PREPARATION USES, AND SOLID FORMS OF OBETICHOLIC ACID

SUMMARY

In one aspect of the present disclosure, there is provided a process of preparing non-crystalline solid form of obeticholic acid comprising less than 1% by weight of chenodeoxycholic acid (CDCA) comprising the steps of:

preparing obeticholic acid by a process comprising the step of purifying an intermediate, E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid, by crystallization;

reacting purified E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas in the presence of a basic solution to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid;

reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form obeticholic acid;

preparing crystalline obeticholic acid by crystallizing obeticholic acid using an organic solvent; and

precipitating non-crystalline solid form of obeticholic acid from a solution prepared from crystalline obeticholic acid.

In another aspect of the present disclosure, there is provided a process of preparing crystalline obeticholic acid comprising preparing obeticholic acid by a process comprising the step of:

purifying 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid by crystallization;

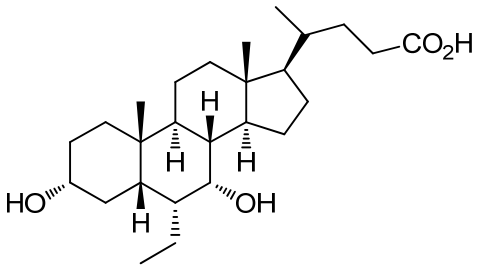
hydrogenating purified E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid;

reducing 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid to form obeticholic acid; and

crystallizing obeticholic acid using an organic solvent selected from the group consisting of heptane and n-butyl acetate.

DESCRIPTION

The present invention relates to obeticholic acid, an agonist for FXR, processes of preparation for obeticholic acid, pharmaceutical formulations comprising obeticholic acid, and the therapeutic use of the same.



obeticholic acid
(also known as INT-747)

The present invention relates to a crystalline obeticholic acid Form C characterized by an X-ray diffraction pattern including characteristic peaks at about 4.2, 6.4, 9.5, 12.5, and 16.7 degrees 2-Theta. The crystalline obeticholic acid Form C is characterized by an X-ray diffraction pattern substantially similar to that set forth in Figure 5 and further characterized by a Differential Scanning Calorimetry (DSC) thermogram having an endotherm value at about 98±2 ºC.

The present invention relates to a process for preparing obeticholic acid Form 1, comprising the step of converting crystalline obeticholic acid to obeticholic acid Form 1.

The present invention relates to a process for preparing obeticholic acid Form 1, comprising the steps of reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid and converting crystalline obeticholic acid to obeticholic acid Form 1.

The present invention relates to a process for preparing obeticholic acid Form 1, comprising the steps of reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid; reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid; and converting crystalline obeticholic acid to obeticholic acid Form 1.

WE CLAIM:

1. A process of preparing non-crystalline solid form of obeticholic acid comprising less than 1% by weight of chenodeoxycholic acid (CDCA) comprising the steps of:

preparing obeticholic acid by a process comprising the step of purifying an intermediate, E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid, by crystallization;

reacting purified E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas in the presence of a basic solution to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid;

reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form obeticholic acid;

preparing crystalline obeticholic acid by crystallizing obeticholic acid using an organic solvent; and

precipitating non-crystalline solid form of obeticholic acid from a solution prepared from crystalline obeticholic acid.

2. The process of claim 1, further comprising the steps of:

reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid;

reacting purified E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas in the presence of a basic solution to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid; and

reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form obeticholic acid.

3. The process of claim 1, further comprising the steps of:

reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with CH_3CHO to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester;

reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid;

reacting purified E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas in the presence of a basic solution to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid; and

reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form obeticholic acid.

4. The process of claim 1, further comprising the steps of:

reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester with $Li[N(CH(CH_3)_2)_2]$ and $Si(CH_3)_3Cl$ to form 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester;

reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with CH_3CHO to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester;

reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid;

reacting purified E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas in the presence of a basic solution to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid; and

reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form obeticholic acid.

5. The process of claim 1, further comprising the steps of:

reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid with CH_3OH and H_2SO_4 to form 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester;

reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester with $Li[N(CH(CH_3)_2)_2]$ and $Si(CH_3)_3Cl$ to form 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester;

reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with CH_3CHO to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester;

reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid;

reacting purified E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas in the presence of a basic solution to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid; and

reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form obeticholic acid.

6. The process of any one of claims 1 to 5, wherein precipitating non-crystalline solid form of obeticholic acid from a solution prepared from crystalline obeticholic acid comprises a step of dissolving crystalline obeticholic acid in aqueous NaOH solution and hydrochloric acid quench.

7. The process of any one of claims 1 to 5, wherein reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form obeticholic acid is carried out at a temperature at 85°C to 110°C in a basic aqueous solution.

8. The process of any one of claims 1 to 5, wherein reacting purified E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas in the presence of a basic solution to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid is carried out at a temperature at 90°C to 110°C.

9. The process of any one of claims 2 to 5, wherein reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid is carried out at a temperature at 20°C to 60°C.

10. The process of any one of claims 3 to 5, wherein reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with CH_3CHO to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester is carried out in a polar aprotic solvent at a temperature at -50°C to -70°C in the presence of boron trifluoride (BF_3) solvated complex.

11. The process of claim 4 or 5, wherein reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester with $Li[N(CH(CH_3)_2)_2]$ and $Si(CH_3)_3Cl$ to form 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester is carried out in a polar aprotic solvent at a temperature at -10°C to -30°C.

12. The process of claim 5, wherein reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid with CH_3OH and H_2SO_4 to form 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester is heated for 3 hours and the pH of the reaction mixture is adjusted with an aqueous basic solution.

13. The process of any one of claims 1 to 12, wherein the organic solvent is heptane or n-butyl acetate.

14. A process of preparing crystalline obeticholic acid comprising preparing obeticholic acid by a process comprising the step of:

purifying 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid by crystallization;

hydrogenating purified E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid;

reducing 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid to form obeticholic acid; and

crystallizing obeticholic acid using an organic solvent selected from the group consisting of heptane and n-butyl acetate.

15. The process of claim 14, wherein non-crystalline solid form of obeticholic acid comprises less than 1% of chenodeoxycholic acid.

16. The process of claim 1 or 14, wherein non-crystalline solid form of obeticholic acid is characterized by a Differential Scanning Calorimetry (DSC) thermogram having an endotherm with an onset at 89°C to 94°C.

17. The process of claim 1 or 14, wherein non-crystalline solid form of obeticholic acid comprises one or more compounds selected from 6β-ethylchenodeoxycholic acid, chenodeoxycholic acid, and 3α(3α,7α-dihydroxy-6α-ethyl-5β-cholan-24-oyloxy)-7α-hydroxy-6α-ethyl-5β-cholan-24-oic acid, and wherein

6β-ethylchenodeoxycholic acid is present in an amount less than about 0.05%,

chenodeoxycholic acid is present in an amount less than about 1%, and

3α(3α,7α-dihydroxy-6α-ethyl-5β-cholan-24-oyloxy)-7α-hydroxy-6α-ethyl-5β-cholan-24-oic acid is present in an amount less than about 0.05%.

18. The process of claim 1 or 14, wherein non-crystalline solid form of obeticholic acid comprises one or more compounds selected from 6β-ethylchenodeoxycholic acid, chenodeoxycholic acid, and 3α(3α,7α-dihydroxy-6α-ethyl-5β-cholan-24-oyloxy)-7α-hydroxy-6α-ethyl-5β-cholan-24-oic acid, and wherein

6β-ethylchenodeoxycholic acid is present in an amount less than about 0.05%,

chenodeoxycholic acid is present in an amount less than about 0.2%, and

3α(3α,7α-dihydroxy-6α-ethyl-5β-cholan-24-oyloxy)-7α-hydroxy-6α-ethyl-5β-cholan-24-oic acid is present in an amount less than about 0.05%.