CORE-SHELL MICROSPHERES

Field

[0001] The invention relates to core-shell microspheres, processes for making them and uses thereof. This application claims priority from US provisional application number 61/495,328, the entire contents of which are incorporated herein by cross-reference.

Background

[0002] In many applications there is a need for controlled release of a substance to a medium. This need has in the past been addressed by encapsulating the substance in particles which release the substance over time. It has been a challenge to accurately control the rate of release of the substance to the medium. A further challenge is to introduce a delay period for release of the substance. Such a delay period may, for example, be desirable in cases where some time is required for the particles containing the substance to reach their desired destination in order to release the substance in the most effective location. Such a delay may also be desirable for the sequential delivery of multiple active substances each at different timepoints in the patient's treatment regime, or for cyclic delivery of multiple different hormones.

[0003] The present invention is designed to at least partially satisfy the above stated needs.

Summary ~~of Invention~~

[0004] Aspects of the disclosure~~invention~~ are as set out below.

[0005] A substance comprising a plurality of microparticles, said microparticles comprising a core comprising a first polymer and a shell surrounding said core and comprising the first polymer and a second polymer, said second polymer being less rapidly degradable than the first polymer. The first polymer in the shell may be in the form of continuous pathways passing through said shell.

[0005a] In one aspect, there is provided a substance comprising a plurality of microparticles, said microparticles comprising: a core comprising a first polymer; and a shell surrounding said core and comprising the first polymer and a second polymer, said second polymer being less rapidly degradable than the first polymer, wherein the first polymer forms a plurality of continuous pathways through the shell.

[0006] The substance of paragraph [0005] wherein the second polymer is less rapidly biodegradable than the first polymer.

[0030] The substance of paragraph [0029] wherein the releasable material is dispersible in, or soluble in, water.

[0031] The substance of any one of paragraphs [0020] to [0028] wherein the releasable material is hydrophobic.

[0032] The substance of paragraph [0031] wherein the releasable material is substantially insoluble in water.

[0033] The substance of any one of paragraphs [0005] to [0032] wherein the microparticles are dispersed in a carrier.

[0034] The substance of paragraph [0033] wherein the carrier is a hydrogel, a membrane or a scaffold.

[0035] The substance of any one of paragraphs [0005] to [0033] wherein the microparticles are at least partially adhered together to form a solid mass.

[0036] A process for making a substance comprising a plurality of microparticles, optionally for making the substance of any one of paragraphs [0005] to [0035], said process comprising: combining a first solution comprising a first polymer in a first solvent, and a second solution comprising a second polymer in a second solvent, to form a mixed polymer solution, said second polymer being less rapidly degradable than the first polymer and the first and second polymers being at least partially immiscible, optionally substantially immiscible, and said first and second solvents being miscible with each other; emulsifying the mixed polymer solution in an aqueous medium to form an emulsion, said aqueous medium being at least partially immiscible with the first and second solvents; aging the emulsion for sufficient time to allow for at least partial separation of the first polymer and the second polymer within droplets of the emulsion so as to form a core comprising the first polymer and a shell surrounding the core and comprising the first polymer and the second polymer; and removing the first and second solvents to form the substance as an aqueous suspension, wherein the microparticles each comprise a core comprising the first polymer and a shell surrounding said core and comprising the first polymer and the second polymer.

[0036a] In another aspect, there is provided a process for making a substance comprising a plurality of microparticles, said process comprising: combining a first solution comprising a first polymer in a first solvent, and a second solution comprising a second polymer in a second solvent, to form a mixed polymer solution, said second polymer being less rapidly degradable than the first polymer and the first and second polymers being at least partially immiscible, optionally substantially immiscible, and said first and second solvents being miscible with each other; emulsifying the mixed polymer solution in an aqueous medium to form an emulsion, said aqueous medium being at least partially immiscible with the first and second solvents, wherein the aqueous medium is at least partially saturated with the first solvent and/or the second solvent; aging the emulsion for sufficient time to allow for at least partial separation of the first polymer and the second polymer within droplets of the emulsion so as to form a core comprising the first polymer and a shell surrounding the core and comprising the first polymer and the second polymer; and removing the first and second solvents to form the substance as an aqueous suspension, wherein the microparticles each comprise a core comprising the first polymer and a shell surrounding said core and comprising the first polymer and the second polymer, wherein the first polymer forms a plurality of continuous pathways through the shell.

[0037] The process of paragraph [0036] wherein the first and second solvents are the same.

aging and solvent extraction are for sufficient time to allow for at least partial separation of the first polymer and the second polymer within droplets of the emulsion so as to form a core comprising the first polymer and a shell surrounding the core and comprising the first polymer and the second polymer.

[0060] The process of any one of paragraphs [0036] to [0059] wherein the first and second solvents are partially miscible with the aqueous liquid and the step of removing the solvent(s) comprises diluting the particulate substance as aqueous suspension with the aqueous liquid which has neither the first nor the second solvent therein.

[0061] The process of any one of paragraphs [0036] to [0060] comprising separating the particulate substance from the aqueous liquid.

[0062] The process of paragraph [0061] comprising heating the separated particulate substance in a mould for sufficient time and at sufficient temperature to cause the microparticles to adhere together so as to form pellets of the particulate substance.

[0063] The process of paragraph [0062] wherein the sufficient temperature is the glass transition temperature of the second polymer.

[0064] The process of paragraph [0062] or [0063] wherein the first solution comprises a releasable material and the sufficient temperature is below the temperature at which said releasable material degrades over the sufficient time.

[0065] In another aspect, there is provided a~~A~~ method for delivering a material to a liquid comprising exposing a substance as described herein~~according to paragraph [0005]~~ to said liquid in the presence of a degrading agent which is capable of degrading the first polymer, said substance being one in which the cores of the microparticles contain the material.

[0066] The method of paragraph [0065] wherein the liquid is, or comprises, the degrading agent.

[0067] The method of paragraph [0065] or [0066] which is for a non-therapeutic, non-diagnostic purpose.

[0068] The method of paragraph [0065] or [0066] wherein the material is a therapeutic substance and the liquid is a bodily fluid, whereby the method is for delivering the therapeutic substance to a patient.

[0069] The method of paragraph [0068] wherein the patient is a non-human.

[0070] The method of any one of paragraphs [0065] to [0069] wherein the microparticles of the substance are adhered together.

[0071] Use of a substance according to paragraph [0020] for the treatment of a condition in a patient, optionally a non-human patient, wherein the releasable material is indicated for treatment of said condition.

[0071a] In another aspect, there is provided the use of a substance as defined above in the manufacture of a medicament for the treatment of a condition in a patient, optionally a non-human patient, wherein the releasable material is indicated for treatment of said condition.

[0072] Use according to paragraph [0071], wherein the condition is pain and the releasable material is an analgesic.

[0073] Use of a substance according to paragraph [0071] wherein the condition is glaucoma, wherein the releasable material is indicated for treatment of glaucoma.

[0074] Use according to paragraph [0073] wherein the releasable material is brimonidine tartarate.

[0075] Use according to paragraph [0071] wherein the releasable material is an antifibrotic agent.

[0076] Use according to paragraph [0075] wherein the antifibrotic agent is fluorouracil.

[0076a] In another aspect, there is provided the substance as defined above for use in therapy.

[0077] In another aspect, there is provided a~~A~~ composite substance comprising at least two different substances, each of said substances being a substance as described herein~~according to any one of paragraphs [0005] to [0033]~~, wherein: the cores of the microparticles of each of the substances comprises a releasable material; and the shells of the microparticles of the different substances are such that they degrade over different times under the same conditions, whereby the releasable materials of in the microparticles of the different substances are capable of releasing sequentially.