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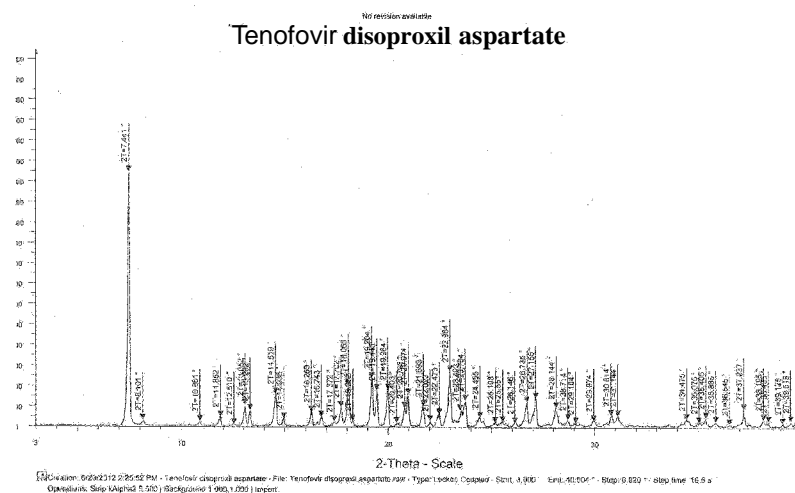
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(54) Title: THE NOVEL TENOFOVIR DISOPROXIL SALT AND THE PREPARATION METHOD THEREOF



(57) Abstract: The present invention relates to a novel tenofovir disoproxil aspartate compound. The aforementioned salt compound allows minimal formation of related substances occurring with passage of time, increasing the stability of the formulation by drastically reducing the formation of impurities during storage. Also, the need for a separate study of toxicological effects is eliminated. Moreover, the salt compound of the present invention possesses superior physicochemical properties, with a significant improvement in stability, hygroscopicity, and solubility, thereby allowing it to be used as an active ingredient along with pharmaceutically acceptable carriers for a pharmaceutical composition for the treatment of HIV infection and chronic hepatitis B.

Description

Title of Invention: THE NOVEL TENOFOVIR DISOPROXIL SALT AND THE PREPARATION METHOD THEREOF

Technical Field

[1] The present invention relates to a novel salt of tenofovir disoproxil and the preparation method thereof.

[2]

Background Art

[3] Tenofovir disoproxil fumarate (hereinafter referred to as "TDF") is a compound whose chemical name is

9-[2-(R)-[[bis [[(isopropoxycarbonyl)oxy] methoxy] phosphinoyl] methoxy] propyl] adenine-fumaric acid (1:1). It is a prodrug which becomes hydrolyzed upon absorption, and it is a phosphonmethoxy nucleotide analog useful for the treatment of HIV-1 infection and chronic hepatitis B.

[4]

[5] TDF was researched and developed by Gilead Sciences and have been in use under the brand name Viread since 2001, when it was approved for the treatment of AIDS. It was approved for the treatment of hepatitis B by the European Medicines Agency in April 2008 and by the U.S. Food and Drug Administration in November 2008. Tenofovir, the active metabolite in TDF, has a similar structure and effect as adefovir (Hepsera) but is less toxic to the kidneys. Thus, it can be used at a much larger dosage of 300mg, as opposed to the dosage of 10mg for adefovir, thus enabling powerful inhibition of the DNA of the hepatitis B virus in patients who are resistant to lamivudine (Zeffix). Furthermore, tenofovir is a Pregnancy Category B (animal studies have failed to demonstrate a risk to the fetus) antiviral agent, as categorized by the U.S. Food and Drug Administration.

[6]

[7] Despite such advantages, securing of a physicochemically stable form of tenofovir has proved to be a difficult challenge. The original developer has initiated various studies in an attempt to overcome this problem. For example, tenofovir disoproxil (hereinafter referred to as "TD") is known to possess a significant stability problem due to the effect of moisture. A publication (Pharmaceutical Research, 2001, 18, 234-237; Pharmaceutical Research, 2000, 17, 1098-1103) reports that TD in the presence of moisture undergoes hydrolysis to generate formaldehyde, and this formaldehyde and the N⁶-amine group of the TD undergo a condensation reaction to generate tenofovir disoproxil dimer, which is an impurity.

[8]

[9] Generally, for a pharmaceutical drug to always demonstrate a consistent effect requires inhibiting not only the reduction of contents of the active ingredients, but also the increase of degradation products of the active ingredients, namely impurities or related substances, immediately after manufacturing and during storage. Thus, preventing inclusion of impurities within a pharmaceutical drug is extremely important for its quality control.

[10]

[11] Looking at each country's official compendium regulations for a purity test, the Korean Pharmacopoeia has a separate regulation for related substances under the purity test section, while the US Pharmacopoeia has regulations for "ordinary impurities", requiring total related substances to be below 2.0% unless otherwise specified, or individually regulating related compounds and chromatographic purity under each article of pharmaceutical drugs. It is regulated as related substances in the European Pharmacopoeia and in the UK Pharmacopoeia, while the amount is regulated as related substances during a purity test in the Japanese Pharmacopoeia.

[12]

[13] Furthermore, the International Conference on Harmonization (ICH), an international agreement for pharmaceutical drugs, provides general descriptions about impurities in new drug substances in Guideline Q3A and impurities in new drug products in Guideline Q3B. Standards of impurities in pharmaceutical products are further subdivided into and regulated as reporting thresholds, identification thresholds, and safety qualification thresholds. The reporting thresholds call for simply reporting the presence of impurities in a brief manner, and the identification thresholds require investigating the physicochemical structures of the impurities, and the safety qualification thresholds require assessing the toxicological effects as well as investigating the physicochemical structures of the impurities in order to provide basis for determining any risks in safety due to the impurities when administered to a human body.

[14]

[15] As shown, controlling impurities contained in pharmaceutical products is an issue of critical importance calling forth an internationally established common agreement.

[16]

[17] Therefore, the ability to maintain the formation of impurities in a TD-containing drug under a certain level during storage of the drug is of great significance because it precludes the necessity for additional investigations on physicochemical structures and/or of toxicological research, allowing economical benefits and also reducing toxicological risks caused by relevant impurities. Accordingly, the drug containing tenofovir disoproxil must be able to keep the impurities formation rate under a certain

level.

[18]

[19] Gilead Sciences, the original developer of tenofovir, developed a tenofovir disoproxil fumarate compound, which is suitable for oral administration and can secure stability of the drug by inactivating N⁶-amine group, inhibiting formation of and increase in the dimer impurities (US Patent No. 5935946). International Patent No. WO2010/142,761 discloses tenofovir disoproxil succinate, which is less hygroscopic than tenofovir disoproxil fumarate and has improved solubility and stability, improving its suitability to be manufactured in tablet form.

[20]

[21] The present inventors put efforts into researching a novel salt that possesses similar or better physicochemical advantages compared to the existing tenofovir disoproxil fumarate while minimizing formation of related substances. As a result of their research, they developed a novel tenofovir disoproxil aspartate by utilizing aspartic acid.

[22]

Disclosure of Invention

Technical Problem

[23]

The object of the present invention is to provide a novel tenofovir disoproxil salt compound that possesses similar or better physicochemical advantages compared to tenofovir disoproxil fumarate and minimize formation of related substances.

[24]

Solution to Problem

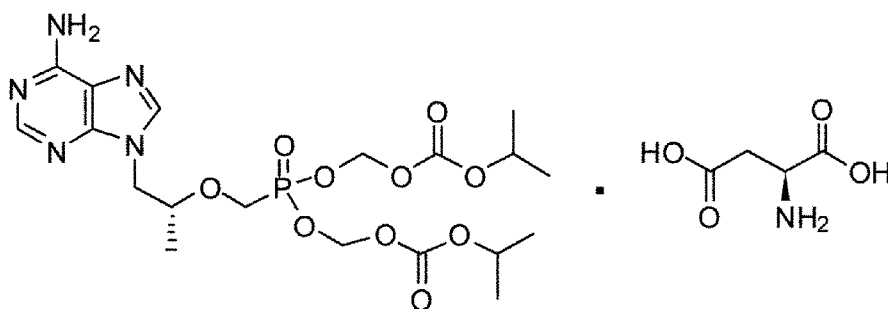
[25]

To achieve the above object, the present invention provides a pharmaceutically acceptable compound of tenofovir disoproxil aspartate, represented by Formula 1 below, which shows an improved physicochemical property, enabling the pharmaceutical composition to be used effectively for the treatment of HIV-1 infection and chronic hepatitis B.

[26]

[27] <Formula 1>

[28]



[29]

[30] Tenofovir disoproxil aspartate of the present invention exists in a salt form where aspartic acid and tenofovir disoproxil free base are ionically bonded in a 1:1 ratio.

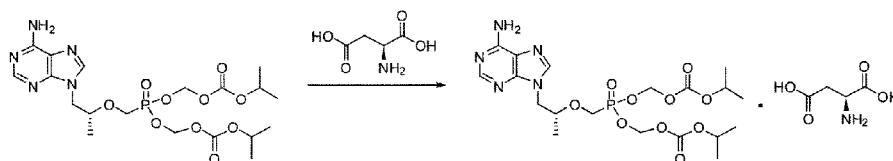
[31]

[32] Tenofovir disoproxil aspartate according to the present invention is prepared by reacting aspartic acid with tenofovir disoproxil free base. The reaction is schematized in the following reaction formula 1.

[33]

[34] <Reaction formula 1>

[35]



[36]

[37] The following is the detailed description of the preparation method of tenofovir disoproxil aspartate according to the present invention.

[38] Step 1) Dissolve tenofovir disoproxil free base in water;

[39] Step 2) Add aspartic acid into the solution of dissolved tenofovir disoproxil free base from step 1, then heat and stir; and

[40] Step 3) Cool the heated and stirred solution from step 2 to room temperature or below, and stir and crystallize to obtain tenofovir disoproxil aspartate.

[41]

[42] From these steps, tenofovir disoproxil aspartate can be prepared.

[43]

[44] Tenofovir disoproxil free base of the present invention can be prepared directly by the known method or can be purchased, and water was used as a solvent for the reaction.

[45]

[46] The preferred amount of aspartic acid used in the preparation method of the present invention is 1 to 3 equivalents with respect to tenofovir disoproxil free base, but it is more preferred to use 1.1 to 1.5 equivalents. Additionally, the preferred amount of water used as a solvent for the reaction of the present invention is 5 to 100mL for 1g of tenofovir disoproxil free base, but it is more preferred to use 10 to 50mL for 1g of tenofovir disoproxil free base.

[47]

[48] In the preparation method of the present invention, the reaction temperature for heating and stirring is room temperature or below the boiling point of the solvent which is 100°C, wherein preferred temperature is 40 to 60°C.

[49]

[50] In the preparation method of the present invention, the reaction time for heating and stirring can be modified according to the reaction temperature, but the preferred time is 10 hours to 15 hours.

[51]

[52] In the present invention, the crystallization method refers to a publicly known crystallization method. For example, cool the solution to room temperature (20 to 30°C) or below, and then stir or leave it as it is to crystallize.

[53]

Advantageous Effects of Invention

[54] Tenofovir disoproxil aspartate according to the present invention can minimize formation of related substances that occur with passage of time compared to tenofovir disoproxil fumarate, thus increasing stability of the formulation as it greatly reduces the formation of impurities during storage of the product containing the above salt compound, and eliminating the need for conducting a separate research on toxicological effect. Furthermore, the salt compound of the present invention has a superior physicochemical property with the improved stability, hygroscopicity, and solubility with respect to changes of pH, thus making it an effective active ingredient for pharmaceutical compositions for the treatment of HIV-1 infection and chronic hepatitis B with a pharmaceutically acceptable carrier.

[55]

[56] Additionally, the present invention makes it possible to obtain purer tenofovir disoproxil through the process of acid salt synthesis, even when the tenofovir disoproxil aspartate is prepared by a simple manufacturing process.

[57]

Brief Description of Drawings

[58] Figure 1 is a graph showing the stability of tenofovir disoproxil fumarate, as a control, at different pH levels.

[59] Figure 2 is a graph showing the stability of tenofovir disoproxil aspartate in accordance with the present invention, at different pH levels.

[60] Figure 3 is an X-ray diffraction record of tenofovir disoproxil fumarate.

[61] Figure 4 is an X-ray diffraction record of tenofovir disoproxil aspartate.

[62] Figure 5 is the differential scanning calorimetry (DSC) spectrum of tenofovir disoproxil fumarate.

[63] Figure 6 the differential scanning calorimetry (DSC) spectrum of tenofovir disoproxil aspartate.

[64] Figure 7 is the ¹H nuclear magnetic resonance (NMR) spectrum of tenofovir

disoproxil fumarate.

[65] Figure 8 is the ¹H nuclear magnetic resonance (NMR) spectrum of tenofovir disoproxil aspartate.

[66]

Mode for the Invention

[67] The present invention is described in detail via the following examples. However, following examples are intended only to illustrate the present invention and do not limit the scope of the present invention.

[68]

[69] In the following examples, Bruker UltraShield™ 400 (400MHz) was used for ¹H NMR; Agilent 1200 series was used for HPLC; and Electrothermal IA9000 and Mettler Toledo DSC 823 for melting points. Unless otherwise stated, reagents and solvents used were purchased from Aldrich, Sigma, and Acros.

[70]

[71] <Reference example 1> Preparation of tenofovir disoproxil free base

[72] Into a 1,000mL reaction unit, add 50.0 g of tenofovir disoproxil fumarate (purity 98.60%, Luna Chemicals, China), 250mL of ethyl acetate, and 250mL of purified water. Suspend and stir for 10 minutes at room temperature. Add saturated sodium bicarbonate solution dropwise until pH 7.0. Stir for 30 minutes and orient the solution for 10 minutes. Discard the aqueous layer. Dry the organic layer with anhydrous magnesium sulfate. Filter and concentrate. When the volume of the concentrate reaches 125 mL, the solids start to precipitate. Stop the concentration and stir at room temperature for 2 hours. Cool the reactor to 5°C and stir for 2 hours. Upon filtering, dry the filtercake for 2 hours at 45°C to obtain 35.0 g of the white title compound, tenofovir disoproxil free base.

[73]

[74] HPLC purity : 99.61%

[75] ¹H NMR (400MHz, D₂O): 8.16(s, 1H), 8.05(s, 1H), 5.52-5.39(m, 3H), 5.33-5.28(m, 1H), 4.89-4.77(m, 2H), 4.34-4.30(m, 1H), 4.16-4.05(m, 2H), 3.93-3.90(m, 1H), 3.80-3.74(m, 1H), 1.27-1.21(m, 15H) ppm

[76] Melting point : 101.5°C

[77]

[78] <Example 1> Preparation of tenofovir disoproxil aspartate

[79] Into a 2,000mL reaction vessel, add 50.0 g of tenofovir disoproxil free base, 750mL of purified water, and 15.4 g of aspartic acid (L-aspartic acid; Aldrich). Heat to 46-51 °C and stir for 2 hours. Cool to room temperature and stir for 15 hours. Filter the solution and wash the filtercake with 50mL of purified water and dry it for 2 hours at 45°C to

obtain 50.6 g of the white title compound, tenofovir disoproxil aspartate.

[80]

[81] HPLC purity : 99.68%

[82] ¹H NMR (400MHz, D₂O): 8.30(s, 1H), 8.18(s, 1H), 5.54-5.42(m, 3H), 5.39-5.34(m, 1H), 4.91-4.83(m, 2H), 4.42-4.38(m, 1H), 4.23-4.18(m, 1H), 4.12-4.06(m, 1H), 3.95-3.92(m, 2H), 3.84-3.78(m, 1H), 2.92-2.86(m, 1H), 2.82-2.75(m, 1H), 1.28-1.24(m, 15H) ppm

[83] Melting point : 109°C

[84]

[85] <Experiment Example 1> Assessment of stability (acceleration, stress) with respect to the degree of related substances formation

[86] Stability tests for pharmaceutical products test the stability of quality with respect to the passage of time, in order to determine the appropriate storage methods, period of use, and other factors. After an appropriate standard is selected, predetermined tests are performed to analyze the pharmaceutical product. Significant changes are evaluated in order to determine appropriacy of the selected standard, and ultimately to establish the expiration dates. Therefore, appropriate stability of a drug is one of the most critical factors to commercial production of a drug.

[87]

[88] Therefore, in order to test stability (acceleration, stress) with respect to the degree of formation of related substances of tenofovir disoproxil aspartate (Example 1) in accordance with the present invention, HPLC (high-performance liquid chromatography) method described in the U.S. Pharmacopoeia was used to analyze the results of acceleration and stress stability tests performed in accordance with the ICH guidelines, using tenofovir disoproxil fumarate (Luna Chemicals, China) as control group. The results are shown in Table 1 and Table 2.

[89]

[90] Table 1

[Table 1]

Acceleration (40 °C ± 2 °C, RH 75% ± 5%)

Related substances	Relative duration	Tenofovir disoproxil fumarate					Tenofovir disoproxil aspartate				
		Initial	3 days	6 days	14 days	30 days	Initial	3 days	6 days	14 days	30 days
Tenofovir	0.14	0.006	0.005	0.009	0.012	0.019	-	-	-	-	-
Adenine	0.16	-	0.001	0.002	0.002	0.001	-	-	-	-	-
Tenofovir isoproxil monoester	0.24	0.724	0.664	0.692	0.702	0.804	0.199	0.119	0.157	0.161	0.189
Tenofovir disoproxil ethyl ester	0.80	-	0.010	0.021	0.025	0.019	-	-	-	-	-
Tenofovir isopropyl isoproxil	0.82	0.082	0.078	0.073	0.083	0.083	-	-	-	-	-
Tenofovir disoproxil carbamate	1.40	0.110	0.114	0.103	0.096	0.096	0.133	0.104	0.108	0.099	0.092
Tenofovir disoproxil dimer	1.76	-	-	-	-	-	-	-	-	-	-

[91]

[92]

Table 2

[Table 2]

Stress (60 °C ± 2 °C)

Related substances	Relative duration	Tenofovir disoproxil fumarate					Tenofovir disoproxil aspartate				
		Initial	3 days	6 days	14 days	30 days	Initial	3 days	6 days	14 days	30 days
Tenofovir	0.14	0.006	0.013	0.032	0.048	0.149	-	-	-	-	-
Adenine	0.16	-	-	0.001	0.002	0.001	-	-	-	-	-
Tenofovir isoproxil monoester	0.24	0.724	0.737	0.838	1.029	1.540	0.199	0.146	0.159	0.224	0.271
Tenofovir disoproxil ethyl ester	0.80	-	0.017	0.022	0.022	0.028	-	-	-	-	-
Tenofovir isopropyl isoproxil	0.82	0.082	0.072	0.071	0.072	0.079	-	-	-	-	-
Tenofovir disoproxil carbamate	1.40	0.110	0.107	0.104	0.104	0.175	0.133	0.110	0.123	0.111	0.111
Tenofovir disoproxil dimer	1.76	-	-	-	-	-	-	-	-	-	-

[93]

[94]

As seen in Table 1 and Table 2 above, tenofovir disoproxil aspartate of the present invention has demonstrated outstanding stability in acceleration and stress conditions compared to tenofovir disoproxil fumarate. Particularly, related substances present with tenofovir disoproxil fumarate rarely occurred with tenofovir disoproxil aspartate of the present invention. Furthermore, formation of the main degradation product,

tenofovir disoproxil monoester, under 60°C stress condition increases to 1.54% (in 30 days) for tenofovir disoproxil fumarate, whereas it increases to merely 0.271% for tenofovir disoproxil aspartate, indicating a large improvement of physicochemical stability.

[95]

[96] Therefore, tenofovir disoproxil aspartate in accordance with the present invention minimizes the occurrences of related substances, allowing long-term maintenance of high purity and outstanding storage stability.

[97]

[98] <Experiment Example 2> Evaluation of stability with pH changes

[99] An orally administered drug passes through the stomach, the duodenum, the small intestine, and other organs before being absorbed into the body. Therefore, securing appropriate stability with respect to pH changes until absorption into the body greatly affects the dissolution of the drug. Therefore, it is ultimately an important factor determining the efficacy of the drug.

[100]

[101] Therefore, in order to assess the stability of the drug by differing pH as it moves through the body, buffer solutions (pH 1.2, pH 3.2, pH 5.2, pH 7.2, pH 9.2) were prepared. Afterward, tenofovir disoproxil aspartate of the present invention and tenofovir disoproxil fumarate as control were each prepared in high concentration (5mg/m³) and dissolved completely in acetonitrile and water (1/19) solution, and diluted with buffer solutions. Each of the prepared samples was put into a 40°C chamber. In order to determine the content change by passage of time, reaction was stopped with acetonitrile and water (1/19) solution at a different time interval for each of the samples. Then, each sample was filtered with a 0.2 μ m filter and measured via high-performance liquid chromatography (HPLC).

[102]

[103] The results of stability by pH change for tenofovir disoproxil aspartate and tenofovir disoproxil fumarate are shown in Figure 1 and Figure 2, respectively.

[104]

[105] As seen in Figure 1 and Figure 2, tenofovir disoproxil aspartate in accordance with the present invention demonstrates equal stability to that of tenofovir disoproxil fumarate at various pH. Both are rapidly degraded in basic environments due to the properties of the drugs (prodrugs to be hydrolyzed).

[106]

[107] <Experiment Example 3> Assessment of hygroscopicity

[108] Low hygroscopicity (or low water sorption) of a chemical compound is a very important property required for a raw material of a pharmaceutical product because it

determines manufacturing and storage of the actual pharmaceutical product. Hygroscopicity of tenofovir disoproxil aspartate of the present invention was assessed.

[109]

[110] 500mg of tenofovir disoproxil aspartate was added into a glass tube for measuring water sorption and was dried with nitrogen at 25°C for 12 hours. Afterwards, mass change of the specimen was automatically measured at relative humidity 15, 35, 55, 75, and 95% with a device for measuring water sorption (Hydrosorb 1000, manufactured by Quantachrome Instruments), and the results are shown in Table 3. Tenofovir disoproxil fumarate was used as a control.

[III]

[112] Table 3

[Table 3]

	Tenofovir disoproxil	
	fumarate	aspartate
Initial mass	0 %	0%
Relative humidity 15%	0.1 %	0%
Relative humidity 35%	0.3 %	0.04%
Relative humidity 55%	0.57%	0.06%
Relative humidity 75%	0.8 %	0.08%
Relative humidity 95%	1.4 %	0.2%

[113]

[114] Under the pharmaceutical ingredient guidelines of the Korea Food & Drug Administration, tenofovir disoproxil fumarate is managed and controlled to a moisture level of 1.0% or below. As seen from Table 3, tenofovir disoproxil fumarate of the control group tended to rapidly absorb moisture from the air with increasing relative humidity, demonstrating unfavorable water sorption property.

[115]

[116] On the other hand, tenofovir disoproxil aspartate in accordance with the present invention demonstrated extremely low absorption of 0.2% or below throughout the entire range of the experiment, indicating its ability to be safely stored even upon exposure to moisture in the air.

[117]

[118] Therefore, tenofovir disoproxil aspartate of the present invention demonstrates superior non-hygroscopicity, which enables outstanding storage stability allowing long-term storage and easier commercialization.

[119]

[120] <Experiment Example 4> Assessment of solubility

[121] Solubility is a very important property of a drug. Many drugs with outstanding efficacy fail to undergo product development because of low solubility. In other words, reduced solubility induces precipitation, which leads to reduced oral absorption. Therefore, securing appropriate solubility is essential to commercialization of a drug.

[122]

[123] Solubility of tenofovir disoproxil aspartate of the present invention was assessed and is shown in Table 4. Tenofovir disoproxil fumarate was used as control.

[124]

[125] 50mg of tenofovir disoproxil aspartate was added to water and pH 1.2, pH 4.0, pH 6.8 solutions each, and shaken at 150 rpm at 25°C for 3 days. Three days later, each sample was filtered with a 0.45/μm filter and diluted with acetonitrile and water (1/19) solution. The product was analyzed with high-performance liquid chromatography (HPLC) and was quantified.

[126]

[127] Table 4

[Table 4]

Medium	Tenofovir disoproxil	
	fumarate (mg/mL)	aspartate (mg/mL)
Distilled Water	6.3	11.2
pH 1.2	35.1	29.4
pH 4.0	4.7	8.8
pH 6.8	6.6	4.1

[128]

[129] As seen from Table 4 above, tenofovir disoproxil aspartate of the present invention demonstrated equivalent or superior solubility to commercially available tenofovir disoproxil fumarate, particularly at pH 4.0 (representative of duodenum, the main absorption site of the drug) where the aspartate was almost as twice as soluble as the fumarate, indicating a major improvement of the physicochemical properties of the drug and thus advantages in absorption and dissolution of the drug.

[130]

[131] <Experiment Example 5> Polymorphism (XRD)

[132] X-ray powder diffraction pattern is a unique property of each drug and is used extensively in identifying crystals and hydrates. As such, X-ray powder diffraction

pattern was determined for tenofovir disoproxil aspartate and commercially available tenofovir disoproxil fumarate.

[133]

[134] X-ray powder patterns of the aforementioned two substances were measured with D8 Advance X-ray diffractometer and Evaluation software system interface manufactured by Bruker AXS GmbH, at scanning rate of $0.020^{\circ}2\Theta$ per minute. They were scanned at 3 and $40^{\circ}2\Theta$ by exposing them to X-ray generator operating at 40kV and 40mA using standard line copper X-ray tube (Siemens) equipped with unidimensional semi-conductor X-ray detector using silicon strips. The weighted average of X-ray wavelength used in calculation is Cu-K α 1.541838Å.

[135]

[136] The results of tenofovir disoproxil fumarate was similar to the data disclosed in a U.S. patent (U.S. Patent No. 5935946), with characteristic X-ray powder diffraction peaks at 4.9° , 10.2° , 10.8° , 18.2° , 21.9° , 24.0° , 25.0° , 25.4° , 27.9° , 30.1° and 30.5° . On the other hand, tenofovir disoproxil aspartate showed characteristic X-ray powder diffraction peaks at 7.4° , 13.0° , 14.5° , 18.2° , 19.2° , 19.4° , 19.9° , 20.9° , 22.9° , 26.7° , 27.1° and 28.1° , confirming that the two are in fact different materials.

[137]

[138] <Experiment Example 6> Differential scanning calorimetry (DSC)

[139] Differential scanning calorimetry is another commonly used method of determining the properties of a drug. As such, thermal analysis was carried out for tenofovir disoproxil aspartate of the present invention and tenofovir disoproxil fumarate. This thermal analysis was obtained in nitrogen atmosphere at a scanning rate of 5°C per minute. Calorie scanning was done using a differential scanning calorimeter (Mettler Toledo; DSC 823e). The amount of specimen used was 3.0mg. As expected, the onset peaks and characteristic peaks of the two compounds differed, as shown in Table 5.

[140]

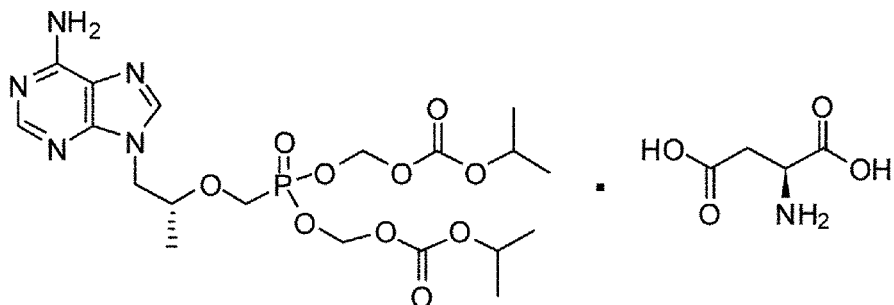
[141] Table 5

[Table 5]

	Onset	Peak
Tenofovir disoproxil fumarate	117.7X2	119.3t
Tenofovir disoproxil aspartate	107.1 $^{\circ}\text{C}$	109.1 $^{\circ}\text{C}$

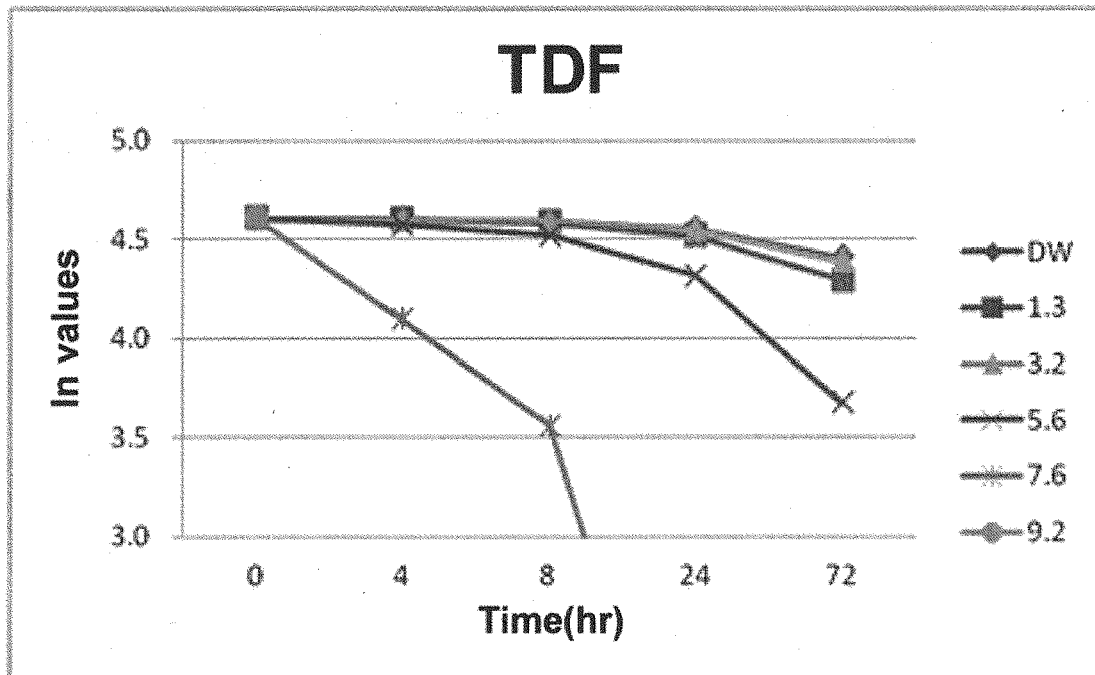
Claims

[Claim 1] Tenofovir disoproxil aspartate of the following Chemical Formula 1:
<Chemical Formula 1>

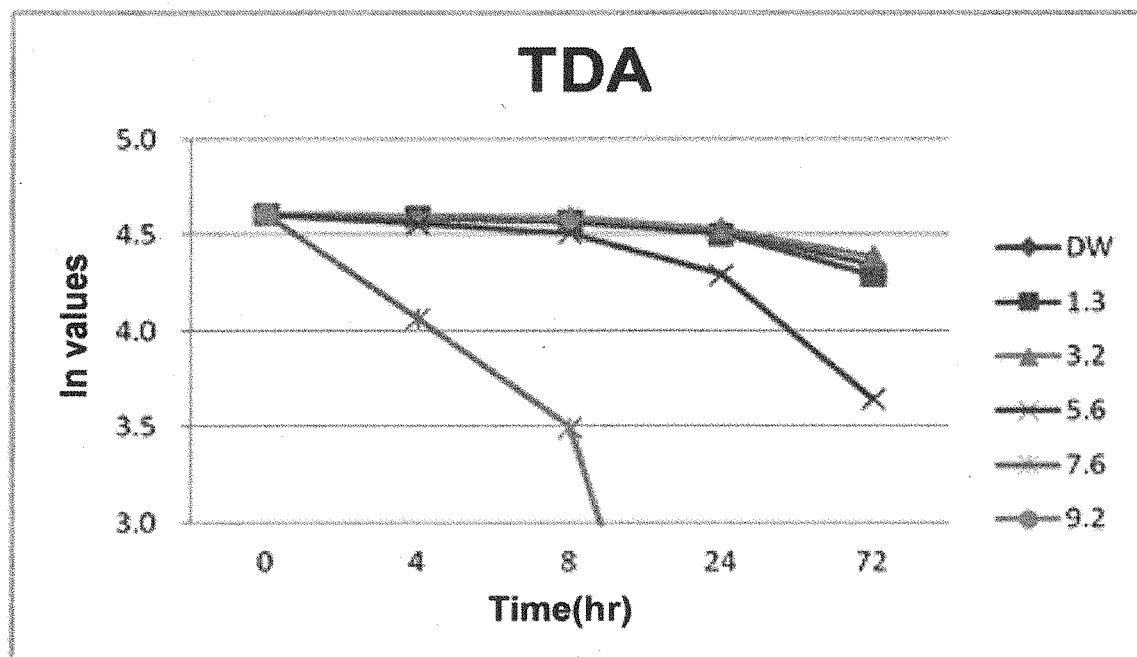


- [Claim 2] The tenofovir disoproxil aspartate of Claim 1, wherein the compound of Chemical Formula 1 is a crystalline solid.
- [Claim 3] The tenofovir disoproxil aspartate of Claim 1, having an X-ray powder diffraction spectrum using Cu-K α radiation comprising peaks at 2 Θ angle values of 7.4°, 13.0°, 14.5°, 18.2°, 19.2°, 19.4°, 19.9°, 20.9°, 22.9°, 26.7°, 27.1° and 28.1°
- [Claim 4] A preparation method of tenofovir disoproxil aspartate comprising the steps of:
- 1) Dissolving the tenofovir disoproxil free base in water;
 - 2) Adding aspartic acid into the solution of dissolved tenofovir disoproxil free base from step 1, followed by heating and stirring; and
 - 3) Cooling the heated and stirred solution from step 2 to room temperature or below, followed by stirring and crystallization to obtain tenofovir disoproxil aspartate.
- [Claim 5] The preparation method of Claim 4, wherein 1-3 equivalent(s) of aspartic acid is used per tenofovir disoproxil free base.
- [Claim 6] The preparation method of Claim 5, wherein 1.1-1.5 equivalent(s) of aspartic acid is used per tenofovir disoproxil free base.

[Fig. 1]

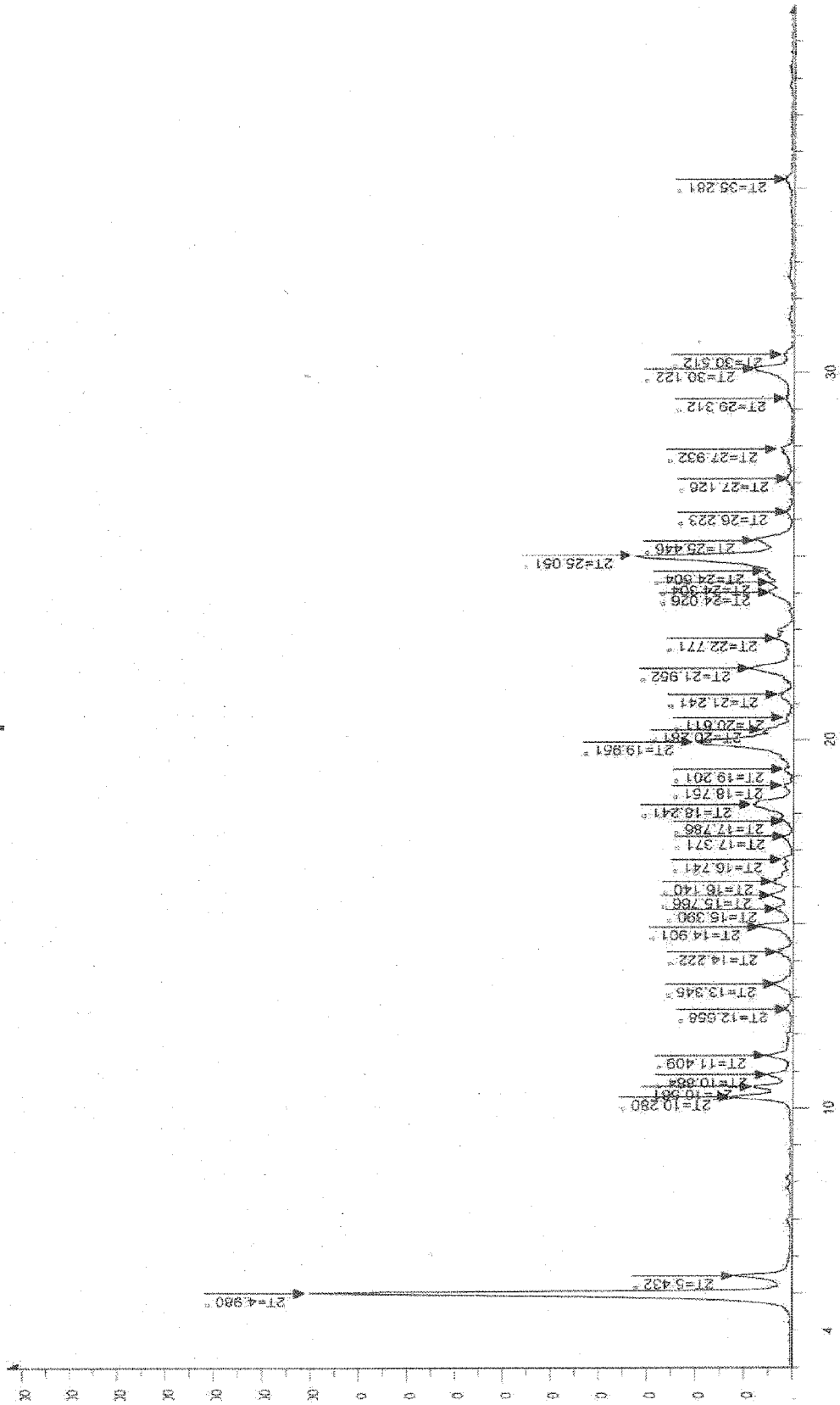


[Fig. 2]



[Fig. 3]

Page 1/1
 C:\DIFFDAT2\customer\Method\Tenofovir disoproxil fumarate.EVA
 Warning: document modified since revision 1 by admin [anonymous administrator], 8/26/2012 2:38:26 PM
Tenofovir disoproxil fumarate

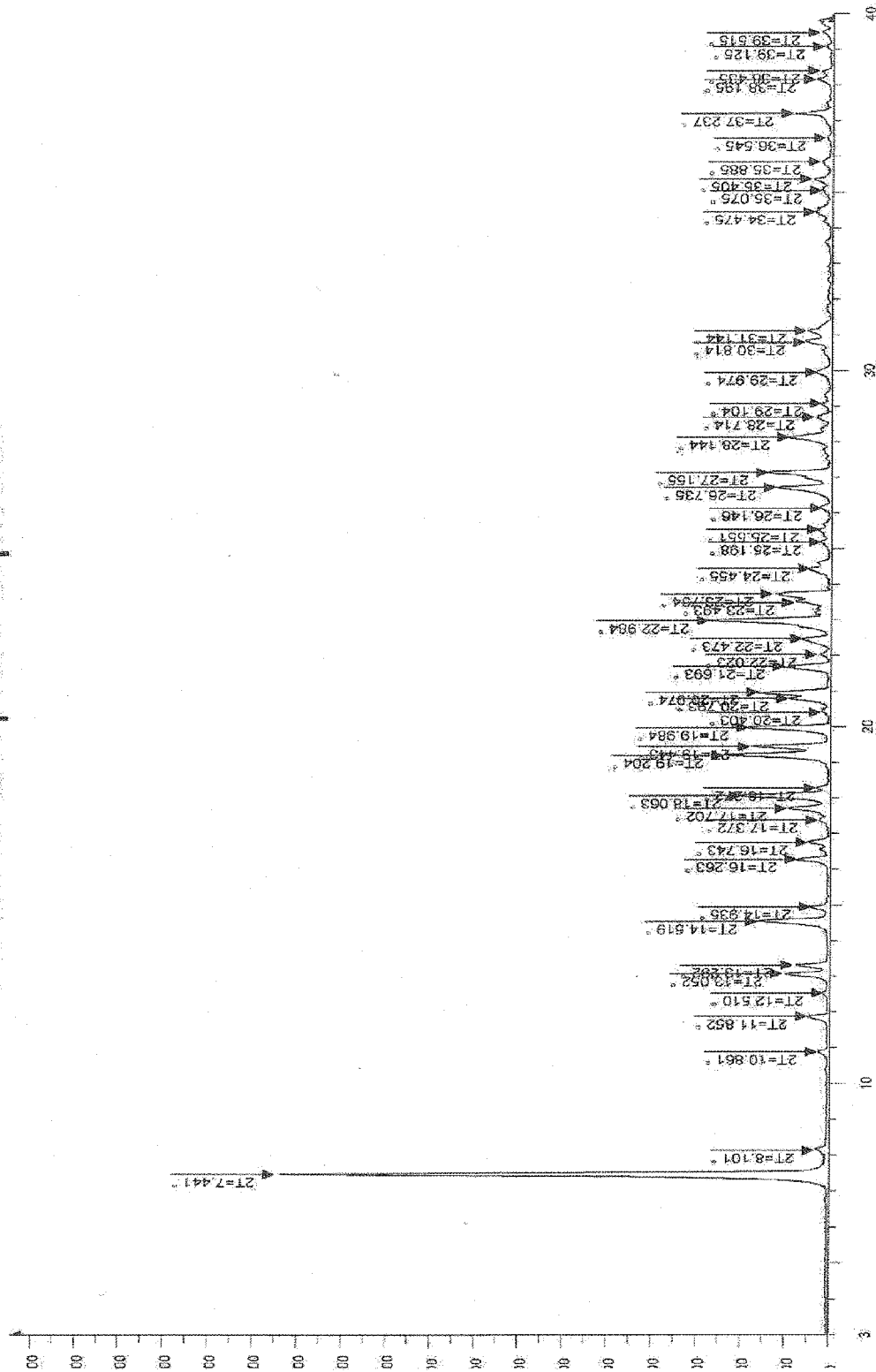


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 Operations: Strip Alpha2 0.500 | Background 1.000 | Import

[Fig. 4]

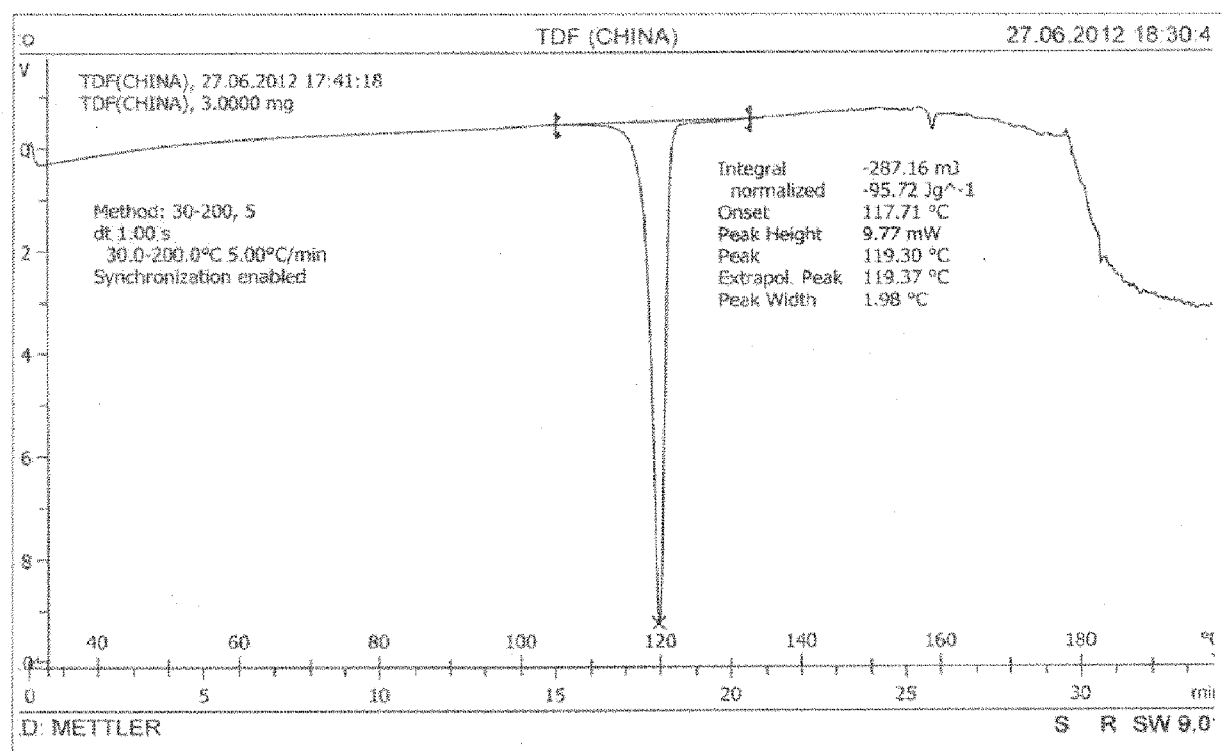
Tenofovir disoproxil aspartate

Page 1/1
No revision available

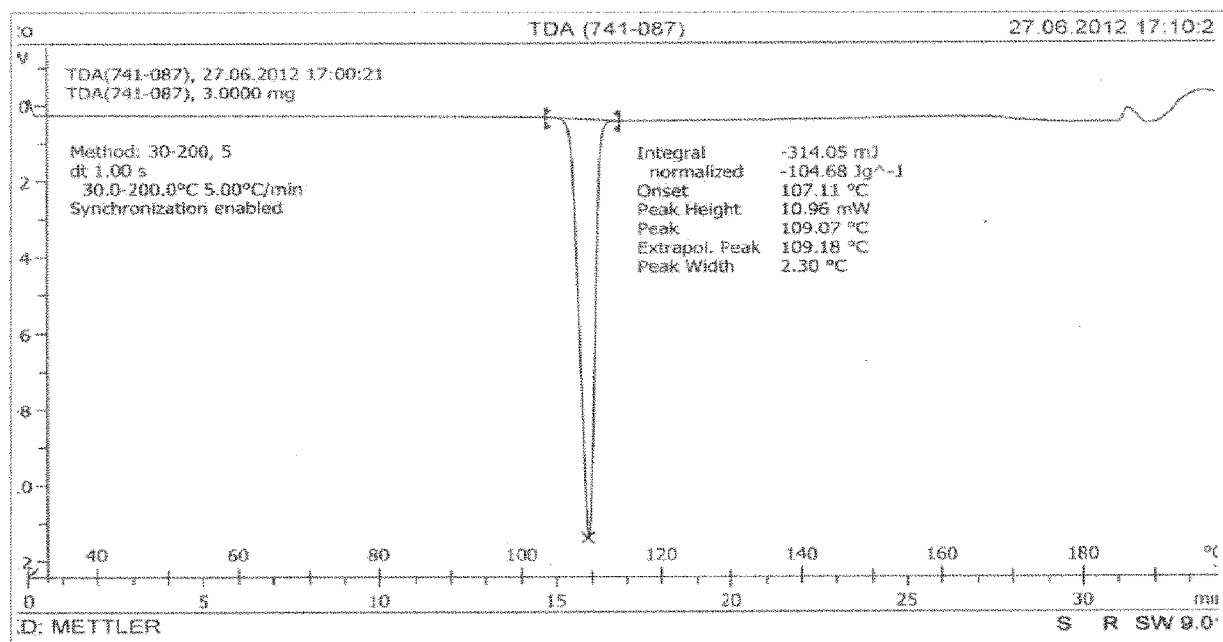


Creation: 6/26/2012 2:25:52 PM - Tenofovir disoproxil aspartate - File: Tenofovir disoproxil aspartate.raw - Type: Locked Coupled - Start: 3.000 - End: 40.004 - Step: 0.020 - Step time: 16.5 s
Operations: Strip (Alpha2 0.500) | Background 1.000 | Import

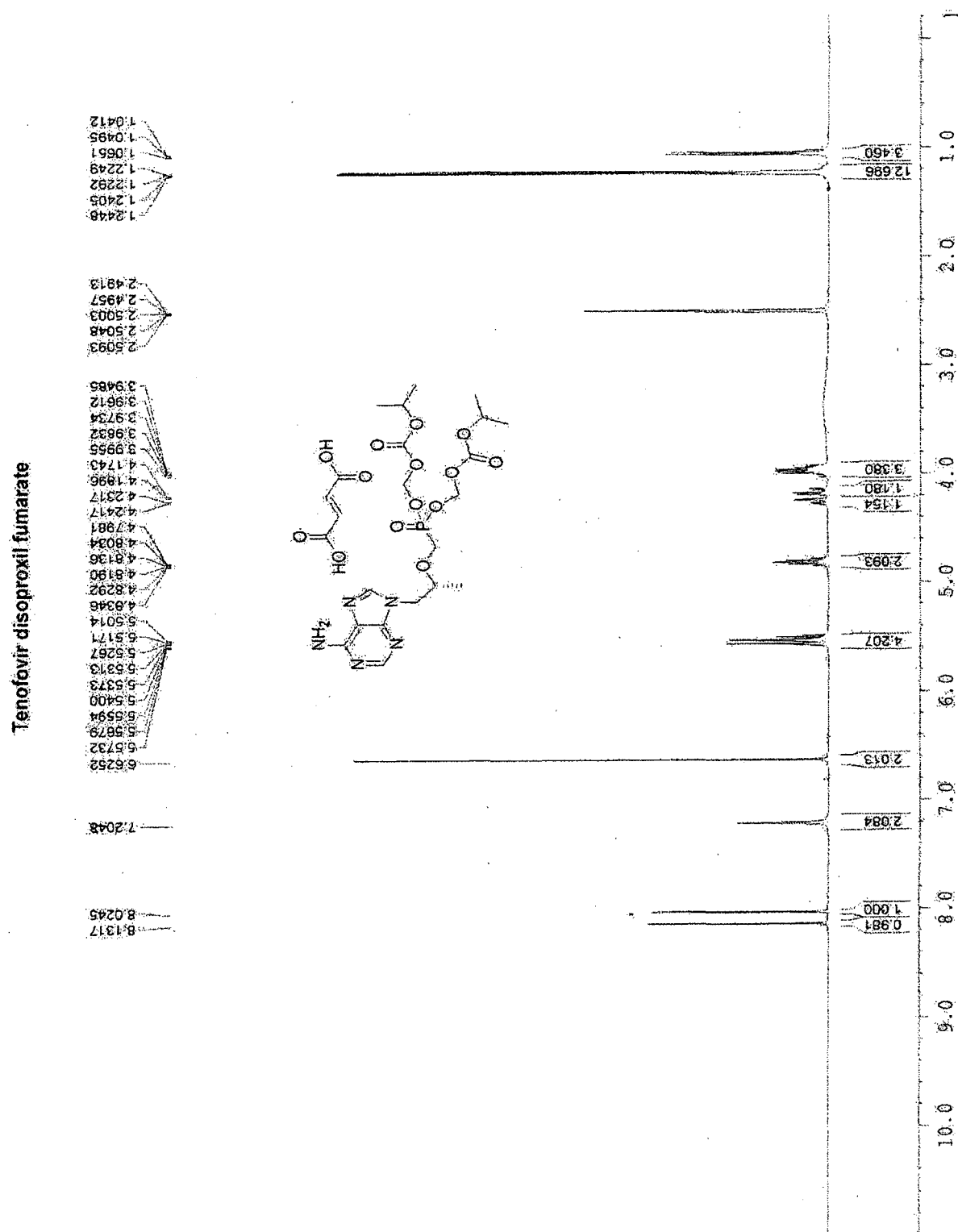
[Fig. 5]



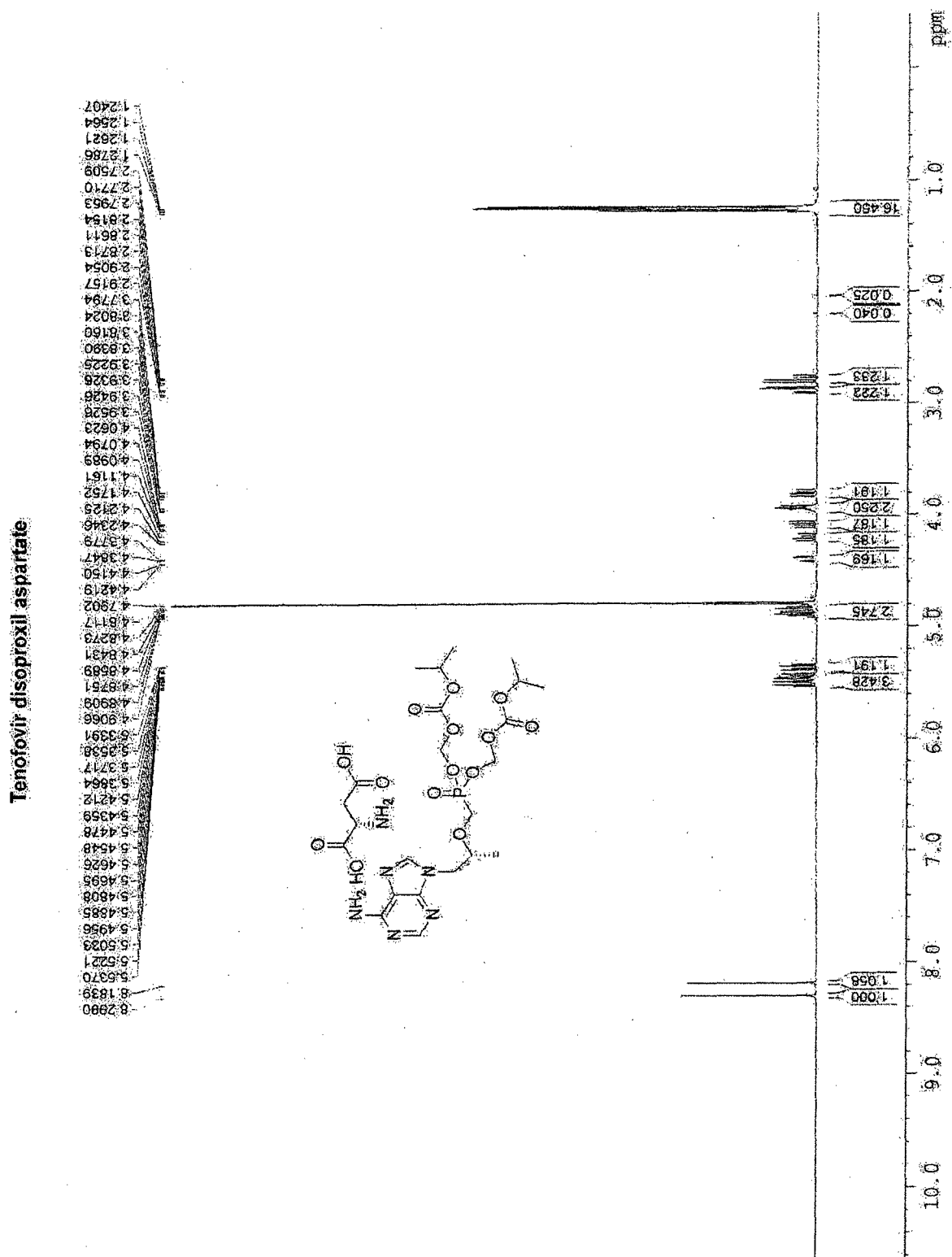
[Fig. 6]



[Fig. 7]



[Fig. 8]



A. CLASSIFICATION OF SUBJECT MATTER**C07D 473/34(2006.01)i, C07F 9/02(2006.01)i, A61K 31/52(2006.01)i, A61P 31/18(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 473/34; C07F 9/6561; A61K 31/675; A61P 31/18; C07F 9/02; A61K 31/52

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: tenofovir disoproxil, crystal, aspartate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	wo 2009-074351 A2 (ULTIMORPHIX TECHNOLOGIES B.V.) 18 June 2009 See claims 1-62	1-6
X	wo 2010-026603 A2 (MATRIX LABORATORIES LIMITED) 11 March 2010 See claims 1-27	1-6
X	wo 2008-143500 A1 (ULTIMORPHIX TECHNOLOGIES B.V.) 27 November 2008 See claims 1-11	1-6

II Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family


Date of the actual completion of the international search

13 November 2013 (13.11.2013)

Date of mailing of the international search report

13 November 2013 (13.11.2013)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2013/006845

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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