REVIEW ARTICLE

Gastroretentive Drug Delivery Systems: A Review

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Abstract
Gastroretentive drug delivery system is gold standard novel delivery system. The purpose of writing this review is to compile the recent literature with special focus on various gastroretentive approaches. In recent years scientific and technological advancements have been provided in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Several approaches are useful in the prolongation of the GRT, including floating drug delivery systems (FDDS), Gastro retentive floating drug delivery systems (GFDDS) are the systems which are retained in the stomach for a longer period of time and leads to improve the bioavailability of drugs.
INTRODUCTION
Oral administration is the most convenient and preferred routes of any drug delivery to the systematic circulation. Oral route remains the prefer route for the administration of therapeutic agents because low cost of therapy and ease of administration leads to higher level of patient compliance. However, conventional delivery had many drawbacks like non-site specificity. Some drugs are absorbed at specific site only. They require release at specific site or a release such that maximum amount of drug reaches to the specific site. Pharmaceutical field has been developed towards such drugs which require site specificity and to improve patient compliance. Gastroretentive delivery system (GRDDS) is one of the site specific deliveries for the delivery of drugs either at stomach or at intestine. A GRDDS can be defined as "a system which retains in the site specific organ like stomach for a sufficient time interval against all the physiological barriers, releasing active moiety in a controlled release pattern, and finally metabolized in the body." A GRDDS can also be a useful tool in delivery of drugs that are primarily absorbed in the duodenum and upper jejunum or those that have an absorption window in the GIT.1-4

Advantage of Using Gastroretentive Drug Delivery
Drugs which are easily absorbed from the gastrointestinal tract and drug having short half-lives are quickly eliminated from the systemic circulation and that’s why frequent dosing is required. To overcome this problem, Gastroretentive drug delivery systems provide to achieve effective plasma drug concentration for longer periods thereby reducing the dosing frequency of drug are being formulated.5-7

PARAMETERS CONTROLLING GASTRIC RETENTION TIME
The following are the parameters controlling the gastric retention time (GRT) of oral dosage forms such as: 10,11

1. Density of the dosage form
2. Gender, posture
3. Shape and size of the dosage form
4. Sex, sleep and body mass index
5. Food intake and its nature (Caloric content and frequency of intake)
6. Administration of drug with effect on GIT e.g: Anticholinergic agents, opiates, prokinetic agents
7. Molecular weight of the drug
8. Particle size of the drug
9. Lipophilicity of the drug depending on its ionization state

Drug Characteristics Required for Gastroretentive Drug Delivery System
The properties of drug candidates that make them suitable or not-suitable for incorporation into gastroretentive delivery system are given in Table 1.8,9

Table 1. Drug candidates for gastroretentive delivery

<table>
<thead>
<tr>
<th>Potential drug candidates for gastroretentive drug delivery</th>
<th>Drug candidates not suitable for gastroretentive drug delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs that locally act in the stomach, e.g., antacids and drugs for H. Pylori therapy, viz., misoprostol</td>
<td>Drugs that have very limited acid solubility, e.g., phenytoin</td>
</tr>
<tr>
<td>Drugs that disturb normal colonic bacteria, e.g. amoxicilin</td>
<td>Drugs with solubility problem in stomach</td>
</tr>
<tr>
<td>Drugs having narrow absorption window in GI tract, e.g., riboflavin, levodopa, cyclosporin, methotrexate</td>
<td>Drugs which undergo extensive first pass metabolism</td>
</tr>
<tr>
<td>Drugs which are primarily absorbed from stomach and upper part of GI tract, e.g., calcium supplements, chloridiazepoxide, cinnarazine.</td>
<td>Drugs with irritant effect in the stomach</td>
</tr>
<tr>
<td>Drugs those are poorly soluble at alkaline pH. e.g. furosemide, diazepam, verapamil.</td>
<td>Drugs that suffer instability in the gastric environment, e.g. erythromycin</td>
</tr>
</tbody>
</table>
**APPROACHES FOR GASTRORETENTIVE DRUG DELIVERY**

Various approaches for development of gastroretentive drug delivery systems are summarized in Fig 1 below:\(^\text{12}\)

**Floating Drug Delivery Systems (FDDS)**

The important points to be considered for floating drug delivery system are: \(^\text{13}\)

- It should release contents slowly to serve as a reservoir
- It must maintain specific gravity lower than gastric contents (1.004 – 1.01 g/cm\(^3\))
- It must form a cohesive gel barrier

FDDS provide a bulk density system which is lower than gastric fluids and hence it remains buoyant in the stomach for a prolonged period of time to float over the gastric content. While the system floats over the gastric contents, the drug is released slowly at the desired rate and thus; the results in an increase in the gastric residence time and thereby a better control of fluctuations in the plasma drug concentrations. Ultimately, when the releasing of drug from the system completed, the residual system is emptied from the stomach. \(^\text{9}\) Floating systems can be further classified as effervescent and non-effervescent systems.

**Non-effervescent Systems**

Non-effervescent systems always incorporate high level of one or more than one gel-forming, highly swellable, cellulosic hydrocolloids such as; hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose, polysaccharides, or matrix forming polymers
(e.g., polycarbophil, polyacrylates, and polystyrene) compressed into tablets or capsules. Whenever the system comes in contact with gastric fluid, these gel formers, polysaccharides and polymers get hydrated and form a colloidal gel barrier, due to which, it controls the rate of fluid penetration into the device and drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and provide buoyancy to the dosage form. This system can be further divided into the following sub-types.\textsuperscript{14}

**Alginate Beads**

They are the multi-unit floating dosage forms developed from freeze dried calcium alginate. The size of spherical beads is approximately 2.5 mm, which is prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. After that process beads are separated, snap-frozen in liquid nitrogen, and freeze-dried at -40 °C for 24 h, leading to the formation of a porous system, due to which it can maintain a floating force for period over 12 h. These floating beads provide a prolonged residence time of more than 5.5 hours.

**Hollow Microspheres (Microballoons)**

Hollow microspheres loaded with drug in their outer polymer shelf and prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer are incorporated into an agitated solution of polyvinyl alcohol (PVA) that is thermally controlled at 40°C. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The microballoons float over the surface of an acidic dissolution media containing surfactant for more than12 h.

**Effervescent (Gas Generating) Systems**

Floatability in this kind of system is achieved by generation of gas bubbles. These buoyant systems utilize matrices which are prepared with swellable polymers like polysaccharides (e.g. chitosan), effervescent components such as sodium bicarbonate, citric acid or tartaric acid.\textsuperscript{15,16} The optimal stoicheometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:117. In this system, carbon dioxide is released and causes the formulation to be float in the stomach. This system can be further divided into the following sub-types:

**Gas-generating Systems**

Principle mechanism of floating in this system is the release of CO\textsubscript{2} gas. These buoyant delivery systems utilize effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO\textsubscript{2}, which gets entrapped in the jellified hydrocolloid layer of the systems, hence decreasing its specific gravity and making it float over chyme.

**Volatile Liquid Containing Systems**

These type of delivery systems containing two chambers which is separated by an impermeable, pressure-responsive, movable bladder. The first chamber contains the drug and the second one chamber contains the volatile liquid. The device inflates, and the drug is continuously released from the reservoir in the gastric fluid.

**Bio/Muco-adhesive systems**

The mechanism of action of Bio/muco-adhesive systems is bind to the gastric epithelial cell surface or mucin, which prolong the GRT of drug delivery in the stomach. Here mucin showing a good surface epithelial adhesive properties have so that it well recognized and applied to the development and formulation of GRDDS based on bio/muco-adhesive polymers. The ability to exhibit adhesion of a drug delivery system to the gastrointestinal wall provides prolong residence time in a organ specific site, hence; producing an improved effect in terms of local action or systemic effect. Binding of polymers to the mucin/epithelial surface can be divided into three categories:\textsuperscript{17}

1. Hydration-mediated
2. Bonding-mediated
3. Receptor mediated

**Hydration-mediated Adhesion**
Some of the hydrophilic polymers imbibe large amount of water and become sticky, so as to provide bioadhesive properties.

**Bonding-mediated Adhesion**
The adhesion of polymers to a mucus/epithelial cell surface involves various bonding mechanisms, such as physical-mechanical bonding and chemical bonding.

The physical-mechanical bonds are produced from the insertion of the adhesive material into the folds or crevices of the mucosa leading to adhesion. The chemical bonds include either covalent (primary) or ionic (secondary) bonds. Secondary chemical bonds exhibit of dispersive interactions (i.e., van der Waals interactions) and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups.

**Receptor-mediated Adhesion**
Some of the polymers whenever bind to specific receptor sites on the cell surfaces, it improve the gastric retention of dosage forms. Various investigators have proposed different mucin-polymer interactions, such as:
- Wetting and swelling of the polymer to permit intimate contact with the biological tissue
- Interpenetration of bioadhesive polymer chains and entanglement of polymer and mucin chains
- Formation of weak chemical bonds
- Sufficient polymer mobility to allow spreading

**Raft Forming Systems**
Raft forming drug delivery systems is popularly known to be delivery of antacids and for gastrointestinal infections and disorders. It can be simply defined as a flat structure, typically made of planks, logs, or barrels, that floats on water and is used for transport or as a platform for swimmers.

The raft forming system contains a gel forming agent (such as alginic acid) and alkaline bicarbonates or carbonates responsible for the formation of CO\textsubscript{2} that make the system less dense (low bulk density created by the formation of CO\textsubscript{2}) and float on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus. The gel forming agent, sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids each portion of the liquid swells forming a continuous layer called a raft.

**High Density Systems**
These type of systems having density of about 3 g/ cm\textsuperscript{3} get retained in the rugae of the stomach and showing a significant effect on peristaltic movements. A density of 2.6-2.8 g/ cm\textsuperscript{3} acts as threshold value and thereby, this system can be retained in the lower part of the stomach. High density formulations include coated pellets. Coating is accomplished by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. They are retained in the antrum of stomach.

**Low Density Systems**
Generally, most of the low density systems are multiple unit systems, also called as “microballoons” because of low-density core. Low density systems (<1g/cm\textsuperscript{3}) provide immediate buoyancy have been advantages to developed these system because, the gas-generating systems showing a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. These are made of low density materials, entrapping air or oil.
Super-porous Hydrogels
This is achieved by a co-formulation of a hydrophilic particulate material, Ac-Di-Sol (crosscarmellose sodium). Super-porous hydrogels, having an average pore size (>100 μm), swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores. Further it tends to swell to a large size (swelling ratio 100 or more) and achieved sufficient mechanical strength to withstand pressure by gastric contractions.\textsuperscript{18,19}

CONCLUSION
Based on the literature surveyed, it may be concluded that drug absorption in the gastrointestinal tract is a highly variable process and prolonging gastric retention of the dosage form extends the time for drug absorption. The major advantage of GRDDS is to get assurance that physiological conditions like GRT will work in favor of developed systems. All these Gastroretentive drug delivery systems (high density, floating, expandable or unfoldable or swelling, Superporous, bioadhesive, magnetic systems etc.) are interesting and present their own advantages and disadvantages. The pricey and difficult job of bioavailability and bioequivalence studies of GRDDS can be smoothly accomplished by understanding regulatory aspects of these studies.

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DECLARATION OF INTEREST
It is hereby declared that this paper does not have any conflict of interest.

REFERENCES