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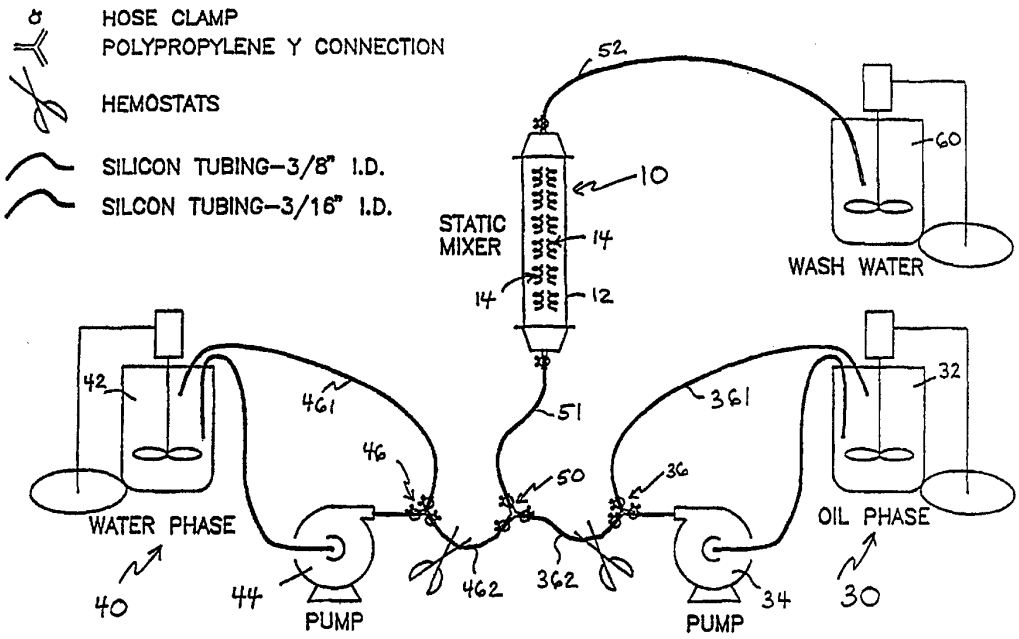
(71) Applicant: MEDISORB TECHNOLOGIES INTERNATIONAL L.P. [US/US]; 6954 Cornell Road, Cincinnati, OH 45242 (US).

(72) Inventors: RAMSTACK, J., Michael; 326 W. Orchard Avenue, Lebanon, OH 45036 (US). HERBERT, Paul, F.; 4 Oak Hill Road, Wayland, MA 01778 (US). STROBEL, Jan; 7753 Brookdale Drive, Westchester, OH 45069 (US). ATKINS, Thomas, J.; 11708 Vauk Valley Lane, Cincinnati, OH 45249 (US). HAZRATI, Azar, M.; 2955 Kimberly Drive, Maineville, OH 45039 (US).

(74) Agents: CORNWELL, David, K., S. et al.; Sterne, Kessler, Goldstein & Fox, Suite 600, 1100 New York Avenue, N.W., Washington, DC 20005-3934 (US).

(54) Title: PREPARATION OF BIODEGRADABLE MICROPARTICLES CONTAINING A BIOLOGICALLY ACTIVE AGENT



(57) Abstract

A process for preparing biodegradable microparticles comprising a biodegradable polymeric binder and a biologically active agent. A first phase, comprising the active agent and the polymer, and a second phase are pumped through a static mixer into a quench liquid to form microparticles containing the active agent. Preferably, a blend of at least two substantially non-toxic solvents, free of halogenated hydrocarbons, is used to dissolve or disperse the agent and dissolve the polymer.

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Preparation of Biodegradable Microparticles Containing a Biologically Active Agent

Cross-Reference to Related Applications

This is a continuation-in-part of co-pending Application Serial No. 08/154,409, filed November 19, 1993, and co-pending Application Serial No. 08/298,787, filed August 31, 1994.

Background of the Invention

1. Field of the Invention

This invention relates to the preparation of microparticles. More particularly, the present invention relates to a method of encapsulating active agents to form controlled-release microparticles through the use of static mixers. The present invention also relates to a solvent system useful in a method of encapsulating active agents to form controlled-release microparticles. By "microparticles" or "microspheres" is meant solid particles that contain an active agent dispersed or dissolved within a biodegradable polymer that serves as the matrix of the particle.

2. Description of the Related Art

A variety of methods is known by which compounds can be encapsulated in the form of microparticles. It is particularly advantageous to encapsulate a biologically active or pharmaceutically active agent within a biocompatible, biodegradable, wall forming material (e.g., a polymer) to

provide sustained or delayed release of drugs or other active agents. In these methods, the material to be encapsulated (drugs or other active agents) is generally dissolved, dispersed, or emulsified, using stirrers, agitators, or other dynamic mixing techniques, in a solvent containing the wall forming material. Solvent is then removed from the microparticles and thereafter the microparticle product is obtained.

An example of a conventional microencapsulation process is disclosed in U.S. Patent No. 3,737,337 wherein a solution of a wall or shell forming polymeric material in a solvent is prepared. The solvent is only partially miscible in water. A solid or core material is dissolved or dispersed in the polymer-containing solution and, thereafter, the core-material-containing solution is dispersed in an aqueous liquid that is immiscible in the organic solvent in order to remove solvent from the microparticles. The substances to be encapsulated or embedded are dissolved or dispersed in the organic solution of the polymer (phase A), using conventional mixers including (in the preparation of a dispersion) vibrators, and high speed stirrers, etc. The dispersion of phase (A), containing the core material in solution or in suspension, is carried out in the aqueous phase (B) again using conventional mixers, such as high-speed mixers, vibration mixers or even spray nozzles, in which case the particle size of the microgranulates will be determined not only by the concentration of phase (A) but also by the particle sizes obtained.

Another example of a process in which solvent is removed from microparticles containing a substance is disclosed in U.S. Patent No. 3,523,906. In this process, a material to be encapsulated is emulsified in a solution of a polymeric material in a solvent that is immiscible in water and then the emulsion is emulsified in an aqueous solution containing a hydrophilic colloid. Solvent removal from the microparticles is then accomplished by evaporation and the product is obtained.

In still another process, as disclosed in U.S. Patent No. 3,691,090, organic solvent is evaporated from a dispersion of microparticles in an aqueous medium, preferably under reduced pressure.

Similarly, U.S. Patent No. 3,891,570 discloses a method in which microparticles are prepared by dissolving or dispersing a core material in a solution of a wall material dissolved in a solvent having a dielectric constant of 10 or less and poor miscibility with a polyhydric alcohol, then emulsifying in fine droplets through dispersion or solution into the polyhydric alcohol and finally evaporating the solvent by the application of heat or by subjecting the microparticles to reduced pressure.

Another example of a process in which an active agent may be encapsulated is disclosed in U.S. Patent No. 3,960,757. Encapsulated medicaments are prepared by dissolving a wall material for capsules in at least one organic solvent, poorly miscible with water, that has a boiling point of less than 100°C, a vapor pressure higher than that of water, and a dielectric constant of less than about 10; dissolving or dispersing a medicament that is insoluble or slightly soluble in water in the resulting solution; dispersing the resulting solution or dispersion to the form of fine drops in a liquid vehicle comprising an aqueous solution of a hydrophilic colloid or a surface active agent, and then removing the organic solvent by evaporation. The size of the fine drops is determined according to the stirring speed, the viscosity of the organic solvent solution containing the medicament and the wall material, and the viscosity and surface tension of the vehicle.

Tice *et al.* in U.S. Patent No. 4,389,330 describe the preparation of microparticles containing an active agent by using a two-step solvent removal process. This two-step solvent removal process is advantageous because it results in microparticles having higher active agent loading and a higher quality than techniques in which solvent is removed in a single step. In the Tice *et al.* process, the active agent and the polymer are dissolved in a solvent. The mixture of ingredients in the solvent is then emulsified in a continuous-phase processing medium that is immiscible with the solvent. A dispersion of microparticles containing the indicated ingredients is formed in the continuous-phase medium by mechanical agitation of the mixed materials. From this dispersion, the organic solvent can be partially removed in the first

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