[0005] Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the United States. This condition is associated with obesity, type-II adult onset diabetes, sedentary lifestyle, and diets high in fat. The earlier stage of NAFLD, fatty liver, is potentially reversible when proper treatment steps are taken. However, left unchecked, it can progress to inflammation of liver cells (non-alcoholic steatohepatitis, or NASH) which is much more difficult to treat. Without treatment, NASH can result in irreversible scarring of liver tissue (steatonecrosis), with the potential to cause cirrhosis, liver failure, and liver cancer.

[0006] 25HC3S has been disclosed as a pharmaceutically acceptable salt, such as a sodium salt, for example (e.g., U.S. Patent 10,144,759 and Ogawa et al., Steroids, 74, 81-87 (2009)). Crystalline solids tend to be more favorable for processing, storage, and stability than non-crystalline solids. However, energetics may not favor the ready formation of suitable crystalline solids and polymorphism may make creating stable crystalline solids of a particular active pharmaceutical ingredient impractical. Herein, the inventors disclose crystalline 25HC3S sodium including stable anhydrates, solvates, and hydrates as well as liquid crystal 25HC3S sodium. Methods for preparing 25HC3S are also provided.

SUMMARY

[0007] In some examples of the present disclosure, crystalline 25HC3S sodium is provided.

[0007a] In one aspect of the present disclosure, there is provided a crystalline 25HC3S sodium.

[0007b] In another aspect of the present disclosure, there is provided a hydrate of crystalline 25HC3S sodium.

[0007c] In a further aspect of the present disclosure, there is provided a Form I of crystalline 25HC3S sodium.

[0007d] In another aspect of the present disclosure, there is provided a Form II of crystalline 25HC3S sodium.

[0007e] In a further aspect of the present disclosure, there is provided a Form XI of crystalline 25HC3S sodium.

[0007f] In another aspect of the present disclosure, there is provided an anhydrous crystalline 25HC3S sodium.

[0007g] In a further aspect of the present disclosure, there is provided a Form XIII crystalline 25HC3S sodium.

[0007h] In another aspect of the present disclosure, there is provided a Form IX crystalline 25HC3S sodium.

[0007i] In a further aspect of the present disclosure, there is provided a use of 25HC3S sodium disclosed herein, in the manufacture of a medicament for treating one or more of hypercholesterolemia, hypertriglyceridemia, and conditions related to fat accumulation and inflammation.

[0007j] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising 25HC3S sodium disclosed herein, and at least one pharmaceutically acceptable excipient.

[0007k] In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition of 25HC3S sodium disclosed herein, in the manufacture of a medicament for treating one or more of hypercholesterolemia, hypertriglyceridemia, and conditions related to fat accumulation and inflammation.

[0007l] In another aspect of the present disclosure, there is provided a composition comprising two or more of Form I 25HC3S sodium, Form II 25HC3S sodium, Form III 25HC3S sodium, Form V 25HC3S sodium, Form IX 25HC3S sodium, Form XI 25HC3S sodium, and Form XIII 25HC3S sodium.

[0007m] In a further aspect of the present disclosure, there is provided a method of producing a 5-cholesten-3β,25-diol-3-sulfate metal salt, the method comprising:

contacting 25-hydroxy-(3β)-cholest-5-en-3-ol with at least one sulfating agent in at least one solvent to produce a 25-hydroxy-(3β)-cholest-5-en-3-sulfate organic cationic salt, wherein the 25-hydroxy-(3β)-cholest-5-en-3-sulfate organic cationic salt has low solubility in the at least one solvent; and

contacting the 25-hydroxy-(3β)-cholest-5-en-3-sulfate organic cationic salt with at least one metal salt to produce the 5-cholesten-3β,25-diol 3-sulfate metal salt.

[0007n] In another aspect of the present disclosure, there is provided a method of producing a 5-cholesten-3β,25-diol 3-sulfate sodium salt, the method comprising:

contacting 25-hydroxy-(3β)-cholest-5-en-3-ol with a sulfur trioxide-pyridine complex in at least one solvent to produce a 25-hydroxy-(3β)-cholest-5-en-3-sulfate pyridinium salt, wherein the 25-hydroxy-(3β)-cholest-5-en-3-sulfate pyridinium salt has low solubility in the at least one solvent; and

contacting the 25-hydroxy-(3β)-cholest-5-en-3-sulfate pyridinium salt with a sodium salt to produce the 5-cholesten-3β,25-diol 3-sulfate sodium salt.

[0007o] In a further aspect of the present disclosure, there is provided a method of producing a 5-cholesten-3β,25-diol 3-sulfate metal salt, the method comprising:

contacting (3β)-cholest-5-en-3-ol with at least one sulfating agent to produce a first (3β)-cholest-5-en-3-sulfate organic cationic salt;

contacting the first (3β)-cholest-5-en-3-sulfate organic cationic salt with an organic base to produce a second (3β)-cholest-5-en-3-sulfate organic cationic salt;

oxidizing the second (3β)-cholest-5-en-3-sulfate organic cationic salt in the presence of at least one surfactant to produce a 25-hydroxy-(3β)-cholest-(5,6-epoxy)-3-sulfate organic cationic salt;

generating a 25-hydroxy-(3β)-cholest-5-en-3-sulfate organic cationic salt from the 25-hydroxy-(3β)-cholest-(5,6-epoxy)-3-sulfate organic cationic salt by deoxygenation; and

contacting the 25-hydroxy-(3β)-cholest-5-en-3-sulfate organic cationic salt with at least one metal salt to produce the 5-cholesten-3β,25-diol 3-sulfate metal salt.

[0007p] In another aspect of the present disclosure, there is provided a composition comprising:

25-hydroxy-(3β)-cholest-5-en-3-sulfate; and

sulfated desmosterol.

[0007q] In a further aspect of the present disclosure, there is provided a composition comprising:

25-hydroxy-(3β)-cholest-5-en-3-sulfate; and

5-cholesten-3β-25-diol-disulfate.

[0007r] In another aspect of the present disclosure, there is provided a method comprising:

sulfating 25-hydroxy-(3β)-cholest-5-en-3-ol to produce 25-hydroxy-(3β)-cholest-5-en-3-sulfate in at least one solvent, wherein 25-hydroxy-(3β)-cholest-5-en-3-sulfate has low solubility in the at least one solvent; and

precipitating 25-hydroxy-(3β)-cholest-5-en-3-sulfate in the solvent.

[0007s] In a further aspect of the present disclosure, there is provided a composition comprising:

25-hydroxy-(3β)-cholest-5-en-3-sulfate; and

byproducts from sulfating 25-hydroxy-(3β)-cholest-5-en-3-ol comprising a first compound comprising a high-pressure liquid chromatography (HPLC) retention time of about 18.3 minutes, a second compound comprising an HPLC retention time of about 37.7 minutes, or any combination thereof, and the 25-hydroxy-(3β)-cholest-5-en-3-sulfate comprising an HPLC retention time of about 7.7 minutes,

wherein the first compound, the second compound, and the 25-hydroxy-(3β)-cholest-5-en-3-sulfate are separated by HPLC comprising a C8 stationary phase operating at about 45 ºC with a first mobile phase comprising a buffer and a second mobile phase comprising one or more organic solvents.

[0007t] In another aspect of the present disclosure, there is provided a 25HC3S sodium disclosed herein, or the pharmaceutical composition disclosed herein, for use in therapy.

[0008] In some examples of the present disclosure, stable crystalline 25HC3S sodium is provided.

[0009] In further examples of the present disclosure, hydrates of crystalline 25HC3S sodium are provided.

[0010] In yet further examples of the present disclosure, monohydrates of crystalline 25HC3S sodium are provided.

[0011] In still further examples of the present disclosure, dihydrates of crystalline 25HC3S sodium are provided.

[0012] In additional examples of the present disclosure, variable hydrates of crystalline 25HC3S sodium are provided.

[0013] In some examples of the present disclosure, anhydrous crystalline 25HC3S sodium is provided.

[0014] In additional examples of the present disclosure, Form I, Form II, Form III, Form IX, Form XI, and Form XIII of crystalline 25HC3S sodium are provided.

[0015] In additional examples of the present disclosure, liquid crystal 25HC3S sodium is provided.

[0016] In some examples of the present disclosure, mesophases of 25HC3S sodium are provided.

[0017] In further examples of the present disclosure, Form V 25HC3S sodium is provided.

[0018] In yet additional examples of the present disclosure, mixtures of two or more of Form I of 25HC3S sodium, Form II of 25HC3S sodium, Form III of 25HC3S sodium, Form V of 25HC3S sodium, Form IX of 25HC3S sodium, Form XI of 25HC3S sodium, or Form XIII of 25HC3S sodium are provided.

[0019] In some examples of the present disclosure, methods of treating one or more of hypercholesterolemia, hypertriglyceridemia, and conditions related to fat accumulation and inflammation, for example, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic hepatitis, acute kidney injury (AKI), psoriasis, or atherosclerosis, comprising administering to a patient in need thereof an effective amount of a compound or pharmaceutical composition thereof of crystalline or liquid crystal mesophase 25HC3S sodium are provided.

[0020] In further examples of the present disclosure, pharmaceutical compositions comprising crystalline 25HC3S sodium or liquid crystal 25HC3S sodium or both and at least one pharmaceutically acceptable excipient are provided.

[0021] In further examples of the present disclosure, pharmaceutical compositions comprising mixtures of two or more of crystalline 25HC3S sodium Form I, crystalline 25HC3S sodium Form II, crystalline 25HC3S sodium Form III, liquid crystal 25HC3S sodium Form V, crystalline 25HC3S sodium Form IX, crystalline 25HC3S sodium Form XI, or crystalline 25HC3S sodium Form XIII and at least one pharmaceutically acceptable excipient are provided.

[0022] Examples of the present disclosure also include methods for preparing 25HC3S. In some cases, methods include contacting 25-hydroxy-(3β)-cholest-5-en-3-ol with a sulfating agent to produce a 25-hydroxy-(3β)-cholest-5-en-3-sulfate organic cationic salt; and contacting the 25-hydroxy-(3β)-cholest-5-en-3-sulfate organic cationic salt with at least one metal salt to produce the 5-cholesten-3β,25-diol 3-sulfate metal salt.

WHAT IS CLAIMED IS:

1. Crystalline 25HC3S sodium.

2. A hydrate of crystalline 25HC3S sodium.

3. Form I of crystalline 25HC3S sodium.

4. Form II of crystalline 25HC3S sodium.

5. Form XI of crystalline 25HC3S sodium.

6. Anhydrous crystalline 25HC3S sodium.

7. Form XIII crystalline 25HC3S sodium.

8. Form IX crystalline 25HC3S sodium.

9. Use of 25HC3S sodium of any one of claims 1-8, in the manufacture of a medicament for treating one or more of hypercholesterolemia, hypertriglyceridemia, and conditions related to fat accumulation and inflammation.

10. A pharmaceutical composition comprising 25HC3S sodium of any one of claims 1-8, and at least one pharmaceutically acceptable excipient.

11. Use of a pharmaceutical composition of 25HC3S sodium of claim 10, in the manufacture of a medicament for treating one or more of hypercholesterolemia, hypertriglyceridemia, and conditions related to fat accumulation and inflammation.

12. The use of claim 9 in the treatment of nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), alcoholic hepatitis, acute kidney injury (AKI), psoriasis, or atherosclerosis.

13. The use of claim 11 in the treatment of nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), alcoholic hepatitis, acute kidney injury (AKI), psoriasis, or atherosclerosis.

14. A composition comprising two or more of Form I 25HC3S sodium, Form II 25HC3S sodium, Form III 25HC3S sodium, Form V 25HC3S sodium, Form IX 25HC3S sodium, Form XI 25HC3S sodium, and Form XIII 25HC3S sodium.

15. A method of producing a 5-cholesten-3β,25-diol-3-sulfate metal salt, the method comprising:

contacting 25-hydroxy-(3β)-cholest-5-en-3-ol with at least one sulfating agent in at least one solvent to produce a 25-hydroxy-(3β)-cholest-5-en-3-sulfate organic cationic salt, wherein the 25-hydroxy-(3β)-cholest-5-en-3-sulfate organic cationic salt has low solubility in the at least one solvent; and

contacting the 25-hydroxy-(3β)-cholest-5-en-3-sulfate organic cationic salt with at least one metal salt to produce the 5-cholesten-3β,25-diol 3-sulfate metal salt.

16. A method of producing a 5-cholesten-3β,25-diol 3-sulfate sodium salt, the method comprising:

contacting 25-hydroxy-(3β)-cholest-5-en-3-ol with a sulfur trioxide-pyridine complex in at least one solvent to produce a 25-hydroxy-(3β)-cholest-5-en-3-sulfate pyridinium salt, wherein the 25-hydroxy-(3β)-cholest-5-en-3-sulfate pyridinium salt has low solubility in the at least one solvent; and

contacting the 25-hydroxy-(3β)-cholest-5-en-3-sulfate pyridinium salt with a sodium salt to produce the 5-cholesten-3β,25-diol 3-sulfate sodium salt.

17. A method of producing a 5-cholesten-3β,25-diol 3-sulfate metal salt, the method comprising:

contacting (3β)-cholest-5-en-3-ol with at least one sulfating agent to produce a first (3β)-cholest-5-en-3-sulfate organic cationic salt;

contacting the first (3β)-cholest-5-en-3-sulfate organic cationic salt with an organic base to produce a second (3β)-cholest-5-en-3-sulfate organic cationic salt;

oxidizing the second (3β)-cholest-5-en-3-sulfate organic cationic salt in the presence of at least one surfactant to produce a 25-hydroxy-(3β)-cholest-(5,6-epoxy)-3-sulfate organic cationic salt;

generating a 25-hydroxy-(3β)-cholest-5-en-3-sulfate organic cationic salt from the 25-hydroxy-(3β)-cholest-(5,6-epoxy)-3-sulfate organic cationic salt by deoxygenation; and

contacting the 25-hydroxy-(3β)-cholest-5-en-3-sulfate organic cationic salt with at least one metal salt to produce the 5-cholesten-3β,25-diol 3-sulfate metal salt.

18. A composition comprising:

25-hydroxy-(3β)-cholest-5-en-3-sulfate; and

sulfated desmosterol.

19. A composition comprising:

25-hydroxy-(3β)-cholest-5-en-3-sulfate; and

5-cholesten-3β-25-diol-disulfate.

20. A method comprising:

sulfating 25-hydroxy-(3β)-cholest-5-en-3-ol to produce 25-hydroxy-(3β)-cholest-5-en-3-sulfate in at least one solvent, wherein 25-hydroxy-(3β)-cholest-5-en-3-sulfate has low solubility in the at least one solvent; and

precipitating 25-hydroxy-(3β)-cholest-5-en-3-sulfate in the solvent.

21. A composition comprising:

25-hydroxy-(3β)-cholest-5-en-3-sulfate; and

byproducts from sulfating 25-hydroxy-(3β)-cholest-5-en-3-ol comprising a first compound comprising a high-pressure liquid chromatography (HPLC) retention time of about 18.3 minutes, a second compound comprising an HPLC retention time of about 37.7 minutes, or any combination thereof, and the 25-hydroxy-(3β)-cholest-5-en-3-sulfate comprising an HPLC retention time of about 7.7 minutes,

wherein the first compound, the second compound, and the 25-hydroxy-(3β)-cholest-5-en-3-sulfate are separated by HPLC comprising a C8 stationary phase operating at about 45 ºC with a first mobile phase comprising a buffer and a second mobile phase comprising one or more organic solvents.

22. The 25HC3S sodium of any one of claims 1-8, or the pharmaceutical composition of claim 10, for use in therapy.