soluble in acidic solutions. Conversely, in basic solutions, iron ions will form insoluble oxides and precipitate from the formulation, unless a chelating agent, such as EDTA is present.

[0009] Soluble ferric pyrophosphate (SFP) is a complex iron salt that has a molecular mass of about 1000 Da and is highly soluble in aqueous solutions, allowing its infusion via aqueous solutions, e.g., dialysate. The administration of SFP overcomes both absolute and functional iron deficiencies in patients, including hemodialysis-dependent CKD (HDD-CKD) patients, and could significantly reduce the amount of erythropoiesis-stimulating agents needed to treat these patients.

[0010] U.S. Patent Nos. 6,689,275; 6,779,468; and 7,857,977; incorporated herein by reference, disclose the addition of SFP to liquid bicarbonate solutions for hemodialysis. However, conventional SFP compositions, such as food grade SFP (FCC-SFP), can dissolve incompletely in aqueous solutions and are not suitable for pharmaceutical applications.

SUMMARY

[0010a] In one aspect of the present disclosure, there is provided a solid particulate formulation of soluble ferric pyrophosphate comprising soluble ferric pyrophosphate having a particle size less than 5 μM, optionally less than 4 μM, wherein the soluble ferric pyrophosphate dissolves in aqueous solution in less than 1 minute.

[0010b] In another aspect of the present disclosure, there is provided a sachet comprising the solid particulate formulation as defined herein.

[0010c] In yet another aspect of the present disclosure, there is provided a use of soluble ferric pyrophosphate for the preparation of a medicament for administering a dialysate to a subject in need thereof, wherein a solid particulate formulation of soluble ferric pyrophosphate is mixed with a hemodialysis solution to form said dialysate.

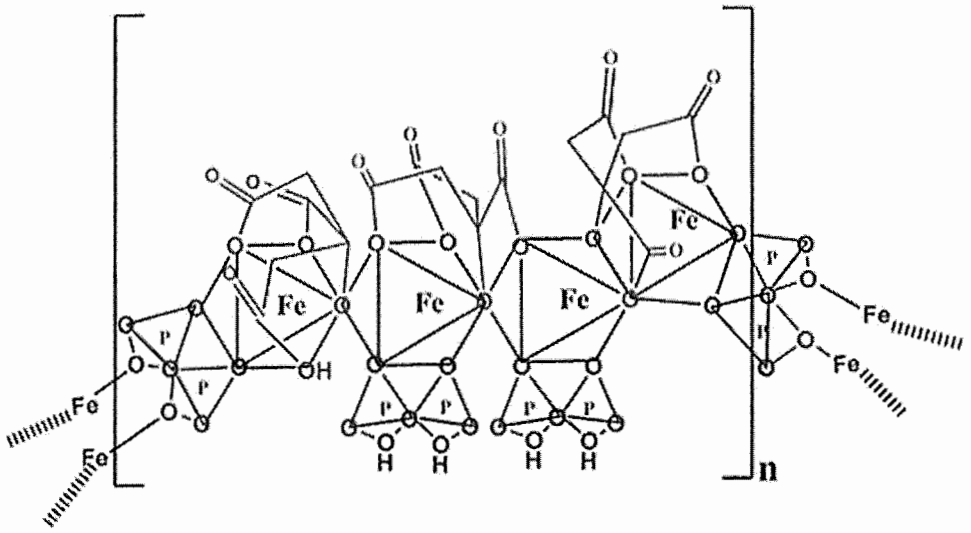
[0010d] In a further aspect of the present disclosure, there is provided a soluble ferric pyrophosphate for use in administering a dialysate, wherein a solid particulate formulation of soluble ferric pyrophosphate is mixed with a hemodialysis solution to form the dialysate.

[0010e] In another aspect of the present disclosure, there is provided a kit comprising the solid particulate formulation of soluble ferric pyrophosphate or sachet as defined herein and a dialysis concentrate formulation in a solid or liquid form.

[0011] The present disclosure is directed to a solid particulate formulation of soluble ferric pyrophosphate (SFP). The present disclosure also provides that the solid particulate formulation of SFP is a powder formulation. The present disclosure further provides that the solid particulate formulation of SFP is a granule formulation. The present disclosure also provides that the dialysis concentrate formulation is an acid. The present disclosure further provides that the dialysis concentrate formulation is a base. The present disclosure further provides a kit comprising a solid particulate formulation of SFP and a dialysis concentrate formulation in a solid or liquid form.

[0012] The present disclosure provides a solid particulate formulation of SFP comprising SFP having a particle size less than about 5 microns, wherein the SFP dissolves in aqueous solution, e.g., dialysis solution or intravenous solution or intravenous fluids, in less than 1 minute. The present disclosure also provides that the solubility of the SFP in aqueous solution is greater than 1 gram per milliliter. The present disclosure further provides that the SFP has an angle of repose less than 45 degrees, optionally less than 42 degrees. The present disclosure also provides that the solid particulate formulation is stable in aqueous solution at ambient temperature for at least 24 months.

[0013] The present disclosure further provides that the solid particulate formulation of SFP comprises SFP comprising iron chelated with citrate and pyrophosphate. The present disclosure also provides that the SFP comprising iron chelated with citrate and pyrophosphate is ferric pyrophosphate citrate (FPC) having structure (I):



(I).

[0014] The present disclosure also provides that the solid particulate formulation comprises SFP comprising iron in an amount of 7% to 11% by weight, citrate in an amount of at least 14% by weight, and pyrophosphate in an amount of at least 10% by weight.

[0015] The present disclosure also provides a sachet (e.g., a packet) comprising a solid particulate formulation of SFP described herein. The present disclosure further provides that the sachet comprises a dose or multiple doses of SFP that will be added to a dialysis solution to form a dialysate and result in a final iron concentration of about 110 mcg/L (about 2 μM) in the dialysate to be administered to a patient e.g., during hemodialysis or hemodiafiltration. The present disclosure also provides that the sachet comprises a dose or multiple doses of SFP that will be added to an intravenous solution to form an intravenous fluid with a final iron concentration of 1 mg per liter to 1 mg per mL, to be administered to a patient via intravenous injection or infusion. The present disclosure further provides that the sachet comprises a dose or multiple doses of SFP that can be mixed with food or drink to provide a nutritional supplement.

[0016] The present disclosure further provides an improved method of administering SFP comprising (a) mixing a solid particulate formulation of SFP with a dialysis solution to form a dialysate and (b) administering the dialysate to a subject in need. The present disclosure also provides that the dialysis solution is an acid solution. The present disclosure further provides that the acid solution comprises citrate or lactate. The present disclosure also provides that the dialysis solution is a base solution. The present disclosure further provides that the base solution comprises bicarbonate. The present disclosure also provides that the solubility of the solid particulate formulation in the base solution is greater than 1 gram per mL. The present disclosure further provides that the mixing of the solid particulate

formulation of SFP with the dialysis solution results in an iron concentration of about 100 mcg per L to about 150 mcg per L in the dialysate.

[0017] The present disclosure also provides that the improved method of administering SFP comprises administering a solid particulate formulation of SFP comprising iron chelated with citrate and pyrophosphate. The present disclosure further provides that the improved method of administering SFP comprises administering a solid particulate formulation of SFP comprising iron in an amount of 7% to 11% by weight, citrate in an amount of at least 14% by weight, and pyrophosphate in an amount of at least 10% by weight. The present disclosure also provides that the improved method of administering SFP comprises administering a solid particulate formulation of FPC comprising iron chelated with citrate and pyrophosphate having structure (I).

[0018] The foregoing summary is not intended to define every embodiment of the present disclosure, and other features and advantages of the present disclosure will become apparent from the following detailed description, including the drawings. The present disclosure is intended to be related as a unified document, and it should be understood that all combinations of features described herein are contemplated, even if the combination of features are not found together in the same sentence, paragraph, or section of this disclosure. In addition, the disclosure includes all embodiments of the present disclosure narrower in scope in any way than the variations specifically mentioned above. With respect to the disclosure described or claimed with "a" or "an," it should be understood that these terms mean "one or more" unless context unambiguously requires a more restricted meaning. With respect to elements described as one or more within a set, it should be understood that all combinations within the set are contemplated. If the disclosure is described as "comprising" a feature, embodiments also are contemplated "consisting of" or "consisting essentially of" the feature. Additional features and variations of the disclosure will be apparent to those skilled in the art from the entirety of this application, and all such features are intended as part of the disclosure.

DETAILED DESCRIPTION

[0019] The present disclosure provides a solid particulate formulation of soluble ferric pyrophosphate (SFP) and a kit comprising a solid particulate formulation of SFP and a dialysis concentrate formulation. The disclosure also provides an improved method of administering SFP comprising mixing a solid particulate formulation of SFP described herein with a dialysis

WHAT IS CLAIMED:

1. A solid particulate formulation of soluble ferric pyrophosphate comprising soluble ferric pyrophosphate having a particle size less than 5 μM, optionally less than 4 μM, wherein the soluble ferric pyrophosphate dissolves in aqueous solution in less than 1 minute.

2. The solid particulate formulation of claim 2, wherein the solubility of the soluble ferric pyrophosphate in aqueous solution is greater than 1 gram per mL.

3. The solid particulate formulation of claim 1 or 2, wherein the soluble ferric pyrophosphate has an angle of repose less than 45 degrees, optionally less than 42 degrees.

4. The solid particulate formulation of any one of claims 1-3 that is stable in aqueous solution at ambient temperature for at least 24 months.

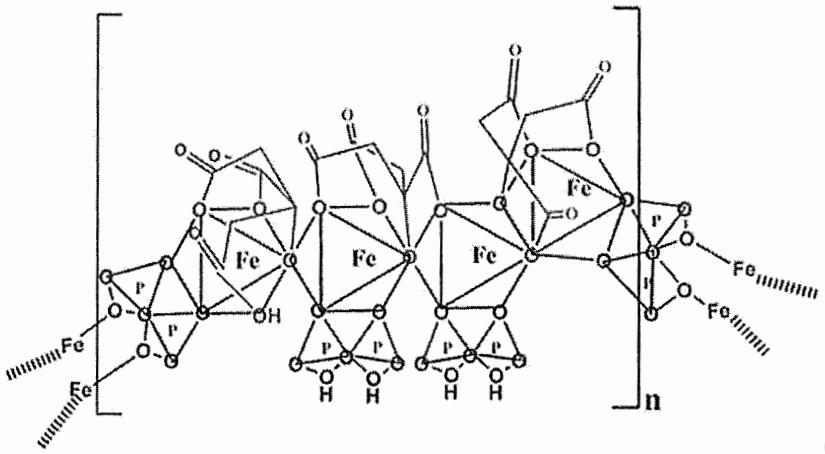
5. The solid particulate formulation of any one of claims 1-4, wherein the soluble ferric pyrophosphate comprises

a) iron in an amount of 7% to 11% by weight, citrate in an amount of at least 14%, and pyrophosphate in an amount of at least 10%,

b) iron in an amount from 7.5-9.0% by weight, citrate in an amount from 15-22% by weight, pyrophosphate in an amount from 15-22% by weight, phosphate in an amount less than 2%, sodium in an amount from 18-25% by weight, and sulfate in an amount from 20-35% by weight, or

c) iron in an amount from 9-14% by weight, citrate in an amount from 30-60% by weight, pyrophosphate in an amount from 5-20% by weight, sodium in an amount from 1-15% by weight, and essentially no sulfate.

6. The solid particulate formulation of any one of claims 1-5, comprising a compound having structure (I):



(I).

7. A sachet comprising the solid particulate formulation of any one of claims 1-6.

8. The sachet of claim 7, comprising a dose of soluble ferric pyrophosphate that will result in a final iron concentration of 110 μg/L or 2 μM in a dialysate to be administered to a patient receiving hemodialysis.

9. Use of soluble ferric pyrophosphate for the preparation of a medicament for administering a dialysate to a subject in need thereof, wherein a solid particulate formulation of soluble ferric pyrophosphate is mixed with a hemodialysis solution to form said dialysate.

10. A soluble ferric pyrophosphate for use in administering a dialysate, wherein a solid particulate formulation of soluble ferric pyrophosphate is mixed with a hemodialysis solution to form the dialysate.

11. The soluble ferric pyrophosphate or use of claim 9 or 10, wherein the dialysis solution is an acid solution or a base solution.

12. The soluble ferric pyrophosphate or use of claim 11, wherein the acid solution comprises water, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, dextrose, and citric or acetic acid or a citrate or acetate salt.

13. The soluble ferric pyrophosphate or use of claim 11 or 12, wherein the solubility of the solid particulate formulation in the acid solution is greater than 1 gram per mL.

14. The soluble ferric pyrophosphate or use of claim 11, wherein the base solution comprises sodium bicarbonate or a combination of sodium bicarbonate and sodium chloride.

15. The soluble ferric pyrophosphate or use of claim 11 or 14, wherein the solubility of the solid particulate formulation in the base solution is greater than 1 gram per mL.

16. The soluble ferric pyrophosphate or use of any one of claims 9-15, wherein the mixing of soluble ferric pyrophosphate results in a final iron concentration of about 100 μg/L to about 150 μg/L in the dialysate.

17. The soluble ferric pyrophosphate or use of any one of claims 9-16, wherein the soluble ferric pyrophosphate comprises

a) iron chelated with citrate and pyrophosphate,

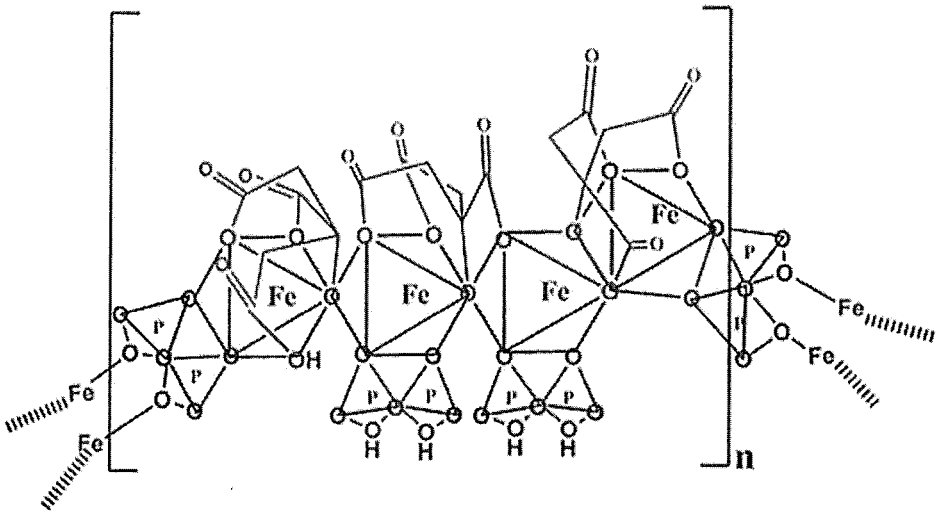
b) iron in an amount of 7% to 11% by weight, citrate in an amount of at least 14%, and pyrophosphate in an amount of at least 10%,

c) iron in an amount from 7.5-9.0% by weight, citrate in an amount from 15-22% by weight, pyrophosphate in an amount from 15-22% by weight, phosphate in an amount less than 2%, sodium in an amount from 18-25% by weight, and sulfate in an amount from 20-35% by weight,

d) iron in an amount from 9-14% by weight, citrate in an amount from 30-60% by weight, pyrophosphate in an amount from 5-20% by weight, sodium in an amount from 1-15% by weight, and essentially no sulfate,

e) iron chelated with citrate and pyrophosphate having at least one of: a Fe-O distance of 2.00 angstroms in the primary coordination shell, a Fe-C distance of 2.98 angstroms, and a Fe-P distance of 3.20 angstroms in the second coordination sphere of Fe.

18. The soluble ferric pyrophosphate or use of any one of claims 9-17, wherein the solid particulate formulation comprises a compound having structure (I):



(I).

19. A kit comprising the solid particulate formulation of soluble ferric pyrophosphate or sachet of any one of claims 1-8 and a dialysis concentrate formulation in a solid or liquid form.

20. The kit of claim 19, wherein the dialysis concentrate formulation is a solid form.

21. The kit of claim 19, wherein the dialysis concentrate formulation is a liquid form.

22. The kit of any of claims 19-21, wherein the dialysis concentrate formulation is an acid.

23. The kit of any of claims 19-21, wherein the dialysis concentrate formulation is a base.