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Biomedical Applications of Microspheres

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ABSTRACT

Microspheres are free flowing particles ranging from 1-1000u. Microspheres are having wide applications in drug delivery system. They are mainly used for targeted drug delivery of anti-cancer agents, ophthalmic agent and can be used for diagnosis purpose. In this article detail discussion was made on the polymers, preparation methods and applications of microspheres in pharmaceutical dosage form development.

Keywords: Microspheres, anti-cancer agents, drug delivery,

INTRODUCTION

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and, therefore, are used for different applications [1, 2]. Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications depending on type of material and size of the material.

Two most common types of polymer

1. Polyethylene microspheres
2. Polystyrene microspheres

Polyethylene microspheres: 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 displays.

Polystyrene microspheres: Polystyrene microspheres are typically used in biomedical applications due to their ability to facilitate procedures such as cell sorting and immuno precipitation. Proteins and ligands adsorb onto polystyrene readily and permanently, which makes polystyrene microspheres suitable for medical research and biological laboratory experiments.[3, 4]

ADVANTAGES

- Microspheres provide constant and prolonged therapeutic effect
- Reduces the dosing frequency and thereby improve the patient compliance.
- They could be injected into the body due to the spherical shape and smaller size.
- 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.

LIMITATIONS [5]

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.

Techniques used in the preparation of microspheres [6, 7]

The choice of the technique mainly depends on the nature of the polymer used, the drug, the equivocally determined by some formulation and technology related factors as mentioned below

- The particle size requirement.
- The drug or the protein should not be adversely affected by the process.
- Reproducibility of the release profile and the method.
- No stability problem.
- There should be no toxic product(s) associated with the final product[16]

Different types of techniques are employed for the preparation of the microspheres using hydrophobic and hydrophilic polymers as matrix materials are,

1. Single emulsion technique [8, 9]

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.

2. Double emulsion technique (Multiple emulsion)

Double emulsion method of microsphere preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w .and is best suited to the water-soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as the synthetic polymers. A number of hydrophilic drugs like luteinizing hormone releasing hormone (LH-RH) agonist, vaccines, protein/peptides and conventional molecules are successfully incorporated in to the microspheres using the method of double emulsion solvent evaporation/extraction.

3. Polymerization techniques

The polymerization techniques conventionally used for the preparation of the microspheres are mainly classified as: I. Normal polymerization

II. 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 polymerization**, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded 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 monomer or 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, but it is very difficult to dissipate the heat of reaction, which can adversely affect the thermo labile active ingredients. On the other hand the suspension and emulsion polymerization can be carried out at lower temperature.

Interfacial polymerization[10]

Interfacial polymerization essentially precedes involving 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. The monomers present in either phases diffuse rapidly and polymerize rapidly at the interface. Monomer droplet, the formed carrier is of capsular (reservoir) type. The interfacial polymerization is not widely used in the preparation of the microspheres because of toxicity associated with the unreacted monomer, high permeability of the film, high degradation of the drug during the polymerization, fragility of microcapsules, non-biodegradability of the microspheres.

Phase separation coacervation technique

The process is based on the principle of decreasing the solubility of the polymer in the organic phase to affect the formation of the polymer rich phase called coacervates. The coacervation can be brought about by addition of the third component to the system which results on the formation of the two phases, one rich in the polymer while the other one, i.e. supernatant, depleted of the polymer. The methods are based on salt addition, non-solvent additi0on, addition of the incompatible polymer or change in pH.

Spray drying [11]

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 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. Microspheres 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's. Thiamine mononitrate and sulpha ethylthiadizole are encapsulated in a mixture of mono- and diglycerides of stearic acid and palmitic acid using spray congealing. Very rapid solvent evaporation, however leads to the formation of porous microsphere.

Non-aqueous solvent evaporation method

In these methods the polymer is dissolved in an organic solvent such as dichloromethane, chloroform, alcohol or ethyl acetate, either alone or in combination. The drug is either dissolved or dispersed into the polymer solution and this solution containing the drug is emulsified in to an aqueous phase to make oil in water emulsion by using a surfactant or an emulsifying agent. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature or by continuous stirring. Solvent evaporation for preparation of embryonic microspheres under pressure or by continuous stirring, determines the size and morphology of the microspheres. It had been reported that the rapid removal of the solvent from the embryonic microspheres leads to the precipitation at the o/w interface. This leads to the formulation of cavity in the microspheres, making them hollow

Ionic gelation method:

Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form hydrogels. These anions forms meshwork structure by combining with the polyvalent cations and induce gelation by binding mainly to the anion blocks. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. The cations diffuses into the drug-loaded polymeric drops, forming a three dimensional lattice of ionically crossed linked moiety.

APPLICATION OF MICROSPHERES [12]

Medical application

- Release of proteins, hormones and peptides over extended period of time.
- Gene therapy with DNA plasmids and also delivery of insulin.

- Vaccine delivery for treatment of diseases like hepatitis, diphtheria, birth control.
- Targeting tumor vessels, targeting of tumor cells, antigens, by intra-arterial application.
- Tumour targeting with doxorubicin and also treatments of leishmaniasis.
- Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
- Used in isolation of antibodies, toxin extraction by affinity chromatography.
- Used for various diagnostic tests for infectious diseases like bacterial, viral, and fungal

Pharmaceutical applications

A number of pharmaceutical microencapsulated products are currently on the market, such as aspirin, theophylline and its derivatives, vitamins, pancrelipase, antihypertensive, potassium chloride, progesterone, and contraceptive hormone combinations. Microencapsulated KCL is used to prevent gastrointestinal complications associated with potassium chloride. The dispersibility of the microsphere and the controlled release of the ions minimize the possibility of local high salt concentrations, which could result in ulceration, haemorrhage, or perforation. Microspheres have also found potential applications as injection or inhalation products.

Microspheres in vaccine delivery [13]

The prerequisite of a vaccine is protection against the microorganism or its toxic product. An ideal vaccine must fulfill the requirement of efficacy, safety, convenience in application and cost. The aspect of safety and minimization of adverse reaction is a complex issue[19] .The aspect of safety and the degree of the production of antibody responses are closely related to mode of application. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of the conventional vaccines. The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies since they offer specific advantages including:

- Improved antigenicity by adjuvant action
- Modulation of antigen release
- Stabilization of antigen.
- Targeting using micro particulate carriers

Surface modified microspheres

Different approaches have been utilized to change the surface properties of carriers to protect them against phagocytic clearance and to alter their body distribution patterns .The adsorption of the poloxamer on the surface of the polystyrene, polyester or poly methyl methacrylate microspheres renders them more hydrophilic and hence decrease their MPS uptake. Protein microspheres covalently modified by PEG derivatives show decreased immunogenicity and clearance. The most studied surface modifiers are:

- Antibodies and their fragments
- Proteins
- Mono-, oligo- and polysaccharides
- Chelating compounds (EDTA, DTPA or Desferroxamine)
- Synthetic soluble polymers

Such modifications are provided on surface of microspheres in order to achieve the targeting to the discrete organs and to avoid rapid clearance from the body.

Monoclonal antibodies mediated microspheres

Monoclonal antibodies are extremely specific molecules. This extreme specificity of monoclonal antibodies (Mabs) can be utilized to target microspheres loaded bioactive molecules to selected sites. Mabs can be directly attached to the microspheres by means of covalent coupling. The free aldehyde groups, amino groups or hydroxyl groups on the surface of the microspheres can be linked to the antibodies. The Mabs can be attached to microspheres by any of the following methods

1. Nonspecific adsorption 2. Specific adsorption 3. Direct coupling 4. Coupling via reagents

Imaging

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 microsphere. The particle size range of microspheres is an important factor in determining the imaging of particular sites. The particles injected, intravenously apart from the portal vein will become entrapped in the capillary bed of the lungs. This phenomenon is exploited for the scintiographic imaging of the tumour masses in lungs using labeled human serum albumin microspheres

Topical porous microspheres

Microsponges are porous microspheres having myriad of interconnected voids of particle size range 5-300 µm. These micro sponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc. These porous microspheres with active ingredients can be incorporated into formulations such as creams, lotions and powders. Microsponges consist of non-collapsible structures with porous surface through which active ingredients are released in a controlled manner.

Microspheres in Gene delivery:

Gene delivery systems include viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems. Viral vectors are advantageous for gene delivery because they are highly efficient and have a wide range of cell targets. However, when used in vivo they cause immune responses and oncogenic effects. To overcome the limitations of viral vectors, non-viral delivery systems are considered for gene therapy. Non-viral delivery system has advantages such as ease of preparation, cell/tissue targeting, low immune response, unrestricted plasmid size, and large-scale reproducible production. Polymer has been used as a carrier of DNA for gene delivery applications.

Microspheres for Oral drug delivery

The potential of polymer films containing diazepam as an oral drug delivery was investigated in rabbits. The results indicated that a film composed of a 1:0.5 drug-polymer mixture might be an effective dosage form that is equivalent to the commercial tablet dosage forms. The ability of polymer to form films may permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make polymer a unique polymer for oral drug delivery applications

Microspheres for DNA delivery:

Microspheres have been recently used as a delivery vehicle for the transfer of plasmid DNA which leads to improve the transfer of plasmid DNA and their stability in the bio- environment. Truong-Le & Coworkers (1998) developed a novel system for gene delivery based on the use of DNA-gelatin microspheres/ nanoparticles formed by salt induced complex coacervation of gelatin & plasmid DNA

Ophthalmic Drug Delivery

Polymer exhibits favorable biological behavior such as bio adhesion, permeability-enhancing properties, and interesting

physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. Due to their elastic properties, polymer hydrogels offer better acceptability, with respect to solid or semisolid formulation, for ophthalmic delivery, such as suspensions or ointments, ophthalmic chitosan gels improve adhesion to the mucin, which coats the conjunctiva and the corneal surface of the eye, and increase precorneal drug residence times, showing down drug elimination by the lachrymal flow.

Nasal drug delivery: The nasal mucosa presents an ideal site for bio adhesive drug delivery systems. Polymer based drug delivery systems, such as micro spheres, gels have been demonstrated to have good bio adhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. Various polymer salts such as chitosan lactate, chitosan aspartate, chitosan glutamate and chitosan hydrochloride are good candidates for nasal sustained release of vancomycin hydrochloride. Nasal administration of Diphtheria Toxoid incorporated into chitosan microparticles results in a protective systemic and local immune response against Diphtheria Toxoid with enhanced IgG production. Nasal formulations have induced significant serum IgG responses similar to secretory IgA levels, which are superior to parenteral administration of the vaccine.

Intratumoral and local drug delivery: Intratumoral and local drug delivery strategies have gained interest as a promising modality in cancer therapy. In order to deliver paclitaxel at the tumour site in therapeutically relevant concentration, polymer films were fabricated. Paclitaxel could be loaded at 31% (w/w) in films, which were translucent and flexible. Polymer films containing paclitaxel were obtained by casting method with high loading efficiencies.

Buccaldrugdelivery:

Polymer has an excellent polymer to be used for buccal delivery because it has muco/bio adhesive properties and can act as an absorption enhancer. Buccal tablets based on chitosan microspheres contain chlorhexidine diacetate gives prolonged release of the drug in the buccal cavity improving the antimicrobial activity of the drug. Polymeric microparticles with no drug incorporated have antimicrobial activity due to the polymer. The buccal bilayered devices (bilaminated films, palavered tablets) using a mixture of drugs (nifedipine and propranolol hydrochloride) and chitosan, with or without anionic cross linking polymers (polycarbophil, sodium alginate, gellan gum) has promising potential for use in controlled delivery in the oral cavity.

Peroral drug delivery: As polymer and most of its derivatives has a mucoadhesive property, a presystemic metabolism of peptides can be strongly reduced leading to a strongly improved bioavailability of many perorally given peptide drugs, such as insulin, calcitonin, and buserelin. Unmodified chitosan has a permeation-enhancing effect for peptide drugs. A protective effect for polymer embedded peptides towards degradation by intestinal peptidases can be achieved by the immobilization of enzyme inhibitors on the polymer.

Recent Applications of Controlled Release Microspheres

Controlled-release microspheres are in development for a number of interesting and important applications, especially for delivery of large, fragile drugs like proteins and nucleic acids. Several recent examples are described below. Controlled-Release Vaccines Vaccination has been highly successful for controlling or even eradicating many important types of infectious diseases, and new or improved vaccines are being heavily investigated for AIDS, hepatitis B, anthrax, and SARS.A frequent problem is the need for repeated administrations. Single-shot Vaccine delivery systems should provide the antigen(s) and adjuvant on a prescribed schedule and maintain the bioactivity of the antigen, both during fabrication of the delivery device and during the often prolonged residence time of the device in the body. To enhance vaccine stability, researchers have been focusing on several approaches, including the use of adjuvants to protect the protein antigens or by choosing different microsphere materials. A major advantage of microspheres for vaccination is that they can be passively targeted to antigen-presenting cells (APCs) such as macrophages and dendritic cells. The ability of APCs to phagocytose particulates is dependent on the particle size. In particular,1- to 10-µm diameter microspheres are optimally taken up by APCs in a number of tissues and have been shown to enhance antigen-specific T-helper lymphocyte (Th) responses thus leading to an enhancement in antigen-specific antibody responses) and elicit a cytotoxic T lymphocyte (CTL) responseT-cell activation in response to antigen encapsulating microspheres has been shown to be 100-1000 fold better than antigen alone.

Diagnostic uses of radioactive microspheres: [14]

- Gated blood pool study.
- Thrombus imaging in deep vein thrombosis.
- Blood flow measurements.
- Investigation of bio distribution and fate of (drug-loaded) microspheres.
- Lung scintigraphy.
- Diagnostic radio embolization.
- Liver and spleen imaging.
- Bone marrow imaging.
- Infection localization.
- Tumour imaging.
- Gastrointestinal transit studies
- Local restenosis prevention in coronary arteries

Some Marketed products of microspheres

Table1: Marketed products of microspheres

Drug	Commercial Name	Company	Technology	Indication
Risperidone	RESPERDA^{R},CONSTA^{R}	Jansenn/Alkermes,inc.	Double emulsion(oil in water)	Schizophrenia;Bipolar1 Disorder
Naltrexone	VIVITROL^{R}	Alkermes	Double emulsion(oil in water)	Alcohol dependence

Octreotide	Sandostatin LAR	Novartis	Phase separation	Acromegaly
Somatropin	Nutropin^{R} Depot^{-a}	Genentech /alkermes	Alkermes prolease^{R}Technology (cryogenic spray drying method)	Growth deficiencies
Bromocriptine	Parlodel LAR	Novartis	Spray drying	parkinsonism
Minocycline	Arestin	Orapharma		Periodontitis

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