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REVIEW ARTICLE

FLOATING MICROSHERES: A NOVEL APPROACH IN DRUG DELIVERY

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ABSTRACT

Floating microspheres (Hollow Microspheres) are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core, free flowing powders consisting of proteins or synthetic polymers, ideally having a size in the range 1-1000 micrometer. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents 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 evaporation methods to create the hollow inner core. Floating microspheres are characterized by their micromeritic properties such as particle size, tapped density, compressibility index, true density and flow properties including angle of repose, scanning electron microscopy, in vitro floatability studies, in vivo floatability studies in dogs, *in-vitro* drug release studies and stability studies etc. In the present review preparation methods, characterization, advantages, mechanism of drug release from microspheres, applications and list of the drugs formulated as floating microspheres are discussed.

Key Words: Floating microspheres, Hollow microspheres, Gastro Retention, Short half-life, Solvent diffusion

INTRODUCTION

Recent advances in novel drug delivery system to enhance the safety and efficacy of the drug molecule by formulating a dosage form being convenient for administration. The high level of patient compliance has been observed in taking oral dosage forms is due to the ease of administration and handling of these forms. There are lot of advancements have been seen in oral controlled drug delivery system in the last few decades, this system has been of limited success in case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). To modify

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the GIT time is one of the main challenge in the development of oral controlled drug delivery system. Gastric emptying of dosage form is extremely variable process and ability to prolong and control the emptying time is valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage forms. Several difficulties are faced in designing controlled released systems for better absorption and enhanced the bioavailability[1].

Conventional oral dosage forms such as tablets, capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of Gastro-retentive floating microspheres[2, 3].

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 proteins 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. The concept of incorporating microscopic quantities of materials within microspheres dates back to the 1930s and to the work of Bungerberg de joing and co-workers on the entrapment of substances within coacervates. The potential uses of microspheres in the pharmaceutical have been considered since the 1960's and have a number of applications. The use of microspheres in pharmaceuticals have a number of advantages Viz., Taste and odor 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. The most important physico-chemical characteristics that may be controlled in microspheres manufacture are; particle size and distribution, polymer molecular weight, ratio of drug to polymer, total mass of drug and polymer

Three decades, various attempts have been done to retain the dosage form in the stomach as a way of increasing retention time:

1.Bio/Mucoadhesive Systems:

The term bioadhesion can be defined as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces[79].

Adhesion of bio-adhesive drug delivery devices to the mucosal tissue offers a possibility of creating an intimate and

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prolonged contact at the site of administration. This prolonged residence time can result in the enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration. The epithelial adhesive properties of mucin have been applied in the development of gastro retentive drug delivery systems [4, 8].

In biological systems, bioadhesion can be classified into 3 types[79]:

- **Type 1:** Adhesion between two biological phases. Example: Platelet aggregation and wound healing.
- **Type 2**: Adhesion of a biological phase to an artificial substrate. Example: Cell adhesion to culture dishes and biofilm formation on prosthetic devices and inserts.
- **Type 3**: Adhesion of an artificial material to a biological substrate. Example: Adhesion of synthetic hydrogels to soft tissues and adhesion of sealants to dental enamel.

2. Floating Systems:

Floating systems 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[9-11].

3. Swelling Systems:

These are capable of swelling to a size that prevents their passage through the pylorus; as a result, the dosage form is retained in the stomach for a longer period of time. Upon coming in contact with gastric fluid, the polymer imbibes water and swells[12-14].

Floating drug delivery system

Floating system was first described by Davis in 1968.Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach for a prolonged period without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system and the residual system is emptied from the stomach. This results in an increased Gastric Residence Time (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. To measure the floating force kinetics, a novel apparatus for determination of resultant weight (RW). 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 intra-gastric buoyancy capability variations[15].

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

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

Types of Floating Drug Delivery System

FDDS can be divided into two systems:

1. Effervescent systems

2. Non-effervescent systems

1. Effervescent Systems

A. Volatile liquid containing systems

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of PVA, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach[16].

B. Gas-generating Systems

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme[17, 18].

These buoyant systems can be prepared by using swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach.

Other approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc.

2. Non-Effervescent Systems

This type of system, after swallowing, swells unrestrained via imbibition of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the 'plug-type systems' since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

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A. Colloidal gel barrier systems

Hydro-dynamically balanced system (HBS) was first design by Sheth and Tossounian in 1975. Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids e.g. HEC, HPMC, NaCMC, Polysaccharides and matrix forming polymers such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsules. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms[19].

B. Microporous Compartment System

This technology is based on the encapsulation of drug reservoir inside a microporous compartment with aperture along its top and bottom wall. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolve drug for continuous transport across the intestine for absorption.

C. Alginate beads

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at -40° for 24 h, leading to the formation of porous system, which can maintain a floating force over 12 h.

D. Hollow microspheres

Hollow microspheres (microballons), loaded with ibuprofen in their outer polymer
shells were prepared by a novel emulsion-solvent diffusion method. The ethanol, dichloromethane solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°.The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 h in vitro.

Advantages of Hollow Microspheres[20-24]

- 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 multi particulate system.
- Improved receptor activation selectivity

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- 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.
- Enhanced first-pass biotransformation
- 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.

Disadvantages[25-26]

- Drugs having irritant effect on gastric mucosa are not suitable candidates for FDDS.eg: NSAIDs, some antibiotics, digoxin,theophylline, corticoster oids, iron (ferrous sulfate), oral contraceptives, and tricyclic antidepressants.
- 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 or microballoons.
- 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.

Development of Floating Microspheres

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs[27]. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric

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contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

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 needed to allow proper achievement of buoyancy[28,29]. Hollow microspheres of acrylic resins, Eudragit, polyethylene oxide, and cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent developments.

Methods of Preparation of Hollow Microspheres

Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by micro encapsulation technique. The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release and these above characters related to rpm, method of cross linking, drug of cross linking, evaporation time, co-precipitation etc. The various methods of preparations are

- **Emulsion solvent evaporation technique**

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0 .2 % sodium of PVP as emulsifying agent. The above 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. Aceclofenac microspheres were prepared by this technique.[30,31]. For emulsion solvent evaporation, 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 process, both the drug and the polymer should be insoluble in water while a water immiscible solvent is required for the polymer.[32] In this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform, or ethyl acetate, either alone or in combination. The drug is either dissolved or dispersed into 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

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the embryonic microspheres leads to polymer precipitation at the o/w interface. This leads to the formation of cavity in microspheres, thus making them hollow to impart the floating properties.[33-36] Oil-in-water emulsion is widely used than water-in-oil due to simplicity of the process and easy cleans up requirement for the final product.[37]

ii) **Oil in oil emulsification solvent evaporation technique**

This oil-in-oil (sometimes referred as water-in-oil) emulsification process is also known as non aqueous emulsification solvent evaporation. In this technique, drug and polymers are co dissolved at room temperature into polar solvents such as ethanol, dichloromethane, acetonitrile etc. 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 revolutions per minute (rpm) and room temperature 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. Span 60 is generally used which is non ionic surfactant. Span 60 has an HLB value of 4.3 and acts as a droplet stabilizer and prevents coalescence of the droplets by localizing at the interface between the dispersed phase and dispersion medium.[38,39]

❖ **Emulsion-solvent diffusion technique**

In order to improve the residence time in colon floating microparticles of ketoprofen were prepared using 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 sodiumlaurylsulphate (SLS) 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. The following microparticles were sieved and collected.[40]

❖ **Ionic Gelation Technique**

Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique. 25 % (w/v) of diclofenac sodium 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 Ca^{2+} /Al^{3+} 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.

❖ **Single Emulsion Technique**

In this method, micro particulate carriers of natural polymers i.e. those of proteins

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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.[41]

❖ **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.[42]

❖ **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 1-100 µm. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively.[42]

❖ **Hot melt encapsulation method**

Lin WJ and Kang WW compared the performance of Indomethacin microparticles and their release properties after coating with chitosan and gelatin, respectively. Here the poly (epsilon-caprolactone) (PCL) micro particles were prepared by the hot-melt encapsulation method. This method is having a disadvantage that thermo-labile substances cannot be used.[43]

Polymers Used In Hollow 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 semi-synthetic substances. Microspheres can be prepared by using both hydrophilic and hydrophobic polymers.

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- **Hydrophilic 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), Polycaprolactone (PCL) and several generic classes such as the poly anhydrides and poly orthoesters.

- ***Non-Biodegradable Hydrophobic 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), Polydimethyl siloxane (PDS), Polyether urethane (PEU), Ethyl cellulose (EC), Cellulose acetate (CA), Polyethylene (PE) and Polyvinyl chloride (PVC), Acrycoat, 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), 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.

Factors to be considered during Formulation[44]

1. **Addition of polymer solution**

As reported that, the high surface tension of water caused the solidification and aggregation of polymer on the surface of aqueous phase. To minimize the contact of polymer solution with the air-water interface and to develop a continuous process for preparing microspheres, a new method of introducing the polymer solution into aqueous phase was developed. The method involves the use of a glass tube immersed in an aqueous phase and the introduction of the polymer solution through the glass tube without contacting the surface of water. This method improved the yield of microspheres and reduced the extent of aggregate formation.

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2. Effect of rotation speed

It is obvious that the rotation speed of propeller affects yield and size distribution of microspheres. As the rotation speed of propeller increases, the average particle size decreases.

3. Effect of temperature

The temperature of the dispersing medium is an important factor in the formation of microspheres as it controls the evaporation rate of the solvents. Microspheres prepared at low temperature (10ºC) were crushed and irregularly shaped. The shell of the microsphere turns translucent during the process, due to slower diffusion rate of ethanol and dichloromethane. At higher temperature (40ºC), the shell of the microsphere became thin and it might be due to the faster diffusion of alcohol in the droplet into aqueous phase and evaporation of dichloromethane immediately after introducing it into the medium.

Characterization of Hollow Microsphere

1.Particle size determination

The particle size can be determined by using an optical microscope under regular polarized light, and mean particle size was calculated by measuring 100 particles with the help of a calibrated oculometer.[45]

2. Bulk density

Bulk density can be determined by three tap method, after filling the weighed quantity of microspheres in a graduated cylinder, the volume occupied by microspheres should be determined.

3. Tapped density

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

$$\text{Tapped density} = \frac{\text{Mass of microspheres}}{\text{Volume of microspheres after tapping}}$$

4. 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 :

$$\%\ \text{Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

$$\text{Hausner Ratio} = \frac{\text{Tapped density}}{\text{Bulk Density}}$$

5. Angle of Repose

The angle of repose θ of the microspheres, which measures the resistance to particle flow, was calculated as

$$\tan \theta = 2H/D$$

Where 2H/D is the surface area of the free standing height of the microspheres heap that is formed after making the microspheres flow from the glass funnel.

6. Yield of Microspheres

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The prepared microspheres were collected and weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

% Yield = (Actual weight of product / Total weight of excipients and drug) x 100

7. Optical Microscopy

This method was used to determine particle size by using optical microscope (Meizer OPTIK) The measurement was done under 450x (10x eye piece and 45x objective) and100 particles were calculated.[46]

8. 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.[47]

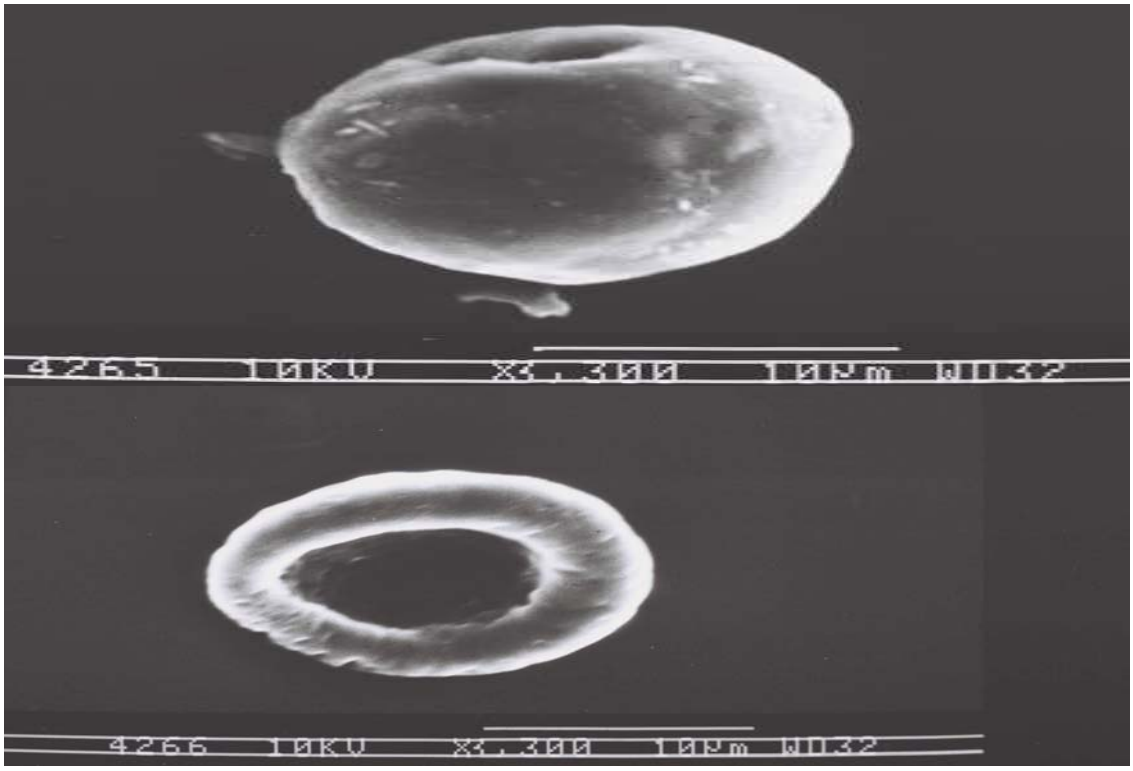

Figure 1: SEM photomicrographs of hallow microspheres: Surface view and Section showing inner cavity[78]

9. Swelling Index

This technique was used for Characterization of sodium alginate microspheres were performed with swelling index technique Different solution (100 mL) were taken such as

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(distilled water, buffer solution of pH(1.2, 4.5, 7.4) were taken and alginate microspheres (100 mg) were placed in a wire basket and kept on the above solution and swelling was allowed at 37°C and changes in weight variation between initial weight of microspheres and weight due to swelling was measured by taking weight periodically and soaking with filter paper.[48]

10. Entrapment Efficiency

Microspheres containing of drug should be crushed and then dissolved in distilled water with the help of ultrasonic stirrer for 3 hr, and was filtered then assayed by UV-vis spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content.[48]

11. Thermal Analysis

Thermal analysis of microsheres and its component can be done by using Differential Scanning Calorimetry (DSC), Thermo Gravimetric Analysis (TGA) and Differential Thermometric Analysis (DTA). Accurately the sample was weighed and heated on alumina pan at constant rate of 10°c/min under nitrogen flow of 40 ml/min.

12. FT-IR (Fourier Transform Infra Red)

The drug polymer interaction and also degradation of drug while processing for microencapsulation can be determined by FTIR.[49]

13. Stability Studies

By placing the microspheres in screw capped glass container and stored them at an ambient humid condition, room temperature (27 ± 2°C), oven temperature (40 ± 2°C) and refrigerator (5°C - 8°C). It was carried out for 60 days and the drug content of the microsphere was analyzed.

13. Zeta potential

The polyelectrolyte shell was prepared by incorporating chitosan of different molecular weight into the W_2 phase and the resulting particles were determined by zeta potential measurement.[50]

14. Floating Behavior

Floating microspheres should be placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0) containing 0.02% w/v Tween 20. The mixture was stirred at 100 rpm with a magnetic stirrer. After 8 hours, the layer of buoyant microspheres 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[51].

Buoyancy (%) = $W_f / W_f + W_s$

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

15. *In-Vitro* Release Studies

The release rate of floating microspheres was determined in a United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus. A weighed amount of floating microspheres equivalent to 50 mg drug was filled into a hard gelatin capsule (No. 0) and placed

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in the basket of dissolution rate apparatus. Five hundred milliliters of the SGF containing 0.02% w/v of Tween 20 was used as the dissolution medium. The dissolution fluid was maintained at 37 ± 1° at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. 5ml samples were withdrawn at each 30 min interval, passed through a 0.25 µm membrane filter (Millipore), and analyzed using LC/MS/MS method to determine the concentration present in the dissolution medium. The initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal. All experiments were run in triplicate.

16. *In-Vivo* Studies

The in-vivo floating behavior can be investigated by X-ray photography of hollow microspheres loaded with barium sulphate in the stomach of beagle dogs. The in-vitro drug release studies are performed in a dissolution test apparatus using 0.1N hydrochloric acid as dissolution media. The in-vivo plasma profile can be obtained by performing the study in suitable animal models (e.g. beagle dogs).

Table1: List of the animal models used for the Evaluation of Floating Drug Delivery Systems[52]

S.No.	Drug	Dosage form	Animal Model	Methodology tested	Results
1	Repaglinide	Microspheres	Male albino rabbits	Gamma scintigraph	Enhanced bioavailability
2	Repaglinide	Microspheres	Male Sprague-Dawley rats	Organ distribution Study	Enhanced bioavailability about 3.17 times in comparison to the marketed products
3	Riboflavin	Microballoons	Healthy human volunteers	Urine excretion Analysis	Prolonged GRT
4	Ranitidine hydrochloride	Microparticles	Rabbits	Pharmacokinetic Studies	Prolonged GRT >12 hrs and Improve the bioavailability
5	Orlistat	Microspheres	Albino rabbits	Gamma scintigraphy	The best floating ability (88% ± 4% buoyancy) in simulated gastric fluid(SGF) as compared with other formulations Prolonged GRT of over 6 hrs was achieved in all rabbits

Applications of Floating Microspheres[53]

- 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. e.g Furosemide, Riboflavin etc.

- The floating microspheres can be used as carriers for drugs with so-called

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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.

- Gastro retentive floating microspheres are very effective in the reduction of major adverse effect of gastric irritation; such as floating microspheres of non-steroidal anti inflammatory drugs i.e. Indomethacin are beneficial for rheumatic patients..
- 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.

- 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. The development of such systems allow administration of non-systemic, controlled release antacid formulations containing calcium carbonate and also locally acting anti-ulcer drugs in the stomach; e.g. Lansoprazole. Buoyant microspheres are considered as a beneficial strategy for the treatment of gastric and duodenal cancers.
- 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.
- 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.
- The drugs recently reported to be entrapped in hollow microspheres include prednisolone, lansoprazole, celecoxib, piroxicam, theophylline, diltiazem, verapamil and riboflavin, aspirin, griseofulvin, ibuprofen, terfenadine.

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Table 2: List of the drugs Formulated as Floating Microspheres

S. No	Drug	Polymers	Method	Reference
1	Atenolol	Ethyl cellulose & HPMC	Emulsion solvent evaporation technique	54
2	Curcumin	Ethyl cellulose, Eudragit S100 & HPMC	Emulsion solvent diffusion method	55
3	Tolperisone	Ethyl cellulose (EC), and HPMC 15 cPs	Non-aqueous solvent evaporation technique	56
4	Famotidine	HPMC and Ethyl cellulose (EC)	Solvent evaporation (Oil-in-water emulsion) technique	57
5	Captopril	HPMC(K4M) and Ethyl cellulose (EC)	Ionotropic gelation technique	58
6	Ketoprofen	Eudragit S100 and Eudragit L 100	Emulsion solvent diffusion method	59
7	Ketorolac trometamol.	Ethyl cellulose, HPMC K4M, Eudragit R100 & Eudragit S100	Emulsion solvent diffusion method	60
8	Glipizide	Acrycoat S100, Eudragit RS100 & Ethyl cellulose	Emulsion solvent diffusion technique	61
9	Rabeprazole	HPMC K15M and Ethyl cellulose	Emulsion solvent Evaporation	62
10	Orlistat	Eudragit S	Emulsion solvent Evaporation	63
11	Esomeprazole	HPMC and Methyl cellulose	Solvent evaporation method	64
12	Cimetidine	HPMC and Ethyl cellulose	Solvent evaporation method	65
13	Stavudine	Eudragit RS100	Emulsion solvent Diffusion	66
14	Metformin	Eudragit RS100 and Eudragit RL 100	Non aqueous solvent evaporation	67
15	Aceclofenac	Ethyl cellulose	Solvent evaporation	68
16	Ketoprofen	HPMC and Ethyl cellulose	Solvent evaporation	69
17	Acyclovir	Ethyl cellulose	Double emulsion solvent evaporation	70
18	Clarithromycin	Ethyl cellulose	Solvent Evaporation Technique	71
19	Cefpodoxime proxetil	Ethyl cellulose	Solvent Evaporation Technique	72
20	Pioglitazone	Ethyl cellulose	Emulsion solvent diffusion-evaporation	73
21	Ranitidine	HPMC (K100), Xanthan gum and Eudragit S100	Solvent Evaporation Technique	74
22	Gabapentin	Sodium alginate	Solvent Evaporation	75
23	Tinidazole	Bovine Serum Albumin	Emulsion cross linking method	76
24	Felodipine	Sodium alginate	Solvent evaporation	77

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CONCLUSION

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. 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. 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. Furthermore, recent innovations in pharmaceutical investigation will surely provide real prospects for establishment of novel and effective means in the development of these promising drug delivery systems.

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