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MICROSPHERES: AN OVERVIEW

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ABSTRACT

Microspheres are potential candidates for the protein drug delivery. Microspheres of various formulations were formulated by using the combination of natural and synthetic materials by solvent evaporation and non-solvent addition methods with an aim to prolong its release. Microspheres produced from molten materials (inorganic, organic, alloys and polymers) can be used for dosing, proportioning, compounding, coloring and light stabilization. Microspheres with dissolved or embedded active agents, with or without coating, are used for numerous pharmaceutical and cosmetic products. There are different methods to prepare microspheres. In recent years the concept of using small colloidal particles for the selective delivery of drugs has been explored experimentally using a variety of different physical systems (for example, phospholipids vesicles (liposome's), triglyceride emulsions, albumin microspheres) and routes of administration. In such studies the aim has been to target a potent pharmacological agent on an organ or tissue site, thereby reducing adverse reactions and side-effects, or to provide a means of controlled release.

Keywords: Microspheres, liposome's, colloidal particles, polymer microspheres etc.

INTRODUCTION

Microsphere is a term used for small spherical particles, with diameters in the micrometer range (typically 1µm to 1000µm (1mm)). Microspheres are sometimes referred to as microparticles.

Microspheres can be manufactured from various natural and synthetic materials. Such as:

- Glass microspheres
- Polymer microspheres

- Ceramic microspheres are commercially available
- Solid and hollow microspheres
    - Vary a lot in density
    - Used as additives to lower the density of a material

Polyethylene and polystyrene microspheres are two most common types of polymer microspheres.

Polystyrene Microspheres are typically used in biomedical applications due to their ability to facilitate procedures such as cell sorting and immunio precipitation. Proteins and ligands absorb 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. Lower melting temperature 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, microscopy techniques, health sciences, process troubleshooting and numerous research applications. Charged polyethylene microspheres are also used in electronic paper digital display.

Glass Microspheres are primarily used as a filler and volumizer for weight reduction, retro-reflector for highway safety, additive for cosmetics and adhesives, with limited applications in medical technology.

Ceramic Microspheres are used primarily as grinding media. [1, 2]

Microspheres vary widely in quality, sphericity, uniformity and particle size and particle size distribution. The appropriate microsphere needs to be chosen for each unique application.

There are different types of microspheres which have different uses such as:

Radioactive Microspheres for Medical Applications

In general radioactive microspheres for diagnostic applications contain one or several gamma-emitters and can be detected by a gamma-camera. The first such "microspheres" in clinical use were actually red and white blood cells, which were taken from a patient, labeled with ^{111}In or ^{51}Cr, and then re-injected in order to measure blood flow and detect regions of infection. Radio labeled blood cells are still used today, although pre-made radioactive microspheres containing different gamma-emitters are often easier to use such as Polystyrene-microspheres labeled with the g-emitters ^{141}Ce, ^{3}H and ^{14}C-labeled microspheres etc. [3, 4]

Biodegradable Microspheres

Controlled release drug delivery employs drug-encapsulating devices from which therapeutic agents may be released at controlled rates for long periods of time, ranging from days to months. Such systems offer numerous advantages over traditional methods of drug delivery, including tailoring of drug release rates, protection of fragile drugs and increased patient comfort and compliance. [5] Various types of biodegradable microspheres can be prepared such as Fluphenazine loaded microspheres etc. [6] By using a new vaccine delivery system, microspheres of a biodegradable polymer may

not only reduce the need for booster shots in some cases, but also appears to stimulate an immune response that traditional vaccines do not.

Polymeric microspheres prepared by electro hydrodynamic atomization

Polymeric microspheres are ideal vehicles for many controlled delivery applications due to their ability to encapsulate a variety of drugs, biocompatibility, high bioavailability and sustained drug release characteristics. Double-walled polymer microspheres for controlled drug one approach to the controlled release of drugs involve incorporation of the drug molecules into the matrix of microscopic polymer spheres or capsules. [7- 17] Existing methods for preparing such micro-particles do not, however, always guarantee a constant release rate, for example because drug molecules may be trapped preferentially at the surface, because they have to diffuse through an increasing thickness of polymer when the particles are non-eroding or because the surface area changes for eroding particles. In other situations pulsed release may be required—an application to which simple polymer microspheres does not readily lend them. Multi-walled microspheres might solve some of these problems. Here we describe a one-step process for preparing double-walled polymer microspheres with diameters ranging from about 20 to 1,000 micrometres.

Microspheres as nasal drug delivery systems

All types of microspheres that have been used as nasal drug delivery systems are water-insoluble but absorb water into the sphere's matrix, resulting in swelling of the spheres and the formation of a gel. The building materials in the microspheres have been starch, dextran, albumin and hyaluronic acid and the bioavailability of several peptides and proteins has been improved in different animal models. Also, some low-molecular weight drugs have been successfully delivered in microsphere preparations. The residence time in the cavity is considerably increased for microspheres compared to solutions. However, this is not the only factor to increase the absorption of large hydrophilic drugs. Microspheres also exert a direct effect on the mucosa, resulting in the opening of tight junctions between the epithelial cells. Starch and dextran microspheres have been administered repeatedly and can be classified as safe dosage forms [18.]

Sustained-Release Microspheres

Sustained release microspheres such as microcapsules of acetazolamide, a short half life carbonic anhydrase inhibitor, was developed to reduce the frequency of drug administration, ease of dose adjustment and improve patient compliance. In this study, sustained release microcapsules of acetazolamide was prepared by solvent evaporation techniques using Eudragit *RL/RS* as polymer and particle size, encapsulation efficiencies and *in vitro* release of the fabricated microcapsules were evaluated. [19]

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. [20- 22]

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

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. [23, 24, 25]

Characterization of Floating Microspheres:

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. The particle size is determined by optical microscopy; true density is determined by liquid displacement method; tapped density and compressibility index are calculated by measuring the change in volume using a bulk density apparatus; angle of repose is determined by fixed funnel method. The hollow nature of microspheres is confirmed by scanning electron microscopy. [26, 27, 28] Floating behavior of hollow microspheres is studied in a dissolution test apparatus by spreading the microspheres on a simulated gastric fluid (pH 1.2) containing tween 80 as a surfactant; the media is stirred and a temperature of 37˚C is maintained throughout the study. After specific intervals of time, both the fractions of the microspheres floating and settled are collected; the buoyancy of the floating microspheres can be calculated using the data.

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). The in-vitro and *in-vivo* data can be correlated.

Applications of Floating Microspheres:

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. Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can also be delivered efficiently thereby maximizing their absorption and improving the bioavailability. [29]

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.[30]

The floating microspheres can be used as carriers for drugs with so-called absorption windows, these substances, for example antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides and Tetracyclines) are taken up only from very specific sites of the GI mucosa. In addition, by continually supplying the drug to its most efficient site of absorption, the dosage forms may allow for more effective oral use of peptide and protein drugs such as Calcitonin, Erythropoietin, Vasopressin, Insulin, low-molecular-weight Heparin and LHRH.

Hollow Microspheres

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. [31] 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. [32-34] The polymers studied for the development of such systems include Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, Polyvinyl acetate, Carbopol, Agar, Polyethylene oxide and Polycarbonates. Hollow microspheres of non-steroidal anti inflammatory drugs are very effective for controlled release as well as it reduces the major side effect of gastric irritation; for example floating microspheres of Indomethacin are quiet beneficial for rheumatic patients. Hollow microspheres of Acrylic resins, Eudragit, PMAA, Polyethylene oxide and Cellulose acetate; Polystyrene floatable shells; Polycarbonate floating balloons and Gelucire floating granules are the recent developments.

The advantages of hollow microspheres include:

- Improves patient compliance by decreasing dosing frequency.
- 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.
- 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.
- Site-specific drug delivery to stomach can be achieved.
- Enhanced absorption of drugs which solublise only in stomach.
- 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 multiparticulate system.

Extra Types of Microsphere -*Phenolic resin and Graphite*

- ✓ Monodispersed aragonite microspheres

- ✓ Protein Conjugated Microspheres
- ✓ Cellulose Microspheres
- ✓ Silica Microspheres
- ✓ Coated microspheres
- ✓ Ceramic Microspheres
- ✓ Over coated microspheres
- ✓ Microspheres for extending drug release
- ✓ Biodegradable microspheres for protein drug delivery [35-42]

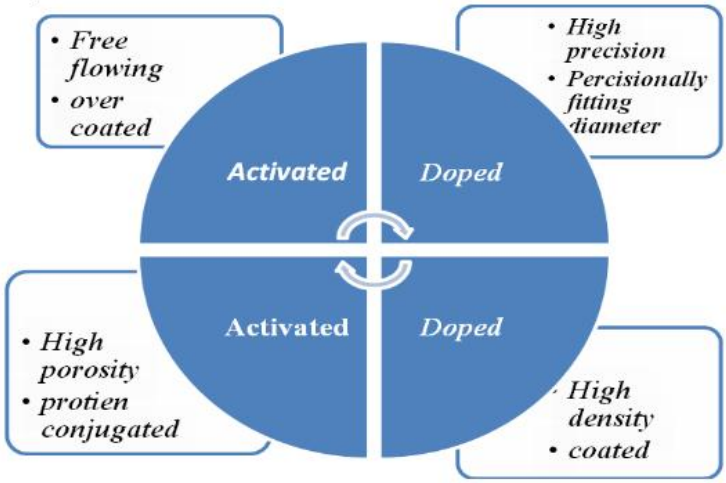

Figure 1: Shows different types of microspheres

Methodology for Production of Microspheres:

Microspheres can be produced:

- ➢ Dry metal oxide Microspheres produced on the basis of a sol (Al_2O_3, ZrO_2, HfO_2, TiO_2, CeO_2, SiO_2, and mixed oxides) can be used as highly interactive press-feed for the production of high-tech ceramics. Through calcining, the pore size and surface area of the Microspheres can be tailored to exacting specifications. These Microspheres make excellent catalyst carriers, homogeneous catalysts, or filtering materials. Unusually effective and abrasion resistant Microspheres for grinding other materials are made from sintered Al, Zr, and Hf-oxides.
- ➢ Microspheres produced from molten materials (inorganic, organic, alloys, and polymers) can be used for dosing, proportioning, compounding, coloring, and light stabilization. Microspheres with dissolved or embedded active agents, with or without coating, are used for numerous pharmaceutical and cosmetic products.
- ➢ Soluble chemical compounds can be incorporated into Microspheres by precipitation for use in the agricultural, food, pharmaceutical, and cosmetics industries.
- ➢ Suspensions are used to produce Microspheres with embedded enzymes or bacteria.
- ➢ With our special double nozzle systems, Microspheres with encapsulated materials can be obtained. Especially for the encapsulation of water, aqueous solutions or cells, a microsphere with a liquid core and a solidified shell can be produced. The shell and the core material can be chosen as

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