MARKED-UP COPY OF CLAIMS

WHAT IS CLAIMED IS

1. – 20. (canceled)

~~21~~1. A plurality of microparticles having diameters ranging from ~~about~~ 2 µm to ~~about~~ 70 µm, as determined by microflow imaging (MFI), comprising a VEGF-Trap protein particle core of ~~about~~ 2 µm to ~~about~~ 12 µm in diameter, as determined by MFI, and a biodegradable polymer cortex, wherein (a) the protein particle core consists of VEGF-Trap, (b) the biodegradable polymer cortex comprises polyorthoester (POE), poly (lactic acid) (PLA), or poly-D,L-lactide-co-glycolide (PLGA), and (c) the VEGF-Trap is released at a rate of 0.01 mg per week to 0.30 mg per week in an aqueous environment over the course of at least 60 days.

~~22~~2. The plurality of microparticles of claim ~~21~~ 1, wherein the VEGF-Trap consists of a dimer of a polypeptide comprising the amino acid sequence SEQ ID NO:1 ~~microparticles degrade at different rates and the protein is released in an aqueous environment over an extended period of time~~.

23. – 29. (canceled)

~~30~~3. The plurality of microparticles of claim 1 or claim 2 for use in a [~~A~~] method of treating [~~a~~] an ocular disease~~, comprising administering to a patient a therapeutically effective amount of a plurality of microparticles of any one of claims 21-29, wherein a therapeutic protein is released from the microparticles over an extended period of time~~.

31. – 32. (canceled)

MARKED-UP COPY OF CLAIMS

~~33~~4. A method of manufacturing a composition comprising a VEGF-Trap protein and a biodegradable polymer selected from the group consisting of POE, PLA, and PLGA, the method comprising the steps of:

a. obtaining a VEGF-Trap protein particle by spray drying a solution comprising the VEGF-Trap protein;

b. suspending the protein particle in a solution comprising the polymer and a solvent; and

c. removing the solvent,

wherein a particle having an average diameter of 15 µm is formed comprising the protein coated with the polymer.

~~34~~5. The method of claim ~~33~~4, wherein the protein particle is obtained by spray drying a solution comprising the protein.

~~35~~6. The method of claim 4[~~34~~], wherein the spray drying is performed by dual-nozzle sonication, single-nozzle sonication, or electrospray.

~~36~~7. The method of claim 6 ~~any one of claims 33-35~~, wherein the solvent is evaporated by creating a dispersion of the protein suspension of step (b) by spray drying.

37. – 50. (canceled)

WHAT IS CLAIMED IS

1. A composition comprising a protein coated with a polymer, wherein the composition is a particle with a diameter of from about 5 μm to about 40 μm.
2. The composition of claim 1, wherein the protein is an antigen-binding protein.
3. The composition of claim 1 or claim 2, wherein the protein comprises an Fc domain.
4. The composition of any one of claims 1-3, wherein the protein is an antibody.
5. The composition of any one of claims 1-3, wherein the protein is a receptor-Fc-fusion protein.
6. The composition of any one of claims 1-4, wherein the protein is an antibody fragment.
7. The composition of claim 5, wherein the protein is a VEGF-Trap.
8. The composition of claim 4, wherein the antibody is a human monoclonal antibody.
9. The composition of any one of claims 1-8, wherein the polymer is a biodegradeable polymer.
10. The composition of any one of claims 1-9, wherein the polymer is selected from the group consisting of poly (lactic acid) (PLA), polyanhydride poly[1,6-bis(p-carboxyphenoxy)hexane] (pCPH), poly(hydroxbutyric acid-cohydroxyvaleric acid) (PHB-PVA), polyethylene glycol-poly (lactic acid) copolymer (PEG-PLA), poly-D,L-lactide-co-glycolide (PLGA), polyorthoester (POE), ethyl cellulose (EC), and poly-ε-caprolactone (PCL).
11. The composition of claim 10, wherein the protein is either a trap or an antibody, and the polymer is a POE.
12. The composition of any one of claims 1-11, wherein the average diameter of the particle is about 15 μm.
13. The composition of any one of claims 1-10, wherein the protein is either a trap or an antibody, and the polymer is a PLGA.
14. A microparticle having a diameter of about 2 μm to about 70 μm comprising a protein particle core of about 2 μm to about 12 μm in diameter and a biodegradable polymer cortex.
15. The microparticle of claim 14, wherein the biodegradable polymer is selected from the group consisting of poly (lactic acid) (PLA), polyanhydride poly[1,6-bis(p-carboxyphenoxy)hexane] (pCPH), poly(hydroxbutyric acid-cohydroxyvaleric acid) (PHB-PVA), polyethylene glycol-poly (lactic acid) copolymer (PEG-PLA), poly-D,L-lactide-co-glycolide (PLGA), polyorthoester (POE), ethyl cellulose (EC), and poly-ε-caprolactone (PCL).

16. The microparticle of claim 14 or claim 15, wherein the protein particle core comprises an antigen-binding protein.
17. The microparticle of any one of claims 14-16, wherein the antigen binding protein is a receptor-Fc-fusion protein.
18. The microparticle of any one of claims 14-17, wherein the protein particle core comprises a VEGF-Trap and the polymer cortex comprises POE, PLA, or PLGA.
19. The microparticle of any one of claims 14-16, wherein the antigen binding protein is an antibody.
20. The microparticle of any one of claims 14-16 and 19, wherein the antibody is a human IgG molecule, and the polymer cortex comprises POE, PLA, or PLGA.
21. A plurality of microparticles having diameters ranging from about 2 μm to about 70 μm comprising a protein particle core of about 2 μm to about 12 μm in diameter and a biodegradable polymer cortex.
22. The plurality of micorparticles of claim 21, wherein the microparticles degrade at different rates and the protein is released in an aqueous environment over an extended period of time.
23. The plurality of microparticles of claim 22, wherein the period of time is at least 3 days.
24. The plurality of microparticles of claim 22 or claim 23, wherein the period of time is at least 60 days.
25. The plurality of microparticles of any one of claims 21-24, wherein the protein is an antigen-binding protein.
26. The plurality of microparticles of any one of claims 21-25, wherein the protein is a receptor-Fc-fusion protein.
27. The plurality of microparticles of any one of claims 21-26, wherein the receptor-Fc-fusion protein is a VEGF Trap and the polymer cortex comprises POE, PLA, or PLGA.
28. The plurality of microparticles of any one of claims 21-25, wherein the antigen-binding protein is an antibody.
29. The plurality of microparticles of claim 28, wherein the antibody is a human IgG molecule and the polymer cortex comprises POE, PLA, or PLGA.
30. A method of treating a disease, comprising administering to a patient a therapeutically effective amount of a plurality of microparticles of any one of claims 21-29, wherein a therapeutic protein is released from the microparticles over an extended period of time.
31. The method of claim 30, wherein the protein is a VEGF-Trap and the polymer is POE, PLA, or PLGA.

32. The method of claim 30 or claim 31, wherein the disease is an ocular disease and the microparticles are delivered to the vitreous of the patient at no less than 60 day intervals.
33. A method of manufacturing a composition comprising a protein and a biodegradable polymer, the method comprising the steps of:
    a. obtaining a protein particle;
    b. suspending the protein particle in a solution comprising the polymer and a solvent; and
    c. removing the solvent,

    wherein a particle is formed comprising the protein coated with the polymer.
34. The method of claim 33, wherein the protein particle is obtained by spray drying a solution comprising the protein.
35. The method of claim 34, wherein the spray drying is performed by dual-nozzle sonication, single-nozzle sonication, or electrospray.
36. The method of any one of claims 33-35, wherein the solvent is evaporated by creating a dispersion of the protein suspension of step (b) by spray drying.
37. The method of any one of claims 33-36, wherein the solvent is removed by heat evaporation, air evaporation, or extraction.
38. The method of any one of claims 33-37, wherein the polymer is selected from the group consisting of poly (lactic acid) (PLA), polyanhydride poly[1,6-bis(p-carboxyphenoxy)hexane] (pCPH), poly(hydroxbutyric acid-cohydroxyvaleric acid) (PHB-PVA), polyethylene glycol-poly (lactic acid) copolymer (PEG-PLA), poly-D,L-lactide-co-glycolide (PLGA), polyorthoester (POE), ethyl cellulose (EC), and poly-ε-caprolactone (PCL).
39. The method of any one of claims 33-38, wherein the protein is a receptor-Fc-fusion protein or an antibody.
40. The method of any one of claims 33-39, wherein the protein is a VEGF-Trap or an IgG molecule, and the polymer is POE, PLA, or PLGA.
41. The method of any one of claims 33-40, wherein the particle has an average diameter of about 15 μm.
42. A method for modulating the release of a protein, comprising the step of (a) combining a protein with a biodegradable polymer to form a protein-polymer complex; followed by the step of (b) contacting the protein-polymer complex with a solvent, wherein the polymer degrades over time and the protein is gradually released into the solvent.
43. The method of claim 42, wherein step (a) is performed according to any one of claims 33-41.

44. The method of claim 42 or claim 43, wherein the protein is a VEGF-Trap or an IgG molecule, and the polymer is POE, PLA, or PLGA.
45. The method of any one of claims 42-44, wherein the particle has an average diameter of about 15 μm.
46. The method of any one of claims 42-45, wherein the protein is released from the protein-polymer complex over at least three days.
47. The method of any one of claims 42-46, wherein the protein is released from the protein-polymer complex over at least 60 days.
48. The method of any one of claims 42-47, wherein the solvent is buffered saline.
49. The method of any one of claims 42-47, wherein the solvent is in vivo.
50. The method of any one of claims 42-47 and claim 49, wherein the solvent is vitreous humour.

CLAIMS

1. A plurality of microparticles having diameters ranging from 2 µm to 70 µm, as determined by microflow imaging (MFI), comprising a VEGF-Trap protein particle core of 2 µm to 12 µm in diameter, as determined by MFI, and a biodegradable polymer cortex, wherein (a) the protein particle core consists of VEGF-Trap, (b) the biodegradable polymer cortex comprises polyorthoester (POE), poly (lactic acid) (PLA), or poly-D,L-lactide-co-glycolide (PLGA), and (c) the VEGF-Trap is released at a rate of 0.01 mg per week to 0.30 mg per week in an aqueous environment over the course of at least 60 days.

2. The plurality of microparticles of claim 1, wherein the VEGF-Trap consists of a dimer of a polypeptide comprising the amino acid sequence SEQ ID NO:1

3. The plurality of microparticles of claim 1 or claim 2 for use in a method of treating an ocular disease.

4. A method of manufacturing a composition comprising a VEGF-Trap protein and a biodegradable polymer selected from the group consisting of POE, PLA, and PLGA, the method comprising the steps of:

a. obtaining a VEGF-Trap protein particle by spray drying a solution comprising the VEGF-Trap protein;

b. suspending the protein particle in a solution comprising the polymer and a solvent; and

c. removing the solvent,

wherein a particle having an average diameter of 15 µm is formed comprising the protein coated with the polymer.

5. The method of claim 4, wherein the protein particle is obtained by spray drying a solution comprising the protein.

6. The method of claim 4, wherein the spray drying is performed by dual-nozzle sonication, single-nozzle sonication, or electrospray.

7. The method of claim 6, wherein the solvent is evaporated by creating a dispersion of the protein suspension of step (b) by spray drying.