A NOVEL CONCEPT – FLOATING DRUG DELIVERY SYSTEM AS A REVIEW


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ABSTRACT
A floating drug delivery system is a novel concept for retaining a dosage form in the stomach for 12 or 24 hrs. Compare this system with the conventional dosage form, the conventional dosage forms are having short action and they are excreted but the floating drug delivery is avoid such a type of problems and give the sustained action. This concept is best for administrator who tried to avoid repeated dose, and also avoid problems occurring from drug which are used in the dosage forms. The various approaches are utilized in the prolongation of gastric retention, such as floating drug delivery system also known as hydrodynamically balance system (HBS), swelling and expanding system, polymeric bioadhesive system, modified-shape system, high-density system and other delayed gastric emptying devices. From the formulation and technological point of view, the floating drug delivery system is considerably easy and logical approach. The purpose of this comprehensive review is to compile the work going on this delivery system. Which provide the valuable information related to formulation aspect to achieve gastric retention and discussed the various factors affect and to overcome it.

Keywords: Gastric-retentive, floating system, hydrodynamically balance system, bioadhesive system.

INTRODUCTION
Historically, the oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. From immediate release to site specific delivery, oral dosage forms have really progressed. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a 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. Gastroretensive systems can remain
in the gastric region for several hours and hence significantly prolong the gastric
residence time of drugs. Prolonged gastric retention improves bioavailability, reduces
drug waste and improves solubility for drugs that are less soluble in a high pH
environment. It has applications also for local drug delivery to the stomach and proximal
small intestines. 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 mechanisms of mucoadhesion,
flotation, sedimentation, expansion modified shape systems or by the simultaneous
administration of pharmacological agent, that delay gastric emptying. This review
focuses on the principal mechanism of floatation to achieve gastric retention\[1\].

Need for controlled release Gastroretentive
Drug Delivery

Dosage form with prolonged GRT, i.e. gastro retentive dosage form (GRDF), will bring
about new and important therapeutic options such as – This application is especially
effective in sparingly soluble and insoluble drugs. It is known that, as the solubility of a
drug decreases, the time available for drug dissolution becomes less adequate and thus
the transit time becomes a significant factor affecting drug absorption. To override this
problem, erodible, gastroretentive dosage forms have been developed that provide
continuous, controlled administration of sparingly soluble drugs at the absorption site.

- Bisphosphonates
- Captopril
- Furosemide
- Metformin
- Gabapentin
- Acyclovir
- Levodopa
- Baclofen
- Ciprofloxacin
GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the submucosal tissue of stomach) making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis, reduce the risk of gastric carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).

GRDFs can be used as carriers for drugs with so-called absorption windows. These substances for e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides, tetracyclines etc.), are taken up only from very specific sites of the GI mucosa.

In general, appropriate candidates for controlled release gastroretentive dosages form (CRGRDF) are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT. Drugs that disturb normal colonic bacteria, e.g., amoxicillin rehydrate.

BIOLOGICAL ASPECTS OF CRGRDFs

Stomach Physiology:
The stomach is an expanded section of the digestive tube between the esophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube, with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions. In the empty state, the stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds called rugae.(fig.1.)
Fig. 1: Physiology of stomach

There are images to four major types of secretary epithelial cells that cover the surface of the stomach and extend down into gastric pits and glands[2]:

**Mucous cells**: secrete alkaline mucus that protects the epithelium against shear stress and acid.

**Parietal cells**: secrete hydrochloric acid.

**Chief cells**: secrete pepsin, a proteolytic enzyme.

**G cells**: secrete the hormone gastrin.

The contraction of gastric smooth muscle serves two basic functions: Ingested food is crushed, ground, mixed and liquefying to form Chyme. Chyme is forced through the pyloric canal into the small intestine, a process called gastric emptying.

**Gastric motility**

Gastric motility is controlled by a complex set of neural and hormonal signals. Nervous control originates from the enteric nervous system as well as parasympathetic (predominantly vagus nerve) and sympathetic systems. A large battery of hormones has been shown to influence gastric motility- for e.g. both gastrin and cholecystokinin act to relax the proximal stomach and enhance contractions in the distal stomach. The bottom line is that the patterns of gastric motility likely are a result from smooth muscle cells integrating a large number of inhibitory and stimulatory signals. Liquid readily pass through the pylorus in spurts, but solids must be reduced to a diameter of less than 1-2
mm before passing pyloric gatekeeper. The gastric volume is important for dissolution of the dosage form *in vivo*. The resting volume of the stomach is 25-50 ml. There is a large difference in gastric secretion of normal and achlorhydric individuals. Gastric pH also has pronounced effect of absorption of drug from delivery system. The pH of fasting stomach is 1.2-2.0 and in fed conditions 2.0-6.0.8\textsuperscript{2,3,1}.

**Gastric empty rate**

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours.\textsuperscript{9}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.

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.

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 forms are subjected to basically complications, that of short gastric residence time and unpredictable gastric emptying rate\textsuperscript{2,3,1}. 

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FACTORS AFFECTING GASTRIC RETENTION

The gastric retention time (GRT) of dosage form is controlled by several factors, that affect their efficacy as a gastroretentive system.

**Density** – GRT is a function of dosage form buoyancy that is dependent on the density.

**Size** – Dosage form units with a diameter of more than 9.5mm are reported to have an increased GRT.

**Shape of dosage form** – Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilopounds 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 coadministration 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, the 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 and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. 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 four 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** – Elderly people, especially those over 70, have a significantly longer GRT.
Posture – GRT can vary between supine and upright ambulatory states of the patient.

Concomitant drug administration – Anticholinergics like Atropine and Propantheline, Opiates like Codeine and Prokinetic agents like Metoclopramide and Cisapride.

Biological factors – Diabetes and Crohn’s disease[^2^,^3^,^7^].

Approaches To Design Floating Dosage Forms:
The following approaches have been used for the design of floating dosage forms of single and multiple unit systems.

Single-Unit Dosage Forms: In low density approaches, the globular shells apparently having lower density than that of gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach. In coated shells popcorn, poprice, and polystyrol have been exploited as drug carriers. Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture. The polymer of choice can be either ethylcellulose or hydroxypropyl cellulose depending on the type of released desired. Finally the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration. Fluid-filled floating chamber type of dosage forms includes incorporation of a gas-filled floatation chamber into a microporous component that houses a drug reservoir. Aperture or opening are present along the top and bottom walls through which the gastrointestinal fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behavior. The device is of swallowable size, remains afloat within the stomach for a prolong time, and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated. Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolong period of time the dosage form must have a bulk density of less than. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. Single
Multiple-Unit Dosage Forms

The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the above mentioned disadvantages of single-unit formulations. In pursuit of this endeavor many multiple unit floatable dosage forms have been designed. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and poly alkyl cyanoacrylate.
dioxide generated in the devices after administration have been described. These 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 (Fig 2 and 3)\[^{8,9,10}\].

**Classification of Floating Drug Delivery:**

Floating drug delivery systems are classified depending on the use of two formulation variables: effervescent and non-effervescent systems\[^{4,5,7,10}\].

![Fig.3. Mechanism of floating system](image)

**Effervescent Floating Dosage Forms:**

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g., sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, C02 is liberate and gas entrapped in swollen hydrocolloids which provides buoyancy to the dosage forms (Fig. 3.)

**Non-effervescent Floating Dosage Forms:**

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type 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.

**Advantages of Floating drug delivery system:**

1. The floating drug delivery systems are advantageous for drugs absorbed through the stomach. E.g., Ferrous salts, antacids.
2. Controlled delivery of drugs.
3. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
4. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
5. Simple and conventional equipment for manufacture.
6. Ease of administration and better patient compliance.
7. Minimizing the mucosal irritation due to drugs, releasing slowly at controlled rate.
8. Site-specific drug delivery
9. Some drugs are having Acidic nature like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
10. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine$^{[1,2,3]}$.

**Disadvantages of floating drug delivery system:**

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat, water.
3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
4. Drugs which are irritant to Gastric mucosa are also not desirable.
5. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted\textsuperscript{[1,2,3]}.

\textbf{Evaluation techniques}\textsuperscript{[1,2,3,4,5]}:

\textit{In vitro evaluation of floating tablets:}
Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

\textbf{1. Pre-compression parameters}

\textbf{a) Angle of Repose}
The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

\[
\tan \theta = \frac{h}{r}
\]
\[
\theta = \tan^{-1} \left( \frac{h}{r} \right)
\]

Where, \( \theta = \) angle of repose
\( h = \) height of the heap
\( r = \) radius of the heap

The relationship between Angle of repose and powder flow is as follows in table 1.

\textbf{TABLE 1: RELATIONSHIP BETWEEN ANGLE OF REPPOSE AND POWDER FLOW}

<table>
<thead>
<tr>
<th>Angle of repose</th>
<th>Powder flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td>Excellent</td>
</tr>
<tr>
<td>25-30</td>
<td>Good</td>
</tr>
<tr>
<td>30-40</td>
<td>Passable</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>Very poor</td>
</tr>
</tbody>
</table>
b) Compressibility Index

The flowability of powder can be evaluated by comparing the bulk density (ρ₀) and tapped density (ρₜ) of powder and the rate at which it packed down. Compressibility index was calculated by –

\[
\text{Compressibility index (\%)} = \frac{\rho_t - \rho_o}{\rho_t} \times 100
\]

Where \( \rho_o \) = Bulk density g/ml

\( \rho_t \) = Tapped density g/ml.

II Post-compression parameters

a) Shape of Tablets

Compressed tablets were examined under the magnifying lens for the shape of the tablet.

b) Tablet Dimensions

Thickness and diameter were measured using a calibrated vernier caliper. Three tablets of each formulation were picked randomly and thickness was measured individually.

c) Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It was expressed in kg/cm². Three tablets were randomly picked and hardness of the tablets was determined.

d) Friability test

The friability of tablets was determined by using Roche Friabilator. It was expressed in percentage (\%). Ten tablets were initially weighed (W initial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W final). The % friability was then calculated by –

\[
\% F = 100 \left(1 - \frac{W_0}{W}\right)
\]

% Friability of tablets less than 1% was considered acceptable.

e) Tablet Density

Tablet density was an important parameter for floating tablets. The tablet would float only when
its density was less than that of gastric fluid (1.004). The density was determined using the following relationship.

\[ V = \pi r^2 h \]
\[ d = \frac{m}{v} \]

\( v = \) volume of tablet (cc)
\( r = \) radius of tablet (cm)
\( h = \) crown thickness of tablet (g/cc)
\( m = \) mass of tablet

f) Weight Variation Test
Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet by U.S. Pharmacopoeia.

g) Buoyancy / Floating Test
The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

h) Swelling Study
The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain, as given by the equation.

\[ WU = \frac{(W_1 - W_0) \times 100}{W_0} \]

\( W_t = \) Weight of dosage form at time \( t \).
\( W_0 = \) Initial weight of dosage form.
REFERENCES


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