[0003] Surfactants are generally used in pharmaceutical compositions comprising therapeutic proteins, e.g., to prevent protein aggregation and stabilize proteins. It is unclear whether surfactants can be used to effectively prevent protein loss due to surface adsorption when proteins are present at low concentrations in pharmaceutical compositions (e.g., 0.1 mg/mL or less).

[0004] There is a need for protein compositions and methods that minimize protein loss due to adsorption to solid surfaces, especially when the compositions comprising protein at low protein concentrations.

SUMMARY

[0005] Disclosed herein are compositions comprising proteins at low protein concentrations as well as methods of administering the compositions to a subject in need thereof. The compositions and methods disclosed herein have the advantage of minimizing or eliminating protein loss due to protein adsorption to solid surfaces and ensure accurate dosing of therapeutic proteins to patients.

[0005a] In another aspect, the present disclosure provides a pharmaceutical preparation comprising an aqueous pharmaceutical composition contained inside a container, wherein the aqueous pharmaceutical composition comprises: a) a bispecific antibody construct at a concentration of between 0.001 μg/ml and 100 μg/ml, and b1) polysorbate at a concentration of at least about 0.25 x of CMC, wherein the container is made of a plastic substantially free of di-2-ethylhexyl phthalate (DEHP) or tri-2-ethylhexyltrimellitate (TOTM), or b2) poloxamer at a concentration of at least 0.25 x of CMC, wherein the container is made of a plastic comprising polyolefin, polyvinyl chloride (PVC), ethyl vinyl acetate (EVA), or polyurethane.

[0005b] In yet another aspect, the present disclosure provides a use of an aqueous pharmaceutical composition comprising a bispecific antibody construct in the manufacture of a medicament for treating cancer in a patient in need thereof, wherein the medicament is an aqueous pharmaceutical

composition inside a container, wherein the aqueous pharmaceutical composition comprises the bispecific antibody construct at a concentration of between 0.001 μg/ml and 100 μg/ml and i) polysorbate at a concentration of at least about 0.25 x of CMC of the surfactant, wherein the container is made of a material substantially free of DEHP or TOTM, or ii) poloxamer at a concentration of at least 0.25 x of CMC, wherein the container is made of a material comprising polyolefin, PVC, EVA or polyurethane, wherein the bispecific antibody construct comprises a polypeptide having the amino acid sequence selected from SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 176, SEQ ID NO: 178, and SEQ ID NO: 192.

[0006] In certain examples, disclosed herein is an aqueous composition comprising a protein and a surfactant, wherein the protein is present in the composition at a concentration of between about 0.001 μg/ml and about 100 μg/ml, and the surfactant is present in the composition at a concentration of at least about 0.25 x of the critical micelle concentration (CMC) of the surfactant.

[0007] In certain examples, the protein is a bispecific antibody construct comprising a first binding domain that binds to a target cell surface antigen, a second binding domain that binds to human CD3 on the surface of a T cell, and optionally, a third domain comprising, in an amino to carboxyl order, hinge-CH2 domain-CH3 domain-linker-hinge-CH2 domain-CH3 domain. In certain examples, the second binding domain comprises a polypeptide having the sequence of SEQ ID NO: 201. In certain examples, the bispecific antibody construct is present at a concentration of between about 0.001 μg/ml and about 50 μg/ml, or between about 0.01 μg/ml to about 50 μg/ml, or between 0.1 μg/ml to about 50 μg/ml, or 0.1 μg/ml to about 10 μg/ml, or 1 μg/ml to about 10 μg/ml.

[0008] In certain examples, the surfactant is a polysorbate, a poloxamer or triton x-100. In certain examples, the surfactant is polysorbate 80, polysorbate 60, polysorbate 40, polysorbate 20, or Triton X-100. In certain examples, the surfactant is poloxamer 188 or poloxamer 407. In certain examples, the surfactant is present at a concentration of between about 0.25x and about 20x of the CMC, or between about 0.25x and about 10x of the CMC of the surfactant.

[0009] In certain examples, wherein the composition further comprising a salt, an amino acid, a saccharide or saccharide derivative, or combinations thereof. In certain examples, the salt is NaCl. In certain examples, the saccharide or saccharide derivative is a monosaccharide, a

CLAIMS

What is claimed:

1. A pharmaceutical preparation comprising an aqueous pharmaceutical composition contained inside a container, wherein the aqueous pharmaceutical composition comprises:

a) a bispecific antibody construct at a concentration of between 0.001 μg/ml and 100 μg/ml, and

b1) polysorbate at a concentration of at least about 0.25 x of CMC, wherein the container is made of a plastic substantially free of di-2-ethylhexyl phthalate (DEHP) or tri-2-ethylhexyltrimellitate (TOTM), or

b2) poloxamer at a concentration of at least 0.25 x of CMC, wherein the container is made of a plastic comprising polyolefin, polyvinyl chloride (PVC), ethyl vinyl acetate (EVA), or polyurethane.

2. The pharmaceutical preparation of claim 1, wherein the aqueous pharmaceutical composition comprises the bispecific antibody construct at a concentration of between 0.001 μg/ml and 50 μg/ml.

3. The pharmaceutical preparation of claim 1 or claim 2, wherein the bispecific antibody construct is present at a concentration of from 0.01 μg/ml to 50 μg/ml, or from 0.1 μg/ml to 50 μg/ml, or from 0.1 μg/ml to 10 μg/ml, or from 1 μg/ml to 10 μg/ml.

4. The pharmaceutical preparation of any one of claims 1-3, wherein the surfactant is polysorbate and is selected from the group consisting of polysorbate 80, polysorbate 60, polysorbate 40, and polysorbate 20.

5. The pharmaceutical preparation of claim 4, comprising from 0.0035% (w/v) to 0.056% (w/v) of polysorbate 20.

6. The pharmaceutical preparation of claim 4, comprising from 0.001% (w/v) to 0.025% (w/v) of polysorbate 80.

7. The pharmaceutical preparation of claim 4, comprising from 0.001% (w/v) to 0.016% (w/v) of polysorbate 80.

8. The pharmaceutical preparation of any one of claims 1-3, wherein the surfactant is poloxamer and is selected from the group consisting of poloxamer 188 and poloxamer 407.

9. The pharmaceutical preparation of claim 8, comprising from 0.2% (w/v) to 3.2% (w/v) of poloxamer 188.

10. The pharmaceutical preparation of claim 8, comprising from 0.002% (w/v) to 0.032% (w/v) of poloxamer 407.

11. The pharmaceutical preparation of any one of claims 1-3, wherein the aqueous pharmaceutical composition comprises the surfactant is at a concentration of between 0.25x and 20x of the CMC or between 0.25x and 10x of the CMC, of the surfactant.

12. The pharmaceutical preparation of any one of claims 1-11, wherein the aqueous pharmaceutical composition further comprising a salt, a buffer, an amino acid, a saccharide or saccharide derivative, or combinations thereof.

13. The pharmaceutical preparation of any one of claims 1-11, wherein the pharmaceutical preparation further comprises a buffer or preservative.

14. The pharmaceutical preparation of claim 12 or claim 13, wherein the pH of the pharmaceutical composition is from 3.5 to 7.5.

15. The pharmaceutical preparation of any one of claims 1-14, wherein the aqueous pharmaceutical composition has a pH of between 4.2 and 7.0.

16. The pharmaceutical preparation of any one of claims 12-15, wherein the salt is NaCl.

17. The pharmaceutical preparation of any one of claims 12-16, wherein the saccharide or saccharide derivative is a monosaccharide, a disaccharide, a cyclic polysaccharide or a sugar alcohol.

18. The pharmaceutical preparation of any one of claims 12-17, wherein the saccharide is sucrose, trehalose, mannitol or sorbitol.

19. The pharmaceutical preparation of any one of claims 12-18, wherein the amino acid is lysine.

20. The pharmaceutical preparation of any one of claims 12-19, wherein the buffer is an acetate buffer, a glutamate buffer, a citrate buffer, a succinate buffer, a tartrate buffer, a fumarate buffer, a maleate buffer, a histidine buffer, or a phosphate buffer.

21. The pharmaceutical preparation of any one of claims 1-20, wherein each of the first and second binding domains of the bispecific antibody construct comprises a VH region and a VL region.

22. The pharmaceutical preparation, according to any one of claims 1-21, wherein the bispecific antibody construct is a single chain antibody construct.

23. The pharmaceutical preparation, according to any one of claims 1-22, wherein the bispecific antibody construct comprises a first binding domain that binds to a target cell surface antigen, a second binding domain that binds to human CD3 on the surface of a T cell, and optionally, a third domain comprising, in an amino to carboxyl order, hinge-CH2 domain-CH3 domain-linker-hinge-CH2 domain-CH3 domain.

24. The pharmaceutical preparation, according to claim 23, wherein the second binding domain comprises a polypeptide having the sequence of SEQ ID NO: 201.

25. The pharmaceutical preparation of any one of claims 1-24, wherein the bispecific antibody construct comprises a polypeptide having the amino acid sequences selected from SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 176, SEQ ID NO: 178, and SEQ ID NO: 192.

26. The pharmaceutical preparation of claim 1, wherein the plastic that is substantially free of DEHP or TOTM is PVC.

27. Use of an aqueous pharmaceutical composition comprising a bispecific antibody construct in the manufacture of a medicament for treating cancer in a patient in need thereof, wherein the medicament is an aqueous pharmaceutical composition inside a container, wherein the aqueous pharmaceutical composition comprises the bispecific antibody construct at a concentration of between 0.001 μg/ml and 100 μg/ml and i) polysorbate at a concentration of at least about 0.25 x of CMC of the surfactant, wherein the container is made of a material substantially free of DEHP or TOTM, or ii) poloxamer at a concentration of at least 0.25 x of CMC, wherein the container is made of a material comprising polyolefin, PVC, EVA or polyurethane,

wherein the bispecific antibody construct comprises a polypeptide having the amino acid sequence selected from SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 176, SEQ ID NO: 178, and SEQ ID NO: 192.

28. The use of claim 27, wherein the aqueous pharmaceutical composition comprises the bispecific antibody construct is at a concentration of between 0.001 μg/ml and 50 μg/ml.

29. The use of claim 27 or 28, wherein the aqueous pharmaceutical composition comprises the surfactant is at a concentration of between 0.25x and 20x of the CMC or between 0.25x and 10x of the CMC, of the surfactant.

30. The use of any one of claims 27-29, wherein the polysorbate is polysorbate 80, polysorbate 60, polysorbate 40, or polysorbate 20.

31. The use of any one of claims 27-30, wherein the poloxamer is poloxamer 188 or poloxamer 407.

32. The use of any one of claims 27-31, wherein the aqueous pharmaceutical composition further comprising one or more selected from a salt, a buffer, an amino acid, a saccharide, and a preservative.

33. The use of any one of claims 27-32, wherein the aqueous pharmaceutical composition has a pH of between 4.2 and 7.0.

34. The use of any one of claims 27-33, wherein the aqueous pharmaceutical composition is prepared by diluting a first composition comprising the bispecific antibody construct with a suitable aqueous solution.

35. The use of claim 34, wherein the first composition is a liquid composition comprising the bispecific antibody construct.

36. The use of claim 34, wherein the first composition is a liquid composition reconstituted from a lyophilized composition comprising the bispecific antibody construct.

37. The use of claim 35 or claim 36, wherein the suitable solution comprises the surfactant at a concentration of at least about 0.25 x of CMC of the surfactant.

38. The use of any one of claims 34-37, wherein the aqueous pharmaceutical composition is prepared by adding the suitable aqueous solution into the container followed by adding an appropriate amount of the first composition into the container.

39. The use of any one of claims 27-38, wherein the aqueous pharmaceutical composition is formulated for IV administration.

40. The pharmaceutical preparation of claim 25 or the use of claim 27, wherein the bispecific antibody construct comprises a polypeptide having the amino acid sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 25, SEQ ID NO: 48, SEQ ID NO: 67, SEQ ID NO: 78, SEQ ID NO: 88, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 178 or SEQ ID NO: 192.