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Salts of the anti-HIV drug lamivudine with phthalic and salicylic acids†

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Salts of the anti-HIV drug lamivudine, with phthalic acid and salicylic acid as counterions, were investigated in this study. Neither the packing of the (lamivudine)⁺(phthalic acid)⁻ ion pairs nor the conformation of the lamivudine moiety itself were similar to those found in other multicomponent molecular salts of the drug, such as hydrogen maleate and saccharinate ones, even though all three salts crystallize in the same *P*₂₁₂₁ orthorhombic space group with similar unit cell metrics. Lamivudine salicylate assumes a different crystal structure to those of the hydrogen maleate and saccharinate salts, crystallizing in the *P*₂₁ monoclinic space group as a monohydrate whose (lamivudine)⁺(salicylic acid)⁻ ion pair is assembled through two hydrogen bonds with cytosine as a dual donor to both oxygens of the carboxylate, such as in the pairing of lamivudine with a phthalic acid counterion. In lamivudine salicylate monohydrate, the drug conformation is related to the hydrogen maleate and saccharinate salts. However, such a conformational similarity is not related to the intermolecular interaction patterns. Lamivudine and water molecules alternate into helical chains in the salicylate salt monohydrate.

Lamivudine (β -L-2',3'-dideoxy-3'-thiacytidine, 3TC) is a nucleoside reverse transcriptase inhibitor (NRTI) widely used in anti-HIV (human immunodeficiency virus) and anti-HBV (hepatitis B virus) therapies.¹ Lamivudine is a cytidine analog featuring an isosteric replacement of the ribose 3'-methylene group with a sulfur atom. This drug has two chiral carbons, namely, C1' and C4', whose absolute configurations are *S* and *R*, respectively. As a consequence of its chirality, all known crystal structures of lamivudine have been solved in non-centrosymmetric space groups. This can be seen in the eleven crystal structures which have already been reported for lamivudine thus far, wherein seven of them were solved in the *P*₂₁ monoclinic space group (form III, (a hemihydrate),² a 3,5-dinitrosalicylate salt hydrate with 2 : 1 : 1

lamivudine : 3,5-dinitrosalicylic acid : H₂O stoichiometry,³ la 4-quinolinone cocrystal,³ a zidovudine cocrystal hydrate with 1 : 1 : 1 lamivudine : zidovudine : H₂O stoichiometry,³ a lamivudine duplex with 8 : 2 : 2 : 1 : 4 lamivudine : maleic acid : HCl : (CH₃)₂CHOH : H₂O stoichiometry,⁴ a hydrochloride salt anhydrate⁵ and a hydrochloride salt monohydrate⁵), three in the *P*₂₁₂₁ orthorhombic space group (form I (a 0.2-hydrate),⁶ a saccharinate salt,⁷ and a hydrogen maleate salt⁸) and one in the *P*₄₃₂₁ tetragonal space group (form II, an anhydrous polymorph).⁶ As can be observed, this drug has been extensively investigated due to its ability to crystallize together with different small molecules in multicomponent molecular solid state phases.

Recently, crystal engineering studies have focused on many drugs.⁹ Concerning lamivudine, we designed a hydrogen maleate salt⁸ by invoking physicochemical principles and recognizing key assembling frameworks in the antecedent structure of lamivudine saccharinate.⁷ The choice of maleic acid to crystallize together with lamivudine was based on chemical and structural similarities to saccharin, such as the acid-ionization constant (p*K*_a) and intramolecular features including hydrogen bonding functionalities and stereochemistry. Lamivudine hydrogen maleate was successfully obtained and a lamivudine saccharinate-like *P*₂₁₂₁ orthorhombic structure was assumed by the designed salt. On the basis of packing and conformational similarities between hydrogen maleate and saccharinate versions of the drug, it was possible to point out a molecular motif present in both the maleic acid and saccharin counterions responsible for the crystal assembly of these two isostructural lamivudine salts.⁸

As part of the ongoing studies in crystal engineering of molecular crystals of lamivudine, other salt formers were investigated in this study. Here, phthalic acid and salicylic acid were selected as salt formers. Their salts with lamivudine were prepared‡ and structurally elucidated by single-crystal X-ray diffraction.§ The experimental X-ray powder diffractograms of the salts were overlaid onto the calculated results from their corresponding crystals structures.¶ The observed Bragg peak positions are in good agreement with the simulated positions, although there are differences in the reflection intensities which resulted from the preferred orientation effects on the X-ray powder diffraction measurements of both salts (Fig. 1). Since neither a pronounced broad hump from an amorphous solid nor extra Bragg peaks from other crystalline phases other than that of the sample were observed in the experimental diffractograms, it

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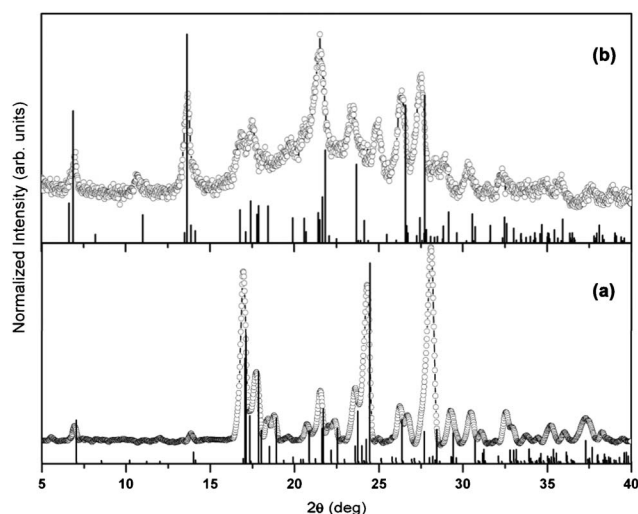
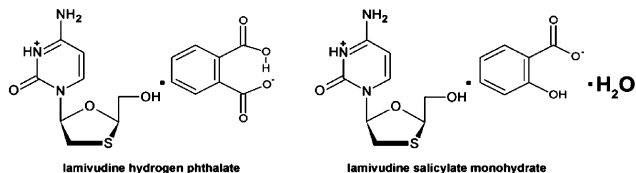


Fig. 1 Calculated (vertical bars) and room-temperature (298 K) experimental X-ray powder diffractograms (continuous line with dots) of (a) lamivudine hydrogen phthalate and (b) lamivudine salicylate monohydrate. The calculated diffractograms were simulated from the corresponding crystal structures, determined at either 298 K (lamivudine hydrogen phthalate) or 107.4 K (lamivudine salicylate monohydrate).

was possible to conclude that the salts were in the bulk of the crystal phases elucidated here.



The acid strengths of the counterions were taken into account when choosing these salts. Both maleic acid and saccharin are deprotonated in the lamivudine salts due to a transfer of one proton from each acid to each lamivudine molecule.^{7,8} It is a fact that their acid strengths for a one-proton dissociation are very similar. Saccharin has a pK_a value of 2.2,^{7,10} while the first proton acid-ionization constant (pK_{a1}) of maleic acid is 1.83.¹¹ However, the acid strengths of phthalic acid and salicylic acid are not similar to those of maleic acid and saccharin. Differing by more than one unit to maleic acid pK_{a1} , phthalic acid has a pK_{a1} of 2.95.¹² Similarly, the pK_a of salicylic acid is 2.97.¹³ Although there are differences in the proton dissociation tendencies of the counterions, fortunately proton transfer to lamivudine occurred in the hydrogen phthalate and salicylate salts as it had in the hydrogen maleate and saccharinate molecules and crystals of lamivudine hydrogen phthalate and lamivudine salicylate were obtained. This can be viewed in Fig. 2 as an ellipsoid plot of their asymmetric units.

Lamivudine hydrogen phthalate was solved in the $P2_12_12_1$ orthorhombic space group with four (lamivudine)⁺(phthalic acid)⁻ ion pairs per unit cell. To assemble each ion pair, the drug donates two hydrogen bonds through the imine and amine moieties of its protonated cytosine ring to the two COO^- oxygens of the hydrogen phthalate counterion, in a pattern equivalent to that observed in lamivudine hydrogen maleate.⁸ In addition to crystallizing in the same crystal system and space group as the

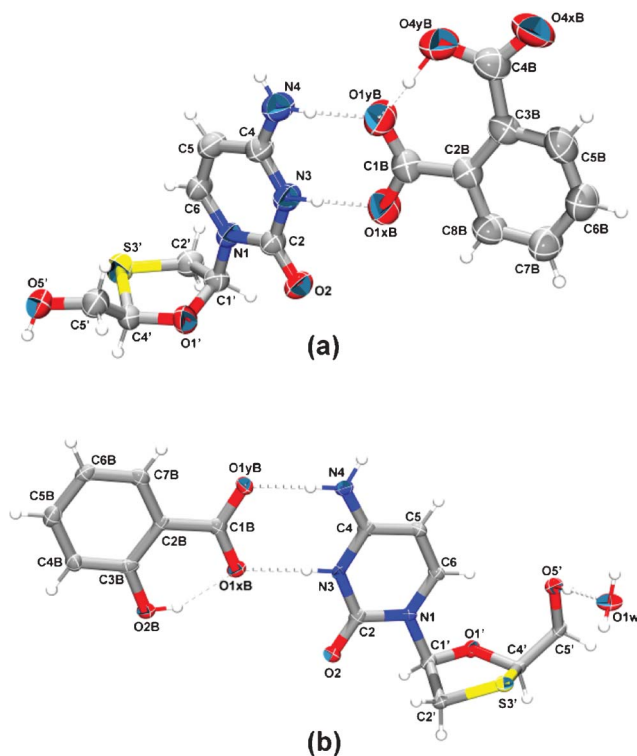


Fig. 2 Asymmetric units of (a) lamivudine hydrogen phthalate (298 K structure) and (b) lamivudine salicylate monohydrate (107.4 K structure). Hydrogens are drawn as arbitrary radius spheres and the ellipsoids of the non-hydrogen atoms are at a 50% probability level.

hydrogen maleate and saccharinate salts, the hydrogen phthalate salt features similar unit cell dimensions. However the structural similarities between lamivudine hydrogen phthalate and the two previously reported isostructural salts end there. Neither the drug conformation (Fig. 3) nor the arrangement of the ion pairs in lamivudine hydrogen phthalate resembles those of the antecedent salts (Fig. 4).

In the hydrogen phthalate salt, the drug skeleton exhibits a very unusual nucleoside conformation, with an intermediate cytosine orientation between the *anti* and *syn* conformations in which the $C2-N1-C1'-O1'$ dihedral angle measures $82.8(2)^\circ$. Its oxathiolane ring possesses a $C2'$ -*exo* pucker conformation ($C1'-O1'-C4'-S3'$ torsional angle of $8.5(2)^\circ$) and the 5'-hydroxyl group is bonded to

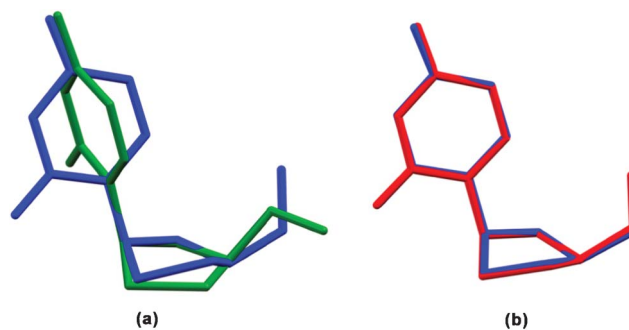


Fig. 3 Superposition of the lamivudine conformer present in the structure of the salt with maleic acid⁸ (blue sticks) with those in the salts with (a) phthalic (green sticks) and (b) salicylic (red sticks) acids. The hydrogen atoms have been hidden for clarity.

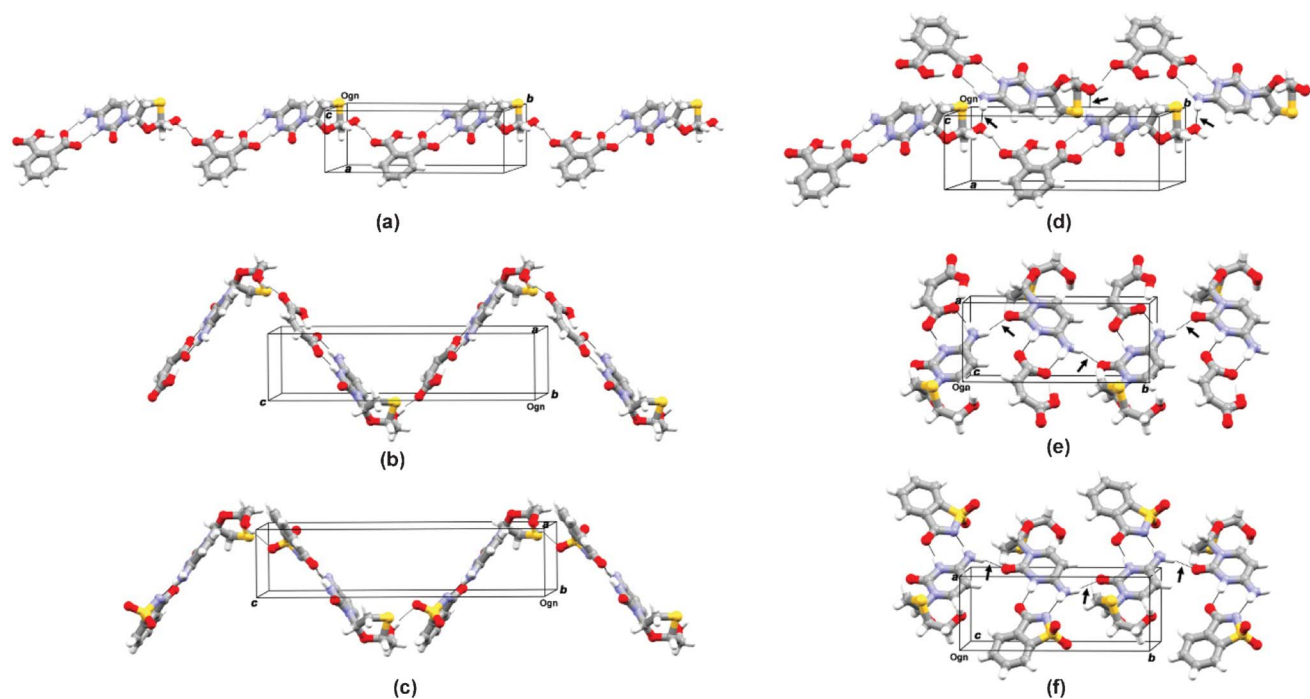


Fig. 4 One-dimensional ribbons of (a) lamivudine hydrogen phthalate, (b) lamivudine hydrogen maleate,⁸ and (c) lamivudine saccharinate⁷ are cross-linked through N–H···O hydrogen bonds (arrows) in which the acceptor is either the 5'-OH group [lamivudine hydrogen phthalate, panel (d)] or the C=O=O moiety (lamivudine hydrogen maleate and lamivudine saccharinate, panels (e) and (f)).

the methylene sp^3 -hybridized carbon in the equatorial position on the same side of the sulfur atom ($O1'-C4'-C5'-O5'$ and $S3'-C4'-C5'-O5'$ dihedral angles measure $-176.4(2)^\circ$ and $62.5(2)^\circ$). In contrast, the cytosine and oxathiolane rings assume *anti* and $C3'$ -*endo* pucker conformations in the lamivudine hydrogen maleate and lamivudine saccharinate salts and the 5'-hydroxyl oxygen is in the axial position on the same side of the cytosine molecule in these two salts.

Concerning the crystal packing of lamivudine hydrogen phthalate, the 5'-OH group of lamivudine is a hydrogen bond donor to (phthalic acid)⁻ with the carbonyl oxygen of the carboxyl group as an acceptor. This interaction assembles (lamivudine)⁺(phthalic acid)⁻ ion pairs along the (010) direction by alternating the cations and anions into a one-dimensional (1D) ribbon wherein each species is related to one another by translation. This same 5'-O–H···O=C hydrogen bond between lamivudine and the counterion also occurs in the hydrogen maleate and saccharinate salts of the drug, but molecules of (lamivudine)⁺ and (maleic acid)⁻ (or saccharinate) are related by a 2_1 -screw axis symmetry and alternate along the (001) direction to form a zigzag 1D ribbon instead (Fig. 4). In these two isostructural salts, there is an N–H···O=C hydrogen bond between the cytosine rings of the neighbouring lamivudine molecules, related by a 2_1 -screw axis symmetry along the (010) direction, whereas the cytosine rings do not interact through hydrogen bonds in the lamivudine hydrogen phthalate salt. In the former, the NH_2 moiety of cytosine, through its hydrogen atom which is not involved in the (lamivudine)⁺(phthalic acid)⁻ pairing, is a hydrogen bond donor to the 5'-hydroxyl oxygen of the lamivudine unit, related by a 2_1 -screw axis symmetry parallel to the (010) direction. This interaction acts as a cross-linker, keeping the linear ribbons running parallel to the *b* axis in contact. To complete the crystal packing difference

between lamivudine hydrogen phthalate and the two antecedent salts, the 5'-hydroxyl oxygen of lamivudine is not a classical hydrogen bond acceptor in the last two crystal phases.

The lamivudine salicylate structure also differs from those of the hydrogen maleate and saccharinate salts. Indeed, lamivudine salicylate crystallizes in the $P2_1$ monoclinic space group as a monohydrate. One water molecule is present in the asymmetric unit together with one (lamivudine)⁺(salicylic acid)⁻ ion pair, assembled through two hydrogen bonds with cytosine as dual donor to both oxygens of the carboxylate, such as in the pairing of lamivudine with the phthalic acid counterion. To the best of our knowledge, a solid state phase of lamivudine salicylate monohydrate has been previously reported,¹⁴ although neither crystal structure of this salt (including any possible solvate) has been elucidated thus far. Likewise, a lamivudine salt with phthalic acid has been reported in the literature,¹⁵ even though no information on its structure has been available up to now. The lamivudine conformation in our structure (Fig. 3) is related to those in lamivudine maleate and lamivudine saccharinate. The cytosine and oxathiolane rings adopt *anti* (the $C2-N1-C1-O1'$ dihedral angle measures $162.2(4)^\circ$) and $C3'$ -*endo* (the $C2'-C1'-O1'-C4'$ torsion measures $-11.8(5)^\circ$) conformations in the lamivudine salicylate monohydrate, with its 5'-hydroxyl oxygen in an axial position (the $O1'-C4'-C5'-O5'$ and $S3'-C4'-C5'-O5'$ dihedral angles measure $70.6(5)^\circ$ and $-49.2(5)^\circ$), similar to both the hydrogen maleate and saccharinate salts. Even the 5'-hydroxyl hydrogen points in the same direction in these salts. It is important to state that comparisons between the 5'-OH hydrogen atom positions in the lamivudine salicylate monohydrate, lamivudine hydrogen maleate and lamivudine saccharinate were possible due to the fact that their coordinates have been accurately found from the refinement. However, such a conformational similarity is not related to the

intermolecular interaction patterns. Lamivudine and water molecules give rise to a helical chain along the (010) direction, in which each 5'-OH group functions as a hydrogen bond donor and acceptor from water molecules that are related by a 2_1 -screw axis symmetry (Fig. 5). These chains are packed along the (100) direction through two hydrogen bonds whose (salicylic acid)⁻ counterion has a dual role as a hydrogen bond acceptor. The same carboxylate oxygen hydrogen-bonded to the NH₂ hydrogen involved in the ionic pairing is also a hydrogen bond acceptor to the other amine hydrogen of a 2_1 -screw axis symmetry related lamivudine molecule (Fig. 6). Finally, the water molecule is also a hydrogen bond donor to the anions by means of a non-classical O-H... π interaction in which the π -system of the phenyl ring is an acceptor moiety. The occurrence of this interaction is supported by taking into account the relatively short separation between the water H2w hydrogen and the centroid, calculated through the phenyl carbons (CgB). The H2w...CgB distance is 2.98(6) Å.

In conclusion, lamivudine hydrogen phthalate and lamivudine salicylate monohydrate were prepared and their structures were elucidated and interpreted based on the crystal assembly and conformational analyses. Both salts differ from the hydrogen maleate and saccharinate versions of the drug, even though the lamivudine conformation in the salicylate salt monohydrate resembles those of the two antecedent phases. Such structural knowledge reported in this study may help to understand the solid state properties, such as the solubility and dissolution kinetics, related to the pharmaceutical performance, resulting in the progression of the solid state chemistry of the drug.

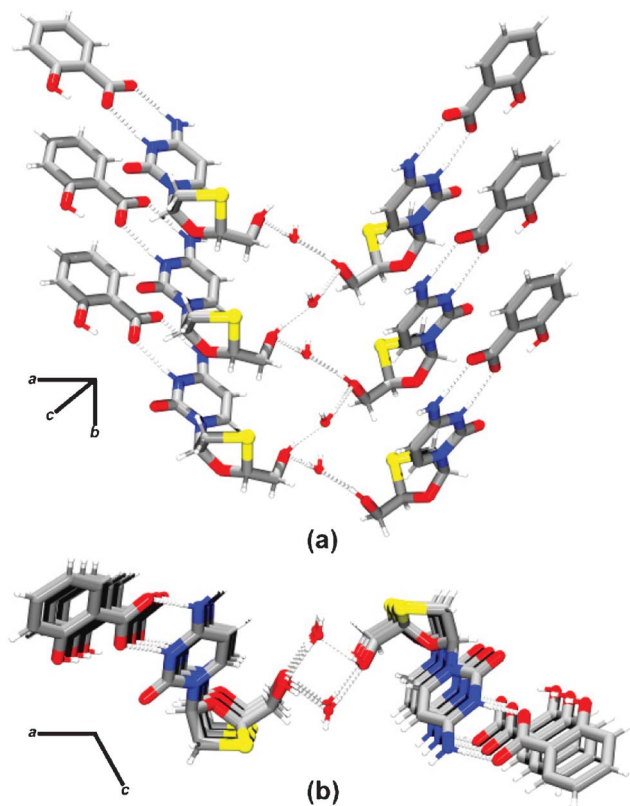


Fig. 5 (a) Lamivudine salicylate monohydrate is assembled as helical chains made up of O-H...O hydrogen bonds between the 5'-OH group and water. (b) Top view of the helical chain projected onto the (010) plane.

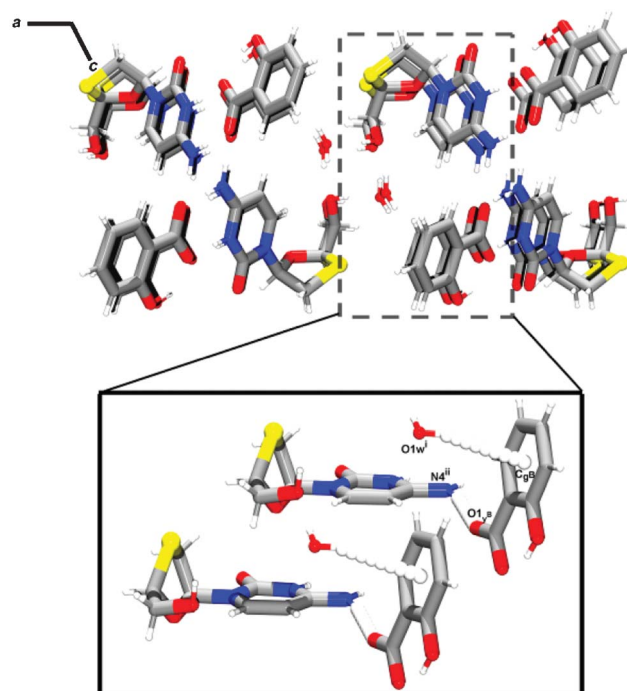


Fig. 6 The dual role of the salicylic acid counterions as cross-linkers between neighbouring helical chains in the lamivudine salicylate monohydrate. The two N-H...O and O-H... π hydrogen bonds involving each counterion as a cross-linker between the chains are shown on the bottom of the depiction. Symmetry codes: (i) = $x + 1, y - 1, z$, (ii) = $-x + 2, y - 0.5, -z$.

Acknowledgements

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References

‡ *Preparation.* For the crystallization batches of each salt, an amount of lamivudine form II (10 mg, 0.04 mmol), whose authenticity and purity were previously checked by single-crystal and powder X-ray diffraction techniques, was dissolved in isopropyl alcohol (5 mL) with stirring for 5 min in a water bath (308 K). This solution was then allowed to cool slowly to room temperature (298 K). Next, an equimolar quantity of the counterion (7 mg of either phthalic acid or salicylic acid) was then added to the newly cooled solution. The resulting mixture was shaken at room temperature until the salt was completely dissolved. This solution was allowed to evaporate slowly upon standing for 5 days at 298 K. Crystals as prisms (lamivudine hydrogen phthalate) or extremely thin needles (lamivudine salicylate monohydrate) were formed on the bottom of the corresponding glass crystallizers.

§ *Structure determination.* Well-grown single crystals of the salts measuring $0.251 \times 0.130 \times 0.078$ mm³ (lamivudine hydrogen phthalate) or $0.293 \times 0.076 \times 0.052$ mm³ (lamivudine salicylate monohydrate) were selected for X-ray diffraction data collection at room (298(2) K, lamivudine hydrogen phthalate) or low (107.4(2) K, lamivudine salicylate monohydrate) temperature. The X-ray diffraction data from lamivudine salicylate

monohydrate had a low intensity even at medium resolution due to the small dimensions of the crystal. For that reason, the X-ray diffraction experiment for this salt was carried out at a low temperature. For lamivudine hydrogen phthalate, a graphite-monochromated X-ray beam (Mo-K α radiation, $\lambda = 0.71073$ Å) was employed using a Kappa-CCD diffractometer with a FR590 generator. In the case of lamivudine salicylate monohydrate, X-ray diffraction data was measured on a Gemini A-Ultra diffractometer equipped with an Atlas CCD detector. Graphite-monochromated Cu-K α radiation ($\lambda = 1.54184$ Å) was used in this case and a multi-scan absorption correction was applied to the raw data set ($T_{\min} = 0.66774$, $T_{\max} = 1.00000$). The X-ray diffraction data was treated as follows: cell refinement and data reduction were treated with HKL Denzo-Scalepack¹⁶ and *CrysAlis PRO*¹⁷ software (there was no absorption correction for lamivudine hydrogen phthalate due to small absorption effects when using a Mo-K α beam), solving by direct methods of phase retrieval with SHELXS-97,¹⁸ refinement by full-matrix least squares on F^2 using SHELXL-97,¹⁸ constrained positions and fixed isotropic thermal parameters [$U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$] for C-H hydrogen atoms following the riding model, localization of N-H, N⁺-H and O-H hydrogen atoms from the difference Fourier map and free refinement of their positions with fixed isotropic thermal parameters [$U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{N})$ or $1.5U_{\text{eq}}(\text{O})$], structure analysis and preparation of the artwork using MERCURY¹⁹ and ORTEP-3.²⁰ *Crystal data for lamivudine hydrogen phthalate.* (C₈H₁₂N₃O₃S)(C₈H₅O₄), MW = 395.39, orthorhombic, $a = 5.3990(1)$ Å, $b = 15.7550(4)$ Å, $c = 20.6980(5)$ Å, $V = 1760.60(7)$ Å³, $T = 298(2)$ K, space group $P2_12_12_1$, $Z = 4$, $D_c = 1.492$ g cm⁻³, $\mu(\text{Mo-K}\alpha) = 0.23$ mm⁻¹, θ -range for data collection = 3.22–26.36, $-6 \leq h \leq 6$, $-19 \leq k \leq 19$, $-25 \leq l \leq 25$, 7211 reflections collected, 3530 unique ($R_{\text{int}} = 0.0360$), completeness to $\theta = 26.36$ of 98.4%, $F_{000} = 824$, 259 parameters refined, $S = 1.022$, $R_1(I > 2\sigma(I)) = 0.0387$, $wR_2(I > 2\sigma(I)) = 0.0958$, R_1 (all data) = 0.0566, wR_2 (all data) = 0.1042, largest diff. peak/hole = 0.135/−0.187 e Å⁻³, Flack parameter = 0.03(8) (1458 Friedel pairs). CCDC 871607. *Crystal data for lamivudine salicylate monohydrate.* (C₈H₁₂N₃O₃S)(C₇H₅O₃)(H₂O), MW = 385.40, monoclinic, $a = 12.7246(12)$ Å, $b = 5.2978(3)$ Å, $c = 13.1688(9)$ Å, $\beta = 106.129(8)^\circ$, $V = 852.80(11)$ Å³, $T = 107.4(2)$ K, space group $P2_1$, $Z = 2$, $D_c = 1.501$ g cm⁻³, $\mu(\text{Cu-K}\alpha) = 2.106$ mm⁻¹, θ -range for data collection = 3.49–66.01, $-15 \leq h \leq 14$, $-2 \leq k \leq 6$, $-15 \leq l \leq 15$ 5257 reflections collected, 2024 unique ($R_{\text{int}} = 0.0651$), completeness to $\theta = 66.01$ of 98.4%, $F_{000} = 404$, 256 parameters refined, $S = 1.064$, $R_1(I > 2\sigma(I)) = 0.0429$, $wR_2(I > 2\sigma(I)) = 0.0933$, R_1 (all data) = 0.0598, wR_2 (all data) = 0.1063, largest diff. peak/hole = 0.279/−0.370 e Å⁻³, Flack parameter = −0.01(3) (375 Friedel pairs). CCDC 871608

¶ For X-ray powder diffraction analysis, crystalline materials obtained from crystallization procedures were powdered and mounted onto a sample holder. Room temperature (298 K) X-ray powder diffractograms were acquired using an X-ray beam (Cu-K α radiation, $\lambda = 1.5418$ Å) generated at 40 kV and 30 mA on a Shimadzu XRD-6000 diffractometer. The diffractograms were acquired at room temperature under a continuous scan mode (scan axis θ - 2θ) with a scan speed of 1.000° min⁻¹. Intensity data was measured at each 0.020° in a 2θ range between 5° and 40°. Crystallographic information files of the structures for lamivudine hydrogen phthalate and lamivudine salicylate monohydrate were used to simulate the X-ray diffractograms with PowderCell software²¹ in order to compare them to the experimental set. It is important to emphasize that single crystal X-ray data of lamivudine salicylate monohydrate was measured at low temperature (107.4 K), while the experimental X-ray powder diffractogram of this salt was acquired at room temperature. Moreover, the comparison between the experimental and theoretical diffractograms from the single crystal structure has allowed us to assign the lamivudine salicylate monohydrate phase to the sample because corresponding simulated and observed Bragg peaks were in agreeing 2θ -positions, even with the temperature difference.

|| Orthorhombic cell parameters of lamivudine hydrogen maleate: $a = 5.4130(1)$ Å, $b = 12.7870(4)$ Å, $c = 21.6501(7)$ Å,⁸ and of lamivudine saccharinate: $a = 5.3464(6)$ Å, $b = 13.7459(14)$ Å, $c = 22.738(2)$ Å.⁷ Both structures were determined at a temperature of 100(2) K, while the X-ray data of lamivudine hydrogen phthalate was measured at room temperature (see crystal data for cell dimension comparisons).

- (a) J. A. V. Coates, N. Cammack, H. J. Jenkinson, I. M. Mutton, B. A. Pearson, R. Storer, J. M. Cameron and C. R. Penn, *Antimicrob. Agents Chemother.*, 1992, **36**, 202; (b) C. N. Chang, V. Skalskiv, J. H. Zhou and Y. C. Cheng, *J. Biol. Chem.*, 1992, **267**, 22414.
- A. Bhattacharya, B. N. Roy, G. P. Singh, D. Srivastava and A. K. Mukherjee, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 2010, **66**, o329.
- P. M. Bhatt, Y. Azim, T. S. Thakur and G. R. Desiraju, *Cryst. Growth Des.*, 2009, **9**, 951.
- F. T. Martins, A. C. Doriguetto and J. Ellena, *Cryst. Growth Des.*, 2010, **10**, 676.
- J. Ellena, N. Papparidis and F. T. Martins, *CrystEngComm*, 2012, **14**, 2373.
- R. K. Harris, R. R. Yeung, R. B. Lamont, R. W. Lancaster, S. M. Lynn and S. E. Staniforth, *J. Chem. Soc., Perkin Trans. 2*, 1997, 2653.
- R. Banerjee, P. M. Bhatt, N. V. Ravindra and G. R. Desiraju, *Cryst. Growth Des.*, 2005, **5**, 2299.
- F. T. Martins, N. Papparidis, A. C. Doriguetto and J. Ellena, *Cryst. Growth Des.*, 2009, **9**, 5283.
- (a) M. Khan, V. Enkelmann and G. Brunklaus, *J. Am. Chem. Soc.*, 2010, **132**, 5254; (b) J. Lu and S. Rohani, *Curr. Med. Chem.*, 2009, **16**, 884; (c) G. P. Stahly, *Cryst. Growth Des.*, 2007, **7**, 1007; (d) C. B. Aakeroy, M. E. Fasulo and J. Desper, *Mol. Pharmaceutics*, 2007, **4**, 317; (e) P. Vishweshwar, J. A. McMahon, J. Bis and M. J. Zaworotko, *J. Pharm. Sci.*, 2006, **95**, 499; (f) P. Vishweshwar, J. A. McMahon, M. L. Peterson, M. B. Hickey, T. R. Shattock and M. J. Zaworotko, *Chem. Commun.*, 2005, 4601; (g) O. Almarsson and M. J. Zaworotko, *Chem. Commun.*, 2004, 1889; (h) S. L. Monisette, O. Almarsson, M. L. Peterson, J. F. Remenar, M. J. Read, A. V. Lemmo, S. Ellis, M. J. Cima and C. R. Gardner, *Adv. Drug Delivery Rev.*, 2004, **56**, 275.
- C. L. Cooke and R. J. Davey, *Cryst. Growth Des.*, 2008, **8**, 3483.
- A. Kütt, I. Leito, I. Kaljurand, L. Sooväli, V. M. Vlasov, L. M. Yagupolskii and I. A. Koppel, *J. Org. Chem.*, 2006, **71**, 2829.
- L. G. Gagliardi, C. B. Castells and M. C. E. Bosch, *J. Chem. Eng. Data*, 2010, **55**, 85.
- M. Ukrainczyk, M. Gredicak, I. Jeric and D. Kralj, *J. Colloid Interface Sci.*, 2012, **365**, 296.
- C. S. Shah, S. D. Sorathia, V. K. Agarwal, V. S. R. Nirogi, K. Pandita, P. R. Patel, S. D. Sorathia, N. V. S. Ramakrishna, *WO 2003027106*, 2003.
- J. Lee, G. S. Lee, M. S. Lee, J. S. Kim, C. Kim, J. Yoo, Y. Moon, S. H. Cho, E. J. Lim, Y. Chang, *KR 840495*, 2009.
- Z. Otwinowski and W. Minor, in *Methods in Enzymology: Macromolecular Crystallography*; ed. C. W. Carter Jr. and R. M. Sweet, Academic Press, New York, 1997, Part a **Vol. 276**, pp 307–326.
- CrysAlis CCD, CrysAlis RED and associated programs*; Oxford Diffraction, Abingdon, England, 2006.
- G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2008, **64**, 112.
- C. F. Macrae, I. J. Bruno, J. A. Chisholm, P. R. Edgington, P. McCabe, E. Pidcock, L. R. Monge, R. Taylor, J. van de Streek and P. A. Wood, *J. Appl. Crystallogr.*, 2008, **41**, 466.
- L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.
- W. Kraus, G. Nolze, *PowderCell for Windows, version 2.3.*, Federal Institute for Materials Research and Testing, Berlin, Germany, 1999.