A NOVEL APPROACH IN GASTRO RETENTIVE DRUG DELIVERY SYSTEM: FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT

The task of achieving efficient delivery of drugs that have poor bioavailability or narrow absorption windows have plagued the pharmaceutically industry for decades. Thus, much research has been dedicated to the development of novel polymeric-based gastro retentive drug delivery technologies that may optimize the bioavailability and subsequent therapeutic efficacy of such drugs. Several technical approaches are currently utilized in the prolongation of gastric residence time, including high-density, swelling and expanding, polymeric mucoadhesive, ion-exchange, raft forming, magnetic and floating drug delivery systems, as well as other delayed gastric emptying devices. The purpose of writing this review on gastro retentive drug delivery systems was to compile the recent literature with special focus on various gastro retentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. In this review, the current technological developments of FDDS and marketed products have been discussed. In addition, the pharmaceutical basis of their design, their advantages and future potential for oral controlled drug delivery are discussed.
**Introduction:** Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance, and cost-effective manufacturing process.\(^1\)

Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as:

1. Drugs with short half-life requires frequent administration, which increases chances of missing dose of drug leading to poor patient compliance.
2. A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.
3. The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the C\(_{SS}\) values fall or rise beyond the therapeutic range.
4. The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs.\(^2\)

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.\(^3\)

**Controlled Drug Delivery Systems:** Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue.\(^4\)

**FIG. 1:** A HYPOTHETICAL PLASMA CONCENTRATION-TIME PROFILE FROM CONVENTIONAL MULTIPLE DOSING AND SINGLE DOSES OF SUSTAINED AND CONTROLLED DELIVERY FORMULATIONS

Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.

1. Delayed release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting

More precisely, controlled delivery can be defined as:-

1. Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
2. Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.

3. Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.

4. Provide physiologically/therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/therapeutic needs of the body.  

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug (Figure 1). Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.

Advantages of Controlled Drug Delivery System:

1. Avoid patient compliance problems.

2. Employ less total drug
   a) Minimize or eliminate local side effects
   b) Minimize or eliminate systemic side effects
   c) Obtain less potentiation or reduction in drug activity with chronic use.
   d) Minimize drug accumulation with chronic dosing.

3. Improve efficiency in treatment
   a) Cures or controls condition more promptly.
   b) Improves bioavailability of some drugs.
   c) Make use of special effects, E.g. Sustained-release aspirin for morning relief of arthritis by dosing before bed time. 

Disadvantages:

1. Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.

2. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.

3. Reduced potential for dosage adjustment of drugs normally administered in varying strengths.


Gastro Retentive Dosage Form (GRDF): It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDF or GRDS). GRDFs extend significantly the period of time.
over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.\textsuperscript{10}

Dosage form with prolonged GRT, i.e. gastro retentive dosage forms (GRDF), will bring about new and important therapeutic options such as:

1. This application is especially effective in sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To override this problem, erodible, gastro retentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.

2. GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the submucosal tissue of stomach) making it possible to treat stomach and duodenal ulcers, gastritis and esophagitis, reduce the risk of gastric carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).

3. GRDFs can be used as carriers for drugs with so-called absorption windows. These substances for e.g. antiviral, antifungal and antibacterial agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides, tetracyclines etc.), are taken up only from very specific sites of the GI mucosa.\textsuperscript{11}

Biological Aspects of GRDFs & Role of GI Tract:

Stomach: The stomach is J-shaped organ located in the upper left hand portion of the abdomen, just below the diaphragm. It occupies a portion of the epigastric and left hydrochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area, it provides barrier to the delivery of drugs to small intestine (Figure 2).

\textbf{FIGURE 2: ANATOMY OF STOMACH}

Approaches to Gastric Retention: A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts \textsuperscript{14, 15}. These include –

a) Floating Systems: Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate (Figure 3). While the system is floating on the
gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems.\textsuperscript{16, 17}

**FIGURE 3: GRAPHIC OF BUOYANT TABLET THAT IS LESS DENSE THAN THE STOMACH FLUID AND THEREFORE REMAINS IN THE FUNDUS**

**b) Bio/Muco-adhesive Systems:** Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane.\textsuperscript{18}

Binding of polymers to the mucin/epithelial surface can be divided into three broad categories:–

- Hydration-mediated adhesion
- Bonding-mediated adhesion
- Receptor-mediated adhesion

c) **Swelling and Expanding Systems:** These are the dosage forms, which after swallowing; swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as “plug type system”, since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state.\textsuperscript{19, 20}

d) **High Density Systems:** These systems with a density of about 3 g/cm\textsuperscript{3} are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm\textsuperscript{3} acts as a threshold value after which such systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. They are retained in the antrum of stomach (Figure 4).\textsuperscript{21}

**FIGURE 4: GRAPHIC OF HEAVY TABLET WHICH IS DENSER THAN THE STOMACH FLUID AND THEREFORE SINKS TO THE ANTRUM**
e) Incorporation of Passage Delaying Food Agents: Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of the stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C_{10}-C_{14}.^{22}

f) Ion Exchange Resins: A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.^{23}

g) Osmotic Regulated Systems: It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment.

Types of Floating Drug Delivery Systems (FDDS): Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS that are:

- Effervescent System, and
- Non-Effervescent System

a) Effervescent System: Effervescent systems include use of gas generating agents, carbonates (e.g. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO$_2$) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature.

These effervescent systems further classified into two types.^{24}

- Gas Generating systems
- Volatile Liquid/Vacuum Containing Systems

I. Gas – Generating Systems:

1. Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS): These are formulated by intimately mixing the CO$_2$ generating agents and the drug with in the matrix tablet (Figure 5). These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.^{25}
2. Intra Gastric Bilayer Floating Tablets: These are also compressed tablet (Fig. 6) and containing two layers.  
- Immediate release layer and  
- Sustained release layer

3. Multiple Unit type floating pills: These systems consist of sustained release pills as ‘seeds’ surrounded by double layers (Figure 7). The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO₂ within the system.  

II. Volatile Liquid/Vacuum Containing Systems:  
1. Intragastric Floating Gastrointestinal Drug Delivery System: This system can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir
is encapsulated inside a microporous compartment (Fig. 8).

FIG. 8: INTRA GASTRIC FLOATING GASTROINTESTINAL DRUG DELIVERY DEVICE

2. Inflatable Gastrointestinal Delivery Systems: In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The drug continuously released from the reservoir into the gastric fluid (Fig. 9).

FIG. 9: INFLATABLE GASTROINTESTINAL DELIVERY SYSTEM

3. Intragastric Osmotically Controlled Drug Delivery System: It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery devices consist of two components; drug reservoir compartment and an osmotically active compartment (Fig. 10).

FIG. 10: INTRAGASTRIC OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM

B. Non Effervescent Systems: The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol. The various types of this system are as:

1. Single Layer Floating Tablets: They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by
the swollen polymer confers buoyancy to these dosage forms.

2. Bilayer Floating Tablets: A bilayer tablet contain two layer one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

3. Alginate Beads: Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence, these floating beads gave a prolonged residence time of more than 5.5 hour.28

4. Hollow Microspheres: Hollow microspheres (microballoons), loaded with drug 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 into 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 an internal cavity in microsphere of polymer with drug. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours in vitro.29

Factors which affect Gastric Retention Time of Dosage Form: The gastric retention time (GRT) of dosage form is controlled by several factors that affect their efficacy as a gastro retentive system.30

- Density – GRT is a function of dosage form buoyancy that is dependent on the density.
- Size – Dosage form units with a diameter of more than 9.5mm are reported to have an increased GRT.
- Shape of dosage form – Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT. 90% to 100% retention at 24 hours compared with other shapes.
- Single or multiple unit formulation – Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
- Fed or unfed state – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (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.
- Nature of meal – Feeding of indigestible polymers or fatty acid salts can change
the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

- **Caloric content** – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.
- **Frequency of feed** – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender** – Mean ambulatory GRT in males (3.4±0.6 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** – Elderly people, especially those over 70, have a significantly longer GRT.
- **Posture** – GRT can vary between supine and upright ambulatory states of the patient.
- **Concomitant drug administration** – Anticholinergic like Atropine and Propantheline, opiates like Codeine and prokinetic agents like Metoclopramide and Cisapride.
- **Biological factors** – Diabetes and Crohn’s disease.

**Advantages of FDDS:** Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery.\(^{31}\) Advantages include:

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.
4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.

**Disadvantages of FDDS:**

1. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
2. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
3. High variability in gastric emptying time due to its all or non-emptying process.

**CONCLUSION:** Floating tablets have plenty of advantages over the conventional tablets. As these floating tablets provide a dosage form which is stable and provides a sustained release dosage form. The most important application of the floating tablets is that they provide a new possibility of treating the stomach infected with Helicobacter pylori. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymer bioadhesive systems, modified shape systems, high density systems and other delayed gastric emptying devices.
TABLE 1: GASTRO RETENTIVE PRODUCTS AVAILABLE IN THE MARKET

<table>
<thead>
<tr>
<th>BRAND NAME</th>
<th>ACTIVE INGREDIENT</th>
<th>REMARKS</th>
<th>REFERENCE NO.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cifran OD ®</td>
<td>Ciprofloxacin</td>
<td>Gas generating floating form</td>
<td>32</td>
</tr>
<tr>
<td>Madopar ®</td>
<td>L-DOPA &amp; Benzerazide</td>
<td>Floating CR capsules</td>
<td>32</td>
</tr>
<tr>
<td>Valrelease ®</td>
<td>Diazepam</td>
<td>Floating Capsules</td>
<td>33</td>
</tr>
<tr>
<td>Topalkan ®</td>
<td>Aluminum -magnesium antacid</td>
<td>Effervescent floating liquid alginate preparation</td>
<td>34</td>
</tr>
<tr>
<td>Almagate Flatcoat ®</td>
<td>Aluminum -magnesium antacid</td>
<td>Floating dosage form</td>
<td>35</td>
</tr>
<tr>
<td>Liquid Gavison ®</td>
<td>Alginic acid</td>
<td>Suppress gastro esophageal reflux and alleviate the heart burn</td>
<td>35</td>
</tr>
<tr>
<td>Conviron</td>
<td>Ferrous sulfate</td>
<td>Colloidal gel forming FDDS</td>
<td>36</td>
</tr>
<tr>
<td>Cytotec®</td>
<td>Misoprostal</td>
<td>Bilayer floating capsule</td>
<td>36</td>
</tr>
</tbody>
</table>

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 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 so, it was seen that these dosage form 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. In addition to this the FDDS is still more important because of the numerous advantages it offers over the conventional dosage form. The popularity of FDDS is a testimony to its usefulness. Day after day the FDDS shows more promise for a bright future.

REFERENCES: