“FLOATING DRUG DELIVERY SYSTEM (FDDS): A REVIEW”
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ABSTRACT
Floating drug delivery system (FDDS) can retain the dosage form in the gastric region for several hrs. Designing the Floating drug delivery system for prolong gastric retention helps in improving bioavailability and improve solubility of the drug that are less soluble in a high pH environment. These are recent technological and scientific research has been devoted to the development of rate controlled drug delivery system to overcome physiological adversities such as unpredictable gastric emptying times and gastric residence time. FDDS are of particular interest of 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 FDDS in specific region of the GIT offers numerous advantages, specially the drugs having narrow absorption window in GIT, primary absorption in the stomach, stability problem in the intestine, poor solubility at alkaline pH, local activity in stomach. This review article is giving detailed information on the pharmaceutical basis of their design, classification, advantages, in vitro and in vivo evaluation parameter and future potential of FDDS. The present review deals with the concept, mechanism, recent innovations and applications of floating drug delivery system.

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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\(^1\). Controlled-release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period; enhancement of activity of duration for short half-life drugs; elimination of side effects; reducing frequency of dosing and wastage of drugs; optimized therapy and better patient compliances\(^2\,^3\).

The successful development of oral controlled drug delivery systems requires an understanding of the three aspects of the system, namely.

1. The physiochemical characteristics of the drug.
2. Anatomy and physiology of GIT and Characteristics of Dosage forms\(^1\)

Good fundamental understanding of the anatomic and physiological characteristics of the human GIT is required to modulate the gastrointestinal transit time of a drug through FDDS for maximal gastrointestinal absorption of drugs and site-specific delivery\(^2\). Gastro retentive system can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines\(^1\).

Basic physiology of gastrointestinal tract
Anatomically the stomach is divided in to three regions: Fundus, Body and Antrum(pylorus). The proximal part made of fundus and body acts as a reservoir for undigested materials, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions (Figure 1). Gastric emptying occurs in both the fasting and fed states. During the fasting state an inter digestive series of electrical events take place which cycle both through stomach and intestine every 2-3 hrs which is called as inter digestive myoelectric cycle or migrating myoelectric cycle which is further divided in to four phases After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state which is also termed as digestive motility pattern\(^3\).
Gastrointestinal retention

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. To successfully modulate the gastrointestinal transit time of a drug delivery system through floating drug delivery system (FDDS) for maximal gastrointestinal absorption of drugs and site-specific delivery, one needs to have a good fundamental understanding of the anatomic and physiological characteristics of the human GIT.

Stomach anatomy

The main function of the stomach is to process and transport food. It serves as a short-term storage reservoir, allowing a rather large meal to be consumed quickly. Substantial enzymatic digestion is initiated in stomach, particularly of proteins. 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 myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases.

1. Phase 1-(Basic phase)-last from 30-60 minutes with rare contractions.
2. Phase 2-(Preburst phase)-last for 20-40 minutes with intermittent action potential and contractions.
3. Phase 3-(Burst phase)-last for 10-20 minutes which includes intense and regular contractions for short period also known as housekeeper wave.
4. Phase 4—last for 0-5 minutes and occurs between phase 3 and phase 1 of 2 consecutive cycles (Period of transition)³.

![Motility pattern in GIT](image)

**Fig. 2: Motility pattern in GIT**

**FACTORS AFFECTING GASTRIC RESIDENCE TIME OF FDDS**

a) **Formulation factors**

**Size of tablets**

Retention of floating dosage forms in stomach depends on the size of tablets. Small tablets are emptied from the stomach during the digestive phase, but large ones are expelled during the housekeeping waves⁵.

**Density of tablets**

Density is the main factor affecting the gastric residence time of dosage form. A buoyant dosage form having a density less than that of the gastric fluids floats, since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. A density of less than 1.0g/ml i.e. less than that of gastric contents has been reported. However, the floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyancy capabilities⁷.

**Shape of tablets**

The shape of dosage form is one of the factors that affect its gastric residence time. Six shapes (ring tetrahedron, cloverleaf, string, pellet, and disk) were screened *in vivo* for their gastric retention potential. The tetrahedron (each leg 2cm long) rings (3.6 cm in diameter) exhibited nearly 100% retention at 24 hr⁷.
Viscosity grade of polymer
Drug release and floating properties of FDDS are greatly affected by viscosity of polymers and their interaction. Low viscosity polymers (e.g., HPMC K100 LV) were found to be more beneficial than high viscosity polymers (e.g., HPMC K4M) in improving floating properties. In addition, a decrease in the release rate was observed with an increase in polymer viscosity.

b) Idiosyncratic factors
Gender
Women have slower gastric emptying time than do men. 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
Low gastric emptying time is observed in elderly than do in younger subjects. Intrasubject and intersubject variations also are observed in gastric and intestinal transit time. Elderly people, especially those over 70 years have a significantly longer GRT.

Posture
i) Upright position
An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size. Floating dosage forms show prolonged and more reproducible GRTs while the conventional dosage form sink to the lower part of the distal stomach from where they are expelled through the pylorus by antral peristaltic movements.

ii) Supine position
This position offers no reliable protection against early and erratic emptying. In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. On moving distally, these units may be swept away by the peristaltic movements that propel the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects.

Concomitant intake of drugs
Drugs such as prokinetic agents (e.g., metoclopramide and cisapride), anti Cholinergics (e.g., atropine or propantheline), opiates (e.g., codeine) may affect the performance of FDDS. The coadministration of GI-motility decreasing drugs can increase gastric emptying time.
Feeding regimen

Gastric residence time increases in the presence of food, leading to increased drug dissolution of the dosage form at the most favorable site of absorption. A GRT of 4-10 h has been reported after a meal of fats and proteins.

SUITABLE DRUGS FOR GASTRO RETENTION

Sustained release in the stomach is useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, from where absorption occurs and contact time is limited. Appropriate candidates for controlled release gastroretentive dosage forms are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.

1. Drugs that have narrow absorption window in gastrointestinal tract (GIT), e.g., riboflavin, para amino benzoic acid, furosemide and levodopa.
2. Basically absorbed from stomach and upper part of GIT, e.g., chlordiazepoxide and cinnarazine.
3. Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.
4. Locally active in the stomach, e.g., antacids and misoprostol.
5. Drugs that are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl and metronidazole.
6. Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide and verapamil HCl.

APPROACHES TO GASTRORETENTION

Several techniques are reported in the literature to increase the gastric retention of drugs.

1) High density systems

These systems, which have a density of ~3g/cm³, are retained in the rugae of stomach and capable of withstanding its peristaltic movements.

The only major drawback with these systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and achieve required density of 2.4-2.8g/cm³. Diluents such as barium sulphate (density= 4.9), zinc oxide, titanium oxide, and iron powder must be used to manufacture such high-density formulation.

2) Swelling and expanding systems

These systems are also called as “Plug type system”, since they exhibit tendency to remain logged in the pyloric sphincters. These polymeric matrices remain in the gastric cavity for several hours even in fed state. By selection of polymer with the proper molecular weight and swelling
properties controlled and sustained drug release can be achieved. The extensive swelling of these polymers is a result of the presence of physical-chemical cross links in the hydrophilic polymer network. On the other hand, a low degree of cross linking results in extensive swelling followed by the rapid dissolution of polymer.

3) Incorporating delaying excipients
Another delayed gastric emptying approach of interest include feeding of digestible polymers or fatty acid salts that changes the motility pattern, of the stomach to a fed stage thereby decreasing the gastric emptying rate and permitting considerable prolongation of the drug release. Prolongation of GRT of drug delivery system consists of incorporating delaying excipients like trietanolamine myristate in a delivery system.

4) Modified systems
Systems with non disintegrating geometric shape molded from silastic elastomers or extruded from polyethylene blends, which extend the GRT depending on size, shape and flexural modules of drug delivery device.

5) Mucoadhesive & bioadhesive systems
Bioadhesive drug delivery systems are used to localize a delivery device within the lumen to enhance the drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc.

6) Floating systems
Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so 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

**CLASSIFICATION OF FDDS BASED ON MECHANISM OF BUOYANCY**

A) Single unit
   - Noneffervescent systems
   - Effervescent systems or gas generating systems

B) Multiple unit
   - Noneffervescent systems
C) Raft forming systems

ADVANTAGES OF FLOATING DOSAGE FORM

(1) These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide.

(2) The fluctuations in plasma drug concentration 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.

(3) The efficacy of the medicaments administered utilizing the sustained release principle of floating formulation has been found to be independent of the site of particular medicaments.

(4) Complete absorption of the drug from the floating dosage form is expected even at the alkaline pH of the intestine. The dissolution of the drug in gastric fluid occurs and then the dissolved drug is available for absorption in the small intestine after emptying of the stomach contents.

(5) Poor absorption is expected when there is vigorous intestinal movement and a shorted transit time as might occur in certain type of diarrhea. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

(6) 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.

LIMITATIONS OF FLOATING DRUG DELIVERY SYSTEMS

(1) A high level of fluid in the stomach is required for drug delivery to float and work efficiently.

(2) Drugs which have stability and solubility problems in GIT are not suitable candidates for these types of systems.

(3) Drugs such as nifedipine, which undergoes first pass metabolism may not be desirable for the preparation of these types of systems.

(4) Drugs which are irritant to Gastric mucosa are also not desirable.

(5) The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems\textsuperscript{14}. 

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IN VITRO AND IN VIVO EVALUATION PARAMETERS OF STOMACH SPECIFIC 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. Although, in vitro floating behavior alone is not sufficient proof for efficient gastric retention so in vivo studies can provide definite proof that prolonged gastric residence is obtained.

1) Hardness, friability, assay, content uniformity (Tablets)

These tests are performed as per described in specified monographs.

2) Floating lag time and total floating time determination

The time between the introduction of the tablet into the medium and its rise to upper one third of the dissolution vessel is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time.

3) Drug release

The test for in vitro drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37°C. Dissolution tests are performed using the USP dissolution apparatus.

4) Drug loading, drug entrapment efficiency, particle size analysis, surface characterization, micromeritics studies and percentage yield (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.

5) Resultant weight determination.

Bulk density and floating duration have been the main parameters to describe the adequacy of a dosage form’s buoyancy Although single density determination does not predict the floating force evolution of the dosage form because the dry material of it is made progressively reacts or interacts with in the gastric fluid to release its drug contents.

6) Weight gain and water uptake (WU)

Weight gain or water uptake can be studied by considering the swelling behavior of Floating dosage form.

7) XRay/ Gamma scintigraphy

For in vivo studies, X-Ray/Gamma Scintigraphy is the main evaluation parameter for floating dosage form.
8) Pharmacokinetic studies
Pharmacokinetic studies include AUC (Area under Curve), Cmax, and time to reach maximum plasma concentration (Tmax) were estimated using a computer. Statistical analyses were performed using a Student t test with p, 0.05 as the minimal level of significance16.

9) Specific Gravity
Displacement method is used to determine the specific gravity of floating system using benzene as a displacing medium19,20.

Commercially available floating products

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug</th>
<th>Dosage form</th>
<th>Polymers used</th>
<th>Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glumetza</td>
<td>Metformin Hcl</td>
<td>Tablet</td>
<td>HPMC</td>
<td>Depomed</td>
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<tr>
<td>Cifran O.D</td>
<td>Ciprofloxacin</td>
<td>Tablet</td>
<td>Xanthan gum and sodiumalginate</td>
<td>Ranbaxy</td>
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<tr>
<td>Liquid Gavison</td>
<td>Mixture of Alginates</td>
<td>Liquid</td>
<td>Alginates</td>
<td>Glaxo Smith Kline</td>
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<tr>
<td>Madopar HBS</td>
<td>Levodopa and Benserazide</td>
<td>Capsule</td>
<td>HPMC</td>
<td>Roche</td>
</tr>
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FUTURE POTENTIAL

FDDS approach may be used for various potential active agents with narrow absorption window, e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines), and antidepressant which are absorbed from very specific regions of GI tract and whose development has been halted due to the lack of appropriate pharmaceutical technologies. In addition, by continual supplying the drug to its most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropoetin, vasopressin, insulin, low molecular weight heparin, and LHRH. Some of the unresolved critical issues related to the rational development of FDDS include, the quantitative efficiency of floating delivery systems in the fasted and fed states and the correlation between prolonged GRT and SR/PK characteristics. However, we are as close as we have ever been to see a greater transition of gastric retention devices from developmental level to the manufacturing and commercial level.

References:


15. Desai S. A Novel Floating Controlled Release Drug Delivery System Based on a Dried Gel Matrix Network [master’s thesis], Jamaica, N. Y: St John’s University; 1984.