However, this formulation is not stable for storage. It was discovered that a liquid formulation of etanercept could be achieved using arginine to stabilize the protein (see US Patent No. 7,648,702). An exemplary liquid formulation consists of 50 mg/mL etanercept, 25 mM phosphate buffer, 25 mM L-arginine hydrochloride, 100 mM NaCl, 1% Sucrose at pH 6.3 in water.

Summary of the invention

[0006] Provided herein are new and improved formulations of etanercept. In particular, the invention provides pharmaceutical compositions containing etanercept that are stable and can be conveniently stored as a liquid at controlled room temperature (CRT) for extended periods of time, even in the absence of an additional buffering agent. In addition, when the pharmaceutical compositions of the invention are injected into subjects, they also demonstrate significantly reduced injection pain as compared to the commercially available prior art formulation. Thus these pharmaceutical compositions are more convenient and advantageous for patients.

[0006a] In one aspect, the invention provides a pharmaceutical composition comprising between 75 mM and 150 mM NaCl, between 5 mM and 100 mM arginine, between 0.5% and 2% (w/v) sucrose, and between 40 mg/mL and 100 mg/mL etanercept, wherein the pharmaceutical composition comprises less than 2.0 mM total additional buffering agent, and the pH of the composition is between 6.1 and 6.5.

[0007] Another aspect of the invention provides methods of formulating pharmaceutical preparations of etanercept at a desired pH but in the absence of additional buffering agent in the final formulation.

[0008] In another aspect, the invention provides a pharmaceutical composition comprising etanercept, NaCl, arginine, and sucrose, wherein the pharmaceutical composition has essentially no additional buffering agent, and the pH of the composition is between 6.1 and 6.5. In one embodiment, the pharmaceutical composition is capable of maintaining the pH between 6.1 and 6.5 when stored at controlled room temperature (CRT) for 2 weeks. In another embodiment, the etanercept concentration is between 40 mg/mL and 100 mg/mL. In another embodiment, the pharmaceutical composition is isotonic. In another embodiment, the pharmaceutical composition contains: between 20 mM and 150 mM NaCl; between 5 mM and 100 mM arginine; and between 0.5% and 2% (w/v) sucrose. In another embodiment, the pharmaceutical composition comprises a surfactant. In another embodiment, the surfactant is polysorbate 20, polysorbate 80, or poloxamer

188. In another embodiment, the surfactant is polysorbate 20 at a concentration (w/v) of between 0.001% and 0.1%. In another embodiment, the surfactant is polysorbate 80 at a concentration (w/v) of between 0.001% and 0.1%. In another embodiment, the surfactant is poloxamer 188 at a concentration (w/v) of between 0.01% to 0.3%. In another embodiment, the pharmaceutical composition maintains a pH of between 5.8 and 6.7 for at least

Claims

What is claimed is:

1. A pharmaceutical composition comprising between 75 mM and 150 mM NaCl, between 5 mM and 100 mM arginine, between 0.5% and 2% (w/v) sucrose, and between 40 mg/mL and 100 mg/mL etanercept, wherein the pharmaceutical composition comprises less than 2.0 mM total additional buffering agent, and the pH of the composition is between 6.1 and 6.5.

2. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises less than 1.5 mM total additional buffering agent.

3. The pharmaceutical composition of claim 2, wherein the pharmaceutical composition comprises less than 1.0 mM total additional buffering agent.

4. The pharmaceutical composition of claim 2, wherein the pharmaceutical composition comprises less than 0.5 mM total additional buffering agent.

5. The pharmaceutical composition of claim 2, wherein the pharmaceutical formulation comprises less than 0.25 mM total additional buffering agent.

6. The pharmaceutical composition of claim 5, wherein the arginine is L-arginine.

7. The pharmaceutical composition of claim 6 comprising about 50 mg/mL etanercept, about 120 mM NaCl, about 25 mM L-arginine hydrochloride, and about 1 % (w/v) sucrose.

8. The pharmaceutical composition of claim 7, wherein less than 28% of the total amount of etanercept is in a misfolded form as assessed using hydrophobic interaction chromatography after two weeks' storage at approximately 25° C.

9. The pharmaceutical composition of claim 7, wherein etanercept consists of a dimer of the amino acid sequence of SEQ ID NO: 1.

10. The pharmaceutical composition of claim 2, wherein the pharmaceutical composition comprises 0.1 mM or less total additional buffering agent.

11. The pharmaceutical composition of claim 10, wherein the arginine is L-arginine.

12. The pharmaceutical composition of claim 11, wherein etanercept consists of a dimer of the amino acid sequence of SEQ ID NO: 1.

13. The pharmaceutical composition of claim 11 comprising about 50 mg/mL etanercept, about 120 mM NaCl, about 25 mM L-arginine hydrochloride, and about 1 % (w/v) sucrose.

14. The pharmaceutical composition of claim 13, wherein etanercept consists of a dimer of the amino acid sequence of SEQ ID NO: 1.

15. The pharmaceutical composition of claim 13, wherein said pharmaceutical composition maintains a pH of between about 6.1 and about 6.5 for at least two weeks during storage at approximately 25° C.

16. The pharmaceutical composition of claim 15, wherein etanercept consists of a dimer of the amino acid sequence of SEQ ID NO: 1.

17. The pharmaceutical composition of claim 1, wherein the arginine is L-arginine.

18. The pharmaceutical composition of claim 17, wherein the L-arginine is L-arginine hydrochloride.

19. The pharmaceutical composition of claim 17, wherein the L-arginine is L-arginine base.

20. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition maintains a pH between 6.1 and 6.5 when stored at controlled room temperature (CRT) for 2 weeks.

21. The pharmaceutical composition of claim 20, wherein the pharmaceutical composition maintains a pH between about 6.2 and about 6.3 when stored at controlled room temperature (CRT) for 2 weeks.

22. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition maintains a pH of between 5.8 and 6.7 for at least two weeks when stored at approximately 25° C. and wherein less than 6% of the total etanercept is aggregated in a high molecular weight form as assessed using size exclusion chromatography.

23. The pharmaceutical composition of claim 1, wherein said pharmaceutical composition maintains a pH of between about 6.1 and about 6.5 for at least two weeks during storage at approximately 25° C.

24. The pharmaceutical composition of claim 1, wherein said pharmaceutical composition maintains a pH of between about 6.2 and about 6.4 for at least two weeks during storage at approximately 25° C.

25. The pharmaceutical composition of claim 1, wherein less than 28% of the total amount of etanercept is in a misfolded form as assessed using hydrophobic interaction chromatography after two weeks' storage at approximately 25° C.

26. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition has an osmolality of about 180 to about 420 milliosmolals.

27. The pharmaceutical composition of claim 26, wherein the pharmaceutical composition has an osmolality of about 250 to about 350 milliosmolals.

28. The pharmaceutical composition of claim 27, wherein the pharmaceutical composition has an osmolality of about 290 to about 310 milliosmolals.

29. The pharmaceutical composition of claim 28, wherein the pharmaceutical composition has an osmolality of about 300 to about 310 milliosmolals.

30. The pharmaceutical composition of claim 1 consisting essentially of about 50 mg/mL etanercept, about 120 mM NaCl, about 25 mM L-arginine hydrochloride, about 1 % (w/v) sucrose and water.

31. The pharmaceutical composition of claim 30, wherein said pharmaceutical composition maintains a pH of between about 6.1 and about 6.5 for at least two weeks during storage at approximately 25° C.

32. The pharmaceutical composition of claim 30, wherein less than 28% of the total amount of etanercept is in a misfolded form as assessed using hydrophobic interaction chromatography after two weeks' storage at approximately 25° C.

33. The pharmaceutical composition of claim 30, wherein etanercept consists of a dimer of the amino acid sequence of SEQ ID NO: 1.

34. The pharmaceutical composition of claim 1 consisting of about 50 mg/mL etanercept, about 120 mM NaCl, about 25 mM L-arginine hydrochloride, about 1 % (w/v) sucrose, and water.

35. The pharmaceutical composition of claim 34, wherein said pharmaceutical composition maintains a pH of between about 6.1 and about 6.5 for at least two weeks during storage at approximately 25° C.

36. The pharmaceutical composition of claim 34, wherein less than 28% of the total amount of etanercept is in a misfolded form as assessed using hydrophobic interaction chromatography after two weeks' storage at approximately 25° C.

37. The pharmaceutical composition of claim 34, wherein etanercept consists of a dimer of the amino acid sequence of SEQ ID NO: 1.

38. The pharmaceutical composition of claim 1, further comprising polysorbate 20.

39. The pharmaceutical composition of claim 38, wherein the polysorbate 20 concentration (w/v) is between about 0.001 % and about 0.1 %.

40. The pharmaceutical composition of claim 39, wherein the polysorbate 20 concentration (w/v) is about 0.005%, about 0.01%, or about 0.015%.

41. The pharmaceutical composition of claim 1, wherein etanercept consists of a dimer of the amino acid sequence of SEQ ID NO: 1.

42. The pharmaceutical composition of claim 1, wherein said solution maintains a pH of between about 6.1 and about 6.5 for at least two weeks during storage at approximately 25° C., and wherein less than 28% of the total amount of etanercept is in a misfolded form as assessed using hydrophobic interaction chromatography after two weeks' storage at approximately 25° C.

43. A kit comprising the pharmaceutical composition of claim 1 in a drug product form and instructions for storage and use.

44. A single-dose container containing the pharmaceutical composition of claim 1.

45. The single-dose container of claim 44 wherein said single dose container is a vial, a syringe, or an autoinjector.

46. The single-dose container of claim 44, containing an aqueous formulation consisting of etanercept at 50.0 mg/mL, sodium chloride at 120 mM, L-arginine hydrochloride at 25 mM, and sucrose at 1.0% (w/v).