



## ORAL FLOATING CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

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### ABSTRACT

This review is to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence times and unpredictable gastric emptying times. Floating tablets are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs. Floating tablets were prepared using directly compression technique using polymer for their gel-forming properties. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to floating systems, and their classification and formulation aspects are covered in detail. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and applications of these systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form.

**Keywords:** Intra-gastric floating system, Hydrodynamically balanced systems, Gastroretentive systems, Buoyant delivery systems.

### 1. INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-subject variations are observed. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine)<sup>1</sup>. The identification of new diseases and the resistance shown towards the existing drugs called for the introduction of new therapeutic molecules. In response, a large number of chemical entities have been introduced, of which some have absorption all over the gastrointestinal tract (GIT), some have absorption windows (i.e. absorption sites, especially the upper part of the small intestine) and some drugs have poor solubility in intestinal media. The drugs belonging to the second and third categories, and the drugs which are required for local action in the stomach, require a

specialized delivery system. All the above requirements can be met and effective delivery of the drugs to the absorption window, for local action and for the treatment of gastric disorders such as gastro-esophageal reflux, can be achieved by floating drug delivery systems (FDDS).

### 2. BASIC PHYSIOLOGY OF GASTROINTESTINAL TRACT

It is well recognized that the stomach may be used as a 'depot' for sustained-release (SR) dosage forms both in human and veterinary applications. The stomach is anatomically divided into three parts: fundus, body, and antrum (or pylorus). The proximal stomach, made up of the fundus and body regions, serves as a reservoir for ingested materials while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying<sup>2</sup>. The process of gastric emptying occurs both during fasting and fed states; however, the pattern of motility differs markedly in the two states. In the fasted state, it is characterized by an interdigestive series of electrical events which cycle both through the stomach and small intestine every 2–3 hr<sup>3</sup>. The activity is called the interdigestive myoelectric cycle or migrating myoelectric complex (MMC), which is often divided into four consecutive phases as described by Wilson and Washington<sup>4</sup>.

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short



period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

- Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate<sup>2</sup>.

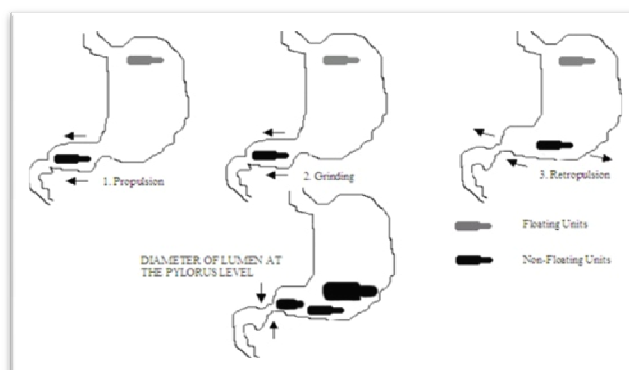
### 3. FACTORS AFFECTING GASTRIC EMPTYING

There are several factors that can affect gastric emptying (and hence GRT) of an oral dosage form.

- Density – gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density,
- Size – dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm<sup>23</sup>,
- Shape of dosage form – tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes<sup>23</sup>,
- Nature of meal – feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release<sup>9</sup>,
- Caloric content – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats<sup>5,6</sup>.

### 4. COMPARISON OF FLOATING & NONFLOATING

It was concluded that regardless of their sizes the floating dosage units remained buoyant on the gastric contents throughout their residence in the gastrointestinal tract, while the nonfloating dosage units sank and remained in the lower part of the stomach. Floating units away from the gastro-duodenal junction were protected from the peristaltic waves during digestive phase while the nonfloating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase (Figure 1). It was also observed that of the floating and nonfloating units, the floating units were had a longer gastric residence time for small and medium units while no significant difference was seen between the 2 types of large unit dosage forms<sup>7</sup>.



**Figure 1:** Intragastric residence positions of floating and nonfloating units.

### 5. APPROACHES IN FLOATING DOSAGE FORMS

Various approaches have been followed to encourage gastric retention of an oral dosage form. Floating systems have low bulk density so that they can float on the gastric juice in the stomach. The problem arises when the stomach is completely emptied of gastric fluid. In such a situation, there is nothing to float on. Floating systems can be based on the following:

- Hydrodynamically balanced systems (HBS) – incorporated buoyant materials enable the device to float;
- Effervescent systems – gas-generating materials such as sodium bicarbonates or other carbonate salts are incorporated. These materials react with gastric acid and produce carbon dioxide, which entraps in the colloidal matrix and allows them to float;
- Low-density systems -- have a density lower than that of the gastric fluid so they are buoyant;
- Bioadhesive or mucoadhesive systems – these systems permit a given drug delivery system (DDS) to be incorporated with bio/mucoadhesive agents, enabling the device to adhere to the stomach (or other GI) walls, thus resisting gastric emptying. However, the mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.
- High-density Systems - 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. Dense pellets (approximately 3g/cm<sup>3</sup>) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on diameter of the pellets, although many conflicting reports stating otherwise also abound in literature.

## 6. METHODS OF FLOATING DOSAGE FORMS

1. Using gel forming hydrocolloids such as hydrophilic gums, gelatin, alginates, cellulose derivatives, etc.
2. Using low density enteric materials such as methacrylic polymer, cellulose acetate phthalate.
3. By reducing particle size and filling it in a capsule.
4. By forming carbon dioxide gas and subsequent entrapment of it in the gel network.
5. By preparing hollow micro-balloons of drug using acrylic polymer and filled in capsules.
6. By incorporation of inflatable chamber which contained in a liquid e.g. solvent that gasifies at body temperature to cause the chambers to inflate in the stomach.

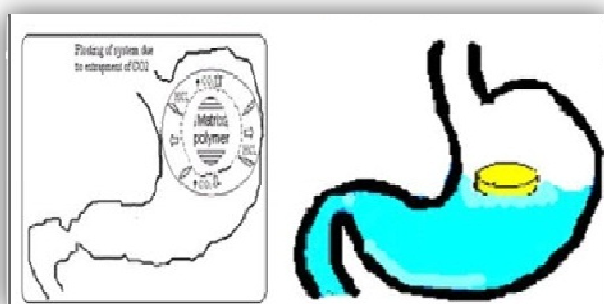


Figure 2: Showing the floating drug delivery in stomach.

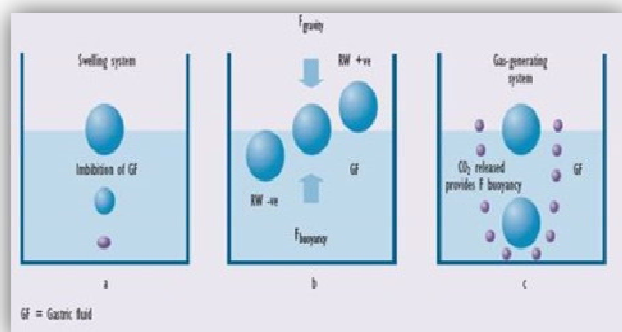


Figure 3: Demonstrate the mechanism of floating drug delivery systems.

## 7. CLASSIFICATION OF FDDS

### 7.1. Effervescent FDDS

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents,  $\text{CO}_2$  is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. Ichikawa et al.<sup>14</sup> developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The

inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sub layers to avoid direct contact between the 2 agents. These sub layers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at  $37^\circ\text{C}$ , it settled down and the solution permeated into the effervescent layer through the outer swellable membrane.  $\text{CO}_2$  was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than  $1.0 \text{ g/mL}$ . It was found that the system had good floating ability independent of pH and viscosity and the drug (para-amino benzoic acid) released in a sustained manner<sup>14</sup> Figure 4, (a) and (b).

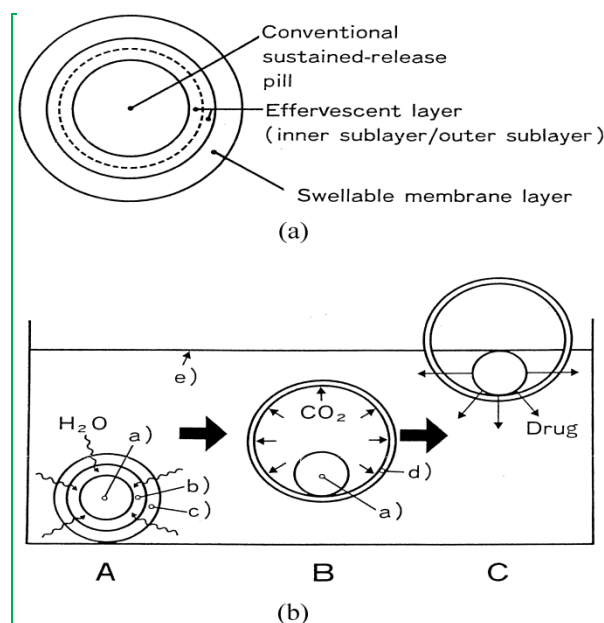


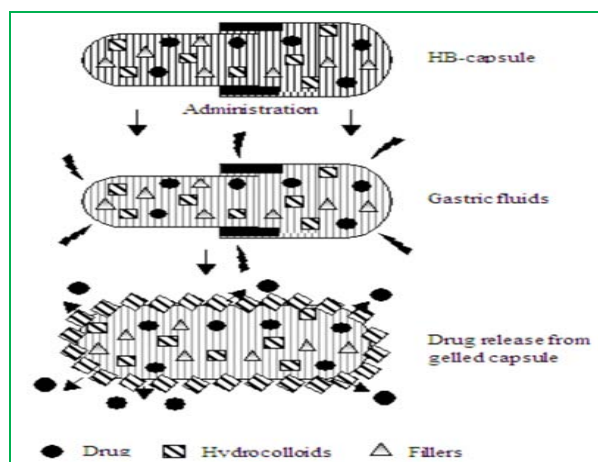
Figure 4: (a) A multiple-unit oral floating dosage system. Reproduced with permission from Ichikawa et al.<sup>14</sup>. (b) Stages of floating mechanism: (A) penetration of water; (B) generation of  $\text{CO}_2$  and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker ( $37^\circ\text{C}$ ). Reproduced with permission from Ichikawa et al.<sup>14</sup>.

### 7.2. Noneffervescent FDDS

The most commonly used excipients in noneffervescent FDDS are gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. One of the approaches to the formulation of such floating dosage forms involves intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier<sup>11</sup>. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

Sheth and Tossounian<sup>16</sup> developed a HBS capsule containing a mixture of a drug and hydrocolloids. Upon

contact with gastric fluid, the capsule shell dissolves, the mixture swells and forms a gelatinous barrier thereby remaining buoyant in the gastric juice for an extended period of time. Ushimaru et al.<sup>25</sup> developed SR capsules containing a mixture of a drug, a cellulose derivative or starch derivative which forms a gel in water, and a higher fatty acid glyceride or higher alcohol or a mixture thereof which is solid at room temperature. The capsules were prepared by filling capsules with the above mixture, then heating them to a temperature above the melting point of the fat / oil component and finally cooling and solidifying the mixture.



**Figure 5:** Working principle of the hydrodynamically balanced system (HBS). The hard gelatin capsule contains a special of the formulation of hydrocolloids, which swell into a gelatinous mass upon contact with gastric fluids. Adapted from Bogentoft<sup>24</sup>.

## 8. IN-VITRO AND IN-VIVO EVALUATION

Various parameters that need to be evaluated in gastro-retentive formulations include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms. In the case of multiparticulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, and mechanical properties are also performed.

The tests for floating ability and drug release are generally performed in simulated gastric fluids at 37°C. In practice, floating time is determined by using the USP disintegration apparatus containing 900 ml of 0.1 N HCl as a testing medium maintained at 37°C. The time required to float the HBS dosage form is noted as floating (or floatation) time. Dissolution tests are performed using the USP dissolution apparatus. Samples are withdrawn periodically from the dissolution medium, replenished with the same volume of fresh medium each time, and then analyzed for their drug contents after an appropriate dilution. Recent methodology as described in USP XXIII states.

The standard dissolution methods based on the USP or British Pharmacopoeia (BP) have been shown to be poor

predictors of *in vitro* performance for floating dosage forms<sup>20,21</sup>. Pillay and Fassihi<sup>20</sup> investigated the application of the helical wire sinker to the swellable floating system containing theophylline (a sparingly water-soluble drug). They observed that the procedure tends to inhibit the three-dimensional swelling process of the dosage form and consequently drug release from the formulation was suppressed. Burns et al.<sup>22</sup> who developed and validated an *in vitro* dissolution method for a floating dosage form which had both rapid release and SR properties. The method, although based on the standard BP (1993) /USP (1990) apparatus 2 method, was modified such that paddle blades were positioned at the surface of the dissolution medium. The results obtained with this modified paddle method showed reproducible biphasic-release dissolution profiles when paddle speeds were increased from 70 to 100 rpm and the dissolution medium pH was varied from 6.0 to 8.0. The dissolution profile was also unaltered when the bile acid concentration in the dissolution medium was increased from 7 to 14 mM.

The *in vivo* gastric retentivity of a floating dosage form is usually determined by g-scintigraphy<sup>7</sup> or roentgenography<sup>8,13,15</sup>. Studies are done both under fasted and fed conditions using F and NF (control) dosage forms. It is also important that both dosage forms are nondisintegrating units, and human subjects are young and healthy.

## 9. ADVANTAGES, LIMITATIONS AND MARKETED PRODUCTS OF FDSS

### 9.1. Advantages

1. The principle of HBS can be used for any particular medicament or class of medicament.
2. The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate.
3. The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.
4. The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments.
5. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.

### 9.2. Limitations

1. The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this





limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach<sup>12</sup>.

2. Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.
3. The dosage form should be administered with a minimum of glass full of water (200-250 ml).
4. The drugs, which are absorbed throughout gastrointestinal tract, which undergo first-pass metabolism (nifedipine, propranolol etc.), are not desirable candidate.<sup>1</sup>
5. Some drugs present in the floating system causes irritation to gastric mucosa.

### 9.3. Marketed products

Product	Active Ingredient
Madopar	Levodopa and benserzide <sup>10</sup>
Valrelease	Diazepam <sup>9</sup>
Topalkan	Aluminum magnesium antacid <sup>18</sup>
Almagate flatcoat	Antacid <sup>19</sup>
Liquid gaviscon	Alginic acid and sodium bicarbonate <sup>17</sup>

## 10. FUTURE POTENTIAL AND CONCLUSIONS

As sustained release systems, floating dosage forms offer various potential advantages evident from several recent publications. Drugs that have poor bioavailability because their absorption is restricted to the upper GI tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailabilities.

The absorption of drug in the gastrointestinal tract is a highly variable procedure and it prolongs gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach towards gastric retention. The currently available polymer-mediated noneffervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be an effective and rational approach to the modulation of controlled oral drug delivery. This is evident from the number of commercial products and a myriad of patents issued in this field. The FDDS become an additional advantage for drugs that are absorbed primarily in the upper segments of GI tract. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique.

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