A REVIEW ON GASTRO-RETENTIVE FLOATING DRUG DELIVERY SYSTEMS

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ABSTRACT
In the recent years, the oral route has been used widely for the delivery of therapeutic medication due to the convenient cost of the therapy and ease of administration. This has led to high levels of patient compliance. More than half of the drug delivery systems which is available in the market are oral drug delivery systems. Gastro-retentive drug delivery systems or Floating systems or Hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents. Moreover, these drug delivery systems tend to keep afloat in the stomach without disturbing the gastric emptying rate for a long period of time. The drug is released at a steady rate from the system while the latter is floating on the gastric juices. The residual system is emptied from the stomach immediately after the drug is released. There is a better control of the fluctuations (irregular rising and falling in number) in plasma drug concentration due to an increased Gastric Residence Time (GRT). Furthermore, a minimal gastric content is required to allow the proper achievement of the buoyancy retention along with a minimal level of the floating force (F) so that the dosage form is kept buoyant/ floating on the surface of the meal. There have been several buoyant systems that have been developed based on granules, powders, tablets, capsules, laminated films and hollow microspheres.

KEYWORDS: Gastro-retentive, Floating systems, Hydrodynamically, Gastric Residence Time, Stomach.

1.1. BASIC GIT PHYSIOLOGY
The GIT (gastrointestinal tract) is a tube which is approximately nine meter long that runs through the centre of the body from the mouth to the anus. This includes throat (pharynx), oesophagus, stomach, small intestine (consisting of the duodenum, jejunum, and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum). The wall of the GIT (Gastro-Intestinal tract) has the same general structure throughout most of its length from the oesophagus to the anus with some local changes for each region.[1] The stomach is located in the left upper part of the abdominal cavity immediately below the diaphragm. The size varies based on the amount of distention: up to (1400-1500) ml following a meal. After food has been emptied, a ‘collapsed’ state is obtained with a resting volume of only 30–50 ml.[2,3]

Anatomically the stomach is divided into 3 regions.
1. Fundus
2. Body
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 actions.[4] 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 cycles both though stomach and intestine every 2 to 3 h. This is called the
interdigestive myoelectric cycle or migrating myoelectric cycle (MMC) which is further divided into following 4 phases.\textsuperscript{[5]}

1. **Phase I (Basal phase)** lasts from 30-60 minutes with rare contractions.
2. **Phase II (Preburst phase)** lasts for 20-40 minutes with intermittent action potential and contractions.
3. **Phase III (Burst phase)** lasts for 10-20 minutes. It includes intense and regular contractions for short period.
4. **Phase IV** lasts for 0-5 minutes and occurs between phases III and I of 2 consecutive cycles.

As the phase progresses, the intensity and frequency also increase gradually.

![Fig. 1.2: Phases involved in gastric emptying.](image1)

When a mixed meal is ingested, the pattern of contractions changes from fasting state to fed state. It is known as the digestive motility pattern and constitutes of continuous contractions as in phase II of a fasted state. These contractions make food size to reduce (less than 1 mm), which are pushed toward the pylorus in a suspension form.\textsuperscript{[6]}

![Fig. 1.3: Gastrointestinal motility pattern.](image2)

1.2. FACTORS AFFECTING GASTRIC RESIDENCE TIME (GRT) OF DRUG

Various approaches such as mucoadhesive, swelling high density and floating system have been developed to increase the GRT of the dosages forms. However, most of these proposals are influenced by various factors that affect their ability as a gastro-retentive system.\textsuperscript{[7]}
1. **Density** – Gastric Residence Time (GRT) is a part of dosage form buoyancy which is dependent on the density.

2. **Size** – Size having diameter 7.5 mm has an increased GRT when compared with the diameter of 9.9 mm.

3. **Shape of dosage form** – Ring and Tetrahedron shaped-devices have better GRT of (90-100) % compared with other shapes.[8]

4. **Single or multiple unit formulations** – Multiple unit formulations show obvious release profile.[9]

5. **Fed/Unfed state** – During the fasting conditions, the GI motility is affected by migrating myoelectric complex (MMC) that occurs every 1.5-2 h. In the fed state, myoelectric complex (MMC) takes time and GRT is considerably longer.[10]

6. **Nature of meal** – Feeding of indigestible polymers or fatty acid salts can decrease the gastric emptying rate and prolong drug release.

7. **Caloric content** – Gastric Residence Time (GRT) can be increased by (4-10) h with a meal rich in proteins and fats.

8. **Frequency of feed** – The Gastric Residence Time (GRT) can increase by over 6.5 hours when successive meals are given compared with a single meal due to the low frequency of myoelectric complex (MMC).

9. **Gender** – Gastric Residence Time (GRT) for males is around (3.4±0.6 h) when compared to Female persons which are around (4.6±1.2 h). Elderly people have a longer GRT.[11]

10. **Posture** – GRT varies between supine and upright ambulatory states of the patient.

11. **Biological factors** – Diabetes and Crohn’s disease, etc.

1.3. **SUITABLE DRUG CANDIDATE FOR GASTRO-RETENTIVE DRUG DELIVERY SYSTEM (GRDDS)**

In general, appropriate candidates for GRDDS are molecules that have poor colonic absorption but are characterised by better absorption properties at the upper parts of the GIT.[12]

1. Acting locally in the stomach.
2. Primarily absorbed in the stomach.
3. Poorly soluble at an alkaline pH.
4. Absorbed rapidly from the GI tract.
5. Degraded in the colon.
6. It should be absorbed primarily in the duodenum and upper jejunum segments.
   e.g. Calcium is mainly absorbed in the duodenum.
7. Drugs which have a short half-life and require frequent dosing. e.g. Cimetidine.
8. Drugs which have a short half-life and extensive first-pass metabolism.
   e.g. Nitroglycerine.
9. Which have poor solubility in intestinal media and poor bioavailability.
10. Drugs that are required for local action in the stomach.
   e.g. Antacids and enzyme preparation.
11. Drugs that cause gastric irritation and produce gastric ulcers. e.g. Aspirin.[13]

1.4. **ADVANTAGES OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEM**

1. Minimised adverse activity in the colon.
2. Reduced fluctuations in drug concentration.
3. Targeted therapy for local ailments in the upper GIT.
4. Reducing the mucosal irritation.
5. Enhanced Bioavailability.
7. Improved drug absorption.
8. Sustained drug delivery/reduced frequency of dosing.
9. Useful in treatment of gastric disorders such as gastroesophageal reflux and peptic ulcers.[14]

1.5. **DISADVANTAGES OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEM**

Low-density dosage forms are unable to retain these systems in stomach unless water is present.

1. The patient must remain in an upright position during the gastric residence time; in a supine position, the pylorus is located above the stomach body. This will allow the accelerated emptying of floating material.[15]
2. Floating systems require the presence of food to delay their gastric emptying.
3. Drugs that have solubility or stability problem in the gastric fluid are not formulated. e.g. Phenytoin.
4. They do not always release the drug at the intended site.
5. Floating systems are not feasible for those drugs to have instability in the gastric acid environment. e.g. Erythromycin.[16]
1.6. CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM

![Diagram of classification of gastro-retentive drug delivery systems](image)

**Formula for Gastro-retentive drug delivery systems**

\[ F = F_b - F_g = (D_b - D_g)gV \]

where,

- \( F \) = total vertical force
- \( F_g \) = force of gravity
- \( D_b \) = object density
- \( V \) = volume
- \( F_b \) = buoyancy force
- \( D_f \) = fluid density
- \( g \) = acceleration due to gravity

gastric emptying rate for a prolonged period.\(^{[19]}\) The drug is released slowly at the desired rate from the floating system and after the complete release, the residual system is expelled from the stomach.\(^{[20]}\)

1.7. GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

1.7.1. Effervescent System

Effervescent systems include the usage of gas generating agents, carbonates (example: Sodium bicarbonate) and another organic acid (examples: tartaric acid and citric acid) present in the formulation.\(^{[17]}\) This produces carbon dioxide (\(\text{CO}_2\)) gas. Thus, it causes the reduction in the density of the system and makes it float on the gastric fluid.\(^{[18]}\)

These effervescent systems further classified into two types.

i. Gas generating systems

ii. Volatile liquid/vacuum systems

i. Gas generating systems

a) *Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS)*

They are formulated by mixing the carbon dioxide generating agents and the drug within the matrix tablet. The bulk density is lower than the gastric fluids and therefore remain floating in the stomach unflattering the

b) *Intra Gastric Bilayed Floating Tablets*

These are also compressed tablet and containing two layers

1. Immediate release layer
2. Sustained release layer
Fig. 1.6: Intragastric floating bilayer tablet.

c) Multiple Unit Type Floating Pill
These are sustained release pills known as ‘seeds’. It is surrounded by double layers wherein the inner layer consists of effervescent agents while the outer layer consists of the swellable membrane layer. After the emersion of the system dissolution medium at body temperature, it sinks at once. This forms swollen pills (balloon-type), which float as they have a lower density. This lower density is due to generation and entrapment of carbon dioxide within the systems.[21]

(b) Stages of floating mechanism
(a) A multi-unit oral floating dosage system.
(b) Stages of floating mechanism.
(A) Penetration of water; (B) Generation of CO₂ and floating; (C) Dissolution of drug.
Key: (a) Conventional SR pills; (b) Effervescent Layer; (c) Swellable Layer; (d) Expanded Swellable Membrane Layer; (e) surface of water in the beaker (37°C).

ii. Volatile liquid / Vacuum containing systems
a) Intragastric Floating Gastrointestinal Drug Delivery System
These systems are buoyant in the stomach because of flotation chamber which may be a vacuum (filled with air or an inert gas) while the drug reservoir is encapsulated inside a microporous compartment.[22]

Fig. 1.7: (a) Multiple-unit oral floating dosage system.

Fig. 1.8: Intragastric floating drug delivery device.
b) Inflatable Gastrointestinal Delivery Systems
These delivery systems are made up of an inflatable chamber which contains liquid ether that becomes a gas at body temperature causing the inflation of the chamber in the stomach. These systems are formulated by incorporating the inflatable chamber with a drug reservoir (drug impregnated polymeric matrix), then by its encapsulation in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir along with the inflatable chamber. The inflatable chamber inflates automatically and retains the drug reservoir into the gastric juices.

![Gastro-inflatable drug delivery device](image1)

Fig. 1.9: Gastro-inflatable drug delivery device.

c) Intragastric Osmotically Controlled Drug Delivery System
It consists of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. The capsule disintegrates very fast in the stomach. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid. This liquid becomes a gas at body temperature to make the bag inflate. The system consists of two components; a drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is surrounded by a pressure responsive collapsible bag. The latter is impermeable to vapour and liquid. In the stomach, the water in the GI fluid is continuously absorbed through the semi-permeable membrane into the osmotically active compartment to dissolve the osmotically salt. This creates an osmotic pressure which acts on the collapsible bag and in turn forces the bag reservoir compartment to decrease its volume. This leads to the activation of the drug through the delivery orifice. The floating support is also made to contain a bio-erodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.

![Intragastric osmotic controlled drug delivery system](image2)

Fig. 1.10: Intragastric osmotic controlled drug delivery system.
1.7.2. Non-Effervescent Systems

It is based on the mechanism of polymer swelling or bioadhesion to mucosal layer in Gastro-Intestinal Tract. The most widely used excipients in non-effervescent floating systems are gel-forming or highly swellable cellulose type. The various types of these systems are as follows.

a) Single layer floating tablets:
These are fabricated by the mixing of drug with a gel-forming hydrocolloid. This leads to its swelling when in contact with gastric fluid. The air trapped by the swollen polymer confers buoyancy to this dosage forms.

b) Bilayer floating tablets
It consists of two layers where one is the immediate release layer which releases the drug immediately from the system while the other layer is a sustained release layer. The latter absorbs gastric fluid which forms an impermeable colloidal gel barrier on its surface, thereby it remains buoyant in the stomach.

c) Alginate beads
Spherical beads can be prepared by dropping sodium alginate solution into a cold solution of aqueous calcium chloride. This leads to the precipitation of calcium alginate causing the formation of the porous system which can maintain a floating force for over 12 hours when compared with solid beads which gave a short residence time of 1 hour. These floating beads give a prolonged residence time of more than 5.5 hours.

d) Hollow microspheres
Hollow microspheres are also known as microballoons. The drug is incorporated in the outer polymer shells. Usually, novel emulsion solvent diffusion method is used. The ethanol: dichloromethane solution of drug and enteric acrylic polymer are poured into an agitated aqueous solution of PVA which is thermally controlled at 400°C. The Hollow microspheres (microballoons) are kept in the floating condition continuously over the surface of acidic dissolution media containing a surfactant for more than 12 hours in vitro.

1.8. APPROACHES TO DESIGN FLOATING DOSAGE FORMS

There are several approaches used to increase the gastric retention of drugs.

1.8.1. High-Density Systems
These types of systems have a density around 3g/cm³. They are held in the rugae of the stomach and they have the capacity to withstand its peristaltic movements.

Examples of diluents used for the manufacture such high-density formulations are
i. Barium sulphate (density= 4.9)
ii. Zinc oxide
iii. Titanium oxide
iv. Iron powder

1.8.2. Swelling and Expanding Systems
Swelling and Expanding Systems are also known as “Plug type system”. The name of “Plug type system” has been coined since they show the tendency to remain logged in the pyloric sphincters. The polymer imbibes water and swells when they come in contact with the gastric fluid.
1.8.3. Incorporation of Delaying Excipients
This is another delayed gastric emptying approach of interest which consists feeding of digestible polymers or fatty acid salts. This leads to changes in the motility pattern of the stomach to a fed stage thereby reducing the gastric emptying rate.\cite{37}

Examples of delaying excipients: triethanolamine myristate.

1.8.4. Modified Systems:
These systems extend the GRT depending on size, shape and flexural modules of drug delivery device.\cite{38}

Examples: Silastic elastomers or extruded from polyethylene blends.

1.8.5. Mucoadhesive & Bioadhesive Systems
These systems are delivery systems which are used to restrict the delivery device to a particular place within the lumen, thus enhancing the drug absorption.\cite{39}

Examples: Gliadin, Polycarbophil, chitosan, carbopol, CMC, lectins.

1.8.6. Floating Systems
These drug delivery systems remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time as they have a bulk density less than gastric fluids.\cite{40,41} This can be achieved by incorporating the floating chamber with inert gas, vacuum or air.\cite{42}
1.9. DRUG RELEASE MECHANISM OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEM

Swelling polymers that are generally employed for the purpose are hydrophilic in nature. The mechanism of release of the drug from the hydrophilic matrices has been reviewed. When swellable hydrophilic dosage forms come in contact with aqueous medium, various events that take place are:

- Partial hydration of the polymer followed by the dissolution of the drug at the surface, resulting in an immediate release.
- Penetration of the solvent molecules into free spaces present on the surface between macromolecular chains.
- If the thermodynamic compatibility of the dissolution medium with the polymer is favourable, the glass transition temperature of the polymer is lowered below the room temperature leading to chain relaxation of the polymer thus resulting in swelling and formation of a gel.
- Water continuously penetrates the matrix, the gel expands and dissolution of drug through the gel layer takes place.
- Simultaneously attrition/erosion of the outermost layer and release of insoluble particles occurs.
- The tailing-off period starts when the water reaches the centre of the system and the concentration of the drug falls below the solubility value. The final stage is characterised by a reduction in the release rate.

Therefore, the release of an active principle by a matrix system is produced by two simultaneous mechanisms.

i. Erosion/attrition of the outermost layer.
ii. Dissolution of the active ingredient in the liquid medium followed by diffusion though the gel barrier when formed.

1.10. MARKETED PREPARATIONS OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

Table 1.1: Marketed preparations of gastro-retentive drug delivery systems.

<table>
<thead>
<tr>
<th>S/N</th>
<th>PRODUCT</th>
<th>ACTIVE INGREDIENT</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glumetza GRTM</td>
<td>Metformin HCl</td>
<td>Metformin HCl Extended-Release Tablet</td>
</tr>
<tr>
<td>2</td>
<td>Cytotec</td>
<td>Misoprostol (100µg/200µg)</td>
<td>Bilayer Floating Capsule</td>
</tr>
<tr>
<td>3</td>
<td>Conviron</td>
<td>Ferrous Sulfate</td>
<td>Colloidal Gel Forming FDDS</td>
</tr>
<tr>
<td>4</td>
<td>Cifran OD</td>
<td>Ciprofloxacin 1g</td>
<td>Gas Generating Floating Form</td>
</tr>
<tr>
<td>5</td>
<td>Valrelease</td>
<td>Diazepam (15mg)</td>
<td>Floating Capsule</td>
</tr>
<tr>
<td>6</td>
<td>Topalkan</td>
<td>Aluminium Hydroxide Antacid</td>
<td>Floating Liquid Alginate Preparation</td>
</tr>
<tr>
<td>7</td>
<td>Almagate Floatcoat</td>
<td>Aluminium Hydroxide Antacid</td>
<td>Floating Dosage Form</td>
</tr>
<tr>
<td>8</td>
<td>Madopar</td>
<td>Levodopa (100mg) and Sodium Bicarbonate</td>
<td>Floating, CR Capsule</td>
</tr>
<tr>
<td>9</td>
<td>Liquid Gaviscon</td>
<td>Alginic Acid and Sodium Bicarbonate</td>
<td>Effervescent Floating Liquid Alginate Preparation</td>
</tr>
</tbody>
</table>

1.11. PATENTS FOR SOME GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

Table 1.2: Patents for some gastro-retentive drug delivery systems.

<table>
<thead>
<tr>
<th>US PATENT No.</th>
<th>PATENT TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>6290989</td>
<td>Expandable gastro-retentive therapeutic system with controlled active substance release in the gastrointestinal tract</td>
</tr>
<tr>
<td>6207197</td>
<td>Gastro retentive controlled release microspheres for improved drug delivery</td>
</tr>
<tr>
<td>5972389</td>
<td>Gastric-retentive, oral drug dosage forms for the controlled-release of sparingly soluble drugs and insoluble matter</td>
</tr>
<tr>
<td>5443843</td>
<td>Gastric retention system for controlled drug release</td>
</tr>
<tr>
<td>5232704</td>
<td>Sustained release, bilayer buoyant dosage form</td>
</tr>
<tr>
<td>4814179</td>
<td>Floating sustained release therapeutic compositions</td>
</tr>
<tr>
<td>4767627</td>
<td>Drug delivery device which can be retained in the stomach for a controlled period of time</td>
</tr>
<tr>
<td>4167558</td>
<td>Novel sustained release tablet formulations</td>
</tr>
<tr>
<td>4140755</td>
<td>Sustained release tablet formulations</td>
</tr>
<tr>
<td>4126672</td>
<td>Sustained release pharmaceutical capsules</td>
</tr>
<tr>
<td>20080220060</td>
<td>Gastro retentive formulations and manufacturing process thereof</td>
</tr>
</tbody>
</table>
1.12. DRUGS USED IN THE FORMULATIONS OF STOMACH SPECIFIC FLOATING DOSAGE FORMS

Table 13: Drugs used in the formulations of stomach-specific floating dosage forms.

<table>
<thead>
<tr>
<th>S/N</th>
<th>DOSAGE FORMS</th>
<th>DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Floating microspheres</td>
<td>Aspirin, Griseofulvin, p-nitroaniline, Ibufrofen, Ketoprofen, Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipryridamol, Tranilast</td>
</tr>
<tr>
<td>2.</td>
<td>Floating granules</td>
<td>Diclofenac sodium, Indomethacin, and Prednisolone</td>
</tr>
<tr>
<td>3.</td>
<td>Films</td>
<td>Cinnarizine, Albendazole</td>
</tr>
<tr>
<td>4.</td>
<td>Floating tablets and Pills</td>
<td>Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin trihydrate, Atenolol, Fluorouracil, Isosorbide mononitrate Para-amino-benzoic acid, Piretanide Theophylline, Verapamil hydrochloride, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol pentoxifylline and Diltiazem</td>
</tr>
<tr>
<td>5.</td>
<td>Floating Capsules</td>
<td>Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid and Pepstatin, and Propranolol</td>
</tr>
</tbody>
</table>

CONCLUSION
In this review, the various types of gastro-retentive drug delivery systems have been discussed along with the different phases involved, drug release mechanisms and their marketed products. Several approaches like floating, bio-adhesion, effervescence, sinking, magnetic, swelling, etc. have been proposed over the years. It has been observed that the major trend formulation-wise has been shifted toward the use of swelling polymer matrix together with effervescence in the design of floating delivery systems. In the market, it is emerging slowly as an important novel drug delivery due to many inherent challenges associated with it in spite of the numerous potential benefits offered by this delivery system. Without any doubt, GRDDS will become a popular drug delivery system in the near future due to its enhanced effectiveness. However, it's in vitro and in vivo studies must be carried out efficiently because of the complexity of pharmacokinetic and pharmacodynamics parameters.

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