Floating Drug Delivery System - A New Era in Novel Drug Delivery System

P. Santhosh Kumar*, GY. Srawan Kumar and J. Kiran Kumar
Department of pharmaceutics, Hindu College of Pharmacy, Guntur, Andhra Pradesh, India.

ABSTRACT
In the recent years, scientific and technological advancements have been made in the research and development of novel drug delivery systems by overcoming physiological troubles such as short gastric residence times and unpredictable gastric emptying times. Several approaches are currently utilized in the prolongation of the gastric residence times, including floating drug delivery systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems and other delayed gastric emptying devices. The management of illness through medication is entering a new era in which growing number of novel drug delivery systems are being employed and are available for therapeutic use. Oral sustained release gastro-retentive dosage forms (GRDFs) offer many advantages for drugs with absorption from upper parts of gastrointestinal tract and for those acting locally in the stomach, improving the bioavailability of the medication. Floating Drug Delivery Systems (FDDS) is one amongst the GRDFs used to achieve prolonged gastric residence time. The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. This review also summarizes the in-vitro techniques, in-vivo studies to evaluate the performance and application of floating systems, and applications of these systems.

Keywords: floating drug delivery systems, single unit, multiple units.

INTRODUCTION
Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. One requisite for successful performance of oral controlled drug delivery system is that drug should have good absorption throughout the gastrointestinal tract, preferably by passive diffusion. These considerations have led to the development of a unique oral controlled release dosage form with Gastroretentive properties. After oral administration, such a dosage form (DF) would be retained in the stomach and releases the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. Gastroretentive dosage forms (GRDFs) 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 of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestine.

CONTROLLED DRUG DELIVERY SYSTEMS
Controlled drug delivery systems (CDDS) have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue. Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.
1. Delayed release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting
ORAL CONTROLLED DRUG DELIVERY SYSTEMS

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either local or systemic action.

The main areas of potential challenge in the development of oral controlled drug delivery systems are:

1) **Development of a drug delivery system:** To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment.

2) **Modulation of gastrointestinal transit time:** To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for a prolonged period of time to maximize the delivery of a drug dose.

3) **Minimization of hepatic first pass elimination:** If the drug to be delivered is subjected to extensive hepatic first-pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.

Conventional oral controlled dosages forms suffer from mainly two adversities are short gastric retention time (GRTs) and unpredictable gastric emptying time (GET). Altering the gastric emptying can overwhelm these problems. Therefore it is desirable, to formulate a controlled release dosage form that gives an extended GI residence time. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDFs or GRDS).

**Anatomy of Stomach**

The stomach is typically a J-shaped enlargement of the gastrointestinal tract directly inferior to the diaphragm in the epigastric, umbilical and left hypochondriac regions of the abdomen. The stomach has four regions:

1. **Cardia:** The cardia surrounds the superior opening of the stomach.
2. **Fundus:** The rounded portion superior to the left of the cardia is the fundus
3. **Body:** Inferior to the fundus is the large central portion of the stomach, called the body
4. **Pylorus:** The region of the stomach that connects to the duodenum is the Pylorus; it has two parts, the pyloric antrum which connects to the body of the stomach, and the pyloric canal, which leads into the duodenum.
Factors Affecting Gastric Retention

Gastric residence time of an oral dosage form is affected by several factors.

1. **Size**: The diameter of the dosage unit is equally important as a formulation parameter. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm.

2. **Shape**: Tetrahedron- and ring-shaped devices have a better gastric residence time as compared with other shapes.

3. **Density**: The density of a dosage form also affects the gastric emptying rate. The density of gastric fluid is reported to be 1.2 g/cm³. A buoyant dosage form having a density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.

**GASTRO RETENTIVE DRUG DELIVERY SYSTEM (GRDDS)**

GRDFs that were designed in large part are based on the following approaches:

a) Low density form of the DF that causes buoyancy in gastric fluid.

b) High density DF that is retained in the bottom of the stomach.

c) Bioadhesion to stomach mucosa.

d) Slowed motility of the gastrointestinal tract by concomitant administration of drugs or Pharmaceutical excipients.

e) Expansion by swelling or unfolding to a large size which limits emptying.
Types of Gastroretentive Dosage Forms⁹-¹³

A. Bio/Mucoadhesive systems

B. Combination of floating, mucoadhesion and swellable systems

C. Expandable systems

D. Floating drug delivery systems
   a. Non-effervescent systems
      i. Colloidal gel barrier system
      ii. Microporous compartment system
      iii. Alginate beads
      iv. Hollow microspheres / Microballons
      v. Floating Microspheres
   b. Gas-generating (Effervescent) systems

A. Bio/Mucoadhesive systems

Bioadhesive drug delivery systems are used as a delivery device within the lumen to enhance drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastroretentive force. Mucoadhesive drug-delivery systems contain a mucoadhesive polymer that adheres itself to the gastric mucosal surface, more specifically the mucus gel layer, thus prolonging its retention in the GIT. The capability to adhere to the mucus gel layer makes mucoadhesive polymers very useful excipients in GRDDS. These polymers can be natural, such as gelatine, sodium alginate, and guar gum, or semi-synthetic/synthetic, such as hydroxypropylmethyl cellulose (HPMC), Carbopol® 934, and sodium carboxymethyl cellulose.¹⁴,¹⁵

B) Combination of floating, mucoadhesion and swellable systems¹⁸

A preferred formulation comprises a mixture of a high or medium viscosity (Hydroxypropylmethylcellulose) and a high or medium viscosity (Hydroxyethylcellulose). It also includes a salt being capable of releasing gaseous carbon dioxide alkaline metal carbonates can be used, an acid may be added, such as citric acid and maleic acid.

C) Expanding Swellable Systems

Another way to retain a dosage form in the stomach is by increasing its size so that it could not be expelled easily through the pylorus into the intestine. Taking patient’s adherence and the impaired swallowing ability of elderly patients or kids, the gastroretentive delivery system should be small initially and swell once it reaches the stomach. The swollen or expanded form should occur as quickly as possible to have sufficient gastric retention. The longer it remains in its swollen or expanded shape, the longer the gastric retention time would be. Moreover, the enlarged form should be strong enough to be able to withstand the powerful housekeeper waves to guarantee 100 percent release of the entire dose.

The expandable GRDFs are usually based on three configurations: a small (‘collapsed’) configuration which enables convenient oral intake; expanded form that is achieved in the stomach and thus prevents passage through the pyloric sphincter; and finally another small form that is achieved in the stomach when retention is no longer required i.e. after the GRDF has released its active ingredient, thereby retained in the stomach where medical intervention enabling evacuation.¹⁹, ²⁰, ²¹
This approach involves retaining the dosage form in the stomach by increasing its size above that of the pyloric sphincter. Due to significant inter-individual variations, the cut off size cannot be given exactly, but its diameter was reported to be 12.8 ± 7.0 mm\(^2\). Streubel et al. estimated, that dosage forms should exhibit a minimum size of 13 mm for being retained in the stomach, however, even bigger units have been reported to be emptied through the pylorus\(^{23,24}\).

D. Floating drug delivery systems\(^{18}\):
Floating drug delivery systems have bulk density less than gastric fluids and so remain buoyant in the stomach without affecting 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, after release of drug; the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. FDDS can be divided into non-effervescent and gas-generating system.

a) Non effervescent systems\(^{18}\)
This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. One of the formulation methods of such dosage forms involves the mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. This system can be further divided into four sub-types:

i. Colloidal gel barrier system:\(^{18}\)
This system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption.

ii. Microporous compartment system:\(^{18}\)
This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

iii. Alginate beads:\(^{18}\)
Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40\(^\circ\)C for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours.

iv. Hollow microspheres / Microballons:\(^{18}\)
Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel
emulsion solvent diffusion. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 hours.

V. Floating Microspheres

Microsphere is a term used for small spherical particles, with diameters in the micrometer range (typically 1µm to 1000µm (1mm)). Microspheres are sometimes referred to as microparticles. Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Floating microspheres are spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins, natural or synthetic polymers. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

b) Gas-generating (Effervescent) systems

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach; carbon dioxide is released, causing the formulation to float in the stomach.

Fig. 7: Intragastric floating tablets

Fig. 8: (A) Multiple-unit oral floating drug delivery system. (B) Working principle of effervescent floating drug delivery system.
Advantages of effervescent tablets

- An opportunity for formulators to improve the taste
- A more gentle action on a patient’s stomach
- Marketing aspects (fizzy tablets may have more consumer appeal than traditional dosage forms).

Fundamentals of Effervescent

Effervescent are soluble organic acid and an alkali metal carbonate salt, one of which is often the API. Carbon dioxide is formed if this mixture comes into contact with water. Typical examples of the acids and alcohols used include

- Citric acid
- Tartaric acid
- Malic acid
- Fumaric acid
- Adipic acid
- Sodium bicarbonate
- Sodium carbonate
- Sodium sesquicarbonate
- Potassium bicarbonate
- Potassium carbonate

Production

Producing effervescent tablets requires a conventional solid dosage form manufacturing process that has been adapted to include additional features. Because of the unique characteristics of the product, the primary material used in the manufacture of effervescent is relatively hygroscopic, that is, it absorbs moisture from the air. However, this must be prevented because it will initiate the effervescent reaction.

ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM

1. The gastroretentive systems are advantageous for drugs absorbed through the stomach.
2. Irritation on the stomach wall caused by acidic substances like aspirin can be avoided by using floating drug delivery system.
3. Administration of floating dosage forms will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid and would be available for absorption in the small intestine after emptying of the stomach.
4. The gastroretentive systems are advantageous for drugs meant for local action in the stomach.
5. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

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.
3. The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
4. Some drugs present in the floating system causes irritation to gastric mucosa.

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS

1. Site-Specific Drug Delivery: These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine.
2. Absorption Enhancement: Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.
3. Sustained Drug Delivery: These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.
No potential approach for gastric retention.

Gastroretentive drug delivery to optimize the bioavailability and controlled delivery of many molecules that exhibit a gastroretentive property has emerged as a unique approach for gastric retention, a large number of companies are focusing toward commercializing this technique.

**CONCLUSION**

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Gastro-retentive floating drug delivery systems have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. The increasing sophistication of delivery technology will ensure the development of increase number of gastroretentive drug delivery to optimize the delivery of molecules that exhibit absorption window, low bioavailability and extensive first pass metabolism. FDDS promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique.

**REFERENCES**

3. Furqan Khan N, Mohamed

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**Table 1: Generally Manufactured Marketed Product**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Brand Name</th>
<th>Drug (Dose)</th>
<th>Company, Country</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Modapar®</td>
<td>Levodopa (100 mg), Benserazide (25 mg)</td>
<td>Roche Products, USA</td>
<td>Floating CR capsule</td>
</tr>
<tr>
<td>2</td>
<td>Valrelease®</td>
<td>Diazepam (15 mg)</td>
<td>Hoffmann- LaRoche, USA</td>
<td>Floating capsule</td>
</tr>
<tr>
<td>3</td>
<td>Liquid Gavis®</td>
<td>Al hydroxide (95 mg), Mg carbonate (358 mg)</td>
<td>Glaxo Smith Kline, India</td>
<td>Effervescent floating</td>
</tr>
<tr>
<td>4</td>
<td>Topalkan®</td>
<td>Al-Mg antacid</td>
<td>Pierre Fabre Drug, France</td>
<td>Liquid alginate preparation</td>
</tr>
<tr>
<td>5</td>
<td>Conviron</td>
<td>Ferrous sulphate</td>
<td>Ranbaxy, India</td>
<td>Colloidal gel forming FDDS</td>
</tr>
<tr>
<td>6</td>
<td>Cifran OD®</td>
<td>Ciprofloxacin (1 gm)</td>
<td>Ranbaxy, India</td>
<td>Gas generating Floating tablet</td>
</tr>
<tr>
<td>7</td>
<td>Cytotec®</td>
<td>Misoprostol (100 mcg/200mcg)</td>
<td>Pharmacia, USA</td>
<td>Bilayer floating capsule</td>
</tr>
<tr>
<td>8</td>
<td>Oflin OD®</td>
<td>Ofloxacin (400mg)</td>
<td>Ranbaxy, India</td>
<td>Gas generating Floating tablet</td>
</tr>
</tbody>
</table>

**List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>DOSAGE FORM</th>
<th>DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TABLETS</td>
<td>Chlorpheniramine maleate, Theophylline, Furosemide, Ciprofloxacin, Pentoxyfillin.</td>
</tr>
<tr>
<td>2</td>
<td>CAPSULES</td>
<td>Nicardipine, L-Dopa and benserazide, Chlordiazepoxide HCl, Furosemide</td>
</tr>
<tr>
<td>3</td>
<td>MICROSPHERES</td>
<td>Verapamil, Aspirin, griseofulvin, p-nitroaniline, Ketoprofen.</td>
</tr>
<tr>
<td>4</td>
<td>GRANULES</td>
<td>Indomethacin, Diclofenac sodium, Prednisolone.</td>
</tr>
<tr>
<td>5</td>
<td>FILMS</td>
<td>Films Drug delivery device, cinnarazine</td>
</tr>
<tr>
<td>6</td>
<td>POWDERS</td>
<td>Several basic drugs</td>
</tr>
</tbody>
</table>

**List of drugs used in manufacture of various effervescent formulations**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>POLYMER</th>
<th>EFFERVESEN T AGENT</th>
<th>DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>HPMC K4M</td>
<td>Sodium bicarbonate</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>2.</td>
<td>HPMCK100M, Carbopol</td>
<td>Sodium bicarbonate &amp; Citric Acid</td>
<td>Glipizide</td>
</tr>
<tr>
<td>3.</td>
<td>K15M</td>
<td>Sodium bicarbonate &amp; Citric Acid</td>
<td>Famotidine</td>
</tr>
<tr>
<td>4.</td>
<td>HPMC, Carbopol</td>
<td>Citric Acid</td>
<td>Zidovudine</td>
</tr>
<tr>
<td>5.</td>
<td>Poly Ethylene Oxide</td>
<td>Calcium carbonate</td>
<td>Propanol HCL</td>
</tr>
<tr>
<td>6.</td>
<td>Poloxamer 188</td>
<td>Sodium bicarbonate</td>
<td>Metoprolol Succinate</td>
</tr>
<tr>
<td>7.</td>
<td>HPMC</td>
<td>Sodium bicarbonate &amp; Citric Acid</td>
<td>Ilevofloxain</td>
</tr>
<tr>
<td>8.</td>
<td>HPMC K100, HPMC K15M, Carbopol 934</td>
<td>Sodium bicarbonate, Citric Acid</td>
<td>Amlodipine</td>
</tr>
<tr>
<td>9.</td>
<td>Poly Ethylene Oxide, HPMCK4M, Guar gum.</td>
<td>Sodium bicarbonate, Citric Acid</td>
<td>Acyclovir</td>
</tr>
</tbody>
</table>

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6. controlled drug delivery by n.k jain
18. Y.manusudhan rao, AV jithan. Advances in drug delivery vol-1
28. B. Rotthäuser,G. Kraus and P.C.


