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Review Article

A Review on Multi-Particulate Floating Microspheres Drug Delivery System with Solvent Evaporation Approach

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ABSTRACT

Gastro-retentive controlled release drug delivery systems are designed to prolong the gastric residence time after oral administration and to control the release of drug to enhance drug therapy thus attracting interest of pharmaceutical formulation. Among the various approaches, floating drug delivery system (FDDS) promises to be a potential approach for gastric retention of drugs. Floating microspheres are multiparticulate gastroretensive systems which have been gaining attention during recent times due to the uniform distribution of these multiple-unit dosage forms which results in more reproducible drug absorption and reduced risk of local irritation in the stomach. These floating microspheres, in strict sense are empty spherical shaped particles having a size less than 200 micrometer comprising of proteins or synthetic polymers without core. The purpose of this review is to bring together the literature with respect to selection of drug, various classifications of floating systems, method of preparation through solvent evaporation, parameters affecting the characteristics, performance and characterization of floating microspheres.

Key words: Floating drug delivery system, multiple unit floating dosage system, microspheres, microballons, multi-particulates and solvent evaporation.

1. INTRODUCTION

Controlled release drug delivery systems (CRDDS) are designed to enhance drug therapy and aimed to control the drug release rate and sustain the duration of the action with or without targeted action.[1] The CRDDS with ability of being retain in the stomach are called gastro-retentive drug delivery system (GRDDS) and they are designed to prolong the gastric residence time of dosage form after oral administration and controlling the release of drug.[2] The controlled gastric retention of formulation may be achieved by the various approaches such as mucoadhesion,

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sedimentation, expansion, floatation and modified shape systems.[3]

Among the various approaches, floating drug delivery system (FDDS) promises to be a better approach for gastric retention of drug. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. FDDS is useful for drugs acting locally in the proximal gastro-intestinal tract and it have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. The systems are also used for drugs which are poorly soluble or unstable in intestinal fluids. However the gastric retention is influenced by many factors such as level of fluids in the stomach, gastric mobility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.[4]

Drug Selection for FDDS System:

Numerous drugs from the category of cardiovascular, anti-diabetic, diuretics etc. have been developed as floating systems. Drug selection becomes quite important for FDDS and selection criteria for floating systems involves various physicochemical characters of drug. Biopharmaceutical classification system (BCS) is vital criteria for drug to be selected. BCS classification is based on solubility and permeability of drug. For FDDS, solubility of drugs should be highly soluble in stomach to achieve better bioavailability. The dissociation constant of the drug of choice should be >2.5 for acidic drug, so that may remain unionised at gastric pH and drug get absorb in the stomach. For lipophilicity, the partition coefficient of the drug should be >1 for rapid absorption across lipoidal membranes. The half life of drug should be shorter (2 to 6 preferably). The drug which possesses acid stability can only be formulated as FDDS. Furthermore, drug should have stomach as its absorption window so as to get absorbed at any segment of stomach. At the same time, drugs showing extensive first pass metabolism are the candidate of choice. Drugs with low therapeutic index are unsuitable for incorporation in FDDS formulations as in case of dose dumping, especially in single unit dosage forms. Inspite of above said factors in finding the suitable drug properties, the physicochemical modification of drugs with poor aqueous solubility and low permeability issue, although quite expensive, may be a great favour in utilization of floating systems as an advantageous tool in the era of controlled delivery of drug.[5]

Ideal drug candidates for FDDS System [6, 7]

1. Drugs those are locally active in the stomach. Eg. Drugs for H.Pylori viz. Misoprostol and antacids etc.
2. Drugs which have narrow absorption window in the GIT. Eg. Furosemide, L-dopa, Para-amino benzoic acid, riboflavin.etc.
3. Drugs that exhibit low solubility at high pH values. Eg. Diazepam, Chlordiazepoxide, Verapamil hydrochloride.
4. Drugs those are unstable in the intestinal or colonic environment. E.g. Captopril, ranitidine HCl, Metronidazole.
5. Drugs that disturb normal colonic microbes. E.g. antibiotics against Helicobacter pylori.
6. Drugs having a specific site of absorption in the upper part of small intestine.

2. CLASSIFICATION OF FDDS [8]

Floating drug delivery systems are classified depending on the mechanism of buoyancy into two different technologies, Effervescent and Non-effervescent systems.

a) Effervescent floating systems: These floating systems are prepared with swellable polymers or polysaccharides and effervescent component containing sodium bicarbonate, citric and/or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. These systems/matrices are fabricated so that upon contact with gastric fluid, carbon dioxide is liberated by the acidity of gastric contents and is entrapped in the gelyfied hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. The carbon dioxide generating components may be intimately mixed within the tablet matrix to produce a single-layered tablet or a bi-layered tablet may be compressed which contains the gas generating mechanism in one hydrocolloid containing layer and the drug in the other layer formulated for the prolonged release.

b) Non effervescent floating systems: In this system commonly used excipients are gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. One of the approaches to the formulation of such floating dosage forms involves intimate mixing of drug with a gel forming hydrocolloid which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier. The air entrapped by the swollen polymer confers buoyancy to these dosage forms. The gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier.

3. PRACTICAL APPROACHES TO DESIGN FLOATING DRUG DELIVERY SYSTEM

The following approaches have been used for the design of floating dosage forms.[9]

A. Single Unit Floating Dosage Systems
B. Effervescent Systems (Gas-generating Systems)
    i. Non-effervescent Systems
C. Multiple Unit Floating Dosage Systems
    i. Effervescent Systems (Gas-generating Systems)
    ii. Non-effervescent Systems
D. Raft Forming Systems

Single unit dosage forms are easy to develop but suffers from the risk of losing their effects too early due to their all or none emptying from the stomach and thus they may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastro intestinal tract.[10]

Multi-particulate drug delivery system

Floating multiparticulate drug delivery systems are gastro-retentive drug delivery systems based on non-effervescent and effervescent approach. They are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm. Multiple-unit dosage forms have the following advantages over single-unit forms.[11, 12]

Table 1: Merits of Multi-unit floating drug delivery system over single – unit floating drug delivery system

Attributes	Multi-particulate	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 integrity of dosage form particularly for hydrophilic matrix
Safety concerns due to dose dumping	Minimal	Significant (drugs with Narran therapeutic index)
Drugs 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 Modulati	Customized profile possible	Somewhat difficult

Classification of multi-particulate floating drug delivery systems:

(A) Effervescent multi-particulate floating Systems :[13, 14]

Multiple unit type of floating pills composed of inner effervescent layer containing sodium bicarbonate and tartaric acid and outer swellable polymeric membrane made up of polyvinyl acetate and purified shellac. The inner layer was further divided into two sub layers to avoid physical contact between sodium bicarbonate and tartaric acid. When the pill was immersed in buffer solution at 37 °C, buffer solution entered in to the effervescent layer through the outer swellable membrane. Carbon dioxide was generated due to reaction between sodium bicarbonate and tartaric acid and formed swollen pills (like balloons) with a density much lesser than 1.0 g/ml. The system was found to float completely within 10 minutes and had a good floating ability independent of pH, viscosity of the medium and drug release in a sustained manner.

(B) Non-effervescent multiparticulate floating Systems

1. **Alginate beads:** 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 h. These alginate floating beads gave a prolonged residence time of more than 5.5 h.[15]
2. **Floating granules/pellets:** Floating granules can be prepared using a drug with suitable lipophilic polymer having low density. The polymers used for these granules are usually meltable at moderate temperature allowing the use of solvent free melt granulation technology for granulation. Pellets are manufactured by both wet and dry granulation techniques or by layering. Extrusion– spheronization is a wet-granulation technique that helps in the preparation of pellets or spherical agglomerates. [16]
3. **Hollow Microspheres/ Micro balloons:** Hollow microspheres are spherical empty particles with characteristic internal hollow core. These microspheres are made from different kind of hydrocolloids (polymers, gel forming agents, polysacharides). Floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents, remain in stomach for prolonged period and release the active compound in controlled manner. General techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. Kawashima and co-workers prepared hollow microspheres (‘microballoons’) with a drug loaded in their outer shells by an emulsion-solvent diffusion method.[17]

Hollow Microspheres/ Micro balloons

Hollow Microspheres/Microballoons are gastro retentive drug-delivery systems with non-effervescent approach and considered as one of the most favourable buoyant systems with the unique advantages of multiple unit systems as well as better floating properties. Microballoons (Hollow microsphere) are in strict sense, empty particles of spherical shape without core. These microspheres are

characteristically free flowing powders comprising of proteins or synthetic polymers, ideally having a size less than 200 micrometer.[18]

The slow release of drug at desired rate and better floating properties of floating microspheres mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation and the release of drug can be modulated by optimizing polymer concentration and the polymer - plasticizer ratio. [17]

Mechanisms of flotation of Hollow Microspheres/Micro balloons: When floating microspheres/microballoons come in contact with gastric fluid, the gel forms 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 outer 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 makes the density lower than the gastric fluid and confers buoyancy to the microspheres. However, a minimal gastric content needed to allow proper achievement of buoyancy. [19]

Table 2: Materials for preparation of Micro balloons[20]

Material and Purpose	Examples
Polymers - controls the drugs release rate	Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, Polyvinyl Acetate, Carbopol, Agar, Polyethylene oxide, Polycarbonates, Acrylic resins and Polyethylene etc.
Solvents - should have good volatile properties so that it should easily come out from the emulsion leaving hollow microspheres.	Ethanol, Dichloromethane (DCM), Acetonitrile, Acetone, Isopropyl alcohol (IPA), Dimethylformamide (DMF)
Processing Medium - used to harden the drug polymer emulsified droplets when the drug polymer solution is poured into it and it should not interact with the former.	Liquid paraffinn, Polyvinyl alcohol and Water
Surfactant - they are stabilizers or emulsifiers, play the role of hardening the microspheres as well.	Tween 80, Span 80 and SLS.
Cross linking agent - used for Chemical cross-linking of microspheres.	Formaldehyde, Glutaraldehyde or by using Di acid chlorides such as Terephthaloyl chloride
Hardening agent - helps to harden the microspheres formed in the processing medium.	n-hexane, Petroleum ether (in case the processing medium is liquid paraffin)

Methods of preparation of Hollow Microspheres/ Micro balloons:

A variety of techniques for the development of floating controlled release microspheres have been developed by various scientific and technological investigators. The selection of the technique depends on the nature of the polymer, the drug and their intended use.[21] Different development techniques are used for the fabrication of floating microspheres such as solvent evaporation, ionotropic gelation method, phase separation, interfacial polymerization and spray drying technique etc.[22] However, the solvent evaporation technique has been extensively used by a large number of researchers worldwide to explore the different vistas of floating microspheres. In solvent evaporation technique, there are basically two systems which include single and multiple emulsion solvent evaporation technique.[23]

Single emulsion solvent evaporation technique

In single emulsion solvent evaporation technique, there are also two systems such as oil-in-water (o/w) and water in oil (w/o). For insoluble or poorly water-soluble drugs, the oil-in water (o/w) method is frequently used. [24] This method is the simplest and effective method for the preparation of floating microspheres. In this method, the polymer is dissolved in organic solvents such as dichloromethane, chloroform or ethyl acetate, either alone or in combination, which had been used by various scientific investigators in their study. The drug is either dissolved or dispersed in polymer solution and this solution containing the drug is emulsified into an aqueous phase to make an oil-in water emulsion by using a surfactant or 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. Solvent removal from embryonic microspheres determines the size and morphology of the microspheres. It has been reported that the rapid removal of solvent from the embryonic microspheres leads to polymer precipitation at the o/w interface. This leads to the formation of cavities in microspheres, thus making them hollow to impart the floating properties.

Oil-in-oil emulsification process is also sometimes referred as water-in-oil or non-aqueous emulsification solvent evaporation. In this process, either drug alone or drug and polymers are codissolved at room temperature into polar solvents such 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 specified revolutions per minute (rpm) and room temperature over a required period of time to ensure complete evaporation of the solvent. The liquid paraffin is decanted and the microparticles are separated by filtration through a filter paper, washed with n-hexane, air dried for 24 h and subsequently stored in desiccators. [25-26]

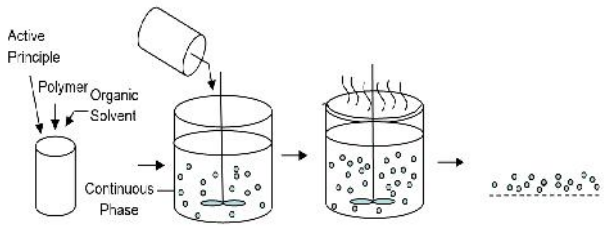

Fig 1: Schematic overview over of principal process steps in microsphere preparation by solvent evaporation technique

Multiple emulsion technique

Multiple emulsion or double emulsion technique is appropriate for the efficient incorporation of water soluble peptides, proteins and other macromolecules. In this process the polymers are dissolved in an organic solvent and emulsified into an aqueous drug solution to form an emulsion. The primary emulsion is re-emulsified into an aqueous solution containing an emulsifier to produce multiple w/o/w dispersion. The organic phase acts as a barrier between the two aqueous phases, preventing the diffusion of the active material toward the external aqueous phase. Microspheres developed by w/o/w method exhibit various characteristics such as porous or nonporous external shell layer enclosing hollow, macroporous, or microporous internal structures depending on different parameters. These methods utilize high-speed homogenization or ultrasonication, followed by evaporation of the solvent, either by continuous magnetic stirring at room temperature or under reduced pressure. Afterwards, the solidified microparticles can be collected by ultracentrifugation and washed with distilled water to remove additives such as surfactants and finally, the product is lyophilized. [27]

Mechanism of formation of hollow microspheres

Ethanol and methanol have been found to be good solvents for most drugs and polymers. Dichloromethane and chloroform are good bridging liquids due to the good linkage between the drug and polymers and to their immiscibility in the external phase. Most of the water-insoluble polymers show higher solubility in dichloromethane than ethanol. However, ethanol has higher solubility in water. As soon as the polymer solution was added to the aqueous medium, the ethanol diffuses rapidly from the droplets of the polymer solution. Simultaneous diffusion of water inside the sphere further decreased the ethanol concentration, hence the polymer precipitated, resulting in the formation of microspheres. Dichloromethane remaining as the central core diffused slowly due to its low water solubility. Therefore, the diffusion of ethanol played an important role in determining the size and shape of the microspheres. The inner porous structure was attributed to the inward diffusion of water, which resulted in the solidification of the polymer and the formation of several smaller pockets of dichloromethane rich entrapments which diffused out together with ethanol. The entrapped dichloromethane diffused slowly out of the pocket giving a porous structure to the wall of the microspheres. Due to the poor miscibility, water could not effectively invade the dichloromethane rich core. Therefore, the diffusion of dichloromethane began late, after the initial solidification, and formed a central hollow structure. During the diffusion of the solvents, the polymer was pulled outward as a result of the dragging force of the solvents and thus the central void space emerged. The central cavity produced by the solvents was gradually filled with water due to the reduced internal pressure. Water escaped out of the cavity during the drying process, ultimately forming hollow microspheres. [28]

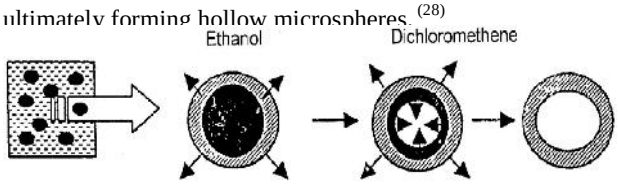

Fig 2: Formulation of floating microspheres

Factors affecting physiochemical properties of Hollow Microspheres/Micro balloons: Microencapsulation by the solvent evaporation method is a complex process, which can be influenced by following process parameters.[29]

1. **Stirring rate:** The stirring rate affects the microsphere - particle size. The size of microspheres decreases with increase of agitation. It may be inferred that the increase in agitation speed break up the bulk of the polymer into finer droplets. [30]
2. **Temperature of preparation:** It affects porosity and surface morphology of Microspheres. The microspheres prepared at lower temperatures (20 or 30ºC) provide porous microspheres having higher porosity with a rough surface. The roundness of hollow microspheres prepared at 40 ºC may close to 1 and surfaces are less rough than those of hollow microspheres prepared at lower temperatures. Hollow microspheres prepared at higher temperature (50 ºC) exhibits no hollow nature and possess high apparent particle density and low buoyancy due to the absence of a cavity. At 40 ºC, polymers and the drug were coprecipitated, and the shell was formed by the diffusion of ethanol into the aqueous solution and simultaneous evaporation of dichloromethane. [31] At the same time as the preparation temperature increases, particle size decreases. This may be at high temperature, emulsion is less viscous and it becomes much easier for the emulsion to be broken down into smaller droplets at the same power of mixing input. [32] Microspheres prepared at high temperature are found to be a uniform internal pore distribution. Microspheres formed at higher temperature gives very slow release rates after their initial drug release. Faster rate of solvent evaporation gives smooth surface, spherical shape and lower encapsulation. [20]
3. **Plasticizers:** It makes the wall of microsphere material more elastic and flexible, so that it never got brittle or ruptured under pressure. The release of the drug from microspheres increases significantly with the increase of plasticizer concentration. [33]
4. **Volume of aqueous phase (Continuous phase):** When the volume of aqueous phase increases the particle size decreases and thus buoyancy increases. The potential advantage of using large volumes of the external aqueous phase is the reduction of the required stirring times. The solubility of dichloromethane in water is 1% w/v and at larger volume (400 to 500 ml), its diffusion into the aqueous phase and solidification of particles

occurred faster when compared to lower volume (200ml) of the external aqueous phase. [34]

5. **Solvent ratio:** The bridging liquid plays a key role in microsphere preparation. When a good solvent diffuses into the poor solvent, which causes the precipitation of the drug and the polymer, a bridge liquid must be present in order to maintain the spherical shape of the microsphere. Too small volume of the bridging liquid can lead to irregularly shaped microspheres while too large volume of bridging liquid could prevent the emulsion droplets from solidifying. Therefore, the amount of dichloromethane needs to be carefully controlled. [35] The ratio of dichloromethane with ethanol affects the morphology of the microspheres so optimized the ratio which can give best spherical shape. The ratio of ethanol to dichloromethane is 2:1 obtains the best result with spherical shape. [34]
6. **Amount of polymer and viscosity:** Smaller microspheres will be formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium, giving rise to faster drug release. [36] The viscosity of the medium increases at a higher polymer concentration, resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities which results in the formation of larger particles. When viscosity is increased, the yield of hollow microspheres is decreases and mean diameter and drug loading amount are increases. [30] Drug dissolution profiles can be slow down by increasing polymer amount in the formulations and that particle size, surface characteristics of microspheres and dissolution rate can be modified through the variation of drug-to-polymer ratio. [37]
7. **Effect of solvent:** Dichloromethane is used as polar internal organic solvent phase for preparation of microspheres because it is a good solvent for most of the polymers and drugs. However, it is observed that the microspheres obtained with it are not at all spherical in shape. To solve this problem, methanol is used along with dichloromethane in the preparation of microspheres. The microspheres so obtained are spherical in shape but lack of smooth texture. To avoid this problem, various solvents are critically screened by researchers on the basis of the boiling points, such as dichloromethane (39.75 ºC), acetone (56.5 ºC), methanol (64.7 ºC) and ethanol (78.4 ºC). It is observed that the boiling point increased from DCM to ethanol and so instead of DCM/methanol, ethanol can be tried for best results. Most of the water-soluble drugs and water-insoluble polymers are dissolved in ethanol and it is non-toxic and considered as good solvent. As ethanol have high boiling point in relation to other organic solvents such as dichloromethane, acetone, methanol etc., which prevents immediate polymer precipitation and the microspheres so obtained are completely spherical, with a smooth surface. [38]
8. **Emulsifier concentration:** The emulsifier (surfactant) decreases the interfacial tension between the dispersed droplets and the continuous phase, as well as to protect the droplets from collision and coalescence. At lower emulsifier concentrations, droplets are more likely to collide and fused to form larger globules as it is insufficient to shield the entire droplet surface. At higher concentration of emulsifier, it reduces the encapsulation efficiency. Hence, the optimum concentration of the emulsifier should be identified. [39]
9. **Release modifiers:** Many drugs are not releases in significant amount from this type of microparticles at the pH of gastric fluids. So, there is a need for some hydrophilic polymers to be added into the formulation. Various agents, such as HPMC, citric acid, PVP, PEG, etc., depending upon their properties can be used to modify the drug release. These are also called as channeling agents.[40]

Characterization of floating multiparticulate microspheres [20, 40, 41]

Micromeritic properties: Floating microspheres are characterized by their micromeritic properties such as particle size, flow properties (Angle of Repose, Hausner's Ratio) and density. Angle of repose is determined by fixed funnel method and compressibility index is determined by measuring the change in volume using a bulk density apparatus.

Drug-Excipient (DE) interactions: This is done using Fourier-transform infrared spectroscopy (FTIR). Appearance of a new peak and/or disappearance of original drug or excipient peak indicate the DE interaction.

Scanning electron microscopy (SEM): Morphological examination of the surface and internal structure of the floating multiparticulates is performed by using a scanning electron microscope (SEM).

X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC): The determination of physical state of the drug in the multiple unit systems is important. There may be chances of change in crystallinity of the drug during the process and such changes may influence the drug release properties. The crystallinity of drug can be studied by X-ray powder diffraction technique (XRD) and differential scanning colorimetry (DSC).

Floating Behavior: Appropriate quantity of the floating microspheres are placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0), the mixture is stirred with a magnetic stirrer. After 12 hours, the layer of buoyant microspheres is pipetted and separate by filtration. Separate the particles in the sinking particulate layer by filtration. Particles of both types are dried in a desiccator until constant weight is achieved. Both the fractions of microspheres are weighed and buoyancy is determined by the weight ratio of floating particles to the sum of floating and sinking particles.

Buoyancy (%) = (W_f / W_f + W_s) × 100

Where, Wf and Ws are the weights of the floating and settled microspheres

Percentage drug entrapment: Appropriate quantity of the floating microspheres are thoroughly triturated and suspended in a minimal amount of solvent. The suspension was filtered to separate shell fragments. Drug contents were analyzed and percentage drug entrapment is calculated by using following equation.

% Drug Entrapment = (Actual drug content /Theoretical drug content) ×100

In Vitro* Dissolution Tests*: In vitro dissolution test is generally done by using USP apparatus with paddle. The in vitro release of drug from floating microspheres is examined by using 900 mil simulated gastric fluid (PH 1.2, without enzymes) as the dissolution medium and maintained at 37°C at a rotation speed of 50-100 rpm. An aliquot of 5 ml of the solution was withdrawn at predetermined time intervals and replaced by 5ml of fresh dissolution medium. Samples were assayed at maximum wave length by any suitable analytical method, such as UV spectroscopy or HPLC, etc.

***In-Vivo Evaluation*:** Although many animal models including rabbits have been reported for in vivo behaviour and human studies are also easily and widely acceptable. In vivo studies are generally conducted in healthy male albino rabbits weighing 2-2.5 kg. The animals are fasted for 24 hours before the experiments. However, they are given free access to food and water during the experiments. Blood samples (2ml) are collected from the marginal ear vein at an appropriate time intervals and samples are analysed with suitable/developed bio analytical method.

Floating behaviour of microspheres can be evaluated through following studies. Type of the study determines the tracing element to be incorporated.

i. **Radiology:** X- ray is widely used for examination of internal body systems. Barium sulphate is widely used Radio opaque marker. So, drug is replaced by BaSO4 and x-ray images are taken at various intervals to view Gastro retention. It is advisable to prepare different concentration of $BaSO_4$ and find out which ratio gives the comparable in vitro floatation. Research experiences shows that 20% of the drug if substituted will give satisfactory results.

ii. **Scintigraphy:** Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is 99Tc (technetium).

iii. **Gastroscopy:** Gastroscopy is peroral endoscopy used with fiber optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of GRDDS.

4. APPLICATIONS OF FLOATING MICROSPHERES [42]

1. 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 gastro-retentive floating microspheres will alter beneficially the absorption profile of the active agent that has poor bioavailability because of their limited absorption in the upper GIT, thus enhancing its bioavailability. e.g Furosemide, Riboflavin etc.
2. 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.
3. Hollow microspheres 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 sub-mucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis.
4. 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. The floating microspheres 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.
6. The development of microspheres allow administration of nonsystemic, controlled release antacid formulations containing calcium carbonate and also locally acting antiulcer drugs in the stomach; e.g. Lansoprazole.
7. Buoyant microspheres are considered as a beneficial strategy for the treatment of gastric and duodenal cancers.
8. These microspheres systems provide sustained drug release behavior and release the drug over a prolonged period of time. The drugs recently reported to be entrapped in hollow microspheres include prednisolone, lansoprazole, celecoxib, piroxicam, theophylline,

diltiazem, verapamil and riboflavin aspirin, griseofulvin, ibuprofen, terfenadine.

5. CONCLUSION

Floating microspheres has emerged as an efficient approach for enhancing the bioavailability and controlled delivery of various therapeutic agents. Floating microspheres as gastro retentive dosage forms precisely control the release rate of target drug to a specific site. These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development.

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