

A review on gastroretentive floating beads

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Abstract

The main aim of any drug delivery system is to bring about the desired concentration of the drug in blood or tissue, which is therapeutically effective and nontoxic for a prolonged period. The recent developments of FDDS are including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems. Floating beads are used for controlled drug release as they have gastro retentive property without affecting the gastric emptying rate. Gastro retentive delivery systems can be retained in the stomach and assist in enhancing absorption and the bioavailability of drug which has a narrow absorption window in a particular region of gastrointestinal tract. This can be achieved by using various natural polymers.

Keywords: Floating dosage form, floating beads, method of preparation, and evaluation of beads.

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1. Introduction

The most convenient and extensively used dosages form of administration is Oral route. This route has high patient acceptability, primarily due to ease of administration. [1-4] The goal of any drug delivery system is to release a therapeutic amount of drug to the specific site in the body and then maintain the desired drug concentration. [5]

Gastric emptying is a complex process that is highly variable and makes the *in vivo* performance of drug delivery systems. Drug delivery systems with prolonged gastric retention time have been investigated to overcome all these physiological problems.

Gastro retentive drug delivery is an approach to enhance gastric residence time, thereby targeting to a specific site and shows local or systemic effects. Floating systems or hydro dynamically controlled systems are low-density systems which have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. [6] While the particulate is floating in the

gastric content; the drug is released slowly from the particulate at a desired rate. Carbon dioxide gas forming agents such as carbonates or bicarbonates are commonly used as material in FDDS.

Floating drug delivery system is classified as effervescent and non-effervescent system. [6,7]

2. Effervescent system

It is a matrix type of system prepared with the help of swellable polymer such as methylcellulose and Chitosan and other effervescent compounds. Example: sodium bicarbonate, tartaric acid, citric acid. These are formulated in such a way that when they come in contact with gastric content, CO₂ is liberated and gets entrapped in swollen hydrocolloid which provides buoyancy to dosage form and making it float over a time.

They are again classified into:

- a) Gas generating system
- b) Volatile liquid containing system

a) Gas generating system:

These buoyant systems utilize effervescent

reaction between carbonate/bicarbonate salts and citric/tartaric acid. The system is so prepared which upon arrival in the stomach, carbon dioxide is released, results in the formulation to float in the stomach. Other materials have been reported like mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that release carbon dioxide when ingested.[9]

b) Volatile liquid containing system:

By incorporating an inflatable chamber which contains a liquid, the GRT of a drug delivery system can be sustained. e.g., ether, cyclopentane, at body temperature it gasifies resulting the inflation of the chamber in the stomach. A bio erodible plug is present in that device which is made up of PVA, Polyethylene, etc. that slowly dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.[10]

3. Non effervescent system

Non-Effervescent FDDS use a gel forming (or) swellable cellulose type of hydrocolloids, formulation which can be done by mixing of the drug with gel forming hydrocolloids which swell in contact with gastric fluid after oral administration and maintains integrity of shape and a bulk density barrier, the air trapped by swollen polymer results in buoyancy to the dosage forms.

They are classified into -

- Colloidal gel barrier systems
- Microporous Compartment systems
- Alginate beads
- Hollow microspheres

• Colloidal gel barrier system:

This system contains drug with gel-forming hydrocolloids which remain buoyant on the stomach contents. This increases GI residence time and enhances drug reaching to absorption site in the solution form which is ready for absorption. In contact with gastric fluid, in the system the hydrocolloid hydrates forms a colloidal gel barrier around its surface. The formed colloidal gel barrier controls the rate of fluid penetration into the device and followed by release of the drug. [8]

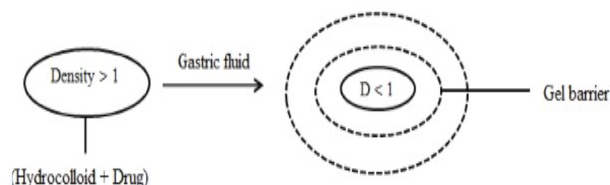


Figure 1: Colloidal gel barrier system

• Microporous Compartment systems:

This system is based on the encapsulation of a drug reservoir inside a Microporous compartment with

aperture along its top and bottom walls. The drug reservoir presents in compartment and its peripheral wall is completely sealed to prevent direct contact of gastric mucosal surface with the undissolved drug. In the stomach entrapped air present in the floatation chamber causing the delivery system to float over the gastric content. Gastric fluid enters through the pores, dissolves the drug and carrier, the dissolved drug for continuous transport across the intestine for absorption. [7]

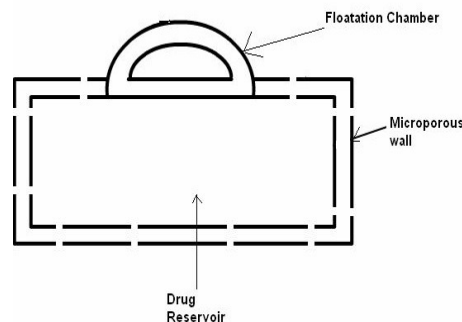


Figure 2: Microporous compartment system

• Alginate beads:

Multi-unit floating dosage forms prepared from freeze-dried calcium alginate by dropping sodium alginate solution into calcium chloride aqueous solution were spherical beads of approx. 2.5 mm in diameter can be prepared beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40°C for 24 hours, resulting in the formation of a porous system, which can float for over 12 hours. These floating beads give an enhanced residence time of more than 5.5 hours. [9]

• Hollow microspheres:

Hollow microspheres carried with drug in their outer polymer shelf which is prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40°C . The gas phase is formed in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. Floating of micro balloon continuously over the surface of an acidic dissolution media for more than 12 h which containing surfactant.[9]

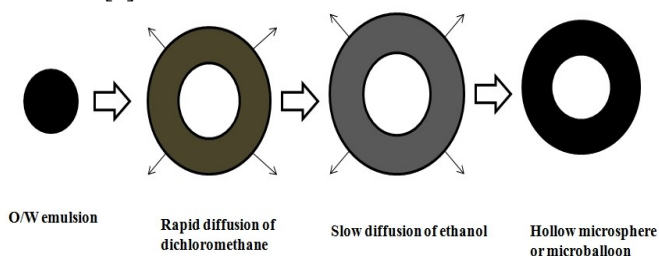


Figure 3: Formulation of floating hollow microsphere or microballoon

4. Mechanism of floating drug delivery system [20,8]

Floating drug delivery systems are low density systems than the gastric contents, which have adequate buoyancy to float over the gastric contents and continue to exist in the stomach for a prolonged period of time. When the system floats over the gastric contents, the drug is released slowly at the desired rate, resulting in enhanced gastro-retention time and minimizes the fluctuation.

However, a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimum level of floating force (F) is also required to keep the dosage form buoyant on the surface. The apparatus works by measuring continuously the force equivalent to F as a function of time that is required to maintain the submerged objects. The object floats better if F is on the higher positive side as shown in figure 4.

This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intra gastric buoyancy capability variations.

$F = F_{\text{buoyancy}} - F_{\text{gravity}}$

$F = (DF - Ds)gv$ (1)

Where,

F= total vertical force,

DF = fluid density,

Ds= object density,

g = acceleration due to gravity

v = volume and

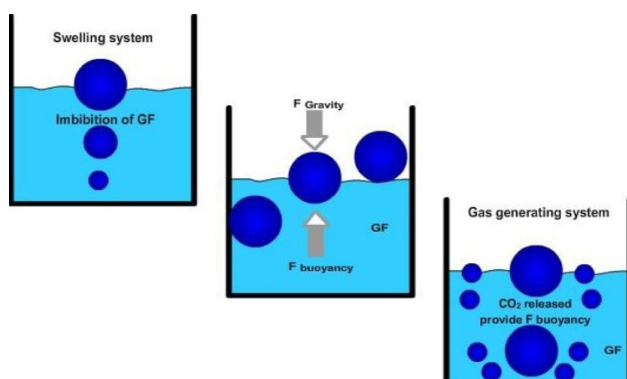


Figure 4: Mechanism of Floating System, GF= Gastric Fluid

5. Gastroretentive floating beads: [2]

Micro beads are small, solid and free flowing particulate carriers, on which the drug is coated or encapsulated in the core of beads. Beads can provide controlled / sustained release properties and as such bioavailability of drugs are enhanced.

Gastro retentive beads are not just to sustain the drug release, but also to enhance gastric residence of the

dosage forms until the entire drugs are completely released at the desired period of time. The multiparticulate dosage forms have many advantages as compared to single unit preparations, such as:

- Greater flexibility
- Avoid dose dumping and incomplete drug release
- Reduction of inter- and intra-subject variability in drug absorption
- Increase bioavailability
- Increase flow property

5.1 Commonly Employed Polymers in Gastro retentive Floating Beads:

• Sodium Alginate:

Sodium alginate is a natural polysaccharide and also an anionic linear polymer containing α -1, 4-linked L-glucuronic acid and β -1, 4-linked D-mannuronic acid residues are randomly arranged with the chains. It is stable gel and contains divalent cations i.e., Ca^{2+} which are used for sustained release of drugs. Alginate having excellent biocompatibility, mucoadhesive aspect, biodegradability and mild gelation conditions. It also used for floating drug delivery because alginate beads are stable in acidic media thereby preventing the degradation of drug in the acidic environment of the stomach.[11,12]

• Pectin:

Pectin is a colloidal polygalacturonic acid where some of the carboxylic groups are esterified with methyl groups. D-galactouronic acid is the main constituent of pectin. It is a low methoxy polysaccharide polymer, with a degree of esterification is $< 50\%$. It can form gels in the presence of calcium ions or other multivalent cations. Pectin minimises the interfacial tension between oil and water phase and used for the preparation of emulsions. The USP 28 reports, pectin as a purified carbohydrate product which is obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. [13,14]

• Chitosan:

Chitosan is a useful excipient for preparing sustained release formulation and for increasing the bioavailability of poorly water-soluble drug. Chitosan obtained by alkaline deacetylation of Chitin, which is a non-toxic, biocompatible, and biodegradable natural polymer. Chitosan-based hydrogel polymeric beads were studied as Nano or micro -particulate carriers in the pharmaceutical and medical fields. [5,15] During the incubation, the presence of calcium ions in the chitosan solution having a great effect on the ability of a gel bead to bind chitosan. As increase in the concentration of calcium chloride, there will be an increase in the rate and extent of chitosan binding process.[18]

- **Guar Gum:**

Guar gum is a galactomannan, obtained from plant *Cyamopsis Tetragonolobus*. It is a polysaccharide consisting of repeating units of galactose and mannose. The backbone is a linear chain of 1, 4-linked mannose residues to which galactose residues are 1, 6-linked at every second mannose, forming short side- branches. Guar gum stable in the range of acidic pH (range 5-7) and temperature. Strong acids (pH 3 or less) and temperature more than 50°C cause hydrolysis and loss of viscosity of guar gum. As the guar gum has more galactose branch points it is more soluble than locust bean gum and is a better emulsifier.[16,17]

5.2 Floating beads can be prepared by:[2,19]

- **Emulsion Gelation Method:**

In this method the polymer is dissolved in distilled water which is kept in a magnetic stirrer. After complete homogenization of polymer required quantity of oil is introduced then followed by drug. The resultant homogenous mixture containing drug, oil and polymer is introduced into 5% calcium chloride through 21G needle, which is left at room temperature. After specific period time the filter the solution, the resultant beads were washed twice through distilled water and dried at room temperature for 12 hrs.

- **Ionotropic gelation method:**

The hydrogel beads are prepared by introducing a drug-loaded polymeric solution into the aqueous solution of polyvalent cations through the 21G needle. The cations tend to diffuse into the drug-loaded polymeric drops, resulting in the formation of a three dimensional lattice of ionically crosslinked moiety. These beads are then dropped in aqueous solution of 1% glutaraldehyde for about 1h. Biomolecules can also be loaded into these gelispheres under mild conditions to retain their three dimensional structure. Beads are dried in an air convection type oven at 40°C for 6 h and in freeze dryer to evaluate the changes in beads.

Evaluation parameters of floating beads:[20,2,19]

- **Percentage yield:**

Prepared floating beads were collected and weighed. Yield can be calculated by the following formula-

$$\% \text{ yield} = \frac{\text{Weight of the prepared beads}}{\text{Total weight of the drug and excipients}}$$

- **Drug Content and Drug Entrapment Efficiency:**

Equivalent weight drug loaded polymer beads will be dissolved in suitable solvent. It will be stirred using magnetic stirrer. The resulting solution will be filtered and filtrate will be suitably diluted with suitable solvent. It can have determined spectrophotometrically.

Drug content and Entrapment efficiency can be determined using equation:

$$\text{Drug content} = \frac{\text{concentration} \times \text{dilution factor}}{1000} \times 100$$

$$\text{Entrapment efficiency} = \frac{\text{Actual yield}}{\text{Theoretical yield}} \times 100$$

- **In-vitro release studies for floating beads:**

The in-vitro dissolution studies were carried out using USP Dissolution Apparatus type II at specific rpm. The dissolution medium contains of 0.1 N HCl (900 ml) maintained at 37±0.5°C. Periodically 5ml sample were withdrawn at specific time interval and replaced with fresh medium to maintain the sink condition. Drug content was determined spectrophotometrically. % CDR is calculated by the calculation.

- **In vitro buoyancy study:**

Required amount of beads were spread over the surface of a USP dissolution apparatus type II, consisting 900 ml of 0.1 N HCl and 0.02% Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 hr. The floating and the settled portions of beads were taken separately. The beads were dried and weighed. Buoyancy percentage was calculated as the ratio of the total mass of beads that remained floating and the total mass of the beads settled.

$$\% \text{ buoyancy} = \frac{Q_f}{Q_f + Q_s}$$

Where,

Q_f = Weight of the floating Beads

Q_s = Weight of settled Beads

- **Scanning electron microscopy (SEM):**

Morphological evaluation of the surface and internal structure of the prepared dried beads can be performed by using a scanning electron microscope (SEM).

- **Stability studies**

The formulated beads were sealed in vials and kept for 90 days at 40°C/75% RH. After 90 days of exposure the beads were studied for drug content determination and in-vitro release.

6. Conclusion

Based on the review it can be concluded that the floating beads show gastro retentive controlled release property. Floating beads having low-density, adequate buoyancy to float over gastric contents and remain in stomach for longer period of time. As a result, the drug released slowly at desired rate from the system which result in the increased gastric retention with low fluctuations in plasma drug concentration. In future by using various other strategies, floating beads may show the better place in novel drug delivery system, exactly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery diseased organ and tissues in the

body. This will enhance the absorption of drugs by slowly releasing in to the site of absorption. The floating beads exhibit better bioavailability characteristic when compared with commercial conventional drugs.

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