tonicity of the formulation. Moreover, such a formulation should be stable in solution so that it readily is available for use and/or can be pre-loaded into a variety of dispensing devices.

Therefore, a need exists for improved pharmaceutical formulations containing furosemide that contain a sufficient concentration of furosemide, and are at an appropriate pH and osmolality, for example, to permit subcutaneous administration of furosemide.

SUMMARY

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

(i) furosemide, or a pharmaceutically acceptable salt thereof;

(ii) one or more pharmaceutically acceptable excipients, wherein the amount of the one or more pharmaceutically acceptable excipients in the liquid pharmaceutical formulation is from 0.1 % (w/w) to 30 % (w/w); and

(iii) a pharmaceutically acceptable buffer, wherein the pharmaceutically acceptable buffer is tromethamine or a pharmaceutically acceptable salt thereof, and the concentration of tromethamine in the liquid pharmaceutical formulation is from 25 mM to 150 mM,

wherein the concentration of furosemide in the liquid pharmaceutical formulation is from 60 mg/mL to 250 mg/mL, and the liquid pharmaceutical formulation has a pH from 6.5 to 8.5.

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

(i) furosemide, or a pharmaceutically acceptable salt thereof;

(ii) from 0.5 % (w/w) to 5 % (w/w) benzyl alcohol; and

(iii) from 25 mM to 250 mM tromethamine or a pharmaceutically acceptable salt thereof,

wherein the concentration of furosemide in the liquid pharmaceutical formulation is from 5 mg/mL to 100 mg/mL and the pH of the liquid pharmaceutical formulation is from 5.5 to 6.5.

In a further aspect of the present disclosure, there is provided a unit liquid pharmaceutical formulation comprising:

(i) from 10 mg to 200 mg furosemide, or a pharmaceutically acceptable salt thereof;

(ii) from 0.1 % (w/w) to 30 % (w/w) of one or more pharmaceutically acceptable excipients selected from the group consisting of ethanol, benzyl alcohol, glycerin, sodium chloride, a polyethylene glycol (PEG), propylene glycol, a polysorbate, a polyvinylpyrrolidone (PVP), and any combination thereof; and

(iii) from 25 mM to 150 mM of a pharmaceutically acceptable buffer comprising tromethamine or a pharmaceutically acceptable salt thereof,

wherein the concentration of furosemide in the liquid pharmaceutical formulation is from 60 mg/mL to 250 mg/mL and the pH of the liquid pharmaceutical formulation is from 6.5 to 8.5.

In another aspect of the present disclosure, there is provided a liquid pharmaceutical formulation disclosed herein, or the unit liquid pharmaceutical formulation disclosed herein, for use in treating congestion, edema, fluid overload, or hypertension in a patient in need thereof.

In a further aspect of the present disclosure, there is provided a use of a liquid pharmaceutical formulation disclosed herein, or the unit liquid pharmaceutical formulation disclosed herein, in the manufacture of a medicament for treating congestion, edema, fluid overload, or hypertension in a patient in need thereof.

In another aspect of the present disclosure, there is provided a kit for the treatment of congestion, edema, fluid overload, or hypertension comprising a liquid pharmaceutical formulation disclosed herein, or the unit liquid pharmaceutical formulation disclosed herein; and instructions for treating the congestion, edema, fluid overload, or hypertension.

In one ~~aspect~~example, the ~~invention~~present disclosure provides a liquid pharmaceutical formulation of furosemide or a pharmaceutically acceptable salt thereof.

In various ~~embodiment~~examples of the ~~invention~~present disclosure, the liquid pharmaceutical formulation comprises:

(i) furosemide, or a pharmaceutically acceptable salt thereof;

(ii) one or more pharmaceutically acceptable excipients; and

(iii) a pharmaceutically acceptable buffer,

wherein the concentration of furosemide in the liquid pharmaceutical formulation is from about 40 mg/mL to about 250 mg/mL. In certain ~~embodiment~~examples, the pH of the liquid pharmaceutical formulation is from about 6.5 to about 8.5.

In certain ~~embodiment~~examples of the ~~invention~~present disclosure, the liquid pharmaceutical formulation comprises:

(i) furosemide, or a pharmaceutically acceptable salt thereof;

(ii) from about 0.1 % (w/w) to about 30 % (w/w) of one or more pharmaceutically acceptable excipients selected from the group consisting of ethanol, benzyl alcohol, glycerin, N-methyl-pyrrolidone (NMP), sodium chloride, a polyethylene glycol (PEG), propylene glycol, a polysorbate, a polyvinylpyrrolidone (PVP), a cyclodextrin, and any combination thereof; and

(iii) from about 25 mM to about 500 mM of a pharmaceutically acceptable buffer selected from the group consisting of histidine, a citrate salt, sodium phosphate, potassium phosphate, tromethamine or a pharmaceutically acceptable salt thereof, and any combination thereof,

wherein the concentration of furosemide in the liquid pharmaceutical formulation is from about 40 mg/mL to about 250 mg/mL and the pH of the liquid pharmaceutical formulation is from about 6.5 to about 8.5.

In certain ~~embodiment~~examples of the ~~invention~~present disclosure, the liquid pharmaceutical formulation comprises:

(i) furosemide, or a pharmaceutically acceptable salt thereof;

(ii) benzyl alcohol; and

(iii) a pharmaceutically acceptable buffer,

wherein the concentration of furosemide in the liquid pharmaceutical formulation is from about 40 mg/mL to about 250 mg/mL.

In certain ~~embodiment~~examples of the ~~invention~~present disclosure, the liquid pharmaceutical formulation comprises:

(i) furosemide, or a pharmaceutically acceptable salt thereof;

(ii) N-methyl-pyrrolidone (NMP); and

(iii) a pharmaceutically acceptable buffer,

wherein the concentration of furosemide in the liquid pharmaceutical formulation is from about 40 mg/mL to about 250 mg/mL.

In certain ~~embodiment~~examples of the ~~invention~~present disclosure, the liquid pharmaceutical formulation comprises:

(i) furosemide, or a pharmaceutically acceptable salt thereof;

(ii) benzyl alcohol;

(iii) N-methyl-pyrrolidone (NMP); and

(iv) a pharmaceutically acceptable buffer,

wherein the concentration of furosemide in the liquid pharmaceutical formulation is from about 40 mg/mL to about 250 mg/mL.

In certain ~~embodiment~~examples of the ~~invention~~present disclosure, the liquid pharmaceutical formulation comprises:

(i) furosemide, or a pharmaceutically acceptable salt thereof;

(ii) from about 0.1 % (w/w) to about 10 % (w/w) benzyl alcohol; and

(iii) from about 25 mM to about 250 mM tromethamine or a pharmaceutically acceptable salt thereof,

wherein the concentration of furosemide in the liquid pharmaceutical formulation is from about 40 mg/mL to about 250 mg/mL.

In certain ~~embodiment~~examples of the ~~invention~~present disclosure, the liquid pharmaceutical formulation comprises:

(i) furosemide, or a pharmaceutically acceptable salt thereof;

(ii) from about 0.1 % (w/w) to about 10 % (w/w) N-methyl-pyrrolidone;

(iii) from about 0.1 % (w/w) to about 10 % (w/w) benzyl alcohol; and

(iv) from about 25 mM to about 250 mM tromethamine or a pharmaceutically acceptable salt thereof,

wherein the concentration of furosemide in the liquid pharmaceutical formulation is from about 40 mg/mL to about 250 mg/mL.

In another ~~aspect~~example, the ~~invention~~present disclosure provides a unit liquid pharmaceutical formulation of furosemide or a pharmaceutically acceptable salt thereof.

In certain ~~embodiment~~examples of the ~~invention~~present disclosure, the unit liquid pharmaceutical formulation comprises:

(i) from about 10 mg to about 200 mg furosemide, or a pharmaceutically acceptable salt thereof;

(ii) from about 0.1 % (w/w) to about 30 % (w/w) of one or more pharmaceutically acceptable excipients selected from the group consisting of ethanol, benzyl alcohol, glycerin, N-methyl-pyrrolidone (NMP), sodium chloride, a polyethylene glycol (PEG), propylene glycol, a polysorbate, a polyvinylpyrrolidone (PVP), a cyclodextrin, and any combination thereof; and

(iii) from about 25 mM to about 500 mM of a pharmaceutically acceptable buffer selected from the group consisting of histidine, a citrate salt, sodium phosphate, potassium phosphate, tromethamine or a pharmaceutically acceptable salt thereof, and any combination thereof,

wherein the concentration of furosemide in the liquid pharmaceutical formulation is from about 40 mg/mL to about 250 mg/mL and wherein the pH of the liquid pharmaceutical formulation is from about 6.5 to about 8.5.

In certain ~~embodiment~~examples of the ~~invention~~present disclosure, the unit liquid pharmaceutical formulation comprises:

(i) from about 10 mg to about 200 mg furosemide, or a pharmaceutically acceptable salt thereof;

(ii) from about 0.1 % (w/w) to about 10 % (w/w) benzyl alcohol; and

(iii) from about 25 mM to about 250 mM tromethamine or a pharmaceutically acceptable salt thereof,

wherein the concentration of furosemide in the unit liquid pharmaceutical formulation is from about 40 mg/mL to about 200 mg/mL.

In certain ~~embodiment~~examples of the ~~invention~~present disclosure, the unit liquid pharmaceutical formulation comprises:

(i) from about 10 mg to about 200 mg furosemide, or a pharmaceutically acceptable salt thereof;

(ii) from about 0.1 % (w/w) to about 10% (w/w) N-methyl-pyrrolidone;

(iii) from about 0.1% (w/w) to about 10 % (w/w) benzyl alcohol; and

(iv) from about 25 mM to about 250 mM tromethamine or a pharmaceutically acceptable salt thereof,

wherein the concentration of furosemide in the unit liquid pharmaceutical formulation is from about 40 mg/mL to about 200 mg/mL.

In certain ~~embodiment~~examples, the liquid pharmaceutical formulation or the unit liquid pharmaceutical formulation comprises one of more of water; a pH adjuster; and an osmolarity adjuster.

Another ~~aspect~~example of the ~~invention~~present disclosure provides a method of treating congestion, edema, fluid overload, or hypertension in a patient in need thereof, the method comprising administering to the patient a liquid pharmaceutical formulation or a unit liquid pharmaceutical formulation described herein.

Another ~~aspect~~example of the ~~invention~~present disclosure provides a kit for the treatment of congestion, edema, fluid overload, or hypertension comprising a liquid pharmaceutical formulation or a unit liquid pharmaceutical formulation described herein.

DETAILED DESCRIPTION

The invention provides liquid pharmaceutical formulations and unit liquid pharmaceutical formulations containing furosemide, medical kits containing the same, and methods of using the liquid pharmaceutical formulations and unit liquid pharmaceutical formulations to treat medical disorders e.g., congestion, edema, fluid overload, or hypertension in a patient in need thereof. In particular, the invention can provide pharmaceutical formulations including an increased concentration of furosemide, or a pharmaceutically acceptable salt thereof, using one or more pharmaceutically acceptable excipients along with a pharmaceutically acceptable buffer, which can maintain an appropriate pH for administration to a patient.

Definitions

To facilitate an understanding of the present invention, a number of terms and phrases are defined below.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

The terms “a” and “an” as used herein mean “one or more” and include the plural unless the context is inappropriate.

WHAT IS CLAIMED:

1. A liquid pharmaceutical formulation comprising:

(i) furosemide, or a pharmaceutically acceptable salt thereof;

(ii) one or more pharmaceutically acceptable excipients, wherein the amount of the one or more pharmaceutically acceptable excipients in the liquid pharmaceutical formulation is from ~~about~~ 0.1 % (w/w) to ~~about~~ 30 % (w/w); and

(iii) a pharmaceutically acceptable buffer, wherein the pharmaceutically acceptable buffer is tromethamine or a pharmaceutically acceptable salt thereof, and the concentration of tromethamine in the liquid pharmaceutical formulation is from 25 mM to 150 mM,

wherein the concentration of furosemide in the liquid pharmaceutical formulation is from ~~about 40~~60 mg/mL to ~~about~~ 250 mg/mL, and the liquid pharmaceutical formulation has a pH from 6.5 to 8.5

~~the one or more pharmaceutically acceptable excipients is selected from the group consisting of ethanol, benzyl alcohol, glycerin, sodium chloride, a polyethylene glycol (PEG), propylene glycol, a polysorbate, a polyvinylpyrrolidone (PVP), and any combination thereof.~~.

2. The liquid pharmaceutical formulation of claim 1, wherein the one or more pharmaceutically acceptable excipients comprises benzyl alcohol.

3. The liquid pharmaceutical formulation of claim 1 or 2, wherein the amount of benzyl alcohol in the liquid pharmaceutical formulation is from ~~about~~ 0.1 % (w/w) to ~~about~~ 10 % (w/w).

4. The liquid pharmaceutical formulation of claim 1 or 2, wherein the amount of benzyl alcohol in the liquid pharmaceutical formulation is from ~~about~~ 0.5 % (w/w) to ~~about~~ 5 % (w/w).

5. The liquid pharmaceutical formulation of ~~any one of claims 1-4~~claim 1, wherein the one or more ~~concentration of the~~ pharmaceutically acceptable ~~buffer in the liquid pharmaceutical formulation is from about 25 mM to about 500 mM~~excipients is selected from the group consisting of ethanol, benzyl alcohol, glycerin, sodium chloride, a polyethylene glycol (PEG), propylene glycol, a polysorbate, a polyvinylpyrrolidone (PVP), and any combination thereof.

~~6. The liquid pharmaceutical formulation of any one of claims 1-5, wherein the pharmaceutically acceptable buffer comprises a buffering agent selected from the group consisting of histidine, a citrate salt, sodium phosphate, potassium phosphate, tromethamine or a pharmaceutically acceptable salt thereof, and any combination thereof.~~

~~7. The liquid pharmaceutical formulation of any one of claims 1-5, wherein the buffering agent is tromethamine or a pharmaceutically acceptable salt thereof.~~

~~8~~6. The liquid pharmaceutical formulation of ~~claim 7~~any one of claims 1-5, wherein the concentration of tromethamine or a pharmaceutically acceptable salt thereof in the liquid pharmaceutical formulation is from ~~about~~ 25 mM to ~~about 250~~ 100 mM.

~~9. The liquid pharmaceutical formulation of claim 7, wherein the concentration of tromethamine or a pharmaceutically acceptable salt thereof in the liquid pharmaceutical formulation is from about 25 mM to about 150 mM.~~

~~10~~7. The liquid pharmaceutical formulation of claim 1, comprising:

(i) furosemide, or a pharmaceutically acceptable salt thereof;

(ii) from ~~about~~ 0.5 % (w/w) to ~~about~~ 5 % (w/w) benzyl alcohol; and

(iii) from ~~about~~ 25 mM to ~~about~~ 150 mM tromethamine or a pharmaceutically acceptable salt thereof,

wherein the concentration of furosemide in the liquid pharmaceutical formulation is from ~~about~~ 60 mg/mL to ~~about 120~~ 250 mg/mL, and the liquid pharmaceutical formulation has a pH from ~~about~~ 6.5 to ~~about~~ 8.5.

~~11~~8. The liquid pharmaceutical formulation of claim ~~10~~7, wherein the amount of benzyl alcohol in the liquid pharmaceutical formulation is from ~~about~~ 1 % (w/w) to ~~about~~3.5 % (w/w).

~~12~~9. The liquid pharmaceutical formulation of claim ~~10~~ 7 or ~~11~~8, wherein the amount of tromethamine or a pharmaceutically acceptable salt thereof in the liquid pharmaceutical formulation is from ~~about~~ 50 mM to ~~about~~ 125 mM.

~~13. The liquid pharmaceutical formulation of any one of claims 1-9, wherein the pH of the liquid pharmaceutical formulation is from about 6.5 to about 8.5.~~

~~14~~10. The liquid pharmaceutical formulation of any one of claims 1-~~12~~9, wherein the pH of the liquid pharmaceutical formulation is from ~~about~~ 7 to ~~about~~ 8.

~~15~~11. The liquid pharmaceutical formulation of claim 1, comprising:

(i) furosemide, or a pharmaceutically acceptable salt thereof;

(ii) from ~~about~~ 1 % (w/w) to ~~about~~ 3.5 % (w/w) benzyl alcohol; and

(iii) from ~~about~~ 50 mM to ~~about~~ 125 mM tromethamine or a pharmaceutically acceptable salt thereof,

wherein the concentration of furosemide in the liquid pharmaceutical formulation is from ~~about~~ 80 mg/mL to ~~about~~ 100 mg/mL and the pH of the liquid pharmaceutical formulation is from ~~about~~ 7 to ~~about~~ 8 ~~and is isosmotic~~.

~~16~~12. A liquid pharmaceutical formulation, comprising:

(i) furosemide, or a pharmaceutically acceptable salt thereof;

(ii) from ~~about~~ 0.5 % (w/w) to ~~about~~ 5 % (w/w) benzyl alcohol; and

(iii) from ~~about~~ 25 mM to ~~about~~ 250 mM tromethamine or a pharmaceutically acceptable salt thereof,

wherein the concentration of furosemide in the liquid pharmaceutical formulation is from ~~about~~ 5 mg/mL to ~~about~~ 100 mg/mL and the pH of the liquid pharmaceutical formulation is from ~~about~~ 5.5 to ~~about~~ 6.5.

~~17~~13. A unit liquid pharmaceutical formulation comprising:

(i) from ~~about~~ 10 mg to ~~about~~ 200 mg furosemide, or a pharmaceutically acceptable salt thereof;

(ii) from ~~about~~ 0.1 % (w/w) to ~~about~~ 30 % (w/w) of one or more pharmaceutically acceptable excipients selected from the group consisting of ethanol, benzyl alcohol, glycerin, sodium chloride, a polyethylene glycol (PEG), propylene glycol, a polysorbate, a polyvinylpyrrolidone (PVP), and any combination thereof; and

(iii) from ~~about~~ 25 mM to ~~about 250~~150 mM of a pharmaceutically acceptable buffer ~~selected from the group consisting of histidine, a citrate salt, sodium phosphate, potassium phosphate,~~comprising tromethamine or a pharmaceutically acceptable salt thereof, ~~and any combination thereof,~~

wherein the concentration of furosemide in the liquid pharmaceutical formulation is from ~~about 40~~ 60 mg/mL to ~~about~~ 250 mg/mL and the pH of the liquid pharmaceutical formulation is from ~~about~~ 6.5 to ~~about~~ 8.5.

~~18~~14. The unit liquid pharmaceutical formulation of claim ~~17~~13, comprising:

(i) from ~~about~~ 60 mg to ~~about~~ 120 mg furosemide, or a pharmaceutically acceptable salt thereof;

(ii) from ~~about~~ 0.5 % (w/w) to ~~about~~ 5 % (w/w) benzyl alcohol; and

(iii) from ~~about~~ 25 mM to ~~about~~ 150 mM tromethamine or a pharmaceutically acceptable salt thereof,

wherein the concentration of furosemide in the unit liquid pharmaceutical formulation is from ~~about 40~~60 mg/mL to ~~about 200~~250 mg/mL and the pH of the liquid pharmaceutical formulation is from ~~about~~ 7 to ~~about~~ 8.

~~19~~15. The liquid pharmaceutical formulation of any one of claims 1-~~16~~12, or the unit liquid pharmaceutical formulation of claim ~~17~~ 13 or ~~18~~14, further comprising one of more of water; a pH adjuster; and an osmolarity adjuster.

~~20~~16. The liquid pharmaceutical formulation or the unit liquid pharmaceutical formulation of claim ~~19~~15, wherein the liquid pharmaceutical formulation comprises a pH adjuster and the pH adjuster is selected from the group consisting of potassium hydroxide, sodium hydroxide, hydrochloric acid, and combinations thereof~~; and the osmolarity adjuster is selected from the group consisting of sodium chloride, potassium chloride, and combinations thereof~~.

17. The liquid pharmaceutical formulation or the unit liquid pharmaceutical formulation of claim 15, wherein the liquid pharmaceutical formulation comprises an osmolarity adjuster and the osmolarity adjuster is selected from the group consisting of sodium chloride, potassium chloride, and combinations thereof.

~~21~~18. A liquid pharmaceutical formulation of any one of claims 1-~~16~~12, or the unit liquid pharmaceutical formulation of claim ~~17~~ 13 or ~~18~~14, for use in treating congestion, edema, fluid overload, or hypertension in a patient in need thereof.

~~22~~19. Use of a liquid pharmaceutical formulation of any one of claims 1-~~16~~12, or the unit liquid pharmaceutical formulation of claim ~~17~~ 13 or ~~18~~14, in the manufacture of a medicament for treating congestion, edema, fluid overload, or hypertension in a patient in need thereof.

~~23~~20. The liquid pharmaceutical formulation for use, the unit liquid pharmaceutical formulation for use, or use of claim ~~21~~18 or ~~22~~19, wherein the liquid pharmaceutical formulation or the unit liquid pharmaceutical formulation is to be administered to the patient by

subcutaneous injection or subcutaneous infusion.

~~24~~21. The liquid pharmaceutical formulation for use, the unit liquid pharmaceutical formulation for use, or use of claim ~~23~~20, wherein the liquid pharmaceutical formulation is to be administered to the patient by subcutaneous infusion using an on-body, subcutaneous delivery system.

~~25~~22. The liquid pharmaceutical formulation for use, the unit liquid pharmaceutical formulation for use, or use of claim ~~24~~21, wherein the on-body, subcutaneous delivery system is a pump device.

~~26~~23. A kit for the treatment of congestion, edema, fluid overload, or hypertension comprising a liquid pharmaceutical formulation of any one of claims 1~~16~~12, or the unit liquid pharmaceutical formulation of claim ~~17~~13 or ~~18~~14; and instructions for treating the congestion, edema, fluid overload, or hypertension.