FLOATING DRUG DELIVERY SYSTEM (FDDS): A NEW WAY FOR ORAL DRUG DELIVERY SYSTEM

Dr. S.D.Pande *
(HOD of pharmaceutics at Vidyabharati College of Pharmacy, Phone no- +919823172064, E mail- drsdpande@gmail.com)
Ku. Pranita V. Vaidya
(M Pharm pharmaceutics, Amravati University, Vidyabharati College of Pharmacy Amravati)
Ku Priyanka N.Gulhane
(M Pharm second year, Amravati University, Vidyabharati college of pharmacy Amravati)

Corresponding Address:
Vidyabharati college of pharmacy, C.K.Naidu, camp road, Amravati – 444601.

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Abstract
The recent scientific literature concluded that an increased interest in novel dosage forms which retained in stomach for prolong and predictable period of time has been shown. Various technological attempts have been made in research and development of rate controlled oral drug delivery systems to overcome short residence times in stomach using stomach specific floating in situ gel system. Several approaches are currently being used to prolong the GRT, including floating drug delivery systems (FDDS), also known as hydro dynamically balanced systems (HBS), swelling and expanding systems, high-density systems, and other delayed gastric emptying devices. Floating dosage form can be prepared as tablets, capsules by adding suitable ingredients as well as by adding gas generating agent. In this review various techniques used in floating dosage forms along with current & recent developments of stomach specific floating drug delivery system for gastro retention are discussed.

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Keywords: Gastric retention time, Gastro retentive systems; floating drug delivery system; Effervescent; non effervescent; floating in situ gel.

INTRODUCTION
The goal of any drug delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve promptly and then maintain a desired drug concentration. Recent development in technology has provided viable dosage alternatives that can be administered via different routes of administration. Various routes that are used include oral, topical, nasal, rectal, vaginal and ocular, etc. but out of these routes oral route of drug delivery is considered as the most favoured and practiced way of delivery, due to following reasons

- Ease of administration
- Ease of production
- Low cost

Drugs which get absorbed from stomach or show local effect should spend maximum time in stomach. This however, is found very difficult to occur. In case of conventional dosage forms.

Floating drug Delivery System
Floating drug delivery systems (FDDS) or hydro dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and 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. After release of drug, the residual system is emptied from the stomach. This results in an increased Gastric retention time and a better control of the fluctuations in plasma drug concentration. 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.
Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres.

**Basic anatomy of stomach and its physiology**

Anatomically the stomach is divided into 3 regions: The Fundus, The body, and the antrum (pylorus). The proximal part made up of fundus and body act as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. The opening nearer to esophagus is called as cardiac end characterized by pyloric spincter. Under fasting conditions the stomach is a collapsed bag with residual volume of 50 ml and contains a small amount of gastric fluid and air.

Basic structure of gastrointestinal tract and stomach as shown in figure. Mucosal lining is covered throughout the stomach under this layer specialized cells are present that secrete gastric juice into stomach.

About 2-3 litres of gastric juice secreted daily by specialized cells in mucosa.

It consist of:
- Water
- Gastric enzymes
- Mucus glycoprotein
- Intrinsic factor

**Gastric emptying and motility**

Gastric emptying occurs during fasting as well as fed states. The passage of drug from stomach to the small intestine is called gastric emptying. It is the rate limiting step for drug absorption because the major site for absorption in intestine. Generally rapid gastric emptying increase bioavailability of the drug. Faster onset requires for drugs that degrade in gastric environment. Delayed gastric emptying promotes dissolution of the drugs, which are poorly soluble drugs and for the drugs that is majorly absorbed from stomach or proximal part of the intestine.

The pattern of motility is however distinct in the two 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. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which are further divided into following 4 phases are:

1. Phase I (basal phase) It lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) It 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 It is a period of transition from phase III and phase I and last for 0 to 5 minutes.

**FACTORS AFFECTING FLOATING DRUG DELIVERY SYSTEM**

There are numerous factors that effects FDDS, some of the important factors are given below.

a. **Density**: Density of the dosage form should be less than the gastric contents (1.004gm/ml) and so remain buoyant in the stomach without affecting the gastric emptying rate for prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at desired rate from the system.

b. **Size and Shape**: Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased Gastric residence time compared to those with a diameter of
9.9 mm. The dosage form with a shape tetrahedron and ring shape devices with a flexural modulus of 48 and 22 kiloponds per square inch (KSI) are reported to have better GIT for 90 to 100 % retention at 24 hours compared with other shapes.

c. 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.

d. 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.

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

f. 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.

g. 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.

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

i. Posture: GRT can vary between supine and upright ambulatory states of the patients

j. Concomitant drug administration: Anticholinergic like atropine and propentheline opiates like codeine and prokinetic agents like metoclopramide and cisapride, affect the gastric emptying and hence gastric residence time of an oral dosage form.

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.

1) High density approach
These approach include coated pellets, 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. this formulation of high density pellet is based on assumption that heavy pellets might remain longer in the stomach, since they are position in lower part of antrum.

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 Hydro dynamically Balanced System (HBS).

Gas generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low density systems with immediate buoyancy have therefore been developed. They are made up of low density materials, entrapping oil or air. Most are multiple systems, and are also called Microballons because of low density core.
B. Multiple Unit Floating Dosage Systems
a) Non-effervescent Systems
b) Effervescent Systems (Gas-generating Systems)
c) Hollow Microspheres
C. Raft Forming Systems

A. Single Unit Floating Dosage Systems:
In single unit systems, such as capsules or tablets, effervescent substances are incorporated in the hydrophilic polymer and CO₂ bubbles are trapped in the swollen matrix. Eg; Bilayer system.

Single unit formulations are associated with problems such as sticking to one another or obstruction to gastrointestinal tract, which may result in local irritation. The main drawback of such systems is the “all or none” phenomenon. In such cases a danger of the dosage form passing into intestine when of house keeper waves are produced.

Multiple unit dosage forms have been designed to overcome this problem.

a) Effervescent Systems (Gas-generating Systems):
These buoyant systems utilised matrices prepared with swellable polymers like HPMC, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. The coating, which is insoluble but Permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach.

Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, Carbopol®, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

Talwar et al. prepared a once-daily formulation for oral administration of ciprofloxacin. The formulation was composed of 69.9% ciprofloxacin base, 0.34% sodium alginate, 1.03% xanthan gum, 13.7% sodium bicarbonate, and 12.1% cross-linked poly vinyl pyrrolidone. The cross linked PVP initially and the gel forming polymers later formed a hydrated gel matrix that entrapped the gas, causing the tablet to float and be retained in the stomach.

Ozdemir et al. prepared floating bilayer tablets with controlled release for furosemide. The low solubility of the drug could be enhanced by using the kneading method, preparing a solid dispersion with β-cyclodextrin mixed in a 1:1 ratio. One layer contained the polymers HPMC 4000, HPMC 100, and CMC (for the control of the drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid.

Radiographic studies on healthy male volunteers showed that floating tablets were retained in stomach for 6 hours and further blood analysis studies showed that bioavailability of these tablets was 1.8 times that of the conventional tablets. On measuring the volume of urine the peak diuretic effect seen in the conventional tablets was decreased and prolonged in the case of floating dosage form.

Penners et al. prepared an expandable tablet containing mixture of polyvinyl lactams and Polyacrylates that swell 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 on the gastric environment.

b) Non-effervescent Systems:
This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the ‘plug-type systems’ since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of 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.

Examples of this type of FDDS include,

- Colloidal gel barrier: Sheth and Tossounian first designated this hydro dynamically balanced system. These types of system contain drug with gel forming hydrocolloids which allow them to remain buoyant on the stomach content. This prolongs to GRT and maximizes the amount of drug at its absorption site in solution form for ready absorption. Suitable hydrocolloids are synthetics, anionic or non ionic like hydrophilic gumes, modified cellulose derivatives. E.g. Acacia, pectin, agar, algimates, gelatin, casein, bentonite, veegum, MC, HPC, HEC, and Na, CMC can be used. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid is having pH 1.2. Although the bulk density of the formulation may initially be more than one, but when gastric fluid is enter in the system.

- Alginate beads: Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence, time of 1 hour, and these
Floating beads gave a prolonged residence time of more than 5.5 hours.

Hollow microspheres\(^4\), Hollow microspheres (microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol; dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40 °C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours.

**B. Multiple Unit Floating Systems:**

Multiple unit floating systems lowers the probability of dose-dumping. It involves development of both non-effervescent and effervescent multiple unit systems. Much research has been focussed and the scientists are still exploring the field of hollow microspheres, capable of floating on the gastric fluid and having improved gastric retention properties.

Multiple unit floating system is subdivided into non-effervescent and effervescent system.

**a) Non-effervescent Systems**

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.

**b) Effervescent Systems (Gas-generating Systems):**

Ikura et al\(^5\) reported sustained release floating granules containing tetracycline hydrochloride. The granules are a mixture of drug granulates of two stages A and B, of which A contains 60 parts of HPMC, 40 parts of polyacrylic acid and 20 parts of drug and B contains 70 parts of sodium bicarbonate and 30 parts of tartaric acid. 60 parts by weight of granules of stage A and 30 parts by weight of granules of stage B are mixed along with a lubricant and filled into capsule. In dissolution media, the capsule shell dissolves and liberates the granules, which showed a floating time of more than 8 h and sustained drug release of 80% in about 6.5 h.

**Eg:** pepstain – floating minicapsules, Sustained release pills.

**c) Hollow Microspheres:**

Hollow microspheres are considered as one of the most promising buoyant systems, as they possess the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere. Polymers such as polycarbonate, Eudragit® S and cellulose acetate were used in the preparation of hollow microspheres.

Eg: AH and Sokar et al\(^6\) The research group of kawashima prepared hollow microspheres based on blends of Eudragit S and HPMC.

**C. Raft Forming Systems\(^7,18\):**

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, where in 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 carbon dioxide. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of Carbon dioxide 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. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus. A patent assigned to Reckitt and Colman Products Ltd., describes a raft forming formulation for the treatment of Helicobacter pylori (H. Pylori) infections in the GIT. The composition contained drug, alginic acid, sodium bicarbonate, calcium carbonate, mannitol and a sweetener. These ingredients were granulated, and citric acid was added to the granules. The formulation produces effervescence and aerates the raft formed, making it float.

Eg: Alginate raft forming floating system

Antacid raft forming floating system.

**Drugs employed in effervescent floating system\(^19,20,21\)**

<table>
<thead>
<tr>
<th><strong>DRUG</strong></th>
<th><strong>FORMULATION TYPE</strong></th>
<th><strong>EXCIPIENTS EMPLOYED</strong></th>
<th><strong>REFERENCES</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pepstain</td>
<td>Minicapsule</td>
<td>Sodium bicarbonate, lactose and HPMC</td>
<td>Umezawa et al</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Floating tablet</td>
<td>Sodium bicarbonate, HPMCK100.</td>
<td>Ozdemir et al</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Floating tablet</td>
<td>Sodium alginate, sodium bicarbonate</td>
<td>Talwar et al</td>
</tr>
<tr>
<td>Famotidine</td>
<td>Bilayer floating tablet</td>
<td>Tartarazine lactose, HPMC, sodium Bicarbonate.</td>
<td>Barhate et al</td>
</tr>
<tr>
<td>Ranitidine HCL</td>
<td>Bilayer tablet</td>
<td>HPMCK,M, carbapol 934, sodium bicarbonate, lactose.</td>
<td>P.Dinesh Kumar et al</td>
</tr>
</tbody>
</table>

**Drugs employed in non effervescent FDDS\(^22,23\)**

<table>
<thead>
<tr>
<th><strong>Drug</strong></th>
<th><strong>Formulation type</strong></th>
<th><strong>Excipient employed</strong></th>
<th><strong>References</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>Tablet</td>
<td>Sodium citrate, mineral oil</td>
<td>Gupta et al</td>
</tr>
<tr>
<td>Claritromycin, metronidazole, Tetracycline.</td>
<td>Triple layer tablet</td>
<td>HPMC, PEO</td>
<td>Vinay kumar et al</td>
</tr>
</tbody>
</table>
Prolongation of gastric retention time\textsuperscript{24,26}

Several approaches have recently been developed to extend gastrointestinal transit time by prolonging the residence time of drug delivery systems in stomach.

I. Hydro dynamically balanced intragastric delivery system.

The formulation of this device must comply with following criteria:

- It must have sufficient structure to form a cohesive gel barrier.
- It must maintain an overall specific gravity lower than that of gastric contents.
- It should dissolve slowly enough to serves as a drug reservoir.

II. Intragastric floating gastrointestinal drug delivery system

A gastrointestinal drug delivery can be made to float in the stomach by incorporating a floatation chamber, which may be vacumm or filled with air or harmless gas. In the Stomach the floatation chamber causes the gastrointestinal drug delivery system to float in gastric fluids. Fluids enter through apertures, dissolve the drug and carry the drug solutes out of drug delivery system for continuous transport to intestine for absorption.

III. Inflatable gastrointestinal drug delivery system

The residence time of drug delivery device in the stomach can also be sustained by incorporation of an inflatable chamber which contains a liquid, eg: ether that gasifies at body temperature to cause the chamber to inflate in stomach.

IV. Intragastric osmotically controlled drug delivery

The osmotic pressure controlled drug release mechanism discussed earlier can also be incorporated in the inflatable gastrointestinal delivery system to control the release of drug in stomach. It consists of two compartments.

- Drug – reservoir compartment
- Osmotically active compartment

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support the deflated drug delivery. The deflated drug delivery is excreted from stomach.

Advantages of FDDS \textsuperscript{27,28}

1. The Floating systems are advantageous for drugs meant for local action in the Stomach e.g. Antacids.
2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.
3. The Floating systems are advantageous for drugs absorbed through the stomach.
4. 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.
5. 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.
6. FDDS provides advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.
7. Certain types of drugs can benefit from using FDDS. These include:
   a) Drugs acting locally in the stomach.
   b) Drugs those are primarily absorbed in the stomach.
   c) Drugs those are poorly soluble at an alkaline pH
   d) Drugs with a narrow window of absorption.
   e) Drugs absorbed rapidly from the GI tract.
   f) Drugs those degrade in the colon

Disadvantages of FDDS\textsuperscript{29}

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. Some drugs present in the floating system causes irritation to gastric mucosa

Drug Candidates Suitable for FDDS

- Drugs that have narrow absorption window in GIT (e.g. L-DOPA, p amino benzoic acid, Furosemide, Riboflavin)\textsuperscript{30}
- Drugs those are locally active in the stomach \textsuperscript{31} (e.g. Misoprostol, Antacids)
- Drugs those are unstable in the intestinal or colonic environment (e.g. Captopril, RanitidineHCI, Metronidazole)
- Drugs that disturb normal colonic microbes (e.g. antibiotics used for the eradication of Helicobacter pylori, such as Tetracycline, Clarithromycin, Amoxicillin)
- Drugs that exhibit low solubility at high pH values (e.g. Diazepam, Chlor Diazepoxide, Verapamil)

<table>
<thead>
<tr>
<th>Sr No.</th>
<th>Brand Name</th>
<th>Drug</th>
<th>Company</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Modapar</td>
<td>Levodopa Benserzide</td>
<td>Roche products</td>
<td>Floating CR capules</td>
</tr>
<tr>
<td>2.</td>
<td>Vairelease</td>
<td>Diazepam</td>
<td>Hoffmann-Laroche</td>
<td>Floating capsules</td>
</tr>
<tr>
<td>3.</td>
<td>Liquid gavison</td>
<td>Al – mg antacid</td>
<td>Glaxo smith</td>
<td>Effervescent floating liquid alginate preparation</td>
</tr>
<tr>
<td>4.</td>
<td>Topalkan</td>
<td>Al-Mg Antacid</td>
<td>Pierre Fabre Drug</td>
<td>Floating liquid alginate preparation</td>
</tr>
<tr>
<td>5.</td>
<td>Cytotec</td>
<td>Misoprostol</td>
<td>Pharmacia</td>
<td>Bilayer floating capsule</td>
</tr>
<tr>
<td>6.</td>
<td>Conviron</td>
<td>Ferrous sulphate</td>
<td>Ranbaxy</td>
<td>Colloidal gel forming FDDS</td>
</tr>
</tbody>
</table>

Stomach specific floating in situ oral gel 35,36

In situ forming drug delivery systems are a revolution in oral drug delivery. These hydrogels are liquids at room temperature but undergo Gelation when in contact of body fluids or change in pH. These have characteristic property of temperature dependent and Cation induced gelation. In situ gel forming systems have been widely studied, for their capability of producing the sustained and controlled delivery. In recent few years, lot of work on development of in situ gelling formulation has been done. The system basically utilizes polymers which undergo transformation from solution to gel like consistency due to change in their physicochemical properties. In situ gel formation can be stimulated by change in temperature, change in pH, change in solvent medium, by radiation exposure or by combination of any of these gastro-retentive in situ gel forming system have provided a suitable way of providing the controlled drug delivery within stomach. Where an environment specific gel forming solution, on conversion to gel, floats on the surface of gastric fluids. (due to less density than gastric contents)

In this technique solution of low viscosity is used which on coming in contact of body fluids, undergo change in polymeric confirmation and a viscous gel of density lower than gastric fluid is produced. This low density gel formation not only provide the much desired gastro-retention to prolong contact time, but also produce the continuous and slow drug release.

Advantages

1. **Prolong gastric retention than conventional dosage form**
   - The system improves gastric retention time for drug in comparison to conventional dosage forms and further minimum effective concentration of drug remains maintained in systemic circulation for longer duration. The system ensures that whole drug delivery system remains in gastric region for longer duration of time.

2. **It prolongs dosing interval**
   - The system prolongs the dosing intervals and thus improves patient compliance. Presence of drug in solution form is the most essential requisite for a drug to get absorbed, but if the solubility of drug is poor then the time required for drug to get dissolve within stomach would be high and transit time becomes most stringent factor, which would in turn affect the absorption of drug. So dose of administration for such drugs should be kept at more frequent intervals in a single day.

3. **To reduce frequent dosing of drug**
   - Floating drug delivery systems provide a support to reduce the frequent dosing of such drug by producing a controlled delivery within stomach for longer duration.

4. **Used in treatment of gastrointestinal diseases**
   - The stomach specific drug delivery system spent more within stomach. It is a perfect way for treating the gastrointestinal diseases with better cure rate eg; Crohn’s disease. The floating in situ gelling system of clarithromycin was prepared using gellan as gelling polymer and calcium carbonate as floating agent for potentially treating gastric ulcers associated with helicobacter pylori.

5. **Site specific delivery**
   - Drugs which are subjected to produce local action can directly targeted to organ site. The stomach specific floating in situ gel of famotidine could be prepared using floating mechanism to increase the residence time of drug in stomach.

6. **Ease of Administration**
   - The gastro-retentive systems are similar in physical design to the conventional dosage forms like tablet, capsule, solution, suspension, which are easy to handle and administer. Oral route remains the prefer route of the administration of therapeutic agents because low cost of therapy and ease of administration leads to higher level of patient compliance.

7. **Patient compliance:**
   - Frequency of dose administration can be reduced remarkably, resulting in better patient compliance.

8. **Less adverse effect of drug**
   - As the drug remains in the stomach till the complete release frequency of adverse effect of drug decreases to greater extent. Such systems also provide higher concentration of drug released around gastric mucosa to efficiently treat gastric diseases like ulcer and gastritis.

Advantages of floating in situ gel forming system over gastro-retentive drug delivery System 37

1. In situ gel forms a low density viscous layer on the gastric contents and hence provides more effective surface area than a tablet, this leads to more drug release and the delivery of drug takes place via various popular routes like Oral, Nasal, Ophthalmic and Vaginal etc.

2. Floating obtained is faster than floating tablets; such systems offer the advantage of easy administration along with improved patient compliance. The low density gel not only provide the much desired gastro retention to prolong the contact time but also produce the continuous and slow drug release.

Disadvantages 38

1. In situ gel forming system is basically formulated in the form of solutions which are more susceptible to stability problems due to chemical degradation.

2. If such systems not stored properly than it may pose instability problems, due to change in pH of system on prolonged storage or on storing in inappropriate temperature.

3. The system requires high level of fluids.

Approaches involved in preparation of in situ gel 39,40,41

1. Based on producing physical changes.
   - This approach involves either swelling or diffusion phenomenon.
   - In swelling, polymer in the system absorbs water from the surrounding environment and swells to form viscous gel. In diffusion, solvent in which the drug and polymer is dissolved or dispersed, diffuse into the surrounding tissues causing the precipitation of polymer to form gel. Eg: N methyl pyrrolidone.

2. Based on producing chemical changes
   - Ionic cross linking: In presence of various ions present in the body fluids eg: Na+, K+, Ca2+, Fe+ ion sensitive
Poly saccharides eg; carrageenan, gellan gum, pectin, etc. undergo transition in phase due to the development of polymeric cross linking.

- Enzymatic cross linking: Enzymes present in the body fluids may also cause cross linking to form a polymer network and is considered, as most convenient method of gel formation.
- Photopolymerization: Exposure of tissues, in which such gel forming is injected, with microwave radiation, uv radiation, or electromagnetic radiation leads to gel formation within tissues.
- In situ formation depending on change in temperature:
  - Polymers such as polyacrylic acid and its derivatives undergo gel formation because of change in pH, due to presence of various ionizable groups in the chemical structure of polymer. A polymer with anionic group leads to increase in swelling with increase in pH, while polymer with cationic groups shows a decrease in swelling.
- Polymers used in floating drug delivery system
  - Use of polymeric material particularly of biodegradable polymers investigated collagen, gelatine.
  - The most of the commercial biodegradable polymers investigated for use in controlled drug delivery come under the class.
    - Lactides / glycolides
    - Polyalhydrides
    - Polycaprolactones
    - Polyoxyethylene
    - Polychloroacetics
    - Polynaphthoic acids

In spite of the advent of many synthetic biodegradable polymers, the use of natural polymers, the use of natural polymers to deliver drug looks to be an active area of research due to obvious reasons of compatibility, inexpensive and ready availability. Out of many natural polymers investigated collagen, gelatine.

### Natural polymers employed in floating drug delivery system

1. Sodium alginate: Sodium alginate is widely used polymer of natural origin. The solution of alginate in water form firm gel in presence of Di or trivalent ions (e.g., calcium and magnesium ions) sodium alginate is mostly used for preparation of gel forming solution, for the delivery of drug and proteins. Alginate salts are considered most favourable because of biodegradable and non toxic nature.
2. Pectin: Pectin undergoes gel formation in presence of divalent ion e.g.; calcium ion which causes cross linking of the galacturonic acid units (ionic cross linking) and also in presence of hydrogen ions.(pH dependent gelling)
3. Gellan gum: Gellan gum undergo gel formation due to change in temperature or presence of cations.eg; sodium ion, potassium ion.
4. Xyloglucan: It is a plant based polysaccharides obtained from the seeds of tamarind. Xyloglucan itself does not undergo gel formation but dilute solution partly degraded by galactosidase exhibit gelling properties on heating. Besides the use in oral drug delivery, it is also being used for ocular and rectal drug delivery.
5. Xanthan gum: Xanthan gum is a high molecular weight extracellular polysaccharide produced by pure culture of aerobic fermentation of carbohydrate with xanthomonas campestris bacteria. This gum develops a weak structure in water which creates high viscosity solution at low concentration. Xanthan gum has an excellent solubility and stability under acidic and alkaline conditions. It is extensively investigated as a possible polymeric material in diverse floating drug delivery technology.
6. Guar gum: Guar gum hydrates and swells in cold water forming viscous colloidal dispersion or sols. It is particularly insoluble in organic solvent. It is compatible with most other plant hydrocolloids such as tragacanth and incompatible with acetone, ethanol, tannin, strong acid and alkalies. The polymeric material has been studied as an inexpensive and flexible carrier for different floating dosage form.

<table>
<thead>
<tr>
<th>Polymers Employed FDDS</th>
<th>Synthetic</th>
<th>Natural</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC K4M</td>
<td>Sodium alginate</td>
<td></td>
</tr>
<tr>
<td>HPMC K 15M</td>
<td>Pectin</td>
<td></td>
</tr>
<tr>
<td>HPMC K100M</td>
<td>Pectin</td>
<td></td>
</tr>
<tr>
<td>Carbopol 934 p</td>
<td>Gelatin</td>
<td></td>
</tr>
<tr>
<td>Polyvinyl alcohol</td>
<td>Carragenan</td>
<td></td>
</tr>
<tr>
<td>Polymides</td>
<td>Guar gum</td>
<td></td>
</tr>
<tr>
<td>Polycarboxylic acid</td>
<td>Chitosan</td>
<td></td>
</tr>
<tr>
<td>Polymethyl methacrylic acid</td>
<td>Okra gum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gellan gum</td>
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</tbody>
</table>
Drug used in FDDS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation type</th>
<th>Excipients employed</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aceclofenac</td>
<td>Tablets</td>
<td>HPMC E, M, Eudragit and NaHCO₃</td>
<td>Ambati Brahma reddy et al., 2011</td>
</tr>
<tr>
<td>Cefpodoxime proxetil</td>
<td>Tablets</td>
<td>HPMCK4M, HPMCK15M, HPMCK100M, sodium bicarbonate, citric acid</td>
<td>Madhu soodan Sharma et al., 2011</td>
</tr>
<tr>
<td>Dipryidamole</td>
<td>Tablets</td>
<td>HPMCK4M, citric acid, sodium bicarbonate</td>
<td>A. senthil, thukkar hardik R., et al., 2011</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>Tablets</td>
<td>SodiumCMC.HPMCK4M, HPMCK15M, sodium bicarbonate</td>
<td>Gottumikkala Jayapal Reddy et al., 2011</td>
</tr>
<tr>
<td>Tizanidine HCl</td>
<td>Tablets</td>
<td>HPMCK4M, HPMCK15M, sodium bicarbonate</td>
<td>Adimoolam Senthil et al., 2011</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Tablets</td>
<td>HPMCK4M, HPMCK15M, HPMC E15</td>
<td>Ajaykumar patil et al., 2011</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>In situ gel</td>
<td>Guaran, sodium alginlate, calcium carbonate</td>
<td>Vinay wamorkar et al., 2011</td>
</tr>
<tr>
<td>Ranitidine HCl</td>
<td>In situ gel</td>
<td>Sodium alginlate, calcium carbonate</td>
<td>Patel R.P., et al., 2011</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>In situ gel</td>
<td>Gellan gum, calcium carbonate</td>
<td>Dipen R. Bhimangeth et al., 2011</td>
</tr>
<tr>
<td>Baclofen</td>
<td>In situ gel</td>
<td>Sodium alginlate, calcium carbonate</td>
<td>Rishad R. Jivami et al., 2010</td>
</tr>
<tr>
<td>Metformin HCl</td>
<td>Mucoadhesive microspheres</td>
<td>SodiumCMC.HPMC</td>
<td>Ram chand dhakar et al., 2010</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Mucoadhesive microspheres</td>
<td>Carbapal 934p</td>
<td>Patel jk et al., 2009</td>
</tr>
</tbody>
</table>

PATENTS FOR SOME FLOATING GASTRO-RETENTIVE DELIVERY SYSTEMS

<table>
<thead>
<tr>
<th>US patent No.</th>
<th>Patent title</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,443,843</td>
<td>Gastric-retention system for controlled drug release</td>
</tr>
<tr>
<td>5,232,704</td>
<td>Sustained-release, bilayer buoyant dosage form</td>
</tr>
<tr>
<td>5,169,638</td>
<td>Buoyant controlled-release powder formulation</td>
</tr>
<tr>
<td>4,814,179</td>
<td>Floating sustained-release therapeutic compositions</td>
</tr>
<tr>
<td>4,767,627</td>
<td>Drug delivery device that can be retained in the stomach for a controlled period of time</td>
</tr>
<tr>
<td>4,167,558</td>
<td>Novel sustained-release formulations</td>
</tr>
<tr>
<td>4,140,755</td>
<td>Sustained-release tablet formulations</td>
</tr>
<tr>
<td>4,126,672</td>
<td>Sustained-release pharmaceutical capsules</td>
</tr>
<tr>
<td>5013876 A1</td>
<td>Novel floating dosage form</td>
</tr>
</tbody>
</table>

Evaluation Parameters of FDDS

Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting gastric residence in vitro floating behavior show prolonged gastric residence in vivo. However, it has to be pointed out that good in vitro floating behavior alone is not sufficient proof for efficient gastric retention in vivo. The effects of the simultaneous presence of food and of the complex motility of the stomach are difficult to estimate. Obviously, only in vivo studies can provide definite proof that prolonged gastric residence is obtained.

1) Measurement of buoyancy capabilities of the FDDS
The floating behavior can be evaluated with resultant weight measurements. The experiment can be carried out in two different media, deionised water and simulated meal, in order to monitor possible difference.

2) Floating time and dissolution:
The test for floating time measurement is usually performed in simulated gastric fluid or 0.1 mole-lit-1 HCl maintained at 37°C. It is determined by using USP dissolution apparatus containing 900 ml of 0.1 mole-lit-1 HCl as the dissolution medium at 37°C. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time.

Apparatus 2 (Paddle): The problem of adherence of the tablet to the shaft of the paddle was observed with the USP dissolution apparatus. The tablet did not stick to the agitating device in the proposed dissolution method. The drug release followed zero-order kinetics in the proposed method. Similarity of dissolution curves was observed between the USP method and the proposed method at 10% difference level (f²=57). The proposed test may show good in vitro-in vivo correlation since an attempt is made to mimic the in vivo conditions such as gastric volume, gastric emptying, and gastric acid secretion rate.

3) Drug release:
Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution.

4) Content uniformity, Hardness, Friability (Tablets)

5) Drug loading, drug entrapment efficiency, particle size analysis, surface characterization (for floating microspheres and beads): Drug loading is assessed by crushing accurately weighed sample of beads or microspheres in a mortar and added to the appropriate dissolution medium which is then centrifuged, filtered and analyzed by various analytical methods like spectrophotometry. The percentage drug loading is calculated by dividing the amount of drug in the sample by the weight of total beads or microspheres. 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 cross-sectional morphology (surface characterization) is done by scanning electron microscope (SEM).

6) X-Ray/Gamma Scintigraphy:
X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form now a day. It helps to locate dosage form in the GIT and 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-rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GI tract.

Pharmacokinetic studies:
Pharmacokinetic studies are the integral part of the in vivo studies and several works has been on that. Sawicki et al. 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 t_{max} and AUC (0-infinity) values for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets. (t_{max} value 1.21 h, and AUC value 224.22 ng.ml-1h). No much difference was found between the Cmax values of both the formulations, suggesting the improved bioavailability of the floating pellets compared to the conventional tablets. An improvement in bioavailability has also been observed with piroxicam in hollow microspheres administered in rabbits. The microspheres showed about 1.4 times more bioavailability, and the elimination half-life was increased by about three times than the free drug.

APPLICATION OF FLOATING DRUG DELIVERY SYSTEM

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follow:

i) Sustained Drug Delivery: FDDS can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of residence time encountered with an oral CR formulation hence can be overcome with these systems. 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.

Eg. Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours).

ii) 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.

Eg. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. Area under Curve obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets.

iii) 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.

Eg. A significantly increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%)

Recent Advances in Stomach Specific Floating Dosage Forms

M. Jaimini et al. prepared a gastroretentive drug delivery system of Famotidine, by employing two different grades of methocel K100 and methocel K15M by effervescent technique; these grades of methocel were evaluated for their gel forming properties. Sodium bicarbonate was incorporated as a gas-generating agent. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, in vitro buoyancy and dissolution studies. The effect of citric acid on drug release profile and floating properties was investigated. The tablet swelled radially and axially during in vitro buoyancy studies. It was observed that the tablet remained buoyant for 6-10 hours. Decrease in the citric acid level increased the floating lag time but tablets floated for longer duration.

Anand Patel et al. developed a novel gastro retentive controlled release drug delivery system of Verapamil HCl in an effort to increase the gastric retention time of the dosage form and to control drug release. Hydroxypropyl methyl cellulose (HPMC), Carbopol, and Xanthan gum were incorporated for gel forming properties. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. In vitro drug release studies were performed, and drug release kinetics was evaluated by the linear regression method. Optimized intragastric floating tablet showed no significant change in physical appearance, drug content, total buoyancy time, or in vitro dissolution pattern after storage at 40°C/75% relative humidity for 3months.

Ninan Ma et al. developed a type of multi-unit floating alginate (Alg) microspheres by the ionotropic gelation method with calcium carbonate (CaCO3) being used as gas-forming agent. Attempts were made to enhance the drug encapsulation efficiency and delay the drug release by adding chitosan (Cs) into the gelation medium and by coating with Eudragit, respectively. The gastrointestinal transit of optimized floating microspheres was compared with that of the non floating system manufactured from identical material by gamma-scintigraphy in healthy human volunteers. It was found that the drug encapsulation efficiency of Cs–Alg microspheres was much higher than that of the Ca–Alg microspheres, and coating the microspheres with Eudragit RS could extend the drug release significantly.

Strübing et al. investigated the mechanism of floating and drug release behaviour of poly (vinyl acetate)-based floating tablets with membrane controlled drug delivery. Propranolol HCl containing tablets with Kollidon® SR as an excipient for direct compression and different Kollidicoat® SR 30 D/Kollidicoat® IR coats varying from 10 to 20 mg polymer/cm2 were investigated regarding drug. Coated tablets with 10 mg polymer/cm2 SR/IR, 8.5:1.5 coat exhibited the shortest lag times prior to drug release.
and floating onset, the fastest increase in and highest maximum values of floating strength. The drug release was delayed efficiently within a time interval of 24 h by showing linear drug release characteristics.

Jang et al has prepared a gastroretentive drug delivery system of DA-6034, a new synthetic flavonoid derivative, for the treatment of gastritis was developed by using effervescent floating matrix system (EFMS). The therapeutic limitations of DA-6034 caused by its low solubility in acidic conditions were overcome by using the EFMS. The release of DA-6034 from tablets in acidic media was significantly improved by using EFMS, which is attributed to the effect of the solubilizers and the alkalizing agent such as sodium bicarbonate used as gas generating agent. DA-6034 EFMS tablets showed enhanced gastro protective effects in gastric ulcer-induced beagle dogs, indicating the therapeutic potential of EFMS tablets for the treatment of gastritis.

Patel R.P. et al studied Formulation, evaluation and optimization of stomach specific in situ gel of clarithromycin and metronidazole benzoate by using sodium alginate as polymer and calcium carbonate was used as a cross linking agent. This study reports that oral administration of aqueous solutions containing sodium alginate results in formation of In situ gel such formulations are homogenous liquid when administered orally and become gel at contact site. Stability study of check point batch after three month showed no change in in-vitro drug release profile, % assay and evaluation parameters. It was concluded that by adopting a systemic formulation approach, an optimum point could be reached in the shortest time with minimum efforts.

R. Rajalakshmi et al studied Development and Evaluation of a Novel Floating In situ Gelling System of Levofloxacin Hemihydrate by using varying concentrations of gellan gum and sodium alginate in deionized water containing sodium citrate, a stomach specific in situ gel of levofloxacin hemihydrate could be prepared using floating mechanism to increase the residence time of the drug in stomach and thereby increasing the absorption. This study shows the feasibility of in vitro gel forming from aqueous solution of sodium alginate and gellan gum containing Ca2+ ions in a complex form. It is concluded that levofloxacin hemihydrate could be targeted to stomach and be released slowly over a period of time.

Ganapati Rohith et al studied Floating drug delivery of a locally acting H2-antagonist An approach using an in situ gelling liquid formulation by using sodium alginate and calcium carbonate. By observing various evaluation parameters for the studied formulations, it can be stated that incorporation of sodium citrate and calcium chloride in the formulation is required to control and sustained the drug release from in situ gel.

Dasharath M. Patel et al studied Formulation and Evaluation of Floating Oral In Situ Gelling System of Amoxicillin by using sodium alginate, calcium chloride, sodium citrate, HPMC K100, and sodium bicarbonate from which concluded that the floating in situ gel system of amoxicillin with increase gastric residence time can be formulated using sodium alginate as a gelling polymer and HPMC K100 as a thickening agent the prepared formulation can provide a site specific delivery of amoxicillin with zero order release kinetics.

CONCLUSION

The currently available polymer-mediated non effervescent and effervescent floating drug delivery system, designed on the basis of delayed gastric emptying and buoyancy Principles, appear to be a very much effective approach in controlled drug delivery. The floating drug delivery system, become an additional advantage for drugs that are absorbed primarily in upper part of GIT. floating drug delivery system play an important role of buoyancy in enhancing gastric retention time of drug and more than that formulation of an ideal dosage form to be given locally to eradicate H. pylori responsible for gastric ulcers worldwide.

By understanding the floating and gel forming behaviour of polymers we can look forward to improve the gastric retention. Similarly, good stability and better drug release than other conventional dosage forms make such system more reliable.

REFERENCES

1. Lovensih Bhawriaj, Pramod Kumar Sharma; A short review on gastro retentive formulations for stomach specific drug delivery: special emphasis on floating in situ gel systems; African journal of basic and applied sciences 3 (2011) 300-312.


43. J. V. Patel, J. R. Chavda; Floating in situ gel based on alginate as carrier for stomach specific drug delivery of Famotidine; Int. journal of pharmaceutical sciences and nanotechnology; (2010) 1092-1104.
Ram Chand Dhakar, Sheo Dutta Maurya; Design and Evaluation of SRM microspheres of metformin hydrochloride, Pharmacie globale, 1, 1-5.


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