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Review Article

A REVIEW ON POLYMERS OF GASTRORETENTIVE DRUG DELIVERY: FLOATING MICROSPHERE

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ABSTRACT

Delivery of the drug at controlled release rate to the specific body site is of paramount importance in the health care system. Gastroretentive drug delivery system helps in increasing the retention of the drugs at the intestinal region which have narrow absorption window, low bioavailability etc. Therefore, different novel strategies have been undertaken for the designing of several Gastroretentive drug delivery systems including floating microspheres. Floating microspheres are one of the novel approaches which are specially gaining attention due to their wide applicability in the targeting of drugs to stomach. These floating microspheres have the advantage that they remain buoyant and distributed uniformly over the gastric fluid to avoid the vagaries of gastric emptying and release the drug for prolonged period of time. The polymers used in the Floating Drug Delivery Systems are mainly involved in controlled release of drug from the delivery system which shows better results on selection of proper polymers and in their optimization. This article mainly emphasis on development techniques, effect of polymers on floating microspheres, characterization and applications.

Key words: Floating microspheres, Gastroretentive drug delivery, Floating Drug Delivery Systems, Polymers.

INTRODUCTION

Over the past three decades, the exploration of devices designed to be retained in the upper part of gastrointestinal tract has advanced consistently in terms of technology and diversity showing a variety of systems such as floating systems which show Gastroretentive drug delivery. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolongation of gastric residence time of a rate-controlled oral drug delivery system reduces inter-subject variability. Moreover, the total gastrointestinal transit time is prolonged thus, the number of dosage regimen can be reduced and solubility can be improved for drugs that are less soluble in a high pH environment [1]. The Gastroretentive drug delivery system can be retained in the stomach and assists in improving the oral sustained delivery of the drugs that have an absorption window in a particular region of the GI tract. These systems help in continuous releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Most drugs are well absorbed throughout the entire intestinal tract, but some compounds usually those that are polar in nature are poorly absorbed from the large intestine. For such drugs, the main area from which absorption occurs is the small intestine. Some of the drugs that are absorbed from gastrointestinal tract include - drugs that are absorbed primarily in the stomach, e.g., albuterol, chlordizepoxide; drugs that absorbed rapidly from the GI tract, e.g., amoxicillin; drugs that have a narrow absorption window and are mainly absorbed from the upper small intestine, e.g., ofloxacin, levodopa, riboflavin, theophylline; drugs having low bioavailability and drugs that degrade in the colon, e.g., ranitidine, metoprolol and drugs that are poorly soluble in intestinal pH, e.g., diazepam, weak bases such as dipyridamole[1].

Several approaches are currently used to prolong gastric retention time. These include floating drug delivery system, swelling and expanding systems, polymeric bioadhesive system, high–density and other delayed gastric-emptying devices. Oral sustained release floating multiparticulate drug delivery system include,

- low density floating micropellets,
- Floating micro beads acrylic resin based,
- Hollow microspheres micro balloons.

High-density systems having density of ~3 g/cm^3 are retained in the rugae of

the stomach. The only major drawbacks with such systems is that it is technically difficult to manufacture them with a large amount of drug >50% and to achieve the required density of 2.4–2.8 g/cm^3.

Swelling systems 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.

Bio/mucoadhesive systems bind to the gastric epithelial cell surface or mucin and extend the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The epithelial adhesive properties of mucin have been applied in the development of Gastro retentive drug delivery systems.

Floating systems first described by Davis 1968 which are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration.

FLOATING DRUG DELIVERY SYSTEM:

Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force F is also required to keep the dosage form reliably buoyant on the surface of the meal. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres[3].

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM:

Various devices such as mucoadhesive, swelling, high-density and floating systems have been developed to increase Gastric Residence Time of a dosage form. In general, FDDS can be divided into Effervescent system and Non Effervescent system.

A. Effervescent system: This system includes carbonate/bicarbonate salts and citric/tartaric acid present in the formulation to liberate CO_2 upon contact with gastric fluid which makes the system buoyant in gastric fluid for its low density. The swellable polymers used are HPMC, chitosan and various effervescent compounds like sodium bicarbonate, tartaric acid, and citric acid. Effervescent system is further classified into: Gas generating systems and volatile liquid or vacuum containing systems.

1. Gas generating systems:

a Hydrodynamically Balanced System HBS: "Hydrodynamically balanced systems" HBS are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity and release drug constantly from the dosage form.

b Intra gastric bilayered floating tablets: These are also compressed tablet that contains two layers i.e., immediate release layer and Sustained release layer.

c Multiple types of floating pills: These systems consist of sustained release pills as seeds surrounded double layer. The inner layer consists of effervescent agents while outer layer is Swellable membrane layer shown in figure 1. When these pills come in contact with gastric fluid it sinks at once and then forms swollen pills like balloons, which float as they have lower density due generation and entrapment of co_2 within the system[4].

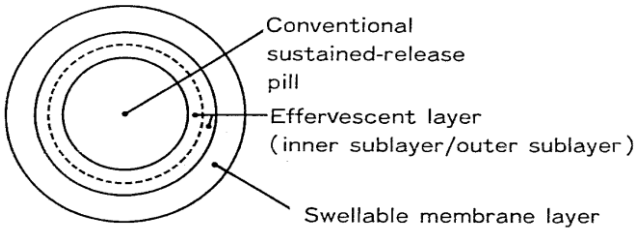

Fig.1.Multiple type of floating pills

2. Volatile Liquid / Vacuum Containing Systems:

a Intra gastric floating gastrointestinal drug delivery system: It is a Fluid-Filled Floating Chamber type of dosage forms and includes incorporation of a gas filled floatation chamber which could be air, under partial vacuum or any other suitable gas, liquid into a microporous component that consists of a drug reservoir. Openings are present along the top and bottom walls through which the gastrointestinal tract

fluid enters to dissolve the drug. The device remains afloat within the stomach for a prolonged time and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated.

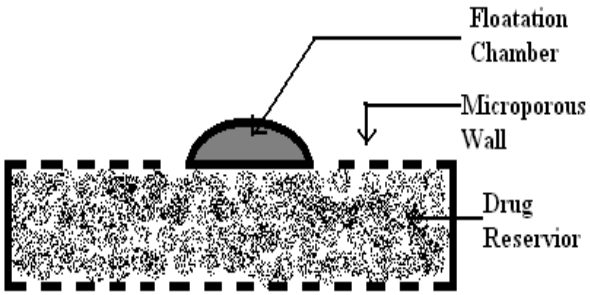

Fig.2.Intragastric floating gastrointestinal drug delivery system

b Inflatable gastro intestinal delivery system: It consists of an inflatable chamber that contains liquid ether which gasifies at body temperature and inflates in stomach region. The inflatable chamber is loaded with drug reservoir and impregnated with biodegradable polymer then encapsulated in gelatin capsule. After administration the inflatable chamber inflates and the drug is continuously released from the system.

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

through the semi-permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

B. Non Effervescent system:

It is based on the mechanism of bioadhesion of polymer to gastric mucosa or swelling of polymer which buoyants in stomach. The polymers used are gel forming or Swellable cellulose type of hydrocolloids, polysaccharides, matrix forming polymers like polycarbonate, polycrylate, polymethacrylate and polystyrene and bioadhesive as chitosan etc. It is further classified to:

1. Single layer floating system: This system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxypropyl cellulose, hydoxyethyl cellulose, hydroxypropyl methyl cellulose HPMC, polysaccharides and matrix forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

2. Bilayer floating system: It contains two layers one is immediate release containing intial dose of drug and second one is sustained release layer which buoyant in stomach by absorbing gastric fluid forming a colloidal gel barrier on its surface and maintains bulk density <1. This type of dosage forms remain in buoyant for period of time about 13 hours.

3. Alginate beads: Spherical beads of 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap- frozen in liquid nitrogen, freeze-dried at -40°C for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours.

4. Hallow micro spheres/Microballons Hollow microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core. The polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing polyvinyl alcohol to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the

temperature under pressure or by continuous stirring. The solvent removal leads to polymer precipitation at the o/w interface of droplets, forming cavity and thus making them hollow to impart the floating properties.

FLOATING MICROSPHERES:

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres, micro balloons or floating micro particles are terms used synonymously for floating microspheres. Hollow microspheres are 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 [2].

A blend of floating and pulsatile principles of drug delivery system would have the advantage that a drug can be released in the upper GI tract after a definite time period of no drug release lag period. The major objectives of the study was to develop a simple, multiparticulate, floating-pulsatile drug delivery system for obtaining no drug release during floating time followed by pulse drug release in small intestine. A pulsatile release of piroxicam was demonstrated by a simple floating drug delivery system which could be useful in chronopharmacotherapy of rheumatoid arthritis.

Advantages [5]:

a) Improves patient comfort and compliance by decreasing dose frequency.
b) Drug releases in a controlled manner for prolonged period of time.
c) Enhances the bioavailability and therapeutic efficacy of drugs with narrow absorption window in the upper part of GIT e.g. para aminobenzoic acid, furosemide, riboflavin.
d) Releases drug uniformly and there is no risk of dose dumping.
e) Efficient absorption of drugs in gastric region that are unstable in the intestinal or colonic environment.
   e.g. captopril, ranitidine HCl, metronidazole.
f) Avoidance of gastric irritation, because of sustained release effect.
g) Enhances drug bioavailability that exhibit low solubility at high pH values.
   e.g. diazepam, chlordiazepoxide, verapamil HCl.
h) Fluctuations in drug concentration are minimized.
   Therefore, concentration dependent adverse effects can be reduced.
i) Advantageous for drugs those are locally active in the stomach. e.g. misoprostol, Antacids.

j) Efficient in correlation with pulsatile drug delivery system in treating arthritis by chronopharmacotherapy.

DEVELOPMENT TEHNIQUES:

The various methods used for the preparation of floating microspheres:

1. Single emulsion technique: The 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. Next cross linking of the dispersed globule is carried out. The cross linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross linking agents used are glutaraldehyde, formaldehyde, di acid chloride etc. Heat denaturation is not suitable for thermolabile substances. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, separation.

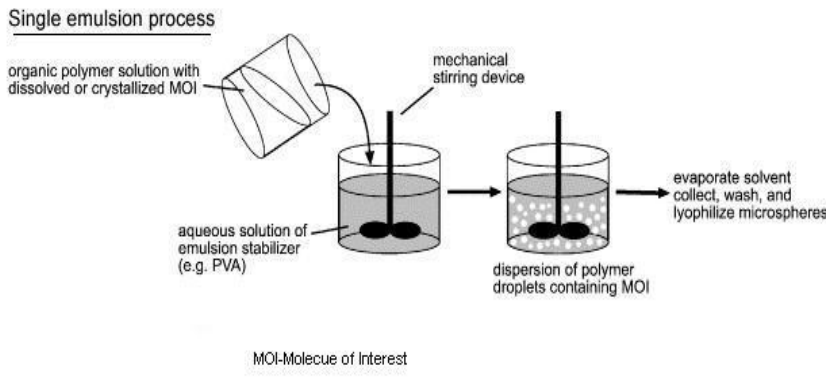

Fig.3.Single emulsion technique

2. Double emulsion technique:

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to water soluble drugs,

peptides, proteins and the vaccines. An aqueous solution of the drug is emulsified in an organic polymer solution, forming the primary water/oil emulsion. The primary emulsion is then introduced into an aqueous solution

with a stabilizer e.g., PVA and emulsified, forming the secondary water/oil/water emulsion. As in the single emulsion method, the speed and duration of agitation with a mechanical stirring device control the size of the droplets formed during each of the

emulsifications. Solvent evaporation yields drug-loaded microspheres dispersed in the PVA solution, which are collected and washed by centrifugation or filtration, and lyophilized.

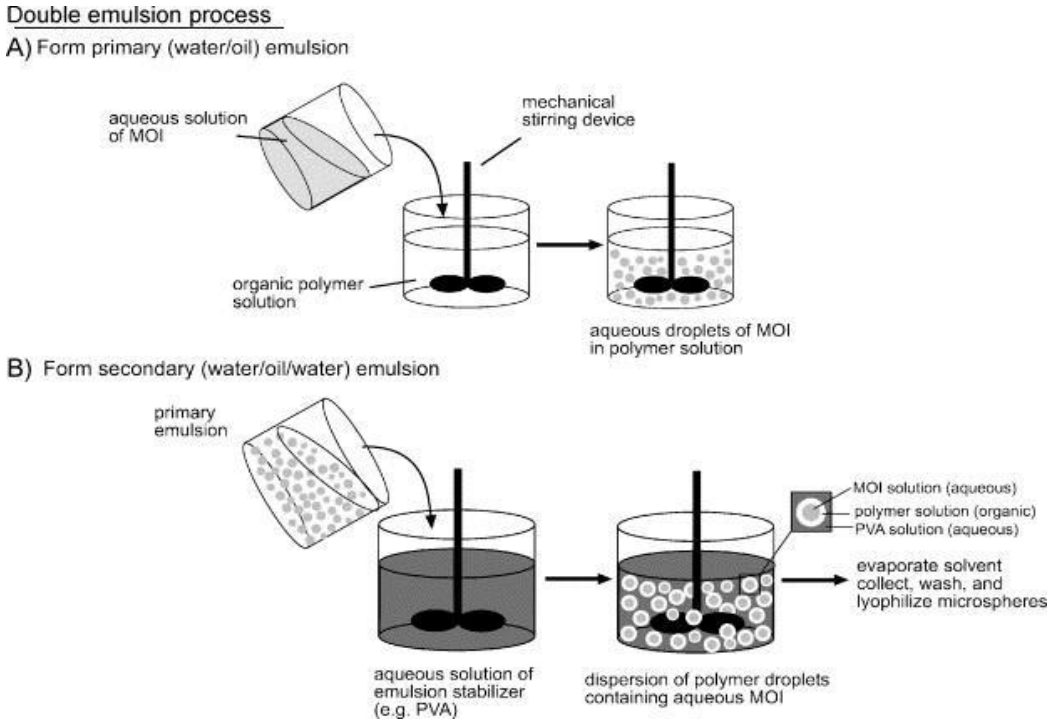

Fig.4.Double Emulsion technique

3. Emulsion solvent evaporation:

Solvent evaporation method is used for the preparation of microparticles, involves removal of the organic phase by evaporation of the organic solvent. The method involves water miscible organic solvents such as isopropanol. Organic phase is removed by evaporation with water. In order for the microsphere to form, the organic solvent must first

diffuse into external phase and then evaporate at the water air interface. As solvent evaporation occurs, the microspheres harden and free flowing microspheres can be obtained after suitable filtration and drying. This process decreases the hardening time for the microspheres. The rate of solvent removal by evaporation method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer [7].

4. 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.

5. Phase separation coacervation technique:

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, 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. Addition of non-solvent results in the solidification of polymer. Poly lactic acid PLA microspheres have been prepared by this method by using butadiene as incompatible polymer [6].

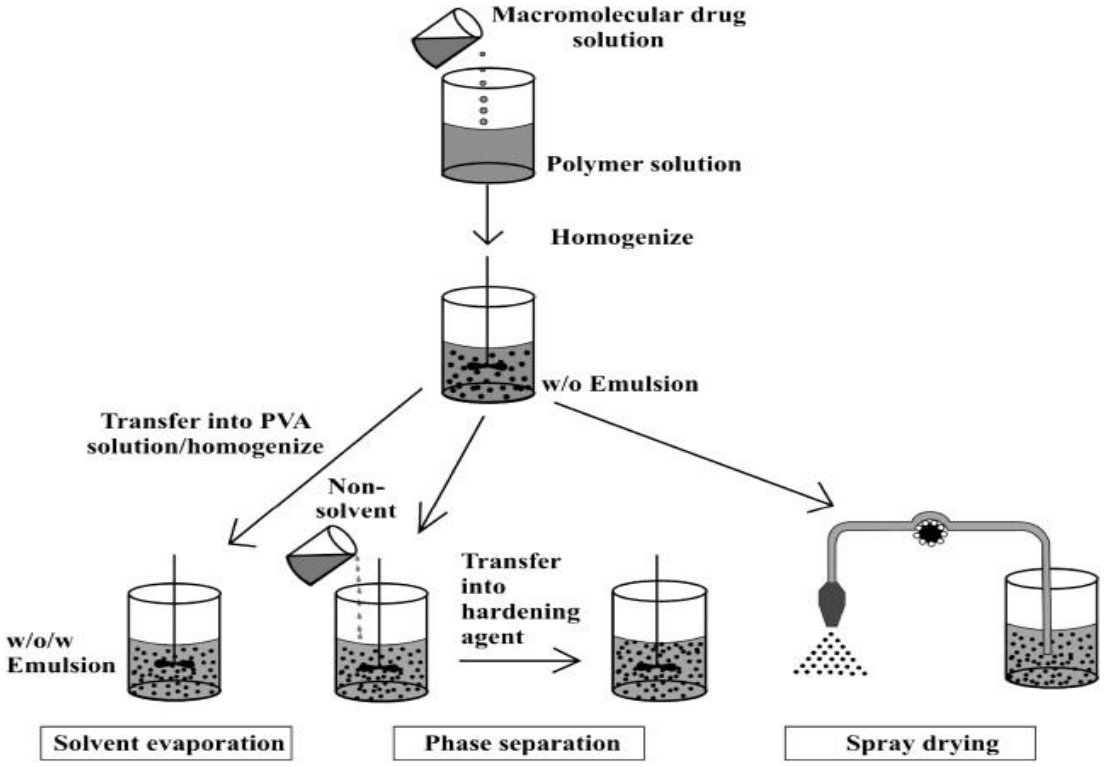

Fig.5.Techniques of Solvent evaporation, Phase separation, Spray drying

6. POLYMERISATION TECHNIQUE:

Mainly involves two methods. a Normal polymerization. b Interfacial polymerization.

a Normal polymerization:

Normal polymerization classified as:

1. Bulk polymerization
2. Suspension/ pearl polymerization
3. Emulsion polymerization

1. Bulk polymerisation: In bulk polymerization, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer obtained may be moulded as microspheres. Drug loading may be done by adding the drug during the process of polymerization.

2. Suspension polymerization: It is carried out at lower temperature and also referred to as pearl polymerization in which the monomer mixture is heated with active drug as droplets dispersion in continuous aqueous phase. Microsphere size obtained by suspension techniques is less the 100 micro meters.

3. Emulsion polymerization: This technique differs from the suspension and polymerization due to presence of initiator in aqueous phase and also

carried out at low temperature as suspension. External phase normally water in last two techniques so through which heat can be easily dissipated. The formation of higher polymer at faster rate is possible by these techniques but sometimes association of polymer with the un- reacted monomer and other additives can occur.

b 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 phase. In this technique two reacting monomers are employed; one is dissolved in continuous phase while other is dispersed in continuous phase aqueous in nature throughout which the second monomer is emulsified.

7. IONIC-GELATION TECHNIQUE:

The core material or drug as fine powder passed through mesh no.120 is added to the polymer solution and mixed to form a smooth viscous dispersion. This dispersion is added drop wise into 10%w/v $CaCl_2$ solution through a syringe with a needle of diameter 0.55mm. The added droplets are retained in $CaCl_2$ solution and allowed to cure for 20 minutes at 200 rpm to produce spherical rigid microsphere. Finally the microspheres are collected and dried in an oven at a temperature 45^{O}C for 12 hrs.

EFFECT OF POLYMERS ON FLOATING MICROSPHERES:

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 mass and total mass of drug and polymer. 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 modified natural substances. A range of microspheres prepared using both hydrophilic and hydrophobic polymers. Hydrophilic polymers includes gelatin, agar, egg albumin, starch, chitosan, cellulose derivatives; HPMC. Hydrophobic polymers include ethyl cellulose, polylactic acid, PMMA, acrylic acid esters etc. The number of polymers and range of formulation variables available to control the rate of drug release from controlled release devices are broad. Selection among these variables is based upon the desired release rate and duration, physical and chemical properties of the drug and the intended site of administration [8]. In general polymers are selected from one of several classes as follows [6, 9]:

1. Synthetic Polymers
2. Natural polymers

1. Synthetic polymers: These are divided into two types.

a. Non-biodegradable polymers: These materials are inert in the environment of use, eliminated intact from the site of administration and serve essentially as a rate limiting barrier to the transport and release of drug from the device.

e.g. Poly methyl methacrylate PMMA, Acrolein, Glycidyl methacrylate, polyethylene vinyl acetate EVA, Polydimethyl siloxane PDS, Polyether urethane PEU, Ethyl cellulose EC, Cellulose acetate CA, Polyethylene PE and Polyvinyl chloride PVC, Acrycoat, Eudragit RS, Eudragit RL etc.

b. Biodegradable polymers: These are moderate molecular weight uncross linked polymers that dissolve in water.

e.g. Lactides -Polylactic acid PLA, Glycolides -poly glycolic acid PGA, Poly anhydrides, Polycaprolactone PCL and poly orthoesters. Other Soluble polymers are polyethylene glycol; uncross linked poly vinyl alcohol or poly vinyl pyrrolidone, hydroxy propyl methyl cellulose Methocel.

Hydrogels like polyhydroxy ethyl methyl acrylate PHEMA, Cross-linked poly vinyl alcohol PVA, cross linked poly vinyl pyrrolidone PVP, poly acryl acids carbopol etc. These polymers swell but do not dissolve when brought in contact with water.

2. Natural polymers: These are obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

Proteins: Albumin, Gelatin, and Collagen.

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch.

Chemically modified carbohydrates: Poly dextran, Poly starch.

Kollidone:

Kollidone is derived from Poly vinyl acetate dispersion and appears as spray dried, non hygroscopic free flowing powder consisting of Poly Vinyl acetate 8 parts w/w and Poly Vinyl pyrrolidone 2 parts w/w. It accelerates the dissolution and bioavailability due to its power to form complexes with many insoluble actives. It acts as disintegrant by absorbing water and subsequent swelling. The insoluble grades of Kollidon are crosslinked polyvinylpyrrolidone manufactured by a polymerization process using an aqueous system, yielding crosslinked insoluble PVP. One of salient features of the soluble Kollidon grades is their universal solubility which extends from extremely hydrophilic solvents, such as water to hydrophobic liquids, such as butanol. It is recommended to add the powder slowly and in small portions to the solvent with vigorous stirring to

ensure that it disperses and dissolves rapidly without forming lumps. Larger lumps dissolve rather slowly. This applies particularly to Kollidon 90 F, as this high-molecular grade of Kollidon dissolves more slowly than the low-molecular grades. In nonpolar solvents such as cyclohexane, hexane, dioxane and ethyl acetate, crospovidone hardly swells at all. Even in acetone it swells much less than in water. In 0.1N hydrochloric acid too, it swells significantly less than in isotonic salt solution. Formulations were formulated using different polymers Kollidone, cellulose acetate, Acrycoat S 100, Methocel K4M, Methocel K15M, Methocel K100M by Emulsion solvent evaporation method. Drug and polymer in proportion 1:2 drug: polymer were dissolved in organic solvent Ethanol and Acetone. Based on physicochemical properties of microspheres developed by individual polymer it was observed that Kollidone SR, cellulose acetate, Acrycoat S 100 are showing good results at which further study was proceeded on change of solvent system with ethyl acetate-acetone ratio and dichloromethane-ethanol ratio. For the all formulations, % drug entrapped was found to vary from 72.9 % to 84.7 % and it shows that the drug entrapment is higher in microspheres containing Kollidone SR and lower in microspheres containing cellulose acetate. All formulations floated for more than 8 hours on the simulated gastric fluid. But more than 60 % microspheres of Kollidone and Acrycoat S 100 were floated for 12 hours. % drug release was 94.75 % at end of 12 h for Kollidone containing microspheres 1:1 which seems to be showing promising results than Acrycoat S 100 and Cellulose acetate. Therefore, drug loaded floating microspheres in combination with Kollidone are a suitable drug delivery system for Hydrochlorothiazide [10].

Ethyl Cellulose: Ethyl cellulose is a derivative of cellulose in which a defined percentage of the hydroxyl groups of the repeating glucose units are substituted with ethyl ether groups. Ethyl cellulose is an inert, hydrophobic polymer and is essentially tasteless, odourless, colorless, and physiologically inert. It has long been used as solvent-based tablet, pellet coating, tablet binder, to prepare microcapsules and microspheres. At high-viscosity grades of ethyl cellulose release of drug is a function of the microsphere wall thickness and surface area. Floating microspheres of Valcyclovir were prepared by W/O emulsification solvent evaporation method using Ethyl cellulose EC as polymer. Entrapment efficiency was carried out by dissolving the microspheres in a dichloromethane and ethanol 1:1 and extracting the drug by dissolution medium of 0.1N HCl and

analysed by UV spectrophotometer. Particle size of optimized floating microspheres was found to be 550.021±0.241 μm. The percentage entrapment efficiency of prepared floating microspheres was 79.88± 2.236%. Floatability studies revealed that 90% of the microspheres were floated for more than 12 hours because of their low densities and internal voids [11]. The floating drug delivery system of ketorolac trometamol was prepared by emulsion solvent diffusion method by using ethyl cellulose, HPMC K4M, Eudragit R 100, Eudragit S 100 polymers in varying concentration. Among all these formulations the microspheres prepared by using ethyl cellulose alone were predominantly spherical in shape with smooth surface than the microspheres prepared by using Eudragit S100, Eudragit R100. Ethyl cellulose with HPMC in the ratio of 1:1 showed highest 82.44 % entrapment efficiency and highest percentage buoyancy 72% [12].

Chitosan: Chitosan, a natural linear biopolyaminosaccharide is obtained by alkaline deacetylation of chitin, which is the second abundant polysaccharide next to cellulose. Chitin is a straight homopolymer composed of beta-1, 4-linked N-acetyl-glucosamine units while chitosan comprises of copolymers of glucosamine and N-acetyl-glucosamine. Chitosan is a weak base and is insoluble in water and organic solvents, however, it is soluble in dilute aqueous acidic solution pH < 6.5, which can convert the glucosamine units into a soluble form R–NH3+. Chitosan microspheres are the most widely studied drug delivery systems for the controlled release of drugs viz., antibiotics, antihypertensive agents, anticancer agents, proteins, peptide drugs and vaccines. Floating microcapsules containing melatonin were prepared by the ionic interaction of chitosan and a negatively charged surfactant, sodium dioctyl sulfosuccinate. The characteristics of the floating microcapsules generated were compared with the conventional non-floating microspheres prepared from chitosan and sodium tripolyphosphate. Swelling studies conducted on various drug-free formulations indicated that dioctyl sulfosuccinate-chitosan microcapsules showed less swelling than tripolyphosphate chitosan microsphere Therefore, it was concluded that the floating hollow microcapsules could form an interesting Gastroretentive controlled drug delivery system. Floating microspheres were prepared by the capillary extrusion technique using chitosan as polymer and sodium lauryl sulphate as cross linking agent. The effects of the stirring rate during preparation, polymer

concentration and cross linking concentration on the percent yield, in vitro floating behavior, drug loading and in vitro drug release were observed. The highest 85% entrapment efficiency was achieved by increasing polymer-drug ratio from 1:1 to 3:1. i.e. increasing the chitosan concentration from 200 to 600 mg. The highest entrapment efficiency was observed with the stirring speed of 400 rpm 95%. The change of stirring speed from 400 rpm to 200 and 600 rpm significantly decrease the entrapment efficiency due to the formation of larger and smaller emulsion droplets. The cumulative release of drug significantly decreased with increase in chitosan concentration. The % cumulative release was 70% for 3:1 ratio of Polymer and Drug whereas it is 90% for 1:1 ratio. Greater swelling was observed in formulation containing highest polymer ratio it is due to the protonation of any excess of the amino groups of the polysaccharide in stomach pH conditions accounts for this effect favoring the hydration and unfolding of the cross-linked polymeric structure and therefore swelling occurs 13.

Cellulose acetate: Cellulose acetate is a polymer derived from cellulose, which is one of the most abundant polysaccharide in the earth. It is considered as potentially useful polymer for biodegradable applications. Cellulose acetate is being used in use in medical applications, such as membrane material for desalination; while other cellulose derivatives such as cellulose acetate butyrate are being used in capsule form as drug-releasing. Floating microspheres loaded with verapamil hydrochloride were prepared using solvent diffusion evaporation method using cellulose acetate F1, Eudragit S100 F2 and acrycoat S100 F3 with 1:1 mixture of solvent system of ethyl acetate and acetone for cellulose acetate, dichloromethane and ethanol for acrycoat S100; dichloromethane, ethanol and isopropyl alcohol 1:1:1 for Eudragit S100. Percentage incorporation efficiency was in the range of 64.31 % to 84.62% at which cellulose acetate microspheres entrapped maximum amount of the drug. Buoyancy percentage of the microspheres was in the range of 46.19 to 69.59% at the end of 12 h. The drug release from floating microspheres was found to be F1> F2 > F3 at the end of 12 h. The nature of polymer influenced the physical characteristics as well as floating behaviour of the microspheres. So, the floating microspheres of verapamil hydrochloride prepared with cellulose acetate, provide a convenient dosage form for achieving best performance regarding release and floating properties [14].

Eudragit: Eudragit is prepared by the polymerization of acrylic and

methacrylic acids or their esters e.g., butyl ester or dimethylaminoethyl ester. Individual types and grades being introduced are Eudragit L 12.5, Eudragit S 12.5, Eudragit E 100, Eudragit L 100, Eudragit RL 30 D, Eudragit RS 30 D. These are known worldwide in the industry under the trade name EUDRAGIT®. The flexibility to combine the different polymers enables us to achieve the desired drug release profile by releasing the drug at the right place and at the right time and, if necessary, over a desired period of time. A floating multiparticulate gastroretentive system for the modified release of zidovudine AZT was obtained with Eudragit S100 and PVA K30 vinyl polymer with emulsifying properties by co-precipitation, after solvent diffusion and evaporation. The interface created by the PVA K30 adsorbed on the coacervate surface prevented the coalescence of the dispersed drops and intercoacervate aggregation. AZT in solid dispersion with the Eudragit S100 present in the most peripheral layer of the microballoon provides the initial burst in the time interval between 2 and 10 h, to initiate the expected pharmacological effect. The second burst release occurring between 10 and 12 h can be attributed to the relaxation of the polymeric chains. The floating was immediate, and floating time was higher than 12 h. The loading rate was 34.0 ± 9.0% and the system obtained had an extended release [15]. A controlled-release system designed to increase residence time in the stomach without contact with the mucosa was achieved through the preparation of floating microspheres by the emulsion solvent diffusion technique, using calcium silicate as porous carrier; glipizide, an oral hypoglycemic agent and Eudragit® S as polymer biodegradable. The characteristics exhibited by the microspheres of without Calcium Silicate WC and with Calcium Silicate were observed for comparative study. The release of glipizide from different formulations followed the order: WC > CS1 > CS2 > CS3 > CS4 > CS5. The series provides an idea about the effect of CS content on drug release from the microspheres i.e., the higher the CS content in microspheres, the lower the drug release. All the CS-based formulations showed good floating ability 83% ± 5%. Formulation CS4 containing 200 mg CS gave the best floating ability 88% in Stomach gastric fluid. The percent drug entrapment in all the formulations was found to be good 81% ± 4.0% at which 80% entrapment was seen in particles whose size range is 500–1000 µm, which is suitable for oral administration and porous carrier-free microspheres are in size of 100–200 µm with 71% entrapment efficiency [16].

Hydroxy Propyl Methyl Cellulose HPMC: HPMC is propylene glycol ether of methyl-cellulose. It is one of the most commonly used hydrophilic biodegradable polymers for developing controlled release formulations, because it works as a pH-independent gelling agent. Swelling as well as erosion of it occurs simultaneously and contributes to overall drug release. It is the most important hydrophilic carrier material used for the preparation of oral controlled drug delivery systems. One of its most important characteristics is the high swellability, which has a significant effect on the release kinetics of an incorporated drug. Upon contact with water or biological fluid, the latter diffuses into the device, resulting in polymer chain relaxation with volume expansion. Subsequently, the incorporated drug diffuses out of the system [17]. Floating microspheres of Rabeprazole were prepared by emulsion solvent evaporation method using HPMC K15M and ethyl cellulose as polymer were developed with six different formulations with increasing polymer concentration. Formulations prepared with HPMC K15M exhibited excellent Micromeritic properties particle size, morphology, texture, angle of repose, percentage yield, in vitro buoyancy, incorporation efficiency and percentage drug release when compared to ethyl cellulose polymer. At which as the concentration of polymer increases it affects the particle size, percentage yield, in vitro buoyancy and drug release of microsphere [18].

Carbopol: Carbopol polymer forms hydrogel that change its swelling behavior upon exposure to an external stimulus such as change in pH, temperature, light or electric field are known as “environmentally responsive polymer”. It consists of chains of polyacrylic acid. In stomach, Carbopol polymer forms hydrogen bonding with the drug and also with the polysaccharides or proteins of mucosa is probably the major mechanism for bioadhesion. On the other hand, under alkaline condition of the intestine, the Carbopol gels are very highly swollen and the chain is stiffened by electrostatic repulsion of the ionic charges. Carbopol polymer gels may provide a gastric retention system by swelling in the stomach and inducing a pseudo fed state, thereby reducing peristaltic contraction. This phenomenon is dependent on viscosity - the higher the viscosity, the lower the contraction. Controlled release Carbopol containing dosage forms release drug for at least 8 to 20 hrs. Carbopol940 and Carbopol934 are such bioadhesive polymers [19]. Floating-bioadhesive microspheres of clarithromycin FBMC were prepared by emulsification-solvent evaporation method using ethyl

cellulose as matrix polymer and Carbopol 934P as mucoadhesive polymer. The formulation variables like polymer concentration and drug concentration influenced the in vitro drug release significantly in simulated gastric fluid pH. 2.0. The in vivo H. pylori clearance efficiency of prepared FBMC in reference to clarithromycin suspension following repeated oral administration to H. pylori infected Mongolian gerbils was examined. The FBMC showed a significant anti-H. Pylori effect in the in vivo gerbil model and the required amount of clarithromycin for eradication of H. pylori was significantly less in FBMC than from corresponding clarithromycin suspension. The prepared microspheres showed a strong mucoadhesive property with good buoyancy [20].

CHARECTERIZATION OF FLOATING MICROSPHERES: [5, 18, 22]:

1. Determination of percentage drug entrapment:

Estimation of drug content in floating microspheres can be carried out by dissolving the weighed amount of crushed microspheres in required quantity of 0.1 N HCl and analysed Spectrophotometrically at a particular wavelength using the calibration curve. Each batch should be examined for drug content in a triplicate manner.

% Entrapment efficiency = Actual drug content / theoretical drug content X100

2. Buoyancy percentage:

In vitro floating tests can be performed in USP type II dissolution test apparatus by spreading the floating microspheres on a simulated gastric fluid pH 1.2 containing the surfactant. The media is stirred at 100 rpm at 37± 0.5 ºC. After specific intervals of time, both the fractions of microspheres floating and settled microspheres are collected and buoyancy of the floating microspheres is determined by using formula:

$$\text{Buoyancy}\,(\%) = \frac{Q_f}{Q_f + Q_s} \times 100$$

Where, Qf and Qs are the masses of floating and settled hollow microspheres, respectively.

3. Swelling ratio:

Swelling property of floating microspheres is studied by soaking the known weight of microspheres at 37 ± 0.5^{0}C in 0.1 N HCl or Phosphate buffer pH 6.8 in a glass beaker for the required period of time. The microspheres are allowed to swell and removed at different time intervals. Their changes in weight are measured and calculated from the formula.

Swelling ratio = We – Wo / Wo

Where, Wo is the initial weight of dry microspheres, We is the weight of swollen microspheres

4. Micromeritic properties:

Angle of repose: It was measured according to fixed funnel standing method.

$$\theta = \tan^{-1} h/r$$

where θ is the angle of repose, r is the radius, and h is the height.

Compressibility index: Also called as Carr's index and is computed according to the following equation.

Carr's Index = tapped density – bulk density x 100 / tapped density

Hausner's ratio: Hausner's ratio of floating microspheres is determined by comparing the tapped density to the fluff density using the equation:

Hausner ratio = tapped density / pour density

5. Percentage yield:

Percentage yield of floating microspheres is 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:

$$\text{Percentage yield} = \frac{\text{Actual weight of floating microspheres}}{\text{Total weight of excipients and drug}} \times 100$$

6. Scanning electron microscopy S.E.M:

Scanning electron microscopy has been used to determine particle size distribution, surface topography, texture and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to simplicity of sample preparation and ease of operation.

7. In vitro drug release studies:

Release rate of drug from hollow floating microspheres is determined using USP dissolution apparatus type I or type II at 37± 0.5ºC. The dissolution test is carried out using 900 mL of 0.1 N HCl dissolution medium at 100 rpm for the required period of time. At an appropriate interval, specific volume of aliquots are withdrawn and replaced with an equivalent volume of fresh dissolution medium to maintain the constant volume of dissolution medium. The sample solutions are filtered through Whatman filter paper and solutions are analysed using UV spectrophotometer.

8. Particle size analysis:

Particle size is measured by using optical microscopy by measuring the mean particle size of 200-300 particles with the help of calibrated optical micrometer. Particle size is determined

by optical microscopy using a quantity of dried microspheres suspended in glycerin.

APPLICATIONS [1, 21]:

1. 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.

2. Efficient protein-based vaccine delivery systems are arrived to achieve a persistent memory immune response capable of detecting and eliminating intracellular pathogens such as Mycobacterium tuberculosis

3. The microspheres have been extensively studied and used for the targeting purposes. Various cells, cell lines, tissues and organs can be imaged using radio labelled microspheres. The particle size range of microspheres is an important factor in determining the imaging of particular sites.

4. Monoclonal antibodies targeting microspheres are immunomicrospheres. These are specially designed microscopic particles that have antibodies or similar molecules chemically bound to their surfaces. The combination of the various new types of synthetic microspheres and the homogeneous antibodies offers new opportunities in research, diagnosis, and therapy.

5. Floating microspheres can be used as carriers for drugs with narrow absorption windows, 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. For weakly basic drugs that are poorly soluble at an alkaline pH, hollow microspheres may avoid the risk of solubility becoming the rate-limiting step in release, by restricting such drugs to the stomach. Positioned gastric release is useful for drugs efficiently absorbed through the stomach, such as verapamil hydrochloride thus Gastroretentive floating microspheres will beneficially alter the absorption profile of the active agent, thus enhanc-ing its bioavailability.

CONLUSION

This article provides an idea about development techniques, effect of different polymers, characterization features and applications of floating microspheres. As the floating microspheres provides definite advantages on the bioavailability, sustained and controlled release of drug from the delivery system which are related with the type, grade,

concentration of polymer used which is mainly involved in controlling of drug release.

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