GASTRORETENTIVE DRUG DELIVERY SYSTEMS: A PROMISING APPROACH

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ABSTRACT

The recent scientific literature showed that more interest in novel dosage forms in GRDDS over several advantages of conventional dosage form which retained in stomach for longer and predictable time period. Many methodological attempts have been tried in the development of rate controlled oral drug delivery systems to overcome short residence times in stomach. Approaches include floating drug delivery systems (FDDS), also known as Hydro dynamically balanced systems (HBS), Swelling & expanding systems, High-density systems, and other Delayed gastric emptying devices. Floating dosage form can be prepared in the form of tablets, capsules by adding suitable ingredients as well as by adding gas generating agent. In this review many techniques used in floating dosage forms along with current & recent developments of stomach specific floating drug delivery system for gastro retention are discussed.

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INTRODUCTION

In the last decades, considerable efforts have been made to develop new pharmaceutically viable & therapeutically effective controlled drug delivery systems [1]. In recent years scientific & technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, like short gastric residence times (GRT) and unpredictable gastric emptying times (GET) [2]. Dosage forms that can be retained in the stomach are called gastro retentive drug delivery systems (GRDDS) [3]. GRDD Devices are primarily site specific drug delivery systems, which gets retained in the stomach for longer period of time, thus helping in absorption of drug for the intended duration of time [4].

Fig. 1 Physiology of stomach.

Floating systems, first described by Davis in 1968, are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period [5]. Floating system is an important category of drug delivery systems with gastric retentive behavior [6]. While the system is floating on the gastric contents and the drug is released slowly at the desired rate from the system [7]. FDDS reside in the stomach for a longer period of time than conventional dosage forms [8]. After release of drug, the residual system is emptied from the stomach [9]. The contribution of floating drug delivery system includes; gastric retention time is increased because of buoyancy, site specific drug delivery to stomach & decreased dosing frequency, targeted therapy for local ailments in the upper GIT, better therapeutic effect of short half life drugs, increase absorption and bypass first pass metabolism of drugs soluble in stomach & reduced fluctuations of drug concentration could be achieved [5].

Pros of Floating Drug Delivery System (FDDS)

- Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs [10].
- Enhancement of the bioavailability for drugs which can metabolized in the upper GIT [11].
- FDDS are advantageous for drugs meant for local action in the stomach e.g., Antacids [12].
- Minimized adverse activity at the colon [13].
- FDDS are advantageous in case of vigorous intestinal movement and in diarrhea to keep the drug in floating condition in stomach to get a relatively better response [14].
- Floating drug delivery systems provide a support to reduce the frequent dosing of such drug by producing a controlled delivery within stomach for longer duration [15].
- The active entity is delivered specifically to the site of action, thus minimizing or eliminating the side effects [16].
- The floating systems are advantageous for drugs absorbed through the stomach e.g., ferrous salts, antacids [17 & 18].

Need for Gastro Retention in GRDDS:

- Drugs that are absorbed from the proximal part of the GIT [21].
- Drugs that are less soluble or that degrade by the alkaline pH the encounters at the lower part of GIT.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal small intestine to treat certain conditions.
- Drugs with variable bioavailability.
- Drugs with short half-life.
- Drugs those degrade in colonic ulcers caused by H. Pylori Infections [3].
Table 1: Gastro retentive Drug Delivery Systems vs. Conventional Drug Delivery Systems \[^{[4 \text{ & 20]}}\].

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Conventional DDs</th>
<th>GRDDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toxicity</td>
<td>High risk of toxicity</td>
</tr>
<tr>
<td>2</td>
<td>Patient compliance</td>
<td>Less</td>
</tr>
<tr>
<td>3</td>
<td>Drug with narrow absorption window in small intestine</td>
<td>Not suitable</td>
</tr>
<tr>
<td>4</td>
<td>Drugs having rapid absorption through GIT</td>
<td>Not much advantageous</td>
</tr>
<tr>
<td>5</td>
<td>Drug which degrades in the colon</td>
<td>Not much advantageous</td>
</tr>
<tr>
<td>6</td>
<td>Drugs acting locally in the stomach</td>
<td>Not much advantageous</td>
</tr>
<tr>
<td>7</td>
<td>Drugs which are poorly soluble at an alkaline pH</td>
<td>Not much advantageous</td>
</tr>
<tr>
<td>8</td>
<td>Dose dumping</td>
<td>High risk of dose dumping</td>
</tr>
</tbody>
</table>

Table 2: Patents for Some Floating Gastro-retentive Delivery Systems \[^{[18]}\].

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5,972,389</td>
<td>Gastric-retentive, oral drug dosage forms for the controlled release of sparingly soluble drugs and insoluble matter.</td>
</tr>
<tr>
<td>5,443,843</td>
<td>Gastric-retention system for controlled drug release.</td>
</tr>
<tr>
<td>5,232,704</td>
<td>Sustained-release, bilayer buoyant dosage form.</td>
</tr>
<tr>
<td>5,169,638</td>
<td>Buoyant controlled-release powder formulation.</td>
</tr>
<tr>
<td>4,814,179</td>
<td>Floating sustained-release therapeutic compositions.</td>
</tr>
<tr>
<td>4,767,627</td>
<td>Drug delivery device that can be retained in the stomach for a controlled period of time.</td>
</tr>
<tr>
<td>4,140,755</td>
<td>Sustained-release tablet formulations.</td>
</tr>
<tr>
<td>4,126,672</td>
<td>Sustained-release pharmaceutical capsules.</td>
</tr>
<tr>
<td>0013876 A1</td>
<td>Novel floating dosage form.</td>
</tr>
<tr>
<td>6,685,962 B2</td>
<td>Gastro retentive controlled release pharmaceutical dosage form.</td>
</tr>
<tr>
<td>6,207,197 B1</td>
<td>Gastro retentive controlled release microspheres for improved drug delivery.</td>
</tr>
<tr>
<td>6,120,803</td>
<td>Prolonged release active agent dosage form adapted for gastric retention.</td>
</tr>
<tr>
<td>0180086 A1</td>
<td>Gastro retentive levodopa delivery dosage form.</td>
</tr>
</tbody>
</table>
Table 3: VARIOUS MARKETED FDDS WITH ACTIVE INGREDIENTS AND DELIVERY TECHNOLOGIES

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Product</th>
<th>Technology</th>
<th>API</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zanocin OD</td>
<td>Effervescent floating system</td>
<td>Ofloxacin</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>2</td>
<td>Riomet OD</td>
<td>Effervescent floating system</td>
<td>Metformine HCl</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>3</td>
<td>Cifran OD</td>
<td>Effervescent floating form</td>
<td>Ciprofloxacin</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>4</td>
<td>Inon Ace tabs</td>
<td>Foam based floating system</td>
<td>Simethicone</td>
<td>SatoPharm, Japan</td>
</tr>
<tr>
<td>5</td>
<td>Gabapentin GR</td>
<td>Polymer swelling: AcuForm</td>
<td>Gabapentin</td>
<td>Depomed, USA</td>
</tr>
<tr>
<td>6</td>
<td>ProQuin XR</td>
<td>Polymer swelling: AcuForm</td>
<td>Ciprofloxacin</td>
<td>Depomed, USA</td>
</tr>
<tr>
<td>7</td>
<td>Glumetza</td>
<td>Polymer swelling: AcuForm</td>
<td>Metformin HCl</td>
<td>Depomed, USA</td>
</tr>
<tr>
<td>8</td>
<td>Metformin GR</td>
<td>Polymer swelling: AcuForm</td>
<td>Metformin HCl</td>
<td>Depomed, USA</td>
</tr>
<tr>
<td>9</td>
<td>Prazopress XL</td>
<td>Effervescent and swelling</td>
<td>Prazosin HCl</td>
<td>SunPharma, Japan</td>
</tr>
<tr>
<td>10</td>
<td>Metformin HCl LP</td>
<td>Minextab Floating</td>
<td>Metformin HCl</td>
<td>Galenix, France</td>
</tr>
<tr>
<td>11</td>
<td>Cafeclor LP</td>
<td>Minextab Floating</td>
<td>Cefaclor</td>
<td>Galenix, France</td>
</tr>
<tr>
<td>12</td>
<td>Tramadol LP</td>
<td>Minextab Floating</td>
<td>Tramadol</td>
<td>Galenix, France</td>
</tr>
<tr>
<td>13</td>
<td>Cipro XR</td>
<td>Erodible matrix system</td>
<td>Ciprofloxacin</td>
<td>Bayer, USA</td>
</tr>
<tr>
<td>14</td>
<td>Baclofen GRS</td>
<td>Floating &amp; swelling</td>
<td>Baclofen</td>
<td>SunPharma, India</td>
</tr>
<tr>
<td>15</td>
<td>Coreg CR</td>
<td>Gastro retention</td>
<td>Carvedilol</td>
<td>Glaxosmithkline</td>
</tr>
<tr>
<td>16</td>
<td>Madopar</td>
<td>Floating, CR capsule</td>
<td>Levodopa</td>
<td>Roche, UK</td>
</tr>
<tr>
<td>17</td>
<td>Liquid gaviscon</td>
<td>Effervescent floating liquid</td>
<td>Alginic acid</td>
<td>R. B. Healthcare.</td>
</tr>
<tr>
<td>18</td>
<td>Valrelease</td>
<td>Floating capsule</td>
<td>Diazepam</td>
<td>Roche, UK</td>
</tr>
<tr>
<td>19</td>
<td>Cytotec</td>
<td>Bilayer floating capsule</td>
<td>Misoprostol</td>
<td>Pharmacia Ltd, UK</td>
</tr>
<tr>
<td>20</td>
<td>Topalkan</td>
<td>Floating liquid alginate</td>
<td>Aluminum magnesium</td>
<td>Perrie Fabrie, France</td>
</tr>
<tr>
<td>21</td>
<td>Conviron</td>
<td>FDDS Colloidal gel</td>
<td>Ferrous sulfate</td>
<td>Ranbaxy, India</td>
</tr>
</tbody>
</table>

Types of Floating Drug Delivery Systems

Various approaches have been made to increase the retention of an oral dosage form in the stomach. These systems include:

- Floating systems
- Bioadhesive systems
- Swelling and expanding systems
- High density systems
- Modified systems

Floating Systems:

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach.

![Fig. 2 Floating Delivery system.](image)

Bioadhesive Systems:

It involves the use of bioadhesive polymers that can adhere to the epithelial surface of the GIT. Binding of polymers to mucin/epithelial surface can be divided into three broad categories: hydration-mediated adhesion, bonding-mediated adhesion and receptor-mediated adhesion. These types of systems adhere to the biological membrane (mucosa) of the stomach and maintain intimate contact with the membrane for a longer time and hence retains in stomach for its prolonged release.
Expandable System:

After being swallowed, these dosage gets swell to a size that prevents their passage through the pylorus [31]. These systems are sometimes referred to as plug type systems because they tend to remain lodged at the pyloric sphincter. A balance between the extent and duration of swelling is maintained by the degree of cross linking of the polymeric chains. A high degree of cross linking retards the swelling ability of the system and maintains its physical integrity for a prolonged period. The swollen system eventually will lose its integrity because of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures because of continuous expansion [31]. This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach [32]. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period [33, 43 & 35].

Yang et al developed a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole, clarithromycin) of Helicobacter pylori–associated peptic ulcers using HPMC and PEO as the rate-controlling polymeric membrane excipients [36]. Swellable polymers: methocel, polysaccharides like chitosan. (37)

![Swellable System](image)

Fig. 3 Swellable System.

High Density Systems:

These systems with a density of about 3g/cm³ are retained in the antrum part of the stomach and are capable of withstanding its peristaltic movements [38]. Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–2.4g/cm³ [39].

Formulation Considerations for GRDDS

- It must be effective for retention in the stomach to suit for the clinical demand.
- It must be convenient for intake to facilitate patient compliance.
- It must possess sufficient drug loading capacity and control drug release profile.
- It must have full degradation and evacuation of the system once the drug release is over.
- It should not have effect on gastric motility including emptying pattern [3].
- It should posses’ low specific gravity (1.004–1.015 g/cm³).

Suitable Drug Candidates for GRDDS

- Drugs that are poorly soluble at alkaline pH, e.g., Furosemide, Diazepam, Verapamil, etc [40 & 41].
- Drugs that degrade in the colon e.g., Ranitidine HCl & Metronidazole [42].
- Basically absorbed from stomach and upper part of GIT, e.g., Chlordiazepoxide and Cinnarazine [43].
- Drugs with narrow absorption window in GI tract, e.g., Para aminobenzoic acid, furosemide, riboflavin in a vitamin deficiency & Levodopa [43].
- Drugs that act locally in the stomach e.g., Antacids and Misoprostol.
- Drugs that are having primary absorption in the stomach e.g., Chlordiazepoxide, Calcium supplements, Cinnarazine, Metronidazole & Tetracycline.
- Drugs with variable bioavailability e.g., Sotalol HCl.
- Drugs Particularly useful for the treatment of peptic ulcers caused by H. Pylori Infection e.g., Antibiotics against [3].
The rapid removal of solvent from the embryonic microsphere leads to polymer precipitation at the o/w interface. This leads to the formation of cavity in microspheres, thus increasing the porosity. Whatman filter paper, washed thrice with n-hexane, air dried for 2 hrs and subsequently stored in desiccators.[18]

### Table 5: Good Candidates for Gastro-retentive Drug Delivery System

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Drug</th>
<th>Category</th>
<th>Half-Life (hrs)</th>
<th>Peak Time (hrs)</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Verapamil</td>
<td>Calcium channel blocker</td>
<td>6</td>
<td>1-2</td>
<td>20-35%</td>
</tr>
<tr>
<td>2</td>
<td>Nifedipine</td>
<td>Calcium channel blocker</td>
<td>2</td>
<td>0.5-0.2</td>
<td>45-65%</td>
</tr>
<tr>
<td>3</td>
<td>Omeprazole</td>
<td>Proton pump inhibitor</td>
<td>1-2</td>
<td>1</td>
<td>35-60%</td>
</tr>
<tr>
<td>4</td>
<td>Atenolol</td>
<td>Antihypertensive</td>
<td>4</td>
<td>3</td>
<td>40-50%</td>
</tr>
<tr>
<td>5</td>
<td>Propranolol</td>
<td>Antihypertensive</td>
<td>4-5</td>
<td>4</td>
<td>26%</td>
</tr>
<tr>
<td>6</td>
<td>Verapamil</td>
<td>Antihypertensive</td>
<td>6</td>
<td>1.8</td>
<td>35%</td>
</tr>
<tr>
<td>7</td>
<td>Diltilazem</td>
<td>Calcium channel blocker</td>
<td>3-4.5</td>
<td>50 min.</td>
<td>40%</td>
</tr>
<tr>
<td>8</td>
<td>Lidocaine</td>
<td>Local Anesthetics</td>
<td>1.5-2</td>
<td>4</td>
<td>35%</td>
</tr>
<tr>
<td>9</td>
<td>Clarithromycin</td>
<td>Antibiotic</td>
<td>3-4</td>
<td>2-2.5</td>
<td>50%</td>
</tr>
<tr>
<td>10</td>
<td>Ramipril</td>
<td>ACE Inhibitor</td>
<td>2-4</td>
<td>3-5</td>
<td>28%</td>
</tr>
</tbody>
</table>

**Method of Preparation of Floating Microspheres**

Wide ranges of developmental techniques are available for the preparation of gastro retentive floating microspheres.

**Solvent Evaporation Technique:**

The development of floating microspheres involves different solvent evaporation techniques to create the hollow inner core. This approach involves the emulsification of an organic solvent (usually methylene chloride) containing dissolved polymer and dissolved/dispersed drug in an excess amount of aqueous continuous phase, with the aid of an agitator. The concentration of the emulsifier present in the aqueous phase affects the particle size and shape. When the desired emulsion droplet size is formed, the stirring rate is reduced and evaporation of the organic solvent is realized under atmospheric or reduced pressure at an appropriate temperature. Subsequent evaporation of the dispersed phase solvent yields solid polymeric micro particles entrapping the drug. The solid micro particles are recovered from the suspension by filtration, centrifugation, or Lyophilization. For emulsion solvent evaporation, there are basically two systems which include oil-in-water (o/w) and water-in-oil (w/o) type.

**Oil in Water Emulsion Solvent Evaporation Technique:**

In this process, both the drugs and the polymer should be insoluble in water. The polymer is dissolved in an organic solvent such as dichloromethane, chloroform, or ethyl acetate, either alone or in combination. The drug is either dissolved or dispersed into polymer solution and this solution containing the drug is emulsified into an aqueous phase to make an oil-in-water emulsion by using a surfactant or an emulsifying agent. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. It has been reported that the rapid removal of solvent from the embryonic microsphere leads to polymer precipitation at the o/w interface. This leads to the formation of cavity in microspheres, thus making them hollow to impart the floating properties.[18]

**Oil in Oil Emulsification Solvent Evaporation Technique:**

In order to increase the encapsulation efficiency, a mixed solvent system comprising 1:1 proportions of Acetonitrile and dichloromethane was used as a dispersed phase, and the corn oil was used as a continuous phase. Microspheres containing anti-hypertensive drug, Felodipine, were prepared by the emulsion solvent evaporation method (o/o) using acrylate methacrylate copolymers. The morphology of the microspheres was evaluated using scanning electron microscope, which showed a spherical shape with smooth surface.[15]. In this technique, drug and polymers are co dissolved at room temperature into polar solvents such as ethanol, dichloromethane, acetonitrile etc. with vigorous agitation to form uniform drug–polymer dispersion. This solution is slowly poured into the dispersion medium consisting of light/heavy liquid paraffin in the presence of oil soluble surfactant such as Span. The system is stirred using an overhead propeller agitator at 500 revolutions per minute (rpm) and room temperature over a period of 2–3 hrs to ensure complete evaporation of the solvent. The liquid paraffin is decanted and the micro particles are separated by filtration through a Whatman filter paper, washed thrice with n-hexane, air dried for 24 hrs and subsequently stored in desiccators [18].

**Ion-tropic Gelation Method:**

Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form beads. The natural polyelectrolytes inspite, having property of coating on the drug core and acts as release retardants contains certain anions on their chemical structure. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. Biomolecules can also be loaded into these beads under mild conditions to retain their three dimensional structure.[14]. In this method, cross linking of the polyelectrolyte takes place in the presence of counter ions to form gel matrix. Microspheres are prepared by dropping drug loaded polymeric solution using syringe into the aqueous solution of polyvalent cations. The cations diffuses into the drug loaded polymeric drops, forming a three dimensional lattice of ionically cross linked moiety. Microspheres formed left into the original solution for sufficient time period for internal gelification and they are separated by filtration.
Emulsion Solvent Diffusion Method:
In this method solution of polymer and drug in ethanol methylene chloride is poured into an agitated aqueous solution of poly (vinyl alcohol). The ethanol rapidly partitions into the external aqueous phase and the polymer precipitate around methylene chloride droplets. The subsequent evaporation of the entrapped methylene chloride leads to the formation of internal cavities within the micro particles.

![Emulsion Solvent Diffusion Method](image)

**Fig. 4 Emulsion solvent diffusion method.**

Single Emulsion Technique:
In this method, micro particulate carriers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil with the help of cross linking agent.

Double Emulsion Technique:
This method involves the formation of the multiple emulsions or the double emulsion such as w/o/w. This method can be used with the natural as well as synthetic.

Phase Separation Coacervation Technique:
It is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase known as co-acervates. The drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles.

Polymerization Technique
The polymerization techniques conventionally used for the preparation of the microspheres are mainly classified as:

Normal Polymerization:
It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. Bulk polymerization has an advantage of formation of pure polymers.

Interfacial Polymerization:
It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed.

Spray Drying and Spray Congealing:
These methods are based on the drying of the mist of the polymer and drug in the air. The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug is then dispersed in the polymer solution under high speed homogenization. This dispersion is then atomized in a stream of hot air. This leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100 μm. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively.

Hot Melt Encapsulation Method:
Lin WJ and Kang WW compared the performance of Indomethacin micro particles and their release properties after coating with chitosan and gelatin, respectively. Here the poly (Epsilon-caprolactone) (PCL) micro particles were prepared by the hot-melt encapsulation method. This method is having a disadvantage that thermo-labile substances cannot be used. \(^{[10]}\).
Mechanism of action involves in multiparticulate floating drug delivery systems

While the system is floating on the gastric, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal.\[46\]

Diffusion:
On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particles. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Erosion:
Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particles.

Osmosis:
In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.\[47\]

Criteria for Selection of Drug Candidate for FDDS

Desirable half-life:
If the drug has a short half-life of less than 2 hours, the dosage form may contain a prohibitively large quantity of the drug.

High therapeutic index:
Drugs with low therapeutic index are not suitable for incorporation in controlled release formulations e.g., Digitoxin.

Small dose:
The dose of a drug in the conventional dosage form is high, its suitability as a candidate for controlled release is seriously undermined.

Aqueous solubility:
Drugs with aqueous solubility make good candidates for controlled release dosage form.

Stability to wide pH range, GI enzymes and flora:
Stability of the drug in the GI contents is important to ensure a complete and reproducible drug input into the body. Typically the drug must be stable in the pH range of 1 to 8.

First pass clearance:
Delivery of the drug to the body in desired concentration is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in controlled release form. Saturable hepatic metabolism may render a drug unsuitable because systemic availability for such drug is highly reduced when the input rate is small.\[48\]

Applications of FDDS:
Enhanced Bioavailability:
The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDFCR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.\[50\]. A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) & enteric coated LASIX-long product (29.5%).\[51\].

Sustained Drug Delivery:
Oral CR formulations are encountered with problems such as gastric residence time in the GIT. These problems can be overcome with the HBS systems which can remain in the stomach for long periods and have a bulk density <1 as a result of which they can float on the gastric contents.\[52\]. Hydrodynamically Balanced System type dosage forms remain in the stomach for several hours, increase the gastric residence time and thus release the drug over a prolonged period of time. Madopar HBS formulation has shown to release levodopa for up to 8 hour in vitro, whereas the standard formulation released levodopa in less than 30 minutes.\[53\]. These systems have a bulk density of e.g., Sustained release floating capsules of nicardipine hydrochloride were developed & were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours).\[54, 55\].
Reduced Fluctuations of Drug Concentration:

The fluctuations in plasma drug concentration are minimized, & concentration-dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index [56].

Site-Specific Drug Delivery:

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets [10].

Enhanced First-pass Biotransformation:

In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (Cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input [57]. Floating microspheres can be used as carriers for drugs with so-called absorption windows, these substances e.g., antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines) are taken up only from very specific sites of the GI mucosa [58].

CONCLUSION

This review provides an overview of concepts available to design pharmaceutical dosages form with increased gastric retention time. Many commercial formulations and patents issued in FDDS area are the evidence of it. The FDDS become additional pros for many API that are absorbed primarily in the upper part of GI tract, i.e., the stomach, duodenum, and jejunum. Gastro-retentive floating drug delivery systems have emerged as an efficient means of improving the bioavailability and controlled delivery of many drugs. The increasing sophistication of delivery technology will provide the development of increase number of gastro retentive drug delivery to optimize the delivery of molecules that exhibit absorption window, low bioavailability and extensive first pass metabolism. It seems that to formulate an efficient FDDS, it is an ideal approach with industrial applicability and feasibility.

REFERENCES

Emerging Concept: Floating Drug Delivery System


