Claims

1. A method of providing at least one diastereoisomer of gemcitabine-[phenyl-benzoxy-L-alaninyl)]-phosphate in a ~~substantially diastereoisomerically pure form,~~diastereoisomeric purity of greater than 85%, the method comprising the steps of:

suspending a mixture of gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*R*)-phosphate and gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate in a solvent or a mixture of solvents to form a slurry; and

filtering the slurry to provide solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-phosphate and a filtrate comprising gemcitabine-[phenyl-benzoxy-L-alaninyl)]-phosphate dissolved in the solvent or mixture of solvents;

wherein the solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-phosphate is ~~substantially diastereoisomerically pure~~ gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*R*)-phosphate in a diastereoisomeric purity of greater than 85% and/or the filtrate comprises ~~substantially diastereoisomerically pure~~ gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate~~.~~ in a diastereoisomeric purity of greater than 85%.

2. A method of claim 1, wherein the slurry is heated once formed; optionally to a temperature from ~~about~~ 30°C to ~~about~~ 80°C.

3. A method of claim 2, wherein the slurry is ~~preferably~~ not cooled prior to filtration.

4. A method of any one of claims 1 to 3, further comprising the step of washing the solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-phosphate.

5. A method of any one of claims 1 to 4, wherein the method is a method of providing gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate in ~~diastereoisomerically pure form~~ a diastereoisomeric purity of greater than 85%and wherein the method further comprises the step of removing the solvent(s) from the filtrate comprising gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate to obtain solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate in a ~~substantially diastereoisomerically pure form.~~diastereoisomeric purity of greater than 85%.

6. A method of claim 5, wherein the step of removing the solvent or mixture of solvents comprises:

removing a portion of the solvent or mixture of solvents from the filtrate comprising gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate by evaporation, e.g. by distillation or evaporation under reduced pressure, to provide a concentrated filtrate comprising solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate;

optionally agitating the concentrated filtrate; and

filtering the concentrated filtrate to obtain gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate as a solid in ~~substantially diastereoisomerically pure form.~~in a diastereoisomeric purity of greater than 85%.

7. A method of claim 5, wherein the step of removing the solvent or mixture of solvents comprises:

cooling the filtrate comprising gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate to provide a cooled filtrate comprising solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate;

optionally agitating the cooled filtrate; and

filtering the cooled filtrate to obtain gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate as a solid in ~~substantially diastereoisomerically pure form.~~in a diastereoisomeric purity of greater than 85%.

8. A method of claim 7, further comprising the step of adding seed material to the filtrate.

9. A method of claim 7 or claim 8, further comprising the step of adding additional solvent to the filtrate.

10. A method of any one of claims 7 to 9, further comprising washing the ~~substantially diastereoisomerically pure~~ solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate~~.~~ in a diastereoisomeric purity of greater than 85%.

11. A method of any one of claims 1 to 4, wherein the method is a method of providing gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*R*)-phosphate in ~~diastereoisomerically pure form.~~a diastereoisomeric purity of greater than 85%;

~~12. A method of claim 11,~~optionally wherein the method further ~~comprising~~comprises the steps:

suspending solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-phosphate obtained from the first filtration in a second solvent or a second mixture of solvents to form a second slurry; and

filtering the second slurry to provide ~~substantially diastereoisomerically pure~~ solid gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*R*)-phosphate~~.~~ in a diastereoisomeric purity of greater than 85%.

~~13~~12. A method of any one of claims 1 to ~~12~~11, wherein the solvent is or the solvent mixture comprises a solvent selected from a polar protic solvent and a polar aprotic solvent.

~~14~~13. A method of claim ~~13~~12, wherein the solvent is or the solvent mixture comprises ~~IPA~~isopropyl alcohol.

~~14.15. A method of claim 14, wherein the solvent is IPA.~~

~~16.~~ A method of claim 13, wherein the solvent is isopropyl alcohol.

15. A method of claim 12, wherein the solvent is or the solvent mixture comprises acetonitrile.

~~17. Gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate obtainable by the method of any one of claims 1 to 16.~~

~~18. Gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*R*)-phosphate obtainable by the method of any one of claims 1 to 16.~~

~~19. A crystalline form of gemcitabine-[phenyl-benzoxy-L-alaninyl)]-(*S*)-phosphate, the crystalline form being form I.~~

~~20. A crystalline form of claim 19, characterised in that said crystalline form has an XRPD pattern with at least two peaks at 2θ selected from 5.0 ± 0.2, 6.7 ± 0.2, 8.0 ± 0.2, 11.3 ± 0.2, 20.2 ± 0.2 and 21.4 ± 0.2 when measured using Cu radiation with a $K_{\alpha2}$ / $K_{\alpha1}$ ratio of 0.5.~~

~~21. A crystalline form of claim 20, characterised in that said crystalline form has an XRPD pattern with at least four peaks at 2θ selected from 5.0 ± 0.2, 6.7 ± 0.2, 8.0 ± 0.2, 11.3 ± 0.2, 20.2 ± 0.2 and 21.4 ± 0.2 when measured using Cu radiation with a $K_{\alpha2}$ / $K_{\alpha1}$ ratio of 0.5.~~

~~22. A crystalline form of claim 21, characterised in that said crystalline form has an XRPD pattern with peaks at 2θ 5.0 ± 0.2, 6.7 ± 0.2, 8.0 ± 0.2, 11.3 ± 0.2, 20.2 ± 0.2 and 21.4 ± 0.2 when measured using Cu radiation with a $K_{\alpha2}$ / $K_{\alpha1}$ ratio of 0.5.~~

~~23. A crystalline form of claim 19, characterised in that said crystalline form has an XRPD pattern substantially as shown in Figure 1.~~

~~24. A crystalline form of any one of claims 19 to 23, characterised in that said crystalline form has an FTIR pattern, when measured as a suspension in Nujol, substantially as shown in Figure 2.~~