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Polymorphism in Carbamazepine Cocrystals

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Abstract

Cocrystals of carbamazepine with nicotinamide and saccharin are shown to be polymorphic. Two polymorphs of carbamazepine-nicotinamide (CBZ-NCT) cocrystals and two polymorphs of carbamazepine-saccharin (CBZ-SAC) cocrystals were grown from solution in the presence of polymer heteronuclei. The two CBZ-NCT polymorphs, CBZ-NCT I and a polymer nucleated (PN) form of CBZ-NCT, were characterized by Raman spectroscopy and powder X-ray diffraction. CBZ-SAC II, a new polymorph, was found to be in the monoclinic space group C2/c with a = 35.72 Å, b = 6.84 Å, c = 16.11 Å, and β = 98.03°. The unique feature of CBZ-SAC II is the formation of a heterosynthon between the carbamazepine and saccharin. These results are notable because CBZ-NCT and CBZ-SAC are among the most widely studied pharmaceutical cocrystals.

Cocystallization has recently been rediscovered as a powerful technique to modify key solid-state properties of pharmaceuticals such as solubility, stability, and dissolution rate.[1,2] From a supramolecular standpoint it is pleasing to see that predictable structural motifs can be introduced by design, offering at least a partial solution to the problem of controlling crystal structure. This element of predictability may be misinterpreted as leading to the formation of a single structure and therefore a lack of crystal polymorphism. Here we investigate this issue for two cocrystals of the highly polymorphic pharmaceutical carbamazepine.[3]

The crystallization properties of carbamazepine-nicotinamide (CBZ-NCT) have been thoroughly investigated[4–7] and the generation of CBZ-NCT cocrystals has been achieved through solution crystal growth,[4,5] slurry conversion,[6] and melt crystallization.[7] From these studies one form of CBZ-NCT cocrystal has been thoroughly characterized and its structure elucidated by single crystal X-ray diffraction.[4] Crystal growth from the melt results in a second form of CBZ-NCT that is metastable.[7]

Our study of CBZ-NCT cocrystals utilized functionalized cross-linked polymers as heteronuclei for crystal growth,[8] a strategy that has previously demonstrated effectiveness in polymorph discovery of pharmaceuticals,[8,9] extended solids,[10] and inorganic complexes.[11] Cocrystals were grown by evaporation of ethanol solutions containing a stoichiometric ratio of carbamazepine and nicotinamide contacting 96 individual polymers in a polymer library. Three separate polymer libraries were utilized derived from monomers with non-polar and aromatic functional groups, polar nitrogen rich functional groups, and polar acidic functional groups (see Supporting Information). Optical microscopy of the resulting crystals revealed needle-like morphologies with no readily distinguishable features. Raman spectroscopy of the crystals identified several crystalline forms including carbamazepine, nicotinamide, CBZ-NCT I, and a cocrystal with a Raman spectrum indistinguishable from that reported for CBZ-NCT II.[7] Powder X-ray diffraction (PXRD, Figure 1) of CBZ-NCT I is in accord with the previously

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reported powder pattern,[7] whereas the pattern of the other form, PN-CBZ-NCT, is closely related to the PXRD of CBZ-NCT II. There are, however, important differences which may indicate that these are indeed structurally related polymorphic forms or that the melt grown form II possesses a high enough level of defects in one or more growth directions that the powder pattern is altered both in 2θ and in the relative intensities of the peaks (see Supporting Information). Dramatic differences in the N-H region are observed by Fourier transform infrared (FTIR) microscopy of form I and PN-CBZ-NCT (Figure 2). The N-H vibrational bands shift from 3446 and 3387 cm^{-1} in form I to 3412 and 3347 cm^{-1} in PN-CBZ-NCT and this shift suggests the formation of a new hydrogen bonding network. PN-CBZ-NCT was found to be stable under ambient conditions, showing no transformation to CBZ-NCT I. PN-CBZ-NCT is best produced in the presence of terpolymers derived from *n*-butyl methacrylate, benzyl methacrylate, and divinylbenzene.

Variable temperature Raman spectroscopy reveals that PN-CBZ-NCT converts to CBZ-NCT I in the temperature range 124 to 128 °C (see Supporting Information). This is in contrast to the previously reported CBZ-NCT II to CBZ-NCT I phase transition, investigated by DSC, in which the phase transformation was found to occur between 83 and 90 °C.[7] This difference can be attributed to PN-CBZ-NCT being a distinct polymorph from CBZ-NCT II or from the production of amorphous material accompanying the melt growth of CBZ-NCT II. Thus, polymer induced nucleation has, at a minimum, produced a polymorph of CBZ-NCT from solution as a pure crystalline phase.

The carbamazepine-saccharin (CBZ-SAC) cocrystal is perhaps the most thoroughly studied of the new generation of pharmaceutical cocrystals and has been the target of several investigations in which high-throughput polymorph screening with the CRYSTALMAX® technology,[12,13] mechanical grinding,[13,14] and slurry conversion experiments[6,13] all resulted in a single form of CBZ-SAC. Our investigation of CBZ-SAC crystallization employed the same polymer libraries utilized for CBZ-NCT crystal growth and was achieved by the evaporation of an equimolar solution of carbamazepine and saccharin in ethanol. Inspection of the resulting crystals by optical microscopy revealed two distinct crystal morphologies: plates and needles. Raman spectra of the two morphologies were closely related suggesting that the two morphologies were indeed polymorphs. In addition, PXRD analysis of the two carbamazepine-saccharin cocrystal morphologies generated two distinct powder patterns (Figure 3). The powder pattern generated from the plate-like crystals is in agreement with that reported for CBZ-SAC I.[14] The first peak in the PXRD pattern of the two forms are readily distinguishable, with 2θ = 6.88° for form I and 2θ = 4.80° for form II. CBZ-SAC II can be produced on 0.2 gram scale as crystals suitable for single crystal X-ray diffraction in the presence of a bead of poly(4-methyl-1-pentene) by evaporation of a 7.2 mM methanol solution.

CBZ-SAC form I has previously been characterized by single crystal X-ray diffraction[4] and is triclinic with a 1:1 molar ratio of carbamazepine and saccharin. As depicted in Figure 4(a), the molecules pack such that a homosynthon (Figure 5) forms between two inversion related carbamazepine carboxamide groups (d = 1.95 Å).[15] The saccharin molecules also form a hydrogen bonded homodimer with C–H···O distances of 2.21 Å. The saccharin N-H forms a hydrogen bond with the carbamazepine carboxyl group (d = 1.75 Å) while the anti N-H of the carbamazepine urea forms a hydrogen bond with the S=O of saccharin (d = 2.47 Å). This results in a 1-D array of molecules in a crinkled tape motif.[4]

In contrast, the new modification of CBZ-SAC has a monoclinic unit cell in the space group C2/c with *a* = 35.72 Å, *b* = 6.84 Å, *c* = 16.11 Å, and β = 98.03°. As demonstrated in Figure 4 (b), a primary feature of the molecular packing of Form II is the formation of a heterosynthon (Figure 5) between the carbamazepine and saccharin molecules. The heterosynthon is formed by a hydrogen bond from the saccharin N-H to the carbamazepine C=O (d = 1.76 Å) and a

hydrogen bond from the carbamazepine N-H to the saccharin C=O (d = 1.97 Å). An additional hydrogen bond is formed between the anti N-H of the carbamazepine urea and the S=O of the saccharin (d = 2.00 Å). The molecules pack in 1-D chains that extend along the crystallographic *c*-axis.

Analysis of CBZ-SAC forms I and II by FTIR (Figure 6) reveals a drastic change in energy of the vibrational bands for the N-H stretching modes in the 3500-3300 cm^{-1} region. The two N-H stretches of form I are found at 3501 cm^{-1} and 3434 cm^{-1}, while the N-H vibrational bands of form II are found at 3430 cm^{-1} and 3350 cm^{-1}. Assuming that the N-H vibrational bands of carbamazepine are always higher in energy than the N-H vibrational band of saccharin,[14] these shifts represent a significant decrease in energy of these modes in form II. This is consistent with the crystal structure of form II in which the measured hydrogen bond distances are significantly shorter than those measured in form I.

Thermogravimetric analysis of CBZ-SAC forms I and II determines an onset of decomposition at 170 °C and 162 °C respectively, with no loss of mass prior to decomposition. The melting temperature of form II, 166.8 °C, is found to be lower than form I by 7 °C; however significant decomposition is observed following the melt. This is also evident in the DSC trace of form I, in which a single non-reversible transition is observed with an onset temperature at 172 °C and ΔH = 57.0 kJ/mol. The DSC trace of form II has a non-reversible transition with an onset at 168 °C and ΔH = 53.1 kJ/mol. This transition is followed by a small non-reversible transition with an onset of 172 °C. The lower free energy of CBZ-SAC form I was demonstrated by slurry conversion of form II to form I at room temperature and this indicates that polymorph II of this cocrystal is more soluble and may present improved bioavailability.

Carbamazepine cocrystals with nicotinamide and saccharin have been found to be polymorphic. The absence of extensive polymorphism in cocrystals may simply result from limitations in screening methods that are compatible with maintaining cocrystal formation rather than a decreased propensity for polymorph formation. Polymer-induced heteronucleation offers a method to access diverse nucleation conditions from a single solvent and is therefore ideal for polymorph discovery in cocrystals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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15. For determination of inter- and intra molecular distances, all carbon-hydrogen bond lengths were normalized to 1.083 Å and all nitrogen-hydrogen bond lengths were normalized to 1.009 Å.

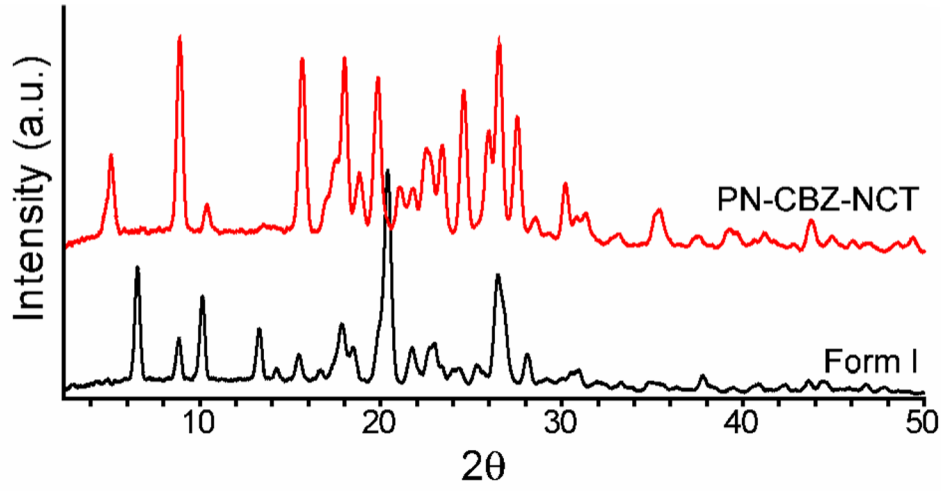

Figure 1.
PXRD of CBZ-NCT I and PN-CBZ-NCT.

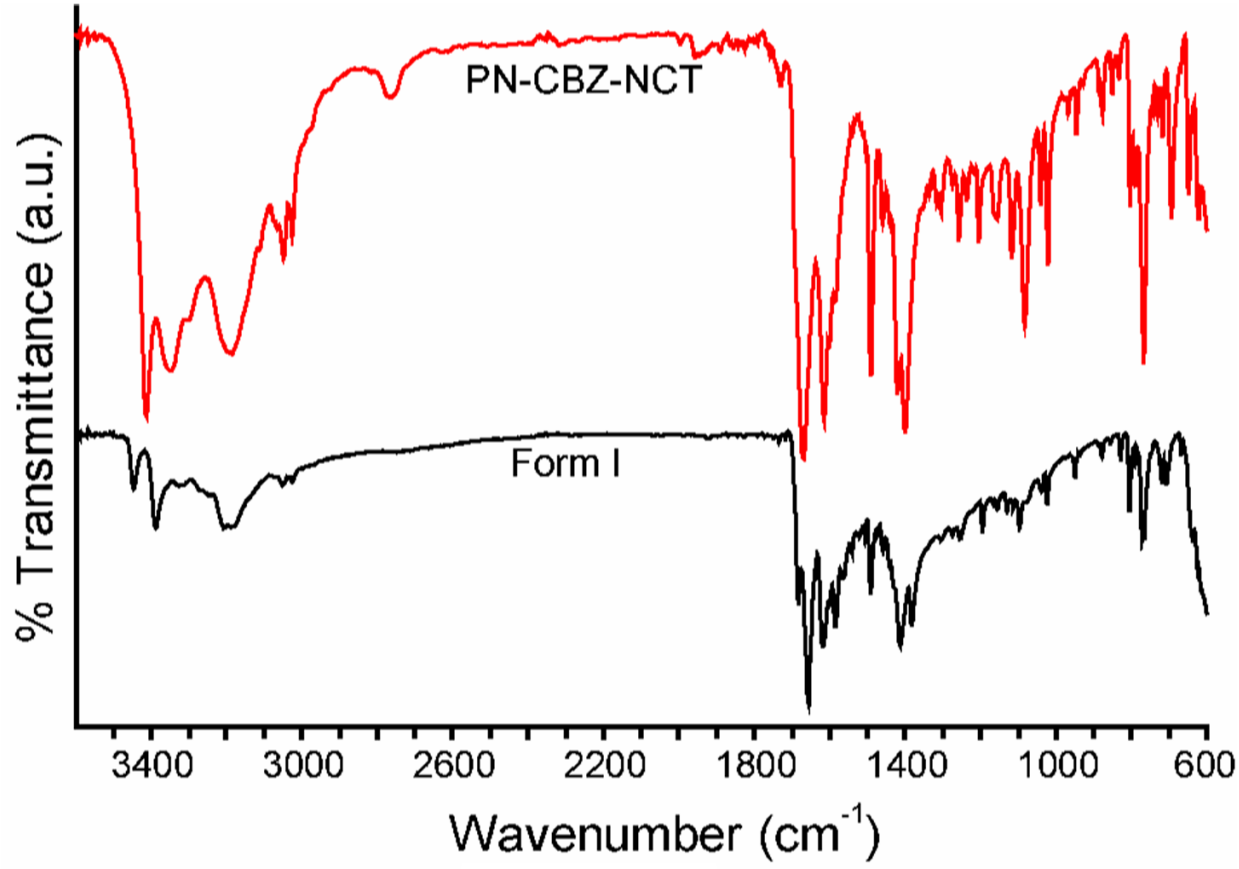

Figure 2.
FTIR spectra of CBZ-NCT I and PN-CBZ-NCT.

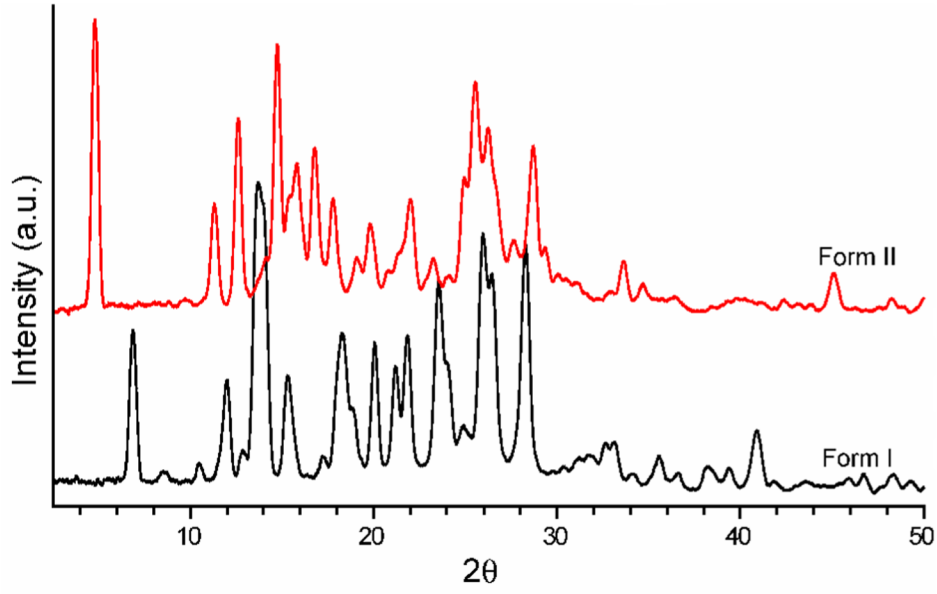

Figure 3.
Powder X-ray diffraction patterns of CBZ-SAC I and CBZ-SAC II.

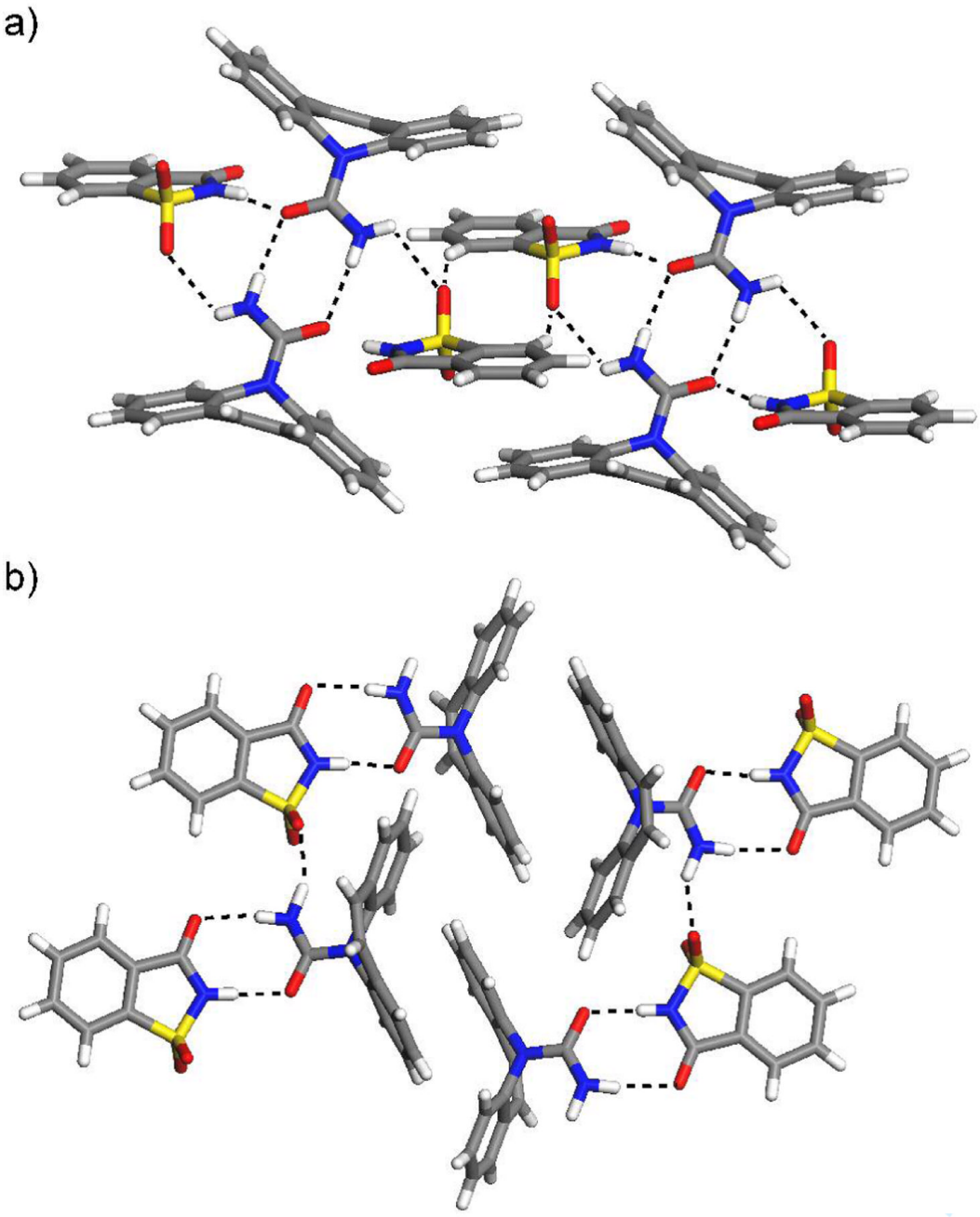

Figure 4.
Molecular packing of a) CBZ-SAC I[4] and b) CBZ-SAC II.

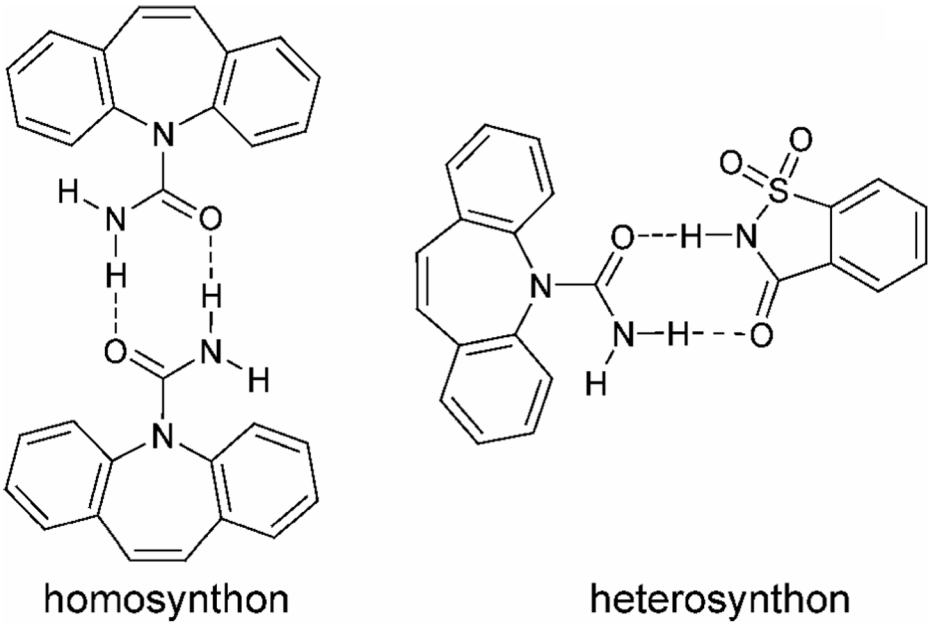

Figure 5.
Representation of the homosynthon between two CBZ molecules in CBZ-SAC I and the heterosynthon between a CBZ and SAC molecule in CBZ-SAC II.

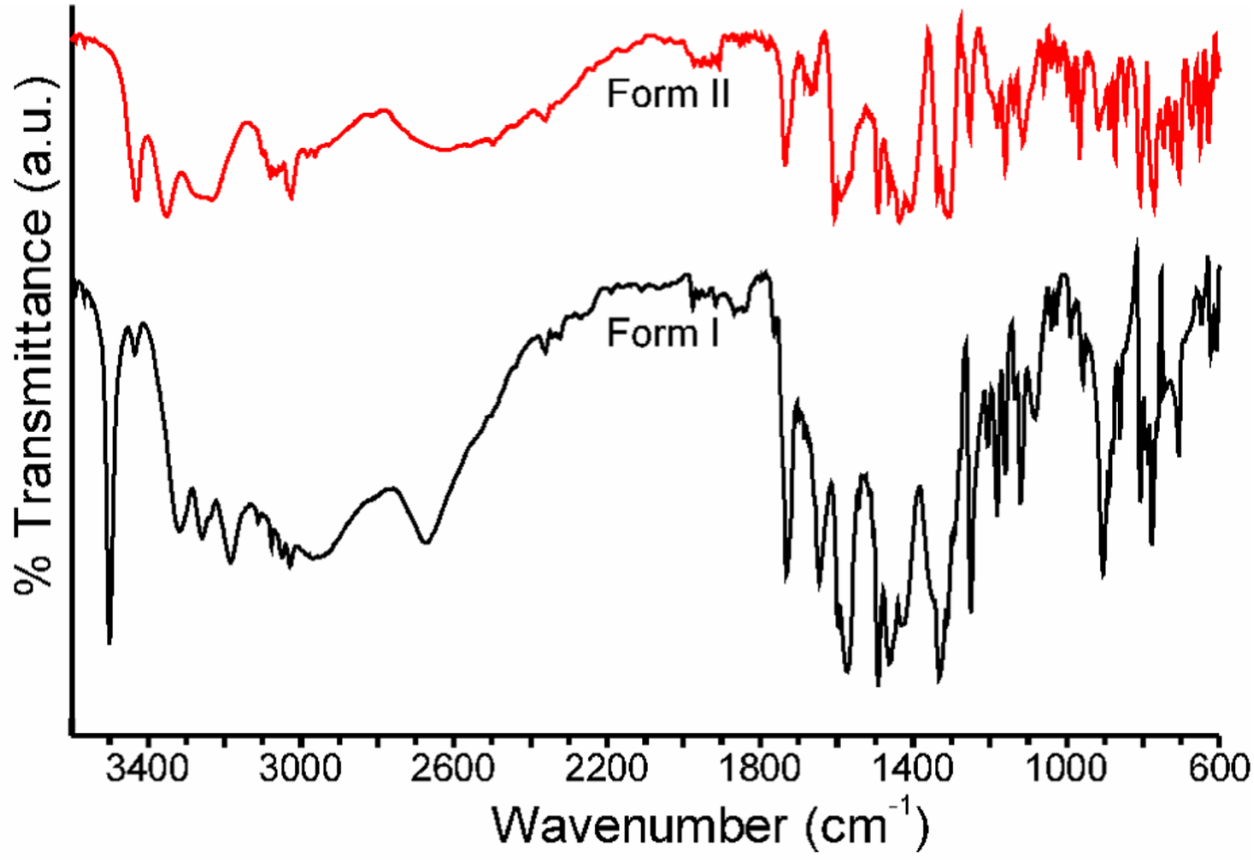

Figure 6.
FTIR spectra of CBZ-SAC I and CBZ-SAC II.