**An Updated Review on Gastro Retentive Drug Delivery System**

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**ABSTRACT**

The very effective and approved method for applying drug has been oral route. Owing to the great curative advantages of oral controlled release dosage types, improved therapeutic advantages are favored as the interesting subject in the pharmaceutical field. One such innovative advance to prolonging gastric residence time is the gastroretentive drug delivery system, which objects site-specific medicine free in the abdomen for systemic or local effect. This technique is especially helpful for the medicine in the upper part of the gastrointestinal tract which have narrow absorption window. The article aims to summarize the various approaches to gastroretentive behavior. We also summarized important factors affecting gastric retention to consider increasing physiological difficulties in achieving gastric retention. Recently implemented gastrointestinal innovations such as expandable, super porous hydrogel; bio / mucoadhesive, elastic, ion-exchange resin; and low- and high-density systems with their merits and demerits have also been studied. Eventually, the criteria of assessment of the gastroretentive drug delivery systems are addressed.

**Keywords:** Gastro retentive system, Floating Delivery, Gastric Residence Time, (GRT), Physiology of Stomach

**INTRODUCTION**

Due to the tremendous curative advantages of the orally controlled release dosage types, the important research subject over the past 3 decades is preferred4. Around 50% of on-the-market drug delivery systems are oral delivery systems with greater benefits due to consumer acceptance and ease of administration5. Due to short gastric retention time (GRT), i.e. the time taken to reach small intestine by the abdomen content3, oral absorption of drugs is also impeded. Drugs that are readily absorbed from GIT & have a short shelf-life are rapidly eliminated from circulation in the blood, and they need repeated dosing. To overcome this restriction, production of oral sustained-controlled release dosage form is an effort to gradually free the medication into the gastrointestinal tract (GIT) and long-term retain an appropriate concentration of the medication in the general circulation. Such a drug delivery should be maintained in the abdomen after oral administration and released in a controlled manner, so that the medication may possibly consistently distributed to its gastrointestinal tract incorporation sites (GIT)4.

Consequently, the “gastro-retentive drug delivery system” is beneficial for these medications by enhancing their bioavailability, therapeutic effectiveness & potential dose decrease. Drug absorption in the “gastrointestinal tract” is a highly variable process which depends on factors such as gastric emptying, the “gastrointestinal transit time of dosage forms”, the release of drugs from the dosage form and the location of drug absorption4,5,6.

**Need for “Gastroretentive drug delivery system”**:7

- Within the pharmaceutical sector traditional oral delivery is commonly used to treat diseases. However, traditional distribution has many inconveniences and main disadvantages are non-site specificity.
- “Gastro-retentive drug delivery” is one of the site-specific routes for drug delivery either in the abdomen or in the intestine. It is administered by maintaining the dosage type in the stomach & the drug is distributed to various locations in the stomach, duodenum and intestine in a controlled manner.

**Stomach**

The stomach is situated just under the diaphragm in the upper left part of the abdomen 14. It occupies a section of the hydrochondriazone and epigastric. The principal purpose of the stomach is to temporarily store the food, grind it and then gradually release it into the duodenum. Too little leakage from the stomach occurs because of its low surface area 15.
Table 1: Suitable Drug Candidates for Gastroretentive Drug Delivery System  

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Suitable Drug Candidates</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Medicines which are absorbed mainly in the abdomen</td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>2</td>
<td>Medications which are freely soluble in basic pH</td>
<td>Diazepam, Furosemide</td>
</tr>
<tr>
<td>3</td>
<td>Medicines which degrade in the colon</td>
<td>Metformin HCl, Ranitidine</td>
</tr>
<tr>
<td>4</td>
<td>Drugs with narrow absorption window</td>
<td>Levodopa, Methotrexate</td>
</tr>
<tr>
<td>5</td>
<td>Medicines which were quickly absorbed from the GI tract</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>6</td>
<td>Medicines which agitate common colonic microbes</td>
<td>Antibiotics against <em>Helicobacter Pylori</em></td>
</tr>
<tr>
<td>7</td>
<td>Medicines which work in the abdomen locally</td>
<td>Amoxicillin, Clarithromycin, Misoprostol</td>
</tr>
</tbody>
</table>

Table 2: Unsuitable drug for Gastroretentive drug delivery system

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Suitable Drug candidates</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drugs which have a very small solubility in acid</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>2</td>
<td>Drugs which suffer from gastric instability</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>3</td>
<td>Medicines targeted for specific release in the colon</td>
<td>5-amino salicylic acid and corticosteroids</td>
</tr>
</tbody>
</table>

Table 3: Advantages and Disadvantages of “Gastroretentive Drug Delivery System”

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>It improves patient observance by raising the regularity of dosing</td>
<td>The limitation of floating systems is so as to they need high levels of stomach fluids for efficient floating. And with such dosage type more water consumption is recommended.</td>
</tr>
<tr>
<td>2</td>
<td>Buoyancy increases the time spent in gastric residence</td>
<td>In supine posture (like sleeping), contractile waves can sweep away the floating dosage type (if not of greater size). Therefore, patient must not take floating formulation just before bedtime.</td>
</tr>
<tr>
<td>3</td>
<td>Better therapeutic efficacy of short-lived drugs</td>
<td>Drugs with problems of stability in a high acidic medium, with very low solubility in acidic medium, and medicine that cause impatience of gastric mucosa cannot be absorbed into the GRDDS.</td>
</tr>
<tr>
<td>4</td>
<td>Site-specific delivery of medication to the stomach</td>
<td>Bio / mucoadhesive systems have problems with high takings of mucus layer, thick mucus layer and related limitations of soluble mucus.</td>
</tr>
<tr>
<td>5</td>
<td>Sustained release can prevent gastric irritation.</td>
<td>Swellable formulations have to able of swelling rapidly before leaving the abdomen and attaining a size greater than pylorus aperture. It has to able of resisting MMC phase III housekeeper waves.</td>
</tr>
<tr>
<td>6</td>
<td>By making particular floating unit such as microspheres release medicine equivalently, no possibility of dumping.</td>
<td>Gastric retention is partial by a number of factors, including gastric motility, pH and food presence. Such variables are never constant and thus we cannot predict the buoyancy.</td>
</tr>
<tr>
<td>7</td>
<td>Delivery of drugs in small intestine region, with narrow absorption window.</td>
<td>The big challenge for a bio-adhesive method is the high rate of gastric mucus turnover.</td>
</tr>
<tr>
<td>8</td>
<td>Longer stomach residence time might be beneficial for local action in upper part of small intestine</td>
<td>Oesophageal binding to bioadhesive drug delivery systems is also possible.</td>
</tr>
</tbody>
</table>

Structure and Function

Stomach is classified by human anatomy into three main parts: fundus, neck, and antrum (pylorus). The proximal part called the fundus, and the body acts as storage for undigested food. The antrum provides the central mixing site, and serves as a gastric emptying pump by propeller actions. The stomach also develops endogenous factor in its parietal cells, in addition to HCl. The intrinsic factor developed at this digestive stage allows the subsequent absorption of vitamin B<sub>12</sub> (cobalamin) into the small intestine. The production of the intrinsic factor is crucial because vitamin B<sub>12</sub> plays a significant role in the development of red blood cells and neurological functions. Many of these products include dehydration-
setting water, some medicines, including aspirin, amino acids, ethanol, caffeine, and certain water-soluble vitamins. In fact, acidic stomach condition can be lethal to several forms of bacteria and other micro-organisms entering the body through ingestion, potentially shielding the body from infection and disease.16-19.

**Physiology**

The primary function of the stomach is food preparation and transport. The stomach allows for reservation of short-term food and fast intake of fairly large meals. The main important enzyme metabolism is encouraged in proteins stomach. Stomach peristalsis mix up and grind eaten food with stomach secretions, transforming it into a diluted liquid shape. The liquefied bulk is transported to the small intestine for further digestion.20-22.

An inter digestive myoelectric cycle or migratory myoelectric cycle (MMC) phenomenon occurs, which is divided into 4 phases as Wilson and Washington have provided. The 4 phases are enumerated below and also shown in Figure 1.

**Factors Controlling GRDDS**

Some of the factors are enumerated below:

**Density**

Dosage type with lesser density in the stomach substance can float to the outside, while greater density sinks to stomach underneath. The proper density necessary for floating properties is lower than 1 gm/cm³.

**Size**

Size must to be higher than 7.5 mm in thickness.

**Shape**

Either in circles or sphere-shaped formulation exhibit improved property associated to other shapes.

**Multiple Unit Formulation**

Multiple units are advantageous due to foretell release profile.

**Nature of Meal**

High concentrations of fatty acid and other indigestible polymers slow down the stomach processing time due to gastric motility variations.

**Frequency of Feed**

Low frequency of myoelectric complex migration (MMC) contributes up to 400 times to GRT, which in turn depends on the level of food intake.

**Age**

GRT is more common in geriatric patients, and less common in neonates and infants. Age over 70 (> 70) shows GRT for longer.

**Concomitant Intake of Drug**

Mixture of some drugs along with gastric motility enhancers or depressants, affect “Gastro retention time”.23, 24, 25.

**Gastroretentive Techniques**

Various strategies have been investigated, including floating, swelling, contraction and adhesion, to improve the gastro-retention of dosage types.26.

**Types of Gastroretentive Dosage Form**

**Floating Systems**

In these systems are devices of low density which have ample buoyancy to float over the gastric content and stay in belly for an extended period of time. As the device floats above the gastric material, the drug is released gradually at the target rate resulting in improved GRT and decreases changeability in the concentration of plasma drugs. The floating drug delivery system and the delivery of bioadhesive drugs are commonly used methods for gastro retention, and floating systems in particular have been thoroughly studied, primarily because the floating mechanism does not adversely affect GI tract motility.
Effervescent and non-effervescent systems may also be listed as floating systems\textsuperscript{27,28}.

**Classification of Floating Drug Delivery System**

**Effervescent system**

The creation of gas bubbles helps bring about floatability. The polymers which are swellable viz. Methyl cellulose, chitosan, as well as various effervescent compounds, such as sodium bicarbonate, citric acid, help to build matrix-type structures of this type\textsuperscript{23}. They are produced in such a way that CO\textsubscript{2} is eventually released into swollen hydrocolloids when it comes to contact with gastric material, rendering dosage forms buoyant \textsuperscript{29}. Such structures are additionally known as:

1. Volatile Liquid Containing System
2. Matrix Tablets Systems
3. Gas Generating Systems

**Non-effervescent System**

The non-effervescent floating dosage forms include swellable hydrocolloid, polysaccharide, and matrix forming polymers such as polycarbonate, polyacrylate, and polystyrene\textsuperscript{25}. The formation has a simple approach, i.e. mixing of medicine and gel, followed by swelling by contracting with gastric fluid after oral administration, thus preserving a relative integrity of the form and retaining a bulk density of less than one (< 1)\textsuperscript{25, 26}. Owing to air trapped in the swelled up matrix the dosage type achieves its buoyancy. This swollen up matrix reserves drug and maintains sustained drug release via gelatinous mass \textsuperscript{26}. The most widely used excipients are hydroxylpropyl methyl cellulose (HPMC), polyacrylate, and polycarbonates \textsuperscript{30}.

1. Hydrodynamically balanced systems
2. Alginate beads
3. Microballoons/Hollow Microsphere
4. Layered Tablet

**A. Single Layered Floating Tablet**

**B. Double Layered Floating Tablet**

**Table 4: Commonly Used Drugs in Formulation of GRDDS\textsuperscript{31,49}**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulation</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tablet</td>
<td>Aceraminophen, Acetylsalicyclic acid, Amoxicillin trihydrate, Atenolol, Ampicillin, Captopril, Cephalexin, Ciproflaxacin, Cinnarazine, Chlorthalidone maleate, Diltiazem, Flurazepam, Furosemide, Isosorbide dinitrate, Isosorbide mononitrate, Losartan, Metformin hydrochloride, Nimodipine, P-Aminobenzoic acid (PABA), Pentaxorfin, Prednisolone, Piretanide, Riboflavin, Sotalol, Theophyllin, Verapamil HCl, Zidovudine</td>
</tr>
<tr>
<td>2</td>
<td>Capsule</td>
<td>Chlordizepoxide HCI, Celiprolol HCI, Diazepam, Furosemide, L-Dopa and Benserazide, Misoprostal, Nicardipine, Pepstatin, Propranol, Urodeoxycholic acid</td>
</tr>
<tr>
<td>3</td>
<td>Films</td>
<td>Albendazole, Cinnarizine, P-Aminobenzoic acid (PABA), Piretanide, Prednisolone, Quinidine gluconate</td>
</tr>
<tr>
<td>4</td>
<td>Microspheres</td>
<td>Aspirin, Cholestyramine, Diprydamol, Flurbiprofen, Griseofulvin, Ibuprofen, Ketoprofen, Nicardipine, Nifedipine, Orlistat, P-nitroaniline, Piroxicam, Rosiglitazone maleate, Terfenadine, Theophylline, Tranilast, Verapamil, amoxicillin</td>
</tr>
<tr>
<td>5</td>
<td>Powders</td>
<td>Several basic drugs-Riboflavin, Sotalol, Theophylline.</td>
</tr>
<tr>
<td>6</td>
<td>Granules</td>
<td>Cinnarizine, Diclofenac sodium, Diltiazem, Fluorouracil, Indomethacin, Isosorbide dinitrate, Prednisolone, Ranitidine HCl</td>
</tr>
<tr>
<td>7</td>
<td>Beads</td>
<td>Beta-cyclodextrin, Curcumin, Diltiazem HCl, Loratidine, Ranitidine HCl</td>
</tr>
</tbody>
</table>

**Non-floating System**

These “Gastro-Retentive Drug Delivery Systems” do not float in the belly but are maintained by different mechanisms.

**Bioadhesive System**

Such types of systems adhere to the stomach’s biological membrane (mucosa) and sustain a longer duration of intimate interaction with the membrane, while maintaining their prolonged release in the stomach. Such systems are formulated using polymers with bio adhesives. \textsuperscript{32}

**Magnetic Systems**

This approach to improving gastric retention time (GRT) is based on the basic premise that the dosage type comprises a small internal magnet and a magnet over the stomach location mounted on the abdomen. While the magnetic device tends to wobble, the external magnet needs to be placed with a degree of accuracy that could impede patient compliance \textsuperscript{33}.

**High-density Systems**

These devices, which have a density of \textasciitilde3 g/cm\textsuperscript{3}, are held in the stomach rugae and are able to withstand the peristaltic movements. These systems may be maintained in the lower part of the stomach above a threshold density of 2.4–2.8 g / cm\textsuperscript{3}. Diluents such as barium sulphate (density = 4.9), zinc oxide, titanium dioxide, and iron powder can be used to manufacture formulations of this high density\textsuperscript{34, 35}.\hfill
Size Increasing System

**Expandable, Unfoldable and Swellable Systems:**

If it is larger than the pyloric sphincter, a formulation in the stomach will tolerate gastric movement. The dosage form must, however, be small adequate to be swallowed, and should not cause stomach obstruction either individually or by accumulation. Their configurations are therefore necessary to build an expandable framework for extending GRT:

Gastoretentivity is thus enhanced by the combination of significant dimension with high dosage shape rigidity to withstand peristalsis and mechanical stomach contractility. Unfoldable and swellable devices have been tested, and a successful delivery of gastoretentive drugs has been recently attempted. Unfoldable structures are constructed from biologically degradable polymers. These are available in various geometric types such as tetrhedron, ring or planner membrane (4-mark disk or 4-limbed cross-shape) of compressed bio erodible polymer inside a capsule that extends in the stomach.

**Raft-forming System:**

Raft System integrates alginate gels which have a carbonate component and create bubbles in the gel when reacted with gastric acid, allowing floating. Rafting formation devices have provided substantial attention for the delivery of drugs for GI infections and disorders. The process involves the creation of viscous cohesive gel in contact with gastric fluids, in which each portion of the liquid swells into a continuous layer called a raft. This raft is floating on gastric fluids due to low bulk density provided by CO₂ formation. An antacid raft forming floating device involves a gel forming agent (e.g. sodium alginate), sodium bicarbonate, and acid neutralizer forming a foaming sodium alginate gel (raft), which, when in contact with gastric fluids, floats on gastric fluids and prevents the reflux of gastric material (e.g. gastric acid) into the esophagus by serving as a barrier between the stomach and esophagus.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Non-floating Systems</th>
<th>Mechanism</th>
<th>Polymer Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bioadhesive systems</td>
<td>Bioadhesive systems bind to the stomach’s biological membrane (mucosa) and sustain a longer period of intimate interaction with the membrane, thereby remaining in the stomach for its prolonged release.</td>
<td>Carbopol, Carboxy methylcellulose, Chitosan, Dextrin, Gliadin, Lectin, Hydroxy methylcellulose, Polyethylene glycol, Polycarbophil, Poly acrylic acid, Sodium alginate, Sucralfate, Tragacanth</td>
</tr>
<tr>
<td>2</td>
<td>Magnetic System</td>
<td>This approach to improving gastric retention time is based on the basic premise that the dosage shape includes a small internal magnet and an external magnet above the stomach location.</td>
<td>Magnet</td>
</tr>
<tr>
<td>3</td>
<td>High Density Systems</td>
<td>Such systems have a greater density than the gastric fluids, because of which the organ sinks to the bottom and stay in the stomach.</td>
<td>Barium sulphate, Iron, Titanium dioxide, Zinc oxide</td>
</tr>
<tr>
<td>4</td>
<td>Swelling Systems</td>
<td>These dosage forms swell to a size after being swallowed which prevents their passage through the pylorus.</td>
<td>Acacia, Agar, Bentonite, Casein, Chitosan, Gellan gum, Hydroxy propyl cellulose, Hydroxy propyl methyl cellulose, Pectin, Sodium carboxy methyl cellulose, Veegum</td>
</tr>
<tr>
<td>5</td>
<td>Raft Forming system</td>
<td>This raft is floating on gastric fluids due to low bulk density provided by CO₂ formation.</td>
<td>Alkaline bicarbonates or carbonates</td>
</tr>
</tbody>
</table>

**CONCLUSION**

“Gastoretentive drug delivery system” has emerged as an effective means of prolonged stomach retention capacity, thereby increasing the gastric residence time of drug and also improving drug bioavailability. Increasing understanding of the effect of gastrointestinal tract physiology on drug delivery will make sure a growing number of drug delivery systems are built to optimize drug delivery of molecules with regional variation of drug absorption. Currently, a lot of work is under way to establish various forms of “gastoretentive delivery systems” of various drugs. These are expected to become increasingly relevant in the future, potentially leading to enhanced efficiencies of various forms of pharmacotherapies.

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**REFERENCES**


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