



MICROSPHERE-BASED DRUG DELIVERY SYSTEMS: A COMPREHENSIVE REVIEW

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ABSTRACT

The targeted drug delivery is designed for endeavoring to concentrate the drug in the tissues of curiosity while reducing relative concentration of medication in the remaining tissues. There for drug is localized on the targeted site. Hence, surrounding tissues are not affected by the drug. Controlled drug delivery system can overcome the problems of conventional drug therapy and gives better therapeutic efficacy of a drug. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000 μm . The range of techniques for the preparation of microspheres 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. Microspheres have a drug located centrally within the particle, where it is encased within a unique polymeric membrane. In future various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene and genetic materials, safe, targeted and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body.

KEYWORDS: Microspheres, controlled drug delivery system, *in vivo* delivery, genetic materials.

INTRODUCTION

Microspheres are small spherical particles, with diameters 10 μm to 1000 μm . Microsphere play an important role to improve bioavailability of conventional drugs and minimizing side effects. The main advantage of applying microspheres as drugs delivery system is the controlled release of the drug content. Microencapsulation used for retarding the drug release from dosage forms and reduced the adverse effects, increased the for compliance. In this technique, aqueous insoluble core (drugs) coated with an aqueous insoluble coat (polymer) by emulsion solvent diffusion evaporation technique for sustain release drug delivery system. Microspheres can be made by a variety of ways including emulsification technique with single or double solvent evaporation system spray-dry technique or phase separation technique. Microspheres can be prepared by dissolving the starting materials in volatile solvents and then dispersing them in another solvent which is not miscible with the previous. Later complete evaporation of the last solvent will produce a fine powder called

microspheres which is soluble in water. There are two types of microspheres;

Types of microspheres

Bio adhesive microspheres

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water-soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc. can be termed as bio adhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, Nano spheres, liposomes, nanoparticles, etc., which modulates the release and absorption of the drug. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity.

Magnetic microspheres

This kind of delivery system is very much important which localizes the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. The different types are therapeutic magnetic microspheres and diagnostic microspheres.

Floating microspheres

In floating types, the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content, increases gastric residence and fluctuation in plasma concentration. It also reduces chances of striking and dose dumping and produces prolonged therapeutic effect. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies.

Polymeric microspheres

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and synthetic polymeric microspheres.

Radioactive microspheres

Radio embolization therapy microspheres sized 10-30 nm are of larger than capillaries and gets trapped in first capillary bed when they come across. They are injected to the arteries that lead to tumor of interest. So these radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters.

Mucoadhesive microspheres

Mucoadhesive microspheres which are of 1-1000 μ m in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it and coupling of mucoadhesive properties to microspheres has additional advantages, *e. g.* efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies, etc. on the surface of the microspheres.

Mucoadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs.

Advantages of microspheres over conventional dosage forms

Microspheres provide prolonged and constant therapeutic effect. Particle size reduction for enhancing solubility of the poorly soluble drug. Microspheres reduce the dosing frequency and therefore improve the patient compliance. Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein. Microspheres provide controlled, sustained and targeted delivery of the drug. Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal. Microspheres produce more reproducible drug absorption. Drug discharge in stomach is hindered and that's why local unwanted effects are reduced. In case of microspheres, better therapeutic effect for short half-life of drugs can be achieved. Microspheres provide freedom from drug and recipients incompatibilities especially with buffer. Microspheres reduce dose dumping. Microspheres provide the protection of drugs against environment. Microspheres also mask the taste and odor. Microspheres avoid the first pass metabolism. Microspheres can be easily injected in body because of their small and spherical size. Microspheres enhance the biological half-life and also improve the bioavailability. Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections. Microspheres also reduce the chances of G. I. irritation.

Limitation

The costs of the materials and processing of the controlled release preparation, are substantially higher than those of standard formulations. Controlled release rate of microspheres may vary due to certain factors like intrinsic or extrinsic factors may be food, rate of transit through gut, mucin turnover rate etc. The fate of polymer matrix and its effect on the environment. There are differences in release from one to another dosage form. Any loss of integrity in release pattern may cause potential toxicity. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers. Reproducibility is less. Low drug loading is done in case of parental microspheres. Process situations like change in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated. Parental delivery of microspheres may interact or form complex with blood components. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents.

Applications of Microspheres in vaccine delivery

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 reactions a complex issue.

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

The concept of targeting, i.e. site-specific drug delivery is a well-established dogma, which is gaining full attention. The therapeutic efficacy of the drug relies on its access and specific interaction with its candidate receptors. The ability to leave the pool in reproducible, efficient and specific manner is enter to drug action mediated by use of a carrier system.

Monoclonal antibodies facilitated microspheres targeting

Monoclonal antibodies targeting microspheres are immune microspheres. This targeting is used to achieve selective targeting to specific sites. 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. Maps can be attached to microspheres by any of following methods:

- Nonspecific adsorption and specific adsorption
- Direct coupling
- Coupling via reagent

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 microspheres. The particle size range of microspheres is a vital 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 abused for the scintigraphic imaging of the tumor masses in lungs using labelled human serum albumin microspheres.

Topical porous microspheres

Micro sponges are porous microspheres having myriads 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., are used as the topical carrier system further, these porous microspheres with active ingredients can be incorporated into formulations such as creams, lotions and powders. Micro sponges

consist of non-collapsible structures with porous surface through which active ingredients are released in a controlled manner.

Nasal drug delivery

Intranasal (IN) administration has many theoretical and practical advantages for the local and systemic delivery of a diverse therapeutic compound. IN delivery is needle free, non-invasive, and essentially painless, does not require sterile preparation, and can be self-administered. The large surface area of the nasal mucosa originated from the presence of a large number of microvilli, a porous endothelial membrane, and a highly vascularized epithelium serves a rapid onset of therapeutic effect. It is describing various systems, devices, formulations, and methods of delivery of drugs to the nose or nasal cavity. Depending on the therapeutic intent, intranasal drugs may be targeted for local treatment or systemic action. In nasal drug delivery, coupling of bioadhesive properties to microspheres is of great importance because of additional advantages: efficient absorption and enhanced bioavailability of the drug, a much more intimate contact with the mucus layer and reduction in frequency of drug administration due to the reduction in mucociliary clearance of drug delivery system adhering to nasal mucosa.

Gastroretentive controlled delivery system

In which Floating systems are low-density systems that have float over the gastric contents and remain in the stomach for a prolonged period than conventional dosage forms. Gastric emptying of dosage form is extremely variable process and ability to control the emptying time is valuable asset for dosage forms, there are several difficulties are faced in designing controlled released systems for better absorption and enhanced the bioavailability. 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. Several polymers are used for gastro retentive controlled delivery system such are Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, Polyvinyl acetate, carbopol, Agar, Polyethylene oxide, Polycarbonates, Acrylic resins and Polyethylene oxide etc.

Implantable devices

Microencapsulation has also been used medically for the encapsulation of live cells and vaccines. Biocompatibility can be improved by the encapsulation of artificial cells and biomolecules such as peptides, proteins, and hormones, which can prevent unwanted immunological reactions that would lead to inactivation or rejection. Microspheres are used for isolating materials until their activity is needed. The biotechnology industry employs microspheres to contain organisms and their recombinant products to aid in the isolation of these products.

Pharmaceutical applications

A number of pharmaceutical microencapsulated products are currently on the market, such as aspirin, theophylline and its derivatives, vitamins, pancreatin's, antihypertensives, potassium chloride, progesterone, and contraceptive hormone combinations. Microencapsulated KCL is used to prevent gastrointestinal complications associated with potassium chloride. The dispersibility of the microcapsules and the controlled release of the ions minimize the possibility of local high salt concentrations which could result in ulceration, hemorrhage, or perforation. Microspheres have also found potential applications as injection, or inhalation products. The number of commercially available products does not reflect the amount of research that has been carried out in this area, nor the benefits that can be achieved using this technology. Economic considerations have been a key factor in determining the number of pharmaceutical microencapsulated products. Most encapsulation processes are expensive and require significant capital investment for equipment. An exception is pan or sprays coating and spray drying, since the necessary equipment may already be available within the company. An additional expense is due to the fact that most microencapsulation processes are patent protected.

Other applications

Fluorescent microspheres can be used for membrane-based technology for flow cytometry, cell biology, microbiology, Fluorescent Linked Immuno-Sorbent Assay. Yttrium can be used for primary treatment of hepatocellular carcinoma and also used for pre transplant management of HCC with promising results. Applications of microencapsulation in other industries are numerous. The best-known microencapsulated products are carbonless copying paper, photosensitive paper, microencapsulated fragrances, such as "scent-strips" (also known as "snap-n-burst"), and microencapsulated aromas ("scratch-n-sniff"). All of these products are usually prepared by gelatin-acacia complex coacervation. Scratch-n-sniff has been used in children's books and food and cosmetic aroma advertising. Microcapsules are also extensively used as diagnostics, for example, temperature-sensitive microcapsules for thermographic detection of tumors. In the biotechnology industry microencapsulated microbial cells are being used for the production of recombinant proteins and peptides.

CONCLUSION

Microspheres are better choice of drug delivery system than many other types of drug delivery system. In future by combining various other strategies, microspheres will find the central and significant place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene and genetic materials, safe, targeted, specific and effective *in vitro* delivery and supplements as miniature version of diseased organ and tissues in the body. Microspheres offer several improvements over existing technologies. These have emerged as an exciting new

platform for biologists to adopt these techniques in the investigation of biomolecules interactions and cellular processes. In recent years there have been increasing numbers of studies in which microspheres have been used in more diverse applications and it is evident that the range of potential applications is enormous. In addition, microspheres have been labeled with a variety of β and emitting radionuclide such as ^{131}I , $^{99\text{m}}\text{Tc}$, $^{113\text{m}}\text{In}$ or ^{51}Cr . Such products have been used to scan the heart, brain, liver and gastro intestinal tracts and in a pulmonary perfusion and inhalation studies. Microsphere is a short term but it is having wide applications in drug delivery systems to get desired biological activity. By combining various strategies, microspheres will find central place in novel drug delivery system mainly particularly in cell sorting, diagnostics and Genetic engineering. From the study it is proved that Microspheres act as effective carriers for the novel drug delivery system.

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