CHAPTER II

FLOATING DRUG DELIVERY SYSTEMS: AN OVERVIEW

Oral delivery of the drug is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in the formulations. From immediate release to site-specific delivery, oral dosage form has really progressed. It is evident from the recent scientific and patented literature that an increased interest in novel dosage forms that are retained in the stomach for prolong and predictable period of time exist today in academic and industrial research groups. Various attempts have been made to develop gastro retentive delivery systems. For example floating, swelling, mucoadhesive, and high-density systems have been developed to increases gastric retention time of the dosage forms. These systems have more flexibility in design of dosage than conventional dosage form. Several new approaches have been developed recently to extend gastrointestinal transit time by prolonging residence time in drug delivery system in the GIT.

The design of oral control drug delivery systems (DDS) should be primarily aimed to achieve more predictable and increased bioavailability. Nowadays most of the pharmaceutical scientists are involved in developing the ideal DDS. This ideal system should have advantage of single dose for the whole duration of treatment and it should deliver the active drug directly at the specific site. Scientists have succeeded to develop a system and it encourages the scientists to develop control release systems. Control release implies the predictability and reproducibility to control the drug release, drug concentration in target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.
Under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substances. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract \(^4\), and the drugs that are less soluble or are degraded by the alkaline pH may benefit from the prolonged gastric retention \(^5,6\). In addition, for local and sustained drug delivery to the stomach and the proximal small intestine to treat certain conditions, prolonging gastric retention of therapeutic moiety may offer numerous advantages including improved bioavailability, therapeutic efficacy and possible reduction of the dose size.\(^7,8\).

**APPROACHES TO GASTRIC RETENTION**

Various approaches have been paused to increase the duration of oral dosage form in the stomach, including floating systems, swelling and expanding systems, modified shape systems, high density systems and other delayed gastric emptying devices (Magnetic systems, super porous biodegradable hydro-gel systems).

1. Hydrodynamically balanced systems (HBS) – incorporated buoyant materials enable the device to float.\(^9,10\)

2. Raft systems incorporate alginate gels – these have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating.\(^9,10\)

3. Swelling type of dosage form is such that after swelling; these products swell to the extent to prevent their exit from the stomach through the pylorus. As a result the dosage form retain in the stomach for a longer period of time. These systems may be referred to as “Plug type systems”, since they exhibit tendency to remain logged in the pyloric sphincters.\(^11\)
4. Bioadhesive or mucoadhesive systems are used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner. The approaches involve the use of bioadhesive polymers that can be adhere to the epithelial surface of the GIT. The proposed mechanism of bio-adhesion is the formation of hydrogen and electrostatic bonding at the mucus polymer boundary.

5. Modified shape systems are non-disintegrating geometric shapes molded from silastic elastomer or exuded from polyethylene blends and extended the GTT depending on the size, shape and flexural modulus of the drug delivery device.

6. High density formulations include coated pellets, and have density greater than that of the stomach content (1.004 gm/cm³). This is accomplishing by coating the drug with a heavy inert material such as barium sulphate, zinc oxide, titanium dioxide. This formulation of high-density pellet is based on assumption that heavy pellets might remain longer in the stomach, since they position in the lower part of the antrum.¹²,¹³

7. Another delayed gastric emptying approaches of interest include sham feeding of digestible polymers or fatty acid salts that charges the motility pattern, of the stomach to a fed stage thereby decreasing the gastric emptying rate and permitting considerable prolongation of the drug release.

**Floating Systems:**

Floating systems, first described by Davis in 1968, have bulk density lower than that of the gastric fluid, and thus remain buoyant in stomach for a prolonged period.
Effervescent Systems:

1. Volatile liquid containing systems:

The GRT of a drug delivery system can be sustained by incorporating an inflatatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of PVA, Polyethylene, etc. that gradually dissolves causing the inflatatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatatable systems from the stomach.\textsuperscript{14}

2. Gas-generating Systems:

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO\textsubscript{2}, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme.\textsuperscript{1, 17, 40} How the dosage form float is shown in the following figure (Figure- 2.1).\textsuperscript{15}

![Figure- 2.1: The Mechanism of Floating Systems\textsuperscript{19}](image-url)
Non-effervescent systems:

1. Colloidal gel barrier systems

Hydrodynamically balanced system (HBS™) was first designed by Sheth and Tossounian in 1975. Such systems contain drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids e.g. HEC, HPMC, NaCMC, Polysaccharides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage form.16

2. Microporous Compartment System

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

3. Alginate beads

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared
by dropping sodium alginate solution in to aqueous solution of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at -40°C for 24 hours, leading to the formation of porous system, which can maintain a floating force over 12 hours.14,16

4. Hollow microspheres

Hollow microspheres (microballoons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hours in vitro.16

FACTORS AFFECTING GASTRIC RETENTION

Density

Density of the dosage form should be less than the gastric contents (1.004gm/ml).

Size and Shape

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5
kilopond per square inch (KSI) are reported to have better GIT @ 90 to 100% retention at 24 hours compared with other shapes.¹

**Fed or Unfed State**

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (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.¹²,¹⁷

**Nature of the meal**

Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release.¹⁸

**Caloric Content**

GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats.

**Frequency of feed**

The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.¹⁶
Gender

Mean ambulatory GRT in meals (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

Age

Elderly people, especially those over 70 years have a significantly longer GRT.

Posture

GRT can vary between supine and upright ambulatory states of the patients

Concomitant drug administration

Anticholinergic like atropine and propentheline opiates like codeine and prokinetic agents like metoclopramide and cisapride.

FORMULATION OF FLOATING DOSAGE FORM

Following types of the ingredients can be incorporated in to HBS dosage form

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

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**Hydrocolloids**

Suitable hydrocolloids are synthetics, anionic or non ionic like hydrophilic gums, modified cellulose derivatives. e.g. Acacia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, MC, HPC, HEC, and Na CMC can be used. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid having pH 1.2. Although the bulk density of the formulation may initially be more than one, but when gastric fluid enter in the system, it should be hydrodynamically balanced to have a bulk density of less than one to assure buoyancy.

**Inert fatty materials**

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

**Release rate accelerant**

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

**Release rate retardant**

Insoluble substances such as dicalcium phosphate, talc, magnesium stearate decreased the solubility and hence retard the release of medicaments.
Buoyancy increasing agents

Materials like ethyl cellulose, which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. It may be adapted up to 80 % by weight.

Miscellaneous

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

IN VITRO AND IN VIVO EVALUATION OF FLOATING SYSTEMS

Physiological Parameters

Age, sex, posture, food, bioadhesion, health of subject and GIT condition

Galenic Parameter

Diametrical size, flexibility and density of matrices

Control Parameter

Floating time, specific gravity, dissolution, content uniformity, hardness and friability

Floating time

The test for buoyancy is usually performed in simulated gastric and intestinal fluid maintained at 37°C. The floating time is determined by using USP dissolution apparatus containing 900 ml of 0.1 N HCl as the testing medium maintained at 37°C. The time for which the dosage form floats is termed as the floating or floatation time.¹
**Specific Gravity**

Specific Gravity of the floating system can be determined by the displacement method using benzene as a displacing medium.\(^{17,21}\)

**Resultant weight**

The in vitro measuring apparatus has been conceived to determine the real floating capabilities of buoyant dosage forms as a function of time. It operates by force equivalent to the force \(F\) required to keep the object totally submerged in the fluid. This force determines the resultant weight of the object when immersed and may be used to quantify its floating or nonfloating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the Victoria sum of buoyancy \((F_{\text{buoy}})\) and gravity \((F_{\text{grav}})\) forces acting on the objects as shown in the equation.

\[
F = F_{\text{buoy}} - F_{\text{grav}}
\]

\[
F = d_f g V - d_s g V = (d_f - d_s) g V
\]

\[
F = (d_f - M/V) g V
\]

In which the \(F\) is total vertical force (resultant weight of the object), \(g\) is the acceleration due to gravity, \(d_f\) is the fluid density, \(d_s\) is the object density, \(M\) is the object mass and \(V\) is the volume of the object.\(^{20}\)

**Advantages of Floating Dosage Form**\(^{22}\)

1. The Principle of HBS may not be limited to any particular medicament or class of medicament.
2. The HBS formulations are not restricted to medicaments, which are absorbed from stomach, since it has been found that these are equally efficacious with medicament, which absorbed from the intestine.

3. Acidic substances like aspirin cause irritation on the stomach wall when come in to contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.

4. The HBS are advantageous for drugs absorbed through the stomach. e.g. Ferrous salts, antacids.

5. The efficacy of the medicaments administered utilizing the sustained release principle of HBS formulation has been found to be independent of the site of particular medicaments.

6. The HBS are advantageous for drugs meant for local action in the stomach. e.g.: Antacids.

7. Administration of prolonged release floating dosage forms, tablets 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 the floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

8. When there is vigorous intestinal movement and a shorted 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.
Limitations/Disadvantages

These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water.

1. Not suitable for drugs that have solubility or stability problem in GIT.

2. Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.

3. Drugs which are irritant to Gastric mucosa are also not desirable or suitable.¹

4. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.¹

5. The dosage form should be administered with a full glass of water (200-250 ml).³

6. These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract.

Application of Floating Drug Delivery System⁵

- Recent study indicated that the administration of Diltiazem floating tablets twice a day may be more effective compared to normal tablets in controlling the B.P. of hypertensive patients.

- Modular® HBS containing L-Dopa and Benzerazide, here the drug was absorbed over a period of 6-8 hours and maintained substantial plasma concentration for Parkinsonian patients. Cytotech® containing Misoprostol, a synthetic prostaglandin –EL analogue, for prevention of gastric ulcer caused by non-steroidal anti-inflammatory drugs (NSAIDS).
• As it provides high concentration of drug within gastric mucosa, it is used to eradicate *H. pylori* (a causative organism for chronic gastritis and peptic ulcers).

• 5-fluorouracil has been successfully evaluated in the patients with stomach neoplasm.

• Developing HBS dosage form for tacrin provide better delivery systems and reduced its GI side effects.

• Treatment of gastric and duodenal ulcer.

**Future Potential**

• Floating dosage form offers various future potential as evident from several recent publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying.

• Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability.

• Buoyant delivery system considered as a beneficial strategy for the treatment of gastric and duodenal cancers.

• The floating concept can also be utilized in the development of various anti-reflux formulations.

• Developing a controlled release system for the drugs, which are potential to treat the Parkinson’s disease.
• To explore the eradication of Helicobacter pylori by using the narrow spectrum antibodies.
Table 2.1: Commercial Gastroretentive Floating Formulations\textsuperscript{3, 23, 24}

<table>
<thead>
<tr>
<th>Name</th>
<th>Type and Drug</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madopar HBS (PropalHBS)</td>
<td>Floating capsule, Levodopa and benserazide</td>
<td>Floating CR capsules</td>
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<td>Valrelease\textsuperscript{34}</td>
<td>Floating capsule, Diazepam</td>
<td>Floating Capsules</td>
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<tr>
<td>Topalkan</td>
<td>Floating Antacid, aluminum and magnesium mixture</td>
<td>Effervescent floating liquid alginate preparation</td>
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<tr>
<td>Amalgate Float Coat\textsuperscript{35}</td>
<td>Floating antacid, Floating gel</td>
<td>Floating dosage form</td>
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<td>Conviron</td>
<td>Ferrous sulphate</td>
<td>Colloidal gel forming FDDS</td>
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<td>Cifran OD</td>
<td>Ciprofloxacin (1 gm)</td>
<td>Gas generating floating form</td>
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<tr>
<td>Cytotech</td>
<td>Misoprostol (100 mcg/200 mcg)</td>
<td>Bilayer floating capsule</td>
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<tr>
<td>Liquid Gaviscone</td>
<td>Mixture of alginate</td>
<td>Suppress gastro esophageal reflux and alleviate the heart burn</td>
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<tr>
<td>S. No.</td>
<td>DRUG</td>
<td>POLYMERS</td>
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</tr>
<tr>
<td>1.</td>
<td>Theophylline</td>
<td>Agar and Light mineral oil</td>
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<td>2.</td>
<td>Frusemide</td>
<td>HPMC, Lactose DC</td>
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<td>3.</td>
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<td>Carbopol 934 P</td>
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<td>Calcium alginate, PVA</td>
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<td>HPMC and Polyethylene Oxide</td>
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<td>8</td>
<td>Metronidazole</td>
<td>Cellulose Derivatives and Starch Derivatives</td>
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<td>Alginate and Amylose</td>
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<td>Pentoxiphylline</td>
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<td>Methoxylated Pectin (LMP), Sodium Alginate</td>
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<td>Furosemide</td>
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<td>Rosiglitazone Maleate</td>
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REFERENCES

1. Garima Chawla, Piyush Gupta, Vishal Koradia and Arvind, K. Bansal,


