AN OVERVIEW ON FLOATING DRUG DELIVERY SYSTEMS

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ABSTRACT

Several approaches are currently utilized in the prolongation of the gastric residence times, including floating drug delivery systems, swelling and expanding systems, polymeric bio-adhesive systems, modified-shape systems, high-density systems and other delayed gastric emptying devices. The present review addresses briefly about the floating drug delivery systems. FDDS are of particular interest for drugs that are locally active and have narrow absorption window in stomach or upper small intestine, unstable in the intestinal or colonic environment, and exhibit low solubility at high pH values. This review article is in pursuit of giving detailed information on the pharmaceutical basis of their design, classification, advantages, in vitro and in vivo evaluation parameters, and the future potential of FDDS.

Key words: Floating drug delivery systems, Effervescent, Non-effervescent.

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INTRODUCTION

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems [1]. Floating systems or hydrodynamically 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 [2]. 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. 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 Gastrointestinal Tract Physiology

Basically stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions (Desai, 1984). Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours (Vantrappen et al., 1979). This is called the inter-digestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington (Wilson and Washington-ton, 1989).

- Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
- Phase II (pre-burst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- 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.
Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate (Desai and Bolton, 1993). Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.

**Floating drug delivery systems**

Floating drug delivery systems (FDDS) or hydrodynamically 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 GRT 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.

**Drug Candidates Suitable for FDDS**

- Drugs that have narrow absorption window in GIT (e.g. L-DOPA, paminobenzoic acid, furosemide, riboflavin) [3].
- Drugs those are locally active in the stomach (e.g. misprostol, antacids) [4].
- Drugs those are unstable in the intestinal or colonic environment (e.g. captopril, ranitidine HCl, metronidazole) [5].
- Drugs that disturb normal colonic microbes (e.g. antibiotics used for the eradication of Helicobacter pylori, such as tetracycline, clarithromycin, amoxicillin) [6].
- Drugs that exhibit low solubility at high pH values (e.g. diazepam, chlordiazepoxide, verapamil) [7].
Table 1: List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems

<table>
<thead>
<tr>
<th>Sl. no</th>
<th>Dosage form</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tablets</td>
<td>Chlophiramine maleate, Theophylline, Furosemide, Ciprofloxacin, Captopril, Acetylsalicylic acid, Nimodipine, Amoxycillin trihydrate, Verapamil HCl, Isosorbid di nitrate, Isosorbid mononitrate, Acetaminophen, Ampicillin, Cinnarazine, Dilitiazem, Florouracil, Prednisolone,</td>
</tr>
<tr>
<td>2</td>
<td>Capsules</td>
<td>Nicardipine, Chlordiazepoxide HCl, Furosemide, Misoprostal, Diazepam, Propranolol, Urodeoxycholic acid.</td>
</tr>
<tr>
<td>3</td>
<td>Microspheres</td>
<td>Aspirin, Griseofulvin, p-nitroanilline, Ketoprofen, Iboprufen, Terfenadine.</td>
</tr>
<tr>
<td>4</td>
<td>Granules</td>
<td>Indomethacin, Diclofenac sodium, Prednisolone</td>
</tr>
<tr>
<td>5</td>
<td>Films</td>
<td>Cinnarazine</td>
</tr>
<tr>
<td>6</td>
<td>Powders</td>
<td>Several basic drugs</td>
</tr>
</tbody>
</table>

Classification of Floating Drug Delivery System: [8-10]

A. Single Unit Floating Dosage Systems
   a. Effervescent system
      ✓ Gas generating system
      ✓ Volatile liquid containing system
   b. Non-effervescent System:
      ✓ Colloidal gel barrier system.
      ✓ Alginate beds.
      ✓ Hollow microspheres / Microballons.
      ✓ Intragastric Floating Drug Delivery Device / Microporous compartment system

B. Multiple Unit Floating Dosage Systems
   ✓ Non-effervescent Systems
   ✓ Effervescent Systems (Gas-generating Systems)
   ✓ Hollow Microspheres

C. Raft Forming Systems

A. EFFERVESCENT SYSTEMS

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the

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acidic gastric contents, CO₂ is liberate and gas entrapped in swollen hydrocolloids which provides buoyancy to the dosage forms.

**a. Volatile liquid containing systems**

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid (like ether, cyclopentane), that gasifies at body temperature to cause the inflationation of the chamber in the stomach. The device may also consist of a bio-erodible plug made up of PVA, Polyethylene, etc. that gradually dissolves and causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

**b. Gas-generating Systems**

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO₂, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme. How the dosage form float.

**B. NON-EFFERVESCENT SYSTEMS**

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allow sustained release of drug through the gelatinous mass.

**a. Colloidal gel barrier systems** [8]

Hydrodynamically balance system (HBSTM) was first design by Sheth and Tossounian in 1975. Such systems contains 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 these dosage forms.

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b. Alginate beads
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°C for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours.

c. Hollow microspheres [9]
Hollow microspheres (microballons), 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 microballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hours in vitro.

d. Intragastric / Microporous compartment system [10]
The system composed of a drug reservoir encapsulated in a microporous compartment having pores on top and bottom surfaces. The peripheral walls of the reservoir compartment were completely sealed to prevent any physical contact of the undissolved drug with walls of the stomach [11,12]. Novel levodopa gastro retentive dosage form based on unfolding polymeric membranes which combines extended dimensions with high rigidity. It was folded into a large size gelatine capsules. In vitro studies showed that unfolded form reached within 15 minutes after administration and it was confirmed in vivo in beagle dogs. The unfolded form was maintained for at least 2 hours.

B. Multiple Unit Floating Systems
In spite of extensive research and development in the area of HBS and other floating tablets, these systems suffer from an important drawback of high variability of gastrointestinal transit time, when orally administered, because of their all-or-nothing gastric emptying nature. In order to overcome the above problem, multiple unit floating systems were developed, which reduce the inter-subject variability in absorption and lower the probability of dose-dumping [17].
a) Non-effervescent Systems

No much report was found in the literature on non-effervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported. Chitosan hydrates and floats in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio. The most commonly used excipient in non-effervescent floating drug delivery system are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polyacrylate, polymethacrylate and polycarbonate. After oral administration these dosage form swells in contact with gastric fluid and attains a bulk density of < 1 (Fig-1).

![Diagram of Gastroretentive drug delivery system (low density and high density systems)](image)

**Fig. 1: Diagram of Gastroretentive drug delivery system (low density and high density systems)**

b) Effervescent Systems (Gas-generating Systems)

There are reports of 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. Floating minicapsules of pepstatin having a diameter of 0.1-0.2 mm has been reported by Umezawa. The system floats because of the CO2 release in gastric fluid and the pepstatin resides in the stomach for prolonged period. Alginates have received much attention in the development of multiple unit systems. Alginates are non-toxic, biodegradable linear copolymers composed of L-glucuronic and L-
mannuronic acid residues. A new multiple type of floating dosage system had developed having a pill in the core, composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sub layers to avoid direct contact between the 2 agents. These sub layers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37°C, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO2 was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/ml.

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. The general techniques involved in their preparation include simple solvent evaporation and solvent diffusion and evaporation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers such as polycarbonate, Eudragit Sand cellulose acetate were used in the preparation of hollow microspheres, and the drug release can be modulated by optimizing the polymer quantity and the polymer-plasticizer ratio. The microspheres showed a drug payload of more than 50%, and the amount of drug incorporated is found to influence the particle size distribution and drug release. The larger proportion of bigger particles was seen at high drug loading, which can be attributed to the increased viscosity of the dispersed phase.

C. Raft Forming Systems

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of to make the system less dense and float on the gastric fluids.

MECHANISM OF FLOATING SYSTEMS

There are various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-
generating systems and swelling or expanding systems, muco-adhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Among these, the floating dosage forms have been most commonly used. While the system is floating on the gastric contents (given in the Figure 3, 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. 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.

The object floats better if F is on the higher positive side (Figure 2). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragas-tric buoyancy capability variations.

\[ F = F_{buoyancy} - F_{gravity} = (D_f - D_s) \cdot g \cdot v \]

Where,
- \( F \) = total vertical force
- \( D_f \) = fluid density
- \( D_s \) = object density
- \( v \) = volume and \( g \) = acceleration due to gravity.

**Fig. 2: Different mechanisms of floating systems**

**FACTORS AFFECTING FLOATING DRUG DELIVERY SYSTEM**

- **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 for 90 to 100 % retention at 24 hours compared with other shapes [13].

- **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 [14].

- **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.

**ADVANTAGES OF FDDS**

- Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.
- FDDS are advantageous for drugs meant for local action in the stomach eg: Antacids.
- FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhoea to keep the drug in floating condition in stomach to get a relatively better response.
- Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.
- The FDDS are advantageous for drugs absorbed through the stomach eg: Ferrous salts, Antacids.
- Drugs with considerably short half life can be administered in this manner to get an appreciable therapeutic activity.
- Enhancement of the bioavailability for drugs which can metabolized in the upper GIT. [15,16].
DIS-ADVANTAGES OF FDDS

✓ Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.

✓ Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.

✓ One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float therein and work efficiently.

✓ These systems also require the presence of food to delay their gastric emptying.

✓ Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.

✓ High variability in gastric emptying time due to its all (or) non-emptying process.

✓ Patients should not be dosed with floating forms just before going to bed [19,20].

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS

Enhanced Bioavailability
The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

Sustained Drug Delivery
Oral CR formulations are encountered with problems such as gastric residence time in the GIT. These problems can be overcome with the HBS systems which can remain in the stomach for long periods and have a bulk density <1 as a result of which they can float on the gastric contents. These systems are relatively larger in size and passing from the pyloric opening is prohibited.

Site-Specific Drug Delivery Systems
These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug.
This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency. Eg: Furosemide and Riboflavin.

**Absorption Enhancement**

Drugs which are having poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

**Minimized Adverse Activity at the Colon**

Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This Pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism’s resistance.

**Reduced Fluctuations of Drug Concentration**

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index [21,22].

**CONCLUSION**

Recently Gastro-retentive floating drug delivery systems have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. Many drugs have been formulated as floating drug delivery systems with an objective of sustained release and restricting the region of drug release to stomach. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. The currently available polymer-mediated non effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be a very much effective approach to the modulation of controlled oral drug delivery. Floating drug delivery system can provide sufficient gastric retention which may help to provide sustained release dosage form with enhanced absorption. Number of commercial product and the most
important criteria which has to be looked into for the productions of a floating drug delivery system is that the density of the dosage form should be less than that of gastric fluid. And hence, it can be concluded that these dosage forms serve the best in the treatment of diseases related to the GIT and for extracting a prolonged action from a drug with a short half life. Finally, this article gives an overview of parameters affecting gastric emptying in humans as well as on the main concepts used to design pharmaceutical dosages form with prolonged gastric retention time.

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