# Dehydration without Heating: Use of Polymer-Assisted Grinding for Understanding the Stability of Hydrates in the Presence of Polymeric Excipients

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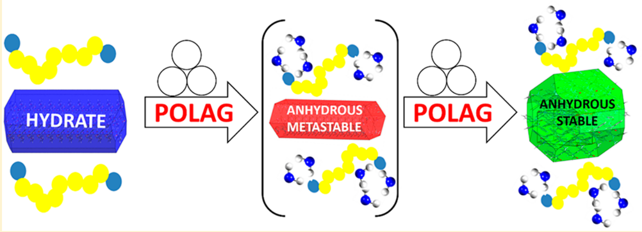
*Supporting Information*



**ABSTRACT:** Hydrates are ubiquitous multicomponent solids of particular interest in the pharmaceutical field. As such, there is a practical need of monitoring the stability of this class of solids, especially when formulated with one or more excipients. In this paper, we propose an innovative solid state method, namely, polymer-assisted grinding (POLAG), for exploring the stability of carbamazepine dihydrate under the simultaneous effects of manufacturing-induced stress (milling) and the presence of polymeric excipients. We demonstrate that, while milling alone did not cause any dehydration, the presence of specific polymers induced partial or total dehydration of the selected model drug carbamazepine dihydrate. Through detailed experimental evidence, it is concluded that the polymer chain length plays a main role in the kinetics of the solid state reaction, while a combination of the amount of polymer and the milling time allowed the isolation of different polymorphic forms of the resulting dehydrated carbamazepine solid. Additional POLAG experiments suggested that polymers of a high molecular weight are less likely to cause dehydration due to their lower affinity for water. POLAG may therefore be used both as a screening method for determining the dehydration propensity of a specific hydrated form in the presence of polymers and for isolating highly metastable forms of the resulting anhydrous product.

## INTRODUCTION

Hydrates are ubiquitous and belong to the class of multicomponent solids known as solvates. A survey of the Cambridge Structural Database (CSD) reveals that approximately 15% of all organic crystal structures entries are solvates,[1] with hydrates representing more than half of the reported solvates. Because of their relative abundance, such multicomponent solids are of particular interest in the pharmaceutical field, with an estimate that more than 60% of marketed active pharmaceutical ingredients (API) are able to form hydrates.[2]

Hydrates may exhibit markedly different physicochemical properties relative to the anhydrous forms.[3,4] There is, therefore, a practical need for monitoring not only the hydration propensity of a drug solid but also the stability of the resulting hydrate/s. Indeed, conversion from the anhydrous form to the hydrate is a frequent phenomenon during API manufacture and storage.[5] This does not mean, however, that the hydrated form is always stable and that the opposite phenomenon cannot occur. In this context, studies addressed on the understanding of phase transformations of several hydrated systems can be divided mainly into two groups: (i) process-induced phase transformations and (ii) phase transformations induced by the interaction of hydrates with excipients, including polymers. As for the first point, some hydrates do indeed revert back to the anhydrous form during processing such as drying,[6] wet granulation,[7] or even when the relative humidity of the environment is decreased.[8,9] On the other hand, the formation and the stability of the hydrates can be affected by the presence of other materials introduced to the final drug product—such as polymeric excipients. For instance, it has been observed that certain polymers such as polyvinylpirrolidone and hydroxypropylcellulose prevented hydrate formation of the anhydrous olanzapine, while polyethylene glycol promoted the formation of a higher hydrate of the same drug.[10]

The formulation pathway of a pharmaceutical hydrate from the pure crystalline solid to the final dosage form (e.g., tablets, granules, etc.) is complex. Therefore, the effect of process-induced stress should be considered simultaneously along with the effect of particular excipients. In this context, we propose an alternative solid state method (namely, polymer-assisted grinding (POLAG)) for exploring the stability of a preformed hydrate under mechanical stress in the presence of polymeric excipients.

POLAG is a new mechanochemical method that uses polymers in association with grinding for promoting and/or accelerating mechanochemical reactions.[11] For instance, the method has been used recently both as a screening technique for new solid forms[12] and in covalent organic reactions for the synthesis of an anticonvulsant drug.[13] In the present study, POLAG is used as a screening technique for the controlled removal of water molecules of a model hydrated API. We selected carbamazepine (CBZ), an anticonvulsant drug used in the treatment of epilepsy and trigeminal neuralgia, as a model system since it is known to crystallize in five different polymorphic forms,[14,15] with Form III being the thermodynamic polymorph and Form II generally accepted as the less stable form (Figure 1).[16] CBZ can also crystallize in the presence of water molecules as a dihydrate (CBZ DH, Figure 1) using a variety of methods such as slurrying,[17] cooling crystallization,[18] and exposure to high humidity.[19] On the other hand, although CBZ DH is relatively stable under normal conditions,[20] many studies have concerned its stability under various stress conditions[20−23] or in the presence of polymeric excipients.[24−26] In the study reported here, different experimental data sets were obtained by modifying polymer chain length, the chemical composition of the polymer, the amount of polymer added, and the grinding time. The effect of each parameter was analyzed qualitatively, and a mechanism of dehydration was proposed based on experimental evidence.

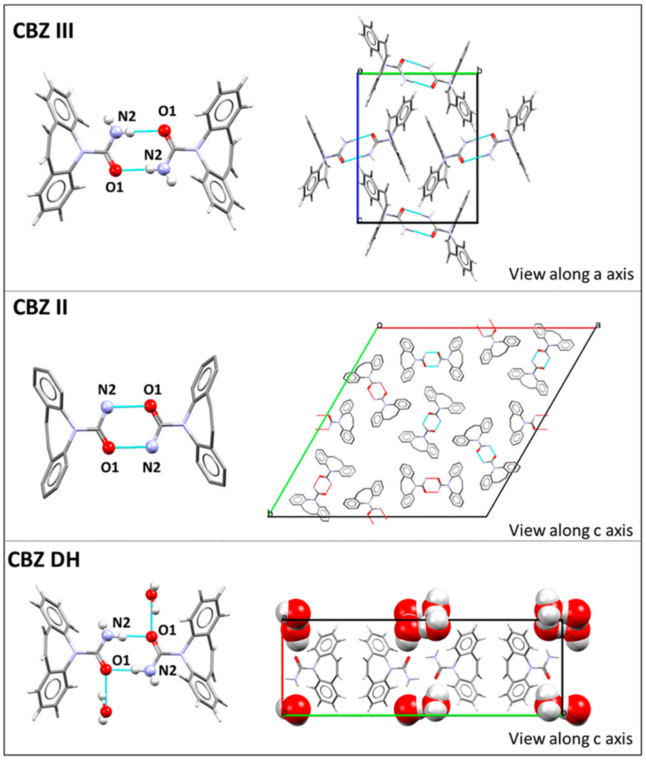


**Figure 1.** Crystal packing of (top) anhydrous CBZ Form III,[27] (middle) CBZ Form II,[28] and (bottom) CBZ DH.[29]

## ■ EXPERIMENTAL SECTION

**Materials.** Carbamazepine 98% (polymorphic Form III) was provided by Alfa Aesar (Thermo Fisher Scientific). Polyethylene glycol (PEG) and the other polymers were purchased from Sigma-Aldrich Company, Ltd. (Gillingham, UK) and used without further purification. PEGs 200, 300, and 400 were liquids, PEG 600 was semisolid, while PEGs with a higher chain length (PEG 1000 and above) were solids at room temperature.

**Grinding Procedure.** POLAG experiments were carried out using a Retsch MM200 grinding mill. In a typical experiment, 200 mg of freshly prepared CBZ DH was transferred in a 15 mL steel jar containing two grinding balls of 7 mm diameter and ground in neat conditions or in the presence of different polymers at a fixed frequency of 25 Hz. While the amount of CBZ DH was kept fixed at 200 mg, the amount of the polymer varied from 25 mg to 400 mg, while the milling time ranged from 1 to 180 min. Product samples were characterized using powder X-ray diffraction within 60 min following their preparation.

**Preparation of CBZ DH by Solution Crystallization.** CBZ DH crystals were prepared following the procedure reported by Khoo et al.[30] Specifically, crystals were obtained from cooling crystallization using ethanol/water (75:25, v-v) solutions. Clear solutions containing approximately 70 mg mL$^{-1}$ of CBZ Form III were prepared under reflux and gentle agitation at 70 °C. The systems were then cooled to room temperature at 5 °C min$^{-1}$, and the resulting crystals were collected by vacuum filtration.

**PXRD Analysis.** Powder X-ray diffraction (PXRD) was performed at room temperature using a Panalytical X'Pert Pro Diffractometer with Ni-filtered Cu-K$\alpha$ radiation (wavelength 1.5418 Å) equipped with an RTMS X'celerator detector. A small amount of powder (20−30 mg) was gently pressed on a glass slide to give a flat surface and subsequently analyzed. The data were collected in the 2 theta range 3−40° using a step size of 0.0334° and a scan speed of 0.142°/s. For each analysis, the total number of steps was 1107 and the total time was 5 min.

## ■ RESULTS

Previous investigations demonstrated that in a POLAG reaction the amount of a PEG polymer present during milling can significantly affect the product outcome.[11] The first experimental data set, therefore, was obtained using different amounts of a series of PEGs of increasing molecular weight. The results are summarized in Figure 2, while the experimental PXRD patterns are reported in Figures 3, 4 and Figures S1−S6.

The results summarized in Figure 2 suggest that both chain length and the amount of the polymer used affected the solid state dehydration of CBZ DH. Partial dehydration was observed when the amount of polymer was increased to 50 mg and 100 mg per 200 mg of CBZ DH, with the resulting PXRD patterns presented a series of diffraction peaks typical of anhydrous CBZ Form III, which is the commercial polymorphic form of CBZ[31] (Figure 3). POLAG experiments with higher amounts (from 150 mg to 400 mg of polymer per 200 mg of CBZ DH) produced pure anhydrous CBZ Form III (Figure 3). The presence of CBZ DH can be noticed particularly from the diffraction reflections at 8.9° and 12.3(5)° of 2$\theta$ angle,[29] while the presence of anhydrous CBZ Form III can be distinguished by characteristic reflections at 13.2°, 14.3°, and 16° of 2$\theta$ angle.[13]

POLAG experiments with different amounts of PEG 300 produced results similar to those obtained using PEG 200 (Figure 2 and Figure S1). In the case of experiments with PEG

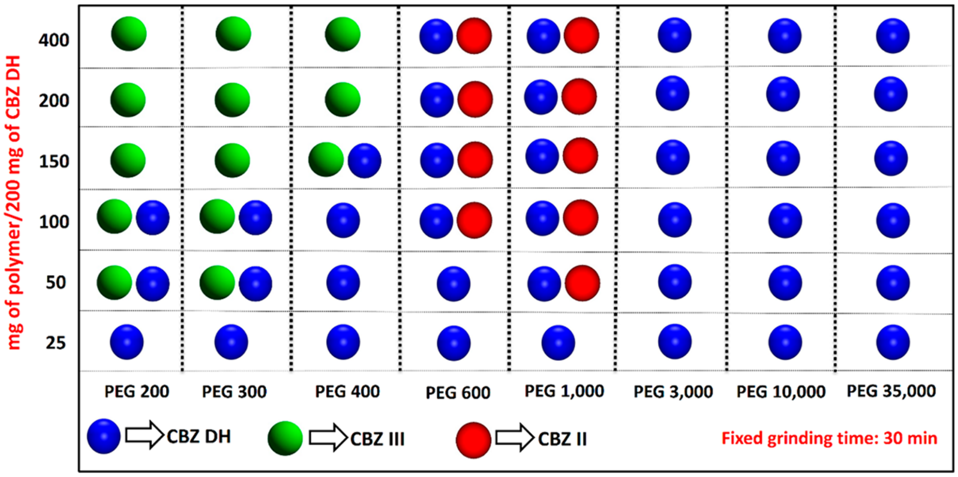


**Figure 2.** Summary of POLAG experiments obtained using polymers with different chain lengths. Blue, green, and red circles represent solid products containing X-ray pure CBZ DH, anhydrous CBZ Form III and Form II respectively, while the presence of two circles indicates that the solid product contained two CBZ forms.

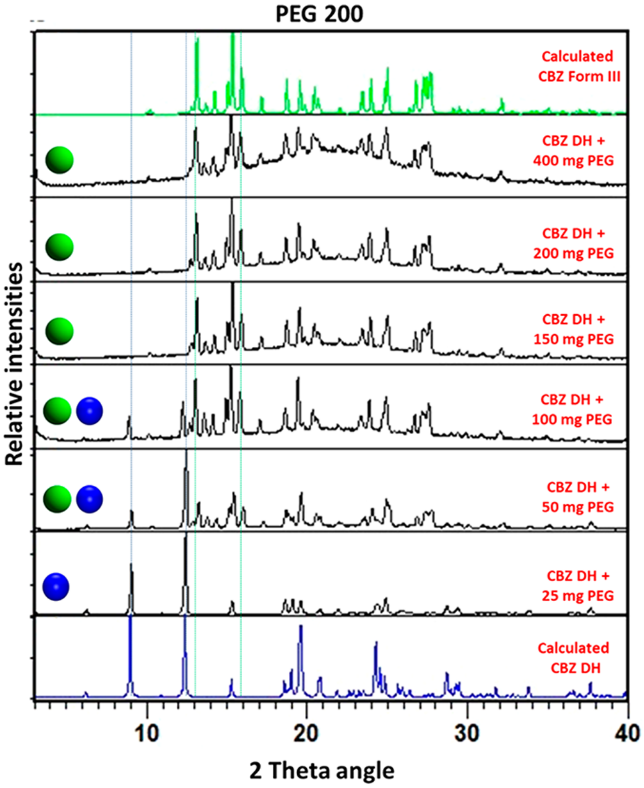


**Figure 3.** PXRD patterns of POLAG products obtained using different amounts of PEG 200. Blue and green circles represent solid products containing X-ray pure CBZ DH and CBZ Form III respectively, while the presence of two circles suggests that the solid product contained two different solid forms.

400, the minimum amount required to partially remove the water molecules from the crystal lattice of CBZ DH increased to 150 mg of polymer. Higher amounts of PEG 400 produced pure anhydrous CBZ Form III. The threshold for partial dehydration was similar also in the case of PEG 600. Importantly, in the case of PEG 600, the PXRD patterns of the solid product obtained 100 mg or higher amount of polymer per 200 mg of CBZ DH, corresponded to a mixture of CBZ DH and anhydrous CBZ Form II, which is one of the less stable polymorphic forms of CBZ.[28]

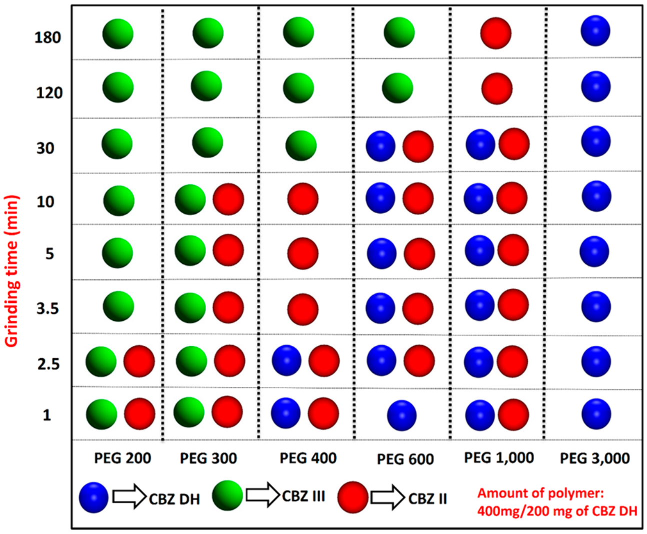


**Figure 4.** Summary of POLAG experiments performed with different PEGs and different grinding times. For each polymer, the amount was kept fixed at 400 mg for 200 mg of CBZ DH. Blue, green, and red circles represent solid products containing X-ray pure CBZ DH, anhydrous CBZ Form III, and Form II, respectively, while presence of two circles suggests that the solid product contained two different solid forms.

In the case of POLAG experiments using different amounts of PEG 1000, the minimum amount of polymer for partially dehydrating 200 mg of CBZ DH was 50 mg. Indeed, PXRD analysis suggested that in all but one case (the product obtained in the presence of 25 mg of polymer) a mixture of CBZ DH and anhydrous CBZ Form II was obtained (see Figure 2 and Figure S4). POLAG experiments with different amounts of higher molecular weights did not produce any dehydrated form of CBZ (see Figures S5−S7).

In order to observe the solid mixtures of CBZ DH and anhydrous CBZ (of either Form III or Form II) obtained after 30 min of grinding equilibrium mixtures, a second experimental data set was produced by maintaining a fixed amount of a specific polymer while varying the grinding time from 1 to 180 min. The results are summarized in Figure 4. In the case of experiments with PEG 200 and 300, the mechanochemical dehydration of CBZ DH was almost instantaneous, with the solid product obtained after 1 min of grinding consisting of a mixture of anhydrous CBZ Form III and Form II (see Figures S8−S9). A mixture of the two polymorphic forms of CBZ was also obtained after 2.5 min of grinding.[32] Longer milling times (from 3 min up to 180 min) produced pure anhydrous CBZ Form III in the case of experiments with PEG 200. In the case of PEG 300, the presence of anhydrous CBZ Form II could be detected up to 10 min of grinding (Figure S9). Solid products obtained with 400 mg of PEG 400 were different; a partial dehydration was observed in the first 2.5 min of grinding. Noteworthy, after 3.5, 5, and 10 min of grinding, the products consisted of pure anhydrous CBZ Form II, while higher milling times generated pure anhydrous CBZ Form III (Figure 5). In the case of POLAG experiments with PEG 600, the mechanochemical dehydration of CBZ DH was slightly slower. Indeed, after 1 min of grinding, it was not possible to detect by PXRD the presence of anhydrous CBZ. Further grinding (up to 30 min) repeatedly produced a mixture of CBZ DH and anhydrous CBZ Form II. Prolonged milling times of 120 and 180 min produced outcomes similar to the experiments with lower chain length PEGs, i.e., the most stable anhydrous CBZ polymorphic Form III (Figure 4). The mechanochemical dehydration of CBZ DH was significantly slower in the case of experiments with 400 mg of PEG 1000 per 200 mg of CBZ DH (Figure 4). A PXRD pattern corresponding to pure anhydrous CBZ Form II was obtained only after 120 and 180 min of grinding. It is also worth noting that in the case of experiments with PEG 1000 it was not possible to detect the presence of anhydrous CBZ Form III even after 180 min of grinding (Figure S11). Finally, experiments using PEG 3000 generated in all cases pure CBZ DH (Figure S12).

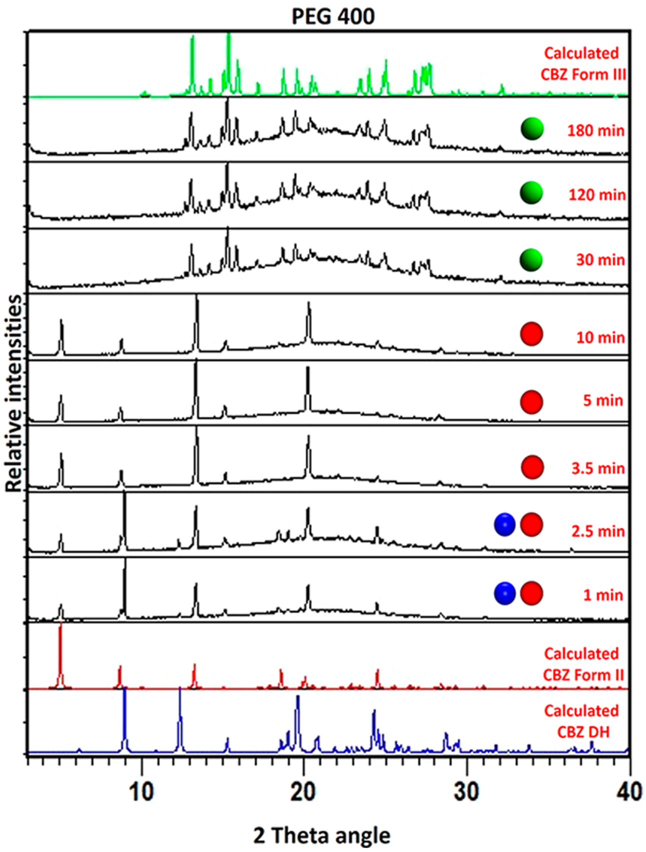


**Figure 5.** PXRD patterns of solid products obtained through POLAG using 400 mg of PEG 400 per 200 mg of CBZ DH. Blue, green, and red circles represent solid products containing X-ray pure CBZ DH, anhydrous CBZ Form III and Form II respectively, while the presence of two circles suggests that the solid product contained two different solid forms.

The results reported in Figures 2 and 4 suggest that mechanochemical dehydration of CBZ DH and the resulting polymorphic form of the produced anhydrous CBZ depended on both the polymer chain length and the grinding time. In order to investigate further the role of the PEG chain length on the rate of the dehydration of CBZ DH, a third experimental data set was obtained. Specifically, 200 mg of polymers of different chain lengths was preground for 30 min at 25 Hz in the presence of 30 $\mu$L of distilled water. Such an amount of water corresponds to the amount of water contained in 200 mg of CBZ DH. Subsequently, 200 mg of anhydrous CBZ Form III (the commercial form) were added to the jar and ground for an additional 30 min. The products were collected and analyzed by PXRD, with the results reported in Figure 6.

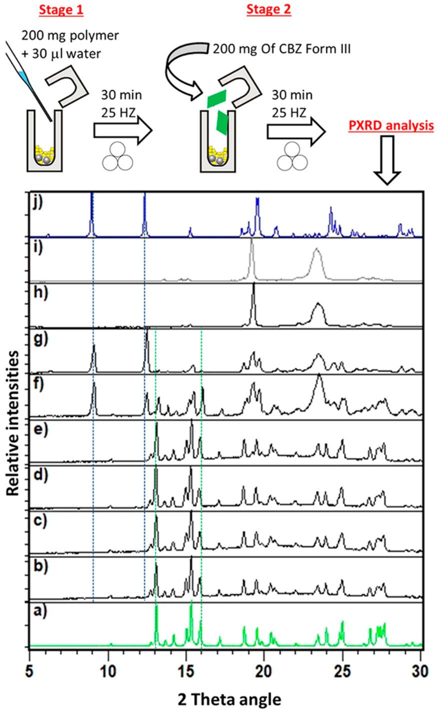


**Figure 6.** PXRD pattern of (a) calculated anhydrous CBZ Form III,[13] (b), (c), (d), (e), (f), (g), products obtained by grinding 200 mg of anhydrous CBZ Form III in the presence of 200 mg of PEG 200, 300, 400, 600, 1,000, and 3,000 respectively, (h) and (i) pure PEG 1000 and 3000 respectively, and (j) calculated CBZ DH.[29] Prior to the addition of CBZ, each polymer was preground for 30 min in the presence of 30 $\mu$L of water.

From Figure 6 it can be observed that anhydrous CBZ Form III did not transform into CBZ DH after 30 min of grinding when 30 $\mu$L of water are predispersed in 200 mg of PEG 200, 300, 400, or 600. Interestingly, in the case of PEG 1000 a partial transformation of anhydrous CBZ Form III into CBZ DH was observed after 30 min of grinding, while in the case of

PEG 3000 the transformation was complete. We may speculate that also in the case of PEG 1000, pure CBZ DH would be eventually generated by longer milling times.

The water−polymer affinity experiments were extended to a series of other polymers commonly used as excipients during formulation development. For such polymers, however, it was not possible to perform a screening using different chain lengths as such choices are not commercially available. We therefore decided to use the most frequent chain length that would be selected during the formulation of a drug. The results reported in Figure 7 suggested that in all cases CBZ Form III transformed almost totally into CBZ DH after 30 min of grinding at 25 Hz in the presence of different polymers presaturated with water. The outcome was similar in all cases, suggesting that the different chemical composition of the chosen polymers did not affect the hydration propensity of anhydrous CBZ.

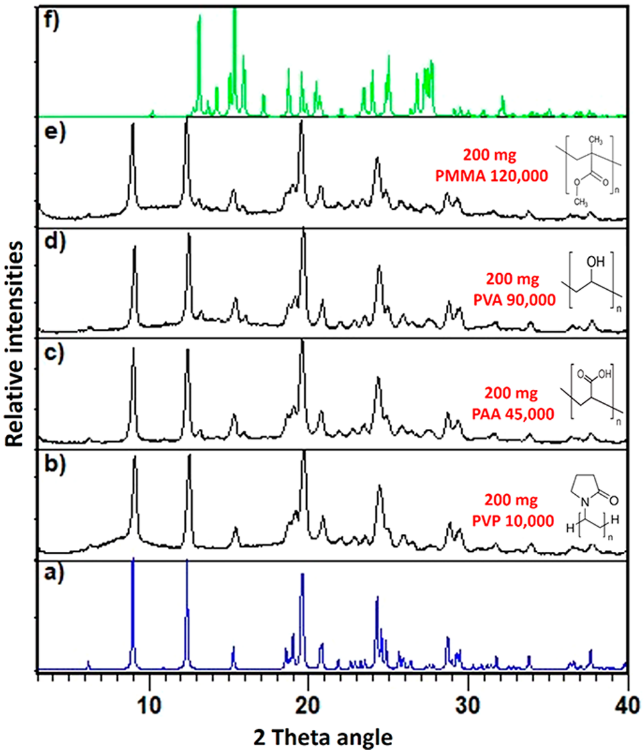


**Figure 7.** PXRD pattern of (a) calculated CBZ DH,[29] (b), (c), (d), (e), products obtained by grinding 200 mg of anhydrous CBZ Form III in the presence of 200 mg of polyvinylpyrrolidone (PVP) 10000, poly(acrylic acid) (PAA) 45000, poly(vinyl alcohol) (PVA) 90000 and poly(methyl methacrylate) (PMMA) 120000 respectively, (f) calculated anhydrous CBZ Form III.[13] Prior to the addition of CBZ each polymer was preground for 30 min in the presence of 30 $\mu$L of water.

## ■ DISCUSSION

The above results indicate that the rate of mechanochemical dehydration of CBZ DH through POLAG depends on the polymer chain length. Indeed, from Figure 2 it is clear that at a fixed grinding time of 30 min, PEGs with a short chain length are highly effective in removing water from CBZ DH crystal lattice, while PEGs with a molecular weight of 3000 or higher did not cause any solid form modification. The mechanochemical dehydration of CBZ DH was also affected by a combined effect of polymer amount and grinding time (Figures 2 and 4). Indeed, although the minimum amount of polymer required for a complete dehydration of 200 mg of CBZ DH increased gradually with PEGs 200, 300, and 400, PEGs with a molecular weight such as PEG 600 and PEG 1000 did not produce pure anhydrous CBZ in 30 min of grinding even when the amount of the polymer used was double to that of CBZ DH. In these later cases, it was necessary to mill CBZ DH for longer times (such as 120 and 180 min) in the presence of large amounts of polymer to obtain a pure anhydrous product. It is also worth noting that in the case of polymers that did cause dehydration, specifically PEGs 200−1000, there was a minimum amount/threshold before dehydration was detected. Such a threshold did not increase regularly by increasing the polymer chain length. For example, in the case of PEG 200 and PEG 300, the minimum amount of polymer required for the dehydration to start was 50 mg per 200 mg of CBZ DH, this value increased to 150 mg when PEG 400 was used, while it decreasing to 100 mg in the case of PEG 600 and to 50 mg in the case of POLAG experiments with PEG 1000 (Figure 2).

The resulting form of the dehydrated product depended strongly on the grinding time. Specifically, the presence of CBZ Form II, a highly unstable polymorph,[16,33,34] was detected with short milling times for all the polymers used, while prolonged grinding produced CBZ Form III (Figure 4). These observations suggest that the first crystal product resulting from mechanochemical dehydration of CBZ DH is CBZ Form II. The reason for such a transformation pathway can be explained based on the Ostwald Rule of Stages.[35] It is expected that the unstable product of dehydration, which could be an isostructural dehydrate lattice or amorphous CBZ, tends to transform into a crystal form via the smallest loss of free energy. According to the literature,[16,36] CBZ Form II is the first metastable state that could be reached with the smallest driving force. CBZ Form II is considered, however, a transient state, and its formation and detection may be strongly affected by several experimental conditions. Specifically, we believe that the detection of the highly unstable CBZ Form II depends on an interplay of grinding time and the properties of the polymer used. With regard to the grinding time, the lower stability of CBZ Form II under mechanical stress is also well-known. Indeed, Kala et al. reported that CBZ Form II promptly converted into Form III under compression.[37]

Additionally, in a recent study, Kulla et al.[38] analyzed the cocrystal formation of pyrazinamide with malonic acid by grinding using in situ PXRD and Raman spectroscopy. The results revealed the presence of a metastable form, which converted quickly into a more stable form upon grinding. The authors therefore highlighted the importance of selecting an appropriate milling time during a mechanochemical reaction that should reflect not only completion (complete transformation of the reactants into a product) but also selectivity toward the desired polymorphic form. What is more interesting, however, is that in the present study the kinetics of the polymorphic conversion of CBZ Form II into Form III appears to be affected by the polymer chain length. In particular, in the case of polymers with a short chain length such as PEGs 200, 300, and 400, CBZ Form II could be detected only at shorter milling times (up to a few minutes), while a further increase of the monomer chain length, such as PEG 1000, made possible the detection of CBZ Form II even after 30 min of high intensity grinding. In a previous study,[12]

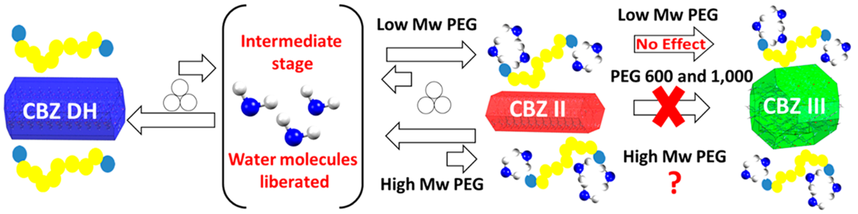


**Figure 8.** Schematic representation of the suggested mechanisms involved in the mechanochemical dehydration of CBZ DH in the presence of different PEG polymers.

we observed that the mechanochemical polymorph transition of a dimorphic cocrystal system could be modified using PEGs with different chain lengths. Indeed, through the calculation of the solubility parameters, it was reported that long chain polymers such as PEG 10000 were less polar compared to short chain PEGs such as PEG 200.[12] We therefore speculate that the presence of polymers with a specific chain length such a PEG 1000 can modify (decelerate) the kinetics of transformation of CBZ Form II into a more stable polymorph that is CBZ Form III. Additionally, since the polymer molecular weight can significantly affect the particle size of a POLAG product,[11] the role of particle size should also be considered. In this context, Navrotsky and coauthors observed that in the case of several inorganic solids the stability of specific polymorph was strongly correlated to the crystal size.[39] In other words: polymorphs which are metastable as micrometer or larger size can often be thermodynamically stabilized at the nanoscale.[40] These observations were recently extended also in the case of liquid-assisted grinding (LAG) reactions.[41,42] Indeed, subjecting a system to specific mechanochemical conditions may move the system to a point in phase space where a metastable polymorphic form becomes the most stable structure.[43] In the present study, the presence and dispersion of CBZ Form II to specific PEGs such as PEG 1000 possibly generates nanocrystals with a specific particle size for slowing down the conversion of CBZ Form II into CBZ Form III.

As mentioned above, neat grinding of CBZ DH for up to 180 min does not result in any dehydration (Figure S13). It is, therefore, clear that the added polymer plays a major role in the mechanical dehydration of CBZ DH. The above results, however, also indicate that the removal of water molecules from the crystal lattice of CBZ DH under POLAG conditions is a complex process. In fact, it is well accepted that in a typical mechanochemical reaction the transformation of reactant solids into a product is likely to occur by the interplay of several mechanisms.[16] Such multimechanism solid state transformations are not limited to ball milling and also can be found in other process-induced dehydration events. Indeed, in a very recent study, Raijada et al. reported that the dehydration of nitrofurantoin monohydrate in the presence poly(ethylene oxide) during melt extrusion occurred through an interplay of two mechanisms, namely, solubilization into the polymer of the hydrate form and subsequent crystallization of the anhydrous form, and heat-induced dehydration.[44] In the present mechanochemical study, it is unlikely that heat-induced dehydration will play a major and can be inferred from the grinding experiments performed with pure hydrate alone where the dihydrate was stable for 180 min of grinding. On the other hand, it cannot be excluded that partial solubilization of CBZ DH into the polymer and subsequent crystallization (due to supersaturation in the polymer) as anhydrous CBZ Form II occurred also during grinding experiments performed here. Such a mechanism alone, however, does not explain completely why polymers with the same chemical composition but different chain length would show such a dissimilar dehydration capability. Consequently, other possible mechanisms should be considered, perhaps related not only to the solubilization kinetics of CBZ into the polymers but rather to the water affinity that can be modified by changing the molecular weight of PEG. Indeed, the experimental data set where polymers were pretreated with a certain amount of water and then coground with anhydrous CBZ Form III showed that water molecules "preferred to stay dispersed" within the polymer matrix in the case of POLAG experiments with PEGs having chain length of up to 1000 monomer units, while in the case of PEG 3000 and a series of other polymers water molecules were incorporated into the CBZ crystal structure forming CBZ DH (Figures 6−7).

A detailed analysis of the interaction strength of water molecules with different polymers and a possible comparison with hydrogen bonding involved within the crystal structure of CBZ DH are beyond the scope of this study, although in a recent study it was reported that the primary criterion for solvate formation is that the solute−solvent affinity must be sufficient to overwhelm the solute−solute and solvent−solvent affinities.[45] We believe that in the case of POLAG experiments where dehydration was detected, the interaction strength between water molecules and polymer was higher compared to the CBZ−water hydrogen bonds present in the crystal structure of CBZ DH (Figure 1). This difference served as the driving force for water molecules to remain "entrapped" within the polymeric network. In the case of long-chain polymers (such polymers are generally less polar than short chain polymers[12]), the interaction strength between polymer and water was not sufficient to overcome the H-bond network of CBZ DH, and thus dehydration was not observed. The differences in the interaction strength between PEGs with different molecular weights can also be related with a different dehydration rate. Indeed, in the case of POLAG experiments with short chain PEGs, dehydration of 200 mg of CBZ DH was completed within a few minutes as the driving force for removing water molecules from the crystal lattice was high (large difference between the strength of polymer−water and CBZ−water interactions), while in the case of PEG 600 and PEG 1000 there was a lower driving force (similar strength of interaction between polymer−water and CBZ−water); thus the dehydration process needed a higher amount of mechanical energy to remove all the water molecules from the crystal lattice of CBZ DH.

On the basis of the comments above, a summary of the suggested mechanisms for the mechanochemical dehydration of CBZ DH in the presence of PEG is reported in Figure 8. In the proposed mechanism, grinding of CBZ DH would initially cause the formation of a highly metastable product as an intermediate where water molecules are "liberated" from the crystal lattice for a very short time. The formation of such a highly energetic intermediate is typical for mechanochemical reactions.[43,46,47] In the case of neat grinding of CBZ DH, the experimental conditions do not allow such a metastable phase to be kinetically trapped and therefore persist as a product. In other words, if the grinding of CBZ DH was considered as a continuous dehydration and rehydration of CBZ, the equilibrium would be completely shifted toward the rehydration reaction in neat grinding conditions. By modifying such conditions through the addition of specific polymers, it is likely that the equilibrium between hydration and dehydration is also modified. Specifically, PEGs with a low molecular would move the equilibrium toward dehydration due to their high affinity for the water molecules. This would cause the formation of an anhydrous product, specifically CBZ Form II as a kinetic form, which in the presence of such polymers converts into the more stable polymorph CBZ Form III. In the case of PEG 600 and 1000, the first equilibrium is also shifted toward the dehydration reaction due to a certain affinity for the water molecules, although the driving force for dehydration is significantly lower compared to POLAG experiments with short chain polymers. On the other hand, PEG 600 and PEG 1000 provide favorable conditions for slowing the transformation of CBZ Form II into Form III. Finally, in the case of polymers with a higher molecular weight, the situation is similar to the neat grinding in that the low affinity of the polymer for water does not affect the dehydration−rehydration equilibrium, while their effect on the polymorphic transition CBZ Form II−CBZ Form III needs further investigations and is beyond the scope of the present study. One possibility would be performing a series of interconversion experiments between CBZ Form II and Form III in POLAG conditions using PEG 3000 or PEG 10000.

## ■ CONCLUSIONS

In summary, we have successfully provided extensive experimental evidence that POLAG is an effective method for the solid state dehydration of carbamazepine dihydrate. The systematic methodology used for exploring the effect of different polymers on the kinetics of the mechanochemical dehydration of the selected model drug suggests that the polymer chain length plays the main role in the kinetics of the solid state reaction, while a combination of the polymer amount and grinding time allows suitable conditions for isolating different polymorphic forms of the resulting dehydrated solid. Indeed, two polymorphs of anhydrous carbamazepine were obtained, namely, carbamazepine Form II (the less stable polymorph) and Form III, the thermodynamic form (at room temperature). To the best of our knowledge, this represents the first time where carbamazepine Form II is obtained by a solid state method. Additional POLAG experiments designed to understand the mechanisms involved in the solid state reactions suggest that the polymer−water interaction strength is a crucial parameter for the mechanochemical dehydration in the presence of a polymer, and must overcome the H-bond interactions between water and drug in the crystal lattice of the hydrate in order to act as a driving force for dehydration to occur. Noteworthy, it was observed that the polymer−water interaction strength decreased by increasing the polymer chain length. Additionally, PEGs with different chain lengths showed different effects toward the conversion of metastable carbamazepine Form II into polymorphic Form III.

The benefits of using POLAG for the dehydration of hydrates can be at least 2-fold. First, such a technique gives important information about the stability of a specific hydrate in the presence of polymeric excipients and can, therefore, be used as a rapid screening method for determining the stability of hydrates during formulation studies. Second, comparable to other already existing dehydration techniques,[48] dehydration via POLAG can be used to isolate highly metastable forms of the resulting dehydrated product. An additional advantage of POLAG would consist of the effect that a specific polymer can have for polymorphs with a high tendency of converting into a more stable form.

Opportunities for future work include extending the study to other hydrate forms and performing POLAG experiments with different chain lengths polymers. This would help confirm the mechanism proposed in this study where polymer affinity toward water played a major role during mechanochemical dehydration of carbamazepine dihydrate. In this context, in situ real time investigations[49−51] would be extremely useful for understanding better the role of polymers during the mechanochemical dehydration of hydrates and also for "knowing when to stop" in order to get the desired anhydrous polymorphic form.[38] Additionally, it would be also interesting to apply POLAG for the controlled dehydration of other multicomponent hydrates such as cocrystal hydrates. In that case, the polymer should be "able" to remove the water molecules and provide favorable conditions for the anhydrous cocrystal being the most stable form—or perhaps for the formation of new cocrystal forms. Finally, we believe that these results can be extended for the mechanochemical desolvation of other solvates in addition to hydrates.

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### Notes

The authors declare no competing financial interest.

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