Novel Amine Salts of Tenofovir, Process for Producing the Same and Use Thereof in Production of Tenofovir Dioproxil

Abstract:

Disclosed herein are novel amine salts of tenofovir and a process for producing the same. In addition, provided is a crystalline form of chloromethyl isopropyl carbonate solvate of tenofovir disoproxil. Furthermore, a process for producing tenofovir disoproxil and its pharmaceutically acceptable salt in high purity and yield employing the novel amine salt of tenofovir and tenofovir CMIC solvate is disclosed.

Title: Novel Amine Salts of Tenofovir, Process for Producing the Same and Use Thereof in Production of Tenofovir Dioproxil

Figure 1
NOVEL AMINE SALTS OF TENOFOVIR, PROCESS FOR PRODUCING THE SAME AND USE THEREOF IN PRODUCTION OF TENOFOVIR DIOPROXIL

FIELD OF THE INVENTION:

The present invention in general relates to tenofovir disoproxil. More particularly the present invention relates to novel amine salts of tenofovir, a process for producing the same and its use thereof to prepare tenofovir disoproxil, its solvate and pharmaceutically acceptable salts.

BACKGROUND OF THE INVENTION:

Tenofovir disoproxil chemically known as 9-[-2-(R)-[[bis[(isoproxy carbonyl) oxy]methoxy]phosphinyl]methoxy]propyl]adenine, is represented by the following structural formula:

![Tenofovir disoproxil](image)

Tenofovir disoproxil fumarate is commercially available as VIREAD®, which has been approved by the United States Food and Drug Administration for use in the treatment of HIV. Tenofovir disoproxil is a highly potent antiviral agent, particularly for the prophylaxis or therapy of retroviral infections and belongs to a class of drugs called nucleotide reverse transcriptase inhibitors (NRTI) which blocks reverse transcriptase, an enzyme crucial to viral production in HIV-infected people.

Tenofovir disoproxil is first disclosed in US 5,922,695, assigned to Gilead. This patent describes the process for the preparation of tenofovir disoproxil and its further isolation as the fumarate salt. Furthermore, the patent discloses that tenofovir disoproxil base is obtained as an oil using the process. The process as disclosed in US 5,922,695 comprises condensation of (R)-9-[2-(phosphonomethoxy)propyl]adenine hydrate with chloromethyl isopropyl carbonate in presence of 1-methyl-2-pyrrolidinone and triethylamine and subsequent treatment with fumaric acid in
presence of isopropanol to produce tenofovir disoproxil fumarate. During the work up process i.e. during extraction of the tenofovir disoproxil fumarate employing solvents, degradation of the tenofovir disoproxil occurs thereby lowering the yield of the final product and the product obtained is of inferior quality.

In the prior art processes tenofovir disoproxil is directly converted to its fumarate salt without isolating the pure tenofovir disoproxil base.

In the existing processes employed, it is difficult to separate the impurities formed during the process from the desired product. The step of purification requires extensive and multiple steps to obtain the required quality of the end product, thereby lowering the yield and increasing the operational cost of the product. The processes are thus not amenable for commercial scale production.

In light of the foregoing discussion there exists a need to develop a new and efficient process for large scale production of tenofovir disoproxil and pharmaceutically acceptable salts thereof that is economical and employs fewer purification steps.

**OBJECT AND SUMMARY OF THE INVENTION**

It is a principal object of the present invention to provide novel amine salts of tenofovir and process for producing the same.

It is another object of the present invention to provide a process for large scale production of tenofovir disoproxil and pharmaceutically acceptable salts thereof employing novel amine salts of tenofovir, wherein the product is obtained in high purity and yield.

It is still another object of the present invention to provide a crystalline form of a solvate of tenofovir disoproxil and a process for producing the same thereof.

The above and other objects of the present invention are further attained and supported by the following embodiments described herein. However, the scope of the invention is not restricted to the described embodiments herein after.

In accordance with one preferred embodiment of the present invention there are provided amine salts of tenofovir.

In accordance with another embodiment of the present invention there is provided a crystalline form of triethylamine salt of tenofovir characterized by powder x-ray diffraction, DSC and TGA as depicted in figure 1, 2 and 3 respectively.
In accordance with yet another embodiment of the present invention there is provided a process for producing tenofovir amine salt wherein the process comprises dehydrating tenofovir hydrate in presence of an amine in a solvent to obtain anhydrous tenofovir amine salt, isolating the anhydrous tenofovir amine salt and optionally purifying the tenofovir amine salt.

In accordance with an embodiment of the present invention, there is provided a process for producing tenofovir amine salt wherein the amine used is selected from triethylamine, diisopropylamine, diisopropyl ethylamine, dicyclohexylamine, cyclohexylamine, or tri n-butylamine, preferably triethylamine.

In accordance with yet another embodiment of the present invention there is provided a process for producing tenofovir amine salt, wherein the process further comprises converting the tenofovir amine salt to tenofovir disoproxil CMIC solvate.

In accordance with still another embodiment of the present invention the process for converting the tenofovir amine salt to tenofovir disoproxil CMIC solvate comprises treating the anhydrous tenofovir amine salt with CMIC in an organic solvent in presence of a base, subsequently isolating the crystalline crude tenofovir disoproxil CMIC solvate using water and purifying the crude crystalline tenofovir disoproxil CMIC solvate employing a solvent to obtain pure tenofovir disoproxil CMIC solvate.

In accordance with yet another embodiment of the present invention, the tenofovir disoproxil CMIC solvate is optionally converted to tenofovir disoproxil free base, wherein the process comprises treating tenofovir disoproxil CMIC solvate in presence of a solvent selected from isopropyl alcohol or cyclohexane and crystallization in ethyl acetate.

In accordance with yet another embodiment of the present invention, the tenofovir disoproxil CMIC solvate is converted to pharmaceutically acceptable salts of tenofovir disoproxil.

In accordance with another embodiment of the present invention there is provided a crystalline form of tenofovir disoproxil CMIC solvate characterized by powder x-ray diffraction, DSC and TGA as depicted in figure 4, 5 and 6 respectively.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Further objects of the present invention together with additional features contributing thereto and advantages accruing there from will be apparent from the
following description of preferred embodiments of the invention which are shown in
the accompanying drawing figures wherein:

Figure 1 illustrates the powder X-ray powder diffraction pattern of crystalline
form of triethylamine salt of tenofovir.

Figure 2 illustrates the Differential Scanning Calorimetric (DSC) thermogram
of crystalline form of the triethylamine salt of tenofovir.

Figure 3 illustrates the Thermo Gravimetric Analysis (TGA) thermogram of
crystalline form of the triethylamine salt of tenofovir.

Figure 4 illustrates the X-ray powder diffraction pattern of crystalline form of
tenofovir disoproxil chloromethyl isopropyl carbonate solvate.

Figure 5 illustrates the DSC thermogram of the crystalline form of tenofovir
disoproxil chloromethyl isopropyl carbonate solvate.

Figure 6 illustrates the TGA thermogram of the crystalline form of tenofovir
disoproxil chloromethyl isopropyl carbonate solvate

DETAILED DESCRIPTION OF THE INVENTION:

While this specification concludes with claims particularly pointing out and
distinctly claiming that, which is regarded as the invention, it is anticipated that the
invention can be more readily understood through reading the following detailed
description of the invention and study of the included examples.

The present invention provides industrial scale process for producing tenofovir
disoproxil and its pharmaceutically acceptable salts with high purity and yield.
Further, the present invention provides novel amine salts of tenofovir and process for
producing the same thereof. The novel amine salts of tenofovir are employed for
producing tenofovir disoproxil and its pharmaceutically acceptable salts, wherein the
process requires fewer purification steps.

In addition, the present invention provides a crystalline form of chloromethyl
isopropyl carbonate solvate (CMIC) of tenofovir disoproxil and a process for
producing thereof.

According to the invention there is provided a novel amine salt of tenofovir.
The amine according to the present invention is selected from triethylamine,
dicyclohexylamine cyclohexylamine or tri n-butylamine, preferably triethylamine.

According to the present invention there is provided a process for producing
the amine salt of tenofovir, wherein the process comprises:
a) dehydrating tenofovir hydrate in presence of an amine in a solvent to obtain anhydrous amine salt of tenofovir amine,
b) isolating the anhydrous amine salt of tenofovir, and
c) optionally purifying the amine salt of tenofovir.

According to the present invention, the amine employed is an organic amine, wherein the amine is selected from the group consisting of triethylamine, diisopropylamine, diisopropyl ethylamine, dicyclohexylamine, cyclohexylamine, tri-n-butylamine, preferably triethylamine.

According to the invention, the solvent used in the step of dehydration is selected from the group consisting of chlorinated hydrocarbons, aliphatic and aromatic hydrocarbons, ketones, ethers, esters or nitriles. The solvent is selected from methylene dichloride, chloroform, acetonitrile, cyclohexane, tetrahydrofuran, xylene, N-methylpyrrolidone, ethyl acetate, acetone, methylisobutyl ketone or toluene, and is preferably cyclohexane.

According to another embodiment of the present invention, purification of amine salt of tenofovir is carried out in presence of an organic solvent selected from acetonitrile, dimethylformamide or N-methylpyrrolidinone.

The anhydrous amine salt of tenofovir, preferably triethylamine salt obtained according to the invention is stable, free from moisture and can be easily handled for subsequent reaction.

According to the invention, the amine salt of tenofovir is further converted to tenofovir disoproxil CMIC solvate by a process comprising treating or condensing the anhydrous amine salt of tenofovir with chloromethyl isopropyl carbonate in an organic solvent in presence of a base to obtain crystalline form of crude tenofovir disoproxil CMIC solvate, subsequently isolating the crystalline form of crude tenofovir disoproxil CMIC solvate using water and purifying the crude tenofovir disoproxil CMIC solvate employing a solvent to get pure crystalline form of tenofovir disoproxil CMIC solvate.

The synthetic scheme for producing tenofovir disoproxil CMIC solvate is depicted below:
According to the present invention, the organic solvent used during condensation of tenofovir amine salt with chloromethyl isopropyl carbonate is selected from the group consisting of acetonitrile, dimethylformamide, N-methylpyrrolidinone, preferably N-methyl pyrrolidinone.

According to the present invention, the base used during condensation of tenofovir organic amine salt with chloromethyl isopropyl carbonate is selected from triethylamine, diisopropylamine, dicyclohexylamine, cyclohexylamirie, tri n-butylamine or diisopropyl ethylamine.

According to the present invention, the condensation of Tenofovir organic amine salt with chloromethyl isopropyl carbonate is carried out at a temperature between 25°C to 80°C and preferably at a temperature between 50-60°C.

Alternatively, the crude tenofyir disoproxil CMIC solvate is obtained directly using cold water without causing degradation of the tenofovir disoproxil, which is further purified employing an organic solvent to get pure tenofovir disoproxil CMIC solvate.

The purification of tenofovir disoproxil CMIC solvate according to the invention is carried out in an organic solvent selected from cyclohexane, n-heptane, n-hexane, ethyl acetate, isopropyl acetate, ethanol or isopropyl alcohol. The crystalline
tenofovir disoproxil CMIC solvate is isolated from the reaction mass at a temperature between 0-35°C, preferably between 10-15°C.

According to the invention, the tenofovir disoproxil CMIC solvate is further converted to pharmaceutically acceptable salts of tenofovir disoproxil.

Moreover, according to the present invention, the tenofovir disoproxil CMIC solvate is optionally converted to tenofovir disoproxil free base by treating the tenofovir disoproxil CMIC solvate in presence of a solvent selected from isopropyl alcohol or cyclohexane followed by crystallization in ethylacetate to yield tenofovir disoproxil free base. The resultant tenofovir disoproxil free base can be further converted to pharmaceutically acceptable salts of tenofovir disoproxil as per the prior art methods.

According to the invention, the pharmaceutically acceptable salt of tenofovir disoproxil, preferably fumarate is prepared by methods known in the art. The tenofovir disoproxil CMIC solvate is reacted with the calculated amount of acid such as fumaric acid in water miscible solvents like alcohols such as isopropyl alcohol (IPA), with subsequent isolation of the salt.

According to the invention, the fumarate salt of the tenofovir disoproxil obtained by the method of the invention is characterized by having high purity, preferably more than 99.0%, most preferably more than 99.5% purity. Alternatively, other pharmaceutically acceptable salts of the tenofovir disoproxil are obtained in a pure form by the process of the present invention.

**Powder X-ray Diffraction (TXRD)**

The crystalline forms of the present invention are characterized by their X-ray powder diffraction pattern. Thus, the X-ray diffraction patterns were measured on **PANalytical, X'Pert PRO** powder diffractometer equipped with goniometer of \(\theta/\theta\) configuration and **X'Celerator** detector. The Cu-anode X-ray tube was operated at 40kV and 30mA. The experiments were conducted over the \(2\theta\) range of 2.0°-50.0°, 0.030° step size and 50 seconds step time.

**Differential Scanning Calorimetry (DSC)**

The DSC measurements of the present invention were carried out on Mettler Toledo 822 star® and **TA Q1000** of TA instruments. The experiments were performed at a heating rate of 10.0 °C/min over a temperature range of 30°C-300°C purging with
nitrogen at a flow rate of 50ml/min. Standard aluminum crucibles covered by lids with three pin holes were used.

**Thermo gravimetric Analysis (TGA)**

TGA was recorded out using the instrument Mettler Toledo TGA/SDTA 851° and TGA Q5000 of TA instruments. The experiments were performed at a heating rate of 10.0 °C/min over a temperature range of 30°C-300°C purging with nitrogen at a flow rate of 25ml/min.

According to a preferred embodiment of the present invention, the amine salt of tenofovir is preferably a crystalline triethylamine salt. The crystalline form of tenofovir triethylamine salt is characterized by powder X-ray diffraction pattern as shown in figure 1 having peaks at 14.67, 18.30, 22.15, 23.15, 24.45 and 28.60 degrees ± 0.2 θ values.

The crystalline Tenofovir triethylamine salt is further characterized by DSC with three endothermic peaks as depicted in figure 2.

The crystalline Tenofovir triethylamine salt is further characterized by TGA data as depicted in figure 3.

According to the present invention, there is provided a crystalline form of tenofovir disoproxil chloromethyl isopropyl carbonate (CMIC) solvate. The crystalline form of tenofovir disoproxil chloromethyl isopropyl carbonate (CMIC) solvate is characterized by powder X-ray diffraction pattern as shown in figure 4 having peaks at 6.81, 8.30, 18.72, 22.89 and 23.18 degrees ± 0.2 θ values.

The crystalline tenofovir disoproxil CMIC solvate is further characterized by DSC with two endothermic peaks as depicted in figure 5.

The crystalline tenofovir disoproxil CMIC solvate is further characterized by TGA data as depicted in figure 6.

The following non-limiting examples illustrate specific embodiments of the present invention. They should not construe it as limiting the scope of present invention in any way.

**Example-1**

**Preparation of tenofovir disoproxil triethylamine salt**

25 gm of (R)-9-[2-(phosphonomethoxy)propyl]adenine, 16.6 gm of triethyl amine and 200 ml of cyclohexane were combined under nitrogen. The reaction mass was then refluxed and water separated by azeotropic distillation. The resultant mass
was cooled to room temperature and filtered. The filtrate was washed with cyclohexane and dried to yield tenofovir disoproxil triethylamine salt.

**Example-2**

**Preparation of tenofovir disoproxil CMIC solvate**

25 gm of (R)-9-[2-(phosphonomethoxy)propyl]adenine, 20 gm of triethyl amine and 200 ml of cyclohexane were combined and heated to remove water and the solvent was distilled off under vacuum. The reaction mass was then cooled to room temperature and 55 ml of N-methyl pyrrolidinone, 20 ml of triethyl amine were added to the reaction mixture. The reaction mass was heated to 50-60°C and 65 gm of chloromethyl isopropyl carbonate was added and the resultant mass maintained for 8 hrs at 50-60°C followed by cooling to 10°C. Subsequently, the reaction mass was diluted with water and precipitated solid product filtered. The mother liquor was extracted with 150 ml methylene chloride and the methylene chloride layer washed with 200 ml of water. The filtered solid and the methylene chloride layer were combined, washed with water and the solvent distilled under vacuum. Ethyl acetate was charged to the precipitated solid. The reaction mass was then cooled to 0-5°C and maintained for 6 hrs. The solid was filtered and dried to produce 22 gm of tenofovir disoproxil CMIC solvate.

**Example-3**

**Preparation of tenofovir disoproxil CMIC solvate**

25 gm of (R)-9-[2-(phosphonomethoxy)propyl]adenine, 25 gm of triethyl amine and 300 ml of cyclohexane were combined and heated to remove water. The solvent was distilled off completely. The reaction mass was cooled to room temperature and 60 ml of N-methyl pyrrolidinone and 16 ml of triethyl amine were added to the reaction mixture. The reaction mass was heated to 50-60°C and 65 gm of chloromethyl isopropyl carbonate was added. The reaction was maintained for 5-9 hrs at 50-60°C and then cooled to 10-15°C. The reaction mass was then diluted with water and precipitated solid product was filtered. The filtrate was extracted with 200 ml of ethyl acetate. The ethyl acetate extraction and filtered solid were combined and washed with 200 ml of water. The solvent was distilled off and the precipitated solid charged with ethyl acetate. The reaction mass was then cooled to 0-5°C and maintained for 6 hrs. The solid was filtered and dried to produce 20 gm of tenofovir disoproxil CMIC solvate.
Example-4
Preparation of tenofovir disoproxil CMIC solvate
25 gm of (R)-9-[2-(phosphonomethoxy)propyl]adenine and 25 gm of triethyl amine are added to 250 ml of cyclohexane and heated to remove water. The solvent was distilled off completely. The reaction mass was cooled to room temperature and 50 ml of N-methyl pyrrolidinone and 25 gm of triethyl amine were added to the reaction mixture. The resultant reaction mixture was heated to 50-60°C and 65 gm of chloromethyl isopropyl carbonate was added. The reaction mass was maintained for 5-7 hrs at 50-60°C and then cooled to 10-15°C. Subsequently, the reaction mass was diluted with water and precipitated solid product filtered. The mother liquor was extracted with 150 ml methylene chloride. The methylene chloride layer was washed with 200 ml of water and the solvent distilled under vacuum. Ethyl acetate was charged to the precipitated solid. The reaction mass was then cooled to 0-5°C and maintained for 6 hrs. The solid was filtered and dried to produce 19 gm of tenofovir disoproxil CMIC solvate.

Example-5
Preparation of tenofovir disoproxil CMIC solvate
25 gm of (R)-9-[2-(phosphonomethoxy)propyl]adenine and 29 gm of dicyclohexyl amine are added to 200 ml cyclohexane under nitrogen. The temperature was raised to reflux and water removed. The solvent was distilled completely and the reaction mass cooled to 25-35°C followed by adding 88 ml of N-methyl pyrrolidinone and 35 gm of dicyclohexyl amine. The reaction mixture was then heated to 50-60°C and 65 gm of chloromethyl isopropyl carbonate was added. The resultant reaction mass was maintained for 6-9 hrs at 50-60°C and then cooled to 10-15°C. To the reaction mixture water was added and product extracted with methylene chloride. Methylene chloride layer was washed with water and distilled off. Ethyl acetate was added to the precipitated solid and the temperature cooled to 0-5°C and maintained for 6 hrs. The solid was filtered and dried to get to produce 24 gm of tenofovir disoproxil CMIC solvate.

Example-6
Preparation of tenofovir disoproxil CMIC solvate
25 gm of (R)-9-[2-(phosphonomethoxy)propyl]adenine and 16 gm of cyclohexyl amine are added to 250 ml of cyclohexane and water was removed. The
solvent was distilled completely and the reaction mass was cooled to room
temperature and 100 ml of N-methyl pyrrolidinone, 20gm of cyclohexyl amine were
added. The reaction mass was heated to 50-60°C and 65 gm of chloromethyl
isopropyl carbonate was added. The resultant reaction mixture was maintained for 6-9
hrs at 50-60°C and then cooled to 10-15°C. To the reaction mixture water was added
and the product was extracted with methylene chloride. The methylene chloride layer
was washed with water and distilled off. Ethyl acetate was added to the precipitated
solid. The resultant reaction mass was cooled to 0-5°C and maintained for 6 hrs. The
solid was filtered and dried to produce 26 gm of tenofovir disoproxil CMIC solvate.

Example-7
Preparation of tenofovir disoproxil CMIC solvate

25 gm of (R)-9-[2-(phosphonomethoxy)propyl]adenine and 31 gm of tri n-
butoxyl amine are added to 250 ml of cyclohexane and water removed by distillation.
The solvent was distilled completely and the reaction mass cooled to room
temperature, followed by adding 90 ml of N-methyl pyrrolidinone and 40 gm of
cyclohexyl amine to the reaction mixture. The reaction mixture was heated to 50-
60°C and 65 gm of chloromethyl isopropyl carbonate was added. The resultant
reaction mass was maintained for 5-7 hrs at 50-60°C and then cooled to 10-15°C. To
the reaction mixture water was added and product was extracted with methylene
chloride. Methylene chloride layer was washed with water and distilled off. Ethyl
acetate was added to the precipitated solid and the temperature cooled to 0-5°C and
maintained for 6 hrs. The solid was filtered and dried to produce 25 gm of tenofovir
disoproxil CMIC solvate.

Example-8
Preparation of tenofovir disoproxil

100 gm of tenofovir disoproxil chloromethyl isopropyl carbonate (CMIC)
solvate was suspended in 400 ml of isopropyl alcohol at 20-25°C. The solvent was
then evaporated under reduced pressure and the residue dissolved in cyclohexane (100
ml). The solvent was again evaporated under reduced pressure and the residue
dissolved in ethyl acetate(300ml). The resultant was cooled to 0-5°C and maintained
for 3 hrs to crystallize the product. The crystallized product was filtered and washed
with chilled cyclohexane (50 ml). The wet cake so obtained was dried under vacuum
below a temperature of 40°C to produce 70 gm of tenofovir disoproxil.
Example-9
Preparation of tenofovir disoproxil fumarate

100 gm of tenofovir disoproxil chloromethyl isopropyl carbonate (CMIC) solvate is suspended in 1000 ml of isopropyl alcohol at 20-25°C. A solution of 38 gm of fumaric acid dissolved in 1500 ml isopropyl alcohol at 45-55°C was added to reaction mixture and the mixture stirred for 1 hr and cooled to 40°C. The reaction mass was then cooled to room temperature and finally to 5-10°C and maintained for 1 hr. The crystallized product was then filtered and washed with 100 ml of isopropyl alcohol. The wet product was dried under vacuum below 40°C to produce 85 gm of tenofovir disoproxil fumarate.

While this invention has been described in detail with reference to certain preferred embodiments, it should be appreciated that the present invention is not limited to those precise embodiments. Rather, in view of the present disclosure, which describes the current best mode for practicing the invention, many modifications and variations would present themselves to those skilled in the art without departing from the scope and spirit of this invention.
We claim:

1. An amine salt of (R)-9-[2-(phosphonomethoxy)propyl] adenine (tenofovir).
2. The amine salt of tenofovir according to claim 1, wherein the amine is selected from triethylamine, dicyclohexylamine cyclohexylamine or tri n-butylamine.
3. A process for producing amine salt of tenofovir of claim 1, wherein the process comprising:
   a. dehydrating tenofovir hydrate in presence of an amine in a solvent to obtain anhydrous tenofovir amine salt;
   b. isolating the anhydrous amine salt of tenofovir; and
   c. optionally purifying the amine salt of tenofovir.
4. The process according to claim 3, wherein the amine used is selected from triethylamine, diisopropylamine, diisopropyl ethylamine, dicyclohexylamine, cyclohexylamine, or tri n-butylamine.
5. The process according to claim 4, wherein the amine is triethylamine.
6. The process according to claim 3, wherein the solvent used is selected from a group consisting of chlorinated hydrocarbons, aliphatic hydrocarbons, aromatic hydrocarbons, ethers, ketones, esters or nitriles.
7. The process according to claim 6, wherein the solvent is selected from methylene dichloride, chloroform, acetonitrile, cyclohexane, tetrahydrofuran, xylene, N-methylpyrrolidone, ethyl acetate, acetone, methylisobutyl ketone or toluene.
8. The process according to claim 6, wherein the solvent is cyclohexane.
9. The process according to claim 3, wherein the purification of amine salt of tenofovir is carried out in presence of an organic solvent selected from acetonitrile, dimethylformamide, tetrahydrofuran or N-methylpyrrolidinone.
10. The process for producing amine salt of tenofovir according to claim 3, wherein the process further comprising converting the amine salt of tenofovir to tenofovir disoproxil CMIC solvate.
11. The process according to claim 10, wherein the process for converting the amine salt of tenofovir to tenofovir disoproxil chloromethyl isopropyl carbonate (CMIC) solvate comprising:
    treating the anhydrous amine salt of tenofovir with CMIC in an organic solvent in presence of a base, subsequently isolating crystalline crude
tenofovir disoproxil CMIC solvate and purifying the crude crystalline
tenofovir disoproxil CMIC solvate employing a solvent to obtain pure
crystalline form of tenofovir disoproxil CMIC solvate.

12. The process according to claim 11, wherein the base used is selected
from triethylamine, diisopropylamine, diisopropyl ethylamine, dicyclohexylamine,
cyclohexylamine, or tri n-butylamine.

13. The process according to claim 11, wherein the organic solvent used is
selected from acetonitrile, dimethylformamide or N-methylpyrrolidinone.

14. The process according to claim 11, wherein the tenofovir disoproxil
CMIC solvate is isolated using water.

15. The process according to claim 11, wherein the purification of
tenofovir disoproxil CMIC solvate is carried out in presence of a suitable organic
solvent selected from cyclohexane, n-heptane, n-hexane, ethyl acetate, isopropyl
acetate, ethanol or isopropyl alcohol.

16. The process according to claim 11, wherein the tenofovir disoproxil
CMIC solvate is optionally converted to tenofovir disoproxil free base.

17. The process according to claim 16, wherein the process for converting
tenofovir disoproxil CMIC solvate to tenofovir disoproxil free base comprises treating
tenofovir disoproxil CMIC solvate in presence of a solvent selected from isopropyl
alcohol or cyclohexane and crystallization in ethyl acetate.

18. The process according to claim 11, wherein the tenofovir disoproxil
CMIC solvate is converted to pharmaceutically acceptable salts thereof.

19. The process according to claim 18, wherein the pharmaceutically
acceptable salt is tenofovir disoproxil fumarate.

20. A crystalline form of (R)-9-[2-(phosphonomethoxy)propyl]adenine
(tenofovir) triethylamine salt.

21. The crystalline tenofovir triethylamine salt according to claim 20,
wherein the crystalline form of tenofovir triethylamine salt is characterized by powder
x-ray diffraction having peaks at 14.67, 18.30, 22.15, 23.15, 24.45 and 28.60 degrees
± 0.2 θ values

22. The crystalline form of tenofovir triethylamine salt according to claim
20, wherein the crystalline form of tenofovir triethylamine salt is having a
substantially similar X-ray powder diffraction pattern as depicted in Figure 1.
23. The crystalline form of tenofovir triethylamine salt according to claim 20, wherein the crystalline form of tenofovir triethylamine salt is characterized by DSC as depicted in Figure 2 and TQA as depicted in Figure 3.


25. The crystalline form of tenofovir disoproxil CMIC solvate according to claim 24, is characterized by powder x-ray diffraction having peaks at 6.81, 8.30, 18.72, 22.89 and 23.18 degrees ± 0.2 θ values.

26. The crystalline form of tenofovir disoproxil CMIC solvate according to claim 24, wherein the crystalline form of tenofovir disoproxil CMIC solvate is having a substantially similar X-ray powder diffraction pattern as depicted in Figure 4.

27. The crystalline form of tenofovir disoproxil CMIC solvate according to claim 24, wherein the crystalline form of tenofovir disoproxil CMIC solvate is characterized by DSC as depicted in Figure 5 and TGA as depicted in Figure 6.