Title: POLYMORPHS OF ETRAVIRINE AND PROCESSES FOR PREPARATION THEREOF

Abstract: The present invention provides novel crystalline forms of etravirine such as forms A, B, D, E, H, J, K, L and M, pharmaceutical compositions comprising the crystalline forms and method of using at least one of the crystalline forms or pharmaceutical compositions to treat HIV.
POLYMORPHS OF ETAVIRINE
AND PROCESSES FOR PREPARATION THEREOF


FIELD OF THE INVENTION

The present invention relates to polymorphs of etavirine, processes for preparing said polymorphs, and pharmaceutical compositions of said polymorphs.

BACKGROUND OF THE INVENTION

Etavirine ("ETV"), 4-(6-amino-5-bromo-2-(4-cyanophenylamino)pyrimidin-4-yl)-3,5-dimethylbenzonitrile of the following chemical structure:

![Chemical Structure](image)

is a drug used for the treatment of HIV. Etavirine is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), designed to be active against HIV with mutations that confer resistance to the two most commonly prescribed first-generation NNRTI's. Etavirine was formerly known as TMC-125, brand name Intelence.

Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule, like Etravirine, may give rise to a variety of polymorphs having distinct crystal structures and physical properties like melting point, thermal behaviours (e.g. measured by thermogravimetric analysis – “TGA”, or differential scanning calorimetry – “DSC”), x-ray diffraction pattern (“XRD pattern”), infrared absorption fingerprint, and solid state NMR spectrum. One or more of these techniques may be used to distinguish different polymorphic forms of a compound.

Discovering new polymorphic forms and solvates of a pharmaceutical product can provide materials having desirable processing properties, such as ease of handling, ease of processing, storage stability, and ease of purification or as desirable intermediate crystal forms that facilitate conversion to other polymorphic forms. New polymorphic forms and solvates of a pharmaceutically useful compound or salts thereof can also provide an opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for formulation optimization, for example by providing a product with different properties, e.g., better processing or handling characteristics, improved dissolution profile, or improved shelf-life. For at least these reasons, there is a need for additional polymorphs of Etravirine.

SUMMARY OF THE INVENTION

In one embodiment the present invention encompasses crystalline etravirine, designated form A characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 10.6, 11.4, 14.0, 21.4 and 23.0 ± 0.2 degrees 2-theta, a powder XRD pattern substantially as depicted in figure 1; a solid state \textsuperscript{13}C NMR spectrum having peaks at 153.9, 142.4, 132.7, and 109.2 ± 0.2 ppm; a solid state \textsuperscript{13}C NMR spectrum substantially as depicted in Figure 27; and combinations thereof.

In another embodiment the present invention encompasses crystalline etravirine, designated form B, characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 11.1, 13.3, 18.3 and 21.6 ± 0.2 degrees 2-theta, a powder XRD pattern substantially as depicted in figure 5; a solid state \textsuperscript{13}C NMR spectrum having peaks at 142.7, 108.6, 107.2, 103.5, and 102.2 ± 0.2
ppm; a solid state $^{13}$C NMR spectrum substantially as depicted in Figure 28; and combinations thereof.

In one embodiment the present invention encompasses crystalline etravirine, designated form D, characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 6.1, 12.2, 17.2 and 25.7 $\pm$ 0.2 degrees 2-theta, a powder XRD pattern substantially as depicted in figure 9; and combinations thereof.

In another embodiment the present invention encompasses crystalline etravirine, designated form E, characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 11.8, 15.3, 16.5 and 19.2 $\pm$ 0.2 degrees 2-theta, a powder XRD pattern substantially as depicted in figure 11; and combinations thereof.

In yet another embodiment the present invention encompasses crystalline etravirine, designated form H, characterized by data selected from the group consisting of: an X-ray powder diffraction pattern having peaks at 16.8, 17.4, 24.2 and 26.2 $\pm$ 0.2 degrees two-theta; and a PXRD pattern substantially as depicted in Figure 16.

In another embodiment the present invention encompasses crystalline etravirine, designated form J, characterized by data selected from the group consisting of: an X-ray powder diffraction pattern having peaks at 5.5, 7.6, 10.9 and 12.2 $\pm$ 0.2 degrees two-theta; a PXRD pattern substantially as depicted in Figure 18; and combinations thereof.

In yet another embodiment the present invention encompasses crystalline etravirine, designated form K, characterized by data selected from the group consisting of: an X-ray powder diffraction pattern having peaks at 6.3, 10.2, 24.5 and 27.4 $\pm$ 0.2 degrees two-theta; a PXRD pattern substantially as depicted in Figure 20; and combinations thereof.

In one embodiment the present invention encompasses crystalline etravirine, designated form L, characterized by data selected from the group consisting of: an X-ray powder diffraction pattern having peaks at 7.3, 11.0, 11.7 and 16.5 $\pm$ 0.2 degrees two-theta; a PXRD pattern substantially as depicted in Figure 21; and combinations thereof.

In another embodiment the present invention encompasses crystalline etravirine, designated form M, characterized by data selected from the group consisting of: an X-ray powder diffraction pattern with peaks at 8.5, 11.2, 25.5 and
30.9 ± 0.2 degrees two-theta; a PXRD pattern substantially as depicted in Figure 24; and combinations thereof.

In one embodiment, the present invention also encompasses a pharmaceutical composition comprising at least one of the above described polymorphs of etravirine of the present invention, and at least one pharmaceutically acceptable excipient. The above described polymorphs of etravirine of the invention can be prepared according to the processes of the present invention.

In another embodiment, the invention encompasses a process for preparing a pharmaceutical composition comprising at least one of the above polymorphs of etravirine, and at least one pharmaceutically acceptable excipient.

In another embodiment, the invention encompasses a method of treating HIV, comprising administering at least one of the above polymorphs of etravirine of the present invention or a pharmaceutical composition comprising at least one of the above polymorphs of etravirine to a patient in need thereof.

One embodiment of the invention provides the crystalline forms of etravirine of the present invention for use as a pharmaceutical formulation.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a powder XRD pattern of polymorphically pure crystalline etravirine form A.

Figure 2 shows a DSC thermogram of polymorphically pure crystalline etravirine form A.

Figure 3 shows a TGA thermogram of polymorphically pure crystalline etravirine form A.

Figure 4 shows a powder XRD pattern of a mixture of crystalline etravirine form A and crystalline Etravirine form F.

Figure 5 shows a powder XRD pattern of crystalline etravirine form B.

Figure 6 shows a DSC thermogram of crystalline etravirine form B.

Figure 7 shows a powder XRD pattern of crystalline etravirine form C, wherein the vertical axis represents intensity (counts).

Figure 8 shows a DSC thermogram of crystalline etravirine form C.
Figure 9 shows a powder XRD pattern of crystalline etravirine form D, wherein the vertical axis represents intensity (counts) and the horizontal axis represents degrees 2θ.

Figure 10 shows a DSC thermogram of crystalline etravirine form D.

Figure 11 shows a powder XRD pattern of crystalline etravirine form E, wherein the vertical axis represents intensity (counts).

Figure 12 shows a powder XRD pattern of crystalline etravirine form F.

Figure 13 shows a DSC thermogram of crystalline etravirine form F.

Figure 14 shows a powder XRD pattern of amorphous etravirine, wherein the vertical axis represents intensity (counts) and the horizontal axis represents degrees 2θ.

Figure 15 shows a powder XRD pattern of crystalline etravirine form G.

Figure 16 shows a powder XRD pattern of crystalline etravirine form H.

Figure 17 shows a powder XRD pattern of crystalline etravirine form I.

Figure 18 shows a powder XRD pattern of crystalline etravirine form J.

Figure 19 shows a DSC thermogram of crystalline etravirine form J.

Figure 20 shows a powder XRD pattern of crystalline etravirine form K.

Figure 21 shows a powder XRD pattern of crystalline etravirine form L.

Figure 22 shows a DSC thermogram of crystalline etravirine form L.

Figure 23 shows a TGA pattern of crystalline etravirine form L.

Figure 24 shows a powder XRD pattern of crystalline etravirine form M.

Figure 25 shows a DSC thermogram of crystalline etravirine form M.

Figure 26 shows a powder XRD pattern of a mixture of crystalline etravirine form B and Etravirine hydrobromide salt, wherein the vertical axis represents intensity (counts) and the horizontal axis represents degrees 2θ.

Figure 27 shows a solid state $^{13}$C NMR spectrum of crystalline etravirine form A.

Figure 28 shows a solid state $^{13}$C NMR spectrum of crystalline etravirine form B.

Figure 29 shows a light microscopic image of crystalline etravirine form A, wherein several of the crystals were measured with a length of about 3.1 μm, 5.8 μm, 6.0 μm, 7.7 μm or 7.9 μm.

DETAILED DESCRIPTION OF THE INVENTION
The present invention relates to polymorphs of etravirine, processes for preparing said polymorphs, and pharmaceutical compositions of said polymorphs.

A crystal form may be referred to herein as being characterized by graphical data “as depicted in” a Figure. Such data include, for example, powder X-ray diffractograms and solid state NMR spectra. The skilled person will understand that such graphical representations of data may be subject to small variations, e.g., in peak relative intensities and peak positions due to factors such as variations in instrument response and variations in sample concentration and purity, which are well known to the skilled person. Nonetheless, the skilled person would readily be capable of comparing the graphical data in the Figures herein with graphical data generated for an unknown crystal form and confirm whether the two sets of graphical data are characterizing the same crystal form or two different crystal forms.

A crystal form (or polymorph) may be referred to herein as substantially free of any other crystalline (or polymorphic) forms. As used herein in this context, the expression “substantially free of any other forms” will be understood to mean that the crystalline form contains from about 0.5% to about 20%, from about 0.5% to about 10%, from about 0.5% to about 5%, from about 0.5% to about 2%, or from about 0.5% to about 1%, of any other forms combined of the subject compound as measured, for example, by XRPD. Thus, polymorphs of Etravirine described herein as substantially free of any other polymorphic forms would be understood to contain about 99.5% to about 80% (w/w), about 99.5% to about 90% (w/w), about 99.5% to about 95% (w/w), about 99.5% to about 98% (w/w) or about 99.5% to about 99% (w/w), of the subject polymorphic form of Etravirine. Accordingly, in some embodiments of the invention, the described polymorphs of Etravirine and may contain from 0.5% to 20% (w/w), 1% to 20% (w/w), from 5% to 20% (w/w), or from 5% to 10% (w/w) of one or more other crystal forms of Etravirine.

As used herein, unless mentioned otherwise, the term "Room temperature" refers to a temperature between about 20° C and about 30° C. Usually, room temperature ranges from about 20° C to about 25° C.

As used herein, unless mentioned otherwise, the term “overnight” refers to a period of between about 8 and about 20 hours, between about 15 and about 20 hours, typically between about 16 to about 20 hours.
As used herein, and unless stated otherwise, the term "anhydrous" in relation to crystalline Etravirine relates to a crystalline Etravirine which contains not more than 1% (w/w) of either water or organic solvents as measured by TGA.

As used herein the term non-hygroscopic in relation to crystalline Etravirine refers to less than 0.2% (w/w) absorption of atmospheric water to the crystalline Etravirine in the conditions specified in this application, as measured by mass weight or Dynamic Vapour Sorption ("DVS"), at a temperature of about room temperature.

In one embodiment the present invention encompasses crystalline etravirine characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 10.6, 11.4, 14.0, 21.4 and 23.0 ± 0.2 degrees 2-theta; a powder XRD pattern as depicted in figure 1; a solid state $^{13}$C NMR spectrum having peaks at 153.9, 142.4, 132.7, and 109.2 ± 0.2 ppm; a solid state $^{13}$C NMR spectrum as depicted in Figure 27; and combinations thereof. This form can be designated as form A.

Form A can be further characterized by additional data selected from the group consisting of: additional XRD peaks at 5.3, 15.6, 17.7, 24.5 and 29.3 ± 0.2 degrees 2-theta; additional solid state $^{13}$C NMR peaks at 162.2, 155.9, 119.5, and 15.5 ± 0.2 ppm; a DSC thermogram as depicted in figure 2; a TGA thermogram as depicted in figure 3; and combinations thereof.


The above crystalline Etravirine form A may be an anhydrous form.

In a preferred embodiment, the above described crystalline Etravirine form A is substantially free of any other forms Etravirine.

In particular, the above described crystalline Etravirine form A is polymorphically pure, wherein the polymorphically pure crystalline etravirine form A contains not more than about 10%, 5% or 1% by weight of crystalline etravirine designated form F, characterized by data selected from the group consisting of: a powder XRD pattern having peaks at 8.8, 9.2, 16.2, 18.4 and 22.0 ± 0.2 degrees 2-theta, a powder XRD pattern as depicted in figure 12; and combinations thereof.

Typically, the amount of crystalline etravirine form F in the crystalline etravirine form A of the present invention can be measured by PXRD using any peak from the group of peaks at: 8.8 and 9.2 ± 0.2 degrees 2-theta.
The above polymorphically pure crystalline etravirine form A is a composition which comprises from about 1% to about 10%, by weight of crystalline etravirine form F and from about 99% to about 90% by weight of crystalline etravirine form A; from about 0.5% to about 10%, by weight of crystalline etravirine form F and from about 99.5% to about 90% by weight of crystalline etravirine form A; from about 0% to about 10%, by weight of crystalline etravirine form F and from about 100% to about 90% by weight of crystalline etravirine form A; from about 1% to about 5%, by weight of crystalline etravirine form F and from about 99% to about 95% by weight of crystalline etravirine form A; from about 0.5% to about 5%, by weight of crystalline etravirine form F and from about 99.5% to about 95% by weight of crystalline etravirine form A; from about 0% to about 5% by weight of crystalline etravirine form F and from about 100% to about 95% by weight of crystalline etravirine form A; from about 0.5% to about 1%, by weight of crystalline etravirine form F and from about 99.5% to about 99% by weight of crystalline etravirine form A; or from about 0% to about 1% by weight of crystalline etravirine form F and from about 100% to about 99% by weight of crystalline etravirine form A.

In more preferred embodiments, the polymorphically pure crystalline etravirine form A is a composition which contains essentially crystalline etravirine form A and crystalline etravirine form F in the above described amounts.

Crystalline Etravirine form A has advantageous properties selected from at least one of: chemical purity, flowability, solubility, morphology or crystal habit, stability – such as storage stability, stability to dehydration, stability to polymorphic conversion, low hygroscopicity, low content of residual solvents. Particularly, Etravirine form A has small crystals with a particle size of less than 100 microns, less than 50 microns, less than 30 microns, or less than 15 microns, and thus provide a bulk product with excellent solubility and flowability properties that are of benefit for pharmaceutical formulations.

Form A can be prepared by a process comprising suspending Etravirine phosphate salt in a mixture of water and NaOH. This process can comprise suspending Etravirine phosphate salt in water, adding NaOH and filtering the crystals from the suspension.

The present invention also encompasses a mixture of crystalline Etravirine form A and crystalline Etravirine form F, that is characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 9.2, 8.8, 10.6, 21.1 and
23.0 ± 0.2 degrees 2-theta; a powder XRD pattern as depicted in figure 4; and combinations thereof; wherein the amount of form F in the mixture is higher than about 1%, preferably higher than about 5%, or more preferably higher than about 10% by weight. The amount of crystalline etravirine form F in the mixture can be measured as described above.

The above mixture can be further characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 9.2, 11.4, 14.0 and 15.5 ± 0.2 degrees 2-theta, a broad peak at about 21.1 ± 0.3 degrees 2-theta; and combinations thereof.

In another embodiment the present invention encompasses crystalline etravirine characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 11.1, 13.3, 18.3 and 21.6 ± 0.2 degrees 2-theta, a powder XRD pattern as depicted in figure 5; a solid state $^{13}$C NMR spectrum having peaks at 142.7, 108.6, 107.2, 103.5, and 102.2 ± 0.2 ppm; a solid state $^{12}$C NMR spectrum as depicted in Figure 28; and combinations thereof. This form can be designated as form B.

Form B can be further characterized by additional data selected from the group consisting of: additional powder XRD peaks at 12.7, 14.7, 19.0 and 27.5 ± 0.2 degrees 2-theta; additional solid state $^{13}$C NMR peaks at 154.0, 121.4, 116.1, 18.7 ± 0.2 ppm; a DSC thermogram as depicted in Figure 6; and combinations thereof.


In a preferred embodiment, the above described crystalline etravirine form B is substantially free of any other forms of Etravirine.

In a preferred embodiment, the above described crystalline etravirine form B is chemically pure, wherein the chemically pure crystalline etravirine form A contains not more than about 10%, 5%, 1% or 0.5% by weight of crystalline etravirine hydrobromide salt.

Typically, the amount of crystalline etravirine hydrobromide salt in the crystalline etravirine form B of the present invention can be measured by PXRD using any peak from the group of peaks at: 9.5, 16.1, 19.4 and 24.8 ± 0.2 degrees 2-theta.
The above chemically pure crystalline etravirine form B is a composition which comprises from about 0% to about 10%, by weight of crystalline etravirine hydrobromide salt and from about 100% to about 90% by weight of crystalline etravirine form B; from about 1% to about 10%, by weight of crystalline etravirine hydrobromide salt and from about 99% to about 90% by weight of crystalline etravirine form B; from about 0.5% to about 10%, by weight of crystalline etravirine hydrobromide salt and from about 99.5% to about 90% by weight of crystalline etravirine form B; from about 0% to about 5% by weight of crystalline etravirine hydrobromide salt; and from about 100% to about 95% by weight of crystalline etravirine form B; from about 1% to about 5%, by weight of crystalline etravirine hydrobromide salt and from about 99% to about 95% by weight of crystalline etravirine form B; from about 0.5% to about 5%, by weight of crystalline etravirine hydrobromide salt and from about 99.5% to about 95% by weight of crystalline etravirine form B; from about 0% to about 1% by weight of crystalline etravirine hydrobromide salt and from about 100% to about 99% by weight of crystalline etravirine form B; or from about 0.5% to about 1%, by weight of crystalline etravirine hydrobromide salt and from about 99.5% to about 99% by weight of crystalline etravirine form B;

In more preferred embodiments, the chemically pure crystalline etravirine form B is a composition which consists essentially of crystalline etravirine form B and crystalline etravirine hydrobromide salt in the above described amounts.

Crystalline etravirine form B has advantageous properties selected from at least one of: chemical purity, flowability, solubility, morphology or crystal habit, stability – such as storage stability, stability to dehydration, stability to polymorphic conversion, low content of residual solvents. Particularly, the crystalline Etravirine form B of the present invention is has better wettability and solubility properties that are of benefit for pharmaceutical formulations.

Form B can be prepared by a process comprising suspending etravirine tosylate salt in a mixture of water and NaOH. The process can comprise suspending etravirine tosylate salt in water, adding NaOH and filtering the crystals from the suspension. Form B can also be prepared by grinding etravirine form D in the presence of water.

In one embodiment the present invention encompasses crystalline etravirine characterized by data selected from the group consisting of: a powder XRD pattern
with peaks at 6.1, 12.2, 17.2 and 25.7 ± 0.2 degrees 2-theta, a powder XRD pattern as depicted in figure 9; and combinations thereof. This form can be designated as form D. Form D can be further characterized by additional data selected from the group consisting of: Additional powder XRD peaks at 15.7, 18.2, 19.9 and 21.4 ± 0.2 degrees 2-theta, and a DSC curve characterized by two thermal events; a first endotherm with maxima at about 173° C, and the second one at about 265° C corresponding to the melting that takes place in parallel with the degradation process as shown in figure 10.

In another embodiment the present invention encompasses crystalline etravirine characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 11.8, 15.3, 16.5 and 19.2 ± 0.2 degrees 2-theta, a powder XRD pattern as depicted in figure 11; and combinations thereof. This form can be designated as form E. Form E can be further characterized by additional powder XRD peaks at 8.8, 13.0, 13.5 and 26.4 ± 0.2 degrees 2-theta.

Also provided herein is amorphous etravirine. The amorphous etravirine can be characterized by a powder XRD pattern as depicted in figure 14.

In another embodiment the present invention encompasses crystalline etravirine characterized by data selected from the group consisting of: an X-ray powder diffraction pattern having peaks at 16.8, 17.4, 24.2 and 26.2 ± 0.2 degrees two-theta; a PXRD pattern as depicted in Figure 16; and combinations thereof. This form can be designated as form H. Form H can be further characterized by additional PXRD peaks at 8.4, 12.2, 25.2 and 33.3 ± 0.2 degrees two-theta.

In one embodiment the present invention encompasses crystalline etravirine characterized by data selected from the group consisting of: an X-ray powder diffraction pattern having peaks at 5.5, 7.6, 10.9 and 12.2 ± 0.2 degrees two-theta; a PXRD pattern as depicted in Figure 18; and combinations thereof. This form can be designated as form J. Form J, can be further characterized by additional data selected from the group consisting of: additional PXRD peaks at 8.1, 17.5, 25.8 and 27.5 ± 0.2 degrees two-theta; a DSC thermogram as depicted in Figure 19; and combinations thereof.

In another embodiment the present invention encompasses crystalline etravirine characterized by data selected from the group consisting of: an X-ray powder diffraction having peaks at 6.3, 10.2, 24.5 and 27.4 ± 0.2 degrees two-theta; a PXRD pattern as depicted in Figure 20; and combinations thereof. This form can be
designated as form K. Form K, can be further characterized by additional PXRD peaks at 9.5, 11.4, 15.3 and 17.5 ± 0.2 degrees two-theta.

In yet another embodiment the present invention encompasses crystalline etravirine characterized by data selected from the group consisting of: an X-ray powder diffraction pattern having peaks at 7.3, 11.0, 11.7 and 16.5 ± 0.2 degrees two-theta; a PXRD pattern as depicted in Figure 21; and combinations thereof. This form can be designated as form L. Form L can be further characterized by data selected from the group consisting of: additional PXRD peaks at 5.5, 12.6, 18.7, 22.0 and 25.0 ± 0.2 degrees two-theta; a DSC thermogram as depicted in Figure 22; a TGA pattern as depicted in Figure 23; and combinations thereof.

In another embodiment the present invention encompasses crystalline etravirine characterized by data selected from the group consisting of: an X-ray powder diffraction pattern with peaks at 8.5, 11.2, 25.5 and 30.9 ± 0.2 degrees two-theta; a PXRD pattern as depicted in Figure 24; and combinations thereof. This form can be designated as form M. Form M can be further characterized by data selected from the group consisting of: additional PXRD peaks at 12.7, 20.0, 22.5 and 32.6 ± 0.2 degrees two-theta; a DSC thermogram as depicted in Figure 25; and combinations thereof.

The present invention also encompasses a mixture of crystalline etravirine hydrobromide salt and crystalline etravirine characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 9.5, 11.2, 13.3 and 18.3 ± 0.2 degrees 2-theta, a powder XRD pattern as depicted in figure 26; and combinations thereof. The above crystalline mixture can be further characterized by additional powder XRD peaks at 12.7, 16.1, 19.0 and 24.7 ± 0.2 degrees 2-theta.

Provided herein a crystalline etravirine characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 8.4, 12.8, 20.4 and 25.3 ± 0.2 degrees 2-theta, a powder XRD pattern as depicted in figure 7; and combinations thereof. This form can be designated as form C. Form C can be further characterized by data selected from the group consisting of: additional powder XRD peaks at 8.8, 11.4, 16.8 and 22.5 ± 0.2 degrees 2-theta, and a DSC curve characterized by two thermal events; a first endotherm with maxima at about 164 °C, and the second one at about 263 °C corresponding to the melting that takes place in parallel with the degradation process as shown in Figure 8; a DSC thermogram as depicted in Figure 8;
and combinations thereof. The above crystalline Etravirine form C is an acetonitrile solvate.

Also provided herein is a crystalline etravirine characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 9.2, 16.2, 18.4 and 22.0 ± 0.2 degrees 2-theta, a powder XRD pattern as depicted in figure 12; and combinations thereof. This form can be designated as form F. Form F can be further characterized by data selected from the group consisting of: additional powder XRD peaks at 8.8, 13.5, 19.4 and 23.5 ± 0.2 degrees 2-theta, and a DSC curve characterized by a thermal event at about 258° C corresponding with the melting that takes place parallel to degradation process of Etravirine as shown in Figure 13; a DSC thermogram as depicted in Figure 13; and combinations thereof. The above crystalline Etravirine form F is an anhydrous form.

Further provided herein is a crystalline etravirine characterized by data selected from a group consisting of: an X-ray powder diffraction having peaks at 16.5, 23.0, 23.9 and 27.5 ± 0.2 degrees two-theta; a PXRD pattern as depicted in Figure 15; and combinations thereof. This form can be designated as form G. Form G can be further characterized by additional PXRD peaks at 8.8, 13.5, 19.3 and 26.0 ± 0.2 degrees two-theta. The above crystalline Etravirine form G is an anhydrous form.

Further provided herein is crystalline etravirine characterized by data selected from a group consisting of: an X-ray powder diffraction pattern having peaks at 7.4, 12.5, 17.1 and 29.2 ± 0.2 degrees two-theta; a PXRD pattern as depicted in Figure 17; and combinations thereof. This form can be designated as form I. Form I can be further characterized by additional PXRD peaks at 8.2, 13.5, 14.7 and 23.3 ± 0.2 degrees two-theta. Crystalline Etravirine form I is a dioxane solvate.

The above forms of etravirine can be used to prepare pharmaceutical compositions. Accordingly, in yet another embodiment, the invention encompasses a pharmaceutical composition comprising at least one of the above described polymorphs of etravirine of the invention, and at least one pharmaceutically acceptable excipient.

The present invention also encompasses a pharmaceutical composition comprising at least one of the above described polymorphs of etravirine, and at least one pharmaceutically acceptable excipient. The polymorphs of etravirine of the invention described above can be prepared according to the processes of the present invention. Accordingly, in another embodiment, the invention encompasses a process
for preparing a pharmaceutical composition comprising mixing at least one of the above-described polymorphs of etravirine of the invention, and at least one pharmaceutically acceptable excipient.

In another embodiment, the invention encompasses a method of treating HIV comprising administering an effective amount of at least one of the above described polymorphs of etravirine of the invention or the pharmaceutical composition comprising at least one of the above described polymorphs of etravirine and at least one pharmaceutically acceptable excipient to a patient in need thereof.

One embodiment of the invention provides the crystalline forms of etravirine of the present invention for use as a pharmaceutical formulation.

**PXRD method**

Samples, after being powdered in a mortar and pestle, were applied directly on silicon plate holder. The X-ray powder diffraction pattern was measured with Philips XPert PRO X-ray powder diffractometer, equipped with Cu irradiation source =1.54184 Å (Ångström), X'Celerator (2.022° 2Θ) detector.

Scanning parameters for forms C, D, forms F-I, a mixture of form B and Etravirine HBr salt and a mixture of form A and F: angle range: 3-40 deg., step size 0.0167, time per step 50 s, continuous scan.

Scanning parameters for form E: angle range: 3-40 deg., step size 0.0167, time per step 100 s, continuous scan.

Scanning parameters for polymorphically pure form A, form B and forms J-M: angle range: 3-40 deg., step size 0.0167, time per step 37.51 s, continuous scan.

**DSC method**

DSC analysis was performed on Q 1000 MDSC TA instruments with heating rate of 10 °C/min up to 320°C, under nitrogen flow of 50 ml/min. Standard aluminum, closed pan (with hole) was used, sample mass was about 1-5 mg.

**TGA method**

TGA analysis was performed on TGA 2950 TA Instruments. Approximately 10 mg of the sample, in a flow rate of nitrogen gas of 60 ml/min, was heated up to 500 °C with heating rate of 10 °C/ min.
NMR method

Solid-state $^{13}$C NMR spectra were recorded with variable amplitude cross polarization, magic angle spinning and high power proton decoupling using a BRUKER Avance II+ spectrometer operating at 125MHz and ambient temperature (about 25°C – not controlled). A probe using 4mm o.d. zirconia rotors was employed. The operation conditions were: contact time: 2ms; recycle delay: 5s; 1024scans and spin rate of 11kHz. Chemical shifts were referenced via a replacement sample of glycine (carboxyl carbon chemical shift assigned as 176.03 ppm relative to the signal of tetramethysilane).

DVS Method

The water sorption isotherms were measured using an accurate humidity- and temperature-controlled microbalance system, Dynamic Vapour Sorption (DVS 1, Surface Management Systems, UK). The RH was raised in steps from 0 to 90% and back to 0% at 26.4 °C. The equilibration condition at each step of the RH for the rate of change in mass with time (dm/dt) was selected.

EXAMPLES

Example 1: Mixture of Etravirine crystalline Forms A and F:

4-(6-Amino-2-(4-cyanophenylamino)pyrimidin-4-yl)oxy)-3,5-dimethylbenzonitrile (4.71 g, 13.22 mmol) was dissolved in glacial acetic acid (147 mL). Bromine solution in acetic acid (0.82 mL/74 mL) was added dropwise over 55 minutes at room temperature. The resulting suspension was stirred for another 45 minutes at room temperature, and the solid which formed was filtered off, washed with 120 mL of water and dried at room temperature under vacuum for 70 h. This yielded 5.03 g of white solid, HPLC purity 80% (20% of starting material).

11.3 g of the product obtained according to the procedure above was suspended in glacial acetic acid (353 mL). Bromine solution in acetic acid (1 mL Br$_2$ in 178 mL of acetic acid) was added dropwise over 45 minutes at room temperature. Another portion of bromine in acetic acid (0.5 mL Br$_2$ in 90 mL of acetic acid) was then added dropwise. The resulting suspension was filtered, and the separated solid was washed with acetic acid and water and dried for 2 h at 80 °C under vacuum and
for an additional 16 h at 25 °C under vacuum. This yielded 10.85 g of Etravirine HBr product (HPLC purity 97.3%).

The above product was suspended in 160 mL of water. 8.5 mL of 10% NaOH (water solution) was added dropwise over 15 minutes. The resulting mixture was stirred 1 h at room temperature. The resulting suspension was filtered and the separated solid was washed with water and dried for 3.5 h at 80 °C under vacuum and for an additional 16 h at 25 °C under vacuum. This yielded 9.31 g of etravirine, HPLC purity 97%.

Example 2: Preparation of polymorphically pure form A:

2.0 g of ETV (Form F) was suspended in acetone (30 ml) and a solution of H₃PO₄ in water (0.34 ml). The resulting suspension was stirred for 30 min at room temperature and then filtered to yield 2.2 g of the phosphate salt of ETV. The phosphate salt was suspended in water (25 ml) and 10% NaOH (1.98 ml) was added. The resulting suspension was stirred for 30 min at room temperature and then filter to yield polymorphically pure ETV form A (1.7 g).

Example 3: Preparation of Etravirine tosylate:

Etravirine (9.1 g) was suspended in acetone (225 ml) and a solution of p-toluenesulphonic acid (4.4 g) in acetone (45 ml) was added to form a mixture. The mixture was stirred at room temperature for 1 h. The obtained suspension was filtered and the thus-separated crystals were washed with acetone (2×10 ml) yielding 12.4 g of etravirine tosylate salt.

Example 4: Preparation of Etravirine Form B:

Etravirine tosylate (500 mg) was suspended in water (20 ml) and 10% NaOH was added (aqueous, 326.5 μL). The resulting suspension was stirred at room temperature for 45 min and for an additional 1 hour at 0 °C. The suspension was then filtered to provide pure form B of Etravirine.

Example 5: Preparation of Etravirine Form B:

Etravirine tosylate (500 mg) was suspended in water (10 ml) and 10% NaOH was added (aqueous, 326.5 μL). The resulting suspension was stirred at room
temperature for 45 min and for an additional 1 hour at 0 °C. The suspension was then filtered to provide pure form B of Etravirine.

Example 6: Preparation of Etravirine Form B:

About 1 g of Etravirine, form D was ground in a Fritsch, Pulverisette 7, ball mill with a few drops of water. The sample was ground in a 12 mL agate container with 3 agate balls (10mm) with a speed rate of 700 rpm. A crystalline sample of form B was obtained after 15 minutes, 30 minutes and 1 hour of grinding.

Example 7: Preparation of a mixture of Etravirine hydrobromide salt and Etravirine Form B:

4-(6-amino-2-(4-cyanophenylamino)pyrimidin-4-yloxy)-3,5-dimethylbenzonitrile (2.56 g) was dissolved in glacial acetic acid (80 mL) and a bromine solution in acetic acid (0.382 mL Br₂ in 40 mL of acetic acid) was added dropwise over 15 min at room temperature. The resulting suspension was stirred at room temperature for 1 hour and then at 80 °C for 3 hours. The mixture was then left in a refrigerator overnight and vacuum filtered to yield 3.126 g of the product (HPLC purity 88 %).

The product was then suspended in water and 10 % aqueous NaOH solution (1.1 eq) was added dropwise. The reaction mixture was stirred for 1 hour at room temperature and then vacuum filtered to provide a white solid which was dried in vacuo at 80 °C for 2 hours to yield 0.85 g of a mixture of etravirine and Etravirine HBr salt, HPLC purity 93%.

Example 8: Preparation of Etravirine Form C:

Etravirine (20 mg) was dissolved in acetonitrile (5 mL). The solution was filtered and left at room temperature to evaporate. Crystals were formed and separated by vacuum filtering.

Example 9: Preparation of Etravirine Form D:

Etravirine (20 mg) was dissolved in methanol (7 mL). The solution was filtered and left at room temperature to evaporate. Crystals were formed and separated by vacuum filtering.

Example 10: Preparation of Etravirine Form E:
A commercial Intelenze tablet was suspended in water (40 mL) and the resulting suspension was extracted with ethyl acetate (2×30 mL). The organic layer was separated and washed with water (30 mL). The organic layer was then dried over sodium sulphate and concentrated to dryness to yield 35 mg of etravirine form E.

Example 11: Preparation of Etravirine Form F:

Etravirine (20 mg) was dissolved in tert-butyl ethyl ether (TBME) (5 mL). The solution was filtered and left at room temperature to evaporate. Crystals were formed and separated by vacuum filtering.

Example 12: Preparation of amorphous Etravirine:

About 0.5 g of Etravirine (Form F) was ground in a Fritsch, Pulverisette 7, ball mill. The sample was ground in a 12 mL agate container with 6 agate balls (10mm) at a speed rate of 700 rpm. An amorphous sample was obtained after 1h, 2h and 3 hours of dry grinding. PXRD analysis of the sample after three hours of grinding is provided in Figure 14.

Example 13: Preparation of Etravirine Form G:

About 3 mg of amorphous etravirine, was placed in an aluminum sample pan with a small hole on lid under nitrogen set at a flow rate of 35 ml/min. The sample was equilibrated at 20 °C, then heated at a heating rate of 10 °C up to 150 °C, and then cooled at a rate of 10 °C/min down to 20 °C. The prepared sample was analyzed by XRPD.

Example 14: Preparation of Etravirine Form H:

Etravirine (20 mg), form F, was dissolved in 2-pyrrolidinone (1 mL). The solution was filtered and left at room temperature to evaporate. Crystals were formed and separated by vacuum filtering.

Example 15: Preparation of Etravirine Form I:

Amorphous etravirine was placed in a Petri dish in a desiccator in an atmosphere of 1,4-dioxane at room temperature. After 7 days, the sample was analyzed by XRPD and a new crystalline form of Etravirine was found.
Example 16: Preparation of Etravirine Form J:

ETV, Form F, (200 mg) was dissolved in DMF (2 ml) and water was added (5 ml). The resulting suspension was stirred for 30 min. at room temperature and filtered.

Example 17: Preparation of Etravirine Form K:

Etravirine, Form F (200 mg) was dissolved in dimethylsulfoxide (DMSO; 2 mL), and water (3 mL) was added. The resulting suspension was stirred at room temperature for 1 hour. Crystals formed and were separated by vacuum filtering.

Example 18: Preparation of Etravirine Form K:

Etravirine, Form F (200 mg) was dissolved in DMSO (2 mL), and water (1.5 mL) was added. The resulting suspension was stirred at room temperature for 72 hours. Crystals formed and were separated by vacuum filtering.

Example 19: Preparation of Etravirine Form L:

Etravirine, Form F (200 mg) was dissolved in dimethylacetamide (DMA; 2 mL) and water (3 mL) was added. The resulting suspension was stirred at room temperature for 1 hour. Crystals formed and were separated by vacuum filtering.

Example 20: Preparation of Etravirine Form L:

Etravirine, Form F (200 mg) was dissolved in DMA (2 mL) and water (1.5 mL) was added. The resulting suspension was stirred at 0-5 °C for 1 hour. Crystals formed and were separated by vacuum filtering.

Example 21: Preparation of Etravirine Form M:

Etravirine (500 mg) was dissolved in 1,2-dichloroethane (50 ml) and a solution was obtained. The solution was filtered and left at room temperature to evaporate overnight. Crystals formed and were separated by vacuum filtering.
CLAIMS

We Claim:

1. Crystalline Etravirine form A characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 10.6, 11.4, 14.0, 21.4 and 23.0 ± 0.2 degrees 2-theta, a PXRD pattern substantially as depicted in Figure 1, a solid state $^{13}$C NMR spectrum having peaks at 153.9, 142.4, 132.7, and 109.2 ± 0.2 ppm, a solid state $^{13}$C NMR spectrum substantially as depicted in Figure 27, and combinations thereof.

2. Crystalline Etravirine form A according to claim 1, characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 10.6, 11.4, 14.0, 21.4 and 23.0 ± 0.2 degrees 2-theta, a PXRD pattern as depicted in Figure 1, and combinations thereof.

3. The crystalline Etravirine according to claim 2, further characterized by additional XRD peaks at 5.3, 15.6, 17.7, 24.5 and 29.3 ± 0.2 degrees 2-theta.

4. The crystalline Etravirine according to claim 1, characterized by a solid state $^{13}$C NMR spectrum having peaks at 153.9, 142.4, 132.7, and 109.2 ± 0.2 ppm.

5. The crystalline Etravirine according to claim 4, further characterized by additional solid state $^{13}$C NMR peaks at 162.2, 155.9, 119.5, and 15.5 ± 0.2 ppm.

6. The crystalline Etravirine according to any one of claims 1 or 2, further characterized by data selected from the group consisting of: a DSC thermogram substantially as depicted in figure 2; a TGA thermogram substantially as depicted in figure 3; and combinations thereof.

7. The crystalline Etravirine according to any one of claims 1-6, wherein the crystalline Etravirine is anhydrous.
8. Crystalline Etravirine form B characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 11.1, 13.3, 18.3 and 21.6 ± 0.2 degrees 2-theta, a PXRD pattern substantially as depicted in Figure 5, a solid state $^{13}$C NMR spectrum having peaks at 142.7, 108.6, 107.2, 103.5, and 102.2 ± 0.2 ppm, a solid state $^{13}$C NMR spectrum substantially as depicted in Figure 28, and combinations thereof.

9. Crystalline Etravirine form B according to claim 8, characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 11.1, 13.3, 18.3 and 21.6 ± 0.2 degrees 2-theta, a PXRD pattern as depicted in Figure 5, and combinations thereof.

10. The crystalline Etravirine according to claim 9, further characterized by additional XRD peaks at 12.7, 14.7, 19.0 and 27.5 ± 0.2 degrees 2-theta.

11. The crystalline Etravirine according to claim 8, characterized by a solid state $^{13}$C NMR spectrum having peaks at 142.7, 108.6, 107.2, 103.5, and 102.2 ± 0.2 ppm.

12. The crystalline Etravirine according to claim 11, further characterized by additional solid state $^{13}$C NMR peaks at 154.0, 121.4, 116.1, and 18.7 ± 0.2 ppm.

13. The crystalline Etravirine according to any one of claims 8 or 9, further characterized by a DSC thermogram substantially as depicted in figure 6.

14. A pharmaceutical formulation comprising a crystalline form of Etravirine according to any one of claims 1-13 and at least one pharmaceutically acceptable excipient.

15. A crystalline form of Etravirine according to any one of claims 1-13 for use as a pharmaceutical formulation.

16. Use of the polymorph of any one of claims 1-13 for the manufacture of a medicament.
17. A method of treating HIV, comprising administering at least one of the crystalline forms of Etravirine according to any one of claims 1-13, or a pharmaceutical composition comprising at least one of the crystalline forms of Etravirine according to any one of claims 1-13 to a patient in need thereof.
Figure 1 shows a powder XRD pattern of polymorphically pure crystalline etavirine form A.
Figure 2 shows a DSC thermogram of polymorphically pure crystalline etravirine form A.
Figure 3 shows a TGA thermogram of polymorphically pure crystalline etavirine form A.
Figure 4 shows a powder XRD pattern of a mixture of crystalline etravirine form A and crystalline Etravirine form F.
Figure 5 shows a powder XRD pattern of crystalline etravirine form B.
Figure 6 shows a DSC thermogram of crystalline etavirine form B.
Figure 7 shows a powder XRD pattern of crystalline etravirine form C.
Figure 8 shows a DSC thermogram of crystalline etravirine form C.
Figure 9 shows a powder XRD pattern of crystalline etravirine form D.
Figure 10 shows a DSC thermogram of crystalline etravirine form D.
Figure 11 shows a powder XRD pattern of crystalline stavudine form E.
Figure 12 shows a powder XRD pattern of crystalline etravirine form F.
Figure 13 shows a DSC thermogram of crystalline etavirine form F.

Instrument: DSC Q1000 V9.8 Build 296

Size: 0.7500 mg
Method: Ramp

Heat Flow (W/g)

Temperature (°C)

Exo-Down

Universal V4.2E TA Instruments 370 360 350 340 330 320 310 300 290 280 270 260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
Figure 14 shows a powder XRD pattern of amorphous etravirine.
Figure 15 shows a powder XRD pattern of crystalline etavirine form G.
Figure 16 shows a powder XRD pattern of crystalline etravirine form H.
Figure 17 shows a powder XRD pattern of crystalline etravirine form I.
Figure 18 shows a powder XRD pattern of crystalline etavirine form J.
Figure 19 shows a DSC thermogram of crystalline etravirine form J.
Figure 20 shows a powder XRD pattern of crystalline etravirine form K.
Figure 21 shows a powder XRD pattern of crystalline etravirine form L.
Figure 22 shows a DSC thermogram of crystalline etravirine form L.
Figure 23 shows a powder TGA pattern of crystalline etravirine form L.
Figure 24 shows a powder XRD pattern of crystalline etravirine form M.
Figure 25 shows a DSC thermogram of crystalline etravirine form M.

- Temperature (°C)
- Heat Flow (W/g)
Figure 26 shows a powder XRD pattern of a mixture of crystalline etavirine form B and Etavirine hydrobromide salt.
Figure 27 shows a solid state $^{13}$C NMR spectrum of crystalline etavirine form A.
Figure 28 shows a solid state $^{13}$C NMR spectrum of crystalline etavirine form B.
Figure 29 shows a microscope image of crystalline etravirine form A.