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Review Article

Gastro retentive floating microspheres: A review

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ABSTRACT

Drug absorption in the gastrointestinal tract is a highly variable process. Floating Microspheres are promises to be a potential approach for gastric retention enhances the bioavailability and controlled delivery of various therapeutic agents. Gastro retentive floating microspheres are low density systems that have sufficient buoyancy to float over gastric contents and remain and remain in stomach for prolonged period. The drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. Floating microspheres to improve patient compliance by decreasing dosing frequency, better therapeutic effect of short half-life drugs can be achieved. Enhanced absorption of drugs which solubilise only in stomach, gastric retention time is increased because of buoyancy. Floating microspheres are prepared by solvent diffusion and solvent evaporation methods to create the hollow inner core. In the present review preparation, methods, characterization, advantages, mechanism of drug release from microspheres, list of polymers, applications and list of drugs formulated as floating microspheres are discussed.

Keywords: Floating Microspheres, Gastro Retention, Short half- life drugs and Solvent Diffusion.

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INTRODUCTION

Oral controlled release (CR) dosage form (DFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is be filled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of gastrointestinal tract (GIT) due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time (GET) in humans which is normally average 2-3hrs through the major absorption zone, i.e., stomach and upper part of the intestine, can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose [1].

Therefore, control on placement of a variety of important drugs through appropriately designed drug delivery system (DDS) in a specific region of the GI tract offers advantages particularly for those having a narrow absorption window in the GIT or those with stability problems. These considerations have led to the development of a unique oral controlled release dosage form with gastro retentive properties. After oral administration, such a DF would be retained in the stomach and release the drug there in a controlled and prolonged manner so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. Gastro retentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestine [2].

A number of systems have been applied to increase the GRT of dosage forms by employing a variety of concepts. These systems have been classified according to the basic principles of gastric retention [3].

1. Floating drug delivery system (FDDS) with low density providing sufficient buoyancy to float over the gastric contents.
2. Bioadhesive systems enabling the localized retention of the drug in the stomach.
3. Swelling and expanding systems preventing transit from the gastric sphincter.
4. High density systems remaining in the stomach for longer period of time by sedimenting to the folds of stomach. Fig.2: Illustrates the mechanism of these systems in the stomach.

A number of other methods like use of passage delaying agents and modified shape systems have also been used for gastro retention purpose [4,5]. Floating microspheres (Hollow Microspheres) are gastro- retention drug delivery system based on non-effervescent approach. The word floating systems, first described by Davis in 1968, have bulk density lower than that of the gastric fluid and thus remain buoyant in stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is floating on the gastric contents, the drug is released slowly at the desired rate and the system is eliminated from the stomach [6].

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 micrometer. The microspheres are characteristically free flowing powders consisting of protein or synthetic polymers, which are biodegradable in nature. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Microspheres are small in size and therefore have large surface to volume ratios [7]. The use of microspheres in pharmaceuticals have a number of advantages Viz., Taste and odour masking, conversion of oils and other liquids to solids for ease of handling, protection of drugs against environment (moisture, heat, light and oxidation), separation of incompatible materials, to improve flow of powders, production of sustained release, controlled release and targeted medications [8].

Advantages:

1. Superior to single unit floating dosage forms as drug uniformity and there is no risk of dose dumping [9].
2. Avoidance of gastric irritation, because of sustained release effect.
3. Improved receptor activation selectively.
4. Extended time over critical concentration.
5. Less inter and intra subject variability.
6. Flexibility in dosage form design.
7. Improves patient compliance by decreasing dosing frequency.
8. Better therapeutic effect of short half-life drugs can be achieved.
9. Gastric retention time is increased because of buoyancy.
10. Drug release in controlled manner for prolonged period [10].

Disadvantages:

1. Drugs having irritant effect on gastric mucosa are not suitable candidates for FDDS eg: NSAIDs, some antibiotics, digoxin, theophylline, corticosteroids, ferrous sulfate and oral contraceptive.

2. Drugs which are absorbed along the entire GIT and which undergo, first pass metabolism may not be desirable eg: Nifedipine [10].
3. They are not suitable candidates for drugs with stability or solubility problem in stomach eg: Ranolazine.

POLYMERS USED IN FLOATING MICROSPHERES

A number of different substances both biodegradable as well as non-biodegradable have been investigated for the preparation of microspheres; these materials include polymers of natural origin or synthetic origin and also semisynthetic substances. Microspheres can be prepared by using both hydrophilic and hydrophobic polymers.

Hydrophillic Polymers: These are includes gelatin, agar, egg, albumin, starch, chitosan, cellulose derivatives; HPMC, DEAE cellulose.

Hydrophobic Polymers: These are include ethyl cellulose, polylactic acid, PMMA, acrylic acid esters etc.

Biodegradable Polymers: These materials also slowly disappear from the site of administration; however it occurs in response to a chemical reaction such as hydrolysis. Example; Polylactic acid (PLA), Poly glycolic acid (PGA) and Poly caprolactone (PCL) [11].

Non- Biodegradable Polymers: These materials are inert in the environment of use, are eliminated or extracted intact from the site of administration. Example; Polyethylene vinyl acetate (EVA), Poly dimethyl Siloxane (PDS), Polyether urethane (PEU), Ethyl cellulose (EC), Cellulose acetate (CA), Polyethylene (PE), and Polyvinyl chloride (PVC), Acrycoat and Eudragit S etc.

Hydrogels: These polymers swell but do not dissolve when brought in contact with water. As with the hydrophobic polymers, hydrogels are inert, removed intact from the site of administration, and function by forming a rate limiting barrier to the transport and release of drugs Example; Polyhydroxy ethyl methyl acrylate (PHEMA), cross-linked Poly vinyl alcohol (PVA), cross-linked Poly vinyl Pyrrolidone (PVP) and Poly acryl amide etc.

Soluble Polymers: These are moderate molecular weight (less than 75,000 Daltons) uncross linked polymers that dissolve in water. The rate of dissolution decreases with increasing molecular weight. These materials can be used alone or in combination with hydrophobic polymers to provide devices that slowly erode over time. Example; Polyethylene glycol (PEG), uncross linked Poly vinyl alcohol or Poly vinyl Pyrrolidone, hydroxyl propyl methyl cellulose (methocel) and copolymers of methacrylic acid and acrylic acid methyl ester (Eudragit L) etc [11].

MECHANISM OF FLOATING MICROSPHERES

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 is needed to allow proper achievement of buoyancy [12].

MECHANISM OF DRUG RELEASE FROM MICROSPHERES

The mechanism of drug release from multi particulates can occur in the following ways [13]:

Diffusion: On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Erosion: Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.

Osmosis: In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.

METHODS OF PREPARATTION OF FLOATING MICROPSHERES

Solvent Evaporation Method: Floating multi particulate dosage form can be 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 suitable additive (Surfactants/polymer) 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 stirring. The solvent removal leads to polymer precipitation at the oil/water interface of droplets, forming cavity and thus making them

hollow to impart the floating properties. The polymers studied for the development of such systems include cellulose acetate, chitosan, eudragit, acrycoat, methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide and polycarbonate [14].

Ionotropic Gelation Method: Ionotropic gelation is based on the ability of poly electrolytes to cross link in the presence of counter ions to form beads. Since, the use of alginates, gellam gum, chitosan and carboxymethyl cellulose for the encapsulaion of drug and even cells, ionotropic gelation technique has been widely used for this purpose. The natural poly electrolytes 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 hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations [15].

Emulsion Solvent Diffusion Method: In the emulsion solvent diffusion method the affinity between the drug and organic solvent is stronger than that of organic solvent and aqueous solvent. The drug is dissolved in the organic solvent and the solution is dispersed in the aqueous solvent producing the emulsion droplets even though the organic solvent is miscible. The organic solvent diffuse gradually out of the emulsion droplets in to the surrounding aqueous phase and the aqueous phase diffuse in the droplets by which drug crystallizes [15].

Single Emulsion Technique: In this method, micro particulate carriers of natural polymers i.e. those of 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 [16].

Double Emulsion Technique: This method involves the formation of the multiple emulsions or the double emulsion such as w/o/w. this method can be used with the natural as well as synthetic [16].

Polymerization technique:

a. **Normal Polymerization:** Normal polymerization is carried out using different technique as bulk, suspension, precipitation, emulsion and micellar polymerization processes. Pure polymers are formed by bulk polymerization.
b. **Interfacial Polymarization:** 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.

Phase separation Coacervation Technique: It is based on the principle of decreasing the solubility of the polymer rich phase knows as coacervates. The drug particles and an incompatible polymer are added to the system which makes first polymer to phase separate and engulf the drug particles [16].

CHARACTERIZATION OF FLOATING MICROSPHERES

Particle size: The particle size of the microspheres was measured using an optical microscopic method and mean microsphere size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer [17].

Bulk density: Bulk density is defined as the mass of powder divided by bulk volume. Accurately weighed 10gm. Sample of granules was placed into 25ml measuring cylinder. Volume occupied by the granules was noted without disturbing the cylinder and bulk density was calculated using the equation (values expressed in gm/cm^3) [17].

Bulk density = Weight of Sample/ Volume of Sample

Tapped density: The tapping method can be used to calculate tapped densities. The volume of weighed quantity of microspheres was determined after 100taps as well as 1000 taps using tapped density apparatus.

Tapped density = Weight of Sample/ Tapped Volume

Compressibility Index and Hausner Ratio: Compressibility index and hausner ratio was calculated from the values of bulk density and tapped density by using following formulas:

% Compressibility Index = (Tapped density-Bulk density)/Tapped Density × 100

Hausner ratio = Tapped Density/ Bulk Density

Angle of Repose: The angle of repose Ɵ of the microspheres, which measures the resistance to particle flow, was calculated as

TanƟ = h/r

Therefore, Ɵ = Tan^{-1} h/r

Where, Ɵ is angle of repose, h is height of the pile, r is the radius of the pile.

Percentage yield: Percentage yield of floating microspheres was calculated by dividing actual weight of product to total amount of all non-volatile components that are used in the preparation

of floating microspheres and is represented by following formula [18].

%yeild = (Actual weight of product/total weight of drug and excipients) x 100

Drug entrapment efficiency: The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCL repeatedly. The extract was transferred to a 100ml volumetric flask and the volume was made up using 0.1N HCL. The solution was filtered and the absorbance is measured by spectrophotometer against appropriate blank. The amount of drug entrapped in the microspheres was calculated by the following formula [18].

DEE = (Amount of drug actually present/ theoretical drug load expected) x 100

Swelling Studies: Swelling studies were performed to calculate molecular parameters of swollen polymers. Swelling studies may be determined by using dissolution apparatus, optical microscopy and other sophisticated techniques which include H1 NMR imaging, confocal laser scanning microscopy (CLSM), Cryogenic Scanning electron microscopy (Cryo-SEM), Light scattering imaging (LSI) etc. the swelling studies by using dissolution apparatus was calculated as per the following formula [18].

$$\text{Swelling ratio} = \frac{\text{Weigt of wet formulations}}{\text{Weight of formulations}}$$

Scanning Electron Microscopy (SEM): Surface morphology was determined by the method SEM. In this microcapsule were mounted directly on the SEM sample slab with the help of double sided sticking tape and coated with gold film under reduced pressure [19].

In-*Vitro* buoyancy: Microspheres (300mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900ml of 0.1N hydrochloric acid containing 0.02% tween 80. The medium was agitated with a paddle rotating at 100rpm for 12hrs. The floating and the settled portions of microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres [19].

$$\text{Buoyancy (\%)} = \frac{Wf}{Wf - Ws} \times 100$$

Where Wd and Ws are the weight of floating and settled microspheres respectively.

In –*vitro* drug release studies: For such type of studies USP dissolution apparatus at particular speed is used. Distilled water and dissolution fluid is maintained at 37±10°C. Samples withdrawn at periodical intervals and are analyzed spectrophotometrically. The volume was replenished with the same amount of fresh medium to maintain the sink condition [19].

APPLICATIONS OF FLOATING MICROSPHERES

- Floating microspheres are very effective approach in delivery of drugs that have poor bioavailability because of their limited absorption in the upper GIT. These systems efficiently maximize their absorption and improve the bioavailability of several drugs. Eg. Furosemide, Ridoflavin etc [20].
- The floating microspheres can be used as carriers for drug 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.
- Gastro retentive floating microspheres are very effective in the reduction of major adverse effect of gastric irritation; such as floating microspheres of nonsteroidalanti inflammatory drugs i.e. Indomethacin are beneficial for rheumatic patients.
- These systems are particularly advantages for the drugs that are specifically absorbed from stomach or the proximal part of the small intestine eg. Riboflavin frusemide and misoprostol.
- These microspheres systems provide sustained drug release behavior and release the drug over a prolonged period of time. Hollow microspheres of tranilast are fabricated as a floating controlled drug delivery system [20].

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Floating microspheres has emerged as an efficient approach for enhancing the bioavailability and controlled delivery of various therapeutic agents. Significant attempts have been made worldwide to explore these systems according to patient requirements, both in terms of therapeutic efficacy and compliance. Floating microspheres as gastro retentive dosage forms precisely control the release rate of target drug to a specific site and facilitate an enormous impact on health care. Optimized multi- unit floating microspheres are expected to provide clinicians with a new choice of an economical, safe and more bioavailable formulation in the effective management of diverse disease.

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