



FLOATING MULTI-PARTICULATE ORAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

The purpose of this review on floating drug delivery systems is the recent literature with mechanism to achieve gastric retention by floatation. Gastroretentive drug delivery system have advantages besides providing better bioavailability to poorly absorbed drugs and a required release profile thus attracting interest of pharmaceutical formulation. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form. The objectives of the review discuss various parameters affecting the behavior of floating multiparticulate oral dosage form and to focus on the recent advances in the field of formulation, characterization, evaluation and applications of floating multi-particulates drug delivery. A large number of marketed formulations are formulated as gastroretentive dosage forms. Floating multi-particulates is one among the several approaches to gastroretention, like floatation, mucoadhesion, sedimentation, expansion, modified shape systems etc. The review also highlights the advantages with reference to the multi-particulate systems, as well as provides an overview of the future prospective that can take place in this arena.

Keyword: Gastroretentive drug delivery system, floating microspheres, multi-particulates.

INTRODUCTION

One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time by using gastro-retentive dosage forms (GRDFs). It remains in the gastric region for several hours and hence prolongs the gastric residence time of drug. It has several advantages over immediate release dosage form including the minimization of fluctuations in drug concentration in plasma and at the site of action over prolonged periods of time, resulting in optimized therapeutic efficiencies and reduce the side effect, reduction of total dose administered and reduction of administration frequency leading to improved patient compliances^{1,2}. The multi-particulates Floating are gastro-retentive drug delivery systems based on non-effervescent approach. These microspheres are characteristically free flowing powders having a size less than 200 μm and remain buoyant over gastric contents and for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration³.

Approaches to gastric retention

Hydrodynamically balanced systems (HBS): The incorporated buoyant materials enable the device to float.^{4,5}

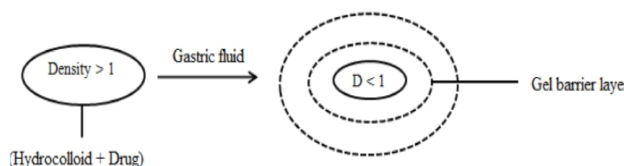


Figure 1: Hydrodynamically balanced system

Raft systems incorporating alginate gels: These have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating.^{6,7}

Bioadhesive or mucoadhesive systems: These systems are used to localize a delivery device within the lumen and cavity of the body to increase the drug absorption process are used that can be adhere to the epithelial surface of the GIT. The proposed gastric mechanism of bioadhesive is the formation

of hydrogen and electrostatic bonding at the mucus polymer boundary.⁵

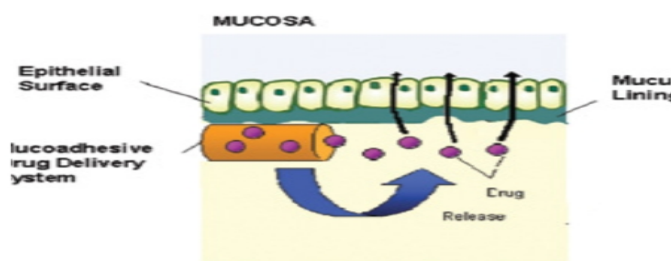


Figure 2: Bioadhesive system

Modified shape systems: These are non-disintegrating geometric shapes molded from silastic elastomer or exuded from polyethylene blends and extended the gastric transit time (GTT) depending on the size, shape and flexural modulus of the drug delivery device.

High density systems: These systems with a density of about 3 g/cm^3 are retained in the rugae of stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm^3 acts as a threshold value after which such systems can be retained in the lower parts of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc.^{8,9}

Swelling and expanding systems: These are dosage forms, which after swallowing; swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in stomach for a long period of time. These systems may be named as "plug type system", since they exhibit tendency to remain logged at the pyloric sphincter.^{10,11,12}

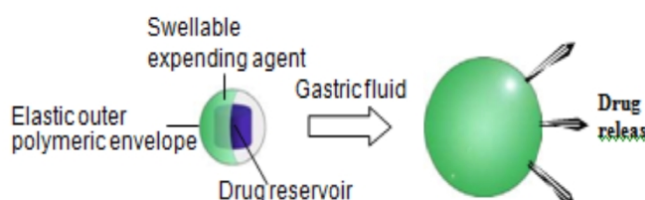


Figure 3: Swelling system

Floating drug delivery systems (FDDS): From the formulation and technological point of view, the floating drug delivery systems are considerably easy and logical approach in the development of Gastro retentive dosage forms (GRDFs).

The multi-particulates floating drug delivery

The floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time and the drug is released slowly at the desired rate from the system. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.¹³

These have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released 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 the fluctuations in plasma drug concentration.¹⁴ However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight (RW) has been reported in the literature. The RW apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if RW is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.¹⁵

$$RW \text{ or } F = F_{\text{buoyancy}} - F_{\text{gravity}} = (D_f - D_s) gV$$

Where, RW = total vertical force, D_f= fluid density, D_s= object density, V = volume and g = acceleration due to gravity.

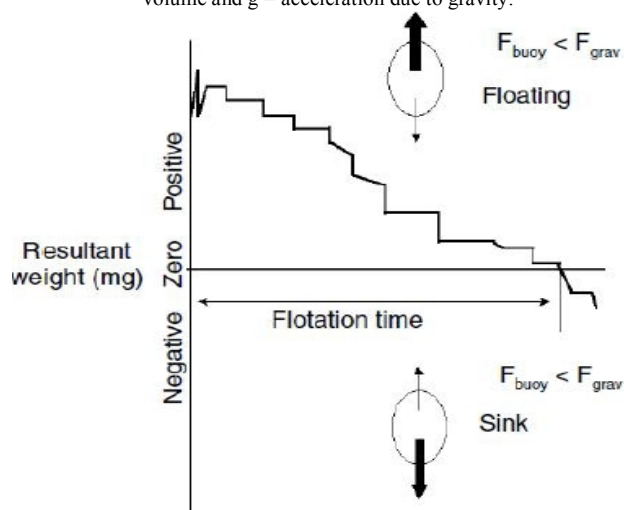


Figure 4: Effect of resultant weight during buoyancy on the floating tendency of FDDS

In recent years, in oral sustained or controlled release multiparticulate drug delivery system extensive research works have been occurs because of its advantages over monolithic dosage form. Now a day's floating concept of multiparticulate reservoir type delivery system more importance.

Oral sustained release floating multiparticulate drug delivery system include low density floating micro pellets, floating

micro beads (acrylic resin based), hollow microspheres (micro balloons) etc. The article published on the development of both effervescent and non-effervescent type of floating drug delivery. Much research has been focused and the scientists are still exploring the field of hollow microspheres.¹⁶

Attributes	Multiparticulate	Single Unit
Gastric Emptying	Uniform	Variable (some effect of unit size)
Inter- and Intra-subject Variability	Low	High
Food Effects (on release)	Minimal	Significant effect on the integrity of dosage form particularly for hydrophilic matrix
Safety concerns due to dose dumping	Minimal	Significant (drugs with narrow therapeutic index)
Drug Loading	Often limited but improved with technology (e.g. extrusion)	High drug loading possible
Compliance	High (often beads in capsules) Less frequent intake	Could be a concern if unit size is large.
Release Modulation	Customized profile possible	Somewhat Difficult

Advantages of floating multiparticulate¹⁷

- Improves patient compliance by decreasing dosing frequency.
- Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration are avoided; a desirable plasma drug concentration is maintained by continuous drug release.
- Better therapeutic effect of short half-life drugs can be achieved.
- Gastric retention time is increased because of buoyancy.
- Drug releases in controlled manner for prolonged period.
- Site-specific drug delivery to stomach can be achieved.
- Enhanced absorption of drugs which solubilise only in stomach.
- Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
- Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multiparticulate system.

Disadvantages

Floating system is not feasible for those drugs that have solubility or stability problem in GIT.

- These systems require a sufficiently high level of fluids in the stomach for enabling the system to float and to work efficiently.
- The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo extensive first pass metabolism, may not be suitable for FDDS as the slow gastric emptying limits the systemic bioavailability.
- Some drugs present in the floating systems cause irritation to gastric mucosa.^{18,19,20}

Applications of floating multiparticulate

- **Sustained Drug Delivery:** These systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems.

These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

- **Site-Specific Drug Delivery:** These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g. riboflavin and furosemide. Floating multiparticulate can greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentrations at the gastric mucosa, thus eradicating *Helicobacter pylori* from the submucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis.
- **Absorption Enhancement:** Floating multiparticulate are especially effective in delivery of sparingly soluble and insoluble drugs. It is known that as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. For weakly basic drugs that are poorly soluble at an alkaline pH, hollow microspheres may avoid chance for solubility to become the rate-limiting step in release by restricting such drugs to the stomach. The positioned gastric release is useful for drugs efficiently absorbed through stomach such as Verapamil hydrochloride. The gastro-retentive floating multiparticulate will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability.
- **As carriers:** The floating multiparticulates can be used as carriers for drugs with so-called absorption windows, these substances, for example antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides and Tetracyclines) are taken up only from very specific sites of the GI mucosa. Pharmacokinetic advantages and future potential: 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.^{19,21}

Methods of preparation of floating multiparticulate

1. Solvent evaporation method: Floating multiparticulate dosage form was prepared by solvent diffusion and evaporation methods to create the hollow inner core. The polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing polyvinyl alcohol to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring⁶, the solvent removal leads to polymer precipitation at the o/w interface of droplets, forming cavity and thus making them hollow to impart the floating properties²².

a. Oil-in-oil emulsion solvent evaporation method: During a great number of microencapsulation techniques for the formation of sustained release drug delivery systems, one of the popular methods is the emulsion solvent evaporation method. In order to increase the encapsulation efficiency, a mixed solvent system comprising 1:1 proportions of Acetonitrile and dichloromethane was used as a dispersed

phase, and the corn oil was used as a continuous phase. Microspheres containing anti-hypertension drug, Felodipine, were prepared by the emulsion solvent evaporation method (o/o) using acrylate methacrylate copolymers. The morphology of the microspheres was evaluated using scanning electron microscope, which showed a spherical shape with smooth surface²³.

b. Foam-based method for floating microparticles: A novel multi-particulate gastro retentive drug delivery system based on low-density foam powder has been proposed in which, The drug and release-rate-controlling polymer were dissolved in Methylene chloride. Polypropylene foam powder was then dispersed within this organic phase. The resulting suspension was subsequently emulsified into an external aqueous Poly (vinyl alcohol) solution and agitated with a stirrer to allow microparticle formation. The microparticles were separated by being sieved, washed with water and dried in a desiccator; they were irregular in shape and highly porous. Importantly, the drug encapsulation efficiency was high and almost independent of the theoretical loading of the system. In all cases, good *in-vitro* floating behavior was observed. Interestingly, a broad spectrum of release patterns could be obtained with the investigated formulations²⁴.

2. Ionotropic gelation method^{25,26}: Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counterions to form beads. Since, the use of alginates, gellan gum, chitosan and carboxymethyl cellulose for the encapsulation of drug and even cells, ionotropic gelation technique has been widely used for this purpose. The natural polyelectrolytes in spite, having property of coating on the drug core and acts as release rate retardants contains certain anions on their chemical structure. These anions forms meshwork structure by combining with the polyvalent cations and induce gelation by binding mainly to the anion blocks. The hydro gel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations.

3. Emulsion solvent diffusion method^{23,27}: Kawashima and colleagues^{5,6} proposed hollow microspheres with drug in their outer polymer shell prepared by novel emulsion solvent diffusion method. Based on Eudragit-S (an enteric polymer), containing the drug in the polymeric shell. The solution of polymer and drug in ethanol methylene chloride is poured into an agitated aqueous solution of poly (vinyl alcohol). The ethanol rapidly partitions into the external aqueous phase and the polymer precipitates around methylene chloride droplets. The subsequent evaporation of the entrapped methylene chloride leads to the formation of internal cavities within the microparticles.

List of polymers used in floating microparticles^{28,29}: Cellulose acetate, ethyl cellulose, chitosan, eudragit, acrycoat, methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide, polycarbonates, acrylic resins and polyethylene oxide.

Evaluation parameters of floating microspheres

1. Micromeritics properties^{30,31}: Floating microspheres are characterized by their micromeritics properties such as particle size, Flow property and Density. Angle of Repose^{13,14} Hausner's Ratio, compressibility index is determined by measuring the change in volume using a bulk density apparatus; angle of repose is determined by fixed funnel method. The hollow nature of microspheres is confirmed by scanning electron microscopy.

2. Floating behavior³²: Appropriate quantity of the floating microspheres were placed in 100 ml of the simulated gastric

fluid (SGF, pH 2.0), the mixture was stirred with a magnetic stirrer. The layer of buoyant microparticulate was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccator until constant weight was achieved. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\text{Buoyancy (\%)} = W_f / (W_f + W_s)$$

Where, W_f and W_s are the weights of the floating and settled microparticles

3. % Drug entrapment³³: Accurately weighed microspheres were taken, thoroughly triturated and suspended in a minimal amount of solvent. The suspension was filtered to separate shell fragments. Drug contents were analyzed and % Drug entrapment is calculated by using following equation.

$$\% \text{ Drug Entrapment} = \text{Actual drug content} / \text{Theoretical drug content} \times 100$$

4. In-vitro release studies³³: The release rate of floating microparticulate was determined in dissolution apparatus. A weighed amount of floating microspheres equivalent to Dose of drug is taken and placed in the basket type of dissolution test apparatus. The dissolution fluid was maintained at $37 \pm 1^\circ\text{C}$ at a rotation speed. Perfect sink conditions prevailed during the drug release study.

5. In-vivo studies³⁴: The *in-vivo* floating behavior can be investigated by X-ray photography of hollow microparticulate loaded with Barium sulphate in the stomach of beagle dogs. The *in vitro* drug release studies are performed in a dissolution test in a dissolution media. The *in-vivo* plasma profile can be obtained by performing the study in suitable animal models.

Dosage form	Drug	Polymer	Method	Ref.
Multiparticulate FDDS	Zolpidem tartarate	(Eudragit® NE 30D)	Gas generation technique	35
Floating microspheres	Cephalexin	EthylCellulose (EC)	Emulsion solvent evaporation	36
Hollow microspheres	Ranitidine HCl	Eudragit RLPO	Solvent evaporation method	37
Floating microparticles	Metoprolol succinate	Polymethacrylate (Eudragit S100, RSPO, RLPO)	Non-aqueous emulsion solvent evaporation method	38
Floating microspheres	Aceclofenac	Eudragit S 100 (ES):Eudragit RL 100	Emulsion solvent diffusion technique	39
Floating microspheres	Aceclofenac	Eudragit RS 100	Emulsification solvent evaporation technique	40
Sustained-release matrices	Metoprolol succinate	Gelucire 43/01 and Gelucire 44/14	Melt-solidification technique	41
Drug-loaded beads	Pantoprazole	Alginate, Sterculia gum	Ionotropic gelation	42
Superporous hydrogen composite	Ranitidine HCl	Sodium carboxymethylcellulose	-	43
Floating alginate beads	Levofloxacin	Hemihydrate Methyl cellulose	Gas generation technique	44

CONCLUSION

Though much research has been conducted to develop controlled or sustained release delivery systems, very few systems, which retained in the stomach for a long time, have been developed so far. These systems mainly consist of swelling and expanding systems, floating and inflating systems and bioadhesive systems. Floating dosage unit is useful for drugs acting loatable in the proximal gastrointestinal tract. These systems are also useful for drugs, which are poorly soluble or unstable in intestinal fluids. The floating properties of these systems help in retaining these systems in the stomach for a long time. Various attempts have been made to develop a floating system. Large number of pharmaceutical and biotech companies is focusing toward commercializing these techniques and still needs further developments for the floating multiparticulate development of pharmaceutical industry.

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