“A REVIEW ON GASTRIC FLOATING DRUG DELIVERY SYSTEMS”

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ABSTRACT
Floating system or dynamically controlled systems are low density systems that have sufficiently buoyancy to float over the gastric contents and buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. This system of drug delivery was studied with special focus on the principle mechanism of floatation to achieve gastric retention. For the drugs that gets absorbed in the upper parts of GIT has advantages to formulate as oral sustained release gastro-retentive dosage form. Gastric emptying rate plays important role to develop the dynamically controlled systems. The recent developments of FDDS are approaches to minimize the variability that increase the retention time of drug delivery system for more than 12 hours. This review also includes the summary of various modern in-vitro techniques that shows the proper performance, advantages and applications of floating systems that compiles with the standard limits. Thus FDDS seems to be the promising delivery systems for control release of drugs.

KEYWORDS
Floating Drug Delivery Systems, Gastro retention time, Hydro dynamically balanced systems and Buoyancy lag time.

INTRODUCTION
Oral route is the most oldest and convient route for the administration of therapeutic agents because of low cost of therapy and ease of administration leads to higher level of patient compliance1. Effective oral drug of delivery may depend upon the factors such as gastric emptying process, GI transit time, drug release from the dosage form and site of absorption2. Gastro retentive drugs can float in the gastric fluid or juice for several hours and hence prolongs the gastric residence time of drugs3. Furthermore, the relatively short gastric emptying time in humans is normally averages 2-3
hours. Through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduce efficacy of the administered dose. Floating systems or dynamically controlled systems are low-density systems that have sufficiently buoyancy to float over the contents of gastric and remain floating in the stomach without affecting the gastric transit time for a longer period. Difficulties are faced like in designing sustained release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to concise the dosage form in the desired area of the gastrointestinal tract. The relatively brief gastric emptying time (GET) in humans which normally averages 2-3 hours through the major absorption zone, i.e, stomach and upper part of intestine can alter drug release from the floating tablets to reduced efficacy of the therapeutic dose.

Different methods are used presently to prolong of the gastric residence times (GRT), including FDDS, Low density systems, Raft systems incorporating alginate gels, Bio adhesive or Mucoadhesive system, High density systems, Super porous hydro gels and magnetic systems. This review gives a briefly idea about the FDDS that it is one of the most promising methodologies in gastro retentive drug formulations. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hallow microspheres. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation.

**Basic Gastrointestinal Tract Physiology**

Anatomically the stomach is divided into 3 regions: Fundus, Body and Antrum. The fundus and body of stomach serves as a reservoir for undigested material, whereas the antrum is the main site for mixing and act as a pump for gastric emptying. The pattern of movement of gastric content is however distinct in the two states. The digestive series of electrical events take place during the fasting state, which regulates both through stomach and intestine every 2 to 3 hours and called as inter digestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases as described below as shown in Figure No.1.

**Phase-I (Basal phase)**

Lasts from 40 to 60 minutes (occurs in time between meals).

**Phase-II (Pre burst phase)**

Lasts for 40 to 60 minutes with inter-mitten action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

**Phase-III (Brust 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 housekepper wave.

**Phase-IV**

Lasts for 0 to 5 minutes and occurs between phase III and I of 2 consecutive cycles.

**Mechanism of Floating Drug Delivery System (FDDS)**

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 floating on the surface of the meal. To measure the floating force kinetics, a novel apparatus is required to maintain the submerged object that measures the force equivalent to F (as a function of time). The dosage form floats better if F is on positive side as shown in fig. This apparatus helps in optimizing FDDS with respect to stability and durability of floating time produced in order to prevent or minimize the drawbacks of unforeseeable intragastric buoyancy capability variations.

\[
F = F_{\text{buoyancy}} - F_{\text{gravity}} = (DF - Ds) \frac{g}{v} \quad (1)
\]

Where,

- \( F \) = Total vertical force,
- \( DF \) = Fluid density,
- \( Ds \) = Object density,
- \( v \) = Volume and
- \( g \) = Acceleration due to gravity.
Approaches to Floating Drug Delivery (FDDS)
Various types of systems have been developed to increase the gastro-retentive time of dosage forms by employing range of concepts.
FDDS have been classified on the basis of principle of gastric retention.

**Floating drug delivery systems (FDDS)**
Systems having low density and floats over the gastric contents.

**Bioadhesive systems**
They bind with stomach mucosa and hence, enable the localized retention of the system.

**Swelling and expanding systems**
Such systems absorb water and hence, enlarged size.

**High density systems**
They remain in the stomach for longer period of time, by sedimenting to the folds of stomach.

**Advantage of FDDS**
1. Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.
2. FDDS are advantageous for drugs which are formulated for local action in the stomach e.g: Aluminum hydroxide gel.
3. FDDS dosage forms are useful in case of vigorous intestinal movement and in diarrhea to keep the drug in floating condition in gastric fluid to get a relatively better response.
4. Drug like aspirin which are acidic in nature causes irritation on the stomach wall when come in contact with it therefore; FDDS formulations will be useful for the administration of such drug and other similar drugs.

**Disadvantage of FDDS**
1. FDDS are not suitable for those drugs that have solubility or stability problems in gastric fluids.
2. Drugs such as Nifedipine, which is well absorbed throughout GIT and undergo significant first pass metabolism, may not be suitable for FDDS.
3. Floating systems a sufficiently high level of fluids in the stomach, so that the drug dosage form float there and work efficiently.
4. These systems also require the presence of food to delay their gastric emptying.

**Classification of FDDS**

<table>
<thead>
<tr>
<th>Effervescent FDDS</th>
<th>Non-Effervescent FDDS</th>
<th>Raft forming system</th>
</tr>
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<tbody>
<tr>
<td>Gas generating system.</td>
<td>Colloidal gel barrier system.</td>
<td>Microscopic compartment system.</td>
</tr>
<tr>
<td>Volatile liquid containing system.</td>
<td>Floating microsphere.</td>
<td>Alginate floating beads.</td>
</tr>
</tbody>
</table>

**Effervescent Floating Dosage Forms**
These are the matrix types of systems which consists of gas generating system and volatile liquid containing system and are prepared by use of swellable materials like methylcellulose, HPMC and chitosan based polymers as well as various effervescent compounds like sodium carbonate, calcium carbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents liberation of CO₂ takes place and gets entrapped in to the swollen hydrocolloids which provides buoyancy to the dosage forms such as Famotidine, Amlodipine besylate.

**Non-Effervescent Floating Dosage Forms**
These dosage forms use a gel forming or swellable cellulose type of hydrocolloids, and other different types of matrix forming polymers like polycarbonates, polymethacrylate and polystyrene. The formulation is prepared by mixing the drug and the gel-forming hydrocolloid which after oral administration swells when it comes in contact with gastric fluid. The floating properties of dosage form is achieved due to the air entrapment into the swollen gel like structure which acts as a reservoir and allows release of drugs in sustained manner through the gelatinous mass. (e.g., Famotidine, Levodopa)
Drugs Suitable for FDDS
1. Drugs those are locally active in the stomach e.g. misoprostol, antacids etc.
2. Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-DOPA, para aminobenzoic acid, furosemide, riboflavin etc.
3. Drugs those are unstable in the basic pH or colonic environment e.g. captopril, ranitidine HCl.
4. Drugs that alters normal colonic microbes e.g. antibiotics against Helicobacter pylori.
5. Drugs that exhibit poor solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.

Drugs Unsuitable for FDDS
1. Drugs that have very limited acid solubility e.g. phenytoin etc.
2. Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
3. Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.28.

Polymer and other Ingredients used for the preparations of Floating Drugs

Polymers
The following polymers used to preparations of floating drugs:- HPMC K4M, Calcium alginate, Eudragit S100, Eudragit RL, Eudragit RS, Propylene foam, Ethyl cellulose, Poly methyl methacrylate, Methocel K4M, Polyethylene oxide, Cyclodextrin, different grades of HPMC CMC, PEG, Polycarbonate, Sodium alginate, Eudragit S, HPMC, Metolose S.M. 100, PVP, PVA, HPCH, Polyox, HPMC K4, Acrylic polymer E4M and Carbopol.

Inert fatty materials (5 - 75%) 
Edible inert fatty materials having a specific gravity of less than one can be used to decrease the solubility property of dosage form and hence increase floating time. E.g. Beeswax, Fatty acids, Long chain fatty alcohols.

Effervescent agents
Sodium bicarbonate, Tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate), CG (Citroglycine), Citric acid

Release rate accelerants (5 - 60%) 
Eg. Lactose, Mannitol.
Release rate retardants (5 - 60%) 
Eg. Dicalcium phosphate, Talc, Magnesium stearate
Buoyancy increasing agents (upto 80%) 
Eg. Ethyl cellulose
Low density material
Polypropylene foam powder (Accurel MP 1000).

LIST OF DRUGS EXPLORED FOR VARIOUS FLOATING DOSAGE FORMS

Microspheres Tablets / Pills
Chlorpheniramine maleate, Aspirin, Griseofulvin, Terfenadine, Acetaminophen, P- Nitroaniline, Acetylsalicylic acid, Ibuprofen, Amoxycillin trihydrate, Tranilast, Atenolol, Ampicillin, , Theophylline, Captopril, Isosorbide dinitrate.

Films
P-Aminobenzoic acid, Doxylamine succinate, Cinnarizine, Prednisolone, Quinidine, Gluconate.

Granules
Cinnarizine, Diclofenac sodium, Diltiazem, Indomethacin, Fluorouracil, Prednisolone, Isosorbide mononitrate, Isosorbide dinitrate.

Powders
Riboflavin phosphate, Sotalol, Theophylline.

Capsules
Verapamil HCl, Chlor Diazepoxide HCl, Diazepam, Furosemide, L- Dopa and Benserazide, Misoprostol, Propranolol HCl, Ursodeoxycholic acid, Nicardipine29.

EVALUATION OF FLOATING DRUG DELIVERY SYSTEM (FDDS)
Various parameters that need to be evaluated in gastro retentive formulations which includes:

Evaluation Parameters
Shape and Size Evaluation
The shape and size of particle plays a major role in determining solubility rate of the drugs and thus potentially its bioavailability. The particle size of the formulation is determined using Sieve analysis, Air elutriation analysis, Photoanalysis, Optical counting method, Microscope, Electro resistance counting methods (Coulter counter), Sedimentation techniques, Laser diffraction methods, Ultrasound
In-Vitro buoyancy study
The test for floating time is usually performed in simulated gastric fluid or 0.1 N HCl which is maintained at 37° C. This study is done by using USP dissolution apparatus containing 900 ml of 0.1 N HCl as the dissolution medium. 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.

Surface Topography
This is determined using Scanning electron microscope (SEM) operated with an acceleration voltage of 10KV, Contact angle meter, Atomic force microscopy (AFM), Contact profilometer.

Swelling Studies
Swelling studies are performed to calculate molecular parameters of swollen polymers. Which can be was determined by using optical microscopy and other sophisticated techniques which include H\textsuperscript{1} NMR imaging, Confocal laser scanning microscopy (CLSM), Cryogenic scanning electron microscopy (Cryo-SEM), Light scattering imaging (LSI) etc. The swelling studies by using Dissolution apparatus was calculated as per the following formula:

\[
\text{Swelling ratio} = \frac{\text{Weight of wet formulations}}{\text{Weight of formulation}}
\]

Determination of the drug content
The amount of the drug present in the formulation gives the percentage drug content which it should not exceeds the limits of the standard monographs. Drug content can be determined by the use of HPLC, HPTLC methods, Near infrared spectroscopy, Microtitrimetric methods, and also by using spectroscopy techniques.

Percentage Entrapment Efficacy
Percentage entrapment efficiency was reliable for quantifying the phase distribution of drug in the prepared formulations. Entrapment efficiency was determined by using three methods such as Microdialysis method, Ultra centrifugation, and pressure Ultra filtration.

In- Vitro Release Studies
The test for in vitro drug release are usually carried out in USP dissolution apparatus using simulated gastric and intestinal fluids maintained at 37 °C. The samples are withdrawn in specific time period and replaced with the same volume of fresh medium each time. The withdrawn samples are analyzed for their drug contents after an appropriate dilution using UV spectroscopy. However, standard dissolution methods based on the USP or British Pharmacopoeia (BP) have been shown to be poor predictors of in vitro performance for floating dosage forms.

Power X-Ray Diffraction
Powder X-ray diffraction is the predominant tool for the study of polycrystalline materials and is highly suitable for the routine characterization of pharmaceutical solid samples. Samples are irradiated with \(\alpha\) radiation and analyzed between 2-60 °C. The voltage and current used are 30KV and 30mA respectively.

Fourier Transform Infrared Analysis (FT-IR)
Fourier transform infrared spectroscopy (FT-IR) is a technique mostly used to determine the functional groups level interaction of organic, polymeric and some inorganic materials. Measurements of pure drug, polymer and drug-loaded polymer formulations and other physical mixture are obtained on FT-IR. The pellets prepared using KBr-press method under hydraulic pressure of 150kg/cm\textsuperscript{2}; and the spectra are scanned over the wave number range of 3600 to 400 cm\textsuperscript{-1} at the ambient temperature.

Differential Scanning Calorimetry (DSC)
DSC is used to characterize water of hydration of pharmaceuticals. Thermo grams of formulated preparations were obtained using DSC instrument equipped with an intracooler. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample preparations were hermetically sealed in pan made up of aluminium and heated at a temperature of 10°C/min; over a temperature range of 25° C - 65° C.

APPLICATION OF FLOATING DRUG DELIVERY SYSTEM (FDDS)
Enhanced Bioavailability
The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the
administration of non-GRDF controlled release polymeric formulations. There are several different processes, related to absorption and movement of the drug in the GIT, that influence the magnitude of drug absorption.

**Sustained Drug Delivery**

Oral sustained release formulations of FDDS may face 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 as a result of which they can float on the gastric contents. These systems are relatively larger in size and their entry 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 distal part of the stomach. The sustained and slow release of drug in the stomach gives sufficient local therapeutic levels and limit the absorption to the drug that reduces side effects 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: Acetazolamide and Vitamin B₂.

**Absorption Enhancement**

Drugs having low bioavailability due to site specific absorption in the upper part of the GIT are suitable to be formulated as floating drug delivery systems, thereby maximizing their absorption.

**Reduced fluctuation of drug concentration**

Continuous administration of the drug following CRGRDF produces blood drug concentrations within a narrower range compared to the conventional dosage forms. Thus, fluctuations in therapeutic drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be avoided and also improve the therapeutic index.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Drug</th>
<th>Category</th>
<th>Half life</th>
<th>Peak time (hrs)</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Verapamil</td>
<td>Calcium channel blocker</td>
<td>6</td>
<td>1-2</td>
<td>20-35%</td>
</tr>
<tr>
<td>2</td>
<td>Nifedipine</td>
<td>Calcium channel blocker</td>
<td>2</td>
<td>0.5-0.2</td>
<td>45-65%</td>
</tr>
<tr>
<td>3</td>
<td>Omeprazole</td>
<td>Proton pump inhibitor</td>
<td>1-2</td>
<td>1</td>
<td>35-60%</td>
</tr>
<tr>
<td>4</td>
<td>Atenolol</td>
<td>Antihypertensive</td>
<td>4</td>
<td>3</td>
<td>40-50%</td>
</tr>
<tr>
<td>5</td>
<td>Propranolol</td>
<td>Antihypertensive</td>
<td>4-5</td>
<td>4</td>
<td>26%</td>
</tr>
<tr>
<td>6</td>
<td>Verapamil</td>
<td>Antihypertensive</td>
<td>6</td>
<td>1.8</td>
<td>35%</td>
</tr>
<tr>
<td>7</td>
<td>Diltiazem</td>
<td>Calcium channel blocker</td>
<td>3-4.5</td>
<td>50 min.</td>
<td>40%</td>
</tr>
<tr>
<td>8</td>
<td>Lidocaine</td>
<td>Local anaesthetic</td>
<td>1.5-2</td>
<td>4</td>
<td>35%</td>
</tr>
<tr>
<td>9</td>
<td>Clarithromycin</td>
<td>Antibiotic</td>
<td>3-4</td>
<td>2-2.5</td>
<td>50%</td>
</tr>
<tr>
<td>10</td>
<td>Ramipril</td>
<td>ACE inhibitor</td>
<td>2-4</td>
<td>3-5</td>
<td>28%</td>
</tr>
</tbody>
</table>

**Table No.2: Marketed preparation of Floating Drug Delivery System (FDDS)**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Product</th>
<th>Active Ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Madopar</td>
<td>Levodopa and Benserzide</td>
</tr>
<tr>
<td>2</td>
<td>Valrelease</td>
<td>Diazepam</td>
</tr>
<tr>
<td>3</td>
<td>Topalkan</td>
<td>Aluminium magnesium antacid</td>
</tr>
<tr>
<td>4</td>
<td>Almagate</td>
<td>Antacid</td>
</tr>
<tr>
<td>5</td>
<td>Liquid gavison</td>
<td>Alginic acid and sodium bicarbonate</td>
</tr>
<tr>
<td>6</td>
<td>Cifran OD</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>7</td>
<td>Glumetza</td>
<td>Metformin HCl</td>
</tr>
</tbody>
</table>

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CONCLUSION
Gastric emptying and other physiological factors are responsible for drug absorption in the GIT which is a variable process. FDDS has proved to be one of the potential approach for gastric retention. The physicochemical properties of the drug and it's physiological events in the GIT should be studied thoroughly for designing a effective GRDDS. An efficient formulation of FDDS is a challenge and the work will extend, until an ideal approach with industrial applicability and feasibility arrives.

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CONFLICT OF INTEREST
We declare that we have no conflict of interest.

BIBLIOGRAPHY


23. Gangadhararappa H V, Pramod Kumar T M and Shiva Kumar H G. Gastric floating drug...
29. Wu W, Zhou Q, Zhang HB, Ma GD, Fu CD. Studies on nimodipine sustained release tablet capable of floating on gastric fluids with prolonged gastric resident time, Yao Xue Xue Bao, 32(10), 1997, 786-790.

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44. Sichina W J. Characterization of Water of Hydration of Pharmaceuticals Using the Pyris, 6 DSC, PETech-54.


