World Applied Sciences Journal 32 (5): 839-847, 2014
ISSN 1818-4952

DOI: 10.5829/idosi.wasj.2014.32.05.84139

Novel Methods of Microsphere Formulation

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Abstract: Microspheres are characteristically free flowing powders consisting of proteins or synthetic/natural polymers having a particle size ranging from 1-1000 µm. There are number of Techniques used for the preparation of microspheres that offers a Variety of opportunities to control aspects of drug administration and enhance the therapeutic efficacy of a given drug. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs also known as micro particles. It is the reliable means to deliver the drug to the target site with specificity, if modified and to maintain the desired concentration at the site of interest. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body.

Key words: Microspheres · Novel Drug Delivery · Controlled Release · Formulation Technologies

INTRODUCTION

Microspheres are small spherical particles, with diameters in the micrometer ranges 1-1000 µm. Microspheres are sometimes referred to as micro particles. Microspheres can be manufactured from various synthetic and natural materials. Polymer microspheres, glass Microspheres and ceramic microspheres are commercially available. The density of hollow microspheres are vary widely therefore, are used for different applications. To lower the density of a material the Hollow microspheres are typically used as additives. Solid microspheres have numerous applications depending on what material they are constructed of and what sizes they are. Polyethylene and polystyrene microspheres are two most common types of polymermicrospheres. Polystyrene microspheres are typically used in biomedical applications and having their ability to facilitate procedures such as cell sorting and immune precipitation. Proteins and ligands adsorb onto polystyrene readily and permanently, which makes polystyrene microspheres suitable for medical research and biological laboratory experiments. Polyethylene microspheres are commonly used as permanent or temporary filler. By lower the melting temperature of microsphere enables polyethylene microspheres to create porous structures in ceramics and other materials. High sphericity of polyethylene microspheres, as well as availability of colored and fluorescent microspheres, makes them highly desirable for flow visualization and fluid flow analysis, as well as microscopy techniques such as, health sciences process, troubleshooting and numerous research applications. In electronic paper digital displays Charged polyethylene microspheres are also used. Glass microspheres are mainly used as filler for retro-reflector for highway safety weight reduction, additive and adhesives for cosmetics, with limited applications in medical technology. Microspheres vary widely in quality, sphericity, uniformity of particle and particle size distribution [1]. The drug administration can be controlled by the range of techniques for the preparation of microspheres. This approach having the

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ability to deliver the accurate or small quantity of the potent drugs reduced drug concentration at the site other than the target site and provides the protection of the labile compound before and after the administration and prior to appearance at the site of action. By coupling the drug to a carrier particle the behavior of the drugs *in vivo* can be manipulated. By The behavior of the carrier the tissue distribution, clearance kinetics, metabolism and cellular interaction of the drug are strongly influenced. The exploitation of these changes in pharmacodynamics behavior may lead to enhanced therapeutic effect. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. Historically oral ingestion, the most convenient and commonly employed route of drug delivery system. Drugs that have short half-life and easily absorbed from the GIT are eliminated quickly from the blood circulation. Oral controlled drug delivery systems have been developed to avoid these problems. Oral controlled drug delivery system releases the drug slowly into the GIT and in the serum as they maintain a constant drug concentration for longer period of time. However, shorter residence time of dosage forms in the upper gastrointestinal tract and incomplete release of the drug, a prominent site for absorption of many drugs, will lead to lower bioavailability. Pharmaceutical industries making efforts to improve oral drug bioavailability and have results in parallel manner. As the number and chemical diversity of drugs has increased, new strategies are required to develop orally active therapeutics. Thus, gastro retentive dosage forms, which prolong the residence time of the drugs in the stomach and improve their bioavailability, have been developed [2]. A proper designed CDDS can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To get maximum therapeutic efficacy, it becomes very important to deliver the drug to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects. There are a lot of approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. Microspheres system as carriers for drugs is one of them. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 μm [3].

Characteristics:

- Microsphere size may be critical to the proper function of an assay, or it may be secondary to other characteristics. Considering traditional diagnostic methods, the test or assay format commonly dictates particle size, such as the use of very small spheres (~0.1- 0.4μm) to ensure satisfactory wicking in lateral flow tests, or the use of larger, cell-sized spheres (~4-10μm) for bead based flow cytometric assays.
- Common microsphere compositions include polystyrene (PS), poly (methyl methacrylate) (PMMA) and silica. These materials possess different physical and optical properties, which may present advantages or limitations for different applications. Polymer beads are generally hydrophobic and as such, have high protein binding abilities. However, they often require the use of some surfactant (e.g. 0.01-0.1% Tween® 20 or SDS) in the storage buffer to ensure ease of handling. During synthesis, functional monomers may be co-polymerized with styrene or methyl methacrylate to develop beads with surface reactive groups. Functional groups may be used in covalent binding reactions and also aid in stabilizing the suspension. Silica microspheres are inherently hydrophilic and negatively charged. Consequently, aqueous silica suspensions rarely require use of surfactants or other stabilizers. Carboxyl- and amine functionalized silica spheres are available for use in common covalent coating protocols and plain silica microspheres may be modified using a variety of silanes to generate functional groups or alter surface properties.
- Microspheres may be coated with capture molecules, such as antibodies, oligonucleotides, peptides, etc. for use in diagnostic or separation applications. Microsphere coatings are typically optimized to achieve desired specific activity, while minimizing nonspecific interactions. Consideration should also be given to the required stability, development time frame and budget and the specific biomolecule to be coated. These factors will aid in determining the most fitting coating strategy for both short- and long-term objectives. Standard microsphere products support three basic coating strategies: adsorption, covalent coupling and affinity binding.
- Many applications in the life sciences demand added properties, such as fluorescence or a visible color, or iron oxide inclusions for magnetic separations.

Polymer spheres (And polymer based magnetic spheres) are often internally dyed via organic solvent swelling and many standard products are available. Dye concentrations can be adjusted to produce beads with different intensities to meet special needs, such as QuantumPlex™ for multiplexed flow cytometric assays, or our Dragon Green or Flash Red Intensity Standards, which support imaging applications and associated instrument QC. Many surface- or internally labeled fluorescent beads are also available as specialized flow cytometrystandards [4].

Advantages:

- Microspheres is used because they provide constant and prolonged therapeutic effect.
- Reduces the dosing frequency and thereby patient compliance are improve.
- Microsphere are smaller in size and having spherical shape so that they can be injected into the body
- Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
- Microsphere morphology allows a controllable variability in degradation and drug release [5].

Limitation: Some of the disadvantages were found to be as follows

- The modified release from the formulations.
- The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
- Differences in the release rate from one dose to another.
- Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
- Dosage forms of this kind should not be crushed or chewed [5].

Methodof Preparation

Spray Drying: In Spray Drying method firstly the polymer solution is prepared in which the polymer dissolved in a suitable volatile organic solvent such as Acetone, dichloromethane etc. homogenizer is used for the uniform dispersion of drug in the polymer solution. Dispersion is atomized by the stream of hot air small droplets or the fine mist is formed. From the resultant solvent is removed by the evaporation which leading the formation of the microspheres which are having the particle size range from 1-100µm. Micro particles are separated by the cyclone separator and then vacuum drying. The process having major advantages such as feasibility of operation under aseptic conditions, the process can be perform very rapidly and this leads to the formation of porous micro particles.

Wet Inversion Technique: In this technique firstly make the Chitosan solution contain with acetic acid was dropped through a nozzle in to an aqueous solution contain with the counter ion sodium tripolyposphate. Microspheres are formed and allow to stand for 1 hour and then cross linked with 5% ethylene glycol diglysidyl ether. Then the prepared Microspheres are washed and dried through the freeze. If we are Change the pH of the coagulation medium the pore structure of CS microspheres are change.

Complex Coacervation: CS microsphere are prepare by complex co acervation method, in this method sodium CMC, sodium polyacrylic acid and Sodium alginate are used with chitosan solution to form microspheres. The microspheres are formed by interionic interaction which are having between oppositely charged KCl& $CaCl_2$ solutions and polymers solutions. The capsule is obtained which become harder in the counter ion solution before washing and drying [6].

Hot Melt Microencapsulation: In the hot melt microencapsulation method firstly the melt the polymer and then mixed with the drug that have been sieved to less than 50 µm. The resultant mixture are suspended with continuous stirring in a suitable non miscible solvent like (Silicone oil) and then heated up to 5°C above the melting point of the polymer. The resultant emulsion is then stabilized and cooled until the polymer particles are solidify and form the microsphere and washed with petroleum ether by decantation process. The major object of this method is to develop a microencapsulation process for the water labile polymers, *e.g.* poly anhydrides. Microspheres are form easily and having diameter of 1-1000 µm and the size of the microspheres can be controlled easily by altering the stirring rate but having onedisadvantage such as in moderate temperature the drug is exposed [6].

Solvent Evaporation: The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer of the core material is disperse in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix – type microcapsules are formed. The core materials may be either water soluble or water in soluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous. The comparison of mucoadhesive microspheres of hyaluronic acid, Chitosan glutamate and a combination of the two prepared by solvent evaporation with microcapsules of hyaluronic acid and gelatin prepared by complex coacervation were made.

Single Emulsion Technique: The microspheres are prepared by single emulsion technique using natural polymers as carrier. The polymers are dispersed in aqueous medium and then dispersion in non-aqueous medium like oil. Next crosslinking 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, acid chloride etc. Heat denaturation is not suitable for thermo labile 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, separation3 The nature of the surfactants used to stabilize the emulsion phases can greatly influence the size, size distribution, surface morphology, loading, drug release and bio performance of the final multiparticulate product [7].

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. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. a number of hydrophilic drugs like luteinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/ extraction[8].

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

- Normal polymerization
- Interfacial polymerization.
- Both are carried out in liquid phase.

Normal Polymerization: It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be molded as microspheres. Drug loading may be done during the process of polymerization. Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomeror mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has an advantage of formation of pure polymers.

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.

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. The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates. Therefore the process variables are critical as they control the kinetic of the formed particles since there is no defined state of equilibrium attainment.

Spray Drying and Spray Congealing: These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively. 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 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 ranges 1-100 µm. Micro particles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying. One of the major advantages of the process is feasibility of operation under aseptic conditions. The spray drying process is used to encapsulate various penicillin. Thiamine mononitrate and sulphaethyl thiadizole are encapsulated in a mixture of mono- and diglycerides of stearic acid and palmiticacid using spray congealing very rapid solvent evaporation, however leads to the formation of porous micro particles.

Solvent Extraction: Solvent evaporation method is used for the preparation of micro particles, involves removal of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvents such as isopropanol. Organic phase is removed by extraction with water. This process decreases the hardening time for then microspheres. One variation of the process involve direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer [8].

Preparation of Microspheres by Thermalcross-linking Citric acid, as a cross-linking agent was added to 30 mL of an aqueous acetic acid solution of Chitosan (2.5%wt. /vol) maintaining a constant molar ratio between chitosan and citric acid (6.90 × 10-3 mol chitosan: 1 mol citric acid). The chitosan cross-linker solution was cooled to 0°C and then added to 25 mL of corn oil previously maintained at 0°C, with stirring for 2 minutes. This emulsion was then added to 175 mL of corn oil maintained at 120°C and cross-linking was performed in a glass beaker under vigorous stirring (1000 rpm) for 40 minutes. The microspheres obtained were filtered and then washed with diethyl ether, dried and sieved [9].

Preparations of Microspheres by Glutaraldehyde Cross Linking: A 2.5% (w/v) chitosan solution in aqueous acetic acid was prepared. This dispersed phase was added to continuous phase (125 mL) consisting of light liquid paraffin and heavy liquid paraffin in the ratio of 1:1 containing 0.5% (wt./vol) Span 85 to form a water in oil (w/o) emulsion. Stirring was continued at 2000 rpm using a 3- blade propeller stirrer). A drop-by-drop solution of a measured quantity (2.5 mL each) of aqueous glutaraldehyde (25% v/v) was added at 15, 30, 45 and 60 minutes. Stirring was continued for 2.5 hours and separated by filtration under vacuum and washed, first with petroleum ether (60°C- 80°C) and then with distilled water to remove the adhered liquid paraffin and glutaraldehyde, respectively. The Microspheres were then finally dried in vacuum desiccators[10].

Evaluation Parameters

Physicochemical Evaluation Characterization: The characterization of the micro-particulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. These microspheres have different micro structures. These microstructures determine the release and the stability of the carrier.

Particle Size and Shape: The most widely used procedures to visualize micro particles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of micro particles. LM provides a control

over coating parameters in case of double walled microspheres. The microspheres structures can be visualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to the LM. SEM allows investigations of the microspheres surfaces and after particles are cross-sectioned, it can also be used for the investigation of double walled systems. Conflocal fluorescence microscopy is used for the structure characterization of multiple walled microspheres. Laser light scattering and multi size coulter counter other than instrumental methods, which can be used for the characterization of size, shape and morphology of the microspheres.

Electron Spectroscopy for Chemical Analysis: The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA). ESCA provides a means for the determination of the atomic composition of the surface. The spectra obtained using ECSA can be used to determine the surficial degradation of the biodegradable microspheres.

Attenuated Total Reflectance Fourier Transform-Infrared Spectroscopy: FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring alternated total reflectance (ATR). The IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material. The ATRFTIR provides information about the surface composition of the microspheres depending upon manufacturing procedures and conditions.

Density Determination: The density of the microspheres can be measured by using a multi volume pycnometer. Accurately weighed sample in a cup is placed into the multi volume pycnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and hence the density of the microsphere carrier is determined.

Isoelectric Point: The micro electrophoresis is an apparatus used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined. The mean velocity at different pH values ranging from 3-10 is calculated by measuring the time of particle movement over a distance of 1 mm. By using this data the electrical mobility of the particle can be determined. The electrophoretic mobility can be related to surface contained charge, ion is able behaviour or ion absorption nature of the microspheres.

Angle of Contact: The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. This thermodynamic property is specific to solid and affected by the presence of the adsorbed component. The angle of contact is measured at the solid/air/water interface. The advancing and receding angle of contact are measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 200C within a minute of deposition of microspheres.

***In vitro* Methods:** There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number of *in vitro* and *in vivo* techniques have been reported. *In vitro* drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc. Sensitive and reproducible release data derived from physic-chemically and hydro dynamically defined conditions are necessary. The influence of technologically defined conditions and difficulty in simulating in vivo conditions has led to development of a number of in vitro release methods for buccal formulations; however no standard in vitro method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed. The dosage form in this method is made to adhere at the bottom of the beaker containing the medium and stirred uniformly using overhead stirrer. Volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed form 60-300 rpm.

***In vivo* Methods:** Methods for studying the permeability of intact mucosa comprise of techniques that exploit the biological response of the organism locally or systemically and those that involve direct local measurement of uptake or accumulation of penetrants at the surface. Some of the earliest and simple studies of mucosal permeability utilized the systemic pharmacological effects produced by drugs after application to the oral mucosa. However the most widely

used methods include in vivo studies using animal models, buccal absorption tests and perfusion chambers for studying drug permeability.

***In vitro-In vivo* Correlations:** Correlations between *in vitro* dissolution rates and the rate and extent of availability as determined by blood concentration and or urinary excretion of drug or metabolites are referred to as "*in vitro-in vivo* correlations". Such correlations allow one to develop product specifications with bioavailability.

(A) Percent of Drug Dissolved *in Vitro* Vs. Peak Plasma Concentration: One of the ways of checking the *in vitro* and *in vivo* correlation is to measure the percent of the drug released from different dosage forms and also to estimate the peak plasma concentrations achieved by them and then to check the correlation between them. It is expected that a poorly formulated dosage form releases amount of drug than a well formulated dosage form and, hence the amount of drug available for absorption is less for poorly formulated dosage form than from a well formulated dosage form.

(B) Percent of Drug Dissolved Vs. Percent of Drug Absorbed: If the dissolution rate is the limiting step in the absorption of the drug and is absorbed completely after dissolution, a linear correlation may be obtained by comparing the percent of the drug absorbed to the percent of the drug dissolved. If the rate limiting step in the bioavailability of the drug is the rate of absorption of the drug, a change in the dissolution rate may not be reflected in a change in the rate and the extent of drug absorption from the dosage form.

© Dissolution Rate Vs. Absorption Rate: The absorption rate is usually more difficult to determine than the absorption time. Since the absorption rate and absorption time of a drug are inversely correlated, the absorption time may be used in correlating the dissolution data to the absorption data. In the analysis of *in vitro* and *in vivo* drug correlation, rapid drug absorption may be distinguished from the slower drug absorption by observation of the absorption time for the dosage form. The quicker the absorption of the drug the less is the absorption time required for the absorption of the certain amount of the drug. The time required for the absorption of the same amount of drug from the dosage form is correlated.

Swelling Index: Swelling index was determined by measuring the extent of swelling of microspheres in the given buffer. To ensure the complete equilibrium, exactly weighed amount of microspheres were allowed to swell in given buffer. The excess surface adhered liquid drops were removed by blotting and the swollen microspheres were weighed by using microbalance. The hydrogel microspheres then dried in an oven at 60° for 5 h until there was no change in the dried mass of sample. The swelling index of the microsphere was calculated by using the formula Swelling index= (mass of swollen microspheres – mass of dry microspheres/mass of dried microspheres) 100[9].

Advancement in Microsphere

Floating Microsphere: Floating microsphere have bulk density less than gastric fluids, thus they remain floating in the stomach without affecting the gastric emptying rate. Therefore gastric retention time is increased and fluctuation in plasma drug concentration is reduced or controlled by floating microsphere. In addition it reduces dumping of dose, dosing frequency, increases therapeutic efficacy, solubility and dispersability [11].

Floating Microsphere Is of Two Types

- Effervescent type-Swellable polymers e.g. methylcellulose, chitosan and various effervescent compound e.g. sodium bicarbonate, citric acid, tartaric acid are used for the preparation of effervescent dosage form. Floating microsphere of effervescent type liberates carbon-dioxide gas due to which the density of the system is reduced and remains in floating condition in stomach for a prolonged period of time, this result in release of drug slowly at a desired rate.
- Non-effervescent type-Highly swellable cellulose type hydrocolloids, polysaccharide and matrix forming polymer such as polycarbate, polyacrylate are used to form non effervescent system. This is prepared by thoroughly mixing the drug and gel forming hydrocolloids. On admonition, it swells up when comes in contact with gastric fluid and attain a bulk density i.e. less than 1 g/ml [12]

Radioactive Microsphere: Radioactive microsphere is used in the same way as nonradioactive microsphere. Delivery of high concentration of drug to the target site

does not damage normal surrounding tissue. As compare to drugs, radioactivity substance is not released from the microsphere but proceed from inside a radioactive typical distance. The _ emitters, _ emitters and _ emitters are used as radioactive microsphere. Radioactive microsphere is used for diagnostic and therapeutic purpose [13, 14].

Hollow Microsphere: Hollow microspheres also called as micro balloons is filled up with the drug in their outer polymer shells and are prepared by emulsion-solvent diffusion technique. The ethyl alcohol: dichloromethane solution of the drug and polymer (Enteric acrylic) is transfer into a stirring aqueous solution of PVA which is thermally controlled at 400°C. Gas is generated by dispersing the polymer droplet by evaporation of dichloromethane which leads to formation of an internal cavity in microsphere of polymer with drug. The micro balloons float continuously over the surface of acidic dissolution media containing surfactant for a period of more than 12 hours *in-vitro*. Different drugs can be prepared by hollow microsphere by using various materials e.g. polycarbonate, calcium alginate, Eudragit S 100 etc [15].

Magnetic Microsphere: In magnetic microsphere small amount of magnetically targeted drug is delivering to the target site in place of high amount of free circulating drug. Those materials which responses to magnetic field are used in the preparation of magnetic microsphere are chitosan, dextran etc [16].Magnetic microsphere is used for diagnostic and therapeutic purpose. Superamagnetic iron oxides radiolabelled is used as therapeutic magnetic microsphere for imaging of liver metastasis, distinguish loop of bowel from other abdominal structure, whereas iron carbon particles radiolabelled with isotope 188Re, 90y etc. are used as diagnostic microsphere for liver tumours[14].

Muchoadhesive Microsphere: Muchoadhesive microsphere adhere to mucus layer and release drug at desired rate. In muchoadhesive microsphere the intimate contact time with the mucus surface is increased. This results in an increased drug retention time as well as drug concentration at the targeted site [17, 18].Muchoadhesive formulation can be administered through various routes such as nasal, gastrointestinal, buccal, Ocularetc [19]. Therapeutic efficacy is improved as well as absorption; bioavailability of normally poorly absorbed drug is improved [20].

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Hollow microsphere promises to be potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body.

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