FLOATING DRUG DELIVERY SYSTEM: INCREDIBLE REVOLUTION

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Summary

Oral drug delivery system is most convenient and commonly used route of drug administration. More than 50% of drug available in market are meant for oral administration. The conventional drug therapy results in fluctuation of drug concentration, causing either toxic effect or no therapeutic effect. But now a day, recent technologies have been developed in research. The developments of floating drug delivery system (FDDS) are achievement of these advanced technologies. In this drug is released from swollen matrix. These forms are expected to remain buoyant on gastric content without affecting intrinsic rate of emptying. This results in prolonged gastric retention time of floating forms which improve bioavailability of drug and also improve clinical situations. The present review also reveals the recent development of FDDS including types, approaches for designing the floating dosage forms, their formulation aspects, advantages & disadvantages and evaluation of FDDS.

Introduction

Oral route has been the predominant route of drug delivery for most of the drug. During the last two decades, numerous oral delivery systems have been designed to act as drug reservoirs from which the active drug can be released over a defined period of time at a predetermined and controlled rate[1]. Oral controlled release (CR) dosage forms (DF) of many important medications with improve therapy have been extensively used[2]. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. The extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa[3]. In the development of oral controlled drug delivery system, other main challenge is to modify the GI transit time. Gastric emptying of various pharmaceuticals is highly variable. Normal gastric residence times usually range between 5 minutes and 2 hours and are dependent on the dosage form the fed/fasted state of the stomach[4]. Prolonged gastric retention increases the duration of drug release, improves bioavailability, reduces drug waste and improves the solubility of the drugs that are less soluble in a high pH environment[5]. Also prolonged gastric retention time (GRT) in the stomach could be beneficial for local action in the upper part of the small intestine e.g. treatment of peptic ulcer, etc.
Gastroretentive drug delivery is an approach to prolong gastric residence time because these dosage forms can remain in the gastric region for long periods, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained at the bottom of the stomach[6], low density (floating) systems that causes buoyancy in gastric fluid[7-9], mucoadhesive systems that causes bioadhesion to stomach mucosa[10], superporous hydrogel systems[11], unfoldable, extenidible or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach[12,13], magnetic systems[14] etc.

**Floating drug delivery Systems:** Floating drug delivery systems (FDDS) are those systems which have a bulk density less than gastric fluids and because of this, these systems remains buoyant (3-4 hours) for a prolonged period of time in the stomach without affecting the gastric emptying rate. The drug is released slowly at the desired rate from the system and after release of the drug; the residual system is emptied from the stomach. As a result GRT is increased and fluctuations in plasma drug concentration can be better controlled[15].

**Drug Candidates suitable for floating Drug Delivery:**

1. Drugs which shows site-specific absorption in the stomach or upper parts of the small intestine. For example: furosemide, riboflavin-5-phosphate.
2. The drugs which are unstable in the lower part of GIT. For example: captopril.
3. Drugs required to exert local therapeutic action in the stomach. For example: antacids, anti-H. pylori agents, misoprostol.
4. Drugs with variable bioavailability. For example: satolol HCl.
5. Drugs which are insoluble in intestinal fluids. For example: quinidine, diazepam[16].

**Anatomy and physiology of GIT:** Anatomically stomach can be is divided into 3 parts: fundus, body, and antrum (pylorus). The uppermost part is called fundus, middle part is body which acts as a reservoir for undigested material, whereas the lowest part is antrum which is the main site for mixing motions and act as a pump for gastric emptying by propelling actions[17]. Gastric emptying occurs during fed states and is also continue in fasting states as well. But, the pattern of motility is different in the two states. During fasting a series of electrical events occurs, which cycle every 2 to 3 hours both through stomach and intestine[18]. This cycle of series of electrical events is known as the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which has following four phases: Phase I (basal phase) which lasts from 40 to 60 minutes with rare contractions. Phase II (preburst phase) has a duration of 40 to 60 minutes with intermittent action potential and contractions and the intensity and frequency also increases gradually as the phase progresses. Phase III (burst phase) lasts for 4 to 6 minutes. In this phase intense and regular contractions occurs for short period. These contractions produce a wave, called housekeeper wave cause all the undigested material to sweep out of the stomach down to the small intestine. Phase IV occurs between phases III and I of 2 consecutive cycles and its duration is 0 to 5 minutes [19].
During the fed state onset of MMC is delayed due to which gastric emptying rate is slowdown. After the ingestion of food, the pattern of contractions changes from fasted to that of fed state and is also called digestive motility pattern. It includes continuous contractions as in phase 2 of fasted state. These contractions reduce the size of food particles to less than 1 mm, which are propelled toward the pylorus in a suspension form[20].

Factors affecting gastric residence time of FDDS:

a. **Density of tablets:** Gastric retention time (GRT) is depends upon the dosage form buoyancy which is further dependent on the density. Density of the dosage form that is used for FDDS should be less than the gastric contents (1.004gm/ml).

b. **Size and Shape:** Dosage form unit with a diameter of more than 7.5 mm are more suitable candidate as compared to those which have a diameter of 9.9 mm because they have an increased GRT. Similarly the dosage form having a tetrahedron shape and ring shape devises with a flexural modulus of 48 and 22.5 kilopond per square inch (KSI) are reported to have better GIT for 90 to 100% retention and hence more suitable for FDDS as compared with other shapes[21,22].

C. **Viscosity of polymer:** Viscosity of polymer and their interaction greatly affect the drug release and floating properties of FDDS. Low viscosity polymers (e.g., HPMC K100 LV) were found to be more suitable candidates for FDDS than high viscosity polymers (e.g., HPMC K4M) because they improve floating properties. Also, with an increase in polymer viscosity a decrease in the release rate was observed[23].

d. **Fed or Unfed State:** Under fasting conditions, the GRT of the unit is expected to be very short because of the periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5to 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 then obviously GRT of the dosage form expected to be very short. But, in the fed state, GRT is considerably longer because MMC is delayed[24].

e. **Nature of meal:** Motility pattern of the stomach can change to fed state when indigestible polymers or fatty acid salts are fed and because of this the gastric emptying rate is decreased and drug release is prolonged[25].

f. **Frequency of feed:** When successive meals are given, the GRT can increase by over 40 minutes compared with a single meal because of the low frequency of MMC[26].

g. **Gender:** Mean GRT of a male in meals (3.4±0.4 hours) is less compared to the female of the same age and race (4.6±1.2 hours), regardless of the height, weight, and body surface of the two[27].

h. **Age:** Elderly people have a significantly longer GRT, especially those who are over 70 years of age[28].
i. Posture: Floating forms are protected by an upright position against postprandial emptying because at this position, the floating form remains above the gastric contents irrespective of its size[29]. While the conventional dosage form sink to the lower part of the distal stomach at this position from where they are expelled by antral peristaltic movements through the pylorus[30]. But supine position offers no such protection against early and erratic emptying of floating dosage forms. Only large dosage forms (both conventional and floating) experience prolonged retention when they are anywhere between the lesser and greater curvature of the stomach. On moving distally, these units show significant reduction in GRT compared with upright subjects because of peristaltic movement[31].

Approaches to design the various floating dosage form: Two types of floating Dosage systems i.e. Single- and multiple-unit floating dosage systems have been designed by using the following approaches[32].

1. Single-unit dosage forms:

Low-density approach: In this approach, the globular shells with density lower than that of gastric fluid can be used as carrier for drug for making single-unit floating dosage form. Popcorn, polystyrol and poprice have been used as drug carriers in coated shells[33]. For the undercoating of these shells sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been exploited. These shells are then further coated with a mixture of drug-polymer. Depending on the type of release desired, either of the polymer ethyl cellulose or hydroxypropyl cellulose can be used. The product floats on the gastric fluid and gradually releases the drug for a long period of time.

Fluid- filled floating chamber: In this type of dosage forms, a gas-filled floatation chamber is incorporated into a microporous component that covers the drug reservoir. Along the top and bottom walls there are provision for opening through which the GIT fluid enters into the device to dissolve the drug. The side walls in contact with the fluid are sealed to ensure undissolved drug remains in the device. The fluid present in the system for floatation could be air or any other suitable gas, liquid, or solid that has an appropriate specific gravity and should be inert. This device should be of swalloable size. Device remains floats within the stomach for a long period of time and slowly releases the drug. After the complete release of the drug, the shell disintegrates, goes to the intestine, and finally eliminated from the body[34].

Hydrodynamically balanced systems (HBS): These systems enhance the absorption because they are designed such that they stay in GIT for prolong time. Drugs which have a better solubility in acidic environment and site-specific absorption in the upper part of GIT are suitable candidates for such systems. These dosage forms must have a bulk density of less than 1. It should maintain its structural integrity and should constantly release the drug. The solubility of chlorodiazepoxide hydrochloride[35] is 150 mg/mL at pH 3 to 6 and is ~0.1 mg/mL at neutral pH. So, HBS capsule of this drug is a better than conventional one to solve the solubility problem.
Bilayer and matrix tablets: Floatable characteristics also shown by some types of bilayer and matrix tablets. The polymers which have been exploited are sodium carboxymethylcellulose (CMC), hydroxypropyl cellulose, hydroxypropyl methylcellulose, ethyl cellulose and Crosspovidone.

3-layer principle: By the development of an asymmetric configuration drug delivery system\(^3\), 3-layer principle has been improved. 3-layer principle helps in modulating the release extent and for achieving zero-order release kinetics. The design of the system is such that it floats on the stomach content and prolong gastric residence time which further results in longer total transit time which maximize the absorptive capacity and hence better bioavailability is achieved. These benefits can be applicable to drugs with pH-dependent solubility, drugs which are absorbed by active transport mechanism from the small intestine or the drugs with narrow absorption window.

Problems with single-unit formulations: Single-unit formulations can stick together or being obstructed in the GIT, which can cause irritation.

2. Multiple-Unit Dosage Forms:

Multiple-unit dosage form is designed to develop a reliable formulation that provide all the benefits of a single-unit form and also overcome the disadvantages of single-unit formulations. Microspheres have been used because of their high loading capacity. The polymers such as albumin, starch, gelatin, polyacrylamine, polymethacrylate and polyalkylenacyonacrylate have been used for the preparation of microspheres. Microspheres show an excellent in vitro floatability because of its characteristic internal hollow structure\(^3\). Several devices of carbon dioxide multiple-unit oral formulations\(^3\) have been described in the recent patent literature with features that unfold, extend or are inflated by carbon dioxide generated in the devices after administration.

Classification of FDDS:

a) Effervescent Systems (Gas-generating Systems): These systems remain buoyant on gastric fluid and contain matrices prepared by using:
1. Swellable polymers such as hydroxypropyl methylcellulose (HPMC).
2. Polysaccharides such as chitosan.
3. Effervescent components such as sodium bicarbonate, tartaric acid and citric acid or chambers containing a liquid that gasifies at body temperature.

The stoichiometric ratio of citric acid and sodium bicarbonate should be optimum for gas generation and is reported to be 0.76:1. For the preparation of these systems, firstly resin beads are loaded with bicarbonate and then coating with ethylcellulose is done. This coating is insoluble in water but allows permeation of water through it. This cause liberation of carbon dioxide due to which beads float in the stomach\(^3\). Most commonly used excipients in these systems includes HPMC, polyvinyl acetate, polyacrylate polymers, sodium alginate, polyethylene oxide, calcium chloride, Carbopol®, agar, , and polycarbonates.
b) Non-effervescent Systems: The Non-effervescent FDDS is the system which is based on mechanism of bioadhesion to mucosal layer in GI tract or swelling of polymer. The excipients which are most commonly used in non effervescent FDDS are gel forming or highly swellable cellulose type hydrophilic gums, hydrocolloids, polysaccharides and matrix forming materials such as polymethacrylate, polystyrene, polycarbonate, polyacrylate and bioadhesive polymers such as carbopol and Chitosan as well[39,40]. These dosage form swells when come in contact with gastric fluids a bulk density of < 1 is attained by them. Buoyancy of the dosage form is due to the air entrapped within the swollen matrix. This swollen gel-like structure so formed acts as a reservoir and it gives sustained drug release through the gelatinous mass.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drugs</th>
<th>Polymers Used</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Tetracycline, metronidazole and clarithromycin</td>
<td>Hydroxy propyl methyl cellulose (HPMC) and poly (ethylene oxide) (PEO)</td>
<td>41</td>
</tr>
<tr>
<td>2.</td>
<td>Furosemide</td>
<td>HPMC 4000, HPMC 100, and CMC</td>
<td>42</td>
</tr>
<tr>
<td>3.</td>
<td>Ciprofloxacin</td>
<td>Sodium alginate,xanthan gum, cross linked poly vinyl pyrrolidine</td>
<td>43</td>
</tr>
<tr>
<td>4.</td>
<td>Cephalexin</td>
<td>HPMC K4M, xanthan gum, guar gum, Microcrystalline cellulose (MCC) HPMC</td>
<td>44</td>
</tr>
<tr>
<td>5.</td>
<td>5-fluorouracil (5-FU)</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>6.</td>
<td>Furosemide</td>
<td>Povidone, polymethacrylates</td>
<td>46</td>
</tr>
<tr>
<td>7.</td>
<td>Ranitidine hydrochloride</td>
<td>Guar gum, xanthan gum, and HPMC</td>
<td>47</td>
</tr>
<tr>
<td>8.</td>
<td>Para-amino benzoic acid</td>
<td>Polyvinyl acetate and purified shellac</td>
<td>48</td>
</tr>
<tr>
<td>9.</td>
<td>Ciprofloxacin</td>
<td>HPMC</td>
<td>49</td>
</tr>
<tr>
<td>10.</td>
<td>Domperidone maleate</td>
<td>Methocel K4M, K100M</td>
<td>50</td>
</tr>
<tr>
<td>11.</td>
<td>Nimesulide</td>
<td>Guar gum, Carbopol, HPMC of low and high viscosity</td>
<td>51</td>
</tr>
<tr>
<td>12.</td>
<td>Loratidine</td>
<td>Pectin, sodium Alginate, ethyl cellulose</td>
<td>52</td>
</tr>
<tr>
<td>13.</td>
<td>Domperidone maleate</td>
<td>Xanthan gum, methocel K4M, K15M, K100 LV</td>
<td>53</td>
</tr>
<tr>
<td>14.</td>
<td>Paracetamol</td>
<td>Methyl Cellulose, PVP K30, HPMC(K4M, K15M, K100M)</td>
<td>54</td>
</tr>
<tr>
<td>15.</td>
<td>Dipyridamole</td>
<td>Methocel K4M CR, K15M CR, K100CR</td>
<td>55</td>
</tr>
<tr>
<td>16.</td>
<td>Celiprolol HCl</td>
<td>HPMC (K4M, K15M, K100M), EC, polyethylene oxideWSR-60K</td>
<td>56</td>
</tr>
<tr>
<td>17.</td>
<td>Famotidine</td>
<td>Methocel K4M, K15M</td>
<td>57</td>
</tr>
<tr>
<td>18.</td>
<td>Rosiglitazone maleate</td>
<td>Acrylic polymers</td>
<td>58</td>
</tr>
</tbody>
</table>
### Advantages of FDDS:

1. **Sustained drug delivery**: Floating drug dosage forms can remain in the stomach for prolonged time and enhance the GRT of numerous drugs. Also, these dosage forms are large in size due to which don’t pass through pylorus (0.9-1.9 cm opening)[75]. So, FDDS provides sustained drug delivery.

2. **Site-specific drug delivery**: Some drugs such as furosemide, riboflavin show site-specific absorption site in the upper part of GIT. In fact, the major site of absorption is stomach for furosemide, followed by the duodenum. So, floating dosage form of furosemide can be beneficial to prolong the GRT, hence it increases the bioavailability[76].

3. **Local action in stomach**: The FDDS are beneficial for drugs that are desire to produce local action in the stomach. For example: antacids.

4. **Reduce irritation of acidic drugs**: Acidic drugs, after administration may cause irritation on the stomach wall. Hence Floating dosage forms may be advantageous for the administration of acidic drugs such as aspirin and other[77,78].

5. **Advantageous to drugs which are unstable in intestine environment**: Drugs such as captopril, ranitidine HCl, metronidazole which are unstable in the intestinal or colonic environment can be administered by making floating dosage forms [79].

<table>
<thead>
<tr>
<th>19. Piroxicam</th>
<th>Eudragit S 100</th>
<th>59</th>
</tr>
</thead>
<tbody>
<tr>
<td>20. Pentoxyfilline</td>
<td>HPMC K4M, Na CMC, Ac-Di-Sol</td>
<td>60</td>
</tr>
<tr>
<td>21. Sotolol HCl</td>
<td>Na CMC, HPC</td>
<td>61</td>
</tr>
<tr>
<td>22. Aspirin, griseofulvin, p-nitroaniline</td>
<td>Bisphenol</td>
<td>62</td>
</tr>
<tr>
<td>23. Glipizide</td>
<td>Eudragit RS100, HPMCK4M</td>
<td>63</td>
</tr>
<tr>
<td>24. Captopril and carbopol 934P</td>
<td>HPMC (4000 and 15 000 cps)</td>
<td>64</td>
</tr>
<tr>
<td>25. Amoxycillin</td>
<td>Alginate</td>
<td>65</td>
</tr>
<tr>
<td>26. Nimodipine</td>
<td>HPMC and PEG 6000, poloxamer-188</td>
<td>66</td>
</tr>
<tr>
<td>27. Theophylline</td>
<td>Methocel K100M and methocel K15MCR</td>
<td>67</td>
</tr>
<tr>
<td>28. Diltiazem</td>
<td>Ethyl cellulose (EC) and eudragit RS-100</td>
<td>68</td>
</tr>
<tr>
<td>29. Verapamil</td>
<td>Cellulose acetate, acrycoat S100 and eudragit S100</td>
<td>69</td>
</tr>
<tr>
<td>30. Rosiglitazone maleate</td>
<td>EC and HPMC</td>
<td>70</td>
</tr>
<tr>
<td>31. Cefpodoxime proxetil</td>
<td>HPMC K15M, EC</td>
<td>71</td>
</tr>
<tr>
<td>32. Metformin</td>
<td>HPMC K4M and EC</td>
<td>72</td>
</tr>
<tr>
<td>33. Cimetidine</td>
<td>HPMC and EC</td>
<td>73</td>
</tr>
<tr>
<td>34. Ketoprofen</td>
<td>Eudragit RS and eudragit RL</td>
<td>74</td>
</tr>
</tbody>
</table>
6. **Beneficial to drugs that show low solubility at high pH**: Some drugs such as diazepam, chlordiazepoxide, verapamil show low solubility at high pH. FDDS can be useful because it enhance the GRT of these drugs and hence increase the bioavailability of these drugs by increasing absorption [80].

7. **Pharmacokinetic advantages**: FDDS maintain constant blood level because of sustain released nature of these dosage forms, easy in administration and patient compliance is also improved.

**Limitation of FDDS:**
1. These systems are not suitable for those drugs that have solubility or stability problems in the stomach.
2. There is need of high level of fluid in the stomach for success of these systems.
3. Drugs which under goes first pass metabolism are not suitable for the FDDS. For example: nifedipine.
4. Drugs that cause irritation in stomach mucosa are not suitable candidates for FDDS.

**Evaluation parameters of Floating dosage form (Tablets):**

1) **Hardness, friability, assay, content uniformity**: These tests are performed according to specified monographs.

2) **Determination of floating lag time and total floating time**: Floating lag time is the time between the introduction of the tablet into the medium and its rise to upper one third of the dissolution vessel and floating or flotation time is the time for which the dosage form floats. For the determination of floating lag time and total floating time, simulated gastric fluid or 0.1 mole.lit-1 HCl which is maintained at 37°C and USP dissolution apparatus containing 900 ml of 0.1 molar HCl as dissolution medium is used[81].

3) **Measurement of buoyancy capabilities of the FDDS**: The floating behavior was evaluated by the measurement of resultant weight. Two different media i.e. deionized water and simulated meal is used to carry the experiment, so that possible differences can be monitored. It was found that the higher molecular weight polymers with slower rate of hydration had enhanced floating characteristics and these enhanced floating characteristics was observed more in simulated meal medium as compared to deionized water[82].

4) **Drug release**: Dissolution tests are performed for the vitro drug release studies using the USP dissolution apparatus by using simulated gastric and intestinal fluids maintained at 37°C. Drug release is analysed by withdrawing the samples periodically from the dissolution medium and same volume of fresh medium is added each time in dissolution apparatus.
5) Drug loading, particle size analysis, drug entrapment efficiency, surface characterization, micromeritics studies and percentage yield (for floating microspheres and beads): To find out drug loading accurately weighed sample of beads or microspheres is crushed in a mortar and this crushed sample is added to the appropriate dissolution medium. This mixture is then centrifuged, filtered and finally analyzed by the use of various analytical methods like spectrophotometry. Then percentage drug loading is the result of division of the amount of drug in the sample by the weight of total beads or microspheres. For the determination of particle size and the size distribution of beads or microspheres, the optical microscopy method is used but the sample should be kept in the dry state. Scanning electron microscope (SEM) can be used for the surface characterization. The total percentage yield of floating microspheres can be calculated by dividing the measured weight of prepared microspheres by total amount of all non-volatile components used for the preparation[83,84].

6) Specific Gravity: Determination of the specific gravity of floating system is done by using displacement method and benzene is used as a displacing medium[85].

7) Weight gain and water uptake: Swelling behavior of floating dosage form can be considered as an important parameter to study weight gain or water uptake. For this study, dosage form is immersed in simulated gastric fluid at 37°C. Then dimensional changes like tablet diameter and/or thickness are determined at regular 1-h time intervals until 24h. After this tablets were removed from beaker and excess liquid from the surface of tablet was carefully removed using the paper. Then this swollen tablets were reweighed and by using the following equation water uptake (WU) is measured in the terms of percent weight gain:

\[
\text{WU} = \frac{W_t - W_0}{W_0} \times 100
\]

where \(W_t\) is the weights of the dosage form at time \(t\) and \(W_0\) is the weights of the dosage form at time \(t=0\)[86].

8) Pharmacokinetic studies: It include the study of AUC (Area under Curve), Cmax (maximum plasma concentration) and time to reach maximum plasma concentration (Tmax) and these parameters are evaluated by using computer. Student t test is used for the Statistical analysis and for this p, 0.05 is taken as minimal level of significance[87].

9) X-Ray/Gamma Scintigraphy: For in vivo studies, it is a very popular evaluation parameter for floating dosage form[88]. Gastric emptying time and the passage of dosage form in the GIT can be predicted and correlated by X-Ray/Gamma Scintigraphy because it helps to locate dosage form in the GIT. In this radio-opaque material is included into a solid dosage form which enables it to be visualized by X-rays. Similarly, when a \(\gamma\)-emitting radionuclide is included in a formulation then by using a \(\gamma\)-camera or scintiscanner, indirect external observation can be taken[89]. In \(\gamma\)-scintigraphy, the \(\gamma\)-rays
emitted by the radionuclide are focused on a camera, with the help of which location of the dosage form in the GI tract can be monitored[90].

Conclusion

For achieving a prolonged and predictable drug delivery profiles in the gastrointestinal tract, gastric retention is one of the most feasible approaches and FDDS is a potential approach for gastric retention. Number of commercial product of floating dosage forms and patent issued in this field are evident of the potential of FDDS. Although there are still some difficulties which have to be removed to achieve desired gastric retention by FDDS. A large number of companies are focusing toward it.

References


