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New Look at Naltrexone Hydrochloride Hydrates: Understanding Phase Behavior and Characterization of Two Dihydrate Polymorphs

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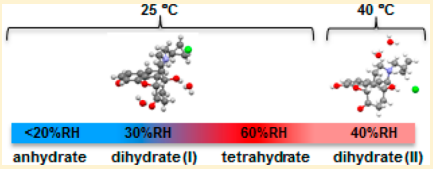
Supporting Information

ABSTRACT: The phase behavior and characterization of two forms of naltrexone hydrochloride dihydrate are presented. A metastable form was isolated first in the solid state under kinetically controlled conditions, namely dehydration of a higher hydrate followed by exposure to ∼38% relative humidity. The second, more thermodynamically stable polymorph was isolated from an aqueous slurry at an elevated temperature. The phase transition boundaries between naltrexone hydrochloride anhydrate and the metastable hydrate species are established through a combination of slurry and moisture sorption experiments to provide a detailed mechanistic understanding of the hydration/dehydration behavior.



INTRODUCTION

Pharmaceutical drug development programs place heavy emphasis on active pharmaceutical ingredient (API) form selection, which can have a profound impact on both the drug substance and drug product when the active ingredient is in contact with excipients.[1] It is estimated that one-third of pharmaceutically active substances are capable of forming crystalline hydrates.[2] During formulation and processing, small changes in seasonal and/or environmental conditions can drastically affect the hydration/dehydration behavior of a crystalline solid. The risks associated with uncontrolled hydration or polymorphic transformations include variations in physicochemical properties,[3] such as solubility,[4] stability,[5] dissolution rate, and bioavailability.[6] It is now common for new chemical entities to undergo solid form screening while in early stages of drug development in order to interrogate and understand the molecule's propensity for form diversity, if any.[7,8] Importantly, case studies, which continue to emerge in the literature on new forms of old compounds, signal the need for continuous understanding and evaluation of solid-state chemistry and an even greater emphasis on examining molecular interactions between API and excipients.[9,10] Simply put, consideration of form does not end with form screening; it merely begins the pursuit of developing products that consistently meet the critical quality attributes of the intended dosage form.

Naltrexone, Figure 1, is an opioid receptor antagonist and has been shown to be effective in the treatment of alcohol and opioid dependence.[11,12] Form diversity of naltrexone has been extensively studied with several reported forms, including salts, solvates, and a monohydrates.[13,14] Oral naltrexone is marketed in a generic form as the hydrochloride (HCl) salt and has also been widely studied. Naltrexone HCl readily forms solvates, but only one hydrate crystal structure is described in the Cambridge Structural Database.[15] Guguta[16] and co-workers report that, at elevated relative humidity, naltrexone hydrochloride anhydrate proceeds through an unspecified hydrate to then provide a stable tetrahydrate. In the present study, we elucidate the structure of the previously unspecified hydrate and report the discovery of a new polymorphic form of that hydrate.

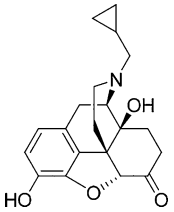


Figure 1. Chemical structure of naltrexone.

EXPERIMENTAL SECTION

Materials. Naltrexone hydrochloride anhydrate was obtained from Cilag. The preparation procedures for the hydrate/anhydrate forms are described below. The new polymorphs were studied and characterized by powder X-ray diffraction (PXRD), dynamic vapor sorption (DVS), differential scanning calorimeter (DSC), and thermogravimetric analysis (TGA).

Preparation of Naltrexone Hydrochloride Tetrahydrate. The tetrahydrate was prepared by slurry at room temperature from an aqueous solution containing excess naltrexone hydrochloride anhydrate. The slurry was stirred with a magnetic stir bar for 24 h before it was filtered to then provide a filter cake of naltrexone tetrahydrate.

Preparation of Naltrexone Hydrochloride Anhydrate. The anhydrate was obtained by dehydrating naltrexone hydrochloride tetrahydrate crystals over desiccant (calcium sulfate) in a sealed chamber under vacuum for 24 h. The anhydrous crystal form was characterized by DSC and PXRD.

Preparation of Naltrexone Hydrochloride Dihydrate Form I. Crystalline naltrexone hydrochloride anhydrate was equilibrated for

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Table 1. Unit-Cell Parameters of Hydrates

	naltrexone hydrochloride anhydrate[a]	naltrexone hydrochloride dihydrate I	naltrexone hydrochloride dihydrate II	naltrexone hydrochloride tetrahydrate[a]
crystal system	orthorhombic	orthorhombic	orthorhombic	orthorhombic
space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a (Å)	7.8420(2)	7.8621(3)	8.1599(3)	7.768(1)
b (Å)	14.9942(4)	15.1732(6)	13.4040(4)	15.926(6)
c (Å)	15.5338(4)	48.8188(14)	18.1530(6)	18.099(5)
V (Å^3)	1826.53	5823.8(4)	1985.49(11)	2239.08

[a]Unit cell data from ref 12; cells in the two cases are transformed to the conventional setting of $a < b < c$.

24 h in a 33% RH salt chamber (saturated aqueous magnesium chloride solution). The naltrexone hydrochloride was removed from the salt chamber after equilibration and provided dihydrate form I crystals, as characterized by DSC and PXRD.

Preparation of Naltrexone Hydrochloride Dihydrate Form II. Naltrexone dihydrate form II was prepared by slurry at 90 °C from an aqueous saturated naltrexone hydrochloride solution. The slurry was stirred with a magnetic stir bar for 24 h, whereupon it was filtered to then provide a filter cake of naltrexone dihydrate form II. The dihydrate form II crystals were confirmed by DSC, TGA, PXRD, and single crystal X-ray diffraction.

Conditions To Provide X-ray Crystals of Naltrexone Hydrochloride Dihydrate Form I from Naltrexone Hydrochloride Tetrahydrate. X-ray quality crystals of dihydrate form I could not be grown directly from solution. The dihydrate form I crystals were obtained by dehydrating X-ray quality tetrahydrate crystals over calcium sulfate desiccant in a sealed chamber for 24 h. The crystals were then hydrated to the dihydrate form I at 33% RH in a saturated aqueous magnesium chloride salt chamber (as described previously) for 24 h. The dihydrate form I crystals were then characterized by DSC, TGA, PXRD, and single crystal X-ray diffraction. Naltrexone tetrahydrate crystals were grown from a distilled water solution containing naltrexone anhydrate (50 mg of naltrexone to 1 mL of H_2O). The naltrexone solution was filtered through a 0.45 μm filter, and the filtrate was left in a sealed vial for one month. Large needle-shaped crystals of the tetrahydrate were obtained.

Analytical Methodology. *Single Crystal X-ray Diffraction.* All operations were performed on a Bruker-Nonius Kappa Apex2 diffractometer, using graphite-monochromated Mo Kα radiation. All diffractometer manipulations, including data collection, integration, scaling, and absorption corrections, were carried out using the Bruker Apex2 software.[17]

Powder X-ray Diffraction (PXRD). Powder X-ray diffraction patterns of naltrexone hydrochloride anhydrate, dihydrate polymorphs, and tetrahydrate were performed using a Rigaku Miniflex II Desktop X-ray diffractometer, with Cu Kα radiation at 15 mA and 30 kV. Each sample was mounted on a zero background sample holder. A scan speed of 7.5°/min 2θ was chosen, coupled with a sampling width of 0.2° 2θ and a start and stop angle of 2° and 40° 2θ.

DVS Analysis. DVS studies were performed with a DVS TA Instruments Q5000 SA. Experiments were conducted at a constant temperature setting of either 25 or 40 °C. Approximately 20 mg of naltrexone hydrochloride sample was used in each experiment. Samples were equilibrated at 0% RH for 3 h prior to starting any sorption studies, unless otherwise noted. Typical DVS testing parameters included an absorption/desorption cycle repeated twice. Each cycle began at 0% RH with an absorption cycle up to 90% RH, and a 10% RH step change. The mass change over time setting for each step was set to a mass constancy of ±0.002% over 30 min. Phase changes were characterized directly by PXRD.

To determine the precise %RH at which phase changes occurred, additional DVS studies were conducted at a 1% RH step change. The specific RH ranges of interest included 20−30% RH and 50−60% RH. Studies were conducted at 25 °C with approximately 20 mg of naltrexone, and the samples were equilibrated at 0% RH for 3 h prior to starting any sorption study. The equilibrium conditions for each step were set to a mass constancy of ±0.002% over 30 min. Phase changes were characterized directly by PXRD.

Differential Scanning Calorimetry (DSC). Differential scanning calorimetry was performed with a TA Instruments Q2000 DSC. Approximately 3−6 mg of sample was accurately weighed into hermetic pans. Dry nitrogen was used as a purge gas (50 mL/min nitrogen), and a heating rate of 1 or 5 °C min^{-1} to 270 °C was applied.

Thermogravimetric Analysis (TGA). Thermogravimetric analysis curves were generated using a TA Instruments Q500 TGA. The instrument was temperature calibrated with an indium standard. A weight calibration was performed using standard weights under a nitrogen purge. Approximately 5−15 mg of sample was weighed into a platinum pan. A heating rate of 1 °C min^{-1} to 300 °C was applied, and dry nitrogen was used as a purge gas (sample purge: 25 mL min^{-1}, balance purge: 10 mL min^{-1}).

Microscopy. Polarized light micrographs were taken with a Carl Zeiss AXIO Scope A1 polarized light microscope. Approximately 1 mg of naltrexone hydrochloride sample was loaded into a GenRH-Mcell humidity chamber combined with a GenRH-Ambient relative humidity generator. Each absorption cycle starts at 0% RH with an absorption cycle up to 90% RH and a 10% RH step change. The humidity airflow rate was set between 100 and 200 mL/min.

RESULTS AND DISCUSSION

Naltrexone Hydrochloride Dihydrate Form I. Initial examination of the putative metastable dihydrate crystals revealed that most were of very poor quality. X-ray quality crystals of dihydrate form I could not be grown directly from solution. A series of solid-state transformations carried out on X-ray quality single crystals of naltrexone hydrochloride tetrahydrate was necessary to afford the metastable dihydrate. The initial unit cell determinations on several samples suggested an approximately tripled orthorhombic unit cell of dimensions ≈ 7.9 × 15.2 × 48.9 Å, with a volume of ca. 5800 Å^3, and 12 molecules per unit cell (Z' = 3), as shown in Tables 1 and 2. All determinations gave similar results for cell constants, and after an exhaustive search of over a dozen samples, a plausible candidate was selected for data collection. Preliminary cell constants were obtained from three sets of 12 frames. Data collection was carried out at 120 K, using a frame time of 30 s and a detector distance of 70 mm. The optimized strategy used for data collection consisted of two φ and five ω scan sets, with 0.5° steps in φ or ω; completeness was 99.7%. A total of 1322 frames were collected. Final cell constants were obtained from the *xyz*-centroids of 5521 reflections after integration; final redundancy was 5.9.

From the systematic absences, the observed metric constants, and intensity statistics, space group $P2_12_12_1$ was chosen initially; subsequent solution and refinement confirmed the correctness of this choice. The structure was solved using SIR-2011,[18] and the remaining atoms were located on electron density difference maps. The structure was refined (full-matrix-least-squares) using the Oxford University Crystals for Windows program.[19,20] The asymmetric unit contains three molecules of naltrexone

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Table 2. Additional Crystallographic Data for Forms I and II

compound	form I	form II
chemical formula	$C_{20}H_{28}NO_6Cl$	$C_{20}H_{28}NO_6Cl$
a, Å	7.8621(3)	8.1599(3)
b, Å	15.1732(6)	13.4040(4)
c, Å	48.8188(14)	18.1530(6)
V, Å^3	5823.8(4)	1985.49(11)
Z, *Z*′	12, 3	4, 1
formula wt. g/mol	413.90	413.90
space group	$P2_12_12_1$	$P2_12_12_1$
T, K	120(1)	120(1)
λ, Å	0.71073	0.71073
ρ_{calc}, g cm^{-3}	1.416	1.385
μ, mm^{-1}	0.235	0.230
θ_{max}; transmission factors	30.00°; 0.84−0.85	28.90°; 0.45−0.46
R^a	0.0868	0.0262
$R_w{}^b$	0.1731	0.0671
S^c	1.056	0.989
no. reflections (all; $I > 2\sigma(I)$)	9529, 11812	5399, 5784
no. parameters	822	275

hydrochloride and six water molecules (for the hydrochloride, $Z = 12$; $Z' = 3$). The second and third molecules are numbered similarly to the first, with atom sequence numbers of exactly 100 and 200, respectively, greater than those of the reference molecule. All non-hydrogen atoms were refined using anisotropic displacement parameters. After the H atoms on electron-density difference maps were located, the H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C−H in the range of 0.93−0.98 Å and U_{iso} (H) in the range 1.2−1.5 times U_{eq} of the parent atom), after which, the positions were refined with riding constraints.[21] All but three of the acidic H atoms were located on electron-density difference maps using a low-angle cutoff to help enhance the contributions of H atoms to the electron density. Acidic protons were refined using isotropic displacement parameters.

The crystallographic data confirm the observation made previously by Guguta[12] and co-workers during their solid-state NMR studies; the kinetic metastable dihydrate is not a mixture of hydrates, and the three distinct carbon signals observed by NMR arise from the presence of three independent molecules in the asymmetric unit (Figure 2). Figure 3 shows a view projected

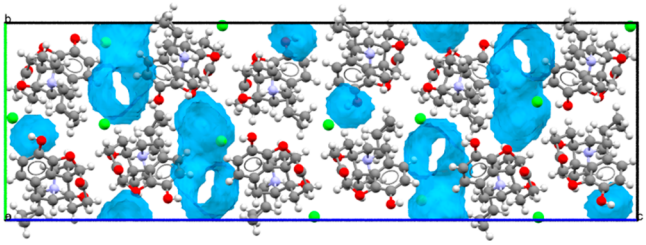

Figure 2. Packing and hydration voids of naltrexone hydrochloride dihydrate form I viewed down the *a*-axis.

down the crystallographic *a*-axis of the modulation/pseudo-symmetry among the three independent molecules, arranged along the long *c*-axis. The labeled 1-series and 100-series molecules are related by an approximate pseudotranslation of ≈ (0.14, −0.02, 0.35), while the 1-series and 200-series molecules are related by a pseudo-2-fold-screw rotation/translation along the *a*-axis of ≈ (*x*, 0.52, 0.18)/(0.33, 0, 0).

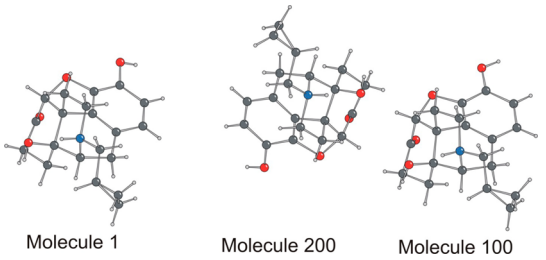

Figure 3. Cutaway view of the asymmetric unit of naltrexone hydrochloride dihydrate form I ($Z' = 3$) viewed down the *a*-axis, showing the modulation and pseudosymmetry present in the asymmetric unit.

The known absolute structure was confirmed using Flack parameter refinement ($x = 0.05(9)$).[22] Post-refinement analysis revealed consistent answers to the latter value, with a Hooft parameter of −0.02(3) and a Parsons difference parameter of 0.01(3).[23−26] The final least-squares refinement converged to $R_1 = 0.0868$ ($I > 2\sigma(I)$, 9529 data) and $wR_2 = 0.1731$ (F^2, 11812 data, 822 parameters). Restraints were used for a few C atom ADPs and also in the refinement of acidic H atoms; details are available in the CIF file, which is available as the Supporting Information.

Naltrexone Hydrochloride Dihydrate Form II. Large crystals of dihydrate form II were grown directly from a 70 °C saturated aqueous solution of naltrexone hydrochloride. Preliminary cell constants were obtained from three sets of 12 frames. Data collection was carried out at 120 K, using a frame time of 10 s and a detector distance of 60 mm. The optimized strategy used for data collection consisted of three *φ* and four *ω* scan sets, with 0.5° steps in *φ* or *ω*; completeness was 99.9%. A total of 2081 frames were collected. Final cell constants were obtained from the *xyz*-centroids of 9938 reflections after integration; final redundancy was 9.6. The crystal faces observed were ± (101), ± (100), ± (1 0−1), ± (010), and ± (001).

From the systematic absences, the observed metric constants, and intensity statistics, space group $P2_12_12_1$ was chosen initially; subsequent solution and refinement confirmed the correctness of this choice. The structure was solved using SIR-92.[18] The structure was refined (full-matrix-least-squares) using the Oxford University Crystals for Windows program.[15] The asymmetric unit contains one molecule of naltrexone hydrochloride and two water molecules (for the hydrochloride, $Z = 4$; $Z' = 1$). All non-hydrogen atoms were refined using anisotropic displacement parameters. After the H atoms on electron-density difference maps were located, the H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C−H in the range of 0.93−0.98 Å and U_{iso} (H) in the range of 1.2−1.5 times U_{eq} of the parent atom), after which, the positions were refined with riding constraints.[17] Acidic protons were refined using isotropic displacement parameters. The known absolute structure was confirmed using Flack parameter refinement ($x = 0.00(3)$).[18] Post-refinement analysis revealed consistent answers to the latter value, with a Hooft parameter of 0.024(14) and a Parsons difference parameter of 0.026(14).[19−22] The final least-squares refinement converged to $R_1 = 0.0262$ ($I > 2\sigma(I)$, 5399 data) and $wR_2 = 0.0671$ (F^2, 5784 data, 275 parameters). The final CIF file is available as Supporting Information.

The crystal structure of the form II dihydrate, including the hydration voids, is shown in Figure 4. Structural analyses of the hydrate voids were performed using a development version of

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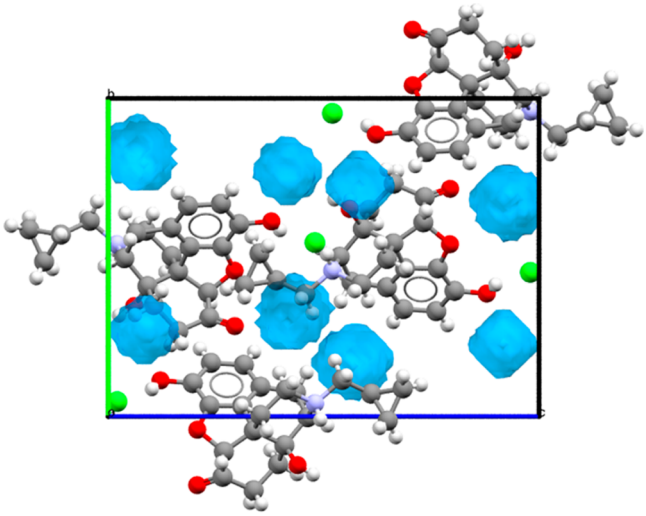

Figure 4. Packing and hydration voids of naltrexone hydrochloride dihydrate form II viewed down the *a*-axis.

Mercury 3.6.[27] The crystal packing diagrams of naltrexone form II dihydrate and that of the known naloxone hydrochloride dihydrate[28−30] are remarkably similar (Figure S4). Considering Megaw's precise and pertinent definition of strict isomorphism,[31] the two structures are indeed strictly isomorphous with the coordinates being nearly identical, except for the three-atom difference in the structure, as shown in Figure 5.

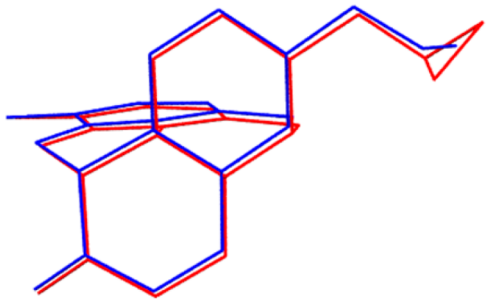

Figure 5. Structural overlay of naltrexone dihydrate form II (red) and naloxone dihydrate (blue).

The overlay in Figure 5 highlights the single terminal atom of the vinyl group in naloxone hydrochloride dihydrate in relationship to the two final atoms of the cyclopropyl group in naltrexone hydrochloride dihydrate form II.

Powder X-ray Diffraction (PXRD). Since it was difficult to grow X-ray quality single crystals of naltrexone hydrochloride dihydrate form I in the early stages of this work, PXRD was employed to provide preliminary and definitive conformation of the phase identity. Samples of naltrexone hydrochloride anhydrate were placed in a humidity chamber containing a specific salt solution known to provide a well-defined humidity. After the naltrexone hydrochloride at 35% RH[32] was equilibrated for 48 h, a PXRD pattern was then collected, and a complete conversion of naltrexone anhydrate to the dihydrate form I was observed. The naltrexone dihydrate form I PXRD pattern contains sharp peaks observed between 7.8−12.7 2θ and is offset from the anhydrate pattern (Figure 6). Slurry conversion experiments led to the discovery of dihydrate form II. Naltrexone hydrochloride dihydrate form II was precipitated from a hot slurry of aqueous naltrexone hydrochloride, and the powder was characterized by PXRD. Above 58 °C in an aqueous slurry, the thermodynamically preferred naltrexone hydrochloride form is dihydrate II. The PXRD pattern of dihydrate form II has a distinctive overlapping peak with form I at 11.8 2θ followed by two characteristic broad peaks at ∼13.0 2θ.

Naltrexone Hydrochloride Phase Boundaries. The kinetic hydration/dehydration behavior of naltrexone hydrochloride was elucidated by DVS. Storage of naltrexone hydrochloride anhydrate in a desiccator under vacuum, followed by a 3 h drying cycle in the DVS chamber, ensured that bulk surface water was removed, and that a constant weight could be achieved. The anhydrate was investigated across a range of moisture conditions from 0% RH to 90% RH with a 10% RH step rate at 25 °C. Two separate phase equilbria were observed in the kinetic DVS plot (Figure 7). The first phase boundary near 30% RH is the transformation of the anhydrate to dihydrate form I. A mass % change from anhydrate to dihydrate form I was recorded (+8.8%) for the single transition. The second phase boundary is observed near 60% RH and is the transformation of dihydrate form I to the tetrahydrate. A mass % change from the anhydrate to the tetrahydrate was recorded (+18.8%) for the two steps. The stoichiometric ratio of water to naltrexone for each hydrate was then calculated (1.8 at or near 30% RH and 3.9 at or near 60% RH), where weight gain and molecular weight are WG and MW (Figure 8). Separately, a narrow RH range (20−30% and 50−60%) in DVS was selected to define the phase transition boundaries of naltrexone dihydrate form I and tetrahydrate. The RH step change was set to 1% RH to better define the key phase transitions. At 1% RH step change, the phase transition for the dihydrate form I and tetrahydrate are observed at

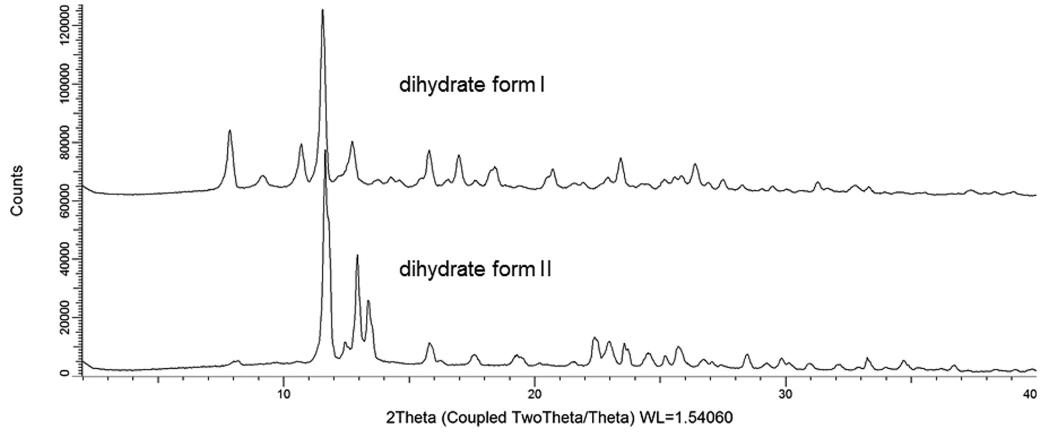

Figure 6. X-ray powder diffraction of naltrexone hydrochloride dihydrate form I and form II.

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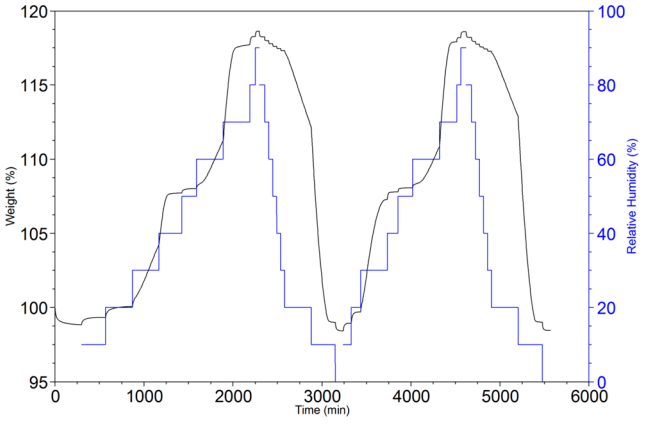


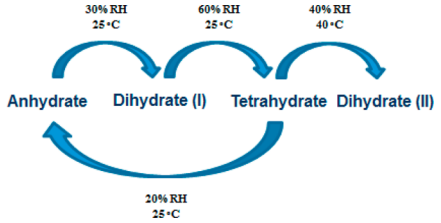
Figure 7. DVS data for naltrexone hydrochloride anhydrate at 25 °C.

$$n\mathrm{H_2O} = \frac{\mathrm{WG}}{100} + \frac{MW}{18.02}$$

Figure 8. Water stoichiometry formula.

28% RH and 58% RH, respectively (see the SI). Dehydration of the tetrahydrate proceeds directly to the anhydrate, apparently without going through dihydrate form I, as shown in Scheme 1.

Scheme 1. Environmental Conditions where Solid State Hydration and Dehydration of Naltrexone HCl Occur



The hysteresis between the sorption/desorption isotherms clearly shows that the solid-state crystal hydration occurs via a two-step process, followed by a one-step dehydration (see the SI).

A second DVS study, conducted at 40 °C, led to the discovery of a new phase transition not previously seen at 25 °C and the characterization of naltrexone HCl dihydrate form II. The range of moisture conditions considered included 0−90% RH with a 10% RH step size. The dihydrate form II phase transition is observed during the desorption cycle at 30% RH and is followed by a rapid dehydration (Figure 9). A second sorption/desorption cycle clearly shows that dihydrate form II does not proceed to the tetrahydrate, and the mass % change from anhydrate to dihydrate form II is +9.5% or 2.2 waters per naltrexone.

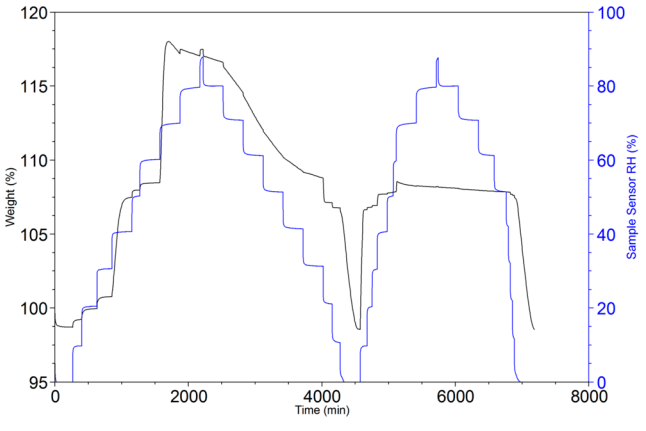


Figure 9. DVS data for naltrexone hydrochloride anhydrate at 40 °C.

Slurry conversion experiments were performed in an effort to measure the thermodynamic critical water activities of naltrexone hydrochloride hydrates. Water activity was controlled in ten different solvents across a range of water/solvent ratios. However, all of the solvents considered formed solvate complexes with naltrexone HCl, thus halting identification of the critical water activities (see the SI).

Determination of form stability was investigated through a series of temperature-dependent aqueous slurry experiments. Slurrying of naltrexone tetrahydrate at 58 °C leads to dihydrate form II, as confirmed by PXRD. Further heating of the slurry up to 100 °C revealed no further phase transitions. The results indicate that the higher energy forms of naltrexone are dihydrate form I and the anhydrous form. Slurry bridging experiments between the two dihydrate polymorphs were then carried out to rank order the thermodynamic stability. When the two polymorphs are seeded into a hot slurry across a range of temperatures, dihydrate form II is formed exclusively. The kinetic and thermodynamic stability data both point to a metastable dihydrate form I and a thermodynamically stable dihydrate form II.

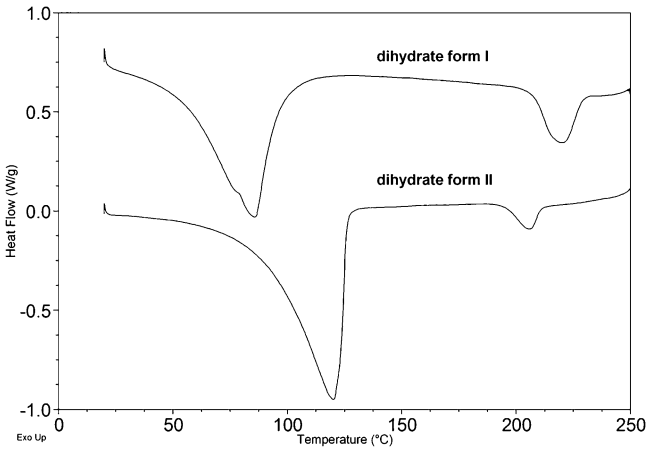


Figure 10. DSC thermogram at 5 °C/min of naltrexone dihydrate form I and form II.

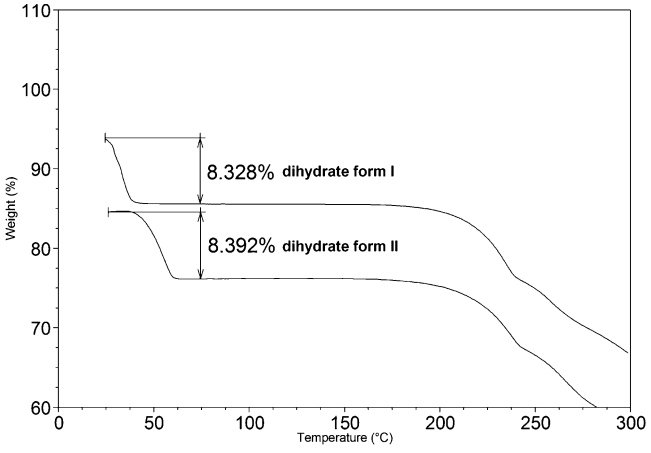


Figure 11. TGA thermogram at 1 °C/min of naltrexone dihydrate form I and form II.

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Differential Scanning Calorimetry (DSC). The thermal behavior of naltrexone hydrochloride dihydrate polymorphs is shown in Figure 10. The comparison of DSC curves for each polymorph shows a single dehydration endotherm due to solvent loss and formation of the anhydrate between 20−120 °C. The loss of water and the formation of the anhydrate are followed by a naltrexone anhydrate melt onset at ∼203 with decomposition.

Thermal Gravimeteric Analysis (TGA). Dehydration and water loss by weight for naltrexone dihydrate polymorphs were characterized by TGA. The metastable dihydrate form I is characterized by continuous mass loss upon heating (25−42 °C) with a total mass loss of 8.3% (Figure 11). Dehydration of the thermodynamically preferred dihydrate form II does not occur until 38 °C, with a total mass loss of 8.4%. A comparison of the total mass loss by TGA to weight % gain by DVS provides similar values and is consistent with the theoretically calculated 8.5% weight water loss for the dihydrate.

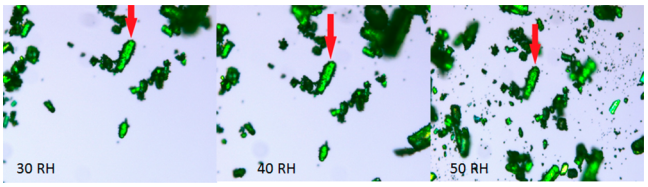

Figure 12. Humidity stage polarizing microscopy images.

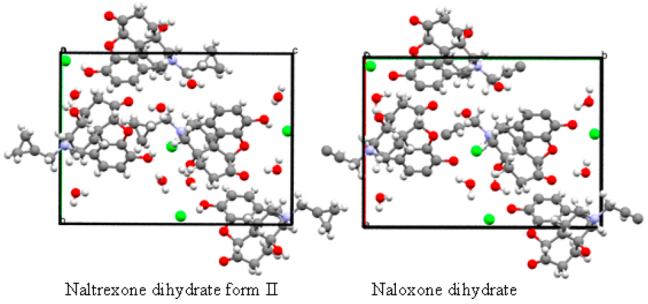

Figure 13. Comparison of naltrexone and naloxone crystal packing.

Polarized Light Microscopy. Solid-state form changes were carried out in a humidity-controlled cell and observed by polarized light microscopy. Naltrexone HCl anhydrate crystals were placed in a humidity cell at 0% RH, which was then slowly increased to 90% RH. As previously described, the solid-state phase transitions of naltrexone HCl occur at 28% RH (dihydrate form I) and 58% RH (tetrahydrate). At no point during the humidity-driven form change could microcrystalline domain growth be seen, nor was a loss in crystal transparency observed (Figure 12). It should be noted that crystal-to-crystal transitions characteristically retain crystal shape and transparency throughout form changes, and that directly monitoring structural changes of naltrexone hydrochloride hydration/dehydration should be possible by variable-humidity X-ray diffraction.

CONCLUSION

A hydration/dehydration scheme showing the allowed phase transitions and conditions for all known naltrexone hydrochloride hydrates has been shown. Naltrexone HCl is known to form solvates (or hydrates if water is the solvent) readily, owing to its characteristic structure.[16] The persistent T-shape contributes to defined lattice voids and is responsible for the stoichiometric solvate formation. Hydration voids in the crystal lattice of the naltrexone HCl dihydrate form I and dihydrate form II vary greatly and most likely contribute to their varied kinetic

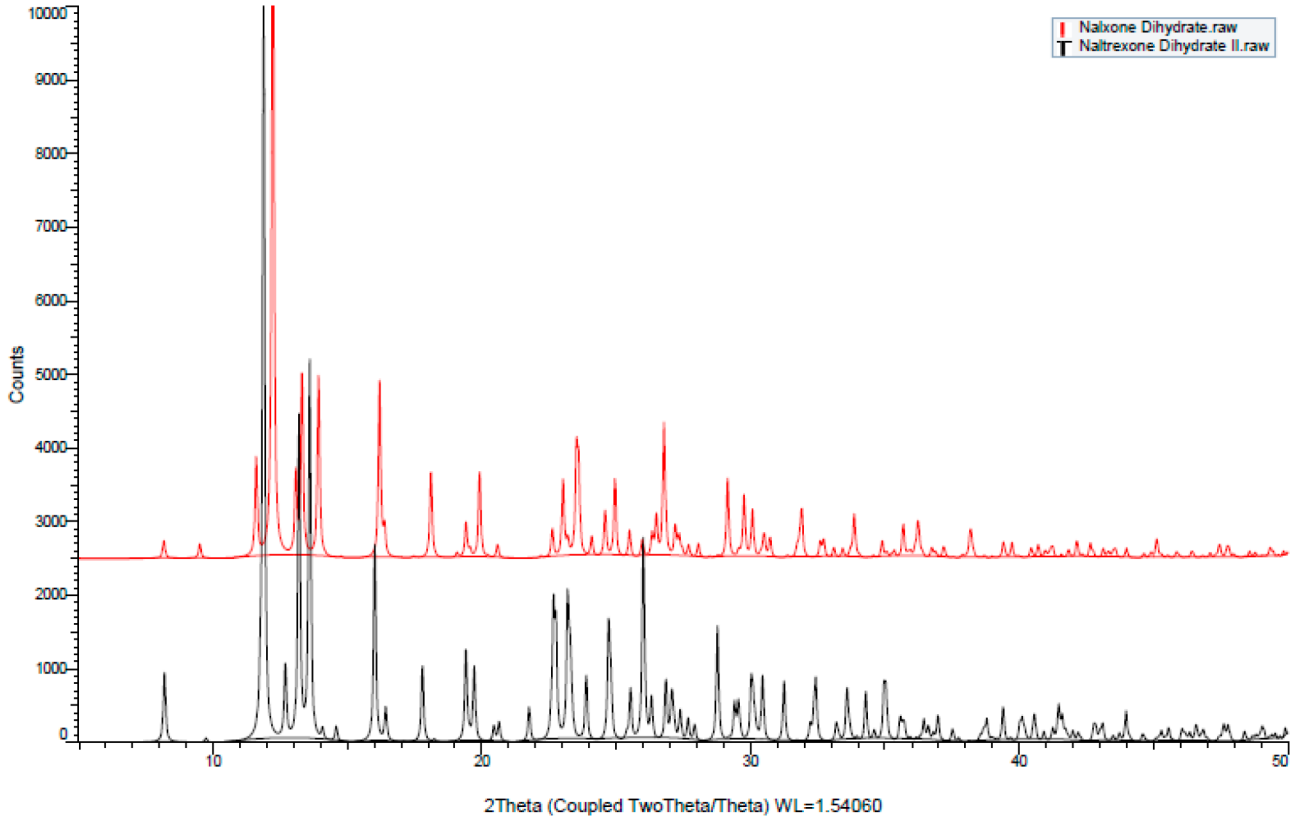

Figure 14. Calculated X-ray powder diffraction patterns of naltrexone hydrochloride dihydrate form II and naloxone hydrochloride dihydrate.

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sorption profiles and the thermodynamic stability of form II (Figures 2 and 4). We have shown that the asymmetric unit of dihydrate form I contains three independent molecules of naltrexone ($Z' = 3$), while the asymmetric unit of dihydrate form II contains only one independent molecule of naltrexone ($Z' = 1$). The humidity stage microscopic analysis of the crystal hydration pathways points to crystal-to-crystal transitions, which are now being investigated further. Finally, the observation that one of the dihydrates of naltrexone HCl and naloxone HCl is isomorphous is noteworthy (Figures 13 and 14). We are actively studying the crystal-to-crystal transitions of several naloxone and naltrexone forms and solvates and hope to report on these findings in the future. The message is clear and highlights that form exploration is not isolated to the single active molecule present in a drug class, but it is predicated upon an understanding of available crystallographic data and the curiosity to exploit more fully the chemical diversity within a class of chemically related compounds. In the case of naltrexone HCl, this work confirms that the most suitable form for development as an oral product remains the anhydrous form, and that minor changes in moisture sorption over time would not impact the performance attributes of the drug.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.8b00262.

Experimental conditions to generate hydrates accompanied by physicochemical data and crystallographic data (PDF)

Accession Codes

CCDC 1823323−1823324 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; Fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

API, active pharmaceutical ingredient; LAI, long acting injectable; XRPD, X-ray powder diffraction; DVS, dynamic vapor sorption; DSC, differential scanning calorimeter; TGA, thermogravimetric analysis

■ REFERENCES

(1) Ticehurst, M. D.; Marziano, I. Integration of Active Pharmaceutical Ingredient Solid Form Selection and Particle Engineering into Drug Product Design. *J. Pharm. Pharmacol.* **2015**, *67*, 782−802.

(2) Vippagunta, S. R.; Brittain, H. G.; Grant, D. J. W. Crystalline Solids. *Adv. Drug Delivery Rev.* **2001**, *48*, 3−26.

(3) Ohannesian, L.; Streeter, A. Form Selection of Pharmaceutical Compounds. In *Handbook of Pharmaceutical Analysis*; Newman, A. W., Stahly, G. P, Eds.; Marcel Dekker: New York, 2001; Chapter 1, pp 1−57.

(4) Pudipeddi, M.; Serajuddin, A. T. Trends in Solubility of Polymorphs. *J. Pharm. Sci.* **2005**, *94*, 929−39.

(5) Yu, L.; Stephenson, G. A.; Mitchell, C. A.; Bunnell, C. A.; Snorek, S. V.; Bowyer, J. J.; Borchardt, T. B.; Stowell, J. G.; Byrn, S. R. Thermochemistry and Conformational Polymorphism of a Hexamorphic Crystal System. *J. Am. Chem. Soc.* **2000**, *122*, 585−591.

(6) Byrn, S. R; Pfeiffer, R. R; Stowell, J. G. *Solid-State Chemistry of Drugs*; SSCI: West Lafayette, IN, 1999; pp 91−101.

(7) Almarsson, O.; Hickey, M. B.; Peterson, M. L.; Morissette, S. L.; Soukasene, S.; McNulty, C.; Tawa, M.; MacPhee, J. M.; Remenar, J. F. High-Throughput Surveys of Crystal Form Diversity of Highly Polymorphic Pharmaceutical Compounds. *Cryst. Growth Des.* **2003**, *3*, 927−933.

(8) Aaltonen, J.; Alleso, M.; Mirza, S.; Koradia, V.; Gordon, C. K.; Rantanen, J. Solid Form Screening - a review. *Eur. J. Pharm. Biopharm.* **2009**, *71*, 23−37.

(9) Surwase, A. S.; Boetker, P. J.; Saville, D.; Boyd, J. B.; Gordon, C. K.; Peltonen, L.; Strachan, J. C. Indomethacin: New Polymorphs of an Old Drug. *Mol. Pharmaceutics* **2013**, *10*, 4472−4480.

(10) Domingos, S.; Andre, V.; Quaresma, S.; Minas da Piedade, M. F.; Duarte, M. T.; Martins, I. C. B. New Forms of Old Drugs: Improving Without Changing. *J. Pharm. Pharmacol.* **2015**, *67*, 830−846.

(11) Ginzburg, H. M.; Glass, W. J. The Role of the National Institute on Drug Abuse in the Development of Naltrexone. *J. Clin. Psychiatry.* **1984**, *45*, 4−6.

(12) Saxson, A. J. Treatment of Opiod Dependence. In *Research and Development of Opioid-Related Ligand*; Ko, M., Husbands, S. M., Eds.; ACS Symposium Series; American Chemical Society: Washington, DC, 2013; Vol. *1131*, pp 61−102.

(13) Scheins, S.; Messerschmidt, M.; Morgenroth, W.; Paulmann, C.; Luger, P. Electron Density Analyses of Opioids: A Comparative Study. *J. Phys. Chem. A* **2007**, *111*, 5499.

(14) Brittain, H.; Dickason, D.; Hotz, J.; Lyons, S.; Ramstack, J.; Wright, S. Polymorphic Forms of Naltrexone. U.S. Patent US20060142320A1, June 29, 2004.

(15) Le Dain, C. A.; Madsen, W. B.; Skelton, W. B.; White, H. A. Crystal-Structure of Naltrexone Hydrochloride: Implications for Location of the Nicotinic Receptor Noncompetitive Inhibitor Binding Site. *Aust. J. Chem.* **1992**, *45*, 635.

(16) Guguta, C.; van Eck, E. R. H.; de Gelder, R. Structural Insight into the Dehydration and Hydration Behavior of Naltrexone and Naloxone Hydrochloride. Dehydration-Induced Expansion versus Contraction. *Cryst. Growth Des.* **2009**, *9*, 3384−3395.

(17) *Apex2, Version 2 User Manual, M86-E01078*; Bruker Analytical X-ray Systems: Madison, WI, 2006.

(18) Burla, M. C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; Giacovazzo, C.; Mallamo, M.; Mazzone, A.; Polidori, G.; Spagna, R. SIR2011: A New Package for Crystal Structure Determination and Refinement. *J. Appl. Crystallogr.* **2012**, *45*, 357−361.

(19) Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. CRYSTALS Version 12: Software for Guided Crystal Structure Analysis. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

(20) Prout, C. K.; Pearce, L. J. *CAMERON*; Chemical Crystallography Laboratory: Oxford, UK, 1996.

(21) Cooper, R. I.; Thompson, A. L.; Watkin, D. J. CRYSTALS Enhancements: Dealing with Hydrogen Atoms in Refinement. *J. Appl. Crystallogr.* **2010**, *43*, 1100−1107.

(22) Flack, H. D. On Enantiomorph-Polarity Estimation. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **1983**, *39*, 876−881.

DOI: 10.1021/acs.cgd.8b00262
Cryst. Growth Des. 2018, 18, 3502−3509

(23) Thompson, A. L.; Watkin, D. J. CRYSTALS Enhancements:Absolute Structure Determination. *J. Appl. Crystallogr.* **2011**, *44*, 1017−1022.
(24) Flack, H. D.; Sadki, M.; Thompson, A. L.; Watkin, D. J. Practical Applications of Averages and Differences of Friedel Opposites. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2011**, *67*, 21−34.
(25) Parsons, S.; Pattison, P.; Flack, H. D. Analysing Friedel Averages and Differences. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2012**, *68*, 736−749.
(26) Hooft, R. W. W.; Straver, L. H.; Spek, A. L. Determination of Absolute Structure Using Bayesian Statistics on Bijvoet Differences. *J. Appl. Crystallogr.* **2008**, *41*, 96−103.
(27) Macrae, C. F.; Bruno, I. J.; Chisholm, J. A.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Rodriguez-Monge, L.; Taylor, R.; van de Streek, J.; Wood, P. A. Mercury CSD 2.0 - New features for the visualisation and investigation of crystal structures. *J. Appl. Crystallogr.* **2008**, *41*, 466−470.
(28) Karle, I. On the Conformation of Naloxone, a Narcotic Antagonist. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1974**, *30*, 1682−1686.
(29) Sime, R. L.; Forehand, R.; Sime, R. J. The Crystal Structure of a Narcotic Antagonist: Naloxone Hydrochloride Dihydrate. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1975**, *31*, 2326−2330.
(30) Klein, C. L.; Majeste, R. J.; Stevens, E. D. Experimental Electron Density Distribution of Naloxone Hydrochloride Dihydrate, a Potent Opiate Antagonist. *J. Am. Chem. Soc.* **1987**, *109*, 6675−6681.
(31) Two substances are strictly isomorphous if they have identical symmetry, and if their atomic positions can be described with the same set of arbitrary parameters.

DOI: 10.1021/acs.cgd.8b00262
Cryst. Growth Des. 2018, 18, 3502−3509