ADVANCES IN GASTRORETENTIVE DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Oral route of drug delivery has been the most conventional and accepted route of drug delivery, among these controlled release (CR) dosage forms have been extensively used to improve therapy. Controlled release drug delivery systems that retain in the stomach for a long time have many advantages over sustained release formulations. Gastroretentive dosage forms (GRDF) has received significant interest in the past few decades as they can improve the limitation of most conventional and oral controlled release drug delivery system related to fast gastric-emptying time. An optimum GRDF system can be defined as a system which retains in the stomach for a sufficient time interval against all the physiological barriers, releases active moiety in a controlled manner. Gastric retention may increase solubility for the drugs which are poorly soluble in intestine due to alkaline pH before they are emptied, resulting in improved bioavailability. Gastroretentive drug delivery system has applications for local drug delivery to the stomach and also for proximal small intestine. Gastro retention helps to provide better availability of new products with new therapeutic possibilities. This article gives an overview of the different approaches of GRDF as well as on the evaluation of GRDF.

KEYWORDS: Gastroretentive Dosage Forms, Gastrointestinal Tract, Bioadhesive Systems, Unfolding Systems, Density Controlled Systems.

INTRODUCTION

Now days the oral route represents the predominant and most preferable route for drug delivery for the administration of therapeutic agents. Numerous oral extended release drug
delivery systems have been developed to prolong drug release. An important prerequisite for successful performance for an oral extended release drug delivery system is that the drug should have good absorption throughout the whole gastrointestinal tract (GIT) to ensure continuous absorption of released drug.\textsuperscript{[1, 2]} But for large number of drugs, transport across the intestinal epithelium in each segment of GIT is not uniform and often limited to a particular segment (window) only. So, the oral extended release drug delivery becomes more difficult due to the inability to restrain and localize the drug delivery system within the desired region of GIT. Under such conditions, one of the most feasible approach for achieving a prolonged and predictable drug delivery profile in GIT is to control the gastric residence time by designing a delivery system that is able to reside in stomach or preferably prior to absorption window that would increase the absorption of drugs. The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance. These considerations have led to development of unique oral controlled release dosage forms with gastroretentive properties.\textsuperscript{[3, 4]}

**WHY GASTRORETENTIVE DRUG DELIVERY??**

Drugs which are easily absorbed from the gastrointestinal tract and those with short half-lives are quickly eliminated from the systemic circulation due to which frequent dosing is required. To overcome this problem, gastroretentive drug delivery systems which provide effective plasma drug concentration for longer periods thereby reducing the dosing frequency are being formulated. It also has an advantage of minimising the fluctuations in plasma drug concentration by delivering the drug in a controlled and reproducible manner.\textsuperscript{[5, 6, 7]}

**ADVANTAGES\textsuperscript{[8, 9]}**

- Slow release of the drug into the body reduces the counter activity to minimum level leading to higher drug efficiency.
- FDDS reduces the drug concentration fluctuation that makes it possible to obtain certain selectivity in the exact pharmacological effect of drugs that are supposed to activate different types of receptors at different concentrations.
- Retention of the drug in the gastric formulation at stomach minimizes the amount of drugs that reaches the colon, thereby preventing the degradation of drug that degrades in the colon.
• GRDDS is highly advantageous in case of drugs having local action e.g. Antacids. The bioavailability of many drugs increases when formulated as Floating dosage form. e.g. Riboflavin Controlled release Gastroretentive Dosage form (CR-GRDF) is highly bioavailable than non GRDF-CR polymeric formulations.

• Drugs like aspirin that cause irritation to gastric mucosa when come in contact with it. Therefore to overcome this formulation of such drugs is prepared for administration.

DISADVANTAGES\[10\]
• These systems require a high level of fluid in the stomach for drug delivery the stomach, so that the drug dosage form float and work efficiently.
• Not suitable for drugs that have solubility or stability problem in GIT.
• This system is not suitable for drugs that irritate the gastric mucosa and the drugs that are not stable in the stomach’s acidic environment.
• These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract.
• Certain drugs get well absorbed along the gastric tract and undergo significant first pass metabolism, may not be suitable for floating systems because of the slow gastric empting that leads to reduced systemic bioavailability.

REQUIREMENTS FOR THE GASTRORETENTIVE FORMULATIONS
• It must form a cohesive gel barrier to facilitate retention.
• It must maintain specific gravity lower than gastric contents.
• It should release contents slowly to serve as a reservoir.

Selection of excipients is an important strategic decision for designing a dosage form with consistence and controlled residence in the stomach. Water soluble cellulose derivatives represent a typical class of polymers best suited for such purposes. It has been suggested that higher molecular weight polymers and slower rates of polymer hydration are usually associated with better floating behaviour.\[11\]

Table 1: Table showing drug candidates suitable for Gastroretentive Systems\[12\]

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Drug candidate</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drugs acting locally in the stomach</td>
<td>Antacids and drugs for H. Pylori viz., Misoprostol</td>
</tr>
<tr>
<td>2</td>
<td>Drugs that are primarily absorbed in the stomach</td>
<td>Amoxicillin</td>
</tr>
</tbody>
</table>
3 | Drugs that are poorly soluble at alkaline pH | Furosemide, Diazepam, Verapamil, etc.  
4 | Drugs with a narrow window of absorption | Cyclosporine, Methotrexate, Levodopa, etc.  
5 | Drugs which are absorbed rapidly from the GI tract. | Metronidazole, tetracycline.  
6 | Drugs that degrade in the colon. | Ranitidine, Metformin HCl.  
7 | Drugs that disturb normal colonic microbes | Antibiotics against Helicobacter pylori

### APPROACHES FOR GASTRIC RETENTION

**Fig. 1: Figure showing various approaches for gastroretentive drug delivery system**

A. **Floating System**

The bulk density of this system is greater than gastric fluids and therefore, remains buoyant in the stomach without causing any effect on the gastric emptying rate for a long time period. The drug releases slowly while the system is floating on the gastric fluid. After drug is released, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. This can be further divided effervescent and non-effervescent system.

1. **Effervescent systems**

A drug delivery system can be made to float in the stomach by incorporating a floating chamber which may be filled with vacuum, air or inert gas. The gas in the floating chamber can be introduced either by the volatilization of an organic solvent or by the effervescent reaction between organic acids and bicarbonate salts.

2. **Non-Effervescent systems**

These are a type of floating gastro retentive drug delivery systems in which gel forming hydrocolloids, polysaccharides and matrix forming polymers like polycarbonate, polystyrene, polymethacrylate etc are used. These are further classified as follows,
i. **Hydrodynamically balanced systems**

This system contains drug with gel forming hydrocolloids formulated into a single unit dosage form. Upon contact with gastric fluids, the hydrocolloids swell to form a gel barrier which facilitates the system to remain buoyant in the stomach.

ii. **Microballoons / hollow microspheres**

These systems contain outer polymer shell loaded with drug. The outer polymer shell is made up of polymers like polycarbonate, cellulose acetate, calcium alginate, agar, etc. Buoyancy lag time and drug release from the system is dependent on the quantity of polymers used in the formulation. These are prepared by emulsion-solvent diffusion method. The steps involved are summarized in Figure 2.[13]

![Flowchart showing steps involved in preparation of microballoons](image)

**Fig. 2:** Flowchart showing steps involved in preparation of microballoons

### B. Bioadhesive Systems

The term bioadhesion is defined as adhesion to biological surface i.e. mucus and/or mucosal surface. In instances when the polymeric system interacts with mucus layer only, it is referred as mucoadhesion. In order to develop an ideal oral bioadhesive system, it is important to have a thorough understanding of mucosa, bioadhesive polymers and mucin-polymer interactions in the physiological environment. Intestinal mucosa is composed of high molecular weight glycoproteins hydrated and covering the mucosa with a continuous adherent blanket. Mucin glycoproteins are rich with fucose and sialic acid groups at the terminal ends which provide a net negative charge in the acidic environment. The thickness of the mucin gel layer varies in different regions of the GIT with thickness ranging between 50-500μm in stomach to 15-150μm in the colon. Cohesion of the mucin gel is dependent upon the glycoprotein
concentration. The mucus layer is created biologically to play a number of important functions of protecting the underlying tissues from various diffusing/corrosive elements such as enzymes, acid and other toxic molecules. Also being a visco-elastic gel, it helps in the passage of food over the epithelium, thereby minimizing potential erosive damages. The mucus layer, in addition to providing protection, provides a barrier to drug absorption.\[14\]

### C. High Density Systems

Gastric contents have a density close to water (1.004 g/cm\(^3\)). When the patient is upright small high-density pellets sink to the bottom of the stomach where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. A density close to 2.5 g/cm\(^3\) seems necessary for significant prolongation of gastric residence time and barium sulphate, zinc oxide, iron powder, titanium dioxide are used as excipients.\[15\]

![Fig. 11: Figure showing the high density systems which are at the bottom of the stomach and low density systems which are floating.](image)

### D. Swellable/Expandable systems

These systems are capable of expanding and retain in the stomach for longer periods. These are usually formulated as a capsule containing dosage form in folded and compact form. After being exposed to stomach environment, capsule shell disintegrates and dosage form expands preventing its exit through the stomach. By using a suitable polymer, sustained and controlled drug delivery can be achieved.\[16\]
Marketed Products\textsuperscript{[17, 18]}

Table 2: Table showing various marketed products with their product name, active ingredient and use

<table>
<thead>
<tr>
<th>S.No</th>
<th>Product name</th>
<th>Active ingredient</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Valrelease®</td>
<td>Diazepam</td>
<td>Treatment of depression</td>
</tr>
<tr>
<td>2</td>
<td>MadoparHBS®</td>
<td>Levodopa and benserazide</td>
<td>Anti-parkinsonism</td>
</tr>
<tr>
<td>3</td>
<td>Gaviscon®</td>
<td>Alginic acid</td>
<td>Antacid</td>
</tr>
<tr>
<td>4</td>
<td>Conviron®</td>
<td>Ferrous sulphate</td>
<td>Antianaemic</td>
</tr>
<tr>
<td>5</td>
<td>Cifran OD®</td>
<td>Ciprofloxacin</td>
<td>Systemic treatment of infections</td>
</tr>
</tbody>
</table>

Evaluation

Measurement of buoyancy capabilities of the FDDS

The floating behaviour was evaluated with resultant weight measurements. The experiment was carried out in two different media like deionised water and simulated meal, in order to monitor possible difference. The results showed that higher molecular weight polymers with slower rate of hydration had enhanced floating behavior and which was more in simulated meal medium compared to deionised water.\textsuperscript{[19]}

Floating time

The test for floating time is usually performed in simulated gastric fluid or 0.1 N HCl maintained at 37°C, 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.\textsuperscript{[20]}

In vitro drug release

Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution.

Drug loading, drug entrapment efficiency, particle size analysis, surface characterization (for floating microspheres and beads)

Drug loading is assessed by crushing accurately weighed sample of beads or microspheres in a mortar and added to the appropriate dissolution medium which is then centrifuged, filtered and analyzed by various analytical methods like spectrophotometry. The percentage drug loading is calculated by dividing the amount of drug in the sample by the weight of total beads or microspheres. The particle size and the size distribution of beads or microspheres
are determined in the dry state using the optical microscopy method. The external and cross-sectional morphology (surface characterization) is done by scanning electron microscope (SEM).[21]

**Resultant weight**

The in vitro measuring apparatus has been conceived to determine the real floating capabilities of buoyant dosage forms as a function of time. It operates by force equivalent to the force, \( F \) required to keep the object totally submerged in the fluid. This force determines the resultant weight of the object when immersed and may be used to quantify its floating or non floating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the Victoria sum of buoyancy (\( F_{\text{buoy}} \)) and gravity (\( F_{\text{grav}} \)) forces acting on the objects as shown in the equal,

\[
F = F_{\text{buoy}} - F_{\text{grav}}
\]

\[
F = dfgV - ds gV = (df-ds) gV
\]

\[
F = (df - M/V) gV
\]

In which the \( F \) is total vertical force (resultant weight of the object), \( g \) is the acceleration due to gravity, \( df \) if the fluid density, \( ds \) is the object density is the object mass and \( V \) is the volume of the object.[22]

**Fig. 3:** Schematic view of resultant weight measuring system

**CONCLUSION**

This article provides information regarding the gastroretentive drug delivery systems and its evaluation process. The foregoing shows that gastroretentive drug delivery systems have great potentials, for formulating both hydrophobic and hydrophilic active substance into
promising deliverable drugs. To optimize this drug delivery system, greater understanding of
the different mechanisms of biological interactions, and polymer is required. In spite of
number of difficulties to be worked out to achieve prolonged gastric retention, many
pharmaceutical companies are focussing towards commercialization of this technique.

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