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A New Strategy of Transforming Pharmaceutical Crystal Forms

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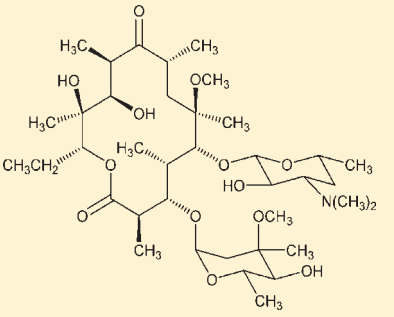
Supporting Information

ABSTRACT: The robust nature of network materials allows them to (for example) respond to external stimuli such as pressure, temperature, light, or gas/solvent adsorption and desorption. There is difficulty in retaining long-range order in purely molecular organic solids, due to weak intermolecular interactions such as van der Waals forces. Here, we show gas-induced transformations of the well-known pharmaceuticals clarithromycin and lansoprazole. For clarithromycin, the stimulus is capable of converting the kinetic solvate and guest-free crystal forms to the commercial thermodynamically stable polymorph with a huge saving in energy cost relative to industrially employed methods. The synthesis of the marketing form of lansoprazole involves a solvate that readily decomposes and that is stirred in water, filtered, and dried intensively. Our method readily circumvents such synthetic problems and transforms the sensitive solvate to the marketed drug substance with ease. Such expedient transformations hold great implications for the pharmaceutical industry in general when considering the ease of transformation and mild conditions employed.



INTRODUCTION

Pharmaceutical crystals represent one of the most important classes of organic solids due to their inherent importance to human health. The phenomenon of polymorphism is a major factor in the pharmaceutical industry, as different polymorphs can display markedly disparate stabilities, solubility, and/or bioavailability.[1−4] Numerous efforts have currently been devoted to polymorph control of drug substances during the preformulation stage to meet technological and biopharmaceutical requirements. Clarithromycin (**1**, 6-*O*-methylerythromycin A, Figure 1A) is a semisynthetic macrolide antibiotic that has been widely studied in this regard and that exhibits excellent activity against various bacteria.[5,6] It has been shown (through numerous synthetic routes, including various methods of crystallization) that **1** can exist in five different crystalline forms designated **0**,[7] **I**,[8] **II**,[9,10] **III**,[11,12] and **IV**[13] (although **III** and **IV** have not to our knowledge been commercialized). Form **0** crystals exist as a solvate form and both form **I** and form **II** crystals are anhydrous. Clarithromycin is currently marketed in the United States under the trademark Biaxin, and is formulated using form **II**. A key step in the process of isolation of form **II** involves heating form **I** at ∼110−115 °C overnight (∼ 18 h).[9] An additional problem in pharmaceutical processing is that some materials can only be desolvated through techniques that are difficult to apply on an industrial scale. Lansoprazole (**2**, Figure 1B) is a proton pump inhibitor (PPI) that is currently the No. 8 best selling drug in the United States market under the trademark Prevacid.[14] Commercially important crystal forms of **2** include a solvate form (1:1 ethanol hydrate) and a solvent-free form. The stable solvent-free marketing agent is currently isolated by stirring the 1:1 ethanol hydrate of **2** (that is prone to decomposition) in water, followed by filtration and intensive drying to remove surface water.[15] Here, we show that gas-induced transformations rapidly transform either of forms **0** and **I** of clarithromycin (**1**) to form **II** readily under mild conditions (100−350 psi CO_2 at room temperature), and the sensitive ethanol hydrate of lansoprazole (**2**) to the stable marketing agent with relative ease. In the past decade, extreme pressure (generally 1000−100 000 bar) compression[16] and or utilization of supercritical fluid[17] have been intensively explored for polymorphic transformation of drug substances. However, to the best of our knowledge, there is no report on gas-induced solid state transformation of pharmaceutical crystal forms.[18]

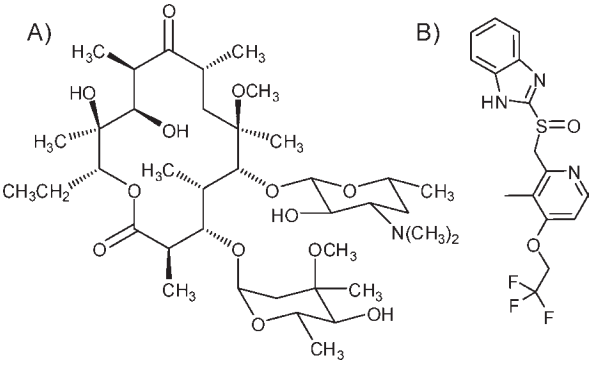


Figure 1. Schematic of clarithromycin (**1**) and lansoprazole (**2**).

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EXPERIMENTAL SECTION

General Information. **1** and **2** were extracted from commercially available Biaxin and Prevacid tablets, respectively. Crystalline form **0** of **1** was prepared by crystallization from absolute ethanol (~1 g/10 mL).[7] The ethanol hydrate of **2** was isolated by crystallization from a mixture of ethanol/water (9:1).[15] XRPD patterns were obtained on a Rigaku advanced diffraction system using Cu Kα radiation (λ = 1.5418 Å) with a variable divergent slit, solid-state detector, and a routine power of 1400 W (40 kV, 35 mA). Powder samples were dispersed on low-background quartz XRD slides. Solid-state NMR data were collected on a Bruker 300 MHz spectrometer. All chemical shifts are quoted in parts per million (ppm) from external TMS standard.

Treatment of Pharmaceutical Solids by CO_2 or Other Gases with Modest Pressures. About 200 mg of each pharmaceutical crystalline form (form **0** and **I** of **1**, ethanol hydrate of **2**) was placed in a gas cell of volume ca. 15 cm^3 at room temperature (ca. 296 K) and evacuated for 1 min using a vacuum line prior to the introduction of dry carbon dioxide at pressures specified in the manuscript. The carbon dioxide used in the experiments was purchased from Air Liquide USA (Purity: 99.999%). The gas adsorption experiments of each form of **1** and **2** are performed using a custom built volumetric gas analyzer.

X-ray Crystallography. Single-crystal X-ray structure determination of form **0** (ethanol solvate) of **1** and ethanol hydrate of **2** was performed on Bruker Apex II diffractometer equipped with a fine-focus sealed-tube X-ray source (Mo Kα radiation, λ = 0.71073 Å). Raw data for all structures were processed using SAINT and absorption corrections were applied using SADABS.[19] The structures were solved by direct method and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for non-H atoms using SHELX-97.[20] The hydrogen atoms on the carbon were placed in calculated position with isotropic displacement parameters set to 1.2 × *U*eq of the attached atom. CCDC 700729 and 784841 contain the supplementary crystallographic data for the form **0** of **1** and ethanol hydrate of **2**, respectively.

RESULTS AND DISCUSSION

Clarithromycin, 1. All of the above-mentioned forms of **1** have been characterized by powder X-ray diffraction (XRPD) and or differential scanning calorimetry (DSC).[7−13,21] Form **0** exists as a solvate of **1** that can be prepared by crystallization from suitable solvents such as ethanol (preferred), isopropanol, tetrahydrofuran, and isopropyl acetate.[7] The solvate **0** may subsequently be converted to nonsolvated **I** through solvent removal either by drying under vacuum in a temperature range between 0 and 50 °C,[8] or by exposure to air at room temperature (Figure 2). Form **II** is reported to be thermodynamically stable compared to form **I** and can be isolated either by heating forms **0** or **I** at a temperature ≥ ~70−80 °C, or by slurrying either form **0** or **I** in water for ~2 h (Figure 2).[8,13,21]

The single crystal X-ray structure of form **0** has been elucidated, and is in an orthorhombic crystal system.[22] However, good diffraction quality single crystals of form **I** are yet to be isolated and their structure realized, although it is known that they are also of orthorhombic symmetry.[8] Our single crystal X-ray diffraction studies of form **0** show molecules of **1** to be stacked in a double bilayer arrangement containing solvent channels. Within each bilayer, the molecules of **1** are arranged in a head-to-head fashion (Figure 3A). Single crystals of form **II** can be obtained by sublimation of **1** under vacuum. Structural analysis demonstrates that in form II the molecules are in the most thermodynamically stable phase, arranged in a densely packed zigzag arrangement (Figure 3C).[23,24]

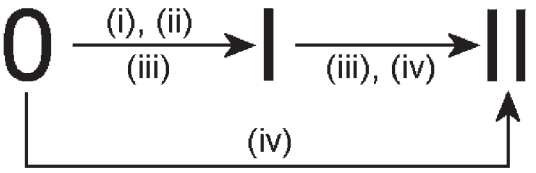

Figure 2. Schematic of known conditions for various phase tranformations of crystalline **1**: (i) drying in vacuum in the temperature range of 0−50 °C, (ii) exposure to air at room temperature, (iii) heating either form **0** or **I** at a temperature ≥ ~70−80 °C (preferred 110−115 °C), and (iv) slurrying either form **0** or **I** in water for ~2 h.[7,13,14] Note that these methods are preformed separately and are not combined.

For our studies, the wet solids of form **0** crystals of **1** were collected from the crystallization system and dried under reduced pressure for ~5 min in order to remove residual solvent from the surface of the crystalline material. Although ethanol loss from form **0** is possible under these conditions, XPRD studies confirmed the sample to be homogeneous form **0**. This solid was kept for further use in a sealed vial and was found (by sequential XRPD analysis) to be stable for up to 1 week. Form **0** was heated for the required times at relevant temperatures to afford anhydrous forms **I** and **II** as pure crystalline materials.[8] We have examined four sets of conditions that are outlined separately for clarity.

1 atm (14.7 psi) CO_2. Upon examination, all three pure forms (**0**, **I**, and **II**) display adsorption of dry carbon dioxide to varied extents at room temperature under 1 atm pressure (indicated by the adsorption isotherms in Figure 3). XRPD studies on form **0** after CO_2 uptake had reached equilibrium (~15 min under these conditions) suggest that there is no onset of phase change at that point. Peak broadening is evident in the powder pattern which may be due to partial solvent loss from the crystalline material (Figure 3A). Similar analysis of forms **I** and **II** also shows no change in phase over analogous time periods under these conditions (Figure 3C).

It is important to note that occasionally form **I** will display evidence of the onset of phase transformation under 1 atm CO_2 gas over a period of ~24 h (Figure 4A). We believe that different particle sizes may affect the rate of transformation at these low pressures, and upon raising this pressure to 2 atm CO_2, phase change onset toward pure form **II** is typically observed (Figure S1). During the course of these experiments, we identified an intermediate phase with XRPD peaks that are characteristic for a mixture of both forms **0** and **II**. This suggests that, prior to reaching form **II**, form **I** first transforms to an isomorphic form (**0′**) of form **0** in which CO_2 molecules fill the nanochannels in place of solvent molecules, but that will escape from the lattice upon release of gas pressure. It was noted that the resulting form **0′** is metastable, which will slowly transform to form **I** in air or vacuum but will transform to form **II** with the interaction of CO_2.

23.8 atm (350 psi) CO_2. Given our observations at 1 atm CO_2, we pressurized a sample of form **0** at 350 psi CO_2 and monitored sample composition as a function of time (sampling at 0, 1, 2, 3, and 4 h) through XRPD experiments and comparison with literature powder patterns.[7−9] As mentioned above, the ethanol solvate of form **0** can be slowly transformed to desolvated **I** by exposure to air at room temperature. In addition, and as stated in the Introduction, heating at a temperature ~110−115 °C results in the transformation of form **0** to form **II** via form **I** over a time period of approximately 24 h (Figure 2).[8] We found that exposure of form **0** to the 350 psi CO_2 atmosphere at room

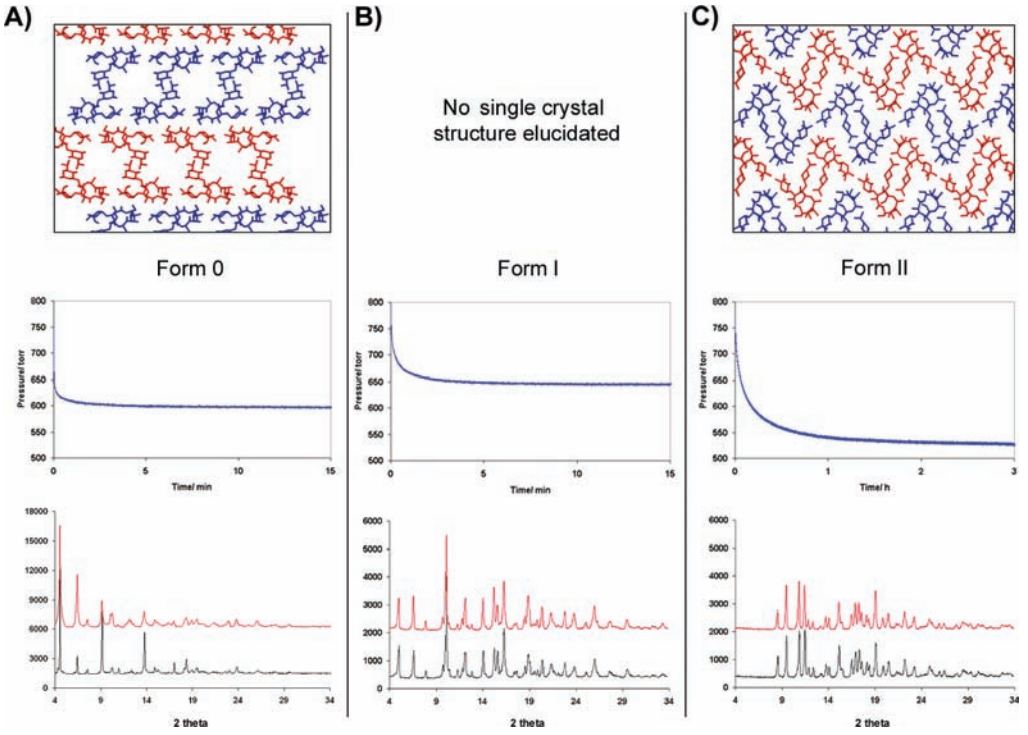

Figure 3. Crystal structures (the *bc* plane of forms **0** and **II**), gas adsorption isotherms (1 atm CO_2), and XRPD studies of forms **0**, **I**, and **II** of **1**.[7,22−24] XRPD studies were performed before (black) and after (red) CO_2 uptake equilibration (after ∼15 min). (A) Molecules of **1** in form **0** are arranged in a bilayer packing mode containing ∼6 × 8 Å solvent occupied channels. (B) Structure of form **I** not known. (C) Molecules of **1** in form **II** arranged in a densely packed zigzag arrangement. Hydrogen atoms have been omitted for clarity in both panels A and C. Solvent molecules have been omitted in panel A.

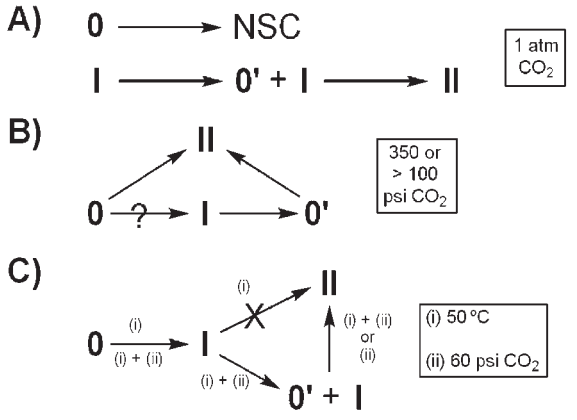

Figure 4. Schematics representing the phase transformations of **1** described. (A) Postequilibration of CO_2 gas uptake at 1 atm, form **0** displays no significant phase change (NSC). Under these conditions, form **I** will transform to a mixture of **0′** and **I**, prior to full transformation to pure form **II**. (B) Higher pressures of CO_2 cause form **0** to transform to form **II** with no evidence for the presence of form **I**. Under analogous conditions, form **I** rapidly transforms to form **II** via form **0′**. (C) Normal heating regimes transform solvated form **0** to desolvated form **I**, with no further phase changes. The presence of CO_2 gas facilitates transformation to form **II** via form **0′**.

temperature for just 4 h resulted in complete transformation directly to form **II** without evidence for the existence of form **I** (from XRPD analysis, Figure 4B).

The possibility of dissolution and recrystallization of **1** from liquid or supercritical CO_2 can be ruled out under these conditions.[17b] Although we are uncertain of the exact mechanism involved in the transformation, a number of possibilities exist. These include (a) that CO_2 molecules cause molecules of **1** to slide over one another with concomitant removal of solvent to the gas phase, and (b) that the dynamic CO_2 molecules break the hydrogen bonds associated with molecules of ethanol and **1**, forcing the molecules of **1** to move closer together. In either case, the result is that the crystal volume shrinks by ∼15% (as calculated by the change in unit cell volume), and the fact that such a phase change produces a crystalline product suggests that the substantial motion must be concerted. The transformation can be completed within only 4 h and results in a pure form **II** phase as evidenced by XRPD (Figure 5A). Solid state NMR analysis of the resulting crystalline form **II** shows that CO_2 molecules are trapped in lattice voids (approximately 83 $Å^3$ volume) that are present in the organic solid (Figure S2).[24] This thermodynamic phase is stable upon release of gas pressure or under vacuum, does not revert to the starting phase, and is found to release the cavity bound CO_2 molecules over a short time (∼ 2 h).

As expected, desolvated form **I** can be transformed to form **II** with greater ease under analogous conditions. Pressurization of form **I** (350 psi CO_2) results in transformation to form **II** within just several minutes (Figures 4B and S3) (see Supporting Information). We believe that the greater ease associated with this transformation may be due to (at least) three contributing factors: (1) Form **I** is desolvated, and as such, there is no need to pay the energy price of breaking interactions between molecules of solvent and **1**. (2) There are no ethanol molecules in the sample chamber that may hinder the transformation process. (3) Form **I** is more thermodynamically stable than form **0** in air and a CO_2 atmosphere. The energy 'price' (which must be paid by CO_2) in this case is clearly less compared to the transformation of form **0** to form **II**.

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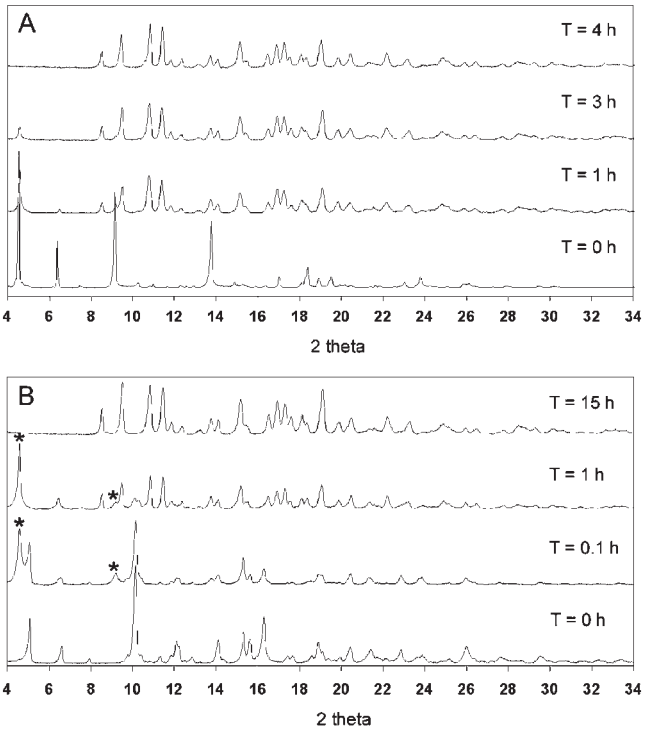

Figure 5. X-ray powder diffraction patterns of samples performed at 296 K. (A) The transformation of crystalline form **0** to form **II** under 350 psi of CO_2. (B) The transformation of form **I** to form **II** by using 100 psi of CO_2. The asterisk (*) label is used for peaks that are indicative for the formation of form **0′**.

6.8 atm (100 psi) CO_2. We also found that the transformation of form **0** to form **II** takes place at a lower pressure (7 atm, 100 psi) of CO_2 but over a longer time period (~6 days, Figure S4). As was the case for higher pressure, there was no evidence for the formation of form **I** in this process. In addition, these conditions effect the transformation of form **I** to form **II** via form **0′** in ~15 h (Figure 5B), and are significantly more facile when compared to currently employed industrial technology and the subsequent energy cost of this processing.

4.1 atm (60 psi) CO_2 at 50 °C. As we had investigated only changes in pressure, we investigated the introduction of pressure at a temperature known to only transform form **0** to **I** (Figure 4C).[8] By gently heating the sample at 50 °C under 60 psi CO_2, we found that the transformation can be completed within ~4 days (Figure S5). At this temperature, form **0** is ultimately transformed to a mixture of form **0′** and **I** which, as described above, is related by transforming form **I** to **0′** prior to the final transformation of form **0′** to **II**. Therefore, without the presence of CO_2, it will not be possible to isolate form **II** at this temperature.[8]

Different gases including H_2, He, CH_4, N_2, O_2, air, and N_2O were studied for this phenomenon. Among these, it was found that 350 psi of N_2O also completely effects the transformation of form **0** to form **II** (Figure S6), but over a longer time period (30 h) relative to that with carbon dioxide (4 h). Gases with smaller molecular weights consistently failed to cause the phase changes described above, even with a pressure as high as 600 psi (40 atm).

Lansoprazole, 2. As stated in the Introduction, the solvent-free form of **2** is used as the marketing agent. This form is more thermodynamically stable than the readily prepared ethanol hydrate, which is reflected by the fact that it does not show any change even when stored for 1 year at either room or elevated temperature. Although the ethanol hydrate displays high stability when stored for 1 year at low temperature (0 °C or lower) and also has excellent solubility, it shows onset of change in the crystalline state at elevated temperature.[15] In addition, it is very difficult to desolvate the ethanol hydrate **2** by vacuum drying due to this ready decomposition.[15] Furthermore, even exposure to air at room temperature in an open container will result in solvate decomposition within several days. As this is the case, special techniques to obtain the solvent free marketing agent are required, and the currently employed method is to stir the crystalline ethanol hydrate in water, which has the effect of expelling both solvents from the material to afford the solvent free-form. While this is effective, intensive drying is required to remove surface water from the product following filtration. Given the prominence of **2** in the world drug market, there has been an outstanding demand for a supply of the solvent−free form and, in particular, the development of effective and highly workable desolvation technology.

The ethanol hydrate of **2** was isolated by literature crystallization from ethanol/water (9:1) as a solvate containing one molecule of both water and ethanol.[25] As no atomic coordinates could be located for the ethanol hydrate of **2** in the Cambridge Structural Database, single crystal X-ray diffraction studies were performed and showed the solvent molecules to form a well ordered hydrogen bonding ring with acceptor atoms in **2** (Figure S7) (see Supporting Information). The ethanol hydrate of **2** was crystallized in bulk and the structure was confirmed by XRPD studies (Figures 6A and S8).

34.0 atm CO_2 (500 psi). Upon examination, both ethanol hydrate and solvent-free forms of **2** are unable to absorb carbon dioxide under STP (Figures S9). When the ethanol hydrate is pressurized with 500 psi CO_2 at room temperature, the transformation to the more thermodynamically stable solvent-free form begins (Figure 6). Examination after a 2 day period shows that a gas−solid equilibrium has been established within the sample chamber. This rate of desolvation of the ethanol hydrate of **2** implies a stronger interaction between the molecular components relative to the ethanol solvate of **1**, and it appears that liberated ethanol and water molecules (that are trapped in the sealed gas cell) slow subsequent transformation, resulting in a mixture of solvate and solvent-free forms (Figure 6B). Further exposure to the same carbon dioxide/ethanol/water atmosphere in the gas cell up to 8 days did not result in any further transformation, but release and reintroduction of an additional 34 atm of CO_2 resulted in complete transformation to the pure solvent-free form within 24 h (Figure 6C,D). As a result, the crystal volume shrinks by 20%, as calculated from known single crystal unit cell volumes,[26] and the solvent molecules have been fully extruded from the bulk material which is confirmed by X-ray powder diffraction (Figures 6D and S9) and solid-state NMR studies (Figure S11).

In line with our experiments with various forms of **1**, the same transformation takes place at a lower pressure (24 atm, 350 psi) of CO_2 but over a longer time period (3 days to reach equilibrium and an additional 2 days to complete transformation). As for **2**, different gases were also studied for this phenomenon. Among these we found that N_2O and CH_4 (500 psi in both cases) can also completely transform ethanol hydrate form to the solvent-free form. The transformation requires a similar time scale when using N_2O, but slightly longer when using CH_4 (3 days to reach equilibrium and an additional 3 days to complete transformation).

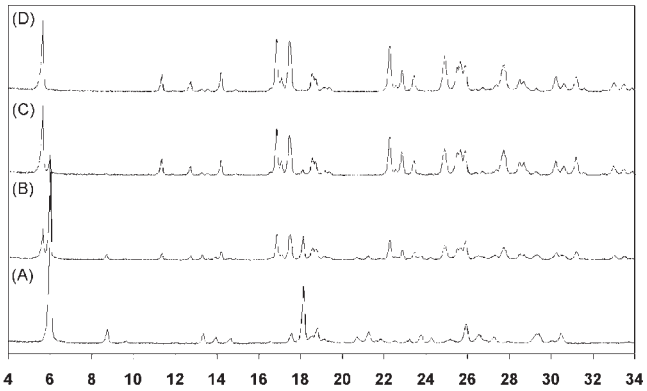

Figure 6. X-ray powder diffraction patterns of samples performed at 296 K showing the transformation of the crystalline ethanol hydrate of **2** to the stable solvent-free form.[15] (A) Fresh ethanol hydrate of **2**. (B) Ethanol hydrate of **2** after 2 days exposure to 500 psi CO_2. (C) Ethanol hydrate of **2** after 12 h exposure following reintroduction of 500 psi CO_2 atmosphere. (D) Ethanol hydrate of **2** fully converted to solvent-free form obtained after 24 h exposure following reintroduction of a 500 psi CO_2 atmosphere.

No transformation was observed when using 600 psi of H_2 or He. These results also confirm that the energy of the van der Waals interaction of the gas molecules with the walls of host molecules is an important factor.

CONCLUSIONS

We have shown that simple pressurization of polymorphic forms of a pharmaceutical agent (**1**) can effect phase transitions among the forms with ease. From our experiments, it appears that the large thermodynamic barrier which must be surmounted by heating to effect the phase transformations outlined above is greatly reduced (given that onset can occur at low pressure of CO_2). Our studies also indicate that low temperature can be introduced to increase the rate of transformation, a feature we are further investigating. For **2**, a material sensitive to degradation, we have shown that conversion between crystal forms can also be performed with relative ease. We conclude that these transformations can only be related to kinetics, with greater pressure effecting faster transformations. Clearly such a transformation process will have huge implications for the pharmaceutical industry, can potentially streamline processing with milder conditions relative to some of those currently employed, or can offer processing routes that circumvent difficult techniques on an industrial scale. Given our evidence that more than one gas can perform the functions outlined above, there remains the possibility that other gases can effect phase transformations in equally disparate materials. A feature such as this would be invaluable from the view point of furthering control over pharmaceutical polymorphism and processing in general.

ASSOCIATED CONTENT

Supporting Information. Crystallographic information file (CIF) and structural description of **1** form **0** (ethanol solvate) and **2** ethanol hydrate, XPRD patterns, and ^{13}C solid-state NMR data of polymorphic transformation. This material is available free of charge via the Internet at http://pubs.acs.org.

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