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Floating Drug Delivery System- A Review

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A B S T R A C T

Formulation of floating drug delivery system (FDDS) is a topic of current interest in pharmaceutical product development. (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Controlled release floating drug delivery system is a promising delivery system for a drug candidate having limited absorption window sparingly soluble and insoluble drugs, drugs those locally release in stomach and shows degradability in colon or poor colonic absorption. In this review various techniques used in floating dosage form along with its mechanism, types and applications are discussed.

Keywords: Floating, Gastric Emptying, Buoyant

A R T I C L E I N F O

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1. Introduction

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. 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.

Unfortunately, in most cases, the important variability of the gastrointestinal tract physiology and of its transit time leads to unpredictable bioavailability and non reproducible therapeutic effects. One requisite for the successful performance of oral controlled release drug delivery systems is that the drug should have good absorption throughout the gastrointestinal tract, preferably by passive diffusion [1,2,3]. Floating systems first described by Davis 1968 which are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration. Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for 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. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. 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. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres [4]

Advantages of floating drug delivery system:

- 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 multi particulate system.
- Extended time over critical (effective) concentration
- Less inter- and intra-subject variability.
- Flexibility in dosage form design.
- Improves patient compliance by decreasing dosing frequency.
- 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.
- Sustained drug delivery/reduced frequency of dosing
- Targeted therapy for local ailments in the upper GIT
- Extend patent protection, globalize product, and provide new business opportunities.
- Site-specific drug delivery to stomach can be achieved.
- Enhanced absorption of drugs which solubilize only in stomach.
- Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release. [5,6]

Disadvantages of floating drug delivery system:

- Drugs which are absorbed along the entire GIT and which undergo first pass metabolism may not be desirable e.g. nifedipine.
- They are not suitable candidates for drugs with stability or solubility problem in stomach. Eg .ranolazine
- Single unit floating capsules or tablets are associated with an "all or none concept," but this can be overcome by formulating multiple unit systems like floating microspheres.
- FDDS require sufficiently high level of fluid in stomach so that the system can float and thus sufficient amount of water (200- 250 ml) of water to be taken together with FDDS.[5]

2. Mechanism of floating microspheres

Floating systems or Hydro dynamically controlled drug delivery systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in stomach 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 concentration. When microspheres come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy.[6,7]

Techniques used in the preparation of microspheres

The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release. The various methods of preparations are

Emulsion solvent evaporation technique

The drug is dissolved in chloroform and then dissolved in polymer and the resulting solution is added to aqueous phase containing 0.2 % sodium of PVP (emulsifying agent). This mixture was agitated at 500 rpm then the drug and polymer (Eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hrs. For these techniques, there are basically two systems which include oil-in-water (o/w) and water-in-oil (w/o) type.

i) Oil in water emulsion solvent evaporation technique

In this technique, both the drug and the polymer should be insoluble in water while a water immiscible solvent is required for the polymer.The polymer is dissolved in an organic solvent such as dichloromethane, chloroform, or ethyl acetate. The drug is either dissolved or dispersed into polymer solution and this solution is emulsified into an aqueous phase to make an oil-in water emulsion by using an emulsifying agent. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring.

ii) Water-in-oil emulsification solvent evaporation technique

This water-in-oil emulsification process is also known as non aqueous emulsification solvent evaporation. Drug and polymers are co dissolved at room temperature with vigorous agitation to form uniform drug–polymer dispersion. This solution is slowly poured into the dispersion medium consisting of light / heavy liquid paraffin in the presence of oil soluble surfactant such as Span. The system is stirred using an overhead propeller agitator at 500 rpm over a period of 2–3 h to ensure complete evaporation of the solvent. The liquid paraffin is decanted and the micro particles are separated by filtration through a Whitman filter paper, washed thrice with n-hexane, air dried for 24 h and subsequently stored in desiccators.

Emulsion-solvent diffusion technique

The drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture was added drop wise to sodiumlauryl sulphate solution. The solution was stirred with propeller type agitator at room temperature at 150 rpm for 1 hr. Thus the formed floating microspheres were washed and dried in a desiccator at room temperature.

Ionic Gelation Technique

The drug was added to 1.2 % (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added drop wise to a solution containing Ca2+ /Al3+ and chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for 24 hr for internal gellification followed by filtration for separation. The complete release was obtained at pH 6.4-7.2 but the drug did not release in acidic pH. Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique.

Single Emulsion Technique

Micro particulate carriers of natural polymers (proteins and carbohydrates) are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil with the help of cross linking agent.

Double Emulsion Technique

This method involves the formation of the multiple emulsions or the double emulsion such as w/o/w.

Phase Separation Coacervation Technique

It is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase known as co-acervates. The drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles.

Polymerization Technique

The polymerization techniques conventionally used for the preparation of the microspheres are mainly classified as:

1. Normal Polymerization

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. Bulk polymerization has an advantage of formation of pure polymers.

2. Interfacial Polymerization

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed.

Spray drying and spray Congealing

These methods are based on the drying of the mist of the polymer and drug in the air. The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100μm. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively. [5,7,8]

Types of Floating Drug Delivery System [9]

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:

1. Effervescent System
2. Non-Effervescent System

1. Effervescent System

Effervescent systems include use of gas generating agents, carbonates (e.g. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature.

These effervescent systems further classified into two types.

A) Gas generating systems

Volatile liquid/vacuum system Gas generating systems

Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS)

These are formulated by intimately mixing the CO2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the grt and a better control over fluctuation in plasma drug concentration.

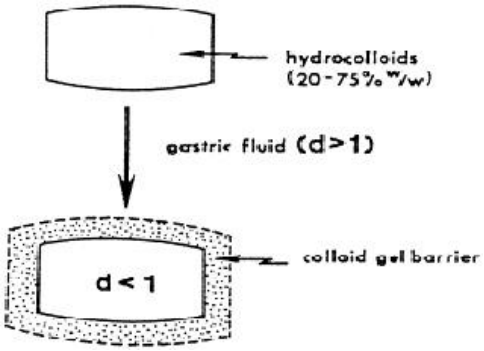

Figure 1: Intragastric floating tablet

Intra Gastric Bilayed Floating Tablets

These are also compressed tablet as shown in Fig and containing two layer i.e.(1)Immediate release layer (2) Sustained release layer.

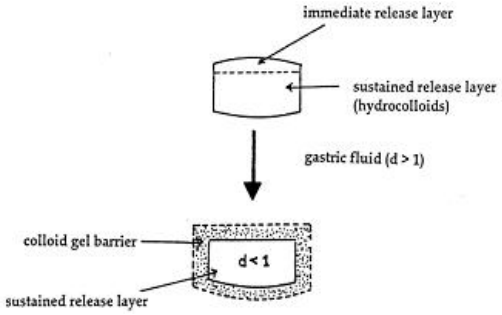

Figure 2: Intragastric floating bilayer tablet

Multiple Unit Type Floating Pills

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the systems.

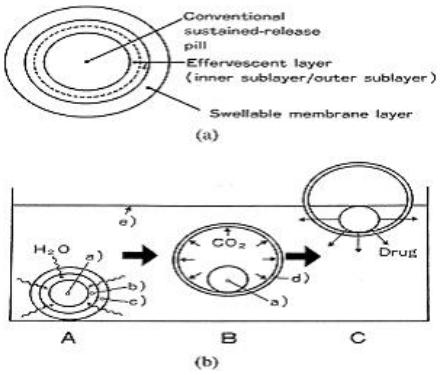

Figure 3: (a) Multiple-unit oral floating dosage system. (b)Stages of floating mechanism

Intragastric Floating Gastrointestinal Drug Delivery System

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment.

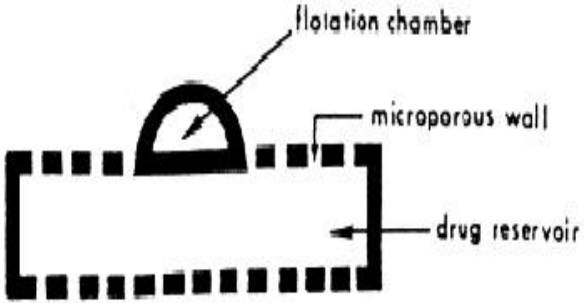

Figure 4: Intragastric floating drug delivery device

B) Inflatable Gastrointestinal Delivery Systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir into the gastric fluid.

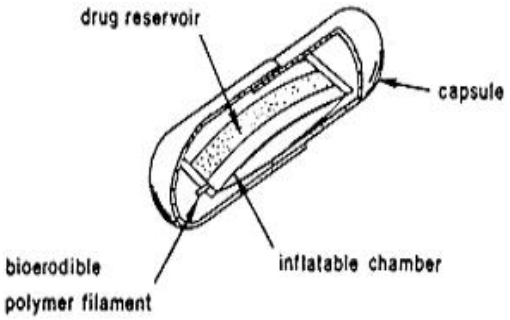

Figure 5: Gastro-inflatable drug delivery device

Intragastric Osmotically Controlled Drug Delivery System

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components: drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi-permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi-permeable membrane into osmotically active compartment to dissolve the osmotically salt. An osmotic pressure is then created which acts on the

collapsible bag and in turn forces the bag reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice. The floating support is also made to contain a bio-erodible plug that erodes after a predetermined time to deflat the support. The deflated drug delivery system is then emptied from the stomach.

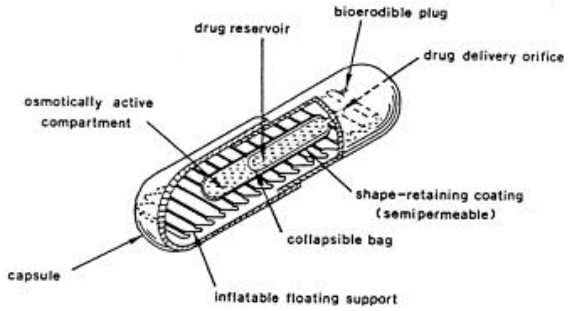

Figure 6: Intragastric osmotic controlled drug delivery system

2. Non Effervescent Systems

The non effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bio-adhesive polymer such as chitosan andcarbopol. The various type of this systems are as follows:

Single layer floating tablets

They are formulated by intimate mixing of drug with gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

Bilayer floating tablets

A bilayer tablet contain two layer immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

Alginate beads

Multi unit floating dosage forms are developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence, time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.

Hollow microspheres

Hollow microspheres (microballons), loaded with drug in their outer polymer shells were prepared by a novel emulsion solvent diffusion method. The ethanol: dichloromethane solution of drug and enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 400 C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro*.

3. Evaluation of Floating Drug Delivery System [10,11,12]

However, it has to be pointed out that good *in vitro* floating behaviour alone is not sufficient proof for efficient gastric retention *in vivo*. The effects of the simultaneous presence of food and of the complex motility of the stomach are difficult to estimate. Obviously, only *in vivo* studies can provide definite proof that prolonged gastric residence is obtained.

1) Measurement of buoyancy capabilities of the FDDS

The floating behaviour was evaluated with resultant weight measurements. The experiment was carried out in two different media, deionised water and simulated meal, in order to monitor possible difference. The results showed that higher molecular weight polymers with slower rate of hydration had enhanced floating behaviour and it was observed more in simulated meal medium compared to deionised water.

2) Floating time and dissolution

The test for floating time measurement is usually performed in stimulated gastric fluid or 0.1 mole.lit-HCl maintained at 37° C. It is determined by using USP dissolution apparatus containing 900 ml of 0.1 mole HCl as the dissolution medium at 37° C. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time. A 100 ml glass beaker was modified by adding a side arm at the bottom of the beaker so that the beaker can hold 70 ml of 0.1 mole.lit-1 HCl dissolution medium and allow collection of samples. A burette was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 ml/min to mimic gastric acid secretion rate. The performance of the modified dissolution apparatus was compared with USP dissolution Apparatus 2 (Paddle). The problem of adherence of the tablet to the shaft of the paddle was observed with the USP dissolution apparatus. The tablet did not stickto the agitating device in the proposed dissolution method. The drug release followed zeroorder kinetics in the proposed method. Similarity of dissolution curves was observed between the USP method and the proposed method at 10% difference level (f2=57). The proposed test may show good *in vitro-in vivo* correlation since an attempt is made to mimic the *in vivo* conditions such as gastric volume, gastric emptying, and gastric acid secretion rate.

3) Drug release

Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution.

4) Drug loading, drug entrapment efficiency, particle size analysis, surface characterization

Drug loading is assessed by crushing accurately weighed sample of beads or microspheres in a mortar and added to the appropriate dissolution medium which is then centrifuged, filtered and analyzed by various analytical methods like spectrophotometry. The percentage drug loading is calculated by dividing the amount of drug in the sample by the weighttotal beads or microspheres.The particle size and the size distribution of beads or microspheres is determined in the dry state using the optical microscopy method. The external and cross sectional morphology (surface characterization) is done by scanning electron microscope (SEM).

5) X-Ray/Gamma Scintigraphy

X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form now a day. It helps to locate dosage form in the GIT and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a emitting radionuclide in a formulation allows indirect external observation using a camera or scintiscanner. In case of scintigraphy, the rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GI tract.

6) Pharmacokinetic studies:

Pharmacokinetic studies are the integral part of the *in vivo* studies and several works has been on that. Sawicki studied the pharmacokinetics of verapamil, from the floating pellets containing drug, filled into a capsule, and compared with the conventional verapamil tablets of similar dose (40 mg). The tmax and AUC (0-infinity) values (3.75 h and 364.65 ng.ml-1h respectively) for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets. (tmax value 1.21 h, and AUC value 224.22 ng.ml- 1h).

No much difference was found between the Cmax values of both the formulations, suggesting the improved bioavailability of the floating pellets compared to the conventional tablets. An improvement in bioavailability has also been observed with piroxicam in hollow polycarbonate microspheres administered in rabbits. The microspheres showed about 1.4 times more bioavailability, and the elimination half-life was increased by about three times than the free drug. [13]

4. Applications of Floating Microspheres [4,14]

- Gastro retentive floating microspheres are very effective in the reduction of major adverse effect of gastric irritation; such as floating microspheres of nonsteroidal anti inflammatory drugs i.e. Indomethacin are beneficial for rheumatic patients.
- Continuous input of the drug following control release floating drug delivery dosages form administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.
- Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. The absorption of bromocriptine is limited to 30% from the gastrointestinal tract. However a hydrodynamically balanced system (HBS) of the bromocriptine can enhance the absorption.
- Floating microspheres 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 microspheres will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability.
- These systems are particularly advantages for drugs that are specifically absorbed from stomach or the proximal part of the small intestine e.g. riboflavin frusemide and misoprostol. By targeting slow delivery of misoprostol to the stomach, desired therapeutic level could be achieved and drug waste could be reduced.

5. Conclusion and Summery

Drug absorption in the gastrointestinal tract is a highly variable process and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promise to be a potential approach for gastric retention. Floating dosage form offers various future potential as evident from several recent publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying.

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