

Effect of varying quantities of polymer on preparation and stability evaluation of carbamazepine cocrystals with dicarboxylic acid cofomers

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Abstract: The current study is an attempt to explore the effect of varying quantities of hydroxypropyl cellulose (HPC) polymer on carbamazepine (CBZ) cocrystal formation with dicarboxylic acid cofomers *i.e.*, malonic acid (MA), succinic acid (SA), glutaric acid (GA), and adipic acid (AA). The cocrystals were first prepared without polymer by slurry crystallization method and then tried with different quantities of the polymer. The prepared samples were characterized by Powder X-ray Diffraction (XRPD). The characterization results indicate that in methanol pure carbamazepine-malonic (CBZ-MA) and carbamazepine-adipic acid (CBZ-AA) cocrystal can be prepared, while in ethanol and acetone pure carbamazepine-succinic (CBZ-SA) and carbamazepine-glutaric acid (CBZ-GA) cocrystals can be obtained respectively. The same cocrystals were tried using HPC polymer in three different quantities. The characterization results showed that a higher quantity of HPC polymer transforms CBZ-MA cocrystal polymorph-I to polymorph-II. The CBZ-SA and CBZ-GA cocrystal formation somehow inhibited as the concentration of HPC polymer increases. But on the other side, the formation of CBZ-AA cocrystal utterly not inhibited in the presence of varying quantities of HPC polymer. Furthermore, 11 different quantities of HPC were tried to know about the inhibitory concentration of HPC on CBZ-AA cocrystal formation. The CBZ-AA cocrystal preparation was not inhibited even at higher quantities of HPC compared to the cofomer. Additionally, the effect of three different quantities of HPC on the thermal stability of the CBZ-AA cocrystal was investigated. Moreover, the stability of pure CBZ at 92% relative humidity (RH) condition was compared to CBZ-AA cocrystal with and without HPC polymer. The CBZ-AA cocrystal with and without HPC polymer was more stable than pure CBZ.

Keywords: Carbamazepine, hydroxypropyl cellulose, malonic acid, succinic acid, glutaric acid, adipic acid

INTRODUCTION

The design and synthesis of multi-component pharmaceutical cocrystals have gained immense interest in the last decade. A cocrystal is a crystalline form containing two or more components held together via noncovalent interactions (Chadha *et al.*, 2012). It is a special challenge for the pharmaceutical industry to enhance the solubility of low soluble drugs without changing the structure (Syarifah *et al.*, 2015). Pharmaceutical cocrystallization is a good technique to attain improved physicochemical properties including solubility, dissolution without changing the nature of the molecule (Aitipamula *et al.*, 2018) retaining the pharmacological effect of the drug (Panzade *et al.*, 2017).

The two main methods of cocrystal preparation are (a) solution based; solution mediated transformation, solvent evaporation, cooling or antisolvent crystallization (b) mechanochemical approaches like neat and liquid assisted grinding method. According to the biopharmaceutical system of classification, carbamazepine (CBZ) is a class II drug having poor water solubility whilst high permeability (Limwikanant *et al.*, 2012). CBZ is a therapeutically important antiepileptic drug. So far, many of the cocrystals of CBZ have been reported with various cofomers, including saccharine, nicotinamide, 4-aminobenzoic acid, 4, 4'-bipyridine and carboxylic acids (Childs *et al.*, 2009; Janz and Frey, 1985). Hydroxypropylcellulose (HPC, IUPAC name 1-[[[(2R,3R,4S,5R)-3, 4, 5-tris (2-hydroxypropoxy)-6-[(2R,

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3R, 4S, 5R, 6R)-4, 5, 6-tris (2-hydroxypropoxy)-2-(2-hydroxypropoxymethyl)oxan-3-yl]oxyoxan-2-yl]methoxy]propan-2-ol) is ether derivative of cellulose in which hydroxypropyl is present instead of hydroxyl groups on the cellulose backbone. Hydroxypropylation of hydroxyl groups at high temperature and pressure on cellulose backbone is obtained by reaction of alkali cellulose with propylene oxide. It is highly water-soluble and soluble in other polar organic solvents mainly, methanol, ethanol, and acetone (Narang and Badawy, 2018; Ma *et al.*, 2015). It is frequently used as a viscosity builder, dispersion stabilizer and a binder in tablet formulation. Moreover, it is also used as a film-coating agent for drug release (Ma *et al.*, 2015; Nancy and Donald, 1997). The purpose of this study was to check the effect of the polymer on cocrystal preparation. In this research CBZ was carefully chosen as a model drug while, dicarboxylic acids like malonic acid (MA, IUPAC name propanedioic acid), succinic acid (SA, IUPAC name butanedioic acid), glutaric acid (GA, IUPAC name pentanedioic acid) and adipic acid (AA, IUPAC name hexanedioic acid) as cofomers and HPC as the representative polymer. The molecular structures of CBZ, MA, SA, GA, AA and HPC are shown in fig. 1.

MATERIALS AND METHODS

Materials

The pure CBZ (purity >97.0%) and HPC polymer (average Mw of ~80,000; 20 mesh particle size) were purchased from TCI (Europe) and Sigma-Aldrich (Belgium) respectively. The dicarboxylic acids cofomers like adipic (purity 99%), malonic (purity 99%), succinic (purity 99%) and glutaric acid (purity >99%) were purchased from Acros Organics (Geel-Belgium) and Sigma-Aldrich (Belgium) respectively. The analytical-grade solvents obtained from the commercial sources.

Cocrystals preparation without HPC

Slurry crystallization was used to prepare CBZ-MA (methanol), CBZ-SA (ethanol), CBZ-GA (acetone), and CBZ-AA (methanol) in 1:1, 2:1, 1:1 and 1:1 molar ratios respectively. The solvent was added to the solid mixture, without reaching full dissolution. The mixtures were stirred for 72 hours in a screw-capped glass vial at room temperature using a magnetic stirring bar. For further characterization, the resulting powder was rapidly filtered and dried (Childs *et al.*, 2008).

Cocrystals preparation in HPC solution

Add and mix the solid materials of CBZ and dicarboxylic acid cofomers (DCA's) in specific proportions to HPC (three different quantities) in a suitable solvent, and stirred it for 72 h. The subsequent powder was quickly filtered and dried for further characterization.

X-ray Powder Diffraction (XRPD)

The solid-state properties of pure CBZ, pure DCA's, pure HPC polymer, solid materials obtained from slurry crystallization with and without HPC were characterized employing X-Ray powder diffraction (XRPD) method on Siemens D5000 diffractometer equipped with a Cu X-ray source operating at 40 kV and 40 mA and a secondary monochromator allowing selection of the $K\alpha$ radiation of Cu ($\lambda = 1.5418 \text{ \AA}$). The samples were measured with a continuous scan rate of $0.01^\circ/\text{s}$ from $2-50^\circ$ at 2θ (Song *et al.*, 2018). Data collected was compared with the literature and structures enlisted in the Cambridge Structural Database (CSD).

Fourier-transform infrared spectroscopy (FT-IR)

Infrared spectra of prepared samples were recorded with PerkinElmer FTIR spectrophotometer. Finely grounded samples were compressed and then at a wavelength range ($450-4000 \text{ cm}^{-1}$) the FT-IR spectral analysis was carried out (Witika *et al.*, 2020).

Thermogravimetric Analysis (TGA)

The TGA scans of prepared samples were obtained on a Mettler Toledo TGA-SDTA 851e. The TGA thermograms were recorded at a temperature range of $30-600^\circ\text{C}$ with a scanning rate of $10^\circ\text{C}/\text{min}$ under a nitrogen purge of 50 mL min^{-1} . The solid samples of masses around 8-10mg were analyzed using aluminium oxide crucible (Buol *et al.*, 2019).

Stability studies

CBZ pure, CBZ-AA and CBZ-AA-HPC (***) were subjected to stability studies at accelerated condition, 92% relative humidity (RH), for 1 month in stability chamber at 25°C (Huynh-Ba and Zahn, 2009), then samples were tested by XRPD and TGA.

STATISTICAL ANALYSIS

All collected data was analyzed using OriginPro 9.0. However, rest of all values were registered as by using conventional statistical methods.

RESULTS

XRPD Analysis

The XRPD characterization results of CBZ-MA cocrystal screening products, the original materials of CBZ, MA and the reference data for CBZ-MA are shown in fig. 2. Cocrystal CBZ-MA was successfully prepared in methanol without HPC as it is in good agreement with the reported CBZ-MA cocrystal, but there is a mixture of pure CBZ and CBZ-MA cocrystal polymorph-I formed in two varying quantities of HPC polymer. Interestingly, at a higher quantity of HPC CBZ-MA cocrystal polymorph-II is formed. The CBZ-MA-HPC1 and CBZ-MA-HPC2 have similar features and are in good agreement with CBZ-MA cocrystal polymorph-I (Code= XOBCEX),

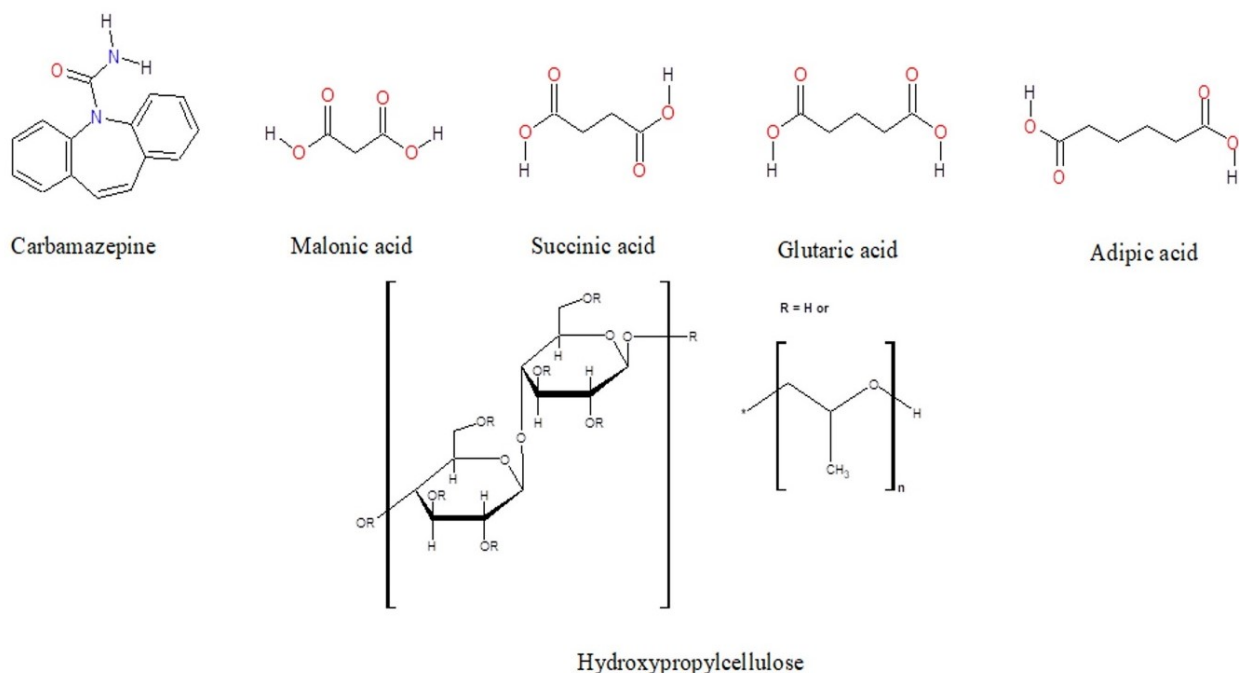


Fig. 1: Structure of API, cofomers and polymer.

Table 1: Molar ratios of carbamazepine, cofomers and quantity of HPC.

CBZ-CF	molar ratio	HPC (mg)	Code
CBZ-MA	(50mg, 22.01mg) 1:1	8.00	CBZ-MA-HPC3
CBZ-MA	(50mg, 22.01mg) 1:1	2.00	CBZ-MA-HPC2
CBZ-MA	(50mg, 22.01mg) 1:1	0.27	CBZ-MA-HPC1
CBZ-SA	(50mg, 12.49mg) 2:1	8.00	CBZ-SA-HPC3
CBZ-SA	(50mg, 12.49mg) 2:1	2.00	CBZ-SA-HPC2
CBZ-SA	(50mg, 12.49mg) 2:1	0.27	CBZ-SA-HPC1
CBZ-GA	(50mg, 27.9mg) 1:1	8.00	CBZ-GA-HPC3
CBZ-GA	(50mg, 27.9mg) 1:1	2.00	CBZ-GA-HPC2
CBZ-GA	(50mg, 27.9mg) 1:1	0.27	CBZ-GA-HPC1
CBZ-AA	(50mg, 30.92mg) 1:1	8.00	CBZ-AA-HPC6
CBZ-AA	(50mg, 30.92mg) 1:1	2.00	CBZ-AA-HPC4
CBZ-AA	(50mg, 30.92mg) 1:1	0.27	CBZ-AA-HPC-1

while CBZ-MA-HPC3 has the same XRPD pattern to CBZ-MA polymorph-II (Code= MOXVUR).

As shown in fig. 3, CBZ-SA was successfully prepared in ethanol without HPC as it is in good agreement with the reported CBZ-SA cocrystal. On the other hand CBZ-SA cocrystal also formed in three different quantities of HPC polymer, though the XRPD patterns are not perfectly matched with the reported CBZ-SA and the ones prepared without HPC polymer due to preferential orientation. The CBZ-SA-HPC1, CBZ-SA-HPC2 have similar XRPD peaks but a bit different from CBZ-SA-HPC3 showed that as the quantity of HPC polymer increases the formation of cocrystal somehow inhibited.

Cocrystal CBZ-GA was successfully prepared in acetone with and without HPC as the XRPD diffractogram is

similar to that of reported CBZ-GA cocrystal as shown in fig. 4. Some extra peaks appeared at position 7 θ and 16.2 θ in CBZ-GA-HPC1, CBZ-GA-HPC2, and CBZ-GA-HPC3 which confirm the presence of pure CBZ. A higher concentration of pure CBZ is probably observed as the quantity of HPC polymer increases.

CBZ-AA was successfully prepared in methanol without HPC as the XRPD diffractogram is similar to that of reported CBZ-AA cocrystal. The CBZ-AA cocrystals can be obtained using three different quantities of HPC polymer. The XRPD patterns of powder materials of CBZ-AA in different quantities of the polymer are perfectly matched to the reported CBZ-AA cocrystal as shown in fig. 5. Furthermore, 11 varying quantities of HPC polymer for the preparation of CBZ-AA cocrystal were tried to know the cocrystal inhibitory concentration

of HPC polymer. The HPC concentration started from 0.27mg and an even greater quantity of HPC (more than the cofomer quantity) did not inhibit CBZ-AA cocrystal formation table 2.

Table 2: Varying quantities of HPC used for CBZ-AA (50mg, 30.92mg) cocrystal preparation.

HPC (mg)	Code
0.27	CBZ-AA-HPC-1*
0.57	CBZ-AA-HPC-2
1.04	CBZ-AA-HPC-3
2.00	CBZ-AA-HPC-4
4.00	CBZ-AA-HPC-5
8.00	CBZ-AA-HPC-6
12.00	CBZ-AA-HPC-7 ⁺
16.00	CBZ-AA-HPC-8
23.00	CBZ-AA-HPC-9
31.00	CBZ-AA-HPC-10
38.00	CBZ-AA-HPC-11 ⁺

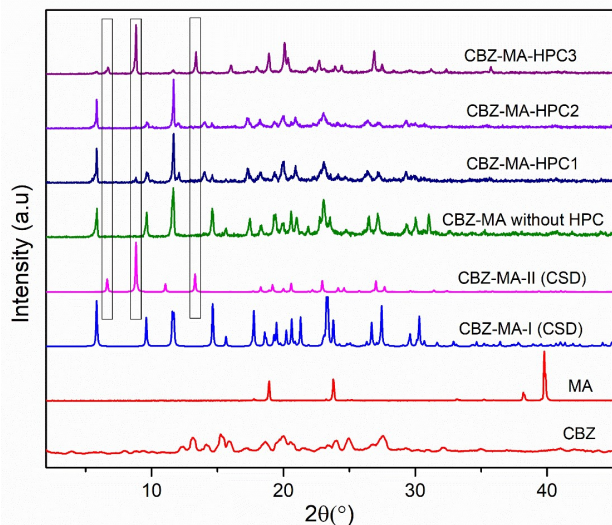


Fig. 2: XRPD pattern of pure CBZ, MA, CBZ-MA-I (CSD), CBZ-MA-II (CSD), CBZ-MA without HPC, CBZ-MA-HPC1, CBZ-MA-HPC2 and CBZ-MA-HPC3.

FT-IR Analysis

CBZ FTIR spectrum showed (fig. 6) the absorption bands of the primary amide group for asymmetrical anti-NH (free) and symmetrical syn-NH (hydrogen-bonded) stretching vibration at 3,465 and 3,157 cm^{-1} respectively (Rahman *et al.*, 2012). The peak for carbonyl in adipic acid and CBZ observed at 1688 and 1682 cm^{-1} respectively. In CBZ the shift in carbonyl stretching was observed at 1654 and in CBZ the stretching due to primary -NH group was shifted to 3356 cm^{-1} in the cocrystal. All the changes observed in FTIR spectra showed the interaction between AA and CBZ molecule in their solid-state and therefore cocrystal formation. The

FTIR spectrum of CBZ-AA cocrystal without HPC is identical to CBZ-AA cocrystal with HPC.

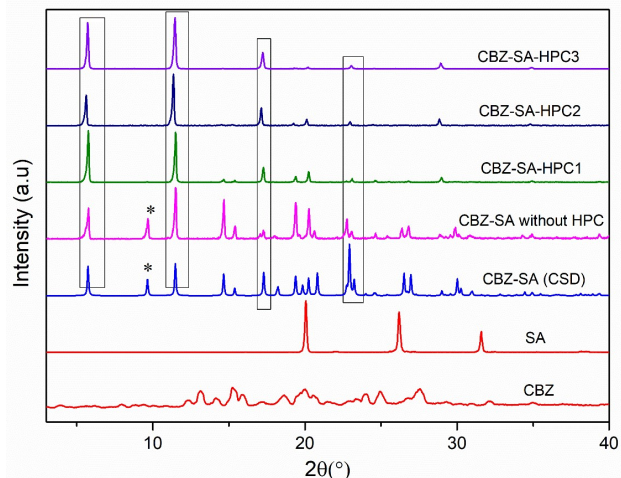


Fig. 3 : XRPD pattern of pure CBZ, SA, CBZ-SA CSD, CBZ-SA without HPC, CBZ-SA-HPC1, CBZ-SA-HPC2, and CBZ-SA-HPC3.

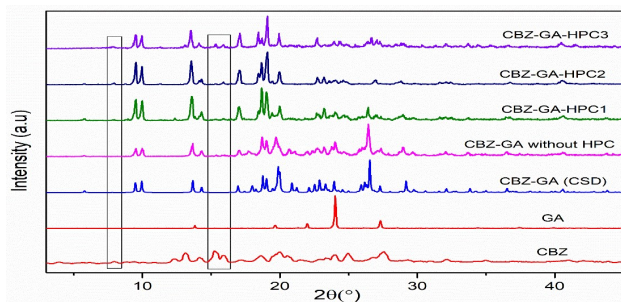


Fig. 4: XRPD pattern of pure CBZ, GA, CBZ-GA CSD, CBZ-GA without HPC, CBZ-GA-HPC1, CBZ-GA-HPC2 and CBZ-GA-HPC3.

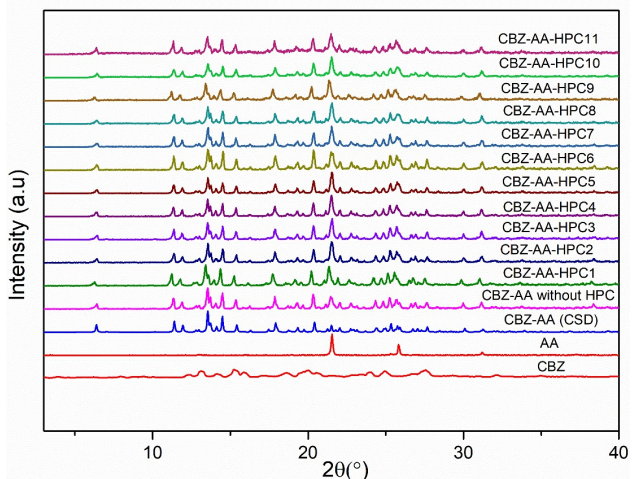


Fig. 5: XRPD pattern of pure CBZ, AA, CBZ-AA CSD, CBZ-AA without HPC, CBZ-AA-HPC1, CBZ-AA-HPC2, CBZ-AA-HPC3, CBZ-AA-HPC4, CBZ-AA-HPC5, CBZ-AA-HPC6, CBZ-AA-HPC7, CBZ-AA-HPC8, CBZ-AA-HPC9, CBZ-AA-HPC10 and CBZ-AA-HPC11.

TGA analysis

The fig. 7, shows TGA thermo grams of CBZ, AA, HPC and CBZ-AA cocrystal without HPC. The thermogram of cocrystal CBZ-AA without HPC was identical to CBZ-AA cocrystal present in the literature (Childs *et al.*, 2008). The TGA thermograms of CBZ-AA without HPC, CBZ-AA-HPC1, CBZ-AA-HPC7, and CBZ-AA-HPC11 were similar, but as the concentration of HPC polymer increases the second degradation peak intensity increases as shown in fig. 8.

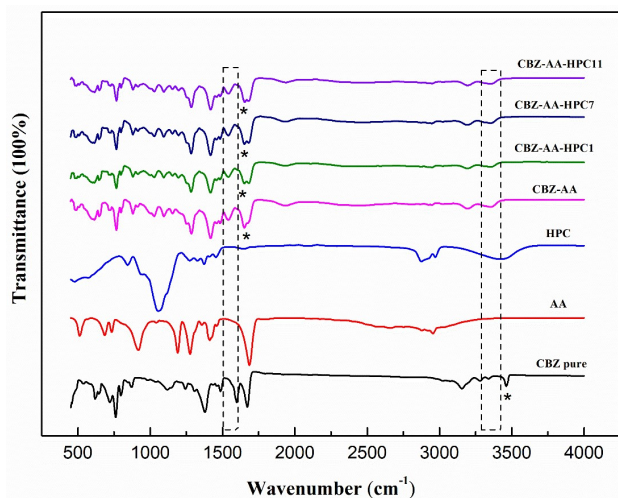


Fig. 6: The FTIR spectra of CBZ, AA, HPC, CBZ-AA without HPC, CBZ-AA-HPC1, CBZ-AA-HPC7, and CBZ-AA-HPC11.

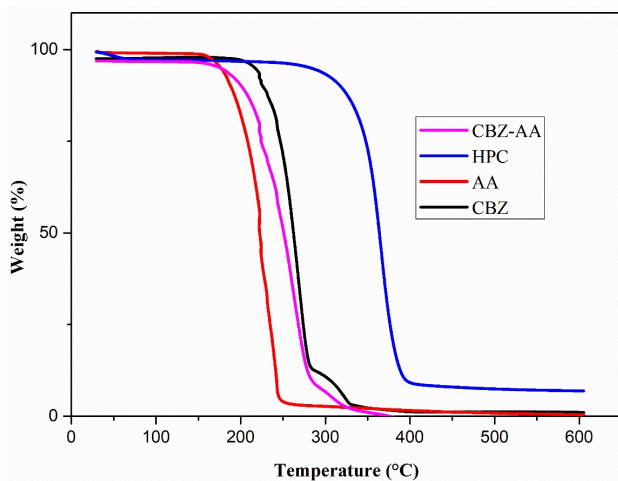


Fig. 7: TGA thermograms of CBZ, AA, HPC, and CBZ-AA cocrystal without HPC.

Stability analysis

After stability samples were checked by XRPD and TGA. The samples were stable as confirmed by XRPD results, after one month of the RH study. These samples were also analyzed for water absorption by TGA, and results showed that CBZ-AA cocrystal with and without HPC remained stable except the pure CBZ, which absorbed 6.69% water as shown in fig. 9 and fig. 10.

DISCUSSION

In this research anhydrous pure CBZ (polymorph form III) is used as the distinctive peaks appeared at $2\theta = 15.4$ and 27.5 (Hickey *et al.*, 2007). Four cocrystals of CBZ were prepared without HPC polymer successfully and confirmed by comparison of corresponding XRPD patterns in the literature and CSD.

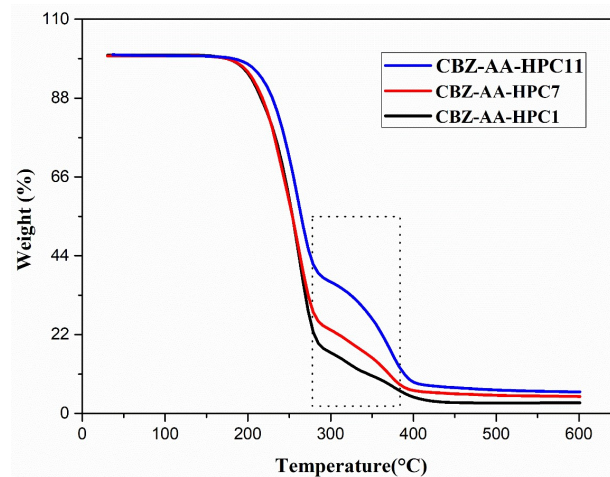


Fig. 8: TGA thermograms of CBZ-AA-HPC1, CBZ-AA-HPC7, and CBZ-AA-HPC11.

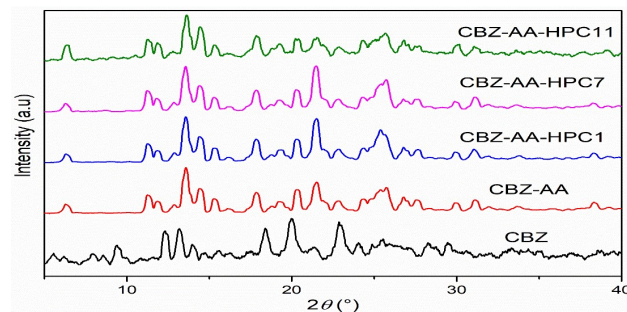


Fig. 9: XRPD pattern of pure CBZ, CBZ-AA cocrystals with and without HPC (variable quantities^{*^*^*}).

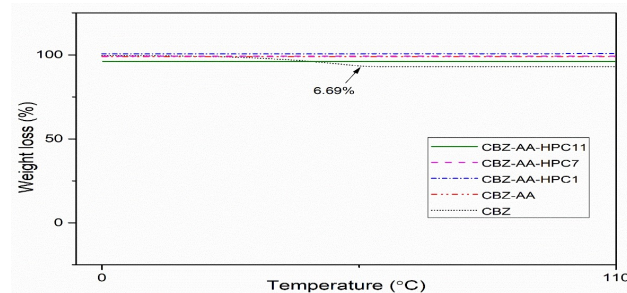


Fig. 10: TGA thermograms of CBZ, CBZ-AA cocrystal with and without HPC (variable quantities^{*^*^*}).

Cocrystal CBZ-MA was formed with and without HPC polymer, but as the quantity of HPC polymer increases the CBZ-MA cocrystal polymorph-I is transformed into CBZ-MA cocrystal polymorph-II as shown in fig. 2.

Polymer concentration dependent cocrystal polymorphs transformation have not been reported to our knowledge in the field of pharmaceutical cocrystallization. Previously, a study conducted by Thakuria *et al* on RH based polymorphs transformation of caffeine-glutaric acid cocrystal form-I to form-II. The cocrystal polymorphic transformation rate enhanced with the rise in RH (Thakuria *et al.*, 2019). The use of polymer for solubility and dissolution enhancement of drug and cocrystal is quite common. For example, by using hydroxypropyl methylcellulose acetate succinate (HPMCAS) enhanced the carbamazepine-succinic acid cocrystal solubility about 4 times compared to carbamazepine dihydrate (Ullah *et al.*, 2019). Similarly, HPC polymer improved dissolution by 3 times of exemestane-maleic acid cocrystal (Jasani *et al.*, 2019). Moreover, different polymorphs may exhibit variable bioequivalence (Gadade and Pekamwar, 2016). But, a polymer optimized concentration has never been considered important yet in cocrystal formulations. As in this research, varying quantities of HPC were used to investigate the effect on cocrystal formation. But, the use of a high quantity of HPC polymer induced cocrystal polymorph transformation as shown in fig. 2. The cocrystal CBZ-SA was prepared with and without HPC polymer, but as the quantity of HPC polymer increases the formation of CBZ-SA cocrystal somehow inhibited as shown in fig. 3. The sample CBZ-GA prepared in HPC was characterized as a physical mixture of cocrystal and pure CBZ. The fig. 4, showed that as the concentration of HPC increases the pure CBZ concentration increases. The CBZ-AA cocrystals were successfully prepared with and without HPC polymer as shown in fig. 5. Furthermore, varying quantities of HPC polymer (table 2) were tried to know about the inhibitory concentration of HPC polymer on CBZ-AA cocrystal formation. The CBZ-AA cocrystal preparation was not inhibited even at higher quantities of HPC compared to the cofomer as shown in fig. 5. A similar study was conducted on carbamazepine cocrystal formation with saccharine and nicotinamide with and without polyvinyl pyrrolidone (PVP) polymer in a mixture of ethanol-water solvents (1:1). In this study carbamazepine-saccharine, cocrystal formation was facilitated by the addition of PVP polymer, while inhibiting carbamazepine-nicotinamide cocrystal formation (Zhang *et al.*, 2017).

Furthermore, the effect of three different quantities (***) of HPC polymer (table 2) on the thermal stability of the CBZ-AA cocrystal was investigated, but no prominent change was observed. The TGA thermograms of CBZ-AA cocrystal with and without HPC polymer were found similar, but the only difference noticed as the concentration of HPC polymer increases the second degradation peak intensity increases as shown in fig. 8. Additionally, at room temperature and 92% RH condition, the RH stability of pure CBZ, CBZ-AA cocrystals with and without HPC polymer was compared. The cocrystals

with and without HPC polymer were found to be more stable than the pure CBZ. The pure CBZ absorbed 6.69% water as shown in fig. 10. So, in the preclinical formulation, a polymer can be used for cocrystals stabilization (Bhardwaj *et al.*, 2017).

CONCLUSION

As a whole, our study designed to investigate the effect of varying quantities of HPC polymer on CBZ-MA, CBZ-SA, CBZ-GA, and CBZ-AA cocrystal formation. The study results showed that a higher quantity of HPC polymer transforms CBZ-MA cocrystal polymorph-I to polymorph-II. The CBZ-SA and CBZ-GA cocrystal formation somehow inhibited as the quantity of HPC polymer increases. The CBZ-AA cocrystal formation cannot be inhibited entirely in the presence of varying quantities of HPC polymer. Concerning 92% RH stability, CBZ-AA cocrystals with and without polymer in varying quantities were stable, except pure CBZ which absorbed 6.69% water. The properties of polymers change with the monomer types, molecular weight, degree of substitution and distribution, etc. Similarly, the properties of cocrystals correspondingly change with different APIs and CFs as they are complex macromolecules. Additional investigation is needed to expand and improve the conclusion.

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