Interaction of native cyclodextrins and their hydroxypropylated derivatives with carbamazepine in aqueous solution. Evaluation of inclusion complexes and aggregates formation

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Supporting Information

Results

\textit{Fourier transform infrared spectroscopy (FTIR)}

The presence of inclusion complexes in samples can be responsible for shifts in vibrational wavelength of both CDs and drug\textsuperscript{1}. To obtain more knowledge on the possible interaction between CBZ and CDs, we performed vibrational spectroscopy, namely FTIR method on solid samples obtained from the phase-solubility studies of the various systems.

Due to the existence of different polymorphic forms of CBZ and in order to determine which are present, the spectra of raw carbamazepine (as received) and carbamazepine collected from the phase-solubility experiment at zero CD concentration (CBZ SE) were determined (Figure S1). As stated by different authors\textsuperscript{2-7}, the most characteristic bands for the two most common CBZ polymorphs were selected and presented in Table S1.
Table S1. The Fourier transform infrared (FTIR) spectra: Summary of most characteristic peaks positions (cm\(^{-1}\)) for two most common CBZ polymorphic forms described in literature (a\(^2\); b\(^3\); c\(^4\); d\(^7\); e\(^5\); f\(^6\)).

|                          | Polymorphic form                                                                 |
|--------------------------|----------------------------------------------------------------------------------|
|                          | Type III (band cm\(^{-1}\))          | Type I (band cm\(^{-1}\))          |
| v (-NH stretching vibration) | 3463\(^a\)                          | 3485\(^c\)                        |
|                          | 3462\(^c\)                          | 3483\(^d\)                        |
|                          | 3464\(^d\)                          | 3485\(^e\)                        |
|                          | 3466\(^e\)                          | 3484\(^f\)                        |
| v (-CO-R vibration)      | 1674\(^a\)                          | 1688\(^b\)                        |
|                          | 1678\(^b\)                          | 1683\(^c\)                        |
|                          | 1677\(^c\)                          | 1684\(^d\)                        |
|                          | 1676\(^d\)                          | 1688\(^e\)                        |
|                          | 1677\(^e\)                          | 1686\(^f\)                        |
| v (-C=O and –C≡O vibration and –NH deformation) | 1605 and 1594\(^d\)                      | 1598 and 1591\(^b\)                        |
|                          | 1601 and 1593\(^b\)                      | 1602 and 1593\(^e\)                        |
|                          | 1605 and 1593\(^d\)                      | 1603 and 1593\(^f\)                        |
|                          | 1605 and 1595\(^e\)                      |
| v (NH\(_2\) rocking)     | 1388\(^b\)                          | 1396\(^c\)                        |
|                          | 1379\(^c\)                          | 1392\(^d\)                        |
|                          | 1383\(^d\)                          | 1397\(^e\)                        |
|                          | 1386\(^e\)                          | 1396\(^f\)                        |

FTIR spectra of as received CBZ and CBZ subjected to the phase-solubility conditions (SE) overall appeared to be quite similar (Figure S1). The band observed on the range 3490-3460 cm\(^{-1}\) (-NH stretching vibration) is the same for both spectra (and characteristic for form III), as well as the remaining 3 bands appearing in the region ~1600-1380 cm\(^{-1}\) look to be due to CBZ form III. One small difference can be noticed in both spectra, regarding the -CO-R vibration band. The possible presence of impurities and taking the accuracy of the IR method into account does not support that we can consider these small changes as significant.

This comparison between CBZ sources showed that both spectra (CBZ as received and CBZ SE) have peaks almost coincident with the ones described for form III, suggesting that this is the main polymorphic form present in both.
The values obtained in this study compared to previously published ones sometimes had some deviations in the wavelengths of peak maxima, however, the differences were deemed not to be significant and the tendency for peaks position registered on Table S1 was always the same. For example, -CO-R vibration and -C=C- and –C=O vibration should appear at ~1677 cm\(^{-1}\) and ~1605 cm\(^{-1}\) (Form III) and in our studies it appeared at ~1674 cm\(^{-1}\) and 1603 cm\(^{-1}\).

Afterwards, these vibrational bands were used as reference to study possible changes in the CBZ characteristic bands promoted by the interaction with CDs. These interactions (e.g. the formation of inclusion complexes) may reveal themselves in FTIR by disappearing/shifting of bands or by reducing the band intensity.

Representative samples from all studied CBZ/CD systems were selected (highest concentration point for A\(_L\)-types and one point before and another beyond the plateau region for B-types). The selected FTIR spectra are depicted on Figures S2 (CBZ/native CDs) and S3 (CBZ/HP-CDs).

**Figure S1.** FTIR spectrograms obtained for raw material CBZ (as received) and CBZ solid phase collected from solubility experiment (SE).
On top part of Figure S2 the system CBZ/αCD 15% (percentage represents the theoretical CD concentration which was used to produce this CBZ/CD complex) which showed A_L-type on phase-solubility studies is represented. The solid phase obtained from CBZ/αCD 15% is mainly constituted by CBZ (characteristic peaks from CBZ form III are detectable) but also by some small traces of αCD. Although the characteristic broad peak between 3500-3000 cm\(^{-1}\) is not present, some peaks characteristics from αCD around 1000 cm\(^{-1}\) can be seen in the spectrum. Due to the A_L-type nature of this complex and the very low apparent association constants it is unlikely that insoluble complexes have been formed, meaning that the presence of αCD most likely have been caused by contamination from liquid phase during isolation of the solid phase.

The next analyzed system was also a representative of A_L-type profile, CBZ/βCD 1.5%. FTIR analysis showed a spectrum identical to CBZ without presence of any βCD characteristic bands. This may also be expected due to the limited solubility of βCD making the possibility of detection of a contamination (as in the case of αCD) or a formed complex in a large surplus of CBZ unlikely.
Due to the nature of the CBZ/γCD system (B₅-type), the composition of the solid phase showed significant differences in the recorded spectra dependent on the γCD concentration. CBZ/γCD 1% (representing the linear part of the phase-solubility curve) was tested and results were in accordance with previous experiments. Saturation of complex was not yet achieved at this γCD concentration, so mainly CBZ will be detectable as solid phase for this system (as CBZ is still in surplus even if γCD is present it will be in trace amounts below the limit of detection). However, a solid phase selected immediately after the plateau region of the phase-solubility curve (CBZ/γCD 10%) gave a considerable different spectrum. The 4 characteristic peaks of the CBZ spectrum described in Table S1 shifted or disappeared and characteristic bands from γCD are visible in 3500 cm⁻¹ (broad band that overlap CBZ 3464 cm⁻¹ peak) and 1000 cm⁻¹ regions. These observations suggest that most likely at this γCD concentration the solid phase is mainly composed by a new entity, most probably an insoluble CBZ/γCD complex. Although quite unlikely at this stage, pure CBZ may also be present (if it is still available from initial excess) but in so small amounts that peaks of complex will stand out and dominate the spectrum.

Comparing the data from the most characteristic peaks of the spectra presented in Figure S2 to the ones obtained in Figure S1, we can suggest that CBZ present in the solid phases from CBZ/native CDs systems is mainly present in the polymorphic form III. This was as expected since CBZ form III is the most stable form at room temperature³-⁴,⁸ Koester et al. also used FTIR to prove the formation of inclusion complexes between CBZ and βCD in solid state⁹. These observations are in accordance with ours since they have shown specific peaks for the CBZ/βCD complex that are absent in our spectra, underlining that our samples only consisted on the surplus CBZ added to the phase-solubility experiment.
All HP-CDs displayed $A_L$-type profiles in the phase-solubility studies with CBZ, so the results interpretation previously made for CBZ/αCD and CBZ/βCD solid phases is similar for CBZ/HP-CD systems (Figure S3).

Spectra presented in Figure S3 for the HP-CDs systems also displayed spectra corresponding to CBZ polymorph III. Some peaks in the 1000 cm$^{-1}$ region (characteristic from CDs) also appeared in the spectra, however, we believe that this is not due to precipitation of complex or HP-CDs but caused by contamination from the liquid phase caused by how the solid phases where collected and dried.

In general, the data underlines as expected that no solid CBZ/HP-CD complexes are to be found in the solid phase as only pure CBZ in its polymorphic form III was detected.

Medarević et al. used FTIR technique to prove the formation of complex between HPβCD and CBZ in solid state$^2$. These results are in accordance with what we have observed since they detected peaks from CBZ/HPβCD on their spectrum which are absent in our samples, reinforcing the observation that these solid phases are mainly composed of solid CBZ.
**Differential Scanning Calorimetry (DSC) studies**

DSC was used to study the complexes formed between drug and CDs in the solid phase. As a result of the interaction between them, shifts/disappearance of melting points from the individual components can occur and these can be detected by this technique.

Phase-solubility results suggested the formation of soluble CBZ/CD complexes for αCD, βCD and all HP-CDs (A_L-type). For γCD insoluble CBZ/γCD complexes are expected after the saturation concentration of CBZ/γCD have been reached. To trace the state and content of the obtained solid phases, DSC analysis was carried out using representative samples from all studied systems (e.g. highest concentration point for A_L-types and one point before and other beyond plateau region for B-types).

**Native cyclodextrins**

As mentioned previously CBZ can be present in different polymorphic forms, although form III and I are the most common. In order to confirm the nature of the polymorphic form present in both CBZ references (as received and SE) we analyzed these samples by DSC (Figure S4).

![DSC thermograms performed for CBZ (as received) and CBZ (SE).](image_url)

**Figure S4.** DSC thermograms performed for CBZ (as received) and CBZ (SE).

CBZ as received presented two well-defined sharp endothermic peaks easily identified on the thermogram. The first corresponds to the melting of
polymorphic form III (~175 °C), followed by recrystallization of CBZ as form I (exothermic peak) and then a second characteristic endothermic peak from melting of form I (~191 °C). Thus, CBZ as received is mainly constituted of polymorph III. Similar data have been presented in the literature and the presented fusion peaks were in accordance with previous works\textsuperscript{2,5,7,10-13}.

Unlike the data obtained by FTIR showing only the presence of polymorph III, the DSC data for the CBZ solid phase from the solubility studies (SE) did not provide elucidative conclusions with respect to the identification of which polymorph(s) were present in the studied sample. The presented thermogram is more similar to CBZ form I\textsuperscript{5,12-13} as apparently the melting peak of form III and crystallization peak of form I prior to a melting peak of form I are missing, although a small peak around 165-170 °C can be seen. This is probably the melting peak of form I which might have shifted to lower values. As it is well known the DSC is highly sensitive and analysis depends on the quality of the instrument, scan-rate, quality of the sample (maybe the drying process could transform CBZ SE to form I or a mixture of polymorphs, impurities could be present and so on). All these causes can be responsible for the inconsistencies between the FTIR and the DSC data for the CBZ SE sample. We believed that CBZ SE should be mostly present in this solid phase as form III (as suggested by the FTIR data). As the one of main focuses of this work is to identify the content of the solid phases (pure CBZ, CBZ/CD complex or a mixture of both), the study and determination of the different CBZ polymorphs that might be formed during phase-solubility process (after contact with water, CDs, drying of solid phase, etc.) is out of scope for this study.
Figure S5. Some representative example of DSC thermograms performed for CBZ (form III) and for CBZ/native CD systems.

Figure S5 depicts representative DSC results from solid phases of all tested phase-solubility samples (A_L: CBZ/αCD 15% and CBZ/βCD 1.5%; B_S: CBZ/γCD 1% and CBZ/γCD 10%). The first shown system is CBZ/αCD, represented by CBZ/αCD 15% solid phase (A_L-type). Although the first endothermic peak is quite small, both melting peaks had similar fusion temperature when compared to CBZ reference (as received, form III). Due to this observation and as they did not show any apparent shift we suggest that this solid phase is mostly constituted by CBZ form III. The contamination of the solid phase with αCD already reported by FTIR (from the liquid phase during sampling process) was also detected by DSC through the broad peak from dehydration of CD visible around 100 °C.

A similar interpretation can be made for the other A_L-type solid phase (CBZ/βCD 1.5%). Even though it is quite small, the endothermic peak referring to the melting of form III is still present around 175 °C. The second melting peak appears at a similar temperature as for the reference, around 190 °C. As it is characteristic of A_L-type systems (soluble complexes), only CBZ (most likely form III) is detected in the solid phase.

Finally, Figure S5 shows an example of B_S-type system represented by two concentration points (CBZ/γCD 1% and 10%). The thermogram obtained for CBZ/γCD 1% (a concentration in linear region of phase-solubility diagram) showed some similarities to the one from CBZ form III (same positions for
melting peaks) although the same difficulties in data interpretation were found (first endothermic peak present but barely visible). Anyway, this confirms that only pure CBZ (probably form III) can be identified in a solid phase taken from initial linear part of B$_5$-type sample.

In the sample produced using high γCD concentration (CBZ/γCD 10%) none of the melting peaks from pure CBZ (both form I and III) could be detected. This means that probably the saturation concentration of the complex has been reached and all the initially added solid CBZ had precipitated as γCD complex. As a consequence, pure CBZ peaks have disappeared and mainly solid CBZ/γCD complex is present on solid phase (pure CBZ can also be present but in so small amount that is beyond the detection limit of the method). The broad endothermic peak (~100 °C) is most likely due to the dehydration of the formed CBZ/γCD complex$_{14-15}$.

![DSC thermograms](image)

**Figure S6.** Example of DSC thermograms performed for CBZ (form III) and CBZ/HP-CDs systems.

**Hydroxypropylated cyclodextrins**

The solid phases from the HP-CD systems are expected to display DSC traces matching the pure drug due to the typical high solubility of complexes between drugs and CD derivatives (yielding A$_L$-types phase-solubility...
diagrams). The CBZ/HP-CDs solid phases are not an exception (Figure S6). Some impurities might be present in these solid phases since the second melting peak (~190-191 ºC) is presented as a double peak instead of the single well-defined sharp peak characteristic of CBZ form III. The endothermic peak corresponding to the melting of polymorph form III is also visible (~175 ºC), although the subsequent recrystallization as form I (exothermic peak) that should appear in between melting points is difficult to find.

After analysis of the data and taking into account the difficulties in interpretation of the DSC thermograms already described, we suggest that also in this group (CBZ/HP-CDs) CBZ present in solid phase are mostly found in its form III.

**X-ray powder diffraction (XRPD) studies**

Any crystalline material in the solid phases has characteristic XRPD pattern that makes their identification possible.

CBZ/native CD solid phases were submitted to XRPD analysis as previous techniques (FTIR and DSC) proved the absence of CBZ/HP-CDs complexes in the solid phases of these systems. As for the two previous presented techniques, we selected samples from one concentration of CD to study the composition of the solid phases from CDs displaying A_L-type profiles (CBZ/αCD and CBZ/βCD) and two concentrations for CDs displaying B_S-type solid phase (CBZ/γCD). High quality diffraction patterns were obtained for all the analyzed diffractograms. Representative samples showing the trends that were obtained for each studied system are presented in Figure S7.
The diffractogram of raw CBZ proved that the main polymorphic form present is form III, in accordance with the data obtained by FTIR and to some extent DSC on the same samples. This XPRD pattern is comparable to those presented by other authors. As demonstrated by FTIR, the XRPD diffractograms also show that CBZ SE is present in polymorph form III. This underlines that the interpretation of the DSC data on these polymorphs are not straightforward and care need to be taken when DSC is used as the only method for identification of CBZ polymorphs.

Taking a closer look at the results we can observe that CBZ only precipitates as CD complexes at high γCD concentrations, which is in accordance with the expectations for the B₅-type profiles from the phase-solubility data. Representing the linear part of phase-solubility diagram the solid phase present at 0.5% (w/v) γCD showed a diffractogram identical to those obtained for pure CBZ without any signs of inclusion complex as expected form the previously presented data. The solid phase obtained with 10% (w/v) γCD (representing the post plateau region) yielded a diffraction pattern that is different from the diffraction pattern of both crystalline raw materials (CBZ and γCD). The results thus suggest then that a new compound, most likely a solid CBZ/γCD inclusion complex, has been formed and constitutes the main component of the solid phase at this CD concentration. These results are also in accordance with the obtained FTIR and DSC results.

Figure S7: XRPD spectra of CBZ (as received and SE), native CDs and some selected solid phases (A₅: CBZ/βCD and CBZ/αCD and B₅: CBZ/γCD).
Figure S7 also shows representative examples of two \( \text{A}_L \)-type profiles: CBZ/\( \alpha \)CD and CBZ/\( \beta \)CD. The solid phase obtained at 15\% (w/v) \( \alpha \)CD is almost identical to the diffractograms obtained with pure CBZ (CBZ as received and CBZ SE). The solubility of the CBZ/\( \alpha \)CD complexes justifies the absence of complexes in the solid phase and, consequently, detection of solid inclusion complexes by XRPD. Although this system displayed \( \text{A}_L \)-type phase-solubility profiles, XRPD showed that some peaks referring to crystalline \( \alpha \)CD are also present in this solid phase. This phenomenon was also registered by FTIR and we believe that it is due to the sample preparation.

Figure S7 shows that even at the highest workable \( \beta \)CD concentration (1.5\% w/v) no CBZ/\( \beta \)CD complex can be detected as exclusively a diffraction pattern representing CBZ crystals was obtained.

After an overall analysis and comparison of studied solid phase diffractograms with CBZ reference we can suggest that apparently CBZ is present in solid phase of all tested systems in its polymorphic form III.

Previously other authors have observed patterns characteristic for solid inclusion complexes of CBZ/\( \beta \)CD using XRPD\textsuperscript{9,11}. Similar pattern was absent in all CBZ/\( \beta \)CD samples and by identifying only CBZ crystals as the main component of the solid phase, we also indirectly proved the formation of soluble CBZ/\( \beta \)CD complexes.

Conclusions

FTIR and XRPD techniques suggested that as received pure CBZ, as well as, CBZ SE (solid phase obtained from phase-solubility studies) were dominated by CBZ polymorph form III. These conclusions were only partially supported by DSC. This technique did not provide clear evidence about which polymorphic form of CBZ was present in each group of tested phases, although the results pointed to the presence of the same polymorphic form as detected by the other techniques.

It can be concluded from solid state techniques results that the formation of water soluble complexes for \( \text{A}_L \)-types (CBZ with \( \alpha \)CD, \( \beta \)CD and HP-CDs) hinders their precipitation and, consequently, only CBZ (and small amount of contaminants of native CD from the sampling procedure) can be detected in
solid phase. For γCD (B_S-type), the composition of the solid phase will vary depending on the CD concentration used. Before the saturation concentration of the complex is achieved (linear part of phase-solubility diagram) only CBZ can be detected. Beyond the plateau region, the solid phase composition consists mainly of a solid CBZ/γCD complex. Throughout the plateau region, depending on the amount of solid CBZ still available, a mixture of pure solid CBZ and solid complex can be present.

However, one of the aim of the work was achieved as we could observe that the type of phase-solubility diagram and CD concentration present in the sample are determinant for the composition of final solid phase (the study and identification of different CBZ polymorphic forms in solid phase was out of the scope of this work).

Materials and Methods

Fourier transformed Infrared (FTIR) spectroscopy

FT-IR spectra were recorded at room temperature in the range of 600–4000 cm\(^{-1}\) with the resolution of 4 cm\(^{-1}\) on a Thermo Nicolet iZ10 spectrometer (Thermo Scientific, Madison, USA) in order to elucidate the nature of the solid phases from the phase-solubility studies. FT-IR spectra of raw materials (CDs, CBZ as received and from solubility experiments, SE) was recorded for reference.

Differential Scanning Calorimetry (DSC)

The DSC thermograms of CBZ (as received and SE), CDs (native and their hydroxypropylated derivatives) and dried solid phases from the phase-solubility studies were recorded on a Netzsch DSC 214 polyma (Netzsch GmbH, Germany). Samples were weighted in an aluminum closed pierced crucible and an identical empty one used as reference. Using a constantly purged nitrogen atmosphere, samples were heated up at a rate of 10 °C/min over 25–200 °C temperature range.

X-ray powder diffraction (XRPD) studies
The crystallinity of the various solid phases was determined using X-ray powder diffractometry (XRPD) (Empyrean, PANalytical). Wide angle XRPD using CuKα radiation with the voltage and working current of 45 kV and 40 mA, respectively, was employed. The scan speed, 2θ scan range and step size was set at 0.0691° per sec, 4–55° and 0.013°, respectively. CBZ (as received and SE), native CDs and solid phases from phase-solubility experiments (CBZ/native CD) were tested.

References

1. Narayanan, G.; Boy, R.; Gupta, B. S.; Tonelli, A. E., Analytical techniques for characterizing cyclodextrins and their inclusion complexes with large and small molecular weight guest molecules. Polym. Test. 2017, 62, 402-439.
2. Medarević, D.; Kachrimanis, K.; Djurić, Z.; Ibić, S., Influence of hydrophilic polymers on the complexation of carbamazepine with hydroxypropyl-β-cyclodextrin. Eur. J. Pharm. Sci. 2015, 78, 273-285.
3. Strachan, C. J.; Howell, S. L.; Rades, T.; Gordon, K. C., A theoretical and spectroscopic study of carbamazepine polymorphs. J. Raman Spectrosc. 2004, 35 (5), 401-408.
4. Czernicki, W.; Baranska, M., Carbamazepine polymorphs: Theoretical and experimental vibrational spectroscopy studies. Vib. Spectrosc. 2013, 65, 12-23.
5. Grzesiak, A. L.; Lang, M.; Kim, K.; Matzger, A. J., Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. J. Pharm. Sci. 2003, 92 (11), 2260-2271.
6. Koester, L. S.; Xavier, C. R.; Mayorga, P.; Bassani, V. L., Influence of β-cyclodextrin complexation on carbamazepine release from hydroxypropyl methylcellulose matrix tablets. Eur. J. Pharm. Biopharm. 2003, 55 (1), 85-91.
7. Rustichelli, C.; Gamberini, G.; Ferioli, V.; Gamberini, M. C.; Ficarra, R.; Tommasini, S., Solid-state study of polymorphic drugs: carbamazepine. J. Pharm. Biomed. Anal. 2000, 23 (1), 41-54.
8. Pinto, M. A. L.; Ambrozin, B.; Ferreira, A. P. G.; Cavalheiro, É. T. G., Thermoanalytical studies of carbamazepine: hydration/dehydration, thermal decomposition, and solid phase transitions. Braz. J. Pharm. Sci. 2014, 50, (4), 877-884.
9. Koester, L. S.; Mayorga, P.; Pereira, V. P.; Petzhold, C. L.; Bassani, V. L., Carbamazepine/βCD/HPMC Solid Dispersions. II. Physical Characterization. Drug Dev. Ind. Pharm. 2003, 29 (2), 145-154.
10. Krahn, F. U.; Mielck, J. B., Relations between several polymorphic forms and the dihydrate of carbamazepine. Pharm. acta Helv. 1987, 62 (9), 247-54.
11. Cvetkovskii, A.; Bettini, R.; Tasic, L.; Stupar, M.; Casini, I.; Rossi, A.; Giordano, F., Thermal Properties of Binary Mixtures of β-Cyclodextrin with Carbamazepine Polymorphs. J. Therm. Anal. Calorim. 2002, 68 (2), 669-678.
12. Bettini, R.; Bonassi, L.; Castoro, V.; Rossi, A.; Zema, L.; Gazzaniga, A.; Giordano, F., Solubility and conversion of carbamazepine polymorphs in supercritical carbon dioxide. Eur. J. Pharm. Sci. 2001, 13 (3), 281-286.
13. Tian, F.; Saville, D. J.; Gordon, K. C.; Strachan, C. J.; Zeitler, J. A.; Sandler, N.; Rades, T., The influence of various excipients on the conversion kinetics of carbamazepine polymorphs in aqueous suspension. J. Pharm. Pharmacol. 2007, 59 (2), 193-201.
14. Muankaew, C.; Jansook, P.; Sigurðsson, H. H.; Loftsson, T., Cyclodextrin-based telmisartan ophthalmic suspension: Formulation development for water-insoluble drugs. *Int. J. Pharm.* 2016, 507 (1-2), 21-31.

15. Jansook, P.; Ritthidej, G. C.; Ueda, H.; Stefansson, E.; Loftsson, T., γCD/HPyCD mixtures as solubilizer: solid-state characterization and sample dexamethasone eye drop suspension. *J. Pharm. Pharm. Sci.* 2010, 13 (3), 336-350.

16. Katz Hendler, I.; Azoury, R.; Friedman, M., Crystalline properties of carbamazepine in sustained release hydrophilic matrix tablets based on hydroxypropyl methylcellulose. *J. Control. Release* 1998, 54 (1), 69-85.

17. O’Mahony, M. A.; Maher, A.; Croker, D. M.; Rasmuson, Å. C.; Hodnett, B. K., Examining Solution and Solid State Composition for the Solution-Mediated Polymorphic Transformation of Carbamazepine and Piracetam. *Cryst. Growth Des.* 2012, 12 (4), 1925-1932.