FLOATING DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT
This is the novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the gastrointestinal tract is to control the gastric residence time, using gastroretentive dosage forms that will provide us with new and therapeutic options. From the formulation and technological point of view, the floating drug delivery system is considerably easy and rational. The discussion of FDDS extends with in-vivo, in-vitro techniques, the floating and swelling characteristics of several excipients and more relevant modified dissolution method. This work focuses on to the current technological developments with pharmaceutical application of FDDS.

Keywords: Floating drug delivery system, GIT, Caloric content, Gastroretention, Bioadhesive system, Absorption enhancement.

INTRODUCTION
Oral ingestion is the most convenient and commonly used method of drug delivery. More than 50% of drug delivery systems available in the market are oral drug delivery systems. These systems have the obvious advantages of ease of administration and patient acceptance. (1)

An ideal drug delivery system that will possess two main properties¹¹
1. It will be a single dose for the whole duration of treatment
2. It will deliver the active drug directly at the site of action.
Such ideal systems are not available usually. Thus scientists try to develop systems that can be as close to an ideal system as possible. This has stimulated the development of systems such as topical delivery systems and bioadhesive systems. Attempt to develop a single-dose therapy for the whole duration of treatment has focused attention on controlled- or sustained release drug delivery systems.\cite{1} Sustained release drug delivery systems describe a drug delivery system with delayed therapeutic action and sustained duration of therapeutic effect. Controlled release implies a predictability and reproducibility in the drug release kinetics. They are primarily used to ensure patient compliance and to improve efficacy of drugs. Increased safety and decreased side effects of drugs help in achieving these objects. Such systems are mainly useful for drugs with narrow therapeutic window where minimum fluctuations in plasma levels are desired.\cite{2} These systems have more flexibility in dosage design than the conventional drug delivery systems. There are many disadvantages of these systems such as longer time to achieve therapeutic blood levels, more variation in bioavailability, enhanced first-pass effect, and dose dumping. These systems are usually more expensive than conventional systems.\cite{1} In spite of their disadvantages, research is continued in this area, as there is much scope to further improve currently available systems. The recent scientific and patent literature shows increased interest in academics and industrial research groups regarding the novel dosage forms that can be retained in the stomach for prolonged and predictable period of time. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the GI tract is to control the gastric residence time (GRT), using gastroretentive dosage forms (GRDFs).\cite{2} It designed on the basis of one of several approaches like, floating dosage form (formulating low density dosage form that remain buoyant above gastric fluid), high-density dosage forms, and bioadhesive dosage form

**GASTRORETENTION**

1. A rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamic profiles is to retain the drug reservoir above its absorption area i.e. in the stomach (gastroretention) and to release drug in a controlled manner.\cite{3} The gastroretentive dosage form resides in the stomach for longer period of time than conventional dosage forms. Gastroretentive systems can remain in gastric region for several hours and hence significantly prolong the gastric retention improves bioavailability, reduces drug waste. \cite{3}Gastroretention is important for drugs that are degraded in intestine due to alkaline pH(1)

2. It is also important for drugs that should act locally in the stomach like antacids(2)
3. Drugs that are erratically absorbed due to variable gastric emptying time.\[^1\]

4. Gastroretention is particularly useful for the treatment of peptic ulcers caused by *H. pylori* infections.

5. If the drugs are poorly soluble in intestine due to alkaline pH, gastric retention may increase. Solubility before they are emptied, resulting in improved bioavailability.\[^4\]

### ADVANTAGES OF GASTRORETENTIVE DELIVERY SYSTEM

1. Gastroretentive systems are advantageous in improving gastrointestinal absorption of drugs with narrow absorption windows.\[^1\]

2. Such systems are useful for drugs that are best absorbed in the stomach. e.g. albuterol.\[^1\]

3. Gastroretention maintains the constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. e.g. beta lactum antibiotics (penicillins)\[^4\]

4. Retention of drug delivery systems in the stomach prolonges overall gastrointestinal transit time thereby increasing bioavailability of system intended for once-a-day administration e.g. Ofloxacin.\[^1\]

### LIMITATIONS OF GASTRORETENTIVE DELIVERY SYSTEMS

1. Gastroretentive systems cannot be used in the case of drugs like aspirin and other nonsteroidal anti-inflammatory drugs that induce gastric lesions\[^5\]

2. Drugs that are unstable in strong acidic environment of stomach, we cannot use gastroretentive system.\[^5\]

### BASIC GASTROINTESTINAL TRACT PHYSIOLOGY

Anatomically the stomach is divided into 3 regions:

1. fundus,
2. body, and
3. antrum (pylorus).

The proximal part made of fundus and body acts 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 action.\[^1\]

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 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.\cite{1}

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) 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 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.\cite{1}

Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complications that of short gastric residence time and unpredictable gastric emptying rate. (Fig.2)\cite{2}

![Fig. 1: REGIONS OF STOMACH](image-url)
1. PARTICLE SIZE
To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm.

2. TYPE OF & CALORIC CONTENT
It does not make any difference whether the meal has high protein, fat, or carbohydrate content as long as the caloric content is the same. Increase in caloric value slows down gastric emptying time. If we take liquids in larger amount, in fasted conditions, faster the emptying time & if take in fed condition, emptying time can be increased. If we take solids, in fasted condition, solids emptied quickly & in fed condition, emptying time can be significantly increased.

3. VOLUME
The resting volume of stomach is 25 to 50 ml. Volume of liquid administered affect gastric emptying time. When volume is large, the emptying is faster. When volume is large, the emptying is faster.
4. BIOLOGICAL FACTORS
In case of elderly persons, gastric emptying is slowed down. Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates.

5. SIZE OF DOSAGE FORM
The effect of size of floating and nonfloating dosage forms on gastric emptying. Dosage form having a diameter of more than 7.5 mm show better gastric residence time compared with one having 9.9 mm.

6. DENSITY OF DOSAGE FORM
A buoyant dosage form having a density of less than that of the gastric fluids floats (approximately less than 1). Since it is away from the pyloric sphincter the dosage unit is retained in the stomach for prolonged time.

DIFFERENT TECHNIQUES OF GASTRORETENTION\textsuperscript{[6]}
1. Floating systems
2. Swelling & expanding systems
3. Bioadhesive systems
4. High density systems

FLOATING DRUG DELIVERY SYSTEM\textsuperscript{[7]}
Floating Drug Delivery System (FDDS) is one of the techniques of Gastroretention\textsuperscript{[7]}. The concept of FDDS was first described in the literature as early as 1968, when Davis disclosed a method for overcoming the difficulty experienced by some person of choking while swallowing medicinal pills. Floating Drug Delivery System offer numerous advantages over other gastric retention systems. These have a bulk density lower than gastric fluids & thus remain buoyant in stomach without affecting gastric emptying rate for prolonged period of time. While system is floating on gastric contents, drug is released slowly at desired rate from stomach. (Fig. II)
LIMITATIONS OF FDDS\textsuperscript{[8]}

1. One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach for the drug delivery dosage form to float therein and to work efficiently.
2. Floating systems are not feasible for those drugs that have solubility or stability problem in gastric fluids and for drugs those are irritant to the gastric mucosa.
3. Gastric emptying of floating dosage forms in supine subjects may occur at becomes highly dependent on the diametric size. Therefore, patients cannot be dosed with floating dosage forms just before going to bed.

APPROACHES TO DESIGN FDDS\textsuperscript{[9]}

1. SINGLE–UNIT DOSAGE FORM
2. MULTIPLE-UNIT DOSAGE FORM

1. SINGLE-UNIT DOSAGE FORM

The globular shells apparently having lower density than that of gastric fluid can be used as a carrier for drug for its controlled release. In coated shells popcorn, poprice, and polystyrol
have been exploited as drug carriers. Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture. The polymer of choice can be either ethylcellulose or hydroxypropyl cellulose depending on the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration. Fluid- filled floating chamber type of dosage forms includes incorporation of a gas-filled floatation chamber into a microporous component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastrointestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine.

**DISADVANTAGES OF SINGLE-UNIT DOSAGE FORM**
The single-unit dosage forms are sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation It also experiences “all or none” pattern.

**MULTIPLE-UNIT DOSAGE FORM**
The purpose of designing Multiple-unit dosage form may be to distribute uniformly the drug content within gastric content, gradually lasting effects & reduced variability in absorption with lower probability of dose dumping. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate. Spherical polymeric microsponges, also referred to as “microballoons,” have been prepared. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability. In Carbon dioxide–generating multiple-unit oral formulations several devices with features that extend, unfold, or are inflated by carbon dioxide generated in the devices after administration have been described in the recent patent literature. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to 18 mm in their expanded state is exceeded.
CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM (FDDS)[9]

Based on mechanism of buoyancy, two distinctly different technologies has been utilized in the development of FDDS,

1. EFFERVESCENT FLOATING DOSAGE FORM
2. NON-EFFERVESCENT FLOATING DOSAGE FORMS

EFFERVESCENT FLOATING DOSAGE FORMS[9]

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g., sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO₂ is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. [9]

NON-EFFERVESCENT FLOATING DOSAGE FORM[9]

Non-effervescent FDDS are based on mechanisms of swelling of polymer or bioadhesion to mucosal layer in gastrointestinal tract. The most commonly used excipients in these dosage forms are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonates, polyacrylate, polymethacrylate, such as chitosan and carbopol. One of the approaches to formation of such floating dosage forms involves intimate mixing of drug with gel forming hydrocolloids, which swell in contact with gastric fluid after oral administration and maintain a relative integrity of shape and bulk density of less than unity within the outer gelatinous barrier. The air trapped by swollen polymer confers buoyancy to these reservoirs for sustained drug release since through gelatinous barrier. In addition, the gel structure acts as the reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier.

FORMULATION ASPECTS[10]

1. Selection criteria for Drug Candidate for FDDS

The drugs that would benefit from gastric retention are,

1. CNS drugs (for Parkinson disease, epilepsy, Alzheimer and migraine)
2. Anti-viral products (for HIV, herpes and hepatitis) and certain antibiotics
3. Anti-hypertension drugs
4. Anti-diabetic agents for Type 2 diabetes
5. Drugs for local treatment of GI infections, and gastric enzyme replacement.
2. Excipients and polymers used in FDDS

Mostly used polymers in FDDS are,
1. Hydroxypropyl methylcellulose (HPMC)
2. Sodium carboxymethylcellulose (CMC Na)
3. Hydroxypropyl cellulose (HPC)
4. Polycarbophil
5. Sodium alginate etc.

Mostly used excipients in FDDS are,

- **For Effervescent dosage forms**
  1. Sodium carbonate
  2. Sodium bicarbonate
  3. Tartaric acid
  4. Citric acid

- **For Non-Effervescent dosage forms**
  1. Swellable cellulose
  2. Polysaccharides
  3. Polycarbonates
  4. Polyacrylaes

**EVALUATION OF POLYMERS**\(^1\)

The excipients used in FDDS are evaluated for their,
1. **Floating characteristics** (Resultant Weight Force i.e. FRW)
2. **Swelling characteristics** (Gravimetric method)

The test media used for evaluation of polymers are,
1. **Deionised water** (air free)
2. **Simulated meal medium** (S.M.M.)

The details of excipient evaluation are given in the reference no.

**EVALUATION OF FLOATING DOSAGE FORM**\(^1\)

The evaluation of floating dosage forms is done in vivo and in vitro.

The various parameters that need to be evaluated include,
1. Floating Lag Time (FLT)
2. Total Floating Time (TFT)
3. Dissolution profiles
4. Specific gravity
5. Content uniformity
6. Hardness
7. Friability (in case of solid dosage forms)

The floating Lag Time (FLT) is the time taken by the tablet to emerge on the surface of dissolution medium and the Total Floating Time (TFT) is the time for which tablet constantly float on the surface of medium. In the case of multiparticulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, and mechanical properties are also performed. Gamma scintigraphy is non-invasive method used to follow gastrointestinal transit of solid dosage forms particularly non-disintegrating single-unit and multiple-unit sustained release forms.

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS\textsuperscript{[11,12]}

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 follows.

SUSTAINED DRUG DELIVERY SYSTEM

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric 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.

Recently 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).
Similarly a comparative study between the Madopar HBS and Madopar standard formulation was done and it was shown that the drug was released up to 8 hours in vitro in the former case and the release was essentially complete in less than 30 minutes in the latter case.

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, e.g., riboflavin and furosemide. 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. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets. A bilayer-floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin E1 used as a protectant of gastric ulcers caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, desired therapeutic levels could be achieved and drug waste could be reduced.

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.

DRUGS FORMULATED AS SINGLE AND MULTIPLE UNIT FORMS OF FLOATING DRUG DELIVERY SYSTEMS

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<tr>
<th>TABLETS</th>
<th>Chlorpheniramine maleate</th>
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<tr>
<td></td>
<td>Furosemide</td>
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<td>Ciprofloxacin</td>
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<td>Captopril</td>
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<td>Amoxycillin trihydrate</td>
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<td>Ibuprofen</td>
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<td>GRANULES</td>
<td>Diclofenac sodium</td>
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<td>Indomethacin</td>
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### MARKETED PREPARATION OF FLOATING DRUG DELIVERY SYSTEM

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<th>PRODUCT</th>
<th>ACTIVE INGREDIENTS</th>
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<tr>
<td>Madopar</td>
<td>Levodopa and Benserzide</td>
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<tr>
<td>Valrelease</td>
<td>Diazepam</td>
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<tr>
<td>Topalkan</td>
<td>Aluminium magnesium antacid</td>
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<tr>
<td>Almagate flatcoat</td>
<td>Antacid</td>
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<tr>
<td>Liquid gavison</td>
<td>Alginate acid and sodium bicarbonate</td>
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### CONCLUSION

Oral ingestion is the most convenient and commonly used method of drug delivery. Patients best accept conventional dosage forms but there are some limitations of these dosage forms like frequent dosing, increase chances of missing dose of drug etc. So these limitations focused attention on controlled- and sustained release dosage forms.

Gastroretention is one of the techniques for sustained-release. The Floating Drug Delivery System (FDSS) is the best technique to achieve gastroretention. FDSS have low bulk density than gastric fluids and thus remain buoyant in stomach. A perfect system, which will be retained in the stomach for longer time, has not yet been developed but some formulations show more bioavailability than the existing. The FDSS are useful for drugs with slow and incomplete intestinal absorption. Although there are some difficulties in manufacturing of FDSS, large numbers of companies are focusing towards commercializing this technique. FDSS those is novel approach by which one can achieve better drug action by eliminating problems related with GIT.

### REFERENCES


