A REVIEW ON FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT

The objective of our review is to compile the recent advancements and literatures regarding the novel dosage form i.e. the floating drug delivery systems (FDDS) that can be retained in the stomach for a prolonged period of time and gives therapeutic action in a predetermined manner. The methodologies used in the development of FDDS by formulating effervescent and non effervescent floating tablets based on buoyancy mechanism. By utilizing above feasible approaches it is possible to deliver drugs which have narrow therapeutic window. Our review article suggests that gastro retentive dosage forms (GRDFs) can be the possible way to improve patient compliance and robustness. Various pharma companies opted advance technologies to make FDDS commercialized in large scale despite of several limitations. So, in future we hope to have a rational GRDF that’s promises to be a potential approach for gastric retention.

KEYWORDS: Floating drug, Effervescent ad Non effervescent, In vitro evaluation

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. from immediate release to site-specific delivery, oral dosage forms have really progressed. However, it is a well accepted fact that it is difficult to predict the real in vivo time of release with solid, oral controlled release dosage form. Thus, drug absorption in the GI tract may be very short and highly variable in certain circumstances. It is evident from the recent scientific and patent literature that an increased interest in novel dosage form that are retained in the stomach for a prolonged and predictable period of time exist today in academic and industrial research group. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT). Dosage form with a prolonged GRT, that is gastro retentive dosage forms (GRDFs), will provide us with new and important therapeutic options [1]. GRDFs extend significantly the period of time over which the drugs may be released. Thus, they not only prolonged dosing intervals, but also increase patient’s compliance beyond the level of existing controlled release dosage forms. This application is especially affective in delivery of sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To address this, oral administration of sparingly soluble drugs is carried out frequently, often several times per day [2].

Gastric retention will provide advantages such as the delivery of drugs with narrow absorption window in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease. Furthermore, improve bio availability is expected for drugs that are absorbed readily upon release in the GI tract. These drugs can be delivered ideally by slow release from the stomach. Many drugs categorized as once a day delivery have been demonstrated to have sub optimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention ill extend the time within which drug absorption can occur in the small intestine. Certain types of drugs can benefit from using gastric retentive devices. These includes (a) drugs locally acting in the stomach (b) drugs having a narrow absorption window in the stomach (c) that are unstable in the intestinal or colonic environments, (d) have low solubility at high pH values.

Physiology of stomach

The stomach is divided into four major regions: fundus, body, antrum, and pylorus. Its functions are mainly:

- reservoir function: achieved through the flexible volume of the stomach
- emptying function: achieved through low sustained pressure produced by the stomach body
- Mixing and homogenizing function: achieved through stomach contraction that produces grinding.
- Size restriction function: the particle sizes of food emptied through the pylorus is less than 1 millimeter during the fed state.

The stomach is an organ with a capacity for storage and mixing. Its fundus and body region are capable of displaying a large expansion to accommodate food without much increase in the intragastric pressure. Whereas, the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions [3]. Under fasting conditions the stomach is a collapsed bag with a residual volume of 50 ml and contains a small amount of gastric fluid (pH 1-3) and air. Under physiological condition, the gastric absorption of most drugs is insignificant as a result of its limited surface area (0.1-0.2 m²) covered by a thick layer of mucus coating, the lack of villi on the mucosal surface, and the short residence time of most drug in the stomach. Rapid gastric emptying, also called dumping syndrome, occurs when undigested food empties too quickly into the small intestine. Stomach emptying is a coordinated function by intense peristaltic contractions in the antrum. At
the same time, the emptying is opposed by varying degrees of resistance to passage of chyme at the pylorus. Rate depends on pressure generated by antrum against pylorus resistance. Chyme = food in stomach which has been thoroughly mixed with stomach secretions. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 - 3 hours \[4\]. This is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington \[5\]. PHASE I the quiescent period, lasts from 30 to 60 mins and is characterized by a lack of secretary, electrical and contractile activity. PHASE II, exhibits intermittent activity for 20-40 min, during which the contractile motions increase in frequency and size. Bile enters the duodenum during this phase, whereas gastric mucus discharge occurs during the latter part of phase II and throughout phase III. PHASE III is a short period of intense large regular contractions, termed "housekeeper waves" that sweep off undigested food and last 10-20 min. PHASE IV is the transition period of 0-5 mins between Phase III & I \[6\].

**Factors affecting gastric emptying**

The most important parameters affecting gastric emptying and, hence, the gastric retention time of oral dosage forms include:

- **Density** – GRT is a function of dosage form buoyancy that is dependent on the density;
- **Size** \[7\] – dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared those with a diameter of 9.9 mm;
- **Shape of dosage form** \[8\] – 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;
- **Single or Multiple unit formulation** \[9\] – Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms;
- **Fed or Unfed state** – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 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, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
- **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.

- **Caloric content** – GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.
- **Frequency of Feed** – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender** – Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
- **Age** – Elderly people, especially those over 70, have a significantly longer GRT.

**Concomitant Drug Administration**  
Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide.

**Biological factors** – Diabetes and Crohn’s disease, stress\[10\] etc.

**Posture** \[11\] – GRT can vary between supine and upright ambulatory states of the patient.

**Designing of FDDS (Floating Drug Delivery System)**

The concept of FDDS was explained in the literature as early as 1968, when Davis disclosed a method for overcoming the difficulty experienced by some persons of gagging or choking while swallowing medicinal pills. The author suggested that such difficulty could be overcome by providing a delivery system having a bulk density less than gastric fluids so that it remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. The system floats on the gastric contents, and it releases slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. These results in an increased GRT and a better control of fluctuations in plasma drug concentration \[12\]. After this, several approaches were used to develop an ideal FDDS. These buoyant formulations include hollow microsphere (micro balloons), granules, powders, tablets, pills, laminated film. Most of the floating systems reported in the literature are in dosage forms of single- and multiple-unit systems\[13\].

**Single-Unit Dosage Forms**

In Low-density approach \[14\] the globular shells apparently having lower density than that of gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach. In coated shells popcorn \[15\], poprice, and polystyrol have been used as drug carriers. Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture. The polymer of choice can be either ethyl cellulose or hydroxypropyl cellulose depending on the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration. Fluid-filled floating chamber \[16\] type of dosage forms includes incorporation of a gas-filled floatation...
chamber into a microporous component that encloses a drug reservoir. Apertures or openings are present at the top and bottom walls through which the GI tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid should have an appropriate specific gravity and an inert behavior. Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastrointestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. The success of HBS capsule as a better system is best exemplified with chlordiazepoxide hydrochloride. The drug is a classical example of a solubility problem wherein it exhibits a 4000-fold difference in solubility going from pH 3 to 6 (the solubility of chlordiazepoxide hydrochloride is 150 mg/mL and is ~0.1 mg/mL at neutral pH).

But Single-unit formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. These systems are also unreliable and non reproducible in prolonging GRT in stomach when orally administered, owing to their fortuitous (all or nothing) emptying process.

Multiple-Unit Dosage Forms

The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form. In pursuit of this endeavor many multiple-unit floatable dosage forms have been designed. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability. Also Carbon dioxide–generating multiple-unit oral formulations have been described in the recent patent literature. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to 18 mm in their expanded state is exceeded. Rouge and coworkers showed that these dosage form decreases the inter subject variability in absorption and reduces probability of dose dumping by uniform distribution within the gastric content and provide longer duration of action.

For designing FDSS following parameters should taken into account

1. Retention in the stomach as per clinical demand or need.
2. Convenience for patient.
3. Ability to load substantial amount of drug with different physiochemical properties and release them in a controlled manner.
4. Complex matrix integrity of sustained release formulation in the stomach, inexpensive optimization between floatation time and release rate, lag time (time taken by the system to float) must be less.

Based on the mechanism of buoyancy two distinctly different technologies Effervescent Floating Drug Delivery System and Non- Effervescent Floating Drug Delivery System has been utilized in the development of FDSS.

Effervescent Floating Drug Delivery System

Effervescent floating delivery systems utilize matrices prepared with swellable polymers such as methocel polysaccharides, e.g., Chitosan, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. Ichikawa et al. 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 sublayers to avoid direct contact between the 2 agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac.

When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO2 was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 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 (Figure 1, A and B).

Stock well et al. prepared floating capsules by filling with a mixture of sodium alginate and sodium bicarbonate. The systems float during in vitro tests as a result of the generation of CO2 that was trapped in the hydrating gel network on exposure to an acidic environment. The carbonates also provide the initial alkaline microenvironment for polymers to gel. Moreover, the release of CO2 helps to accelerate the hydration of the floating tablets, which is essential for the formation of a bioadhesive hydrogel. This provides an additional mechanism (‘bioadhesion’) for retaining the dosage form in the stomach, apart from floatation.

Floating dosage forms with an in situ gas generating mechanism are expected to have greater buoyancy and improved drug release characteristics. However, the optimization of the drug release may alter the buoyancy and, therefore, it is sometimes necessary to separate the control of buoyancy from that of drug release kinetics during formulation optimization.

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, and clarithromycin) in *Helicobacter pylori*-associated peptic ulcers using hydroxy propyl methyl cellulose (HPMC) and poly (ethylene oxide) (PEO) as the rate-controlling
The design of the delivery system was based on the swellable asymmetric triple-layer tablet approach. Hydroxypropylmethylcellulose and poly (ethylene oxide) were the major rate-controlling polymeric excipients. Tetracycline and metronidazole were incorporated into the core layer of the triple-layer matrix for controlled delivery, while bismuth salt was included in one of the outer layers for instant release. The floatation was accomplished by incorporating a gas-generating layer consisting of sodium bicarbonate: calcium carbonate (1:2 ratios) along with the polymers. The in vitro results revealed that the sustained delivery of tetracycline and metronidazole over 6 to 8 hours could be achieved while the tablet remained afloat. The floating feature aided in prolonging the gastric residence time of this system to maintain high-localized concentration of tetracycline and metronidazole (Figure 2).

**NON- EFFERVESCENT FLOATING DRUG DELIVERY SYSTEM**

Table No.1: Commercial products available based on the research activity of floating drug delivery

<table>
<thead>
<tr>
<th>Product</th>
<th>Active ingredient</th>
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<tbody>
<tr>
<td>Madour</td>
<td>Levodopa and benzodiazepine</td>
</tr>
<tr>
<td>Valsekase</td>
<td>Dipeptone</td>
</tr>
<tr>
<td>Topalkan</td>
<td>Aluminum magnesium aspartate</td>
</tr>
<tr>
<td>Aluminate floatout</td>
<td>Antacid [32]</td>
</tr>
<tr>
<td>Liquid gavisos</td>
<td>Alginic acid and sodium bicarbonate [33]</td>
</tr>
</tbody>
</table>

Table No.2: Drugs Reported To Be Used In The Formulating Of Floating Dosage Forms [34]

<table>
<thead>
<tr>
<th>Dosage forms</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Floating microspheres</td>
<td>Aspirin, Griseofulvin, p-nitro aniline, Ibufrofen, Tefnaldane and Tranfast</td>
</tr>
<tr>
<td>Floating granules</td>
<td>Dichloro sodium, Indomethacin and Prednisolone</td>
</tr>
<tr>
<td>Films</td>
<td>Cannazinc</td>
</tr>
<tr>
<td>Floating Capsules</td>
<td>Chlorideazepoxide hydrogen chloride, Duzeyum, Faresinem, Misoprostol, L. Depa, Bensemide, Ursooxycholic acid and Papastatin</td>
</tr>
<tr>
<td>Floating tablets and PIBs</td>
<td>Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Ditiazem, Fluoruracil, Busulfate monomeric, Pyrimino benzoic acid, Prentaneide, Theophylline and Verapamil hydrochloride</td>
</tr>
</tbody>
</table>

Non-effervescence FDDS belongs to the class are usually prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. In 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 1 g/ml. The air trapped by the swollen polymer confers buoyancy to these dosage forms. In addition, the gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier. Sheth and Tossounian [39] postulated that when such dosage forms come in contact with an aqueous medium, the hydrocolloid starts to hydrate by first forming a gel at the surface of the dosage form. The resultant gel structure then controls the rate of diffusion of solvent-in and drug-out of the dosage form. As the exterior surface of the dosage form goes into solution, the gel layer is maintained by the immediate adjacent hydrocolloid layer becoming hydrated. As a result, the drug dissolves in and diffuses out with the diffusing solvent, creating a ‘receding boundary’ within the gel structure.

**Evaluation of floating drug delivery systems**

1. **Determination of hardness of tablet**

Randomly sampled twenty tablets in each batch of formulations should be used for the determination of hardness with the help of Monsanto type hardness tester.

2. **Determination of weight variation**

Twenty tablets selected at the random are weighed accurately and the average weight of the tablet is calculated. Then the deviation of individual weight from the average weight is calculated.

3. **Determination of thickness of the tablet**

The individual crown – to – crown thickness of ten tablets is determined using slide calipers for each batch.

4. **Measurement of Floating Capacity**

Three individual tablets are put in individual flask containing 400ml of 0.1(N) HCL solutions. Then the time in minutes for each tablet to go from the bottom to the top of the flask (floating lag time) and the time for which tablets constantly float on the water surface (duration of floating) are measured. The sample mean and standard deviation are then calculated.

5. **Angle of Repose**

Angle of repose is determined by using funnel method; the accurately weighed spheres are taken in funnel. The height of funnel is adjusted in such a way that the tip of funnel just touches the apex of heap of blends. The blends are then allowed to flow through funnel freely on to surface. The diameter of powder cone was measured; angle of repose is calculated by using following equation.

\[ \tan \theta = \frac{h}{r} \]

Where

- \( h \) – height of pile, \( \theta \) – angle of repose, \( r \) – radius of base pile

- <25-excellent flow, 25–30-good flow, 30–40
- 40–very poor flow

6. **Measurement of the density of the formulation**

The apparent densities of the tablets are calculated from their volumes and masses in triplicate. The volume \( V \) of the cylindrical tablets are calculated from their height \( h \) and radius \( r \) (both determined with a micrometer gauge) using the mathematical equation for a cylinder \( (V = \pi \times r^2 \times h) \).

7. **Determination of drug content in tablets**

Three tablets from each batch are selected randomly and transferred to a 100ml volumetric flask filled up with 0.1(N) HCL. Kept it for 48hours then took 1ml from each of volumetric flask and transferred to the test tubes. Samples are then filtered, suitably diluted and analyzed spectrophotometrically at a suitable wavelength.

8. **Determination of In – Vitro Dissolution Study**

Dissolution study is carried out in USP –II type dissolution apparatus (paddle type). Dissolution study was performed at 50 rpm in 900ml 0.1(N) HCL. 5ml
of sample was withdrawn at a predetermined interval and the volume of dissolution medium was maintained by adding same volume of dissolution medium. The absorption of withdrawn sample was measured spectrophotometrically with suitable dilution and the corresponding concentration was determined from the respective calibration curve.

**Table No.3: In vitro floating and dissolution performance**

<table>
<thead>
<tr>
<th>Drug (Polymer Used)</th>
<th>Floating Media/Dissolution Medium and Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pantoprazole (E-HPMC K 4 M)</td>
<td>300 mL of artificial gastric fluid pH 1.2 (without pepsin) at 100 rpm using USP XXIII dissolution apparatus. The time taken by the tablet to emerge on the water surface (floating lag time) and time until it floats on water surface was measured.</td>
</tr>
<tr>
<td>Amoxicillin beads (Calcium alginate)</td>
<td>For dissolution: 900 mL of deassembled 0.1 M HCl (pH 2.1) at 37 ± 0.5°C in USP XXII dissolution tester at 50 rpm.</td>
</tr>
<tr>
<td>Ketoprofen (Eudragit RL)</td>
<td>20 mL of simulated gastric fluid without pepsin, 50 mg of free micro particles in S100 50 mL beakers were shaken horizontally in a water bath, % age of floating micro particles was calculated. For dissolution: 900 mL of either a 0.1 N HCl or the phosphate buffer (pH 6.8) at 37 ± 0.5°C in USP dissolution apparatus (I) at 100 rpm.</td>
</tr>
<tr>
<td>Captopril (Micro tablet K4M)</td>
<td>900 mL of enzymes-free 0.1 N HCl (pH 1.2) in USP XXII apparatus II (basket method) at 37°C at 75 rpm.</td>
</tr>
</tbody>
</table>

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