There is therefore a need to provide a polymeric system that can suppress the initial burst release that overcomes, or at least ameliorates, one or more of the disadvantages described above.

Summary

According to the disclosure, there is provided a polymeric system for release of an active agent, comprising a first polymeric phase containing the active agent, said first polymeric phase forming discrete regions of a set size range and being dispersed within a second polymeric phase comprising a cross-linked polymer-phenol conjugate for release of the active agent therein.

According to a first aspect, there is provided a polymeric system for release of an active agent, having a first polymeric phase comprising polyethylene glycol (PEG) and containing the active agent as a PEG-conjugated active agent, the first polymeric phase forming discrete regions of a set size range and being dispersed within a second polymeric phase comprising a cross-linked dextran-tyramine conjugate for release of the active agent therein, wherein said PEG conjugated-active agent preferentially partitions to said first polymeric phase as compared to said second polymeric phase.

The first polymeric phase may act as a reservoir for the active agent, and entrap or release the active agent upon changes in the concentration of the active agent in the second polymeric phase. When the active agent is released from the polymeric system, the active agent in the first polymeric phase may move from the first polymeric phase to the second polymeric phase. As a result, the concentration of the active agent in the second polymeric phase advantageously remains substantially constant for prolonged periods of time.

The set size range of the discrete regions of the first polymeric phase may control the rate of release of the active agent. The set size range may be selected by controlling the rate of cross-linking of the second

the discrete regions of the first polymer phase having the active agent therein.

In another aspect, there is provided a method for forming a polymeric system for release of an active agent, having a first polymeric phase comprising polyethylene glycol (PEG) and containing the active agent as a PEG-conjugated active agent, the first polymeric phase forming discrete regions of a set size range and being dispersed within a second polymeric phase comprising a cross-linked dextran-tyramine conjugate for release of the active agent therein, wherein said PEG conjugated-active agent preferentially partitions to said first polymeric phase as compared to said second polymeric phase, the method comprising the steps of:

a. providing an aqueous reaction mixture comprising a first polymeric phase polymer, a dextran-tyramine conjugate and a PEG-conjugated active agent; and

b. controlling the rate of cross-linking of the dextran-tyramine conjugate during formation of the second polymeric phase by adding a catalyst to the aqueous reaction mixture to thereby control the set size range of the discrete regions of the first polymeric phase having the PEG-conjugated active agent therein.

Definitions

The following words and terms used herein shall have the meaning indicated:

The term "phase", as used in the context of the present specification, is intended to refer to a distinct, homogeneous and immiscible part of a polymeric system that may be physically separated from the rest of the polymeric system. One phase of the polymeric system may be dispersed or surrounded by a second phase, which is a continuous phase.

The word "polymer" or "polymeric" refers to a molecule having two or more monomeric repeat units. It includes linear and branched polymer structures, and also encompasses cross-linked polymers as well as copolymers

CLAIMS

1. A polymeric system for release of an active agent, having a first polymeric phase comprising polyethylene glycol (PEG) and containing the active agent as a PEG-conjugated active agent, said first polymeric phase forming discrete regions of a set size range and being dispersed within a second polymeric phase comprising a cross-linked dextran-tyramine conjugate for release of the active agent therein, wherein said PEG conjugated-active agent preferentially partitions to said first polymeric phase as compared to said second polymeric phase.

2. The polymeric system of claim 1, wherein the second polymeric phase has been formed by utilizing an agent that controls the rate of cross-linking during formation of said second polymeric phase to thereby control the set size range of the discrete regions of the first polymer phase.

3. The polymeric system of claim 2, wherein the agent that controls the rate of cross-linking during polymerization is a catalyst.

4. The polymeric system of claim 3, wherein said catalyst is selected from the group consisting of horseradish peroxidase, human myeloperoxidase, lactoperoxidase, eosinophil peroxidase, thyroid peroxidase, prostaglandin H synthases, soybean peroxidase, hemin, hematin, microperoxidase-11, and cytochrome c.

5. The polymeric system of any one of claims 2 to 4, wherein the concentration of said agent is changed in order to control the rate of cross-linking.

6. The polymeric system of any one of the preceding claims, wherein the rate of release of said

active agent from said polymeric system is dependent on the size of said discrete regions.

7. The polymeric system of claim 6, wherein smaller discrete regions result in a slower release rate of said active agent from said polymeric system as compared to larger discrete regions.

8. The polymeric system of any one of the preceding claims, wherein the release rate of said active agent from said polymeric system is 0.5 to 20% per day.

9. The polymeric system of any one of the preceding claims, wherein the size of said discrete regions is in the micron-range or the nano-range.

10. The polymeric system of claim 9, wherein the size of said discrete regions is in the range selected from the group consisting of 1 µm to 150 µm, 1 µm to 10 µm, 1 µm to 20 µm, 1 µm to 30 µm, 1 µm to 40 µm, 1 µm to 50 µm, 50 µm to 150 µm, 10 µm to 150 µm, 20 µm to 150 µm, 30 µm to 150 µm, 40 µm to 100 µm, 5 µm to 100 µm and 1 µm to 100 µm.

11. The polymeric system of any one of the preceding claims, wherein the discrete regions form microdomains, microspheres or microcapsules in said second phase.

12. The polymeric system of claim 1, wherein the degree of substitution of said dextran polymer is from 1 to 30.

13. The polymeric system of any one of the preceding claims, wherein said active agent is selected from the group consisting of proteins, antibodies, peptides, small-molecule drugs, nucleic acid-based drugs, nanoparticulate systems and mixtures thereof.

14. The polymeric system of claim 1, wherein greater than 20% of said conjugated-active agent is

present in said first phase as compared to said second phase.

15. The polymeric system of any one of claims 1 to 14, wherein said PEG conjugated-active agent is PEGinterferon alpha-2a (PEGASYS), PEGylated L-asparaginase (Oncaspar), PEG-adenosine deaminase (Adagen), PEGinesatide (Omontys), PEGylated uricase (Pegloticase), PEGylated hyaluronidase, PEGylated epidermal growth factor, PEGylated tumor necrosis factor, PEGylated tumor necrosis factor-related apoptosis-inducing ligand (PEG-TRAIL), certolizumab pegol (Cimzia), PEGylated erythropoetin (Mircera), PEGaptanib (Macugen), PEGylated recombinant methionyl human granulocyte colony-stimulating factor (Neulasta), PEG-human growth hormone mutein antagonists (Somavert) and PEGylated interferon alpha-2b (Pegintron).

16. The polymeric system of any one of claims 1 to 15, wherein said polymeric system is an injectable hydrogel.

17. The polymeric system of claim 16, wherein said hydrogel is formed *in situ*.

18. A carrier for delivering a biologically active substance or a drug, comprising the polymeric system of claim 16 or 17.

19. A method for forming a polymeric system for release of an active agent, having a first polymeric phase comprising polyethylene glycol (PEG) and containing the active agent as a PEG-conjugated active agent, said first polymeric phase forming discrete regions of a set size range and

being dispersed within a second polymeric phase comprising a cross-linked dextran-tyramine conjugate for release of the active agent therein, wherein said PEG conjugated-active agent preferentially partitions to said first polymeric phase as compared to said second polymeric phase, the method comprising the steps of:

a. providing an aqueous reaction mixture comprising a first polymeric phase polymer, a dextran-tyramine conjugate and a PEG-conjugated active agent; and

b. controlling the rate of cross-linking of said dextran-tyramine conjugate during formation of said second polymeric phase by adding a catalyst to said aqueous reaction mixture to thereby control the set size range of the discrete regions of the first polymeric phase having the PEG-conjugated active agent therein.

20. The method of claim 19, comprising the step of selecting the concentration of said catalyst to thereby control the rate of cross-linking of said second polymeric phase.

21. The method of any one of claims 19 to 20, wherein said cross-linking step involves the formation of a C-C bond or C-O bond between a pair of dextran-tyramine conjugates.

22. The method of any one of claims 19 to 21, comprising the step of adding an oxidizing agent to said reaction mixture.

23. The method of any one of claims 19 to 22, wherein said crosslinking is carried out for 1 to 60 minutes.

24. The method of any one of claims 19 to 23, wherein said crosslinking is carried out at a temperature of 4°C to 40°C.

25. The method of claim 19, wherein said catalyst is an enzyme selected from horseradish peroxidase, human myeloperoxidase, lactoperoxidase, eosinophil peroxidase, thyroid peroxidase, prostaglandin H synthases, soybean peroxidase, hemin, hematin, microperoxidase-11, and cytochrome c.

26. The method of any one of claims 19 to 24, wherein said oxidizing agent is a peroxide selected from hydrogen peroxide, sodium peroxide, potassium peroxide, hydrogen superoxide, potassium superoxide, alkyl peroxides, aryl peroxides, acyl peroxides, organic hydroperoxides, organic peracids, sodium percarbonate, ammonium persulfate and perborates.