

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
12 February 2004 (12.02.2004)

PCT

(10) International Publication Number
WO 2004/012687 A2

(51) International Patent Classification⁷: **A61K**
(21) International Application Number:
PCT/US2003/024987
(22) International Filing Date: 6 August 2003 (06.08.2003)
(25) Filing Language: English
(26) Publication Language: English
(30) Priority Data:
60/401,318 6 August 2002 (06.08.2002) US
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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CRYSTALLINE AND AMORPHOUS FORMS OF BETA-L-2'-DEOXYTHYMIDINE

(57) Abstract: Physical forms of beta-L-2'-deoxythymidine are disclosed that can be characterized by physical appearance, purity levels, Infra-Red and Raman spectroscopy, X-ray powder diffraction patterns, thermal properties, and methods of manufacture. These forms of beta-L-2'-deoxythymidine can be used in the manufacture of other forms of beta-L-2'-deoxythymidine, or in pharmaceutical compositions. Particularly preferred uses are in the treatment of hepatitis B.



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5 **CRYSTALLINE AND AMORPHOUS FORMS OF BETA-L-2'-**
 DEOXYTHYMIDINE

CROSS-REFERENCE OF THE INVENTION

 This application claims priority to U.S. Provisional Application Serial No.
10 60/401,318, filed on August 6, 2002.

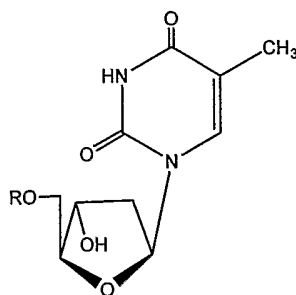
FIELD OF THE INVENTION

 The present invention describes crystalline and amorphous forms of beta-
L-2'-deoxythymidine and mixtures thereof, substantially pure crystalline and
15 amorphous forms of beta-L-2'-deoxythymidine, analytical methods for confirming
the presence and crystalline purity of beta-L-2'-deoxythymidine, pharmaceutical
compositions thereof, and uses for such compositions.

BACKGROUND OF THE INVENTION

20 The synthetic nucleoside beta-L-2'-deoxythymidine (L-dT) is known in
the art. Antonin Holy first disclosed beta-L-2'-deoxythymidine and methods for
preparing beta-L-2'-deoxythymidine in 1972 in "Nucleic Acid Components and
Their Analogs. CLIII. Preparation of 2'-deoxy-L-Ribonucleosides of the
Pyrimidine Series," *Collect. Czech. Chem. Commun.* (1972), 37(12), 4072-87.

25 The compound is represented by the following chemical structure:



wherein R is H.

5 Several authors have reported antiviral activity of beta-L-2'-deoxythymidine against herpes simplex virus. See, e.g., Iotti et al., WO 92/08727; and Spadari et al., *J. Med. Chem.* (1992), 35(22), 4214-20.

 More recently, Gilles Gosselin, Jean-Louis Imbach and Martin Bryant disclosed that the compound and its derivatives and analogues have useful
10 properties against the hepatitis B virus. See WO 00/09531; PCT US01/17301 and PCT US01/19147; U.S. Patent Nos. 6,395,716; 6,569,837; 6,444,652; and 6,566,344. L-dT is currently in advanced clinical development by Idenix Pharmaceuticals, Inc. (Cambridge, Mass.).

 Each of the foregoing references discloses a synthetic process for
15 producing L-dT that relies upon crystallizing the compound from ethanol. None of the references disclose the particular crystalline or physical form of the L-dT that was obtained, or the water content of such L-dT. However, it has been recognized that crystalline, amorphous, hydrated, and various physical forms of the same compound can vary substantially in their biological properties, and in
20 their ease of processing, manufacturing and/or pharmaceutical formulation. In addition, some forms are unstable under ambient conditions and thus require special storage and handling conditions to be maintained, or must be avoided altogether.

 Given the commercial importance of beta-L-2'-deoxythymidine, it would
25 be useful to have additional forms and phases of beta-L-2'-deoxythymidine that may exhibit beneficial properties in manufacturing or other applications. It is therefore an objective of this invention to provide novel forms and phases of beta-L-2'-deoxythymidine.

 It is another objective to provide novel methods for the preparation and
30 isolation of forms and phases of beta-L-2'-deoxythymidine.

 It is still another objective of the invention to provide therapeutic uses of such forms and phases of beta-L-2'-deoxythymidine.

5

SUMMARY OF THE INVENTION

As a result of studies into the crystalline structure and various physical forms of L-dT, Applicants have unexpectedly made a number of significant discoveries. In particular, Applicants have discovered:

- structural forms of crystalline L-dT that can be characterized by their physical appearance;
- an amorphous form of L-dT; and
- mixtures of these two forms.

These discoveries lead to the production of a form of L-dT that is substantially devoid of water and can be maintained for a period of time, or shelf life, of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 11 or 12 months or more, by maintaining the compound under appropriate conditions of low humidity. Given that nucleosides in general are polar, water soluble compounds, and that L-dT in particular contains a pyrimidinedione ring and two free hydroxy groups, it could not be predicted that L-dT, when substantially devoid of waters of hydration, could be maintained for an extended shelf-life.

In addition, Applicants have discovered methods of analyzing the purity of crystalline L-dT for contamination by amorphous L-dT. These analytical methods include diffractional, vibrational, thermal, and other analytical techniques. In still other embodiments the invention includes methods of making the foregoing forms of L-dT.

These forms of L-dT have advantageous properties in the preparation of pharmaceutical compositions and in the treatment of hepatitis B. Beneficial properties can be attributed to these different physical forms including increased solubility, improved bioavailability, ease of chemical processing and/or ease of pharmaceutical formulation.

5

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1 is a XRPD ("X-ray powder diffraction") pattern of crystalline beta-L-2'-deoxythymidine and amorphous beta-L-2'-deoxythymidine.

FIGURE 2 is a graphical depiction of the Infra-Red (IR) spectra of crystalline beta-L-2'-deoxythymidine and amorphous beta-L-2'-deoxythymidine.

10 FIGURE 3 is a graphical depiction of the Raman spectra of crystalline beta-L-2'-deoxythymidine and amorphous beta-L-2'-deoxythymidine.

FIGURE 4 is a graphical depiction of a TGA ("thermogravimetric analysis") scan of crystalline beta-L-2'-deoxythymidine superimposed over a typical DSC ("differential scanning calorimetry") thermogram of the same
15 crystalline beta-L-2'-deoxythymidine, with an endotherm at 189.69°C.

FIGURE 5 depicts in graphical form the moisture sorption and desorption data for crystalline beta-L-2'-deoxythymidine.

FIGURE 6 is a graphical depiction of a TGA scan of amorphous beta-L-2'-deoxythymidine superimposed over a typical DSC thermogram of the same
20 amorphous beta-L-2'-deoxythymidine, with an endotherm at 187.19°C.

FIGURE 7 depicts a DSC thermogram obtained from temperature cycling experiments on amorphous beta-L-2'-deoxythymidine.

FIGURE 8 depicts in graphical form the moisture sorption and desorption data for amorphous beta-L-2'-deoxythymidine.

25

DETAILED DESCRIPTION OF THE INVENTION

Anhydrous L-dT Unassociated with Water

A principal embodiment of the present invention derives from the discovery of crystalline beta-L-2'-deoxythymidine, and to methods of preventing
30 the formation of hydrous forms that could affect the stability of the product. The inventors have surprisingly discovered that L-dT, crystallized from ethanol, and then maintained in an environment of less than or equal to about 45% relative humidity, and is substantially impervious to water. The resulting crystalline L-dT is non-solvated and free of adsorbed or absorbed water. As shown from the TG
35 and DK curves in Figure 4, when L-dT is crystallized and dried in an environment

5 lacking humidity, it is devoid of waters of hydration and association (hence the lack of an endotherm until the substance melts at about 189 °C). As Figure 5 shows, however, crystalline L-dT will associate with water (via adsorption, absorption or hydration) as the relative humidity exceeds about 45% to 55% relative humidity.

10 The fact that L-dT devoid of waters of hydration or association can even be obtained is surprising in view of the fact that L-dT is frequently crystallized from ethanol, which necessarily contains water as an impurity at levels greater than about 1, 2, or 3 vol.%, frequently up to about 5, 7, or 10 volume percent. These discoveries led to the invention of L-dT which is substantially devoid of
15 water for a period of time, or shelf life, of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 11 or 12 months or more, by maintaining the compound under appropriate conditions of humidity. Because nucleosides in general are polar, water soluble compounds, and L-dT in particular contains a pyrimidinedione ring and two free hydroxy groups, two carbonyls, a secondary amine, a tertiary amine, and an internal ether linkage,
20 it could not be predicted that L-dT that is devoid of waters of hydration or association could be maintained for an extended shelf-life.

Therefore, in one embodiment the invention provides crystalline L-dT that is substantially devoid of waters of hydration or association, for periods of time exceeding 4, 6, 8, 10, or even 12 months. In another embodiment the invention
25 provides a method of using crystalline L-dT is substantially devoid of water at the end of the time period. The L-dT is preferably administered to a human after such time period. Humid environments include environments in which the relative humidity exceeds greater than about 10%, 20%, 30%, 40%, or 50%, but preferably not more than about 75%, 65%, or 55% relative humidity. The periods
30 of time during which the L-dT can be exposed to such humid environments are greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or even 12 months, but preferably not more than 3 years, 2 years, or 1½ years. The term "humid environment" means the general ambient conditions to which L-dT or a container of L-dT is exposed. Relative humidities are taken as an average over the recited period of time.

5 This non-solvated crystalline form of beta-L-2'-deoxythymidine is prepared by crystallizing beta-L-2'-deoxythymidine from solution, optionally filtering said crystallized beta-L-2'-deoxythymidine, and drying said beta-L-2'-deoxythymidine in an environment that lacks humidity (i.e. less than 45%, 40%, 35%, 30%, 25%, 20%, 15%, or 10% relative humidity). The substance is
10 preferably present in the substantial absence of amorphous L-dT.

 The term hydrous, when used herein to describe a material, means that the weight of the material is increased by association with water, regardless of the mechanism of association. Thus, the term includes hydrated forms of the material, in addition to material in which water is absorbed or adsorbed. Potential
15 hydrated forms include the monohydrate, the dihydrate, the trihydrate, and the quaternary hydrate.

 As used herein, the term, "substantially pure," when used in reference to a physical form, phase or crystalline form of beta-L-2'-deoxythymidine, refers to a phase or form of beta-L-2'-deoxythymidine which is greater than about 95% pure.
20 This means that the phase or form of beta-L-2'-deoxythymidine does not contain more than about 5% of any other compound and, in one embodiment, does not contain more than about 5% of any other phase[s] or form[s] of beta-L-2'-deoxythymidine. In another embodiments, the term "substantially pure" includes a phase or form of beta-L-2'-deoxythymidine that is greater than about 96% pure.
25 In still another embodiment the term "substantially pure" includes a phase or form of beta-L-2'-deoxythymidine that is greater than about 97%, 99%, 99.5%, or 99.8% pure.

 Similarly, the term "substantially in the absence of a second component" or "substantially free of a second component" when used in reference to a
30 physical form, phase or crystalline form of beta-L-2'-deoxythymidine, refers to a phase or crystalline form of beta-L-2'-deoxythymidine that does not contain more than about 5% of the second component. More preferably, the term "substantially in the absence of a second component" refers to a phase or form of beta-L-2'-deoxythymidine that does not contain more than about 4% of the second

- 5 component, and even more preferably no more than about 3%, 1%, 0.5%, or 0.2% of the second component.

Physical Forms of Crystalline L-dT Characterized by their Physical Appearance

10 In another principal embodiment the invention provides crystalline beta-L-2'-deoxythymidine in various physical forms. Preferred physical forms can be obtained using the methods more fully described in the Examples hereto and include:

- white flakes;
- 15 • clear aciculars;
- white aciculars;
- white solid;
- white powder;
- needles;
- 20 • white chunks;
- white fibers; and
- white plates.

As used herein, the term "flake" is defined as a small flocculent mass of crystals typically in the form of a thin flattened piece or layer. The term
25 "acicular" means a material which incorporates within itself fine, needlelike crystals. A "powder" is a substance composed of fine particles. "Needles" refer to slender pointed objects. A "chunk" refers to a short thick piece often crudely or roughly formed. A "fiber" refers to a structure or object resembling a thread. "Plates" refer to smooth, substantially flat and relatively thin pieces of material.
30 A "solid" material refers to a uniform continuous mass of material obtained upon vaporization of solvent.

The differing physical properties of these physical forms can give rise to numerous unexpectedly beneficial properties including increased solubility, improved bioavailability, ease of chemical processing, and/or ease of
35 pharmaceutical formulation.

5 In a preferred embodiment, one or more of the foregoing forms is present in its preferred orientation. Preferred orientation is the tendency for crystals, usually plates or needles, to align themselves with some degree of order. In various embodiments, the foregoing physical forms are further characterized by purity levels. For example, in one embodiment the crystalline beta-L-2'-
10 deoxythymidine is substantially free of amorphous beta-L-2'-deoxythymidine.

 Still other embodiments relate to methods of manufacturing the foregoing physical forms of beta-L-2'-deoxythymidine. These methods generally require dissolution of beta-L-2'-deoxythymidine in an appropriate solvent, followed by crystallization using one of various techniques. A particularly preferred solvent is
15 ethanol, and especially absolute ethanol, although other solvents can be employed including acetone, acetonitrile, dichloromethane, N,N-dimethylformamide, ethyl acetate, ethyl ether, 1,1,1,3,3,3-hexafluoroisopropanol, hexane, isopropanol, methanol, tetrahydrofuran, toluene, 2,2,2-trifluoroethanol, and water, or mixtures of the foregoing solvents with water.

20 While numerous methods for crystallizing a solute are known and can be employed in the practice of this invention, particularly preferred methods of recrystallization include:

- crystallizing said dissolved beta-L-2'-deoxythymidine via fast evaporation (i.e. evaporation in an open container under ambient conditions);
- 25 • crystallizing said dissolved beta-L-2'-deoxythymidine via slow evaporation (i.e. evaporation in a substantially closed container containing only small holes for escape of vapors under ambient conditions);
- crystallizing said dissolved beta-L-2'-deoxythymidine via slow cooling from an elevated temperature (preferably of about 45-60°C) under
30 substantially ambient conditions (the dissolution is preferably performed at an elevated temperature, followed by rapid filtration of the dissolved beta-L-2'-deoxythymidine before the slow cooling);
- crystallizing said dissolved beta-L-2'-deoxythymidine via crash cooling;
- crystallizing said dissolved beta-L-2'-deoxythymidine via slurry methods.

- 5 Ambient conditions in any of the methods of crystallization can be altered in terms of temperature (i.e. greater than 10 °C, 20 °C, or 30 °C than room temperature), or humidity (i.e. less than 45%, 35%, or 25% relative humidity).

Amorphous L-dT

- 10 An amorphous and hygroscopic form of beta-L-2'-deoxythymidine is also disclosed that can be distinguished from crystalline beta-L-2'-deoxythymidine by Infra-Red and Raman spectroscopy, X-ray powder diffraction patterns, thermal properties, and methods of manufacture. The amorphous phase of beta-L-2'-deoxythymidine exhibits significant hygroscopicity and improved solubility when
15 compared to crystalline beta-L-2'-deoxythymidine, a fact which could result in enhanced bioavailability in vivo. This form of beta-L-2'-deoxythymidine can be used in the manufacture of other forms of beta-L-2'-deoxythymidine, or in pharmaceutical compositions. Particularly preferred uses of this form are the treatment of hepatitis B.

- 20 The amorphous and hygroscopic form of beta-L-2'-deoxythymidine is characterized by the IR and Raman spectra in Figures 2 and 3, the TGA and DSC curves in Figure 6, the DSC temperature cycling characteristics shown in Figure 7, the moisture sorption data shown in Figure 8, and/or the X-ray powder diffraction pattern in Figure 1. This form should be contrasted with crystalline beta-L-2'-
25 deoxythymidine, which can be characterized by the IR and Raman spectra in Figures 2 and 3, the TGA and DSC curves in Figure 4, the moisture sorption data shown in Figure 5, and/or the X-ray powder diffraction pattern shown in Figure 1. Amorphous and crystalline forms of beta-L-2'-deoxythymidine are further characterized in the Examples contained herein.

- 30 Thus, the invention further provides:

- a) an amorphous and hygroscopic phase of beta-L-2'-deoxythymidine, as characterized by X-ray powder diffraction analysis, physical properties, and methods of manufacture;
- b) processes for making an amorphous and hygroscopic phase of beta-
35 L-2'-deoxythymidine;

- 5 c) therapeutic and/or pharmaceutical compositions of the amorphous and hygroscopic phase of beta-L-2'-deoxythymidine, optionally in the presence of a pharmaceutically acceptable carrier; and
- d) novel therapeutic uses for the amorphous and hygroscopic phase of beta-L-2'-deoxythymidine, especially in the treatment of viral
- 10 diseases such as hepatitis B.

Amorphous beta-L-2'-deoxythymidine is obtained when melted beta-L-2'-deoxythymidine is rapidly quenched to below about 40 or 50 °C. A DSC temperature cycling thermogram of amorphous beta-L-2'-deoxythymidine is presented in Figure 7, which shows that the glass transition temperature for this

15 phase is about 50 °C.

Low temperatures and low levels of humidity are preferably observed when storing amorphous beta-L-2'-deoxythymidine. For example, it is preferred to store amorphous beta-L-2'-deoxythymidine at temperatures below 50, 40, 30, 20, 10, or 0 °C. Moreover, it is preferred to store the amorphous beta-L-2'-

20 deoxythymidine at relative humidities of less than 25%, 20%, 15%, 10%, or 5%.

In another embodiment, the invention provides amorphous beta-L-2'-deoxythymidine in substantially pure form i.e., in the absence of crystalline beta-L-2'-deoxythymidine. In still another embodiment the invention provides a pharmaceutical composition that comprises amorphous beta-L-2'-

25 deoxythymidine, further comprising a pharmaceutically acceptable carrier.

Analytical Methods of Assuring the Purity of Crystalline L-dT

In view of the stability issues surrounding amorphous beta-L-2'-deoxythymidine, it is very important to ensure during the manufacturing process that batches of crystalline L-dT are not inadvertently contaminated by the

30 amorphous form. Thus, other embodiments of the present invention relate to methods of detecting crystalline beta-L-2'-deoxythymidine contaminated by the amorphous form of beta-L-2'-deoxythymidine, and to methods of manufacturing crystalline beta-L-2'-deoxythymidine that is substantially free of amorphous beta-L-2'-deoxythymidine. As can be seen by a comparison of Figures 2 and 3,

35 crystalline and amorphous beta-L-2'-deoxythymidine can each be characterized

5 by IR and Raman spectrometry, and the two forms can be distinguished by peak broadening that occurs from the crystalline to the amorphous form. These peak broadenings are observed between 2200-2600, 1600-1800, 1000-1500, or 500-1000 cm^{-1} in an IR spectra, and between 2800-3200, 1600-1675, 1300-1500, or 700-900 in a Raman spectra.

10 Therefore, in various embodiments the invention provides a method of detecting amorphous contamination of beta-L-2'-deoxythymidine, or distinguishing between crystalline and amorphous beta-L-2'-deoxythymidine, comprising:

- 15 subjecting a material that contains beta-L-2'-deoxythymidine to IR spectrometry; and
- evaluating breadth of peaks displayed between 2200-2600, 1600-1800, 1000-1500, or 500-1000 cm^{-1} by reference to a known IR spectra for crystalline beta-L-2'-deoxythymidine.

In other embodiments the invention provides a method of detecting 20 amorphous contamination of beta-L-2'-deoxythymidine, or distinguishing between crystalline and amorphous beta-L-2'-deoxythymidine, comprising:

- subjecting a material that contains beta-L-2'-deoxythymidine to Raman spectrometry; and
- 25 evaluating the breadth of peaks displayed between 2800-3200, 1600-1675, 1300-1500, or 700-900 cm^{-1} by reference to a known Raman spectra for crystalline beta-L-2'-deoxythymidine.

In still other embodiments the invention relates to the manufacture of pharmaceutical compositions of crystalline beta-L-2'-deoxythymidine substantially in the absence of the amorphous form. Thus, the invention provides 30 a method of manufacturing pharmaceutical formulations of crystalline beta-L-2'-deoxythymidine comprising:

- crystallizing two or more batches of beta-L-2'-deoxythymidine from solution;
- subjecting the batches to IR spectrometry;

- 5 • selecting for further processing the batches that do not display significant breadth of peaks (i.e. breadth consistent with the presence of amorphous L-dT) between 2200-2600, 1600-1800, 1000-1500, or 500-1000 cm^{-1} from a known IR spectra for crystalline beta-L-2'-deoxythymidine; and
- 10 • formulating said selected batches into pharmaceutical formulations of beta-L-2'-deoxythymidine.

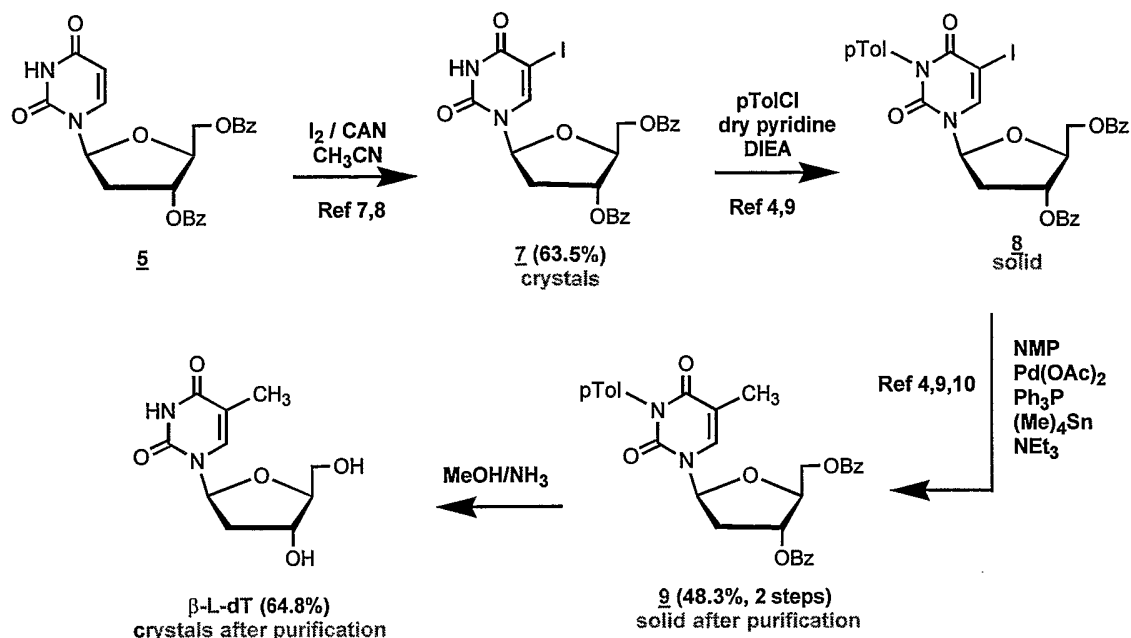
In another embodiment, the invention provides a method of manufacturing pharmaceutical formulations of crystalline beta-L-2'-deoxythymidine comprising:

- 15 • crystallizing two or more batches of beta-L-2'-deoxythymidine from solution;
- 15 • subjecting the batches to Raman spectrometry;
- selecting for further processing the batches do not display significant breadth of peaks (i.e. breadth consistent with the presence of amorphous L-dT) between 2800-3200, 1600-1675, 1300-1500, or 700-900 cm^{-1} from a known Raman spectra of crystalline beta-L-2'-deoxythymidine; and
- 20 • formulating said selected batches into pharmaceutical formulations of beta-L-2'-deoxythymidine.

5

EXAMPLES

Example 1 -- Stereoselective Chemical synthesis of beta-L-2'-deoxythymidine



3',5'-Di-O-benzoyl-2'-deoxy-5-iodo-β-L-uridine (7)

A mixture of compound **5** (105.8 g, 0.242 mol), iodine (76.8 g), CAN (66.4 g) and acetonitrile (2550 ml) was stirred at 80°C for 3h then the reaction mixture was cooled at room temperature leading to crystallization of compound **7** (86.6 g, 63.5%); m. p. 192-194°C ; ¹H NMR (DMSO) δ ppm .8.34 (s, 1H, NH), 8.2-7.2 (m, 11H, 2 C₆H₅CO, H-6), 6.31 (q, 1H, H-1', J = 5.5 Hz and J = 8.7 Hz), 5.5 (m, 1H, H-3'), 4.7 (m, 2H, H-5', H-5''), 4.5 (m, 1H, H-4'), 2.7 (m, 1H, H-2'), 2.3 (m, 1H, H-2''); FAB<0, (GT) m/e 561 (M-H)⁻, 237 (B)⁻; FAB>0 (GT) 563 (M+H)⁺; [α]_D²⁰ + 39.05 (c = 1.05 in DMSO); UV (EtOH 95) ν_{max} = 281 nm (ε = 9000), ν_{min} = 254 nm (ε = 4000), ν_{max} = 229 nm (ε = 31000); Anal. Calcd for C₂₃H₁₉IN₂O₇: C, 49.13 H, 3.41 N, 4.98 I, 22.57. Found: C, 49.31 H, 3.53 N, 5.05 I, 22.36.

20

Reagents:

Iodine: Fluka, 99.8%, ref 57650

Cerium ammonium nitrate (CAN): Aldrich, >98.5%, ref 21,547-3

5 **3',5'-Di-*O*-benzoyl-2'-deoxy-3-*N*-toluoyl- β -L-thymidine (9)**

To a solution of compound **7** (86.6g, 0.154 mol) in anhydrous pyridine (1530 ml) containing *N*-ethyldiisopropylamine (53.6 ml) was added, portionwise at 0°C, *p*-toluoyl chloride (40.6 ml). The reaction mixture was stirred for 2 h at room temperature, then water was added to stop the reaction and the reaction
 10 mixture was extracted with methylene chloride. The organic phase was washed with water, dried over sodium sulfate and evaporated to dryness to give crude 3',5'-di-*O*-benzoyl-2'-deoxy-3-*N*-toluoyl-5-iodo- β -L-uridine (**8**) which can be used for the next step without further purification.

A solution of the crude mixture **8**, palladium acetate (3.44 g),
 15 triphenylphosphine (8.0 g) in *N*-methylpyrrolidinone (1375 ml) with triethylamine (4.3 ml) was stirred at room temperature for 45 min. Then, tetramethyltin (42.4 ml) was added dropwise at 0°C under argon. After stirring at 100-110°C overnight, the reaction mixture was poured into water and extracted with diethyl ether. The organic solution was dried over sodium sulfate and concentrated under
 20 reduced pressure. The residue was purified by a silica gel column chromatography [eluant: stepwise gradient of ethyl acetate (0-10%) in toluene] to give compound **9** as a foam (42.3 g, 48.3% for the 2 steps). ¹H NMR (DMSO) δ ppm .8.3-7.2 (m, 15H, 2 C₆H₅CO, 1 CH₃C₆H₄CO, H-6), 6.29 (t, 1H, *H*-1', *J* = 7.0 Hz), 5.7 (m, 1H, *H*-3'), 4.7-4.5 (m, 3H, *H*-5', *H*-5'', *H*-4'), 2.7-2.6 (m, 2H, *H*-2', *H*-2''); FAB<0, (GT) *m/e* 567 (M-H)⁻, 449 (M-CH₃C₆H₄CO)⁻, 243 (B)⁻, 121 (C₆H₅COO)⁻; FAB>0
 25 (GT) 1137 (2M+H)⁺, 569 (M+H)⁺, 325 (M-B)⁻, 245 (B+2H)⁺, 119 (CH₃C₆H₅CO)⁺.

Reagents:

30 *p*-Toluoyl chloride, Aldrich, 98%, ref 10,663-1

Diisopropylethylamine: Aldrich, >99.5%, ref 38,764-9

N-methylpyrrolidinone: Aldrich, >99%, ref 44,377-8

Palladium acetate: Aldrich, >99.98%, ref 37,987-5

Triphenylphosphine: Fluka, >97%, ref 93092

35 Tetramethyltin: Aldrich, >99%, ref 14,647-1

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2'-Deoxy- β -L-thymidine

A solution of compound **9** (42.3 g, 0.074 mol) in methanol saturated with ammonia (1850 ml) was stirred at room temperature for two days. After evaporation of the solvent, the residue was diluted with water and washed several
10 times with ethyl acetate. The aqueous layer was separated, evaporated under reduced pressure and the residue was purified by a silica gel column chromatography [eluant: stepwise gradient of methanol (0-10%) in methylene chloride] to give pure 2'-deoxy- β -L-thymidine (11.62 g, 64.8%) which was crystallized from ethanol; m.p. 185-188°C; ^1H NMR (DMSO) δ ppm 11.3 (s, 1H,
15 NH), 7.70 (s, 1H, *H*-6), 6.2 (pt, 1H, *H*-1'), 5.24 (d, 1H, OH-3', *J* = 4.2 Hz), 5.08 (t, 1H, OH-5', *J* = 5.1 Hz), 4.2 (m, 1H, *H*-3'), 3.7 (m, 1H, *H*-4'), 3.5-3.6 (m, 2H, *H*-5', *H*-5''), 2.1-2.0 (m, 2H, *H*-2', *H*-2''); FAB<0, (GT) *m/e* 483 (2M-H)⁻, 349 (M+T-H)⁻, 241 (M-H)⁻, 125 (B)⁻; FAB>0 (GT) 243 (M+H)⁺, 127 (B+2H)⁺;)⁺; [α]_D²⁰ - 13.0 (*c* = 1.0 in DMSO); UV (pH 1) ν_{max} = 267 nm (ϵ = 9700), ν_{min} = 234
20 nm (ϵ = 2000).

Reagent:

Methanolic ammonia: previously saturated at -5°C, tightly stoppered, and kept in a freezer.

25

Example 2 -- Characterization of Physical Forms of L-dT**EXPERIMENTAL METHODS****Crystallization Studies**

A weighed sample of L-dT (usually 20-30mg) was treated with aliquots of
30 the test solvent. Solvents were either reagent or HPLC grade. The aliquots were usually 100 μ L or 500 μ L. Between additions the mixture was sonicated. When the solids dissolved, as judged by visual inspection, the solution was filtered, then left in an open vial under ambient conditions (fast evaporation). The procedure was repeated, and the resulting solution was left under ambient conditions in a vial
35 with aluminum foil containing pinholes (slow evaporation). Samples were also

5 generated by filtering a warm solution of L-dT into a cold antisolvent (cold precipitation).

Solubilities were estimated from these experiments based on the total solvent used to give a solution. Note that actual solubilities may be greater than those calculated because of the use of too-large solvent aliquots or a slow rate of dissolution. If the dissolution did not occur during the experiment the solubility is
10 expressed as "less than." If the solid dissolved before the whole aliquot of solvent was added the solubility is listed as "greater than."

The solid was also dissolved in a test solvent at an elevated temperature (either 45 or 60° C). The resulting solution was rapidly filtered into a vial kept on
15 the same hotplate. The heat source was then turned off and the hotplate and vial were allowed to cool to room temperature (slow cool). The vial was then allowed to stand at ambient temperature overnight. The presence or absence of undissolved solids was noted; if there were no solids present, or an amount of solid judged too small for XRPD analysis, the vial was placed in a refrigerator overnight. Again
20 the presence or absence of undissolved solids was noted and, if there were none, the vial was placed in a freezer overnight. Solids were removed by filtration and allowed to dry in the air.

Slurry experiments were carried out by making saturated solutions containing excess solid. The slurries were agitated at ambient temperature. The
25 insoluble solids were recovered by filtration. Crystallizations using antisolvent addition were also performed. Solid was dissolved in a solvent and filtered into an antisolvent at either 0° C or -78° C. If no solids immediately formed, the samples were either left to stand under ambient conditions and/or the solvent was removed by rotary evaporation. Any solids formed were removed by filtration and air-
30 dried. Vapor diffusion experiments involved placing a saturated solution of L-dT in a vial. The vial was placed in a larger vial containing an antisolvent which was then sealed and kept at ambient temperature. Samples were also generated by cooling of a melt of L-dT to room temperature and also lyophilization using water.

All samples generated as described above were air-dried and analyzed by
35 X-ray powder diffraction (XRPD).

5

X-ray Powder Diffraction

X-ray powder diffraction (XRPD) analyses were performed using a Shimadzu XRD-6000 X-ray powder diffractometer using Cu K α radiation. The instrument is equipped with a fine focus X-ray tube. The tube voltage and
10 amperage were set to 40 kV and 40 mA, respectively. The divergence and scattering slits were set at 1° and the receiving slit was set at 0.15 mm. Diffracted radiation was detected by a NaI scintillation detector. A theta-two theta continuous scan at 3 °/min (0.4 sec/0.02° step) from 2.5 to 40 °2 θ was used. A silicon standard was analyzed to check the instrument alignment. Data were
15 collected and analyzed using XRD-6000 v. 4.1. Samples were prepared for analysis by placing them in a silicon sample holder or aluminum holder with silicon insert.

Characteristic powder X-ray diffraction pattern peak positions are reported for crystalline forms in terms of the angular positions (two theta) within an
20 allowable variability of plus or minus 0.1°. This allowable variability is specified by the US Pharmacopeia, pages 1843-1844 (1995). The variability of plus or minus 0.1° is intended to be used when comparing two powder X-ray diffraction patterns. In practice, if a diffraction pattern peak from one pattern is assigned a range of angular positions (two theta) which is a measured peak position plus or
25 minus 0.1° and a diffraction pattern peak from the other pattern is assigned a range of angular positions (two theta) which is the measured peak position plus or minus 0.1° and if those ranges of peak positions overlap, then the two peaks are considered to have the same angular position (two theta). For example, if a diffraction pattern peak from one pattern is determined to have a peak position of
30 5.20°, for comparison purposes the allowable variability allows the peak to be assigned a position in the range of 5.10°-5.30°. If a comparison peak from the other diffraction pattern is determined to have a peak position of 5.35°, for comparison purposes the allowable variability allows the peak to be assigned a position in the range of 5.25°-5.45°. Because there is overlap between the two

- 5 ranges of peak positions, the two peaks being compared are considered to have the same angular position (two theta).

Thermal Analysis

Thermogravimetric (TG) analyses were performed using a TA Instruments
10 2050 or 2950 thermogravimetric analyzer. Each sample was placed in an aluminum sample pan and inserted into the TG furnace. Samples were first equilibrated at 25 °C, then heated under nitrogen at a rate of 10 °C/min, up to a final temperature of 350 °C. Nickel and Alumel™ were used as the calibration standards.

15 Differential scanning calorimetry (DSC) was performed using a TA Instruments differential scanning calorimeter 2920. The sample was placed into an aluminum DSC pan, and the weight accurately recorded. The pan was covered with a lid and left uncrimped. Each sample was equilibrated at 25 °C and heated under a nitrogen purge at a rate of 10 °C/min, up to a final temperature of 350 °C.
20 For studies of the glass transition temperature (T_g) of the amorphous material, the sample was heated at a rate of 20° C/min, up to 90° C and held there for 3 minutes. The sample was then allowed to cool and equilibrate at 0° C. The sample was again heated at a rate of 20° C/min, up to 90° C, held there for 3 minutes, and then cooled to 0° C. The sample was then heated at 20° C/min up to a final
25 temperature of 225° C. Indium metal was used as the calibration standard..

Hot stage microscopy was performed using a Linkam hot stage (model FTIR 600) mounted on a Leica DMLP microscope equipped with a Sony DXC-970MD 3CCD camera for collecting images. A 10× objective was used with cross polarizers to view samples. Samples were placed on a glass coverslip. A
30 coverslip was then placed over the sample. Each sample was visually observed as the stage was heated. Images were captured using Linksys version 2.27 (Linkam). The hot stage was calibrated using USP melting point standards.

5 **Spectroscopy**

Infrared spectra were acquired on a Magna-IR 560[®] /or 860[®] Fourier transform infrared (FT-IR) spectrophotometer (Thermo Nicolet) equipped with an Ever-Glo mid/far IR source, potassium bromide (KBr) beamsplitter, and a deuterated triglycine sulfate (DTGS) detector. A diffuse reflectance accessory (the Collector[™], Thermo Spectra-Tech) was used for sampling. Each spectrum represents 256 co-added scans collected at a spectral resolution of 4 cm⁻¹. Sample preparation consisted of placing the sample into a 3-mm diameter cup and leveling the material with a frosted glass slide. A background data set was acquired with an alignment mirror in place. A Log 1/*R* (*R* = reflectance) spectrum was acquired by taking a ratio of these two data sets against each other. Wavelength calibration was performed using polystyrene.

FT-Raman spectra were acquired on an FT-Raman 960 spectrometer (Thermo Nicolet). This spectrometer uses an excitation wavelength of 1064 nm. Approximately 0.5 W of Nd:YVO₄ laser power was used to irradiate the sample. The Raman spectra were measured with an indium gallium arsenide (InGaAs) detector. The samples were prepared for analysis by placing the material in a glass tube and positioning the tube in a gold-coated tube holder in the accessory. A total of 256 sample scans were collected from 100 – 3600 cm⁻¹ at a spectral resolution of 4 cm⁻¹, using Happ-Genzel apodization. Wavelength calibration was performed using sulfur and cyclohexane.

Moisture Sorption/Desorption

Moisture sorption/desorption data were collected on a VTI SGA-100 Vapor Sorption Analyzer. Sorption and desorption data were collected over a range of 5% to 95% relative humidity (RH) at 10% RH intervals under a nitrogen purge. Samples were not dried prior to analysis. Equilibrium criteria used for analysis were less than 0.0100% weight change in 5 minutes, with a maximum equilibration time of 3 hours if the weight criterion was not met. Data were not corrected for the initial moisture content of the samples. NaCl and PVP were used as calibration standards.

5

RESULTS

Approximate Solubilities

Approximate solubilities of L-dT in various solvents at ambient temperature were determined during the crystalline screen, and are summarized in Table 1. L-dT was found to be most soluble in 1:1 THF:water (127 mg/mL), followed by *N,N*-dimethylformamide (72 mg/mL), 1:1 methanol:water (58 mg/mL), 4:1 acetone:water (51 mg/mL), water (32 mg/mL), 1,1,1,3,3,3-hexafluoro-2-propanol (22 mg/mL), methanol (11 mg/mL), 2,2,2-trifluoroethanol (8 mg/mL) and EtOH (>4 mg/mL). L-dT is sparingly soluble in acetone, acetonitrile, ethyl acetate, diethyl ether, isopropanol, methylene chloride, and toluene

Crystallization Studies

Crystallization studies were also carried out to generate different solid forms of L-dT. The technique involved generation of solid L-dT under a variety of conditions and characterization of the resulting samples by XRPD. The experiments performed are summarized in Tables 2 and 3. One distinct crystalline XRPD pattern was found, termed crystalline L-dT, as well as an amorphous form. Amorphous material was generated by quenching a melt of the material on a cold countertop or lyophilization from aqueous solution. Many of the generated samples exhibited preferred orientation. Preferred orientation can affect peak intensities, but not peak positions, in XRPD patterns. The sections below summarize the characterization of the crystalline and amorphous materials.

5

Characterization of Crystal Form

The XRPD pattern of the initial material received for the crystallization screen is shown in Figure 1, and was termed representative of crystalline L-dT. Almost all of the crystallizations performed during the course of the screen
10 resulted in crystalline L-dT material. The IR and Raman spectra for crystalline L-dT are shown in Figures 2 and 3, respectively.

The thermal data for crystalline L-dT is shown in Figure 4 and listed in Table 4. The TG curve displays minimal weight loss up to 175 °C, indicating an unsolvated material. The DSC curve displays an endotherm at 190 °C. The
15 moisture sorption data for crystalline L-dT is shown in Figure 5 and summarized in Table 5. The material gains a relatively small amount of weight up to 45% RH, but above this point the material gains weight up to a total of 1.1% at 95% RH. All of this weight is lost upon lowering the relative humidity to 5%RH.

20 Characterization of Amorphous Form

Amorphous material was prepared by quenching a melt of the material to room temperature or by lyophilization from aqueous solutions. The IR and Raman spectra of amorphous are shown in Figure 2 and Figure 3, respectively. The IR spectra for the amorphous material differs from the crystalline material in that the
25 peaks from the amorphous material are broader and vary in shape between 1500-1900 cm^{-1} . The peaks in the Raman spectrum of the amorphous material also are broader than those seen for the crystalline material; however, the amorphous Raman spectrum displays significant peak shifts around 2800-3200, 1600-1675, 1300-1500, and 700-900 cm^{-1} .

30 The thermal data for the amorphous is shown in Figure 6. The TG curve shows a 0.5% weight loss up to 175 °C. The material displays an exothermic event at about 135 °C, which is likely a crystallization, followed by a melting endotherm at about 187 °C. A DSC temperature cycling experiment, shown in Figure 7, demonstrates that the glass transition temperature for the amorphous material is
35 ~50 °C.

5 The moisture sorption data for amorphous L-dT is shown in Figure 8. The material loses ~0.4% of its weight upon equilibration at about 5% RH, and gains ~2.3% up to about 55% RH. Above this point, the material loses some of this weight and continues to gain weight above about 85% RH. The material loses almost all of this weight upon lowering the relative humidity from about 95%RH
 10 to about 5% RH. The XRPD pattern of the material after the experiment matches that of crystalline L-dT. It is likely that the sudden weight drop above about 55% RH is indicative of a recrystallization and the concomitant loss of water.

Table 1. Approximate Solubilities of crystalline L-dT

15

Solvent	Solubility (mg/mL) ^a
acetone	< 4
acetone:water (4:1)	51
acetonitrile (ACN)	< 4
dichloromethane	< 3
<i>N,N</i> -dimethylformamide (DMF)	72
ethanol (EtOH)	>3.6*
ethyl acetate (EtOAc)	< 4
ethyl ether	< 3
1,1,1,3,3,3-hexafluoroisopropanol	22
hexane	< 4
isopropanol (IPA)	< 3
methanol (MeOH)	11
MeOH:water (1:1)	58
tetrahydrofuran (THF)	4
THF:water (1:1)	127
toluene	< 4
2,2,2-trifluoroethanol	8
water	32

^a Solubilities are calculated based on the total solvent used to give a solution; actual solubilities may be greater because of the volume of the solvent portions utilized or a slow rate of dissolution. If a clear solution was not obtained the values for the solubilities are listed as "less than." If the solid dissolved before the whole aliquot of solvent was added the solubility is listed as "greater than." Values are rounded to the nearest mg/mL.

* after 2 hours, all solid was dissolved.

25 **Table 2. Crystallization Screen of L-dT**

Solvent	Conditions ^a	Habit	XRPD Results ^b
acetone	slurry	small white aciculars	crystalline
acetone	1 day slurry (50°C)	needles	crystalline
acetone:water (4:1)	FE	unknown	crystalline
	1 day slurry (50°C)	needles	crystalline
acetonitrile	slurry	small white aciculars	crystalline
	1 day slurry (50°C)	needles	crystalline
dichloromethane	slurry	small white aciculars	crystalline
diethyl ether	slurry	small white aciculars	crystalline
N,N-dimethyl- formamide (DMF)	FE	white chunks	crystalline
	SE	white needles, chunks	crystalline(PO)
	SC (60 °C)	no solid	-
ethanol	FE	white flakes, chunks	crystalline
	SE	clear aciculars	crystalline
	SC (60° C)	Unknown white solid	crystalline
	CC	white solid	crystalline
	1 day slurry (50°C)	needles	crystalline
ethyl acetate	slurry	small white plates	crystalline
hexafluoroisopropanol	FE	small white flakes	crystalline
	SE	white flakes	crystalline
	SC (60 °C)	no solid	-
	rotovap	white solid	crystalline
hexanes	slurry	small white aciculars	crystalline
isopropanol	slurry	white powder	crystalline
	1 day slurry (50°C)	needles	crystalline
methanol	FE	white needles	crystalline
	SE	white needles, flakes	crystalline
	SC (60°C)	white chunks	crystalline
	CC	white solid	crystalline
	rotovap	white solid	crystalline
MeOH:water(1:1)	FE	needles	crystalline
	1 day slurry (50°C)	no solids	-
	CC freezer	no solids	-
toluene	slurry	white powder	crystalline
tetrahydrofuran	FE	clumps of white fibers	crystalline

Solvent	Conditions ^a	Habit	XRPD Results ^b
(THF)	SE	white aciculars	crystalline(PO)
	SC (60 °C)	white needles	crystalline
	CC	white solid	crystalline
	rotovap	white solid	crystalline
THF:Water (1:1)	FE	needles	crystalline
	1 day slurry (50°C) CC freezer	no solids no solids	- -
2,2,2-trifluoroethanol	FE	white needles, flakes	crystalline
	SE	white needles	crystalline
	SC (60 °C)	no solid	-
	rotovap	white solid	crystalline
water	FE	unknown white solid	crystalline
	SE	clear aciculars	crystalline
	SC (60 °C)	no solid	-
	1 day slurry (50°C)	needles	crystalline
	freeze dry	white solid	crystalline
	freeze dry	fluffy white solid	amorphous
	freeze dry	-	crystalline
	melt/quench	clear solid	amorphous
	melt/quench	clear solid	crystalline + amorphous
	melt/quench	clear solid	amorphous
	melt/quench	clear solid	amorphous
	melt/quench	clear solid	amorphous

5 ^a FE = fast evaporation; SE = slow evaporation; SC = slow cool, CC = crash cool, rotovap = rotary evaporator

^b PO = preferred orientation; LC = low crystallinity; SS = small sample; IS = insufficient sample

10 **Table 3. Cold Precipitation Crystallizations**

Solvent	Anti-solvent	Habit	XRPD Results
<i>N,N</i> -dimethylformamide	acetone	no solid	-
	toluene	white solid	crystalline
ethanol	acetone	no solid	-
	ethyl acetate	white solid	crystalline
methanol	acetone	no solid	-
	dichloromethane	white solid	crystalline
	diethyl ether	white solid	crystalline
tetrahydrofuran	acetone	no solid	-
	diethyl ether	white solid	crystalline

	hexanes	white solid	crystalline
water	acetone	no solid	-
	acetonitrile	no solid	-
	isopropanol	no solid	-

5 * solid dissolved in solvent at 60°C, hot filtered into vial containing cold antisolvent (cooled in dry-ice/acetone slurry) None of these yielded solid immediately, solid formed after samples had been in freezer several days.

Table 4. Thermal Data for L-dT Forms

10

Form	DSC Results (°C) ^a	TG Results ^b
crystalline	endo 190	< 0.1
amorphous	transition ~44, exo 135, endo 187	0.5
amorphous	T _g ~50	-

^a maximum temperature reported; endo = endotherm; exo = exotherm; T_g = glass transition

^b percent volatiles measured at 175 °C

15

Table 5. Summary of Moisture Sorption/Desorption Data for For Crystalline L-dT Solid Forms

Lot No.	Moisture Balance Results	XRPD Results
1	<0.1 % weight loss at 5% RH 1.1 % weight gain at 95% RH 1.1 % loss from 95-5% RH	crystalline
2	-0.4% weight loss at 5% RH 2.8% weight gain at 95% RH 2.7% loss from 95-5% RH	crystalline

20

PHARMACEUTICAL COMPOSITIONS

Humans suffering from viral diseases such as HBV can be treated by administering to the patient an effective amount of the forms of the compound of the present invention, or a pharmaceutically acceptable prodrug or salt thereof in the presence of a pharmaceutically acceptable carrier or diluent. The active materials can be administered by any appropriate route, for example, orally, parenterally, or intravenously, in liquid or solid form.

25

A preferred dose of the compound for HBV will be in the range from about 1 to 75 mg/kg, preferably 1 to 50 or 20 mg/kg, of body weight per day,

5 more generally 0.1 to about 100 mg per kilogram body weight of the recipient per day. The effective dosage range of the pharmaceutically acceptable salts and prodrugs can be calculated based on the weight of the parent nucleoside to be delivered. If the salt or prodrug exhibits activity in itself, the effective dosage can be estimated as above using the weight of the salt or prodrug, or by other means
10 known to those skilled in the art.

The compound is conveniently administered in any suitable dosage form, including but not limited to one containing 7 to 3000 mg, preferably 70 to 1400 mg of active ingredient per unit dosage form. An oral dosage of 50-1000 mg is usually convenient.

15 Ideally the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.2 to 70 μM , preferably about 1.0 to 10 μM . This may be achieved, for example, by the intravenous injection of a 0.1 to 5% solution of the active ingredient, optionally in saline, or administered as a bolus of the active ingredient.

20 The concentration of active compound in the drug composition will depend on absorption, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be
25 adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of
30 smaller doses to be administered at varying intervals of time.

A preferred mode of administration of the active compound is oral. Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with
35 excipients and used in the form of tablets, troches, or capsules. Pharmaceutically

5 compatible binding agents, and/or adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch
10 or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above
15 type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compound can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in
20 addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The compound or a pharmaceutically acceptable prodrug or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics,
25 antifungals, anti-inflammatories, or other antivirals, including other nucleoside compounds. Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial
30 agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or
35 plastic.

5 If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

 In a preferred embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and
10 microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation.

15 Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) are also preferred as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome
20 formulations may be prepared by dissolving appropriate lipid(s) (such as stearyl phosphatidyl ethanolamine, stearyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound or its monophosphate,
25 diphosphate, and/or triphosphate derivatives is then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

 It will be apparent to those skilled in the art that various
30 modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope
35 and spirit of the invention being indicated by the following claims.

5 We Claim:

1. A non-solvated crystalline form of beta-L-2'-deoxythymidine devoid of waters of association.
2. A non-solvated crystalline form of beta-L-2'-deoxythymidine substantially in the absence of amorphous beta-L-2'-deoxythymidine.
- 10 3. Amorphous beta-L-2'-deoxythymidine.
4. Amorphous beta-L-2'-deoxythymidine in substantially pure form.
5. A substantially pure phase of beta-L-2'-deoxythymidine prepared by quenching cooling the melted beta-L-2'-deoxythymidine.
6. The beta-L-2'-deoxythymidine of claim 1 prepared by crystallizing beta-L-
15 2'-deoxythymidine from solution, optionally filtering said crystallized beta-L-2'-deoxythymidine, and drying said beta-L-2'-deoxythymidine in an environment comprising less than about 40% relative humidity.
7. A physical crystalline form of beta-L-2'-deoxythymidine in the form of white flakes.
- 20 8. A physical crystalline form of beta-L-2'-deoxythymidine in the form of clear aciculars.
9. A physical crystalline form of beta-L-2'-deoxythymidine in the form of white aciculars.
10. A physical crystalline form of beta-L-2'-deoxythymidine in the form of a
25 white solid.
11. A physical crystalline form of beta-L-2'-deoxythymidine in the form of a white powder.
12. A physical crystalline form of beta-L-2'-deoxythymidine in the form of needles.
- 30 13. A physical crystalline form of beta-L-2'-deoxythymidine in the form of white chunks.
14. A physical crystalline form of beta-L-2'-deoxythymidine in the form of white plates.

- 5 15. A method of detecting amorphous contamination of beta-L-2'-deoxythymidine, or distinguishing between crystalline and amorphous beta-L-2'-deoxythymidine, comprising:
- a) subjecting a material that contains beta-L-2'-deoxythymidine to IR spectrometry;
- 10 b) evaluating breadth of peaks displayed between 2200-2600, 1600-1800, 1000-1500, or 500-1000 cm^{-1} by reference to a known IR spectra for crystalline beta-L-2'-deoxythymidine.
16. A method of detecting amorphous contamination of beta-L-2'-deoxythymidine, or distinguishing between crystalline and amorphous beta-L-2'-deoxythymidine, comprising:
- 15 a) subjecting a material that contains beta-L-2'-deoxythymidine to Raman spectrometry;
- b) evaluating the breadth of peaks displayed between 2800-3200, 1600-1675, 1300-1500, or 700-900 cm^{-1} by reference to a known Raman spectra for crystalline beta-L-2'-deoxythymidine.
- 20 17. A process of manufacturing pharmaceutical formulations of crystalline beta-L-2'-deoxythymidine comprising:
- a) crystallizing two or more batches of beta-L-2'-deoxythymidine from solution;
- 25 b) subjecting the batches to IR spectrometry;
- c) selecting for further processing the batches that do not display significant breadth of peaks between 2200-2600, 1600-1800, 1000-1500, or 500-1000 cm^{-1} from a known IR spectra for crystalline beta-L-2'-deoxythymidine; and
- 30 d) formulating said selected batches into pharmaceutical formulations of beta-L-2'-deoxythymidine.
18. A process of manufacturing pharmaceutical formulations of crystalline beta-L-2'-deoxythymidine comprising:
- a) crystallizing two or more batches of beta-L-2'-deoxythymidine from solution;
- 35

- 5 b) subjecting the batches to Raman spectrometry;
- c) selecting for further processing the batches that do not display
 significant breadth of peaks between 2800-3200, 1600-1675, 1300-
 1500, or 700-900 cm^{-1} from a known Raman spectra of crystalline
 beta-L-2'-deoxythymidine; and
- 10 d) formulating said selected batches into pharmaceutical formulations
 of beta-L-2'-deoxythymidine.
19. A pharmaceutical formulation of crystalline beta 2'-deoxythymidine
 prepared by the process of claim 17 or 18.
20. A process of making a non-solvated crystalline form of beta-L-2'-
15 deoxythymidine that is devoid of waters of association, comprising:
- a) crystallizing beta-L-2'-deoxythymidine from solution;
- b) optionally filtering said crystallized beta-L-2'-deoxythymidine; and
- c) drying said filtered beta-L-2'-deoxythymidine in an environment
 comprising less than about 40% relative humidity.
- 20 21. A process of preparing substantially pure amorphous beta-L-2'-
 deoxythymidine comprising:
- a) melting a beta-L-2'-deoxythymidine, and
- b) quench cooling the melt to avoid recrystallization.
22. The process of claim 21 further comprising cooling the beta-L-2'-
25 deoxythymidine to below about 50 °C.
23. The process of claim 21 further comprising maintaining the relative
 humidity below about 20%.
24. A pharmaceutical composition comprising the compound or composition
 of any one of claims 1-8, 13, 14, or 16-19, and a pharmaceutically
30 acceptable carrier.
25. A method of treating hepatitis B virus comprising administering to a
 patient afflicted with the disease a treatment effective amount of the
 compound of any one of claims 1-8, 13, 14, or 16-19.
26. β-L-dT which is substantially devoid of water for a period of time of at
35 least 4 months.

- 5 27. β -L-dT which is substantially devoid of water for a period of time of at least 6 months.
28. β -L-dT which is substantially devoid of water for a period of time of at least 8 months.
29. β -L-dT which is substantially devoid of water for a period of time of at
10 least 10 months.
30. β -L-dT which is substantially devoid of water for a period of time of at least 12 months.
31. A method of manufacturing a form of β -L-dT comprising exposing said β -
15 L-dT to an environment comprising not more than 10% relative humidity for a period of time of at least 4 months, wherein said L-dT is substantially devoid of water at the end of the 4 months.
32. A method of manufacturing a form of β -L-dT comprising exposing said L-
20 dT to an environment comprising not more than 20% relative humidity for a period of time of at least 4 months, wherein said L-dT is substantially devoid of water at the end of the 4 months.
33. A method of manufacturing a form of β -L-dT comprising exposing said L-
 dT to an environment comprising not more than 30% relative humidity for a period of time of at least 4 months, wherein said L-dT is substantially devoid of water at the end of the 4 months.
- 25 34. The method of claim 33 further comprising, after the 4 month time period, administering said L-dT to a human.
35. A use of the compound of any one of claims 1-14 or 26-30, in the manufacture of a medicament for treating a patient afflicted with hepatitis B virus.

Figure 1. XRPD patterns of crystalline L-dT and amorphous L-dT

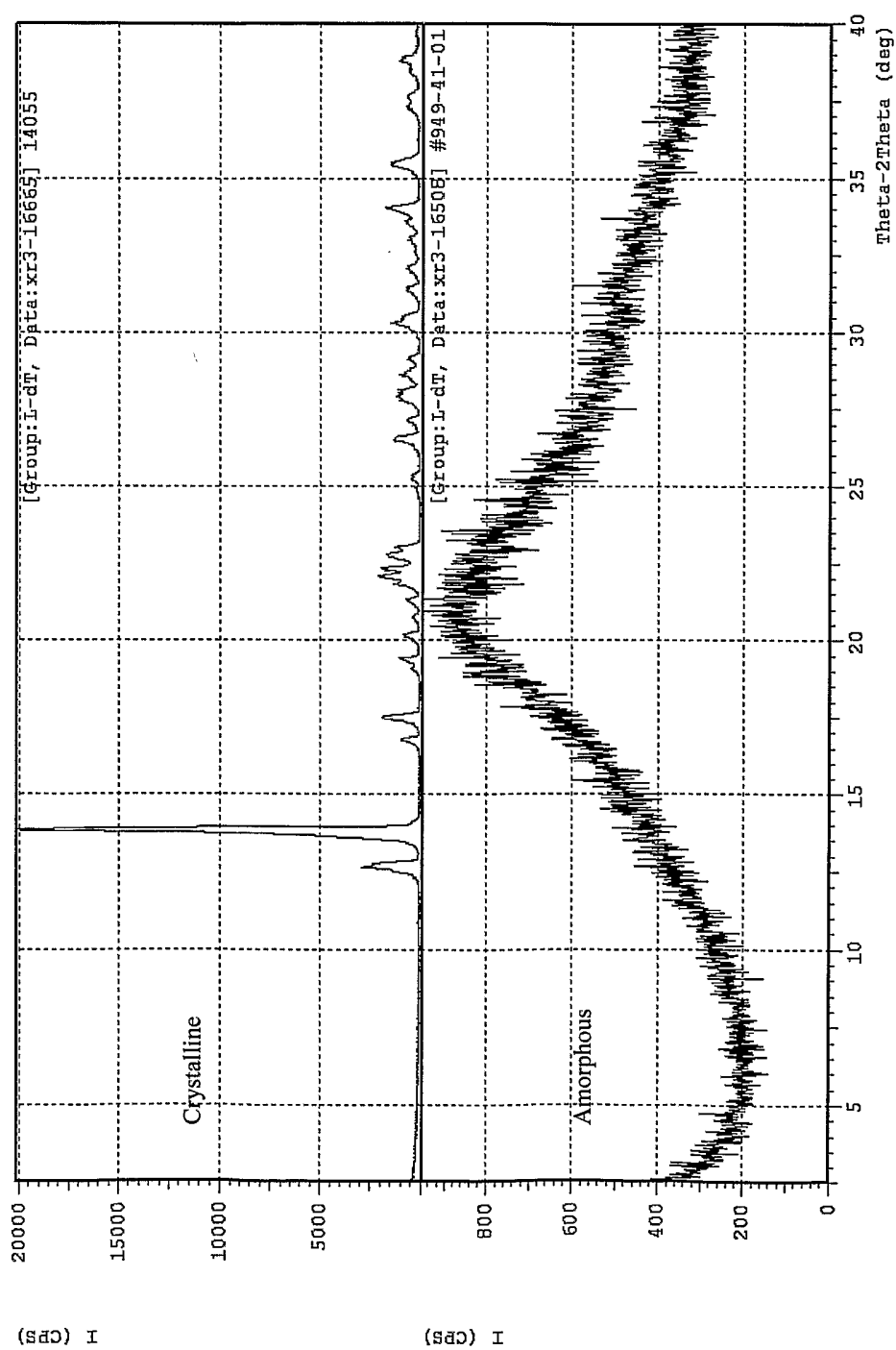


Figure 2. IR spectra for crystalline and amorphous L-dT

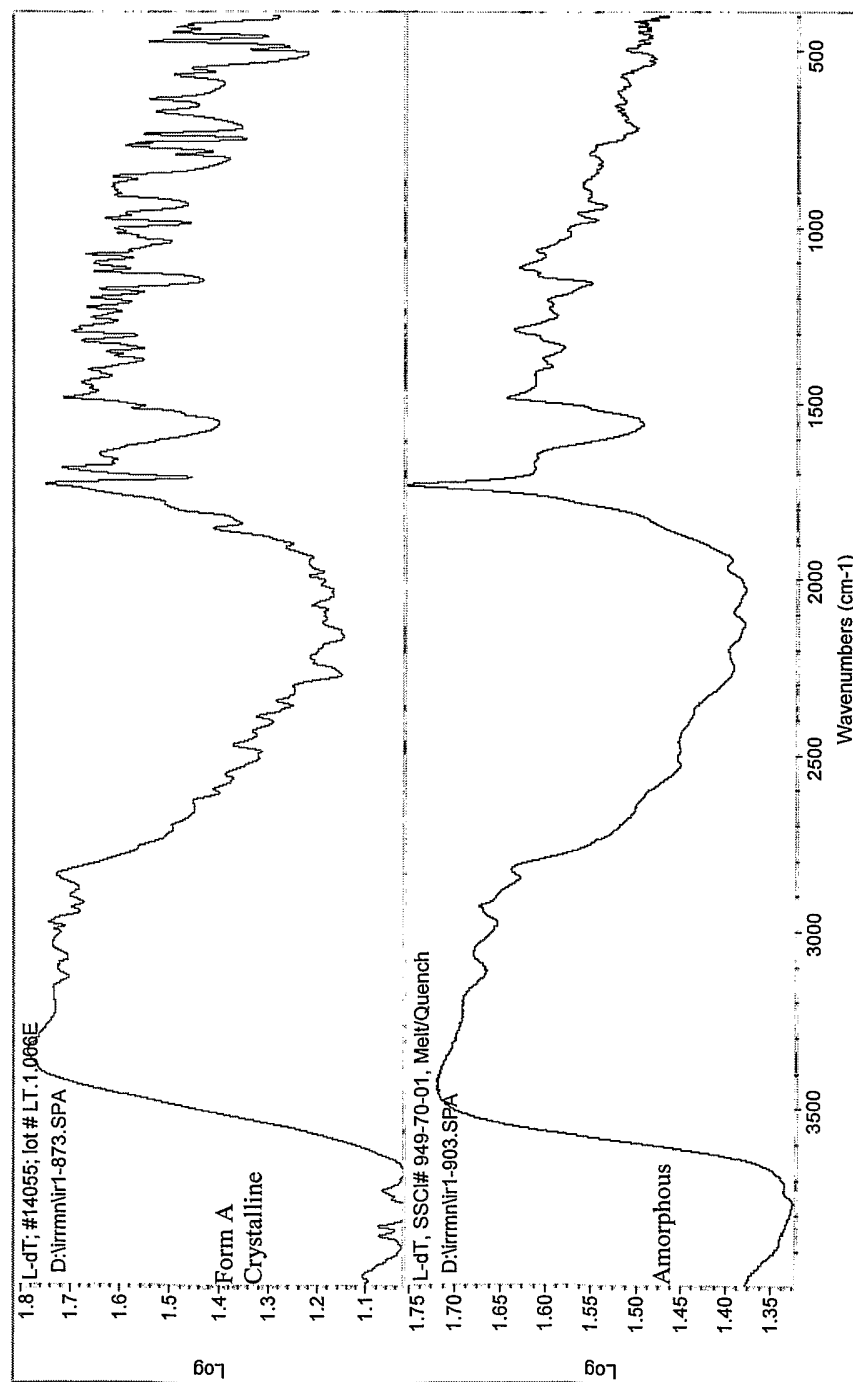


Figure 3. Raman spectra for crystalline and amorphous L-dT

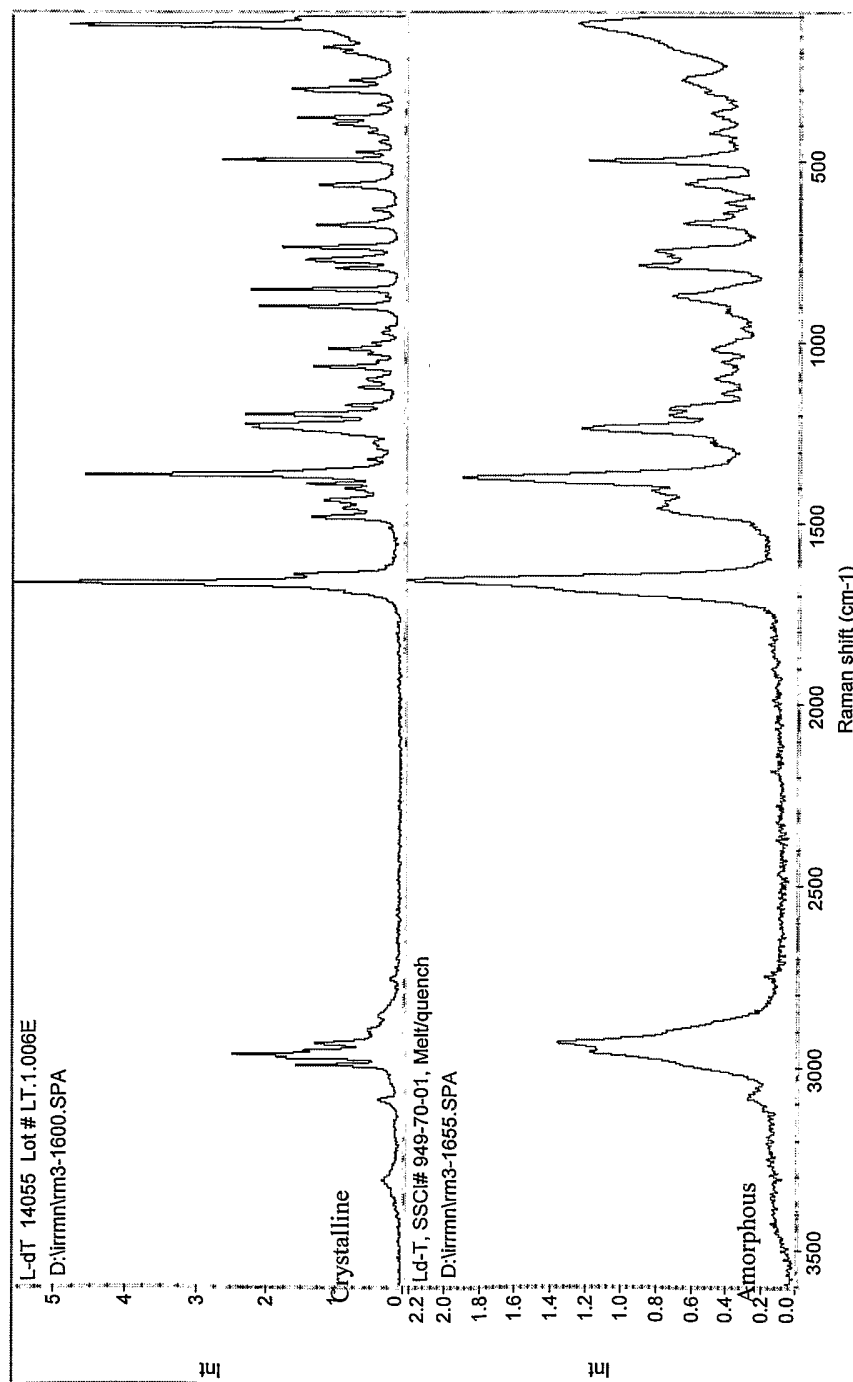


Figure 4. TG and DSC curves for crystalline L-dT

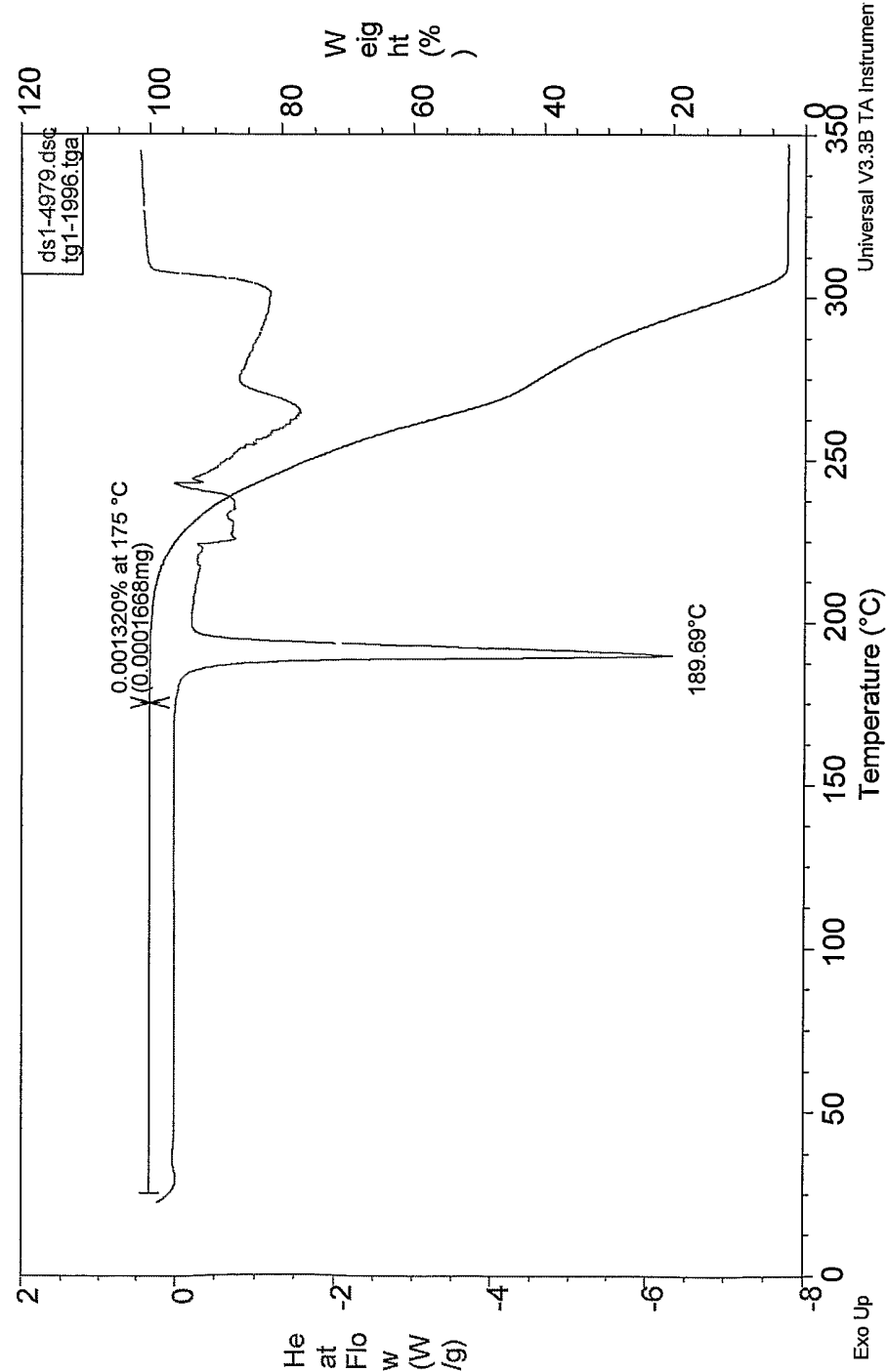


Figure 5. Moisture sorption data for crystalline L-dT

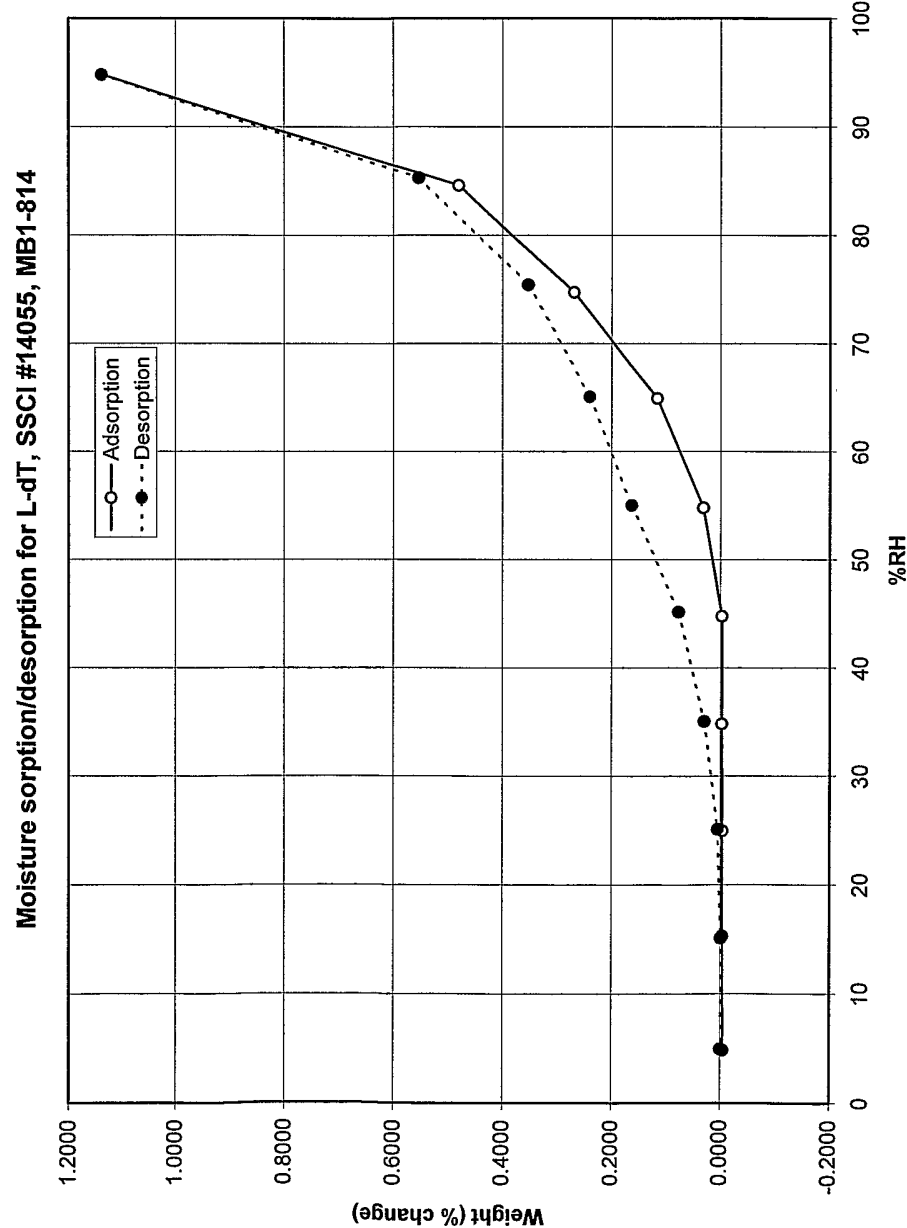


Figure 6, TG (top) and DSC (bottom) curves for amorphous L-dT

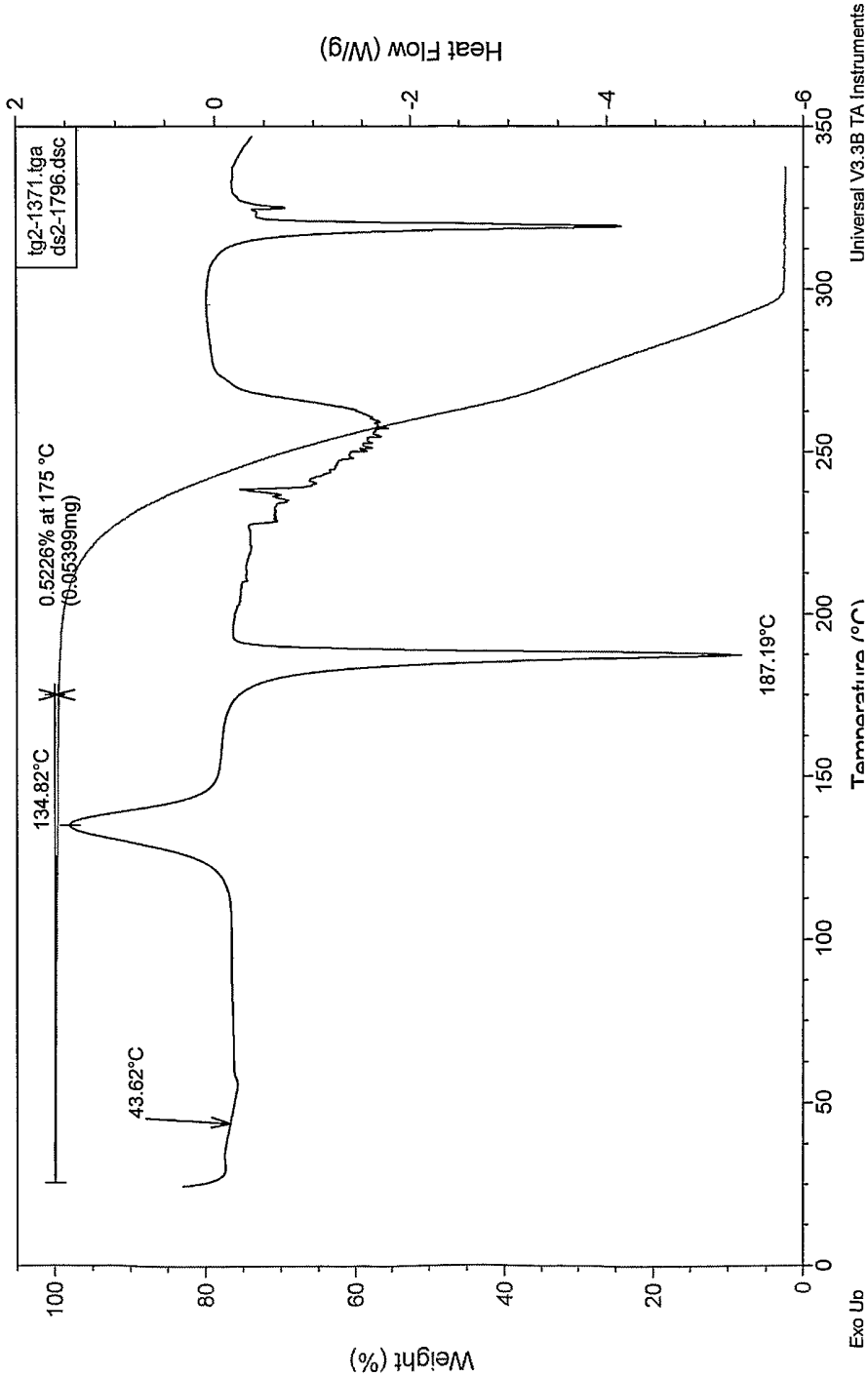


Figure 7. DSC temperature cycling experiments on amorphous L-dT

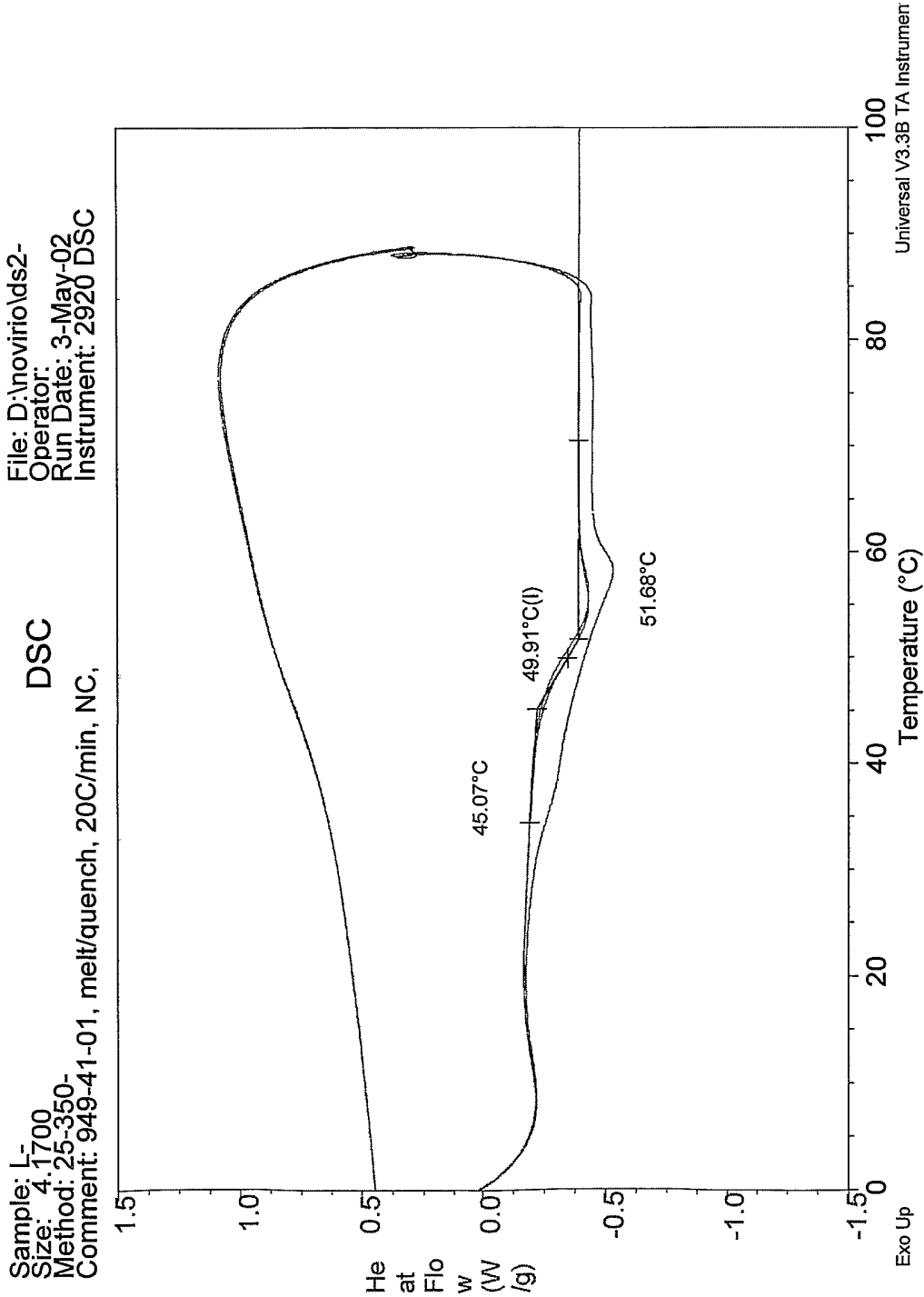


Figure 8. Moisture sorption/desorption curves for amorphous L-dT

