight of powder in equation (2) gives the bulk density.

c) Percentage porosity
   Whether the powder is porous or nonporous, the total porosity expression for the calculation remains the same. Porosity provides information about hardness, disintegration, total porosity etc.

\[
\% \text{ porosity}, \epsilon = \frac{\text{void volume}}{\text{true volume}} \times 100
\]

Bulk volume

\[
\% \text{ porosity}, \epsilon = \left(\frac{\text{bulk volumeture volume}}{\text{true volume}}\right) \times 100
\]

True density

2) Evaluation of floating tablets

a) Measurement of buoyancy capabilities of the FDDS:
   The floating behaviour is evaluated with resultant weight measurements. The experiment is carried out in two different media, deionised water and simulated meal. The results showed that higher molecular weight polymers with slower rate of hydration had enhanced floating behaviour and it was observed more in simulated meal medium compared to deionised water.

b) In Vitro floating and dissolution behaviour:
   The dissolution tests are generally performed on various drugs using USP dissolution apparatus. USP 28 states “the dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started”. A small, loose piece of nonreactive material with not more than a few turns of a wire helix may be attached to the dosage units that would otherwise float. However, standard USP or BP methods have not been shown to be reliable predictors of in vitro performance of floating dosage forms. Pillay et al applied a helical wire sinker to the swellable floating system of theophylline, which is sparingly soluble in water and concluded that the swelling of the system was inhibited by the wire helix and the drug release also slowed down. To overcome this limitation, a method was developed in which the floating drug delivery system was fully submerged under a ring or mesh assembly, and an increase in drug release was observed. Also, it was shown that the method was more reproducible and consistent.

   However, no significant change in the drug release was observed when the proposed method was applied to a swellable floating system of diltiazem, which is a highly water soluble drug. It was thus concluded that the drug release from swellable floating systems was dependent upon uninhibited swelling, surface exposure, and the solubility of the drug in water.
In practice, composite samples of tablets (usually 10) are taken and weighed throughout the compression process. The composite weight divided by 10, however, provides an average weight but contains a problem of averaged value. To help alleviate this problem, the United States Pharmacopeia (USP) provides limits for the permissible variations in the weights of individual tablets expressed as a percentage of the average weight of the sample. The 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.

d) Hardness & friability:
Hardness is defined as the “force required to break a tablet in diametric compression test.” Hardness is hence, also termed as the tablet crushing strength. Some devices which are used to test hardness are Monsanto tester, strong Cobb tester, Pfizer tester, etc. The laboratory friability tester is known as the Roche Friabilator. This consists of a device which subjects a number of tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm & drop the tablet to a distance of six inches with each revolution. Normally, a pre weighed tablet sample is placed in the friabilator which is then operated for 100 revolutions. Conventional compressed tablets that lose less than 0.5 to 1.0 % of their weight are generally considered acceptable. Most of the effervescent tablets undergo high friability weight losses, which accounts for the special stack packaging that may be required for these types of tablets.

e) Particle size analysis, surface characterization (for floating microspheres and beads):
The particle size and the size distribution of beads or microspheres are determined in the dry state using the optical microscopy method. The external and crosssectional morphology (surface characterization) is done by scanning electron microscope (SEM).

f) XRay/ gamma scintigraphy:
X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form nowadays. It helps to locate dosage form in the gastrointestinal tract, by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here 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 γ-emitting radionuclide in a formulation allows indirect external observation using a γ-camera or scintiscanner. In case of γ-scintigraphy, the γ-ray emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GIT.

g) Pharmacokinetic studies:
Pharmacokinetic studies are an integral part of the in vivo studies and several works have been reported on these. Sawicki studied the pharmacokinetics of verapamil, from the floating pellets containing drug, filled into a capsule, and compared with the conventional verapamil tablets of similar dose (40 mg). The tmax and AUC (0-infinity) values (3.75 h and 364.65ng/ml /1h respectively) for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets. (tmax value 1.21 h, and AUC value 224.22 mg/ml/1h)

Recent advances in stomach specific floating dosage forms:
Sungthongjeen et al have prepared a floating multilayer coated tablets based on gas formation. The system consists of a drugcontaining core tablet coated with a protective layer (hydroxylpropyl methyl cellulose), a gas forming layer (sodium bicarbonate) and a gas-entrapped membrane, respectively. Eudragit RL 30D was chosen as a gas-entrapped membrane due to its high flexibility and high water permeability.

The obtained tablets enabled to float due to the CO2 gas formation and the gas entrapment by polymeric membrane. The effect of formulation variables on floating properties and drug release was investigated. The floating tablets using direct-compressed cores had shorter the time to float and faster drug release than those using wet granulated cores. The increased amount of a gas forming agent did not affect time to float but increased the drug release from the floating tablets.
Table 2: Some of the marketed formulations available as GRDDS

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Brand name</th>
<th>Delivery system</th>
<th>Drug Category</th>
<th>Company name</th>
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<tbody>
<tr>
<td>1</td>
<td>Topalkan®</td>
<td>Floating liquid alginate preparation</td>
<td>Al – Mg Antacid</td>
<td>Pierre Fabre Drug, France</td>
</tr>
<tr>
<td>2</td>
<td>Conviron®</td>
<td>colloidal gel forming FDDS</td>
<td>Ferrous sulphate Antianemic</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>3</td>
<td>Cifran OD®</td>
<td>Gas generating floating form</td>
<td>Ciprofloxacin Antibiotic</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>4</td>
<td>Valreleas e®</td>
<td>Floating capsule Diazepam</td>
<td>CNS depressant</td>
<td>LaRoche, USA</td>
</tr>
<tr>
<td>5</td>
<td>Madopar®</td>
<td>Floating, CR capsule</td>
<td>Benserazide and L-Dopa Antiparkinsons</td>
<td>Roche Products, USA</td>
</tr>
</tbody>
</table>

while increasing the coating level of gas entrapped membrane increased the time to float (more than 8 hours) and slightly retarded, but sustained drug release. Rajnikanth et al have developed a floating in situ gelling system of clarithromycin (FIGC) using gellan as gelling polymer and calcium carbonate as floating agent for potentially treating gastric ulcers, associated with Helicobacter pylori (H.pylori). Gellan based FIGC was prepared by dissolving varying concentrations of gellan in deionized water, to which varying concentrations of the drug and sucralfate were dispersed well. The addition of sucralfate to the formulation significantly suppressed the degradation of clarithromycin at low pH. FIGC showed a significant antiH. pylori effect than that of clarithromycin suspension. The in situ gel formulation with sucralfate cleared H.pylori more effectively than that of formulation without sucralfate. In addition, the required amount of clarithromycin for eradication of H.pylori was found to be less from FIGC than from the corresponding clarithromycin suspension. It was concluded that prolonged gastrointestinal residence time and enhanced clarithromycin stability resulting from the floating in situ gel of clarithromycin might contribute better for complete clearance of H. pylori than the corresponding clarithromycin suspension.

Gastroretentive products available in market

Table 3 Gastroretentive Products Available in Market

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cifran OD</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Madopar</td>
<td>L-DOPA and Benserazide</td>
</tr>
<tr>
<td>Valreleas</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Topalkan</td>
<td>Aluminum -magnesium antaci</td>
</tr>
<tr>
<td>Almagate FlatCoat</td>
<td>Aluminum -magnesium antacid</td>
</tr>
<tr>
<td>Liquid Gavison</td>
<td>Aluminium hydroxide,</td>
</tr>
<tr>
<td>Conviron</td>
<td>Ferrous sulfate</td>
</tr>
<tr>
<td>Liquid Gavison</td>
<td>Alginic acid , Sodium bicarbonate</td>
</tr>
</tbody>
</table>
Companies involved in developing gastric retention technologies37

Table 4: Names of Companies Developing GR Products

<table>
<thead>
<tr>
<th>Company</th>
<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intec Pharma, Israel</td>
<td>Expandable (unfolding)</td>
</tr>
<tr>
<td>Kos Pharmaceuticals, New Jersey</td>
<td>Expandable (swelling absorbent, porous hydrogel)</td>
</tr>
<tr>
<td>DepoMed, Inc., California</td>
<td>Expandable (absorbing, swelling tablet)</td>
</tr>
<tr>
<td>Ranbaxy, India</td>
<td>Expandable, floating (gas generation)</td>
</tr>
<tr>
<td>Akina Pharmaceuticals, Indiana</td>
<td>Expandable</td>
</tr>
<tr>
<td>Spherics Inc., Rhode Island</td>
<td>(swelling absorbent, porous hydrogel)</td>
</tr>
<tr>
<td>Flamel Technologies, France</td>
<td>Mucoadhesion</td>
</tr>
<tr>
<td>Flamel Technologies, France</td>
<td>Mucoadhesion</td>
</tr>
</tbody>
</table>

Patents on FDDS38

Table 5: Patents on Floating Drug Delivery System

<table>
<thead>
<tr>
<th>S.No</th>
<th>Type of formulation</th>
<th>Patent no</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gastro retentive dosage form</td>
<td>U.S-7,413,752</td>
<td>Devane et al., 2008</td>
</tr>
<tr>
<td>2</td>
<td>Multiple unit floating dosage form</td>
<td>European patent (EP)</td>
<td>Vanderbist et al., 2007</td>
</tr>
<tr>
<td>3</td>
<td>Bilayer tablet</td>
<td>EP-002445</td>
<td>Lohray et al., 2004</td>
</tr>
<tr>
<td>4</td>
<td>Floating Tablet</td>
<td>U.S-66,352279</td>
<td>Kolter et al., 2003</td>
</tr>
<tr>
<td>5</td>
<td>Microspheres</td>
<td>U.S-6207197</td>
<td>Ilum et al., 2001</td>
</tr>
<tr>
<td>6</td>
<td>3-layer tablet</td>
<td>U.S-5780057</td>
<td>Conte et al., 1998</td>
</tr>
<tr>
<td>7</td>
<td>Foams (or) hollow bodies</td>
<td>U.S-5626876</td>
<td>Muller et al., 1997</td>
</tr>
<tr>
<td>8</td>
<td>Floating tablet</td>
<td>U.S-5169639</td>
<td>Baichwal et al., 1992</td>
</tr>
<tr>
<td>9</td>
<td>Granule</td>
<td>U.S-4844905</td>
<td>Ichikawa et al., 1989</td>
</tr>
<tr>
<td>10</td>
<td>Floating capsules</td>
<td>U.S-4814178,-79</td>
<td>Sheth et al., 1989</td>
</tr>
<tr>
<td>11</td>
<td>Tiny pills</td>
<td>U.S-4434153</td>
<td>Urguhart et al., 1984</td>
</tr>
<tr>
<td>12</td>
<td>Floating capsule</td>
<td>U.S-4126672</td>
<td>Sheth et al., 1978</td>
</tr>
<tr>
<td>13</td>
<td>Floating device</td>
<td>U.S-4055178</td>
<td>Harrigan et al., 1977</td>
</tr>
<tr>
<td>14</td>
<td>Empty globular shells</td>
<td>U.S-3976164</td>
<td>Watanabe et al., 1976</td>
</tr>
</tbody>
</table>

Commonly used drugs in Formulation of FDDS

Table 6: Commonly used FDDS Formulations

<table>
<thead>
<tr>
<th>Dosage forms</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Floating Tablets</td>
<td>Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbid mononitrate, p-Aminobenzoic acid (PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil,Nicardipine,Nimodipine,piretanide</td>
</tr>
<tr>
<td>Floating Capsules</td>
<td>Chlordiazepoxide HCl, Diazepam, Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin</td>
</tr>
<tr>
<td>Floating Microspheres</td>
<td>Aspirin, Griseofulvin, P-nitroaniline, Ibuprofen, Terfenadine, Tranilast,ketoprofen</td>
</tr>
<tr>
<td>Floating Granules</td>
<td>Diclofenac sodium, Indomethacin, Prednisolone, Diltiazem,</td>
</tr>
<tr>
<td>Powders</td>
<td>Riboflavin , sotalol ,theophylline</td>
</tr>
<tr>
<td>Films</td>
<td>Cinnarizine,Piretanide,Prednisolone,Quinidine guconate</td>
</tr>
</tbody>
</table>
Conclusion:
Recently many drugs have been formulated as floating drug delivery systems with an objective of sustained release and restricting the region of drug release to stomach. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. The currently available polymer-mediated noneffervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be a very much effective approach to the modulation of controlled oral drug delivery. The most important criteria which has to be looked into for the productions of a floating drug delivery system is that the density of the dosage form should be less than that of gastric fluid. And hence, it can be concluded that these dosage forms serve the best in the treatment of diseases related to the GIT and for extracting a prolonged action from a drug with a short half life.

References:
15. Seth SD. Text book of pharmacology, Reed Elsevier Ltd. 2005
33. Wu W, Zhou Q, Zhang HB, Ma GD, Fu CD. Studies on nimodipine sustained release tablet capable of floating on gastric fluids with prolonged gastric resident time. Yao Xue Xue Bao. 1997; 32:786-790