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Role of polymers in solution and tablet based carbamazepine cocrystal formulations

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The aim of this study was to evaluate the influence of three chemically diverse polymers of Hydroxypropylemthylcellulose acetate succinate (HPMCAS), Polyvinylpyrrolidone (PVP) and PolyEthylene Glycol (PEG) on the phase transformation of three carbamazepine (CBZ) cocrystals of carbamazepine-nicotinamide (CBZ-NIC), carbamazepine-saccharin (CBZ-SAC) and carbamazepine-cinnamic acid (CBZ-CIN) in solution and tablet based formulations. Based on the solubility and powder dissolution studies, it demonstrates that cocrystals can be easily formulated through a simple solution formulation or powder formulation to generate supersaturated concentrations and faster dissolution rates to overcome those drugs with solubility and/or dissolution limited bioavailability. However, a polymer based CBZ cocrystal tablet formulation has not shown any advantage of an improved CBZ release rate compared with the formulation of CBZ III or physical mixtures of CBZ III and coformers. This is contradictive to the solution behaviours of CBZ cocrystals in the solubility and powder dissolution tests because crystallization of the stable solid form of CBZ dihydrate (CBZ DH) within the tablet has taken place, leading to a reduced drug release rate and incomplete release. The mechanism of a polymer inhibition effect on the drug precipitation in solution has been elucidated through investigating the molecular interactions among CBZ, coformers and polymers in solution using infrared spectroscopy. Finally the formulation strategy has been proposed to capture the significant advantage of cocrystals.

Introduction

Solubility and dissolution rate are the most important physicochemical properties of active pharmaceutical ingredients (APIs) in drug discovery and development. Many candidates with promising pharmacological properties have to be withdrawal from development due to their poor aqueous solubility and/or dissolution rates. There has been significant ongoing research in improving the aqueous solubility and dissolution rates of such drug candidates, in particular those of BCS II compounds with high permeability and low solubility [1]. Among many effective methods, such as particle size reduction, solid dispersion, salt formation and cyclodextrin complexing agents, pharmaceutical cocrystals have been recognised as an alternative approach to improve the solubility and bioavailability of poorly water soluble drugs [2-7]. In order to form cocrystals with higher solubility than its parent drugs, different solubility coformers are required [2, 8]. When these cocrystals are dissolved, they can create supersaturated states of the parent drug concentrations which exceed its equilibrium solubility. Although a higher drug concentration can increase its oral absorption, the drug is thermodynamically unstable at such high concentrations, leading to crystallisation of less soluble solid forms of the parent drugs. This phenomenon is called solution mediated phase transformation (SMPT) [9]. In our previous work, we have demonstrated that the SMPT of cocrystals can significantly compromise the advantages of the improved solubility and dissolution rates [10, 11].

In order to benefit from the supersaturated state of drugs in solution generated by dissolution of cocrystals, it is essential to develop effective formulations to maintain the increased drug concentrations for a time period for absorption to overcome solubility limited bioavailability. This could be achieved through inclusion of pharmaceutical excipients as precipitation (or crystallisation) inhibitors in the formulation. A large number of excipients have been explored as precipitation inhibitors to maintain drugs in other supersaturating drug delivery systems such as solid dispersions and lipid-based formulations [12-14]. These excipients including polymers, surfactants and cyclodextrins can interfere with drug nucleation and/or crystal growth to inhibit and/or retard the drug precipitation from solution. However, very limited research has been carried out to study a supersaturating cocrystal system in order to capture the solubility advantages [11, 15-19]. In an earlier study, it has been found that the combinations of celecoxib-nicotinamide (Cel-Nic) cocrystal with both 1–10% solid SDS and PVP can have up to 4-fold more bioavailable than marketed Cel-III in contrast with the neat Cel-Nic cocrystal formulation which

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dissolves more slowly than commercial Cel-III into 1% SDS solution [17]. In another study, it has been demonstrated that the advantage of the improved solubility of a 1:1 danazole-vanillin cocrystal can only be captured by a suitable formulation containing 1% vitamin E-TPGS and 2% Klucel LF Pharm hydroxypropylcellulose [16]. In the meantime, several previous studies have revealed that inclusions of the excipients of polymers and surfactants in formulations have not shown the effectiveness to capture the enhanced solubility advantage of the cocrystals of indomethacin-saccharin and carbamazepine-nicotinamide [15, 18]. Therefore, the selections of both excipients and coformers are essential for success of enabling cocrystal formulations [11, 19]. In our previous study it has been found that the rate difference between the cocrystal dissolution and formation of a soluble complex between the parent drug and polymer in solution is a vital factor to inhibit the precipitation of the drugs at supersaturated concentrations [19]. In parallel, our very latest work has shown that through selection of a suitable coformer to form stable cocrystals in solution the dissolution advantage can be easily captured in a cocrystal formulation [11]. In order to select the optimal polymer and coformer for a given API in a cocrystal formulation, more systematic investigation is needed to provide guides to avoid potential performance risks of the cocrystal formulations.

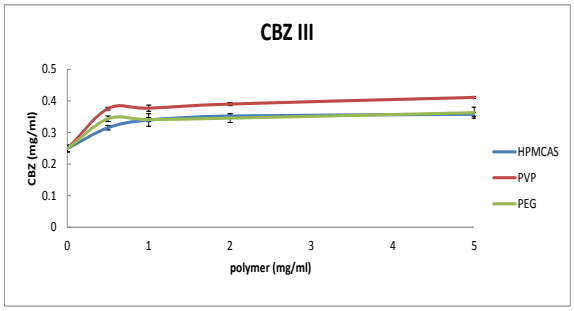
The aim of the current study was to evaluate the effects of three chemically diverse polymers on phase transformation and release profiles of three carbamazepine cocrystals with significantly different solubility and dissolution rates including 1:1 carbamazepine-nicotinimide (CBZ-NIC), 1:1 carbamazepine-saccharin (CBZ-SAC) and 1:1 carbamazepine-cinnamic acid (CBZ-CIN) cocrystals [11, 18-21]. Three chemically diverse polymers including hydroxypropylemthylcellulose acetate succinate (HPMCAS), polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) were selected in the study because they have been widely used as precipitation inhibitors in other supersaturating drug delivery systems and approved orally commercial products [12-14, 22]. In order to evaluate the effectiveness of these polymers on inhibiting the phase transformation of cocrystals, the study was carried out with polymers in both pre-dissolved solution and tablet based formulations. Two types of dissolution testing experiments were conducted: 1) cocrystal powder dissolution tests in the dissolution medium of pH6.8 phosphate buffer solution (PBS) in the absence and presence of pre-dissolved polymers to investigate the polymer effects on the drug precipitation and 2) dissolution tests for tablets of mixture of the cocrystals (or physical mixtures of drug and coformers) and polymers to assess the effects of the polymer release kinetics on the cocrystal release profiles. Both of powder and tablet dissolution tests were carried out under sink conditions with aims to identify the rate difference between the cocrystal dissolution and interaction of the drug and polymer in solution [19]. In order to investigate the mechanism of a polymer inhibition effect on the drug precipitation in solution, the molecular interactions among CBZ, coformers and polymers in solution were investigated using infrared spectroscopy. In the meantime, the apparent equilibrium solubility of the CBZ cocrystals and parent drug CBZ III in ph6.8 PBS in absence and presence of different concentrations of the selected polymers was measured to evaluate the polymer solubilization effects in solution formulations. By comparing the behavior of cocrystals with that of physical mixtures or the pure parent drug, it was expected to elucidate the role of polymers in solution and tablet based cocrystal formulations.

Results

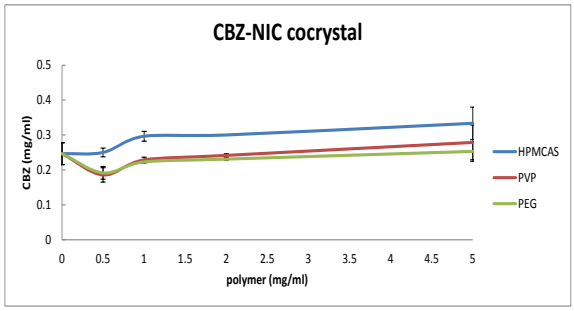
Solubility studies

Figs. 1(a)-(d) show the CBZ concentrations after the solubility tests of CBZ III and cocrystals of CBZ-NIC, CBZ-SAC, and CBZ-CIN in the absence and presence of the different concentrations of a pre-dissolved polymer of HPMCAS, PVP or PEG in pH6.8 PBS at equilibrium after 24h.

It is revealed that all three polymers of HPMCAS, PVP and PEG can enhance the solubility of CBZ III shown in Fig. 1(a). The equilibrium concentration of CBZ in solution increased with increasing a polymer concentration and reached its maximum at 1 mg/mL for all the polymers and then was constant. It is found that the solubility enhancement by the polymers was limited, which was 1.5 fold increase by polymers of both of HPMCAS and PEG and slightly higher increase of 1.6 fold by PVP. The solubility enhancement was caused by formation of the soluble complex through hydrogen bonding between CBZ and polymers [19, 23]. However, these polymers show significantly different precipitation inhibition abilities. HPMCAS can completely inhibit the transformation of CBZ III into CBZ dihydrate (CBZ DH). In contrast, either PVP or PEG can inhibit the transformation of CBZ III into CBZ DH. This was confirmed by the DSC thermographs of the solid residues retrieved from the solubility tests. Fig. 2 shows the comparison of DSC thermographs of original samples and the solid residues obtained from the solubility tests in the absence and presence of a 2 mg/mL polymer in pH6.8 PBS. In pH6.8 PBS without a polymer, the solid residues of the CBZ III test were CBZ DH crystals, showing that the dehydration process happened between 80-120°C under DSC heating. After dehydration, CBZ DH converted back to CBZ III which melted around 175°C and then recrystallized a more stable form CBZ I which was melted around 196°C [19]. In the presence of 2 mg/mL PVP or PEG in pH6.8 PBS, CBZ DH crystals were found in the solid residues of the CBZ III test, showing a similar DSC thermograph as that of solid residues in pH6.8 PBS in the absence of a polymer. However, the dehydration peak of the DSC thermograph from the test in the presence of PVP or PEG was significantly lower than that of the solid residues in the absence of a polymer, indicating the solid residues were the mixture of CBZ DH and CBZ III. Therefore PVP or PEG can partially inhibit the transformation of CBZ III into CBZ DH. In the presence of 2 mg/mL HPMCAS in pH6.8 PBS, the DSC thermograph of the solid residues was the same of the starting materials CBZ III due to HPMCAS inhibition effect. Similar as HPMC, the hydroxyl groups of HPMCAS can attach to CBZ at the site of water binding to form stable CBZ-HPMCAS complexes, resulting in inhibiting CBZ transformation to the dihydrate form CBZ DH [11, 19, 23]. SEM photographs of solid residues obtained from the tests in Fig. S1 in the Supporting information have further supported the above analyses. Similar results can be found in the other solubility tests in the presence of different concentrations of a polymer of HPMCAS, PVP or PEG, including 0.5 mg/mL, 1 mg/mL and 5 mg/mL by the DSC



(a)



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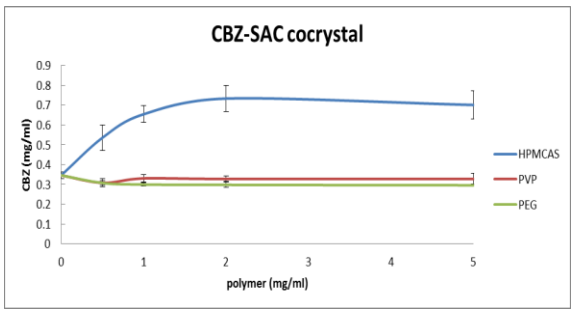

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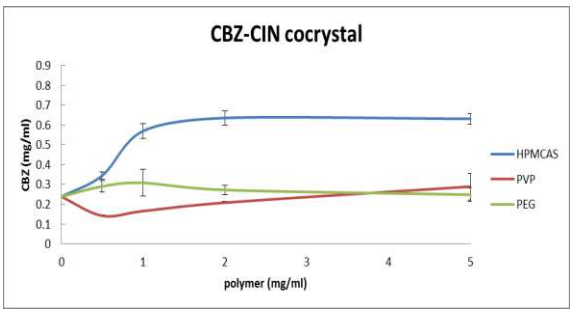
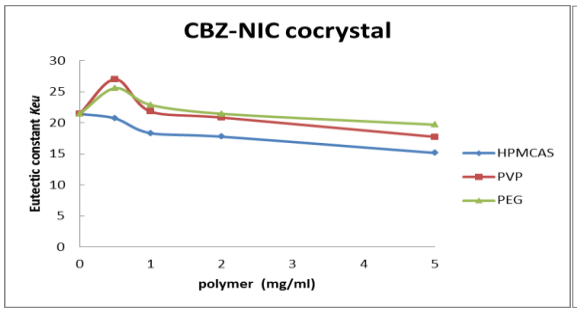


(d)



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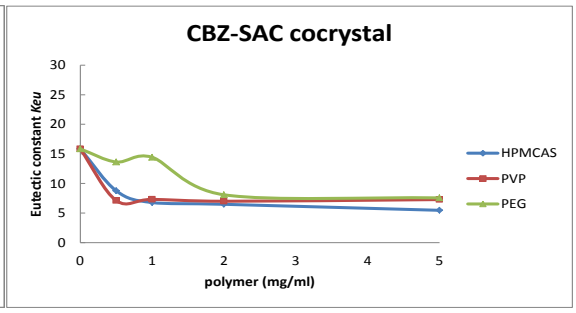
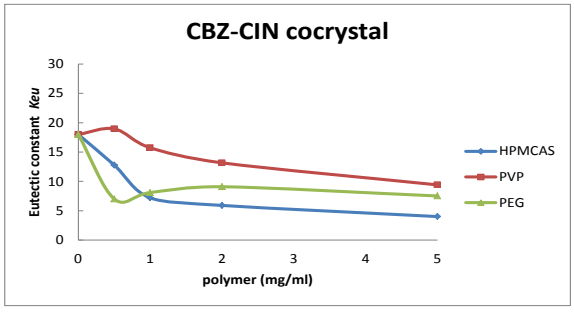


(f)



(g)

Fig. 1 CBZ concentrations in the absence and presence of the different concentrations of pre-dissolved polymers in pH6.8 PBS at equilibrium after 24 H: (a) CBZ III; (b) CBZ-NIC cocrystal; (c) CBZ-SAC cocrystal; (d) CBZ-CIN cocrystal; (e) eutectic constant for CBZ-NIC cocrystal; (f) eutectic constant for CBZ-SAC cocrystal; (g) eutectic constant for CBZ-CIN cocrystal

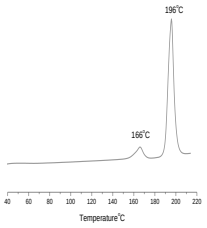
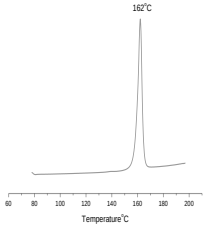
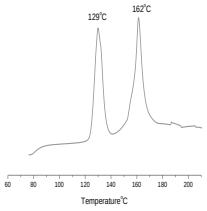
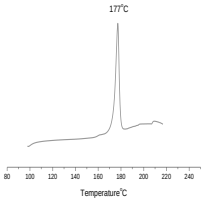
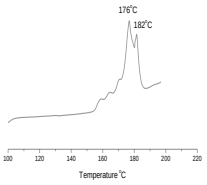
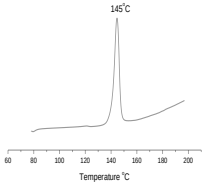
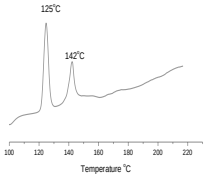
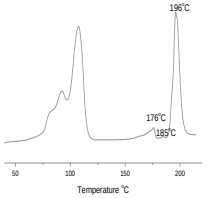
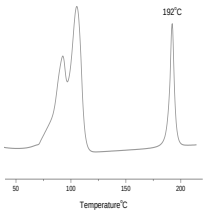
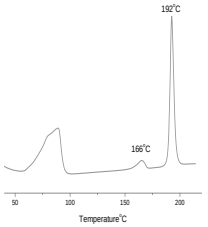
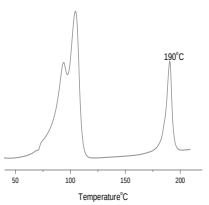
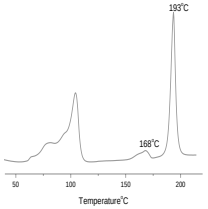
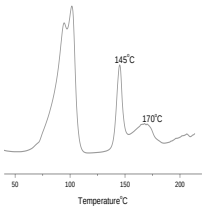
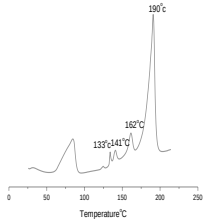
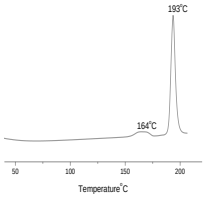
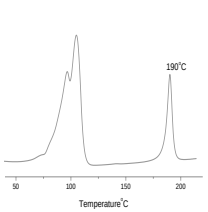
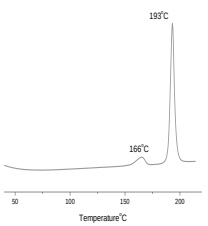
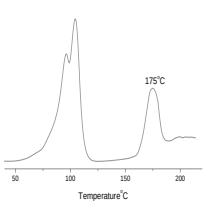
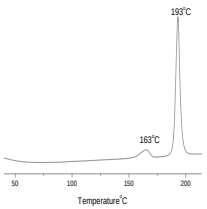
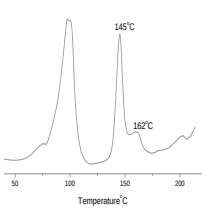
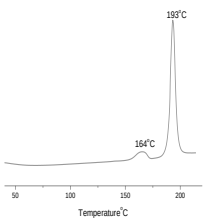
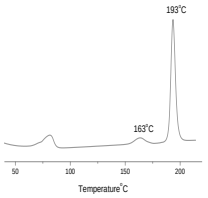
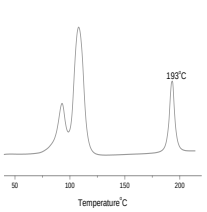
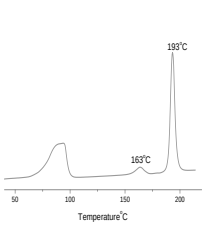
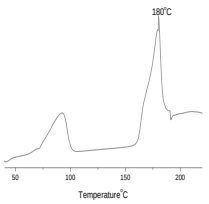
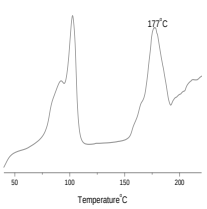
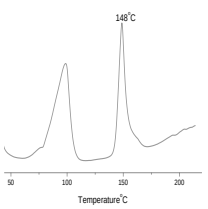
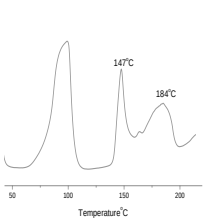
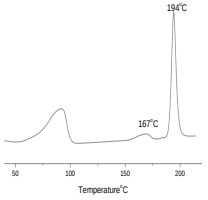
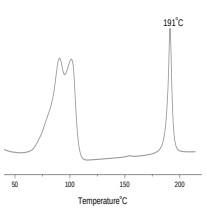
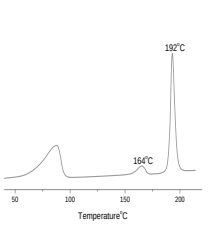
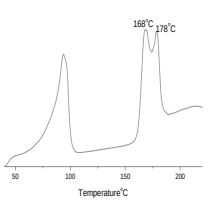
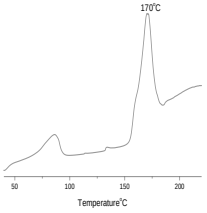
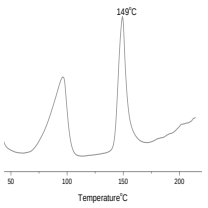
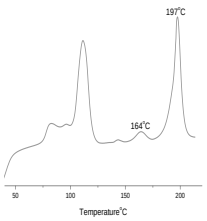
		CBZ III	CBZ-NIC cocrystal	CBZ-NIC mixture	CBZ-SAC cocrystal	CBZ-SAC mixture	CBZ-CIN cocrystal	CBZ-CIN mixture
Original samples								
pH 6.8 PBS								
pH 6.8 PBS in the presence of 2mg/ml	HPMCAS							
	PVP							
	PEG							

Fig. 2 DSC thermographs of original samples and solid residues retrieved from solubility studies in the absence and presence of 2 mg/ml polymer in pH6.8 PBS

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thermographs of the solid residues in Fig. S2 and SEM photographs in Fig. S3 in the Supporting information.

For CBZ-NIC cocrystal, the apparent CBZ concentration was the same as that of CBZ III in pH6.8 PBS in the absence of a polymer. It was increased slightly with increasing the concentration of HPMCAS up to 1 mg/mL in pH6.8 PBS and then was constant. A pre-dissolved polymer of PVP or PEG in pH 6.8 PBS at any concentration tested did not affect the apparent CBZ concentration of CBZ-NIC cocrystal which was the same as the solubility of CBZ III in pH6.8 PBS in the absence of a polymer, although the apparent CBZ concentration was slightly decreased in a low polymer concentration shown in Fig. 1(b). Having examined the DSC thermographs and SEM photographs of solid residues after the solubility tests in Fig. 2 and Fig. S1 in the Supporting information (Fig. S2 and Fig. S3 show the results in the other polymer concentrations in the Supporting information), it is clearly shown that the original CBZ-NIC cocrystals have completely transferred into needle-like CBZ DH crystals, indicating that none of the polymers of HPMCAS, PVP, and PEG can inhibit the crystallisation of CBZ DH from solution, which is similar to the polymer of HPMC in our previous publication [19]. Based on the solubility test of the physical mixture of CBZ III-NIC, it has been found that NIC did not affect the apparent solubility of CBZ III in the absence and presence of a polymer in pH6.8 PBS shown in Fig. S4 in the Supporting information. A pre-dissolved HPMCAS in pH6.8 PBS can inhibit the transformation of CBZ into CBZ DH for the physical mixture of CBZ III-NIC, confirmed by the DSC thermographs in Fig. 2 and SEM photographs in Fig. S1 in the Supporting information.

The apparent CBZ concentration of CBZ-SAC cocrystal (about 0.35 mg/mL) in pH6.8 PBS in the absence of a polymer was 1.4 fold of that of CBZ III (0.25 mg/mL), indicating the enhanced solubility advantage of the cocrystals. Based on the SEM photograph of the solid residues after the test in Fig. S1, it was found that part of CBZ-SAC cocrystals had transferred into needle-like CBZ DH crystals. When HPMCAS was pre-dissolved in pH6.8 PBS, the apparent CBZ solubility of CBZ-SAC cocrystal increased dramatically and it reached its maximum 0.74 mg/mL at 2 mg/mL of HPMCAS concentration, which was 2.1-fold of the solubility of CBZ III in the same polymer solution and 3-fold solubility of CBZ III in pH6.8 PBS in the absence of HMPCAS. Although the CBZ DH crystals were found in the solid residues of the tests shown in the DSC thermographs in Fig. 2 (other results in Fig. S2 in the Supporting information), its percentage was significantly lower than those in the absence of HPMCAS in pH6.8 PBS shown in the SEM photographs in Fig. S1, indicating that HPMCAS can partially inhibit the precipitation of CBZ from solution. Pre-dissolved PVP in pH6.8 PBS did not affect the apparent CBZ concentration of CBZ-SAC cocrystal, showing the constant CBZ concentration with different concentrations of PVP shown in Fig. 1. The solid residues were the mixture of CBZ-SAC cocrystals and CBZ DH crystals confirmed by the DSC analysis in Fig. 2 (other results in Fig. S1 in the Supporting information) and SEM photographs in Fig. S1 (other results in Fig. S3 in the Supporting information), indicating the pre-dissolved PVP can partially inhibit the crystallisation of CBZ DH, but it was less effective than HPMCAS. Pre-dissolved PEG in pH6.8 PBS slightly decreased the apparent CBZ concentration of CBZ-SAC cocrystal in comparison with that of CBZ-SAC cocrystal in the absence of the polymer, showing that PEG enhanced the precipitation of CBZ DH from solution, which was confirmed by the SEM photographs in Fig. S1 (other results in Fig. S3 in the Supporting information), in which large amount of needle-like CBZ DH crystals was found in the solid residues after the tests. The solubility of SAC decreased slightly when a polymer of HPMCAS, PVP or PEG was pre-dissolved in pH6.8 PBS shown in Fig. S4(a) in the Supporting information. Therefore SAC can change the CBZ concentration of the physical mixture of CBZ III-SAC in the presence of a polymer in pH6.8 PBS shown in Fig. S4(a) in the Supporting information.

Fig. 1(d) shows the apparent CBZ concentration of CBZ-CIN cocrystals in absence and presence of a polymer in solution. The apparent CBZ concentration of CBZ-CIN cocrystal in pH6.8 PBS was same as that of CBZ III. When HPMCAS was pre-dissolved in the solution, the apparent CBZ concentration of CBZ-CIN cocrystal increased significantly. At 2 mg/mL of HPMCAS concentration the CBZ-CIN cocrystal can increase 2.7 fold of the solubility of CBZ III in pH6.8 PBS, which is slightly lower than that of CBZ-SAC cocrytal in the same condition. In the presence of PVP in pH6.8 PBS, it is shown that PVP has a profound effect on the apparent CBZ concentration of CBZ-CIN cocrystal. At a lower concentration of 0.5 mg/mL PVP, the apparent CBZ concentration of CBZ-CIN cocrystal was significantly lower than that of CBZ III and at a higher PVP concentration (2 mg/mL or 5 mg/mL) the CBZ concentration of CBZ-CIN cocrystal increased to the same level of the solubility of CBZ III. PEG pre-dissolved in solution did not significantly affect the apparent CBZ concentration of CBZ-CIN cocrystal, showing a nearly constant CBZ concentration in different concentrations of PEG. The solid residues of CBZ-CIN cocrystal in pH6.8 PBS in the absence and presence of a polymer of HPMCAS, PVP, or PEG were physical mixtures of CBZ DH and CBZ-CIN cocrystal confirmed by DSC analysis in Fig. 2 and SEM photographs in Fig. S1. The CBZ concentration of the physical mixture of CBZ III-CIN was constant in the absence and presence of a polymer in pH6.8 PBS showing in Fig. S4 in the Supporting information and is lower than that CBZ III or CBZ-CIN cocrystal. However, the components of the solid residues from the tests were different. In the absence of a polymer, the solid residues contained mixtures of CBZ DH, CIN and CBZ-CIN cocrystal. In the presence of HPMCAS in solution, the solid residues were CBZ III, indicating that HPMCAS completely inhibited the transformation of CBZ III to CBZ DH. In contract, in the presence of PVP or PEG in solution, both CBZ DH and CBZ-CIN cocrystal were found in the solid

residues. DSC analysis in Fig. 2 and SEM photographs in Fig. S1 support the above analyses.

Figs. 1(e)-(g) show the ratios of CBZ and its corresponding coformer concentrations for the three CBZ cocrystals. This parameter is also called the cocrystal eutectic constant K_{eu}, which can be used as an indicator of the stability of cocyrstals in solution [11, 15]. Detailed discussion will be given in the discussion section.

Powder dissolution studies

Fig. 3 presents the effect of a pre-dissolved 2 mg/mL concentration of HPMCAS, PVP or PEG on the powder dissolution profiles of CBZ III and cocrystals of CBZ-NIC, CBZ-SAC and CBZ-CIN. It has been found that a pre-dissolved polymer did not improve the dissolution rate of CBZ III. Actually a pre-dissolved polymer of HPMCAS or PVP decreased the release rate of CBZ III while as the pre-dissolved PEG did not affect the dissolution rate of CBZ III. The reduced dissolution rate is most likely caused by the reduced diffusion coefficient of CBZ in solution due to the change of the bulk solution properties, in particular the increased viscosity of solution with a pre-dissolved polymer.

In contrast, all three pre-dissolved polymers in pH6.8 PBS can increase the dissolution rates of three CBZ cocrystals. PEG shows the smallest effect on increasing the dissolution rates of the CBZ cocrystals. HPMCAS and PVP have the similar effects on increasing the dissolution rates of the CBZ cocrystals. Although the physicochemical properties are significantly different between CBZ-NIC and CBZ-CIN cocrystals, the dissolution profiles (p>0.05) are similar in the absence or presence of a polymer of 2 mg/mL concentration in pH6.8 PBS, which are faster than those of CBZ-SAC cocrystals. In the meantime, all three cocrystals show a significant advantage of an improved dissolution rate than that of CBZ III. In the presence of a 2 mg/mL HPMCAS in pH6.8 PBS, the cocrystals of CBZ-NIC and CBZ-CIN can be dissolved about 80% within 5 minutes in comparison with 10% of CBZ III in the same condition and period.

CBZ release profiles from HPMCAS, PVP and PEG based tablets

Fig. 4 presents the comparisons of CBZ release profiles from different polymer-based tablets. It has been found that none of the cocrystal formulations shows a better performance compared with the CBZ III formulation.

Depending on a coformer, the dissolution profile of a physical mixture formulation can vary significantly (p<0.05). Generally a physical mixture of the CBZ III-NIC formulation had a similar release performance as that of the CBZ III formulation. The dissolution performance of a physical mixture of the CBZ III-SAC in HPMCAS or PVP tablets was in the middle of the formulations of CBZ III and CBZ-SAC cocrystal. For the PEG based tablets, the release profiles of the physical mixture of CBZ III-SAC were better than those of CBZ III based formulations. The dissolution performance of a physical mixture of CBZ III-CIN varied with different polymers. In HPMCAS or PVP based tablets, CIN reduced the release rate of CBZ III, indicating that the release profile of a physical mixture of CBZ III-CIN was lower than that of CBZ III alone. In a HPMCAS based tablet, the physical mixture of CBZ III-CIN had a lower release profile than that of the cocrystal formulation up to 4 hours. In a PVP based tablet, the physical mixture of CBZ III-CIN shows a lower release profile

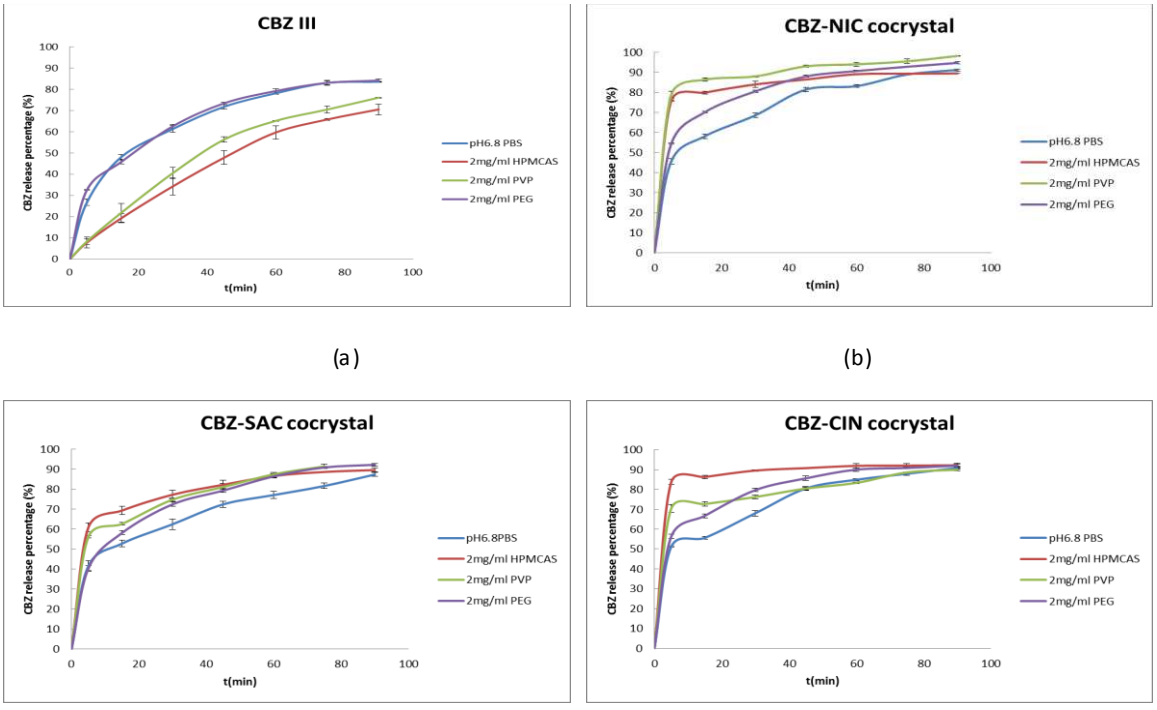
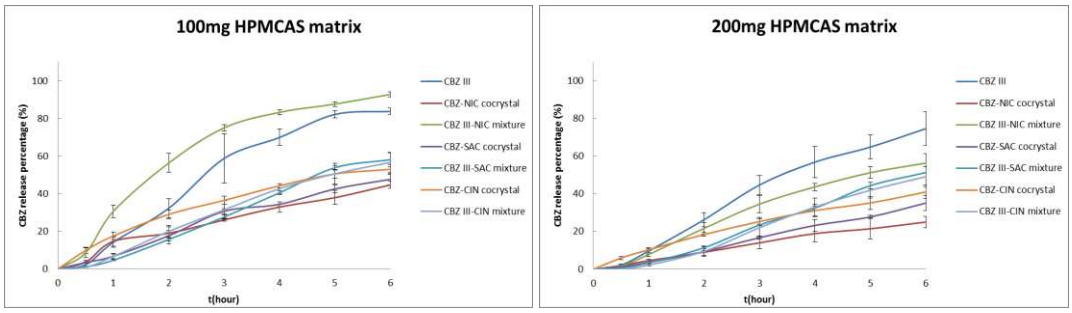
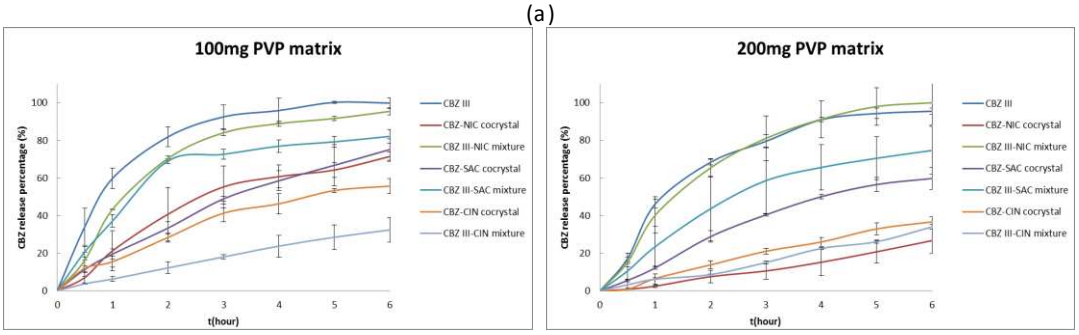


Fig. 3 Powder dissolution profiles in the absence and presence of a 2 mg/ml pre-dissolved polymer in pH6.8 PBS: (a) CBZ III; (b) CBZ-NIC cocrystal; (c) CBZ-SAC cocrystal; (d) CBZ-CIN cocrystal



(a)



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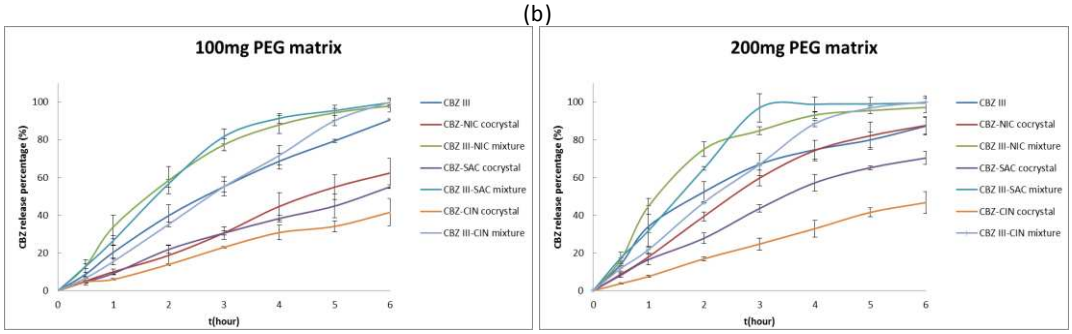

(c)

Fig. 4 CBZ release profiles of CBZ III, cocrystals of CBZ-NIC, CBZ-SAC and CBZ-CIN from 100mg and 200mg polymer based tablets: (a) HPMC based tablets; (b) PVP based tablets; (c) PEG based tablets

than that of the cocrystal formulation over the whole dissolution period. In a PEG based tablet, the physical mixture of CBZ III-CIN had a higher release profile than that of the cocrystal formulation. Up to 3-hour dissolution, the physical mixture of CBZIII-CIN formulation shows a lower rate profile than that of CBZ III alone in PEG based tablets.

In the meantime, the drug release profile is also affected by the percentage of a polymer in the tablet, varying with different polymers. PEG shows the different effects on the performance of the formulations in comparison with the polymers of HPMCAS and PVP. Increasing the percentage of PEG in a formulation increased the dissolution of the drug. In contrast, increasing the percentage of HPMCAS or PVP in a formulation slowed down the drug release.

The solid residues of different formulations after the dissolution tests (if any reasonable amount of the solids can be collected for testing) have been analysed by XRPD in Fig. 5 (DSC in Fig. S5 and SEM in Fig. S6 in the Supporting information). It has been shown that all cocrystal formulations had solid residues left after 6-hour dissolution except of the 100 mg PVP based CBZ-SAC cocrystal formulation. The solid residues from these cocrystal formulations were the mixture of CBZ cocrytals and CBZ DH crystals confirmed by XRPD patterns in Fig. 5, indicating that the CBZ DH crystals were precipitated during dissolution. Tablets of the CBZ III formulations and physical mixture of CBZ III-NIC had dissolved completely. The solid residues collected from the 200 mg HPMCAS-based physical mixture of CBZ III-SAC were CBZ III, indicating HPMCAS can completely inhibit the transformation of CBZ III into CBZ DH during tablet dissolution. For the HPMCAS based physical mixture of CBZ III-CIN formulations, the solid residues were the mixture of the original materials of CBZ III and CIN shown in XRPD patterns in Fig. 5. However, for the PVP based physical mixture of CBZ III-CIN formulation, the solid residues were the mixture of three components of CBZ III, CIN and CBZ DH, indicating PVP cannot inhibit the transformation of CBZ III into CBZ DH during tablet dissolution.

For any of PEG based formations, there was no solid residue collected because the tablet was either broken into fine particles or dissolved completely.

Spectroscopic investigation of CBZ, coformers and polymers interaction in solution

Fig. 6 shows comparison of the spectra of CBZ cocrystal solids with solution spectra of individual components and mixture in absence and presence of different polymers. The IR spectrum of CBZ-NIC cocrystal solids in Fig. 6(a) shows the strong characteristic peak of 1681 cm^{-1} due to the intermolecular hydrogen bonding between the carboxamide groups from both CBZ and NIC [10]. The IR spectra of the individual components of CBZ and NIC in Methanol show the strong bands at 1686 and 1674 cm^{-1} due to the carboxamide groups. When two components are mixed in solution, it can be seen that a new strong peak at 1681 cm^{-1} which is exactly same as that of the CBZ-NIC cocrystal solids is formed and the individual bands of the two components disappear, indicating the formation of CBZ-NIC complex through the molecular interaction in solution. By adding a polymer of HPMCAS, PVP, or PEG in solution, the spectrum of the mixed CBZ and NIC solution is kept as the same, indicating that none of the polymers has interacted with CBZ, NIC or CBZ-NIC complex.

The characteristic peak of CBZ-SAC cocrystal at 1724 cm^{-1} can be clearly seen in Fig. 6(b) due to the intermolecular hydrogen bonding between the carbonyl groups from both CBZ and SAC [11]. The IR spectra of individual components of CBZ and SAC in Acetonitrile show the strong bands at 1686 and 1743 cm^{-1}. There is no new characteristic peak formed when two components are mixed in solution, showing no interaction between CBZ and SAC in solution. By adding a polymer of HPMCAS, PVP, or PEG in solution, the spectrum of the mixed CBZ and SAC in solution has changed. For example, in the presence of PVP in solution both characteristic bands of CBZ at 1686 cm^{-1} and SAC at 1743 cm^{-1} have shifted to 1681 and 1740 cm^{-1}, indicting the intermolecular bonding can be formed between the polymer and CBZ or SAC.

For CBZ-CIN cocrystal solids, one of the characteristic peaks in Fig 6(c-1) is at 1697 cm^{-1} due to the intermolecular hydrogen bonding between the amide and acid groups from CBZ and CIN [11]. The IR spectra of individual components of CBZ and CIN in Acetonitrile show the strong bands at 1686 and 1716 cm^{-1}. Although the characteristic peaks at 1697 cm^{-1} of the CBZ-CIN cocrystal solids disappears in Fig. 6(c-1) when two components are mixed in solution, a new characteristic peak is formed at 1311 cm^{-1} in Fig. 6(c-2), showing the formation of CBZ-CIN complex in solution. By adding a polymer of HPMCAS, PVP, or PEG in solution, the spectrum of the mixed CBZ and CIN in solution has changed significantly. For example, in the presence of HPMCAS in solution both characteristic bands of CBZ at 1686 cm^{-1}, CIN at 1743 cm^{-1} and CBZ-NIC complex at 1311 cm^{-1} have shifted, indicating that the intermolecular bonds can be formed between the polymer and CBZ, CIN or CBZ-CIN complex. The full IR spectral data can be found in Fig. S7 in the Supporting information.

Discussion

From a theoretical point of view, cocrystals can significantly improve the solubility of a drug compound with solubility limited bioavailability through selection of suitable coformers [24]. However, the reality is that the improved drug solubility by the cocrystals cannot be sustained in the supersaturated solution generated due to the solution mediated phase transformation, resulting in precipitation of a less soluble solid form of the parent drug. The drug precipitation process can occur simultaneously with the dissolution of cocrystals, showing that the apparent drug solubility of cocrystals has not been improved in comparison with that of the stable form of the parent drug. Study on maintaining the advantages of cocrystals is of importance [11, 15-19].

Cocrystals in pre-dissolved polymer solutions

In the absence of a polymer in pH6.8 PBS, the solubility advantage of CBZ cocrystals has not been seen, in which both CBZ-NIC and CBZ-CIN cocrystals generated the same apparent CBZ concentrations as that of the parent drug CBZ III while as the CBZ-SAC cocrystal produced a slightly higher value shown in Fig. 1. This was due to crystallisation of CBZ DH from the supersaturated solution generated by the dissolution of CBZ cocrystals, confirmed by DSC analyses in Fig. 2. When HPMCAS with a concentration of 2 mg/mL or higher was pre-dissolved in solution, both CBZ-SAC and CBZ-CIN cocrystals can generate significantly higher CBZ supersaturated solutions with around three-fold increase in the solubility of CBZ III. This supersaturated state had been maintained for more than 24 hours and therefore it can certainly allow sufficient CBZ absorption for increasing bioavailability.

Based on the solution IR spectra of the individual components and mixture in the absence and presence of a polymer of HPMCAS, PVP or PEG, it was concluded that the mechanism of the supersaturated state of CBZ can be adjusted through the polymer interaction with induvial components and/or complex of the API and a coformer. For the mixture of CBZ and NIC in solution, none of three polymers of HPMCAS, PVP and PEG can interact with CBZ or NIC due to the strong bonds of the CBZ-NIC complex in Fig. 6(a), showing a constant apparent CBZ solubility of CBZ-NIC cocrystal in the absence and presence of a polymer in Fig1(b). Based on the IR spectroscopic results in Fig. 6(b), it was found that a polymer of HPMCAS, PVP or PEG can interact with both CBZ and SAC, resulting in the change of the apparent CBZ solubility of CBZ-SAC cocrystal, notably 2.1 fold increase of the solubility of CBZ III in the presence of HPMCAS. The similar situation is applied to the mixture of CBZ and CIN in solution in which a polymer of HPMCAS, PVP or PEG can affect the apparent solubility of CBZ-CIN cocrystal through intermolecular binding between the polymer and CBZ, CIN and/or CBZ-CIN complex. It is worth noting that a solvent used in the spectroscopic investigation was different from the dissolution medium used in the solubility measurements due to the limitation of the IR approach. Therefore the results did not provide the information on selection of the best polymer for maintaining the CBZ supersaturation in solution.

Based on the powder dissolution studies, all three cocrystals showed at least two-fold increase of the drug release compared with that of CBZ III in pH6.8 PBS in the absence of a polymer at 5 minutes. In the presence of 2 mg/mL HPMCAS in pH6.8 PBS, the drug release of CBZ-NIC or CBZ-CIN cocrystal was increased to

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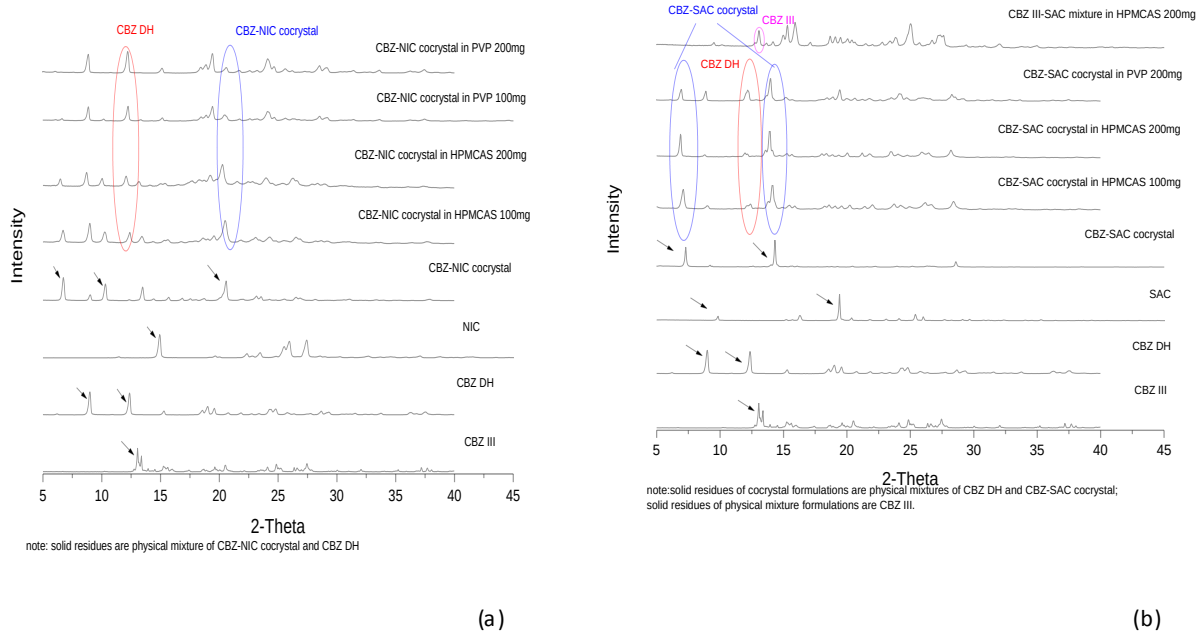
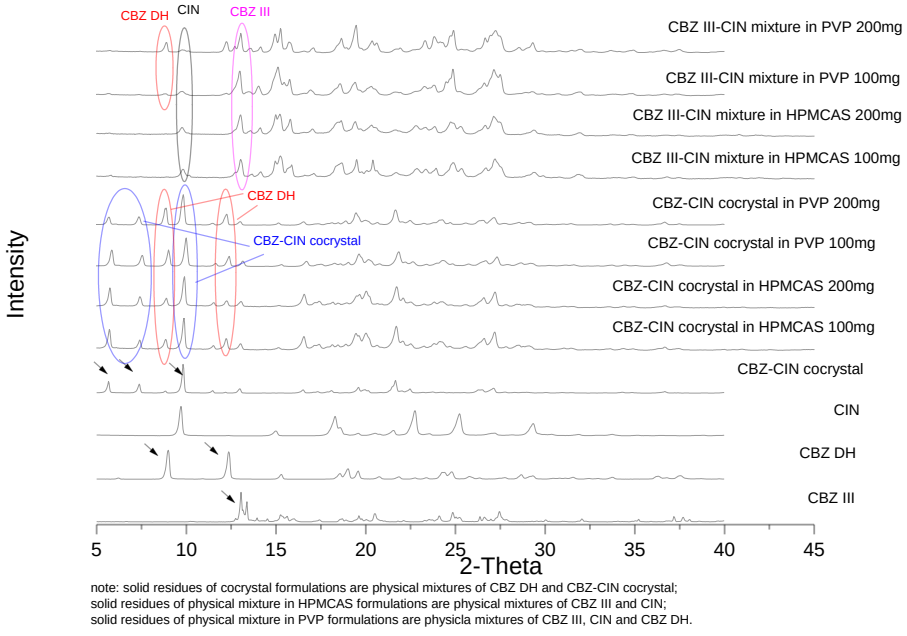


(a) (b)



(c)

Fig. 5 XRPD patterns of solid residues of different formulation after dissolution tests: (a) CBZ-NIC cocrystal formulations (b) CBZ-SAC cocrystal and physical mixture formulations; (c) CBZ-CIN cocrystal and physical mixture formulations

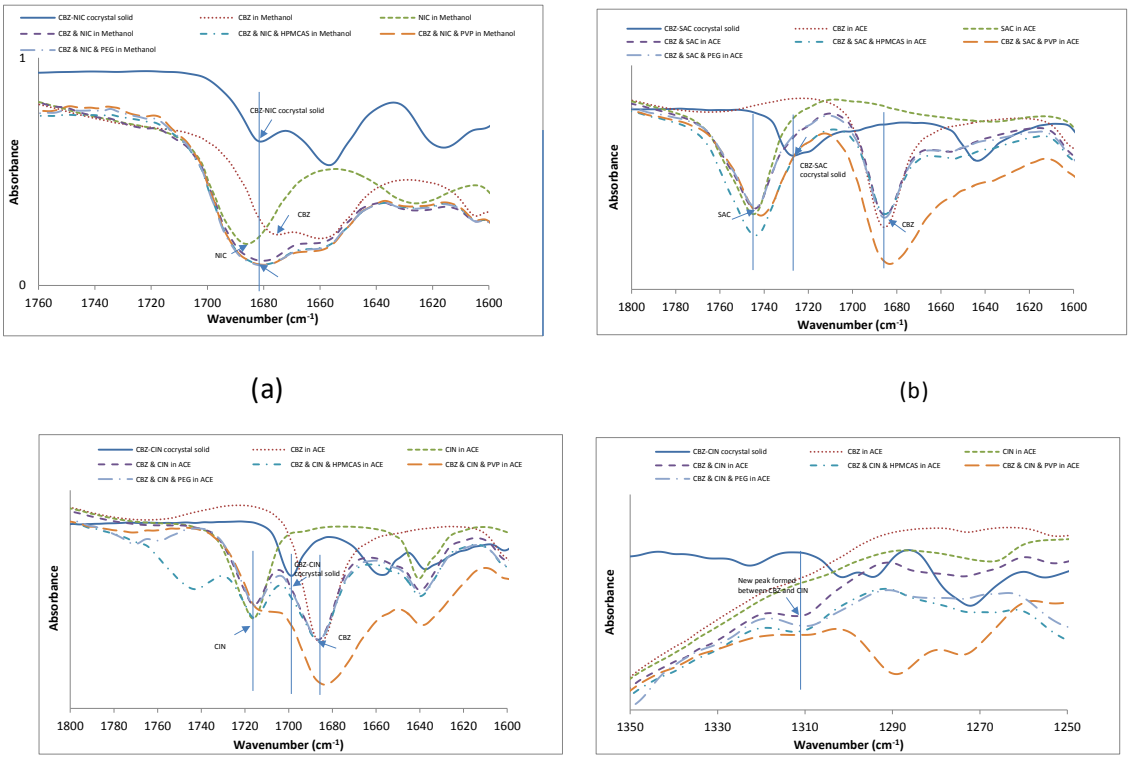


Fig. 6 IR spectra: (a) comparison of CBZ-NIC cocrystal solids with individual components and mixture in solution in absence and presence of polymers; (b) comparison of CBZ-SAC cocrystals solids with individual components and mixture in solution in absence and presence of polymers; (c) comparison of CBZ-CIN cocrystals solids with individual components and mixture in solution in absence and presence of polymers;

around 8 times of that of CBZ III in the same condition at 5 minutes. These results are much better than those of previous work based on a solid dispersion approach [25, 26]. Therefore, the implication of these observations is of significance because it demonstrates that cocrystals can be easily formulated through a simple solution formulation or powder formulation to generate supersaturated concentrations and faster dissolution rates to overcome those drugs with solubility and/or dissolution limited bioavailability. This conclusion has been supported by a similar work which has recently been done for development of an enabling danazol-vanillin cocrystal formulation, although a relatively complicated approach has been used containing both a surfactant and polymer in the formulation [16]. Therefore the cocrystal approach should have the same priority to be considered for formulating drug compounds with solubility and/or dissolution limited bioavailability as many other successfully supersaturating drug delivery approaches, such as solubilized formulations, solid dispersions, nanoparticles, and crystalline salt forms and particle size reduction [13].

In order to develop an enabling cocrystal formulation, a mechanistic understanding of the role of a polymer on inhibiting the phase transformation of cocrystals is required. Base on this study with our previous work [11, 19], it has been found that the key factors in controlling the maintenance of the apparent parent drug supersaturating level of a cocrystal include the cocrystal stability in solution, rate difference between the cocrystal dissolution/dissociation and formation of a soluble complex between the parent drug and polymer, stability of the complexes of the drug and polymer. A schematic diagram that summarizes the important processes during dissolution of cocrystals is given in Fig. 7. It can be seen that when the cocrystal molecules dissolve into solution, they can be dissociated into the parent drug and coformer molecules completely or partially depending on the stability of cocrystals in solution. If a pre-dissolved polymer in solution cannot form soluble complexes with the drug molecules, the solid crystals will be certainly precipitated from solution due to supersaturated states. On the other hand, although a pre-dissolved polymer can form soluble complexes with the API in solution, precipitation of the drug crystals can also occur if the rate of cocrystal dissolution and dissociation is faster than the rate of the formation of the soluble complexes. Finally, the stability of the soluble complex of the drug and polymer formed in solution is another factor to determine the precipitation of the drug solid forms from solution. Therefore, if we want to completely inhibit the crystallisation of the stable solid form of the parent drug in a formulation, two different approaches can be taken as:

Scheme 1: selecting cocrystals which are stable in solution. This can be achieved through selection of a suitable coformer. The scheme is particularly suitable to formulate drug compounds with dissolution limited bioavailability because most of cocrystals have

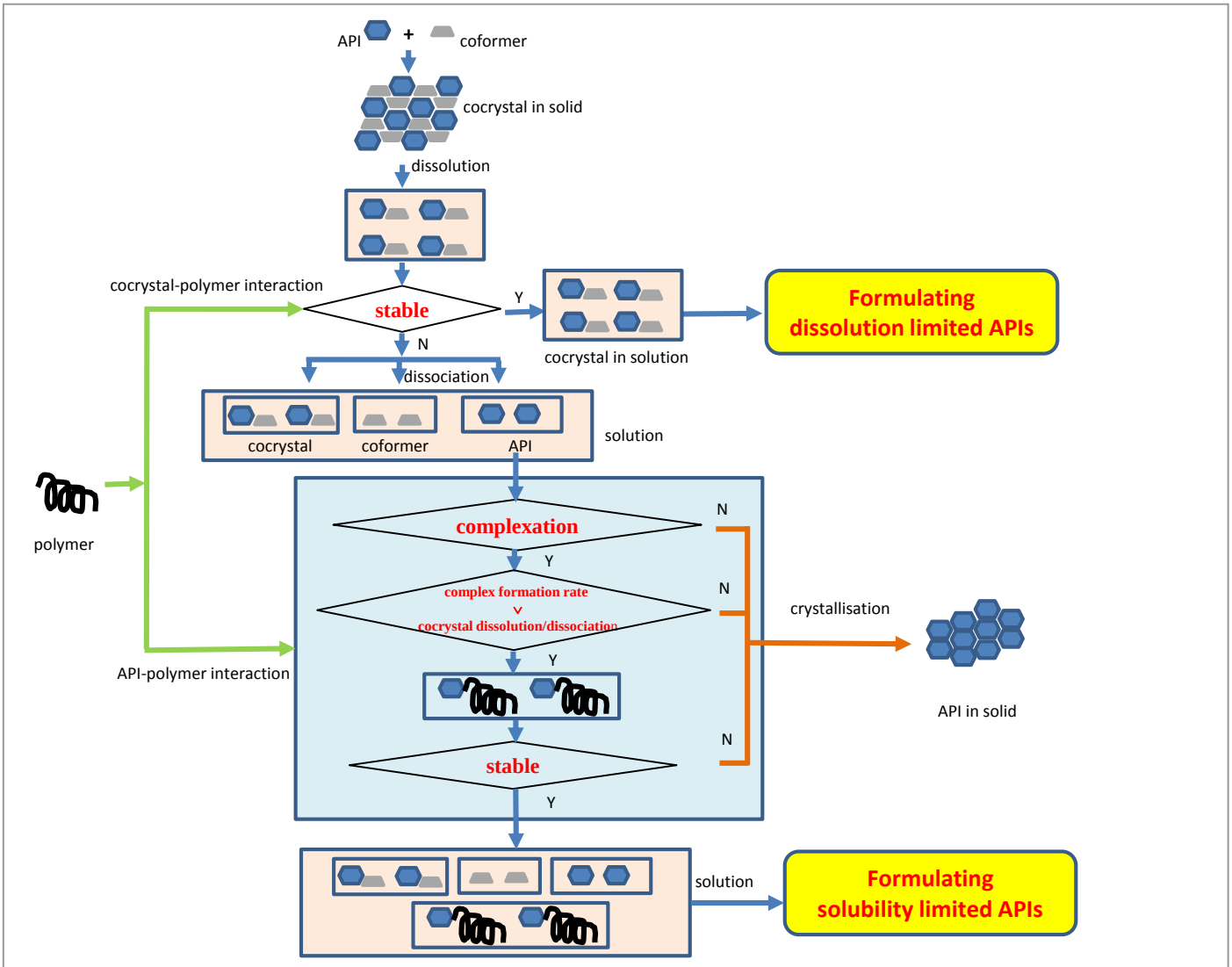


Fig. 7 Illustration of factors affecting the phase transformation of cocrystals

faster dissolution rates, although the apparent solubility of the parent drug has not been improved.

Scheme 2: balancing the rate difference between the cocrystal dissolution and formation of a soluble complex between the drug and polymer in solution. This can be realised through selection of both a polymer and coformer. The scheme is particularly suitable to formulate drug compounds with solubility limited bioavailability because a stable supersaturated drug concentration can be generated to enhance the drug absorption.

It has to be stressed that when a polymer is pre-dissolved in solution, both of the dissolution rate of solid cocrysals and stability of the cocrystals in solution will be affected due to change of the bulk properties of the dissolution medium and the solubility of both the parent drug and coformer. The cocrystals in solution intend to be stable if the solubility difference between the drug and coformer in a pre-dissolved polymer solution becomes smaller to form a congruent system.

Based on the solubility tests of CBZ III in this study, it was found that all three polymers of HPMCAS, PVP and PEG can interact with CBZ in solution to form soluble complexes through hydrogen bonding, indicating the increased solubility of CBZ III in pH6.8 PBS in the presence of a pre-dissolved polymer shown in Fig. 1(a) [19, 23]. However, the stability of the formed soluble complexes is different. Due to the rigorous structure and rich hydrogen-bond acceptors of HPMCAS in comparison of PVP and PEG, CBZ-HPMCAS complexes are stable in solution. Therefore, the supersaturated CBZ solution can be stabilized, indicating that HPMCAS can completely inhibit the precipitation of CBZ from solution shown in DSC analyses of the solid residues of the tests in Fig. 2.

The solubility tests in the absence of a polymer in pH6.8 PBS show that all three CBZ cocrystals of CBZ-NIC, CBZ-SAC and CBZ-CIN are not stable, indicating that the eutectic constants K_{eu} in Figs. 1(e)-(g) are significantly higher than the critical value of 1 [11, 15]. Therefore when they are dissolved, the cocrystal molecules are dissociated into CBZ and coformers in solution, resulting in crystallisation of CBZ DH crystals from solution confirmed by DSC analyses in Fig. 2. Because of the smallest value of the eutectic constant, CBZ-SAC cocrystal in solution is relatively more stable

than the other two cocrystals of CBZ-NIC and CBZ-CIN, leading to a higher apparent CBZ concentration.

A pre-dissolved polymer in pH6.8 PBS can improve the stability of cocrystals of CBZ-SAC and CBZ-CIN significantly due to reduced solubility differences between CBZ and coformers (coformer solubility is shown in Figure S4(a) in the Supporting information), indicating decreases of the eutectic constants K_{eu} shown in Fig. 1(f)-(g). In addition, HPMCAS is the best polymer to stabilize the cocrystal of CBZ-SAC or CBZ-CIN in solution because of the smallest value of the eutectic constant K_{eu}, indicating the significant improvement of the supersaturating level of CBZ in solution shown in Figs. 1(c)-(d). However, the values of K_{eu} in different concentrations of HPMCAS solutions are well above the critical value of 1 and therefore the crystallisation of CBZ DH takes place. There is a small change of the eutectic constants K_{eu} for CBZ-NIC cocrystal in the presence of HPCAS, PVP or PEG in solution so that the apparent concentration of CBZ is almost constant shown in Fig. 1(b).

All three CBZ cocrystals show significantly improved dissolution rates compared with that of CBZ III based on the powder dissolution tests in the absence and presence of a polymer in pH6.8 PBS shown in Fig. 3. Selection of a coformer is the key factor to affect the dissolution rate of cocrystals. Although there is a significant difference of NIC and CIN in term of solubility, it is found that both CBZ-NIC and CBZ-CIN cocrystals have similar dissolution rates, which are higher than that of CBZ-SAC cocrystal. A pre-dissolved polymer in the dissolution medium of pH6.8 PBS can further improve the dissolution rates of the cocrystals. One possible explanation is that the presence of a polymer in solution can increase the solubility of the cocrystals, resulting in an increased driving force for faster dissolution. In the meantime, because of the improved stability of cocrystals in solution in the presence of a pre-dissolved polymer, the dissolved cocrystal will be stable in solution to avoid crystallisation of the parent drug, indicating that the eutectic constants K_{eu} were close to the critical value of 1 shown in Fig. S6 in the Supporting information. The experiments generally show that HPMCAS is the best excipient to be included in solution to improve the dissolution rates as well as solubility of the cocrystals. In contract, the presence of HPMCAS or PVP in solution decreased the dissolution rate of CBZ III, which is the similar to our previous work on HPMC [11]. This could be caused by the slightly increased viscosity of the dissolution medium, resulting in a reduced molecular mobility of CBZ III. In the meantime, the polymer of HPMCAS or PVP can also be adsorbed on the surfaces of CBZ III particles to hinder its dissolution.

Cocrystals in polymer-based matrix tablets

A polymer based cocrystal tablet formulation has not shown any advantage to improve CBZ release rate in comparison with the formulation of CBZ III or physical mixtures of CBZ III and coformers shown in Fig. 4. This is contradictive to the solution behaviors of CBZ cocrystals studied in the solubility and powder dissolution tests. Drug release performance from a tablet is complex and highly dependent not only on each individual component properties (such as solubility, dissolution rate, partide size, and wettability) but also on manufacturing factors (e.g., compression forces, tablet shape, and drug loads). These factors affect the tablet dissolution kinetic processes, including the polymer dissolution kinetics, drug dissolution kinetics, and kinetics of the physical form change of the tablet. Based on this study and our previous work [11, 19], it is found that the polymer hydration process is the critical factor to determine the cocrystal release performance.

PEG used in this study is highly soluble and exhibits good wettability. Due to the poor gelling ability, all PEG based tablets were eroded quickly and eventually disintegrated completely. Therefore there was no solid residue left for any PEG based tablets after dissolution. PEG based tablets of CBZ III and physical mixtures of CBZ III and coformers exhibited complete drug release because of the sink conditions. The PEG based cocrystal tablets had an incomplete release profile, which was believed to be caused by the precipitation of CBZ DH. Once a cocrystal tablet was immersed into the dissolution medium PEG was dissolved quickly to form channels to allow water to penetrate the inside of the tablet. Because of the faster dissolution rate, dissolution of the cocrystal started immediately inside the tablet before its erosion and disintegration, resulting in crystallisation of CBZ DH from the micro-environmentally supersaturated states.

Similar to PEG, PVP can be dissolved quickly in the water. However, PVP which is a good gelling agent can form a gel matrix to modify the drug release profile in an extended release formulation. Due to a loosen structure of the gel matrix formed by PVP, the dissolution medium can easily penetrate inside the tablet to dissolve the drug. Because of highly viscous environment inside the matrix, the dissolved drug can not diffuse into the bulk solution immediately. When the drug concentration was built up to exceed its solubility, crystallisation of a stable solid form of the drug occurred. The three CBZ cocrystals used in this study had significantly improved dissolution rates compared with that of CBZ III therefore the concentration of the cocrystals inside the tablets quickly exceeded their solubility. In the meantime, the formation of the soluble complexes between the drug and polymer was slower. Therefore a PVP based cocrystal formulation has a slower and incomplete release compared with that of the CBZ III or physical mixture formulations because of crystallisation of CBZ DH inside the tablet, shown in Fig. 4(b) and analyses of the XRPD in Fig. 5. The formulation of physical mixture of CBZ III and CIN had significantly slower release rate of CBZ III formulation. It is believed that poor solubility and slow dissolution rate of CIN retarded the hydration and dissolution of CBZ III inside the tablet.

HPMCAS based cocrystal formulations have showed an improved release rate at the early stage of the tablet dissolution test, which are similar to our previous work on HPMC based cocrystal formulations [11, 19]. This is caused by the slower hydration property of HPMCAS. At the beginning of the dissolution test, cocrystal dissolution can only take place at the surface of the tablet and therefore the dissolved cocrystal can diffuse into the bulk of dissolution medium directly to avoid the supersaturated states of the drug concentration, which is similar to the powder dissolution tests. Once the gel layer formed, the water can penetrate inside the tablet to dissolve the cocrystals, resulting in crystallization of CBZ DH inside the tablet.

Conclusion

The influence of three chemically diverse polymers of HPMCAS, PVP and PEG on the phase transformation of three CBZ cocrystals of CBZ-NIC, CBZ-SAC and CBZ-CIN in solution and tablet based formulations has been investigated. The study has shown that the improved CBZ solubility of the three CBZ cocrystals cannot be sustained in the supersaturated solution generated due to the solution mediated phase transformation, resulting in precipitation of a less soluble solid form of CBZ DH. When HPMCAS with a concentration of 2 mg/mL or higher was pre-dissolved in solution, both CBZ-SAC and CBZ-CIN cocrystals can generate significantly higher CBZ supersaturated solutions with around three-fold increase in the solubility of CBZ III, which can be sustained for more than 24 hours. All three cocrystals showed at least two-fold increase of the drug release compared with that of CBZ III in the absence of a polymer in pH6.8 PBS at 5 minutes. In the presence of 2 mg/mL HPMCAS in pH6.8 PBS, the drug release of CBZ-NIC or CBZ-CIN cocrystal was increased to around 8 times of that of CBZ III in the same condition and time period. These results demonstrate that cocrystals can be easily formulated through a simple solution formulation or powder formulation to generate supersaturated concentrations and faster dissolution rates to overcome those drugs with solubility and/or dissolution limited bioavailability. However, a polymer based CBZ cocrystal tablet formulation has not shown any advantage of an improved CBZ release rate compared with the formulation of CBZ III or physical mixtures of CBZ III and coformers. This is contradictive to the solution behaviours of CBZ cocrystals in the solubility and powder dissolution tests because crystallization of the stable solid form of CBZ DH within the tablet has taken placed, leading to a reduced drug release rate and incomplete release. Finally it is worth noting that the investigation of CBZ and polymer interactions were based different solvent systems because of the IR strong absorption in aqueous media. The direct evidence for the polymer-cocrystal and polymer-API interactions in aqueous solutions is required, which is part of ongoing research in the group.

Experimental section

Anhydrous CBZ (CBZ III) was purchased from Zhenjiang Jiuzhou Pharmaceutical Co., Ltd (Taizhou, China). Nicotinamide (NIC, purity ≥99.5%), Saccharin (SAC, purity ≥98%) and *trans*-Cinnamic acid (CIN, purity ≥99%) were purchased from Sigma-Aldrich (Dorset, UK). Hydroxypropylemthylcellulose acetate succinate (HPMCAS, Hypromellose Acetate Succinate AS-MF) was provided by Shin-Etsu Pharma & Food Materials Distribution GmbH (Stevenage, UK) as an in-kind contribution. PolyEthylene Glycol (PEG, average M_w 4000) and Polyvinylpyrrolidone (PVP, K30 and average M_w 40,000) were purchased form Sigma-Aldrich (Dorset, UK). Sodium lauryl sulphate (SLS, purity ≥99%), methanol (HPLC grade) and Ethyl acetate (EtOAc, purity >99%) were purchased from Fisher Scientific (Loughborough, UK) and used as received. Double distilled water was generated from a Bi-Distiller (WSC044.MH3.7, Fistreem International Limited, Loughborough, UK) and used throughout the study.

Formation of the carbamazepine cocrystals

CBZ-NIC cocrystal and CBZ-SAC cocrystal were prepared by reaction crystallisation method. The CBZ-CIN cocrystal was prepared by slow evaporation method. Detailed methods can be found in our previous publications [11, 19]. XRPD, Raman spectroscopy and DSC were used to confirm the formation of the carbamazepine cocrystals.

pH6.8 phosphate buffer solution (PBS)

The dissolution medium used for solubility and dissolution tests was pH6.8 PBS prepared according to British Pharmacopeia 2010 [27]. 250 mL of 0.2 M potassium dihydrogen phosphate (KH_2PO_4) and 112 mL of 0.2 M sodium hydroxide (NaOH) were mixed and diluted to 1000.0 mL with double distilled water.

Preparation of tablets

The formulations of the matrix tablets for each polymer are provided in Table 1 and therefore in total there were 42 formulations studied. Cylindrical tablets were prepared by direct compression of the blends, using a laboratory press fitted with a 13 mm flat-faced punch and die set and applying 1ton force. All tablets contained the equivalent 200 mg CBZ III.

Solubility analyses of CBZ III, physical mixtures of CBZ III and coformers and CBZ cocrystals in pH6.8 PBS with a pre-dissolved polymer of HPMCAS, PVP or PEG

An excess of each of test samples including cocrystals (i.e., CBZ-NIC, CBZ-SAC and CBZ-CIN), CBZ III and the physical mixtures (i.e., CBZ III-NIC, CBZ III-SAC and CBZ III-CIN), all of which were slightly grinded and sieved by 60 mesh sieve (250 µm), was added into a small vial containing 10 mL of pH6.8 PBS or with a pre-dissolved polymer of HPMCAS, PVE or PEG and shaken with stirring for 24 h. Aliquots were filtered through 0.45 µm filters (thermo Scientific Nalgene) and diluted properly for determination of the concentrations of the parent drug CBZ and coformer of NIC, SAC or CIN by HPLC. Solid residues retrieved from the tests were dried at room temperature for one day and analysed by DSC, Raman and SEM. The concentrations of a pre-dissolved polymer of HPMCAS, PEG or PVP in pH6.8 PBS were 0.5, 1, 2 and 5 mg/mL. Each test was done in triplicate.

Powder dissolution studies of CBZ III, physical mixtures of CBZ III and coformers and CBZ cocrystals in pH6.8 PBS in the presence of a pre-dissolved polymer

In order to reduce the effect of particle size on the dissolution rates, all of powders were slightly grinded and sieved by 60 mesh sieve before dissolution tests. Cocrystal powders with 20 mg equivalent of CBZ III were added to beakers with 200 mL of a dissolution medium to ensure the sink conditions. The dissolution tests were conducted at 37±0.5°C with aid of magnetic stirring at 125 rpm. Samples of 2±0.1 mL were taken manually at 5, 15, 30, 45, 60, 75, 90 min. The samples were filtered and measured by HPLC to determine the concentrations of CBZ and coformer of NIC, SAC or CIN. Each dissolution test was carried out in triplicate. The two different dissolution media used for the tests included pH 6.8 PBS

and pH6.8 PBS with a pre-dissolved 2 mg/mL polymer of HPMCAS, PVP or PEG. Each test was done in triplicate

Dissolution studies of the formulated tablets

The dissolution tests of the tablets were carried out by the USP I basket method for 6 h. Rotation speed was 100 rpm and the dissolution medium was 700 ml of pH6.8 PBS with 1% SLS to achieve sink conditions, maintained at 37±0.5°C. Samples of 5±0.1 ml were taken manually at 0.5, 1, 2, 3, 4, 5 and 6 h replaced with an equal volume of the fresh medium to maintain a constant dissolution volume. The samples were filtered and measured by HPLC to determine the concentrations of CBZ and coformer of NIC, SAC or CIN. The dissolution profiles were represented as the cumulative percentages of the amount of drug released at each sampling interval. Each profile was the average of three individual tablets.

After a dissolution test, the solid residues (if available) were collected and dried at room temperature for at least 24 h for the further analyses of XRPD, DSC, and SEM.

High Performance Liquid Chromatography (HPLC)

The concentrations of CBZ and coformer of NIC, SAC or CIN in solution were analysed by Perkin Elmer series 200 HPLC system. A HAISLL 100 C18 column (5μm, 250×4.6mm) (Higgins Analytical, Inc. USA) at ambient temperature was used. The mobile phase was composed of 70% methanol and 30% water, and the flow rate was 1mL/min using an isocratic method.

Scanning electron microscope (SEM)

The solid-state transformation of sample residues after solubility and dissolution tests were investigated by SEM. SEM micrographs were photographed by a ZEISS EVO HD 15 scanning electron microscope (Carl Zeiss NTS Ltd., Cambridge, UK). The sample compacts were mounted with Agar Scientific G3347N carbon adhesive tab on Agar Scientific G301 0.5" aluminium specimen stub and coated with a thin layer of gold (Agar Scientific Ltd., Stansted, UK). The accelerating voltage of the electron beam was 10.00 kV to obtain the SEM images.

X-ray powder diffraction (XRPD)

X-ray powder diffraction patterns of the solid residues of the formulated tablets after dissolution tests were recorded at a scanning rate of 0.5° 2Θ min^{-1} by a Philips automated diffractometer. Cu Kα radiation was used with a voltage of 40 kV and current of 35 mA.

Differential scanning calorimetry (DSC)

DSC measurements were conducted for all test samples using a Perkin Elmer Jade DSC (PerkinElmer Ltd., Beaconsfield, UK). The Jade DSC was controlled by Pyris Software. The temperature and heat flow of the instrument were calibrated using an indium and zinc standards. Test samples (8-10 mg) were analysed in crimped aluminium pans with pin-hole pierced lids. Measurements were carried out at a heating rate of 20 °C/min under a nitrogen flow rate of 20 mL/min.

Infrared spectroscopy

IR spectroscopy has been used to investigate the molecular interaction among CBZ, NIC and polymer (HPMCAS, PEG or PVP) in solution. IR spectra of the solid forms of CBZ, NIC, SAC and CIN were collected using a Bruker ALPHA A4 sized Benchtop ATR-FTIR spectrometer fitted with a horizontal universal ATR accessory. Solution spectra were collected using the same spectrometer fitted with transmission accessory and the Bruker 6500S Circular Aperture liquid cell with size of 32×3 m CaF2 window. The path length was 0.05mm. Methanol was selected for the interaction study of CBZ, NIC and polymers in which the concentration of each material was 50, 23.73 and 2 mg/mL respectively. Acetonitrile was selected for the interaction study of CBZ, SAC (or CIN) and polymers (HPMCAS, PEG and PVP) in which the solution concentration of each component was 25, 19.37 (or 15.67) and 25mg/mL respectively. In all measurements 20 scans were collected per spectrum with resolution of 2 cm^{-1} in the spectral region of 400 to 4000 cm^{-1} using OPUS software. All the spectral data were collectd at ambient temperature between 20 to 23°C.

Statistical analysis

The differences in the CBZ concentrations and release profiles of CBZ III, CBZ cocrystals, and physical mixtures of CBZ III and coformers in different dissolution media were analysed by one-way analysis variance (ANOVA) (significance level was 0.05) using JMP 11 software.

Tab. 1Matrix tablet composition (mg)

Component	Formulation													
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
CBZ III	200							200						
CBZ-NIC cocrystal		304							304					
equal molar mixture of CBZ-NIC			304							304				
CBZ-SAC cocrystal				355							355			
equal molar mixture of CBZ-SAC					355							355		
CBZ-CIN cocrystal						325							325	
equal molar mixture of CBZ-CIN							325							325
HPMCAS or PVP or PEG	100	100	100	100	100	100	100	200	200	200	200	200	200	200

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