In one aspect, there is provided the use of a pharmaceutical formulation in the preparation of a medicament for treating edema, hypertension or heart failure or treating a patient exhibiting the symptoms of edema, hypertension or heart failure, wherein the pharmaceutical formulation comprises:

furosemide, or a pharmaceutically acceptable salt, hydrate or ester thereof; and

a pharmaceutically acceptable buffer comprising

tris(hydroxymethyl)aminomethane, wherein the concentration of

tris(hydroxymethyl)aminomethane in the pharmaceutical formulation is greater than or equal to about 50 mM;

wherein the pharmaceutical formulation has a pH between about 7 to about 8.5 and the molar ratio of tris(hydroxymethyl)aminomethane to furosemide is greater than one.

In one aspect, there is provided a pharmaceutical formulation comprising:

furosemide, or a pharmaceutically acceptable salt, hydrate or ester thereof; and

a pharmaceutically acceptable buffer comprising

tris(hydroxymethyl)aminomethane, wherein the concentration of

tris(hydroxymethyl)aminomethane in the pharmaceutical formulation is greater than or equal to about 50 mM,

wherein the molar ratio of tris(hydroxymethyl)aminomethane to furosemide is greater than one, and the pharmaceutical formulation has a pH between about 7 to about 8.5 and is isosmotic.

In one aspect, there is provided the pharmaceutical formulation as described herein for use as a medicament.

Thus, in ~~one~~ another aspect, the present teachings provide methods for treating a patient with edema or hypertension, which can be due to congestive heart failure, or renal or hepatic insufficiency or failure. The methods generally include administering to a patient a pharmaceutical formulation of the present teachings,

where the pharmaceutical formulation includes furosemide, or a pharmaceutically acceptable salt, hydrate or ester thereof; and a pharmaceutically acceptable buffer including Tris, where the concentration of Tris in the pharmaceutical formulation can be greater than or equal to about 50 mM, and the pharmaceutical formulation has a molar excess of Tris to furosemide and a pH in the range of about 7 to about 8.5. In various embodiments, the pharmaceutical formulation can be isoosmotic.

In particular embodiments, methods of treating a patient with or exhibiting the symptoms of edema, hypertension or heart failure can include administering subcutaneously to a patient using a patch device a pharmaceutical formulation including between about 6 mg/mL to about 10 mg/mL of furosemide, or a pharmaceutically acceptable salt, hydrate or ester thereof; and a pharmaceutically acceptable buffer comprising Tris, where the concentration of Tris in the pharmaceutical formulation is greater than or equal to about 50 mM; and where the molar ratio of Tris to furosemide is greater than or equal to 1.65, and the pharmaceutical formulation has a pH between about 7.2 to about 8 and is isoosmotic.

In another aspect, the present teachings provide pharmaceutical formulations including furosemide, or pharmaceutically acceptable salt, hydrate or ester thereof; and a pharmaceutically acceptable buffer including Tris in an amount greater than or equal to about 50 mM, where the molar ratio of Tris to furosemide is greater than one and the pharmaceutical formulation can have a pH in the range of about 7 to about 8.5 and can be isoosmotic.

The foregoing as well as other features and advantages of the present teachings will be more fully understood from the following figures, description, examples, and claims.

CLAIMS

1. A method of treating a patient with or exhibiting the symptoms of edema, hypertension or heart failure, the method comprising:

administering to a patient a pharmaceutical formulation, wherein the pharmaceutical formulation comprises:

furosemide, or a pharmaceutically acceptable salt, hydrate or ester thereof; and

a pharmaceutically acceptable buffer comprising tris(hydroxymethyl)aminomethane, wherein the concentration of tris(hydroxymethyl)aminomethane in the pharmaceutical formulation is greater than or equal to about 50 mM;

wherein the pharmaceutical formulation has a pH between about 7 to about 8.5 and the molar ratio of tris(hydroxymethyl)aminomethane to furosemide is greater than one.

2. The method of claim 1, wherein the pharmaceutical formulation is isoosmotic.

3. The method of claim 1 or 2, wherein the molar ratio of tris(hydroxymethyl)aminomethane to furosemide is greater than or equal to two.

4. The method of claim 1 or 2, wherein the concentration of tris(hydroxymethyl)aminomethane in the pharmaceutical formulation is in a range of about 50 mM to about 250 mM.

5. The method of any one of claims 1-4, wherein the pharmaceutical formulation has a pH between about 7.2 to about 8.

6. The method of any one of claims 1-5, wherein the amount of furosemide in the pharmaceutical formulation is between about 6 mg/mL to about 10 mg/mL.

7. The method of any one of claims 1-6, wherein administering comprises administering subcutaneously the pharmaceutical formulation.

8. The method of claim 7, wherein administering subcutaneously comprises using a pump device.

9. The method of claim 8, wherein the pump device is a patch device.

10. The method of any one of claims 1-6, wherein administering comprises administering intravenously the pharmaceutical formulation.

11. A method of treating a patient with or exhibiting the symptoms of edema, hypertension or heart failure, the method comprising:

administering subcutaneously to a patient using a patch device a pharmaceutical formulation comprising:

furosemide, or a pharmaceutically acceptable salt, hydrate or ester thereof, wherein the pharmaceutical formulation comprises between about 6 mg/mL to about 10 mg/mL of furosemide; and

a pharmaceutically acceptable buffer comprising tris(hydroxymethyl)aminomethane, wherein the concentration of tris(hydroxymethyl)aminomethane in the pharmaceutical formulation is greater than or equal to about 50 mM;

wherein the molar ratio of tris(hydroxymethyl)aminomethane to furosemide is greater than or equal to 1.65, and the pharmaceutical formulation has a pH between about 7.2 to about 8 and is isoosmotic.

12. A pharmaceutical formulation comprising:

furosemide, or a pharmaceutically acceptable salt, hydrate or ester thereof; and

a pharmaceutically acceptable buffer comprising tris(hydroxymethyl)aminomethane, wherein the concentration of tris(hydroxymethyl)aminomethane in the pharmaceutical formulation is greater than or equal to about 50 mM,

wherein the molar ratio of tris(hydroxymethyl)aminomethane to furosemide is greater than or equal to one, and the pharmaceutical formulation has a pH between about 7 to about 8.5 and is isoosmotic.

13. The pharmaceutical formulation of claim 12, wherein the pharmaceutical formulation comprises between about 6 mg/mL to about 10 mg/mL of furosemide.

14. The pharmaceutical formulation of claim 12 or 13, wherein the pharmaceutical formulation has a pH between about 7.2 to about 8.

15. The pharmaceutical formulation of any one of claims 12-14, wherein the pharmaceutical formulation is substantially pH stable at room temperature for at least one year.

16. The pharmaceutical formulation of any one of claims 12-14, wherein the pharmaceutical formulation is substantially API stable at room temperature for at least one year.

17. The pharmaceutical formulation of any one of claims 12-14, wherein the pharmaceutical formulation exhibits increased pH stability when exposed to a temperature of about 70 °C for three months compared to a substantially identical pharmaceutical formulation but for the molar ratio of tris(hydroxymethyl)aminomethane to furosemide being about 1:1.

18. The pharmaceutical formulation of any one of claims 12-14, wherein the pharmaceutical formulation exhibits increased API stability when exposed to a temperature of about 70 °C for three months compared to a substantially identical pharmaceutical formulation but for the molar ratio of tris(hydroxymethyl)aminomethane to furosemide being about 1:1.

19. The pharmaceutical formulation of any one of claims 12-14, wherein the pharmaceutical formulation exhibits increased API stability when exposed to light compared to a substantially identical pharmaceutical formulation but for the molar ratio of tris(hydroxymethyl)aminomethane to furosemide being about 1:1.

20. The pharmaceutical formulation of any one of claims 12-14, wherein the pharmaceutical formulation exhibits increased API stability under termination

sterilization conditions compared to a substantially identical pharmaceutical formulation but for the molar ratio of tris(hydroxymethyl)aminomethane to furosemide being about 1:1.

21. The pharmaceutical formulation of any one of claims 12-14, wherein the pharmaceutical formulation exhibits increased API stability at room temperature for two years compared to a substantially identical pharmaceutical formulation but for the molar ratio of tris(hydroxymethyl)aminomethane to furosemide being about 1:1.

22. The pharmaceutical formulation of any one of claims 12-14, wherein the pharmaceutical formulation is loaded in a pump device.

23. The pharmaceutical formulation of claim 19, wherein the pump device is a patch device.

CLAIMS

1. Use of a pharmaceutical formulation in the preparation of a medicament for treating edema, hypertension or heart failure or treating a patient exhibiting the symptoms of edema, hypertension or heart failure, wherein the pharmaceutical formulation comprises:

furosemide, or a pharmaceutically acceptable salt, hydrate or ester thereof; and

a pharmaceutically acceptable buffer comprising tris(hydroxymethyl)aminomethane, wherein the concentration of tris(hydroxymethyl)aminomethane in the pharmaceutical formulation is greater than or equal to about 50 mM;

wherein the pharmaceutical formulation has a pH between about 7 to about 8.5 and the molar ratio of tris(hydroxymethyl)aminomethane to furosemide is greater than one.

2. The use of claim 1, wherein the pharmaceutical formulation is isoosmotic.

3. The use of claim 1 or 2, wherein the molar ratio of tris(hydroxymethyl)aminomethane to furosemide is greater than or equal to two.

4. The use of claim 1 or 2, wherein the concentration of tris(hydroxymethyl)aminomethane in the pharmaceutical formulation is in a range of about 50 mM to about 250 mM.

5. The use of any one of claims 1-4, wherein the pharmaceutical formulation has a pH between about 7.2 to about 8.

6. The use of any one of claims 1-5, wherein the amount of furosemide in the pharmaceutical formulation is between about 6 mg/mL to about 10 mg/mL.

7. The use of any one of claims 1-6, wherein the pharmaceutical formulation is administered subcutaneously.

8. The use of claim 7, wherein the pharmaceutical formulation is administered subcutaneously using a pump device.

9. The use of claim 8, wherein the pump device is a patch device.

10. The use of any one of claims 1-6, wherein the pharmaceutical formulation is administered intravenously.

11. The use of claim 1 wherein the pharmaceutical formulation is administered subcutaneously using a patch device;

wherein the pharmaceutical formulation comprises between about 6 mg/mL to about 10 mg/mL of furosemide; and

wherein the molar ratio of tris(hydroxymethyl)aminomethane to furosemide is greater than or equal to 1.65, and the pharmaceutical formulation has a pH between about 7.2 to about 8 and is isoosmotic.

12. A pharmaceutical formulation comprising:

furosemide, or a pharmaceutically acceptable salt, hydrate or ester thereof; and

a pharmaceutically acceptable buffer comprising tris(hydroxymethyl)aminomethane, wherein the concentration of tris(hydroxymethyl)aminomethane in the pharmaceutical formulation is greater than or equal to about 50 mM,

wherein the molar ratio of tris(hydroxymethyl)aminomethane to furosemide is greater than one, and the pharmaceutical formulation has a pH between about 7 to about 8.5 and is isoosmotic.

13. The pharmaceutical formulation of claim 12, wherein the pharmaceutical formulation comprises between about 6 mg/mL to about 10 mg/mL of furosemide.

14. The pharmaceutical formulation of claim 12 or 13, wherein the pharmaceutical formulation has a pH between about 7.2 to about 8.

15. The pharmaceutical formulation of any one of claims 12-14, wherein the pharmaceutical formulation is substantially pH stable at room temperature for at least one year.

16. The pharmaceutical formulation of any one of claims 12-14, wherein the pharmaceutical formulation is substantially API stable at room temperature for at least one year.

17. The pharmaceutical formulation of any one of claims 12-14, wherein the pharmaceutical formulation exhibits increased pH stability when exposed to a temperature of about 70 °C for three months compared to a substantially identical pharmaceutical formulation but for the molar ratio of tris(hydroxymethyl)aminomethane to furosemide being about 1:1.

18. The pharmaceutical formulation of any one of claims 12-14, wherein the pharmaceutical formulation exhibits increased API stability when exposed to a temperature of about 70 °C for three months compared to a substantially identical pharmaceutical formulation but for the molar ratio of tris(hydroxymethyl)aminomethane to furosemide being about 1:1.

19. The pharmaceutical formulation of any one of claims 12-14, wherein the pharmaceutical formulation exhibits increased API stability when exposed to light compared to a substantially identical pharmaceutical formulation but for the molar ratio of tris(hydroxymethyl)aminomethane to furosemide being about 1:1.

20. The pharmaceutical formulation of any one of claims 12-14, wherein the pharmaceutical formulation exhibits increased API stability under termination sterilization conditions compared to a substantially identical pharmaceutical formulation but for the molar ratio of tris(hydroxymethyl)aminomethane to furosemide being about 1:1.

21. The pharmaceutical formulation of any one of claims 12-14, wherein the pharmaceutical formulation exhibits increased API stability at room temperature for two years compared to a substantially identical pharmaceutical formulation but for the molar ratio of tris(hydroxymethyl)aminomethane to furosemide being about 1:1.

22. The pharmaceutical formulation of any one of claims 12-14, wherein the pharmaceutical formulation is loaded in a pump device.

23. The pharmaceutical formulation of claim 22, wherein the pump device is a patch device.

24. The pharmaceutical formulation of any one of claims 12-23 for use as a medicament.