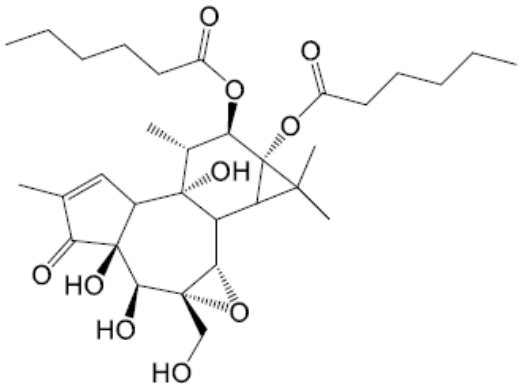
The present disclosure is based at least in part on the discovery of a polymorphic form of EBC-1013 (crystalline form I) having desirable properties for use in a pharmaceutical product, such as stability and lack of hygroscopicity. Furthermore, a process facilitating production of EBC-1013 form I *via* production of further polymorphic forms (crystalline forms II, IIA, IIB, IIC or IID), which enables the form I material to be produced reproducibly in high purity and good yield, and which is amenable to scale up, has also been discovered.

In a first aspect, there is provided a crystalline form (Form I) of a compound of formula (I):



(I),

wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at each of 5.1, 6.5, 9.7 and 15.9 degrees 2θ ±0.3 2θ as measured by X-ray powder diffraction.

In some examples, the crystalline form exhibits an X-ray powder diffraction pattern comprising one or more peaks at 8.9, 10.2, 11.0, 12.1, 13.1 17.1, 18.3 and 18.5 degrees 2θ ±0.3 2θ.

In some examples, the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at each of 5.1, 6.5, 8.9, 9.7, 10.2, 11.0, 12.1, 13.1, 15.9, 17.1, 18.3 and 18.5 degrees 2θ ±0.3 2θ.

In some examples, the crystalline form exhibits an X-ray powder diffraction pattern substantially as shown in Figure 7.

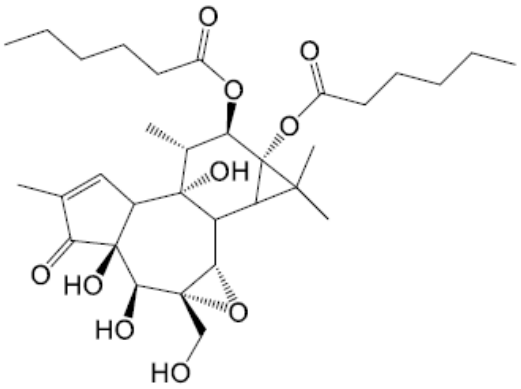
In some examples, the crystalline form has a differential scanning calorimetry profile showing an endothermic peak with peak onset at 77°C ±5°C and peak at 87°C ±5°C.

In some examples, the crystalline form exhibits loss of not more than 0.3% mass during heating to 100°C when subjected to thermogravimetric analysis.

In some examples, the crystalline form is substantially unsolvated.

In some examples, the compound of formula (I) has a purity of at least 98% by mass.

In another aspect, there is provided a crystalline form of a compound of formula (I) selected from the group consisting of Form II, Form IIA, Form IIB, Form IIC, and Form IID:



(I),

wherein the crystalline form II exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.6, 13.3 and 20.0 degrees 2θ ±0.2 2θ as measured by X-ray powder diffraction;

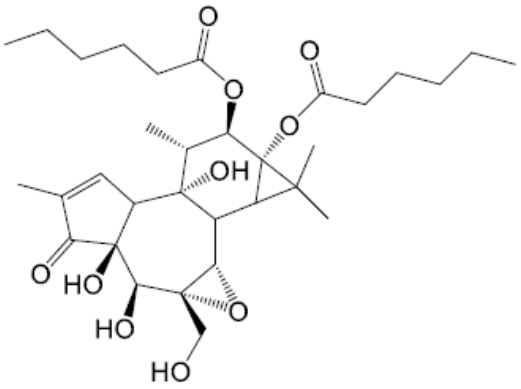
wherein the crystalline form IIA exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.7, 9.5, 13.3, 18.8 and 19.9 degrees 2θ ±0.2 2θ as measured by X-ray powder diffraction;

wherein the crystalline form IIB exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.4, 9.3, 13.1 and 17.7 degrees 2θ ±0.2 2θ as measured by X-ray powder diffraction;

wherein the crystalline form IIC exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.5, 9.4 and 13.1 degrees 2θ ±0.2 2θ as measured by X-ray powder diffraction; and

wherein the crystalline form IID exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.4, 9.3 and 13.1 degrees 2θ ±0.2 2θ as measured by X-ray powder diffraction.

In another example, there is provided a crystalline form (Form II) of a compound of formula (I):



(I),

wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.6, 13.3 and 20.0 degrees 2θ ±0.2 2θ as measured by X-ray powder diffraction.

In some examples, the crystalline form exhibits an X-ray powder diffraction pattern comprising one or more peaks at 7.4, 9.4, 16.9, 17.9, 18.6, 20.9 and 22.5degrees 2θ ±0.2 2θ.

In some examples, the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.6, 7.4, 9.4, 13.3, 16.9, 17.9, 18.6, 20.0, 20.9 and 22.5 degrees 2θ ±0.2 2θ.

In some examples, the crystalline form exhibits an X-ray powder diffraction pattern substantially as shown in Figure 11.

In some examples, the crystalline form has a differential scanning calorimetry profile showing an endothermic peak with peak onset at 75°C ±5°C and peak at 81°C ±5°C.

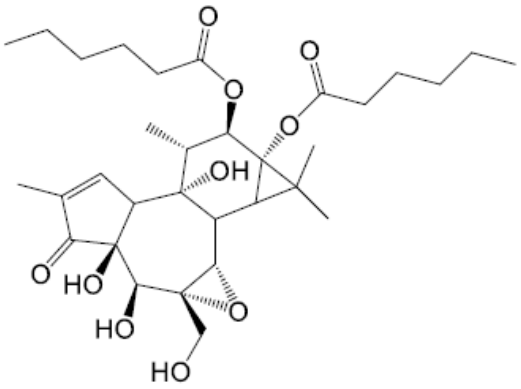
In some examples, the crystalline form exhibits loss of at least 1.5% mass during heating to 100°C when subjected to thermogravimetric analysis.

In some examples, the crystalline form is a solvate.

In some examples, the solvate is an acetone solvate.

In some examples, the compound of formula (I) has a purity of at least 97.5% by mass.

In another example, there is provided a crystalline form (Form IIA) of a compound of formula (I):



(I),

wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.7, 9.5, 13.3, 18.8 and 19.9 degrees 2θ ±0.2 2θ as measured by X-ray powder diffraction.

In some examples, the crystalline form exhibits an X-ray powder diffraction pattern comprising one or more peaks at 7.6, 11.3, 16.9, 17.8, 21.1 and 22.5 degrees 2θ ±0.2 2θ.

In some examples, the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.7, 7.6, 9.5, 11.3, 13.3, 16.9, 17.8, 18.8, 19.9, 21.1 and 22.5 degrees 2θ ±0.2 2θ.

In some examples, the crystalline form exhibits an X-ray powder diffraction pattern substantially as shown in Figure 15.

In some examples, the crystalline form has a differential scanning calorimetry profile showing an endothermic peak with peak onset at 61°C ±5°C and peak at 68°C ±5°C.

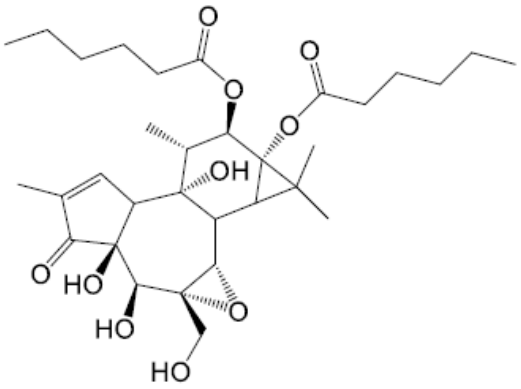
In some examples, the crystalline form exhibits loss of at least 1.5% mass during heating to 100°C when subjected to thermogravimetric analysis.

In some examples, the crystalline form is a solvate.

In some examples, the solvate is an isopropanol solvate.

In some examples, the compound of formula (I) has a purity of at least 97.5% by mass.

In another example, there is provided a crystalline form (Form IIB) of a compound of formula (I):



(I),

wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.4, 9.3, 13.1 and 17.7 degrees 2θ ±0.2 2θ as measured by X-ray powder diffraction.

In some examples, the crystalline form exhibits an X-ray powder diffraction pattern comprising one or more peaks at 7.3, 11.1, 16.7, 18.4, 18.7, 19.0, 19.7, 19.8, 20.9, 21.6, 22.0 and 22.2 degrees 2θ ±0.2 2θ.

In some examples, the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.4, 7.3, 9.3, 11.1, 13.1, 16.7, 17.7, 18.4, 18.7, 19.0, 19.7, 19.8, 20.9, 21.6, 22.0 and 22.2 degrees 2θ ±0.2 2θ.

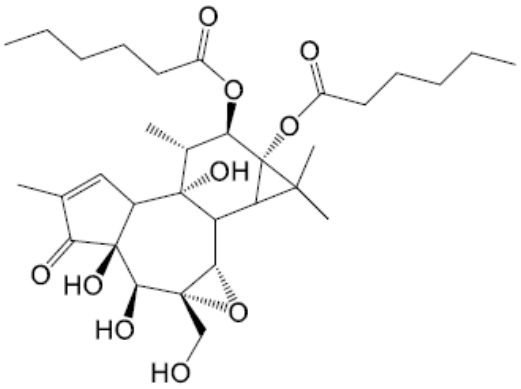
In some examples, the crystalline form exhibits an X-ray powder diffraction pattern substantially as shown in Figure 17.

In some examples, the crystalline form is a solvate.

In some examples, the solvate is a tert-butanol solvate.

In some examples, the compound of formula (I) has a purity of at least 97.5% by mass.

In another example, there is provided a crystalline form (Form IIC) of a compound of formula (I):



(I),

wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.5, 9.4 and 13.1 degrees 2θ ±0.2 2θ as measured by X-ray powder diffraction.

In some examples, the crystalline form exhibits an X-ray powder diffraction pattern comprising one or more peaks at 7.3, 11.3, 13.4, 16.5, 18.1, 18.8, 19.6, 20.3, 20.9 and 21.9 degrees 2θ ±0.2 2θ.

In some examples, the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.5, 7.3, 9.4, 11.3, 13.1 13.4, 16.5, 18.1, 18.8, 19.6, 20.3, 20.9 and 21.9 degrees 2θ ±0.2 2θ.

In some examples, the crystalline form exhibits an X-ray powder diffraction pattern substantially as shown in Figure 18.

In some examples, the crystalline form has a differential scanning calorimetry profile showing an endothermic peak with peak onset at 54°C ±5°C and peak at 62°C ±5°C.

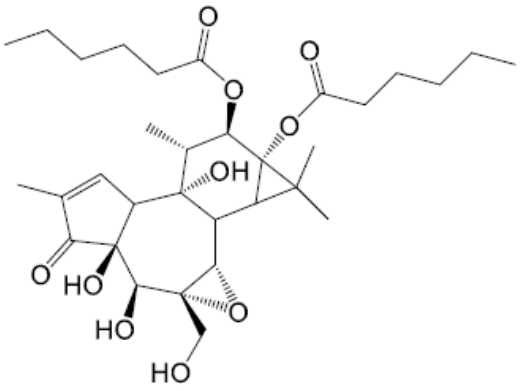
In some examples, the crystalline form exhibits loss of at least 1.25% mass during heating to 100°C when subjected to thermogravimetric analysis.

In some examples, the crystalline form is a solvate.

In some examples, the solvate is a methyl ethyl ketone solvate.

In some examples, the compound of formula (I) has a purity of at least 97.5% by mass.

In another example, there is provided a crystalline form (Form IID) of a compound of formula (I):



(I),

wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.4, 9.3 and 13.1 degrees 2θ ±0.2 2θ as measured by X-ray powder diffraction.

In some examples, the crystalline form exhibits an X-ray powder diffraction pattern comprising one or more peaks at 7.3, 13.2, 16.6, 17.8, 19.6, 20.1, 20.9 and 22.1 degrees 2θ ±0.2 2θ.

In some examples, the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.4, 7.3, 9.3, 13.1, 13.2, 16.6, 17.8, 19.6, 20.1, 20.9 and 22.1 degrees 2θ ±0.2 2θ.

In some examples, the crystalline form exhibits an X-ray powder diffraction pattern substantially as shown in Figure 20.

In some examples, the crystalline form is a solvate.

In some examples, the solvate is a tetrahydrofuran solvate.

In some examples, the compound of formula (I) has a purity of at least 97.5% by mass.

In another aspect, there is provided a process for producing crystalline form II, IIA, IIB, IIC or IID of a compound of formula (I) as defined herein, comprising:

gradually adding water to a solution of the compound of formula (I) in an organic solvent selected from the group consisting of acetone, isopropanol, methyl ethyl ketone, THF and *tert*-butanol,

producing a solid precipitate, and

separating the solid precipitate from the water:organic solvent mixture.

In some examples, the crystalline form is form II, and the organic solvent is acetone.

In some examples, the water is added to the solution of the compound of formula (I) in organic solvent at a temperature in the range of from 20 to 30°C.

In some examples, following addition of water, the mixture is cooled to a temperature in the range of from 0 to 5°C.

In some examples, the mixture is cooled over a period in the range of from about 90 minutes to 3 hours, optionally about 2 hours.

In some examples, following cooling, the mixture is maintained at the cooled temperature for a period in the range of from about 90 minutes to 3 hours, optionally about 2 hours.

In some examples, the amount of organic solvent in which the compound of formula (I) is dissolved is in the range of from 2 to 15 volumes, optionally about 10 volumes.

In some examples, the amount of water added to the solution of compound of formula (I) in organic solvent is in the range of from 5 to 40 volumes, optionally about 10 volumes.

In some examples, the solid precipitate is separated from the water:organic solvent mixture by filtration.

In some examples, the separated solid precipitate is washed with water, optionally an amount of water in the range of from 1 to 5 volumes, optionally about 2 volumes of water.

In another aspect, there is provided a process for producing crystalline form I of a compound of formula (I) as defined herein, comprising:

subjecting the crystalline form II, IIA, IIB, IIC or IID of a compound of formula (I) as defined herein, to vacuum conditions at a temperature of up to 70°C, thereby producing the crystalline form I.

In some examples, crystalline form II, IIA, IIB, IIC or IID is obtained by carrying out a process as defined herein.

In some examples, crystalline form II, IIA, IIB, IIC or IID is subjected to vacuum conditions at a temperature in the range of from 30 to 60°C.

In some examples, crystalline form II, IIA, IIB, IIC or IID is subjected to vacuum conditions for a period in the range of from 6 to 120 hours.

In some examples, crystalline form II, IIA, IIB, IIC or IID is subjected to vacuum conditions for a period in the range of from 12 to 18 hours.

In another aspect, there is provided a pharmaceutical composition comprising crystalline form I of the compound of formula (I) as defined herein, and a pharmaceutically acceptable excipient.

In another aspect, there is provided crystalline form I of the compound of formula (I) as defined herein, or a pharmaceutical composition comprising the crystalline form, for use in treating a wound; promoting wound healing; treating, preventing and/or reducing scarring; preventing or treating a bacterial infection; preventing or treating an inflammatory skin disorder such as psoriasis or eczema; treating an ulcer; and/or treating burns.

In another example, there is provided a method of treating a wound; promoting wound healing; treating, preventing and/or reducing scarring; preventing or treating a bacterial infection; preventing or treating an inflammatory skin disorder such as psoriasis or eczema; treating an ulcer; and/or treating burns in a subject, comprising administering an effective amount of crystalline form I of the compound of formula (I) as defined herein, or an effective amount of a pharmaceutical composition comprising the crystalline form, to the subject.

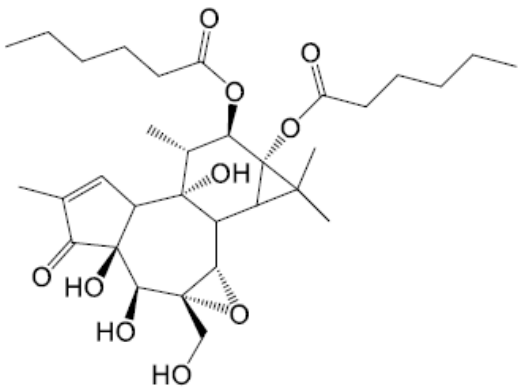
In another aspect, there is provided use of crystalline form I of the compound of formula (I) as defined herein, in the manufacture of a medicament for treating a wound; promoting wound healing; treating, preventing and/or reducing scarring; preventing or treating a bacterial

infection; preventing or treating an inflammatory skin disorder such as psoriasis or eczema; treating an ulcer; and/or treating burns.

In another example, there is provided use of crystalline form I of the compound of formula (I) as defined herein, for the manufacture of a medicament for treating a wound; promoting wound healing; treating, preventing and/or reducing scarring; preventing or treating a bacterial infection; preventing or treating an inflammatory skin disorder such as psoriasis or eczema; treating an ulcer; and/or treating burns.

Claims

1. A crystalline form (Form I) of a compound of formula (I):



(I),

wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at each of 5.1, 6.5, 9.7 and 15.9 degrees 2θ ±0.3 2θ as measured by X-ray powder diffraction.

2. The crystalline form as claimed in claim 1, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising one or more peaks at 8.9, 10.2, 11.0, 12.1, 13.1 17.1, 18.3 and 18.5 degrees 2θ ±0.3 2θ; and/or

wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at each of 5.1, 6.5, 8.9, 9.7, 10.2, 11.0, 12.1, 13.1, 15.9, 17.1, 18.3 and 18.5 degrees 2θ ±0.3 2θ.

3. The crystalline form as claimed in claim 1 or 2, wherein the crystalline form exhibits an X-ray powder diffraction pattern substantially as shown in Figure 7.

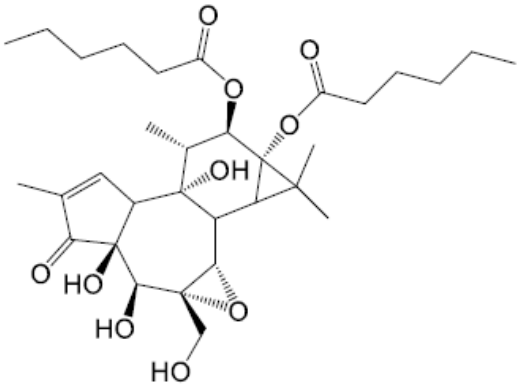
4. The crystalline form as claimed in any of claims 1 to 3, wherein the crystalline form has a differential scanning calorimetry profile showing an endothermic peak with peak onset at 77°C ±5°C and peak at 87°C ±5°C.

5. The crystalline form as claimed in any of claims 1 to 4, wherein the crystalline form exhibits loss of not more than 0.3% mass during heating to 100°C when subjected to thermogravimetric analysis.

6. The crystalline form as claimed in any of claims 1 to 5, wherein the crystalline form is substantially unsolvated.

7. The crystalline form as claimed in any of claims 1 to 6, wherein the compound of formula (I) has a purity of at least 98% by mass.

8. A crystalline form of a compound of formula (I) selected from the group consisting of Form II, Form IIA, Form IIB, Form IIC, and Form IID:



(I),

wherein the crystalline form II exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.6, 13.3 and 20.0 degrees 2θ ±0.2 2θ as measured by X-ray powder diffraction;

wherein the crystalline form IIA exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.7, 9.5, 13.3, 18.8 and 19.9 degrees 2θ ±0.2 2θ as measured by X-ray powder diffraction;

wherein the crystalline form IIB exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.4, 9.3, 13.1 and 17.7 degrees 2θ ±0.2 2θ as measured by X-ray powder diffraction;

wherein the crystalline form IIC exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.5, 9.4 and 13.1 degrees 2θ ±0.2 2θ as measured by X-ray powder diffraction; and

wherein the crystalline form IID exhibits an X-ray powder diffraction pattern comprising peaks at each of 6.4, 9.3 and 13.1 degrees 2θ ±0.2 2θ as measured by X-ray powder diffraction.

9. A process for producing crystalline form II, IIA, IIB, IIC or IID of a compound of formula (I) as claimed in claim 8, comprising:

gradually adding water to a solution of the compound of formula (I) in an organic solvent selected from the group consisting of acetone, isopropanol, methyl ethyl ketone, THF and *tert*-butanol,

producing a solid precipitate, and

separating the solid precipitate from the water:organic solvent mixture.

10. The process as claimed in claim 9, wherein any one or more of the following apply:

the crystalline form is form II, and the organic solvent is acetone; and/or

the water is added to the solution of the compound of formula (I) in organic solvent at a temperature in the range of from 20 to 30°C; and/or

following addition of water, the mixture is cooled to a temperature in the range of from 0 to 5°C; and/or

the amount of organic solvent in which the compound of formula (I) is dissolved is in the range of from 2 to 15 volumes, optionally about 10 volumes; and/or

the amount of water added to the solution of compound of formula (I) in organic solvent is in the range of from 5 to 40 volumes, optionally about 10 volumes; and/or

the solid precipitate is separated from the water:organic solvent mixture by filtration; and/or

the separated solid precipitate is washed with water, optionally an amount of water in the range of from 1 to 5 volumes, optionally about 2 volumes of water.

11. A process for producing crystalline form I of a compound of formula (I) as claimed in any of claims 1 to 7, comprising:

subjecting the crystalline form II, IIA, IIB, IIC or IID of a compound of formula (I) as claimed in claim 8, to vacuum conditions at a temperature of up to 70°C, thereby producing the crystalline form I.

12. The process as claimed in claim 11, wherein crystalline form II, IIA, IIB, IIC or IID is obtained by carrying out a process as defined in claim 9 or 10.

13. The process as claimed in claim 11 or 12, wherein crystalline form II, IIA, IIB, IIC or IID is subjected to vacuum conditions at a temperature in the range of from 30 to 60°C; and/or

optionally for a period in the range of from 6 to 120 hours, optionally for a period in the range of from 12 to 18 hours.

14. A pharmaceutical composition comprising crystalline form I of the compound of formula (I) as claimed in any of claims 1 to 7, and a pharmaceutically acceptable excipient.

15. Crystalline form I of the compound of formula (I) as claimed in any of claims 1 to 7, or a pharmaceutical composition comprising the crystalline form, for use in treating a wound; promoting wound healing; treating, preventing and/or reducing scarring; preventing or treating a bacterial infection; preventing or treating an inflammatory skin disorder such as psoriasis or eczema; treating an ulcer; and/or treating burns.

16. Use of crystalline form I of the compound of formula (I) as claimed in any of claims 1 to 7, in the manufacture of a medicament for treating a wound; promoting wound healing; treating, preventing and/or reducing scarring; preventing or treating a bacterial infection; preventing or treating an inflammatory skin disorder such as psoriasis or eczema; treating an ulcer; and/or treating burns.