analogs, however, the maximum plasma insulin level is not reached until 50-90 minutes following a subcutaneous injection. This is slower than endogenous insulin release from a normally functioning pancreas and does not always match glucose absorption profiles.

Another avenue to achieve rapid action that has been explored is the use of ingredients or excipients which improve the time action profile of insulin when provided in combination with insulin. For example, U.S. 8,324,157 states that a faster onset of action compared with existing insulin therapies can be achieved by adding a nicotinic compound, such as nicotinamide, and the amino acid arginine, and optionally glutamic acid. US2013/0231281 discloses compositions comprising an insulin and oligosaccharides, either alone or in combination with a polyanionic compound and states that such compositions are fast acting. US2014/0113856 discloses compositions containing insulin in combination with a zinc chelator, such as ethylenediaminetetraacetic acid (EDTA), another excipient described in the publication as a "dissolution/stabilization" agent, such as citric acid or sodium citrate, and a magnesium-containing compound, and states that such compositions have more rapid absorption rates and declines from peak concentrations. US2015/0065423 describes compositions comprising a peptide and a vasodilatory agent, discloses lists of vasodilatory agents from three different categories, and provides data on compositions containing insulin lispro and nitroglycerin and states that such formulations are rapid acting.

Despite these and other efforts, a need remains for insulin compositions that have more rapid uptake of insulin into the blood from the injection site, more rapid onset and/or offset of action than existing insulin products, and chemical and physical stability during storage and use conditions. The present invention seeks to provide compositions which meet one or more of these needs.

Summary

In one aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

a. an insulin;
b. citrate, in a concentration from about 5 to about 25 mM;
c. treprostinil, in a concentration from about 0.04 to about 20 μg/mL;
d. zinc, in a concentration sufficient to provide at least 2 zinc ions per six molecules of insulin;
e. a preservative; and
f. one or more additional stabilizing agents selected from the group consisting of magnesium-containing compounds and sodium chloride;

and having a pH of about 7.0 to about 7.8 at room temperature.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

a. an insulin;
b. citrate, in a concentration from about 5 to about 25 mM;
c. treprostinil, in a concentration from about 0.04 to about 20 μg/mL;
d. a preservative;
e. a stabilizing agent comprising zinc, in a concentration sufficient to provide at least 2 zinc ions per six molecules of insulin; and

and having a pH of about 7.0 to about 7.8 at room temperature.

In a further aspect of the present disclosure, there is provided the pharmaceutical composition disclosed herein for use in therapy.

In another aspect of the present disclosure, there is provided the pharmaceutical composition disclosed herein for use in the treatment of diabetes.

In a further aspect of the present disclosure, there is provided a use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for the treatment of diabetes.

In another aspect of the present disclosure, there is provided an article of manufacture comprising any one of the pharmaceutical compositions disclosed herein.

Description

It has surprisingly been found that compositions containing certain concentrations of both citrate and treprostinil have a more rapid time action profile than existing commercially available insulin compositions, and that the chemical and physical stability of the compositions containing those concentrations of both citrate and treprostinil can be maintained, without eliminating the improvements in time action, by including in the compositions zinc and one or more additional stabilizing agents such as a surfactant, magnesium chloride or sodium chloride.

WE CLAIM:

1. A pharmaceutical composition comprising:
    a. an insulin;
    b. citrate, in a concentration from about 5 to about 25 mM;
    c. treprostinil, in a concentration from about 0.04 to about 20 μg/mL;
    d. zinc, in a concentration sufficient to provide at least 2 zinc ions per six molecules of insulin;
    e. a preservative; and
    f. one or more additional stabilizing agents selected from the group consisting of magnesium-containing compounds and sodium chloride;

    and having a pH of about 7.0 to about 7.8 at room temperature.
2. The pharmaceutical composition of claim 1 wherein the zinc concentration is from about 0.2 to about 2 mM.
3. The pharmaceutical composition of any of claims 1-2 wherein the zinc concentration is from about 0.2 to about 1 mM.
4. The pharmaceutical composition of any of claims 1-3, wherein the zinc concentration is from about 0.6 to about 0.8 mM.
5. The pharmaceutical composition of any of claims 1-4, wherein the one or more additional stabilizing agents comprise a magnesium-containing compound.
6. The pharmaceutical composition of claim 5, wherein the magnesium-containing compound is present in a concentration resulting in a molar ratio of magnesium to citrate from about 1:2 to about 1:10.
7. The pharmaceutical composition of claim 6, wherein the molar ratio of magnesium to citrate is from about 1:3 to about 1:5.
8. The pharmaceutical composition of any of claims 6-7 wherein the magnesium-containing compound is magnesium chloride.
9. The pharmaceutical composition of any of claims 1-8, wherein the insulin concentration is from about 100 to about 300 U/mL.
10. The pharmaceutical composition of any of claims 1-9, wherein the insulin concentration is either about 100 U/mL or about 200 U/mL.

11. The pharmaceutical composition of any of claims 1-10, wherein the insulin is insulin lispro.

12. The pharmaceutical composition of any of claims 1-11, wherein the concentration of citrate is from about 10 to about 25 mM.

13. The pharmaceutical composition of any of claims 1-12, wherein the concentration of treprostinil is from about 0.04 to about 10 μg/mL.

14. The pharmaceutical composition of any of claims 1-13, wherein the concentration of treprostinil is from about 0.5 to about 2 μg/mL.

15. The pharmaceutical composition of any of claims 1-14, wherein the preservative is m-cresol.

16. The pharmaceutical composition of claim 15, wherein the concentration of m-cresol is from about 2.5 to about 3.8 mg/mL.

17. The pharmaceutical composition of any of claims 1-16, wherein the one or more additional stabilizing agents comprise sodium chloride.

18. The pharmaceutical composition of claim 17 wherein the sodium chloride is present in a concentration from about 1 to about 50 mM.

19. The pharmaceutical composition of any of claims 1-18, wherein the total concentration of chloride is from about 10 to about 50 mM.

20. The pharmaceutical composition of any of claims 1-19, further comprising a tonicity agent.

21. The pharmaceutical composition of claim 20, wherein the tonicity agent is glycerol.

22. The pharmaceutical composition of claim 21, wherein the concentration of glycerol is from about 1 to about 15 mg/mL.

23. The pharmaceutical composition of claim 1 comprising:

    a. insulin lispro, in a concentration from about 100 to about 200 U/mL;
    b. citrate, in a concentration from about 5 to about 25 mM;
    c. treprostinil, in a concentration from about 0.5 to about 2 μg/mL; and
    d. zinc, in a concentration from about 0.2 mM to about 2 mM.

24. The pharmaceutical composition of claim 23, wherein the concentration of citrate is from about 15 to about 25 mM.

25. The pharmaceutical composition of any of claims 23-24, wherein the concentration of zinc is from about 0.6 to about 0.9 mM.

26. The pharmaceutical composition of any of claims 23-25, further comprising a magnesium-containing compound, in a concentration resulting in a molar ratio of magnesium to citrate from about 1:3 to about 1:5.

27. The pharmaceutical composition of any of claims 1-26 having a pH of about 7.4.

28. The pharmaceutical composition of claim 23 wherein:

a. insulin lispro is in a concentration of about 100 U/mL;

b. citrate is in a concentration of about 15 mM;

c. treprostinil is in a concentration of about 1 μg/mL; and

d. zinc is in a concentration of about 0.6 mM;

and further comprising:

e. magnesium chloride in a concentration of about 5 mM;

f. m-cresol, in a concentration of about 3.15 mg/mL;

g. glycerol, in a concentration of about 12 mg/mL;

and having a pH of about 7.4.

29. The pharmaceutical composition of claim 23 wherein:

a. insulin lispro is in a concentration of about 200 U/mL;

b. citrate is in a concentration of about 15 mM;

c. treprostinil is in a concentration of about 1 μg/mL; and

d. zinc is in a concentration of about 0.8 mM;

and further comprising:

e. magnesium chloride in a concentration of about 5 mM;

f. m-cresol, in a concentration of about 3.15 mg/mL; and

g. glycerol, in a concentration of about 12 mg/mL;

and having a pH of about 7.4.

30. A pharmaceutical composition comprising:
    a. an insulin;
    b. citrate, in a concentration from about 5 to about 25 mM;
    c. treprostinil, in a concentration from about 0.04 to about 20 μg/mL;
    d. a preservative;
    e. a stabilizing agent comprising zinc, in a concentration sufficient to provide at least 2 zinc ions per six molecules of insulin; and

and having a pH of about 7.0 to about 7.8 at room temperature.

31. The pharmaceutical composition of any one of Claims 1-30 for use in therapy.

32. The pharmaceutical composition of any one of Claims 1-30 for use in the treatment of diabetes.

33. Use of the pharmaceutical composition of any one of Claims 1-30 in the manufacture of a medicament for the treatment of diabetes.

34. An article of manufacture comprising any one of the pharmaceutical compositions of Claims 1-30.

35. The article of manufacture of Claim 34 which is a multi-use vial.

36. The article of manufacture of Claim 34 which is a multi-use cartridge.

37. The article of manufacture of Claim 34 which is a re-usable pen injector.

38. The article of manufacture of Claim 34 which is a disposable pen device.

39. The article of manufacture of Claim 34 which is a pump device for continuous subcutaneous insulin infusion therapy.

40. The article of manufacture of Claim 34 which is a container closure system for use in a pump device for continuous subcutaneous insulin infusion therapy.