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NATURAL POLYMERIC MICROSPHERES FOR DRUG DELIVERY: A REVIEW

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ABSTRACT

Natural polymeric microspheres find application in a many range of applications due to its low production costs non-toxic, biodegradability, biocompatibility. Among other uses microspheres are being used as embolic and drug-delivery particles. Drug delivery has become increasingly important mainly due to the awareness of the difficulties associated with a variety of old and new drugs. The many polymeric drug delivery systems, biodegradable polymers have been used widely as drug delivery systems because of their biocompatibility and biodegradability. The majority of biodegradable polymers have been used in the form of microspheres, from which the incorporated drug is released to the environment in a controlled manner. The factors responsible for controlling the drug release rate are physicochemical properties of drugs, degradation rate of polymers, and the morphology and size of microspheres. Microspheres of the size varies with the application and therefore a huge range of materials has been used to produce microspheres such as 10 µm in size are well suited for regional blood flow in organs such as the kidneys, lungs and heart where as 1µm size are preferred to trace the development of new blood vessels for the study of tumor angiogenesis and micro vascular continuity. In this review, aims to compile the various application of natural polymer in microspheres based drug delivery.

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INTRODUCTION

There has been considerable interest in developing biodegradable, injectable microspheres for the controlled release of proteins and peptides. Mucoadhesive polymers may fulfill the desirable features of a prolonged residence time at the site

of drug absorption owing to increased contact with the absorbing mucosa, resulting in a steep concentration gradient to favor drug absorption, and localization in specified regions to improve and enhance the bioavailability of the drug.[1] With advances in biotechnology, genomics, and combinatorial chemistry, a wide variety of new, more potent and specific therapeutics are being created. Because of common problems such as low solubility, high potency, and/or poor stability of many of these new drugs, the means of drug delivery can impact efficacy and potential for commercialization as much as the nature of the drug itself.

Thus, there is a corresponding need for safer and more effective methods and devices for drug delivery. Indeed, drug delivery systems—designed to provide a therapeutic agent in the needed amount, at the right time, to the proper location in the body, in a manner that optimizes efficacy, increases compliance and minimizes side effects—were responsible for $47 billion in sales in 2002, and the drug delivery market is expected to grow to $67 billion by 2006. Controlled release drug delivery systems are being developed to address many of the difficulties associated with traditional methods of administration. Controlled release drug delivery employs devices—such as polymer-based disks, rods, pellets, or microparticles— that encapsulate drug and release it at controlled rates for relatively long periods of time.

Controlled drug delivery systems offer some advantages compared to the conventional dosage forms, which include reduced adverse reaction, toxicity and frequency of dosing with improved efficacy, patient compliance and convenience. Using the novel microencapsulation techniques and varying the polymer ratio and molecular weight, microspheres can be developed as an optimal drug delivery system which provides the desired release profile. Microsphere-based systems may increase the life span of active constituents and control the release of bioactive agents [2]

The use of natural polymers as drug carriers has received much attention in the pharmaceutical field due to their safety. In particular, the polysaccharides such as sodium alginate and chitosan have been studied for application in the design of dosage forms for controlled release9. The use of natural polymers is valuable based on proven biocompatibility. Chitosan, a natural linear biopolyaminosaccharide, is obtained by alkaline deacetylation of chitin. Properties of chitosan make the polymer suitable for use in biomedical and pharmaceutical formulations. It has also been used for the encapsulation of drugs. Sodium alginate is a natural and hydrophilic polymer suitable for the entrapment of water soluble drugs. [3]

Such systems offer several potential advantages over traditional methods of administration. First, drug release rates can be tailored to the needs of a specific application; for example, providing a constant rate of delivery or pulsatile release. Second, controlled release systems provide protection of drugs, especially proteins that are otherwise rapidly destroyed by the body. Finally, controlled release systems can increase patient comfort and compliance by replacing frequent (e.g., daily) doses with infrequent (once per month or less) injection. While a variety of devices have been used for controlled release drug delivery, biodegradable polymer microspheres are one of the most common types and hold several advantages. Microspheres can encapsulate many types of drugs including small molecules proteins, and nucleic acids and are easily administered through a syringe needle. They are generally biocompatible, can provide high bioavailability, and are capable of sustained release for long periods of time.

Chitosan microspheres are used to provide controlled release of many drugs and to improve the bioavailability of degradable substances such as protein, as well as to improve the uptake of hydrophilic substances across the epithelial layers. These microspheres are being investigated both for parenteral and oral drug delivery. [4]

Chitosan is an non-toxic biodegradable polycationic polymer with low immunogenicity. It is an good candidate for the gene delivery system because cationically charged chitosan can be complexed with negatively charge plasmid DNA and promising results with chitosan as a gene delivery carrier.[5] In this study, an attempt was made to focus on the natural of polymeric microspheres and how these are mostly applied clinically. We will describe how drug delivery of microspheres may improve therapeutic efficiency. In this review we aim to describe how design of natural polymeric microspheres can lead to novel drug delivery.

METHODLOGY

Microspheres are defined as spherical microscopic particles that range in size from 1–1,000 µm [6, 7]. The definition on the basis of size can sometimes be confusing since spheres with a size of over 1,000 µm are still often called microspheres. These particles have a wide variety of possible applications that range from use in the medical field, application as carrier materials for purification purposes in the biochemical sciences [8], to use as flow indicators. Non-polymeric microspheres are mainly produced in a simple method based upon the formation of spheres in an aqueous environment and subsequent drying, and if required, sintering [9, 10]. Here we will focus on medical microspheres that are composed of polymers. The use of polymers for synthesizing microspheres enables the production of uniformly shaped and well-defined spheres in a wide range of sizes. Polymeric microspheres can be synthesized using a variety of different methods.

Natural polymeric microspheres have been fabricated by a variety of technique including:

1) Solvent extraction
2) Spray drying and spray congealing
3) Phase separation co acervation technique
4) Single emulsion technique
5) Double emulsion technique

Solvent extraction:

Solvent evaporation method is used for the preparation of microparticles, 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 the microspheres. One variation of the process involves 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**.**

Spray drying and spray congealing:

Compared to other conventional methods, spray drying offers several advantages [11,12, 13]. It shows good reproducibility, involves relatively mild conditions, allows controlling the particle size, and is less dependent on the solubility of the drug and the polymer. The drug is dissolved or dispersed in the polymer solution, in which volatile solvents (e.g., dichloromethane and acetone) are preferred. The resulting solution or suspension is sprayed in a stream of heated air to produce microparticles.

The size of the microparticles is determined depending on the atomizing conditions. The main disadvantage of this technique is a loss of a significant amount of product, primarily due to adhesion of the microparticles to the inner wall of the spray-drier. In addition, large aggregates are frequently obtained because the microparticles are very sticky before the complete removal of the solvent. In an attempt to minimize aggregation of the microparticles, a double-nozzle spray-drying technique was developed [14]. While the polymer/drug solution is sprayed from one nozzle, aqueous mannitol solution is simultaneously sprayed, which enables the surface of the microparticles to be coated with mannitol. The results indicated that the coating of the microsphere with mannitol reduces the extent of aggregation and augments the yield of the product. A cryogenic, non-aqueous process was used to prepare protein-loaded microparticles [15, 16] .In this technique, the liquid droplets of the polymer/drug solution are produced through the spraying nozzle, collected in liquid nitrogen containing frozen

ethanol, and hardened by placing them at -80 oC where the solvent extraction occurs. This method is known to encapsulate proteins into microparticles without significant loss of their biological activity.

Phase separation co acervation 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.

Single emulsion technique:

This method has been primarily used to encapsulate hydrophobic drugs through oil-in water (o/w) emulsification process. The polymer is dissolved in a water-immiscible, volatile organic solvent such as dichloromethane, and the drug is dissolved or suspended into the polymer solution. The resulting mixture is emulsified in a large volume of water in the presence of an emulsifier [17, 18,]. The solvent in the emulsion is removed by either evaporation at elevated temperatures or extraction in a large amount of water, resulting in formation of compact microparticles. The rate of solvent removal is reported to affect the final morphology of microparticles. The solvent removal rate is determined by the temperature of the medium, the solubility characteristics of the polymer, and the solvent used [19]. This method, however, is only available for the hydrophobic drugs because the hydrophilic drugs may diffuse out or partition from the dispersed oil phase into the aqueous phase, leading to poor encapsulation efficiencies. In an attempt to encapsulate hydrophilic drugs (e.g., peptides and proteins), an oil-in-oil (o/o) emulsification method has recently received considerable attention [20, 21]. In this method, the watermiscible organic solvents are employed to dissolve the drug and polymer, whereas hydrophobic oils are used as a continuous phase of the o/o emulsion. The microparticles are obtained by removing the organic solvents through evaporation or extraction process.

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 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 leutinizing 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.

CLINICAL APPLICATION OF MICROSPHERES:

1. Microspheres in vaccine delivery

The prerequisite of a vaccine is protection against the micro organism 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. 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 [22].

2. Microspheres to Enhance Pulmonary Drug Delivery

The success of microspheres as DDS is limited due to their short residence time at the site of absorption. It would, therefore, be advantageous to have means for providing an intimate contact of the DDS with the absorbing membranes. It can be achieved by coupling bioadhesion characteristics to microspheres and developing novel delivery systems referred to as "bioadhesive microspheres". "Bioadhesion" in simple terms can be described as the attachment of a synthetic or biological macromolecule to a biological tissue. An adhesive bond may form with either, the epithelial cell layer, the continuous mucus layer or a combination of the two. The term "mucoadhesion" is used specifically when the bond involves mucous coating and an adhesive polymeric device, while "cytoadhesion" is the cell-specific bioadhesion. Bioadhesive microspheres include microparticles and microcapsules (having a core of the drug) of 1–1000 µm in diameter and consisting either entirely of a bioadhesive polymer or having an outer coating of it, respectively. Microspheres, in general, have the potential to be used for targeted and controlled release drug delivery; but coupling of bioadhesive 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 drugs to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies, etc. on the surface of the microspheres. Microspheres prepared with bioadhesive and bioerodible polymers undergo selective uptake by the macrophages cells in lung mucosa and by the M cells of Peyer patches in gastrointestinal (GI) mucosa. Bioadhesive microspheres offer unique carrier system for many pharmaceuticals and can be tailored to adhere to any mucosal tissue, including those found in eyes, oral cavity and throughout the respiratory, urinary and gastrointestinal tract. Increased residence time of particulate delivery systems at the mucosal surface may facilitate the increased uptake of such particlres. To this end, muco- or bioadhesive agents provide a strategy that may help to increase the residence time and, hence, the uptake of biodegradable particulate when administered by the pulmonary routes.

3. Microspheres for Inhalation

Aerosolised administration of drugs to the lung has been employed for many years to treat primarily localised disease states within the bronchi. Since this route of administration can deliver therapeutic agents to the diseased regions whilst reducing their distribution to the other organs, it provides an excellent example of targeted drug therapy. Hence, a more favorable therapeutic index can be obtained for the treatment of lung diseases when drugs are administered by inhalation rather than by the oral route. Bronchodilators, anti-inflammatory agents, mucolytics, antiviral agents, anticancer agents and phospholipidprotein mixtures for surfactant replacement therapy are all routinely given as aerosolized formulations whilst more recently, there has been an increasing interest in the delivery of drugs via the lung to treat pulmonary diseases in particular these associated with AIDS. Moreover, the development of potent protein drugs by biotechnology has also stimulated a growth of interest in inhalation aerosols because of the possibility of systemic delivery of these drugs via the airways.

CONCLUSION

Natural polymeric microspheres are frequently used in clinical practice and the number of applications is steadily increasing. They serve diverse roles that range from bulking agent to drug delivery depots. It has become clear that microspheres have advantages that make them well suited for clinical application. First of all, microspheres are easy and relatively cheap to

produce. The polymers that are currently being used for synthesis of commercial spheres are proven to be biocompatible and safe. Furthermore the combination of several drugs in one microspheres or the synthesis of microspheres with different layers containing different drugs can load to a more personalized drug delivery regime. Finally, it is clear that microspheres of naturally polymer are nowdays an important part of the physicians making the treatment of patients easier and with safer. However, there over still important features that need to added to the microspheres pallet to optimize their clinical use.

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