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(54) **PROCESSES FOR MANUFACTURING
POLYMERIC MICROSPHERES**

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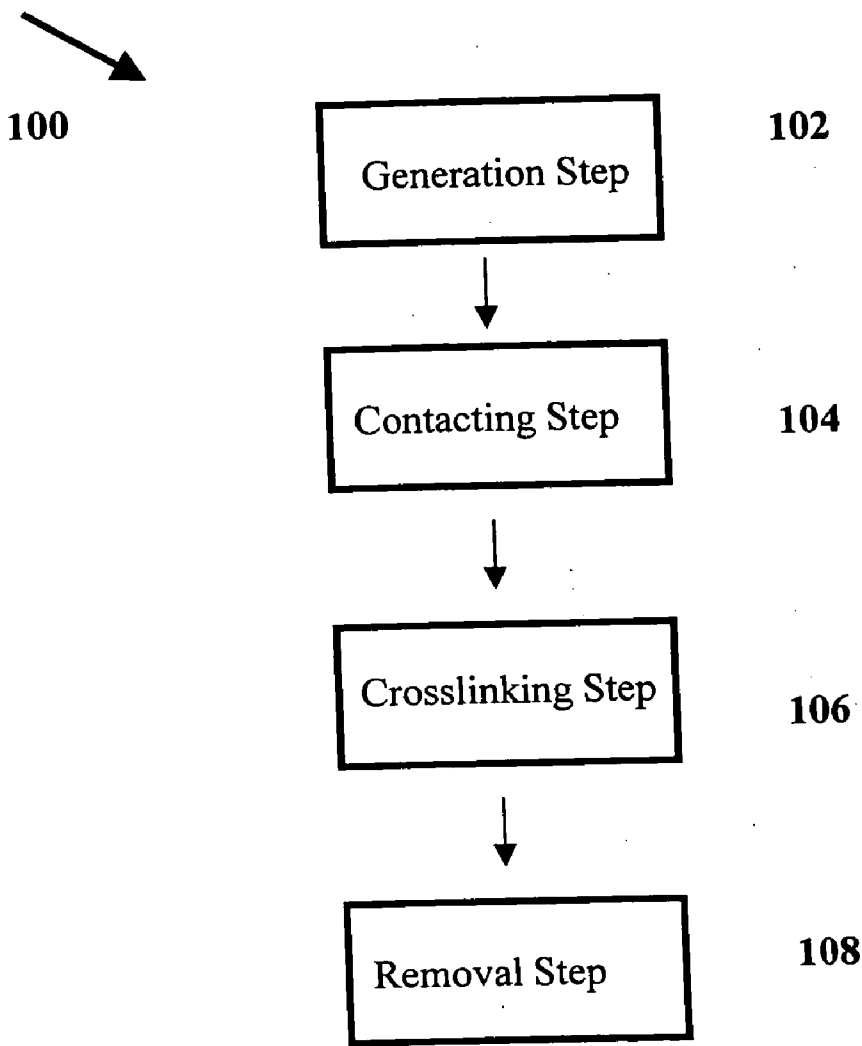
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(57) **ABSTRACT**
Processes of manufacturing polymeric microspheres facilitate the generation of polymeric microspheres of size ranges smaller than 600 microns diameter by forming beads of a predetermined size from a starting material which may include a template polymer, and subsequently contacting the beads with a structural polymer. After crosslinking of the structural polymer has taken place, the template polymer may be removed to form the finished microspheres.

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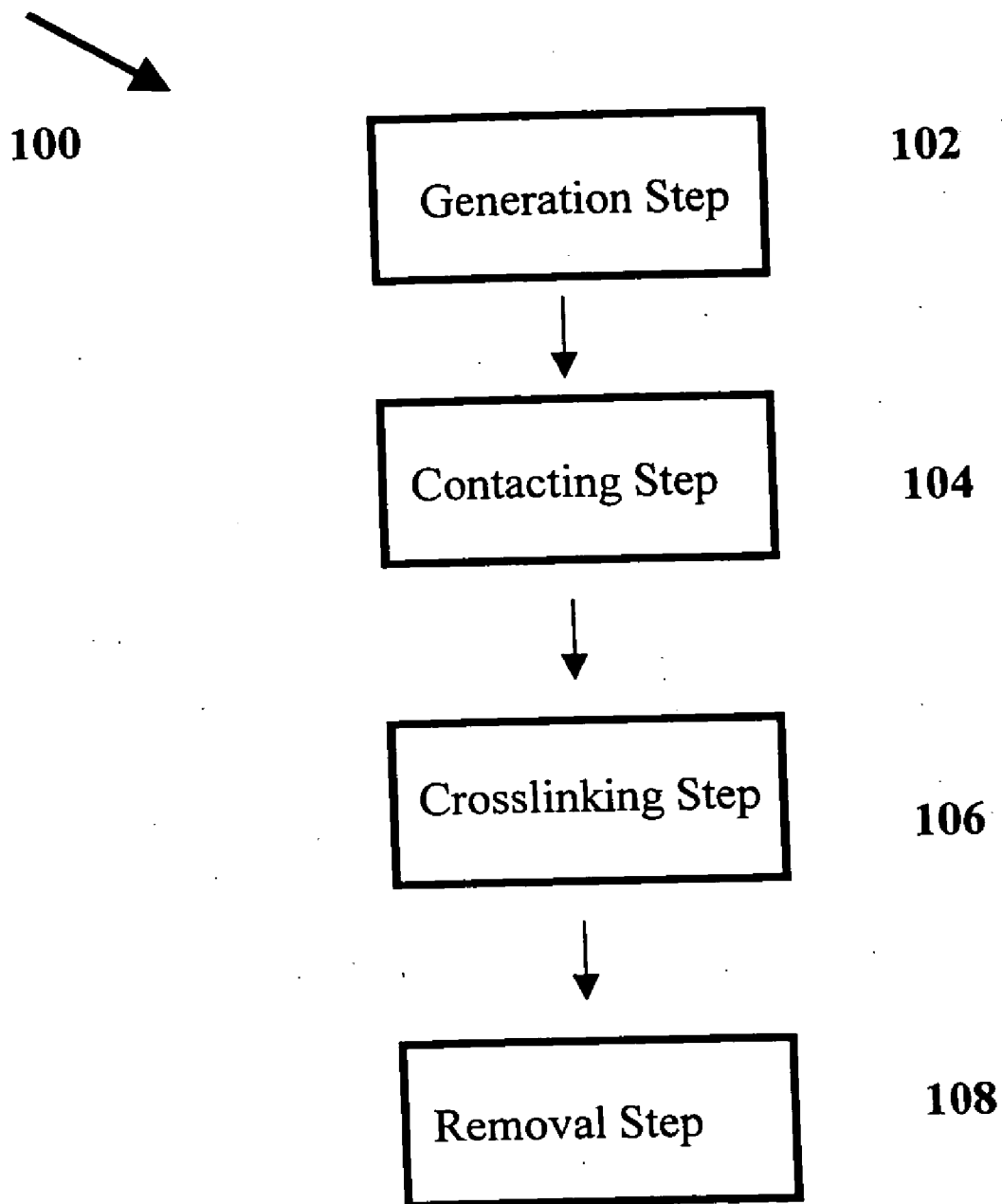


FIG. 1

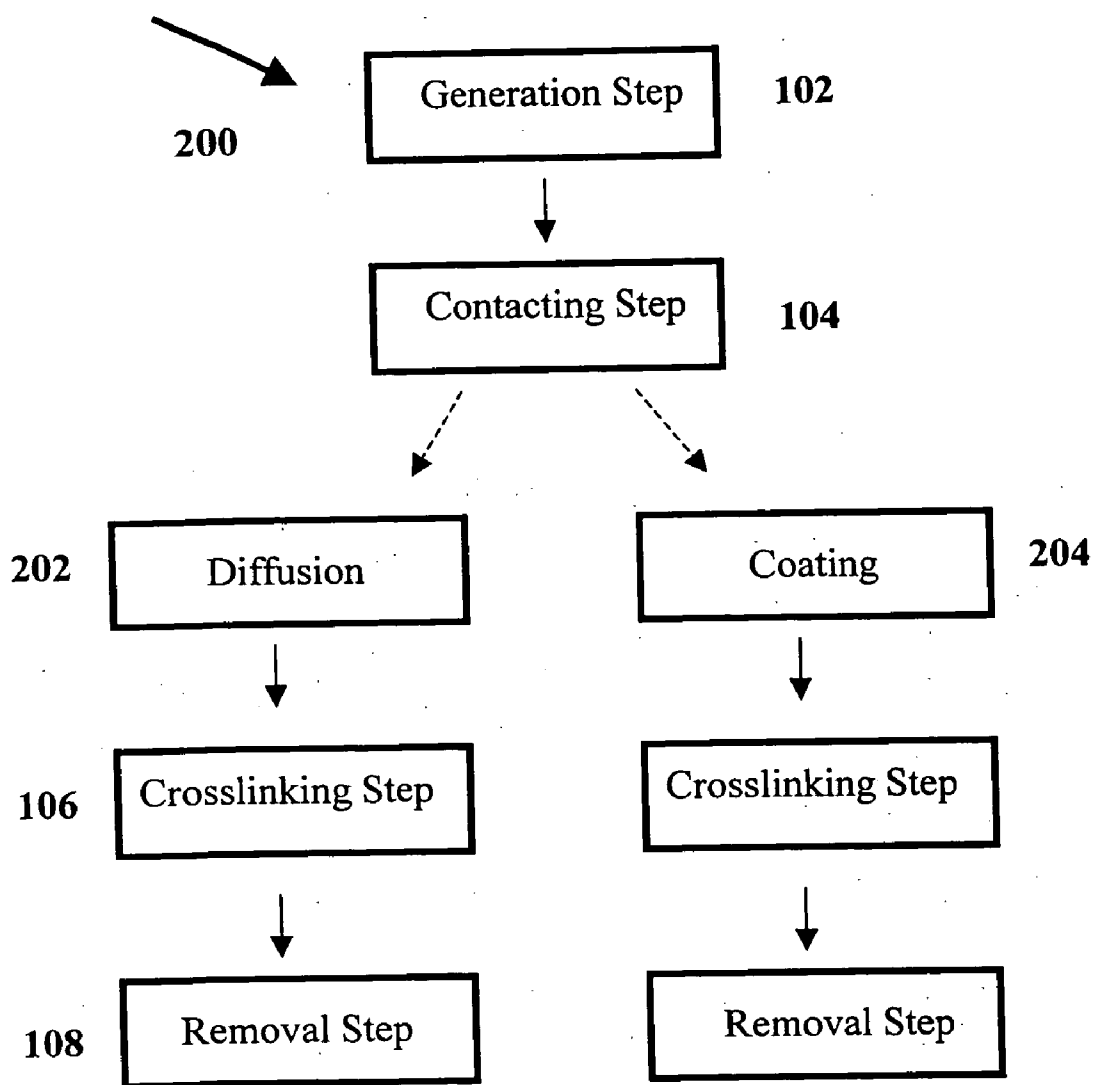


FIG. 2

PROCESSES FOR MANUFACTURING POLYMERIC MICROSPHERES

TECHNICAL FIELD

[0001] This invention generally relates to polymeric microspheres and processes of manufacturing polymeric microspheres.

BACKGROUND INFORMATION

[0002] Microparticles, microcapsules and microspheres have important applications in the medical, pharmaceutical, agricultural, textile and cosmetics industries as delivery vehicles, cell culture substrates or as embolization agents.

[0003] Polymeric microspheres, i.e., microspheres formed (at least in part) from a crosslinkable polymer, have found a variety of uses in the medical and industrial areas. They may be employed, for example, as drug delivery agents, tissue bulking agents, tissue engineering agents, and embolization agents. Accordingly, there are numerous methods directed toward preparing polymeric microspheres. These methods include dispersion polymerization of the monomer, potentiometric dispersion of a dissolved crosslinkable polymer within an emulsifying solution followed by solvent evaporation, electrostatically controlled extrusion, and injection of a dissolved crosslinkable polymer into an emulsifying solution through a porous membrane followed by solvent evaporation.

[0004] Additional methods include vibratory excitation of a laminar jet of monomeric material flowing in a continuous liquid medium containing a suitable suspending agent, irradiation of slowly thawing frozen monomer drops, and continuous injection of a dissolved crosslinkable polymer into a flowing non-solvent through a needle oriented in parallel to the direction of flow of the non-solvent.

[0005] These methods known in the art have shortcomings that may curtail the formation of uniformly sized microspheres of small diameter ranges (e.g., in the range of 100-600 microns) for various applications, particularly when the base material has a high viscosity.

SUMMARY OF THE INVENTION

[0006] The present invention facilitates production of small, uniformly sized polymeric microspheres in a manner not limited, in terms of obtainable size range, by the viscosity or density of the structural polymer.

[0007] In one aspect, a process of the invention includes generating spherical beads or particles of a desired or predetermined size from a suitable template polymer, contacting the beads or particles with a structural polymer, such as polyvinyl alcohol, and crosslinking the structural polymer into the beads or particles. The template polymeric material may subsequently be removed, resulting in polymeric microspheres.

[0008] As used herein, the term "template" polymer refers to a soluble polymer that is used to create temporary particle forms (i.e., beads), which may be porous or non-porous depending on the template polymer that is selected. A "structural" polymer invades or surrounds the temporary form and, following crosslinking, creates the permanent structure of the particle. Structural polymers are generally

chemically crosslinkable, i.e., crosslink through the formation of covalent bonds. Chemically crosslinkable polymers may be crosslinked through, for example, photoinitiation or other application of actinic radiation, by exposure to a chemical crosslinking agent or thermal energy or through freeze-thaw cycles.

[0009] In a preferred embodiment, a process of the invention includes generating spherical beads of a desired size from a starting material including a porous template polymer and a solvent; diffusing the structural polymer into the beads; and crosslinking at least the structural polymer. The solidified template polymer may exhibit a porosity gradient, from the outside to the inside of the beads, which determines the manner and extent to which the structural polymer diffuses into the beads. Alternatively, the template may have homogeneous porosity. The template polymer is subsequently removed, leaving behind a microsphere composed of only the structural polymer. In this way, the process of the invention overcomes the problem associated with generation of smaller-sized polymeric microspheres from viscous polymer solutions, by starting with particles of a desired size and subsequently contacting the particles with a structural polymer.

[0010] In an alternative embodiment of the diffusion method, spherical beads of a desired size are generated from starting material including a template polymer and a crosslinking agent. The structural polymer is diffused into the beads. The inclusion of a crosslinking agent in the starting material causes the structural polymer to crosslink into the beads upon contact therewith. The template polymer is subsequently removed, resulting in the formation of polymeric microspheres.

[0011] In another preferred embodiment, a process of the invention includes generating spherical particles or beads of a desired predetermined size from a starting material including a generally non-porous template polymer, such as methacrylate, and contacting the beads with a structural polymer. To prevent premature damage to the beads, the template polymer in this case should not dissolve in the carrier of the structural polymer. The latter polymer is subsequently crosslinked and the template polymeric material is removed, leaving behind intact hollow polymeric spherical particles. In this embodiment the beads are coated on the outside surface with a generally uniform layer of the structural polymer, as opposed to the structural polymer diffusing within the beads. The beads can be either soaked in a solution containing the structural polymer, or the structural polymer can be sprayed or otherwise applied onto the outer surfaces of the beads. The structural polymer can be crosslinked, whether diffused within or applied onto the outer surface of the particles or beads, by a chemical crosslinking agent such as formaldehyde or glutaraldehyde, or by exposure to actinic or thermal energy.

[0012] The size of the beads can be determined or influenced by passing the mixture including a template polymer through a droplet generator with a nozzle adapted to generate droplets of a predetermined size, and subsequently depositing the droplets into a gelling solution to solidify the droplets, resulting in spherical beads. The size distribution of the beads can be improved by sieving.

[0013] Alternatively, a generally non-porous template polymer, such as methacrylate, can be used for generation of beads using spheronization technology known in the art.

[0014] In a preferred embodiment of the invention, a desired size for the resulting polymeric microspheres is in the range 1-50 microns diameter. Other desirable size ranges for the polymeric microspheres include microspheres in the size range 50-100 microns diameter, microspheres in the size range 100-600 microns diameter and microspheres in the size range 600-1000 microns diameter.

[0015] The foregoing and other objects, aspects, features and advantages of the invention will become more apparent from the following description and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] The foregoing and other objects of the invention and the various features thereof may be more fully understood from the following description when read together with the accompanying illustrative flowcharts in which like reference characters generally refer to the same parts throughout the different illustrations.

[0017] **FIG. 1** is an illustrative flow diagram depicting the basic steps involved in a process of the invention.

[0018] **FIG. 2** is an illustrative flow diagram representing the steps involved in a process of the invention, where the contacting step is carried out by either diffusion or coating.

DETAILED DESCRIPTION OF THE INVENTION

[0019] The methods of the invention facilitate the generation of polymeric microspheres of size ranges smaller than 600 microns diameter by forming template beads or particles of a predetermined size and subsequently contacting the beads with a structural polymer. Polymeric microspheres of size ranges smaller than 600 microns can be generated by diffusing a structural polymer, such as polyvinyl alcohol, within spherical beads of a predetermined size made from a starting material including a template polymer such as alginate, chitosan, etc. Diffusion of the structural polymer into the beads can be achieved by, for example, soaking the beads in a solution of the structural polymer. The porous nature of the beads favors the diffusion of the polymer into the beads. Alternatively, this process may be carried out under conditions that enhance diffusion, e.g., the addition of a surfactant, elevated temperature and/or pressure.

[0020] Polymeric microspheres of size ranges smaller than 600 microns diameter can also be generated by coating the outer surface of prefabricated beads or particles made from a template polymer, such as methacrylate, with a structural polymer. In this case, the beads are generally non-porous in morphology and receive a substantially even coating of the structural polymer either by, for example, soaking the beads in a solution or suspension of a structural polymer or by spraying the outer surface of the beads with such a solution or suspension.

[0021] **FIG. 1** shows a flow chart **100** illustrating the basic steps involved in a process of the invention. The prefabrication or generation step **102** includes formation of spherical beads or particles of a predetermined size from a starting material containing a template polymer. In one embodiment, the starting material includes a template polymer and a solvent.

[0022] In general, the role of the template polymer is to act as a removable carrier to encapsulate or support the struc-

tural polymer, which is introduced in a subsequent step. Accordingly, the template polymer will be soluble in a solvent that does not attack the crosslinked structural polymer, and may be, for example, an ionically crosslinkable material. Omission of the structural polymer at this stage enables the formation of uniformly sized spherical beads of small size ranges, preferably smaller than 600 microns diameter.

[0023] Suitable porous template polymers include, for example, alginates, polysaccharides, carrageenans, chitosan, hyaluronic acid, or other ionically crosslinkable polymers (also known as "shape-forming agents"), such as the classes of carboxylic-, sulfate-, or amine-functionalized polymers. The template polymer can also be generated from a blend of one or more of the above synthetic or naturally occurring materials, or derivatives thereof. In one preferred embodiment of the invention, the template polymer is an alginate, which is ionically crosslinkable.

[0024] The solvent utilized in a process of the invention is chosen based on several considerations. Firstly, the solvent should be easily removable by evaporation, and should therefore have a relatively low boiling point. The solvent should be capable of dissolving the starting material without interfering with the structural polymer crosslinking. Absence of any environmental contaminants and ease of disposal are also worthwhile criteria in the selection of the solvent. Deionized water and saline solution are preferred as solvents; however, solvents can also be selected from polar and nonpolar laboratory solvents, such as, for example, acetone, methane and ethanol (which are polar), or hexane and benzene (nonpolar).

[0025] The generation step **102** is followed by the contacting step **104**, which involves contacting the prefabricated spherical beads or particles with a structural polymer. The crosslinking step **106** involves crosslinking the structural polymer into the beads or particles. The last step **108**, involves the removal of the template polymer from the beads, resulting in the formation of polymeric microspheres. The template polymer is removed by soaking the beads in a suitable solvent.

[0026] The structural polymer utilized in the contacting step **104** can be selected from a wide variety of generally chemically crosslinkable polymers such as, for example, vinyl polymers, polyacrylamides, polyethylene glycol, polyamides, polyureas, polyurethanes, polyvinyl alcohols, and derivatives thereof. For some (e.g., embolic) applications, a hydrophilic polymer, such as polyvinyl alcohol, will be preferred.

[0027] The structural polymer is subsequently crosslinked in step **106** by a crosslinking agent. The crosslinking agent can be a chemical agent such as, for example, formaldehyde or glutaraldehyde, or the like thereof. The structural polymer can also be crosslinked by application of photoinitiation, an ionic agent or actinic radiation such as, for example, ultraviolet or gamma radiation, or an electron beam.

[0028] The porosity of the outer polymeric shell can be controlled by the addition to the polymeric solution of a filler agent, such as starch, that is not crosslinked in the crosslinking step and can be removed easily by rinsing the beads.

[0029] The size of the polymeric particles depends on the method used for generating the spherical beads. Several

techniques can be utilized for the generation of spherical particles or beads from a suitable starting material. A droplet generator can produce spherical droplets of a predetermined diameter by forcing a jet stream of a solution containing a template polymer and a solvent through a nozzle, which is subjected to a periodic disturbance to break up the laminar jet stream into droplets. This may involve the use of a nozzle having, for example, an electrostatic or piezoelectric element. The size of the droplets depends on the frequency at which the element is driven. The uniformly sized droplets fall into a solution containing a positively or a negatively charged agent, such as calcium or barium, or a charged polymer, such as polyacrylic acid, resulting in the conversion of the liquid droplets into solid beads.

[0030] The manner in which liquid droplets are solidified affects the properties of the particles. Ca^{2+} , for example, is a strong gelling ion, so a high concentration of, for example, CaCl_2 will create an inwardly moving gelling zone as the droplet solidifies. This creates a high porosity gradient, with the solidified particle exhibiting a smooth exterior with minimal porosity (e.g., microporous with an average pore size of 10 microns or less) and increasing porosity (e.g., up to about 50 microns) at the particle core. By adding non-gelling ions (e.g., Na^+ in the form of NaCl) to the solution in order to compete with the gelling ions, it is possible to limit the porosity gradient, resulting in a more uniform intermediate porosity throughout the particle. The porosity of the particle, in turn, affects the distribution of the structural polymer. A higher porosity gradient will result in concentration of the structural polymer on the surface of the particle and, following removal of the template polymer, a relatively hollow sphere. A lower porosity gradient, by contrast, will result in a more even distribution of the structural polymer throughout the particle, and a more densely crosslinked finished sphere.

[0031] In an alternative embodiment, beads are generated from a mixture of a template polymer and a crosslinking agent, such as formaldehyde or glutaraldehyde. The beads are contacted with a structural polymer and the template polymer is subsequently removed, resulting in the formation of polymeric spherical particles. Thus, by inclusion of a crosslinking agent in the starting material for generating the beads, this embodiment eliminates the need for a discrete crosslinking step 106.

[0032] FIG. 2 shows a flow chart 200 illustrating the various steps in particular embodiments of the invention, where the contacting step 104 includes diffusion 202 or coating 204. The contacting step employing diffusion 202 is based on diffusing the structural polymer into the prefabricated beads, generated from a starting material including a template polymer and a solvent. Diffusion can be achieved by, for example, soaking the beads in a solution of the structural polymer.

[0033] The contacting step employing coating 204 is based on application of a uniform layer of the structural polymer on the outer surface of the beads. The structural polymer can be applied by, for example, spraying the polymer on the surfaces of prefabricated beads made from a generally non-porous template polymer, such as methacrylate, or soaking such beads in a solution of a structural polymer. An even spray-coating of the microspheres can be achieved by, for example, suspending the beads in air while spraying.

[0034] The structural polymer is crosslinked into the beads in step 106. The template polymer, which generally comprises a porous polymer in the diffusion embodiment 202, and a non-porous polymer in the coating embodiment 204, is subsequently removed in step 108. The end product is microspheres of a desired predetermined size and composed of the structural polymer. Ionically crosslinkable materials, such as, for example, shape-forming agents are dissolved using suitable solvents, such as a solution of sodium hexametaphosphate or ethylene diamine tetraacetic acid (EDTA), that leave the structural polymer intact, thereby resulting in polymeric microspheres. The methacrylate in the coating embodiment 204 can be removed by soaking the beads in acetone or another solvent that removes the methacrylate without dissolving the outer polymeric shell, resulting in hollow polymeric spheres.

[0035] Formation of porous particles is discussed above. To form non-porous beads of suitably small diameter, techniques such as spheronization may be used. Ultimately, the size of the hollow polymeric microspheres can be controlled by the size of the preformed beads and the thickness of the polymeric layer.

[0036] Spheronization techniques, which are well-characterized in the art, generate beads that have low surface to volume ratios and smooth surfaces, to allow for the application of uniform layer of the structural polymer. A device called a spheronizer comprises a rotating frictional plate enclosed within a hollow cylinder with a slim clearance between the edges of the rotating base plate and the cylinder wall. Spheronization typically begins with damp extruded particles, such as particles generated by grinding an agglomerated mass of a soluble polymer, such as methacrylate. The extruded particles are broken into uniform lengths and gradually transformed into spherical shapes while rotating on the base plate of the spheronizer. The resulting spherical beads have low surface to volume ratios and smooth surfaces to achieve even coating of the structural polymer on the surfaces thereof.

[0037] In still another embodiment, the beads are ice crystals. The ice crystals are removed simply by exposing the microspheres to elevated temperatures.

[0038] The invention is illustrated further by the following non-limiting examples.

EXAMPLE 1

[0039] An aqueous solution of 2% sodium alginate was infused through a droplet generator directly into a 2% CaCl_2 bath. The parameters used for the droplet generator were a nozzle 300 microns in diameter; a flow rate of 10 ml/min; and a frequency of 260 Hz. The CaCl_2 solution was decanted and the resulting calcium alginate beads were soaked overnight in an 8% polyvinyl alcohol (PVA) aqueous solution accompanied by slow stirring. The PVA-infused beads were subsequently recovered using a sieve and crosslinked by soaking the beads in a mixture of 3% formaldehyde/20% sulfuric acid at 60° C. for 20 minutes. The alginate was removed from the beads by soaking the beads in 5% sodium hexametaphosphate for 1 hour, resulting in PVA microspheres of 600 microns diameter.

[0040] The absence of non-gelling ions resulted in a heterogeneous distribution of the PVA within the particle,

with a high concentration at the surface of the particle and a relatively low concentration at the center, resulting in a hollow microsphere.

EXAMPLE 2

[0041] A solution of 2% alginate was injected through a droplet generator using a nozzle of 200 micron diameter; a frequency of 660 Hz; and a flow rate of 5 ml/min. The droplets were slowly stirred into a solution of 2% CaCl₂ solution. The resultant calcium alginate beads were soaked overnight in an 8% polyvinyl alcohol solution, sieved and recovered. The polyvinyl alcohol was crosslinked by soaking the beads in a solution of 4% formaldehyde/20% sulfuric acid at 60° C. for 25 minutes. The alginate was removed by soaking the beads in a 5% sodium hexametaphosphate solution at room temperature, resulting in PVA microspheres of 400 microns diameter.

[0042] The absence of non-gelling ions resulted in a heterogeneous distribution of the PVA within the particle, with a high concentration at the surface of the particle and a relatively low concentration at the center, resulting in a hollow microsphere.

What is claimed is:

1.-36. (canceled)

37. A particle comprising a polymer and having a core region and an exterior region, wherein the core region includes first pores having a first average pore size and the exterior region includes second pores having a second average pore size that is smaller than the first average pore size.

38. The particle of claim 37, wherein the polymer is crosslinked.

39. The particle of claim 37, wherein the polymer is selected from the group consisting of vinyl polymers, poly-

acrylamides, polyethylene glycol, polyamides, polyureas, polyurethanes, and derivatives thereof.

40. The particle of claim 37, wherein the polymer comprises a hydrophilic polymer.

41. The particle of claim 37, wherein the polymer comprises polyvinyl alcohol.

42. The particle of claim 37, wherein the first pores have a first average pore size of up to about 50 microns.

43. The particle of claim 42, wherein the second pores have a second average pore size of 10 microns or less.

44. The particle of claim 37, wherein the second pores have a second average pore size of 10 microns or less.

45. The particle of claim 37, wherein the particle has a diameter of smaller than 600 microns.

46. The particle of claim 37, wherein the particle has a diameter of from one micron to 50 microns.

47. The particle of claim 37, wherein the particle has a diameter of from 50 microns to 100 microns.

48. The particle of claim 37, wherein the particle has a diameter of from 100 microns to 600 microns.

49. The particle of claim 37, wherein the particle has a diameter of from 600 microns to 1000 microns.

50. A particle comprising a polymer comprising polyvinyl alcohol, the particle having a core region and an exterior region, wherein the core region includes first pores having a first average pore size of up to about 50 microns and the exterior region includes second pores having a second average pore size of 10 microns or less.

51. The particle of claim 50, wherein the particle has a diameter of smaller than 600 microns.

52. The particle of claim 50, wherein the particle has a diameter of from 600 microns to 1000 microns.

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