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(54) Title: VERY LOW TEMPERATURE CASTING OF CONTROLLED RELEASE MICROSPHERES

(57) Abstract

A process for preparing microspheres using very cold temperatures to freeze polymer-biologically active agent mixtures into polymeric microspheres with very high retention of biological activity and material. Polymer is dissolved in a solvent together with an active agent that can be either dissolved in the solvent or dispersed in the solvent in the form of microparticles. The polymer/active agent mixture is atomized into a vessel containing a liquid non-solvent, alone or frozen and overlayered with a liquified gas, at a temperature below the freezing point of the polymer/active agent solution. The cold liquified gas or liquid immediately freezes the polymer droplets. As the droplets and non-solvent for the polymer is warmed, the solvent in the droplets thaws and is extracted into the non-solvent, resulting in hardened microspheres.

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VERY LOW TEMPERATURE CASTING OF CONTROLLED RELEASE MICROSPHERES

Background of the Invention

This invention generally relates to processes for making polymeric microspheres for controlled release of substances.

A variety of techniques are known by which active agents can be incorporated into polymeric microspheres. An example is spray drying. In spray drying, the polymer and active agent are mixed together in a solvent for the polymer, then the solvent is evaporated by spraying the solution, leaving polymeric droplets containing the active agent. Spray drying is reviewed in detail by K. Masters in "Spray Drying Handbook" (John Wiley & Sons, New York 1984); and Patrick B. Deasy in "Microencapsulation and Related Drug Processes" (Marcel Dekker, Inc., New York 1984). Spray drying works well for many agents but may inactivate some materials, particularly biologically active proteins, due to the heat generated during the process. In addition, considerable amounts of the material can be lost during the spray drying process due to sticking of the polymer to the large surface area on the sides of the chamber.

Solvent evaporation techniques have also been used to form microspheres. These techniques involve dissolving the polymer in an organic solvent which contains either dissolved or dispersed active agent. The polymer/active agent solution is then added to an agitated continuous phase which is usually aqueous and immiscible with the polymer/active agent. Emulsifiers can be included in the aqueous phase to stabilize the oil-in-water emulsion. The organic solvent is then evaporated over a period of several hours or more, thereby depositing the polymer around the core material. Solvent can be removed from the microspheres in a single step, as described in U.S. Pat. No. 3,737,337 and U.S. Pat. No. 3,523,906, or in U.S. Pat. No. 3,691,090 (under reduced pressure), or by the application of heat, as shown in U.S. Pat. No. 3,891,570. A two-step technique is described in U.S. Pat. No. 4,389,330. Freeze drying has also been

used to remove the solvent from microspheres, as reported by Sato, et al, in "Porous Biodegradable Microspheres for Controlled Drug Delivery. I. Assessment of Processing Conditions and Solvent Removal Techniques," Pharmaceutical Research 5, 21-30 (1988).

Solvent evaporation works reasonably well for hydrophobic drugs but the amount of incorporated material is usually lower than the theoretical values due to loss of drug to the aqueous phase, as reported by Benita, et al., in "Characterization of Drug Loaded Poly(d,l-lactide) Microspheres," J. Pharm. Sci. 73, 1721-1724 (1984). If water soluble active agents are used, such as proteins, a much more significant loss of material can occur.

Phase separation techniques have also been used to form microspheres. These techniques involve the formation of a water-in-oil or an oil-in-water emulsion. The polymer is precipitated from the continuous phase onto the active agent by a change in temperature, pH, ionic strength or the addition of precipitants. For example, U.S. Pat. No. 4,675,189 describes the formation of poly(lactic-co-glycolic acid) microspheres containing hormonally active polypeptides. The polypeptide is first dissolved in the aqueous phase of a water-in-oil emulsion. Polymer is then precipitated around the aqueous droplets by addition of a non-solvent for the polymer such as silicon oil. The final product, as with most phase separation techniques, is in the form of a microcapsule. Microcapsules contain a core material surrounded by a polymer membrane capsule. The release kinetics of active agents from these devices can be difficult to control.

Although these phase separation techniques result in the formation of microspheres containing active agents, active agent is often lost during the solvent extraction process. In addition, as with spray drying, biologically active proteins may be denatured during the process.

Cold temperatures have also been employed in certain steps of the microsphere formation process. For example, U.S. Pat.

No. 4,166,800 describes the use of temperatures between -40°C and -100°C along with a phase separation agent to stabilize the polymeric microspheres during phase separation.

A method using low temperature to form microspheres from an ethylene-vinyl acetate co-polymer, but not other polymers such as poly(lactic acid), is reported by Sefton, et al., in "Ethylene-Vinyl Acetate Copolymer Microspheres for Controlled Release of Macromolecules," J. Pharm. Sci. 73, 1859-1861 (1984). Polymer is dissolved in a dispersion of albumin in methylene chloride, added dropwise through a syringe into ethanol in a dry ice-ethanol bath (-78°C), where, upon hitting the cold ethanol, the drops gel and sink to the bottom of the container. After five to ten minutes the container is removed from the dry ice bath and allowed to warm to room temperature to extract the solvent from the microspheres. This system, however, does not work with other polymers such as poly(lactic acid).

Most of these methods result in the loss of some of the material being incorporated, and/or its activity. Many are very specific for a particular type of polymer, in part because the majority of these techniques rely on the use of a two phase system to form the microspheres, which are also very specific for each polymer type.

It is therefore an object of the present invention to provide a method for making microspheres containing biologically active materials with very little loss of activity and material.

It is a further object of the present invention to provide a method for making microspheres which can be used with a broad range of polymers.

It is a still further object of the present invention to provide such a process which is relatively quick, simple, and inexpensive.

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