



FLOATING DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Significant advancements have been made in the field of drug delivery systems, addressing physiological challenges such as short gastric residence periods and unpredictable gastric emptying times. Gastro-retentive Dosage Forms (GRDF) refer to dosage forms designed to remain in the stomach for an extended period. Various methods have been employed to prolong gastric residence time, including floating drug delivery systems, swelling and expanding systems, polymeric bio-adhesive systems, high-density systems and delayed gastric emptying systems. The realm of medication-based disease treatment is entering a new era, with a growing range of innovative drug delivery technologies becoming available for clinical use. Floating Drug Delivery Systems (FD DS) is a gastro-retentive dosage form utilized to achieve prolonged gastric residency time. This review aims to compile recent literature on floating drug delivery systems, focusing particularly on the main mechanisms employed to achieve gastric retention. Sustained oral release of gastrointestinal dosage forms offers numerous advantages for drugs absorbed in the upper sections of the gastrointestinal tract and those with local gastric action. The review covers the physiology of gastric retention, factors influencing gastric retention time, excipient variables that impact gastric retention, approaches to designing single-unit and hydrodynamically balanced systems, multi-unit floating structures, as well as detailed discussions on their classification, formulation, evaluation, and a few applications of these systems.

KEYWORDS: Gastro retentive dosage forms, Floating drug delivery systems.

INTRODUCTION

Drug delivery systems aim to ensure therapeutic efficacy, safety, and stability by delivering drugs in various forms (solid, liquid, or semi-solid) to the intended site in the body. Oral drug delivery systems are widely used due to their cost-effectiveness^[1], patient compliance, and ease of administration. However, their fast emptying from the stomach requires frequent dosing. To address this, drug delivery systems need to provide prolonged gastric residence.^[2]

Gastro retention is key for improving bioavailability, extending drug release, reducing wastage, and enhancing solubility in high pH environments.^[3] Delayed and controlled release in the stomach maximizes therapeutic impact, minimizes side effects, and eliminates the need for frequent dosing. Multilayered/bilayered tablets offer an innovative approach, delivering loading and maintenance doses in a single tablet. They release an initial dose rapidly, while the second layer ensures sustained release, resulting in a prolonged blood level.^[4] This approach optimizes the pharmacokinetics of the drug, providing immediate and long-lasting therapeutic effects.^[5]

Compared to conventional controlled-release forms, layered tablets offer a pharmacokinetic advantage. The rapid release layer rapidly increases drug plasma concentration, followed by sustained release from the second layer. This optimizes the drug's effects by combining immediate action and prolonged release.^[6]

Advantages of Floating Drug Delivery Systems^[7-8]

1. Prolongs gastric residence time, enhancing drug absorption.
2. Provides controlled and sustained drug release.
3. Improves solubility of drugs in high-pH environments.
4. Reduces variability in drug absorption.
5. Enhances patient compliance.
6. Offers versatile formulation options.
7. Enables targeted drug delivery.

Disadvantages of Floating Drug Delivery Systems

1. Limited application to drugs that require absorption in the upper gastrointestinal tract
2. Variability in gastric emptying times can affect drug release and absorption
3. Potential for gastrointestinal side effects, such as bloating or discomfort

4. Dependency on the presence of food or gastric fluids for optimal floating behaviour
5. Need for careful formulation design to ensure consistent floating and drug release
6. Possibility of drug accumulation and local irritation in the stomach
7. Potential for inter individual variations in gastric pH and fluid volume affecting drug performance

Gastric motility^[9] is controlled by a complex interplay of neural and hormonal signals.

Gastric emptying occurs during both fasting states and fed states. During fasting, a series of electrical events known as the inter-digestive mylo-electric cycle or

myoelectric migratory cycle (MMC) takes place every 2 to 3 hours in the stomach and intestines. The MMC consists of four stages:

Phase I (Basal phase): This phase lasts for 40 minutes to 60 minutes and is characterized by infrequent contractions.

Phase II (Preburst phase): Lasting 40 minutes to 60 minutes, this phase features intermittent action potentials and contractions.

Phase III (Burst phase): This phase lasts for 4 minutes to 6 minutes and involves intense and regular contractions over a short period of time.

Phase IV: Occurring between phases III and I of two consecutive cycles, this phase lasts for 0 to 5 minutes.

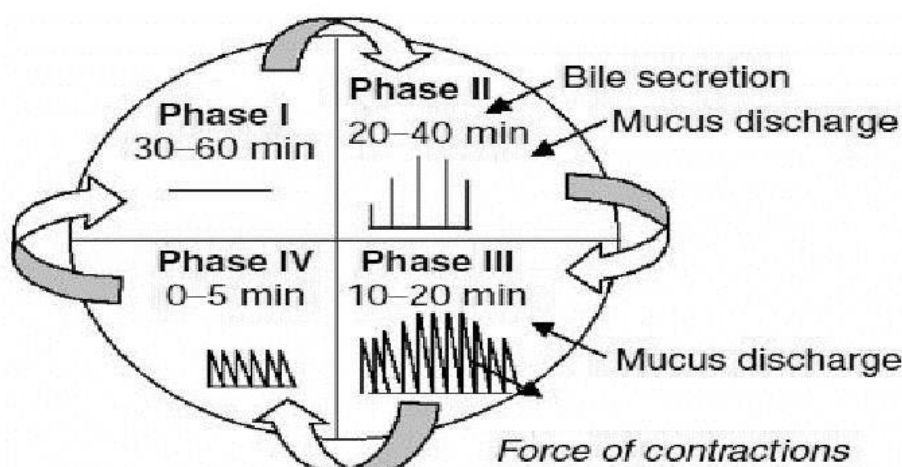


Figure 1: Motility Pattern in GIT^[10] Factors controlling gastric retention time of a dosage form include.^[11]

- Density
- Size and shape,
- Buoyancy,
- Swelling
- Mucoadhesion,
- Drug solubility
- Release rate
- Gastrointestinal motility
- Food intake

Classification of Floating Drug Delivery Systems (FDDS)

I. Formulation based classification

1. **Single-unit systems:** These systems consist of a single dosage form, such as a tablet or capsule that is designed to float on gastric fluids. The buoyancy is typically achieved by incorporating low-density materials or by incorporating gas-generating agents within the formulation.
2. **Multi-unit systems:** These systems are composed of multiple small units, such as beads, pellets, or microspheres. Each unit acts independently and floats in the stomach. Multi-unit systems provide advantages such as improved drug release profile and reduced risk of dose dumping.^[12]

II. Mechanism of buoyancy based classification

1. **Non-effervescent systems:** These systems achieve buoyancy without the generation of gas. They rely on the use of low-density materials or matrices that reduce the overall density of the dosage form, allowing it to float on gastric fluids. Common materials used include hydrocolloids, cellulose derivatives, and polymers with low bulk density.
2. **Effervescent systems:** These systems utilize gas-generating agents, such as carbonates or bicarbonates that react with gastric fluids to release carbon dioxide. The gas bubbles generated within the dosage form increase its volume, thereby reducing its density and causing it to float on the gastric contents.^[13]

III. Dosage form based classification

1. **Floating tablets:** These are solid dosage forms that are specifically designed to float on the gastric fluids. They may contain low-density materials or incorporate effervescent components to achieve buoyancy. Floating tablets provide controlled drug release and prolonged gastric retention, ensuring sustained drug delivery.
2. **Floating capsules:** These are encapsulated dosage forms that contain the drug formulation. The capsules are designed to float on gastric fluids due to

their low-density components or effervescent properties. Floating capsules offer flexibility in drug formulation and dosage adjustments.

3. **Floating beads or microspheres:** These are small spherical units that are prepared using various techniques such as ionotropic gelation or emulsion solvent diffusion. They are typically made from polymers that are buoyant in gastric fluids. Floating beads or microspheres provide a sustained release of drugs and allow for targeted drug delivery.^[15]

Approaches to Design Floating Drug Delivery System For Single Unit Dosage Forms (e.g. Tablets)

- ✓ **Floating Lag Time:** It refers to the duration it takes for the tablet to rise to the surface of the dissolution medium. It is typically measured in seconds or minutes.
- ✓ **In vitro Drug Release and Floating Duration:** This is assessed using USP II devices (paddle) with simulated gastric fluid (pH 1.2 without pepsin) at a stirring speed of 50 or 100 rpm, maintained at a

temperature of $37 \pm 0.20^\circ\text{C}$. Samples are collected at regular intervals and analyzed to determine the drug content. The duration during which the tablets remain buoyant on the surface of the dissolution medium is visually observed and recorded.^[16]

- ✓ **In vivo Gastro Retention Assessment:** This involves X-ray or gamma-scintigraphic testing to observe the transition of the dosage form in the gastrointestinal tract. Additionally, the tablets undergo testing for parameters like hardness and weight variation.
- ✓ **Hydrodynamically Balanced System (HBS):** This drug delivery system is specifically designed to prolong the residence time of medications in the gastrointestinal tract, thereby enhancing absorption. HBS systems are suitable for drugs that have higher solubility in acidic conditions and target a specific absorption site in the upper part of the small intestine. To achieve prolonged gastric retention, the dosage form should have a bulk density less than '1' and maintain a constant drug release.

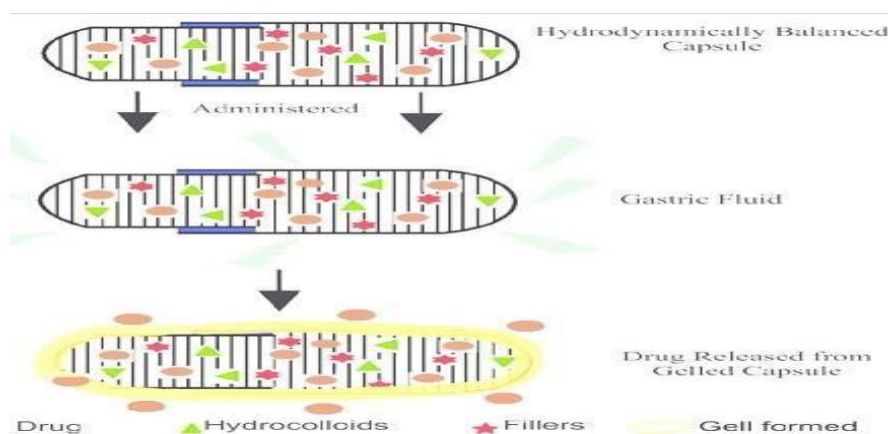


Figure 2: Hydrodynamically Balanced System.^[9]

For Multiple Unit Dosage Forms (e.g. Microspheres)^[17]

- ✓ **Morphological and Dimensional Analysis:** Electron microscopy (SEM) scanning is utilized for the analysis of the microspheres' morphology and dimensions. Optical microscopy can also be employed to determine their size.
- ✓ **In vitro Floating Potential (Buoyancy Level):** A specific quantity of microspheres is dispersed into the surface of a USP dissolution system (Type II), which is filled with 900 ml of 0.1 N HCl containing 0.002% v/v Tween 80. The system is agitated at 100 rpm for 12 hours. After this duration, the floating layer and settled layers are separated, dried in a desiccator, and weighed. The buoyancy is calculated using the formula:

$$\text{Buoyancy (\%)} = \left(\frac{W_f}{(W_f + W_s)} \right) \times 100$$

Here, W_f and W_s represent the weights of the floating and settled microspheres, respectively.

Methods for Developing Floating Drug Delivery Systems (FDDS)^[18]

- **Direct Compression Technique:** This technique involves compressing tablets directly from the powder content without altering the physical structure of the substances. Commonly used carriers include dicalcium trihydrate phosphate and tricalcium phosphate.
- **Effervescent Technique:** By utilizing an effervescent reaction between organic acid (such as citric acid) and bicarbonate salts, the floating chamber of the drug delivery system is filled with inert gas (CO_2).
- **Wet Granulation Technique:** This technique involves wet powder massaging, milling, or drying. Instead of compacting the powders, wet granulation binds them together with an adhesive to shape the granules.
- **Ionotropic Gelation Technique:** In this method, gelation of the anionic polysaccharide sodium alginate (a primary polymer of natural origin) is achieved by utilizing oppositely charged calcium

ions (counter-ions). The goal is to form instant micro-particles.

- **Solvent Evaporation Technique:** The continuous phase in this technique is unable to completely remove the liquid dispersal solvent. The solvent evaporates from the dispersal surface, resulting in hardened microspheres.
- **Spray Drying Technique:** This technique involves the drying of a dispersed solution or suspension using a spray-drying apparatus. The solvent is evaporated, leaving behind solid particles.

Mechanism of Floating System^[19]

Various approaches have been employed to enhance the retention time of dosage forms in the stomach. These approaches encompass floating dosage forms, mucoadhesive systems, high density systems, modified shape systems, and gastric emptying delaying drugs. Among these, floating dosage forms, known as Floating Drug Delivery Systems (FDDS), are widely utilized.

FDDS are designed with a bulk density lower than that of gastric fluids, allowing them to float in the stomach without significantly affecting the gastric emptying rate. While the system remains buoyant in the gastric contents, the drug is gradually released at the desired rate. Once the drug is released, the residual system is eliminated from the stomach. This mechanism leads to an extended Gastric Residence Time (GRT) and better control over fluctuations in plasma drug concentration.

These FDDS can be formulated as oral dosage forms, such as capsules or tablets, specifically designed to prolong the retention time of the drug within the gastrointestinal (GI) tract. Recent literature surveys demonstrate an increased interest in academic and industrial research focused on developing novel dosage forms capable of sustained retention in the stomach for a longer and predictable duration.

Floating drug delivery systems are well-suited for a range of drugs^[20] including:

- Drugs that exert their effects locally in the stomach, such as H₂ receptor antagonists, antacids, and misoprostol. These medications target specific gastric conditions and require a prolonged stay in the stomach to achieve their therapeutic outcomes.
- Drugs that undergo degradation in the colon, like ranitidine HCL and metronidazole. By formulating these drugs as floating delivery systems, their transit through the stomach is slowed, allowing them to reach the colon intact where they can effectively act.
- Drugs that disrupt the normal balance of colonic bacteria, such as amoxicillin trihydrate. Floating drug delivery systems help prolong the drug's residence time in the stomach, enhancing its targeting ability and efficacy against conditions associated with colonic bacteria.^[21]
- Drugs with a small absorption window in the gastrointestinal tract. Floating drug delivery systems

can optimize drug absorption by extending their gastric residence time, ensuring sufficient contact with the absorption sites for enhanced bioavailability.

Evaluation of Stomach Specific FDDS^[22-23]

❖ Floating Lag Time Determination

The mechanism of floating in FDDS is attributed to the presence of insoluble carbonated dispersion within the formulation, which becomes soluble in the acidic environment. As a result, released metal ions and carbonic acid gas cause gelation of the compound, trapping the gas within the gel matrix, leading to the floating of the system.

❖ Gelling Capacity Assessment

The gelling capacity is determined by adding 10 cubic centimeters of the solution to 100 cubic centimeters of stirred gastric fluid at 37±0.5°C. The formation of gel is visually assessed, noting the time taken for gelation and dissolution. Different weights are assigned based on gel integrity, weight, and rate of gel formation over time.

❖ In Vitro Gelling Capacity

To evaluate the in-vitro gelling capacity of the formulation using a visual technique, colored solutions of the in-place gel-forming drug delivery system are prepared. The prepared formulation is placed in a 15ml glass tube and maintained at a temperature of 37±1°C. A measured amount of colored formulation solution is added to the tube, and the formation of gel is observed. The *in vitro* gelling capacity is classified into 3 categories based on gelation time and duration for which the gel remains intact.

❖ **pH Measurement:** The pH of each Na alginate-based in-place solution is measured using a digital pH meter at a temperature of 27°C.

❖ **Physical Appearance:** The clarity, gel formation time, floating duration, and type of gel formed are assessed for all prepared in-place gels. Measurements are conducted in triplicate, and the average results are recorded.

Applications of Floating Drug Delivery Systems (FDDS)^[24]

Floating drug delivery systems offer various applications for drugs with poor bioavailability due to the narrow absorption window in the upper part of the gastrointestinal tract. They retain the drug at the site of absorption, thereby enhancing its bioavailability.

These applications can be summarized as follows:

1. **Sustained Drug Delivery:** Floating drug delivery systems can overcome the limited gastric retention time associated with conventional formulations. HBS systems can remain in the stomach for extended periods, allowing for the sustained release of the drug over a prolonged period. For example, sustained-release floating capsules of amlodipine

complex were developed and evaluated *in vivo*.

2. **Site-Specific Drug Delivery:** These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine. For instance, diuretics and vitamin B2 are primarily absorbed from the stomach. By developing a monolithic floating dosage form with prolonged gastric retention, their bioavailability can be enhanced. The AUC (area under the curve) obtained with the floating dosage form was approximately 1.8 times higher than that of the conventional dosage form.
3. **Absorption Enhancement:** Drugs with poor bioavailability due to site-specific absorption in the upper gastrointestinal tract are good candidates for development as floating drug delivery systems. These systems can improve drug absorption. For example, floating dosage forms have demonstrated significantly increased bioavailability compared to commercially available dosage forms.
4. **Maintenance of Constant Blood Levels:** Floating drug delivery systems provide a convenient method for maintaining constant blood levels of drugs, ensuring easy administration and better patient compliance.

CONCLUSION

The development of floating drug delivery systems aims to prolong the gastric retention time of the dosage form and control drug release. This approach offers a viable strategy to achieve extended and predictable drug delivery profiles in the gastrointestinal tract, providing new and valuable therapeutic options. Floating matrix tablets are specifically designed to prolong gastric retention time at a specific site and regulate drug release, making them particularly useful for achieving prolonged gastric retention. Many organizations are focusing on commercializing this approach due to its potential benefits.

In summary, the establishment of floating drug delivery systems presents a promising approach to enhance drug delivery and provide improved therapeutic options. By extending the gastric retention time and controlling drug release, these systems offer new possibilities for optimizing drug therapy in the future.

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