Improved *in vitro* and *in vivo* performance of carbamazepine enabled by using a succinic acid cocrystal in a stable suspension formulation

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Abstract: Currently cocrystals are considered as an established approach for making crystalline solids with overall improved physico-chemical properties. However, some otherwise well behaving cocrystals undergo rapid dissociation during dissolution, with ultimate conversion to parent drug and thus apparent loss of improved solubility. The polymeric carriers are long known to manipulate this conversion during dissolution to parent crystalline drug, which may hinder or accelerate the dissolution process if used in a dosage form. The goal of this study was to deliver *in vivo* a more soluble carbamazepine-succinic acid (CBZ-SUC) cocrystal in suspension formulation utilizing Hydroxypropyl methyl cellulose (HPMC-AS) as a crystallization inhibitor and Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer® as solubilizer. The concentration of these polymers were systemically varied during *in vitro* dissolution studies, while selected formulations from dissolution studies were tested *in vivo*. Pharmacokinetic studies (PK) in rabbits demonstrated that formulation F_7-X (1% cocrystal, 1% HPMC-AS and 2% Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer®) caused almost 6fold improvement in $AUC_{0\text{-}72}$ (****P ℜ 0.05*) as well as much higher C_{max} of 4.73µg.mL^{-1} to that of 1.07µg.mL^{-1} of unformulated 'neat' cocrystal given orally. When reference formulation of CBZ (F_5-X) with similar composition to F_7-X were given to rabbits, cocrystal formulation gave 1.37fold (****P ℜ 0.05*) bioavailability than CBZ reference formulation. C_{max} of reference formulation observed was 3.9µg.mL^{-1}.

Keywords: Cocrystal, suspension, bioavailability, carbamazepine, crystallization inhibitor.

INTRODUCTION

Cocrystallization is a valuable crystal engineering approach for modifying pharmaceutical performance by managing API (s) overall solid state properties (Sun, 2013). In general literature survey ratifies improved bioavailability of APIs by cocrystallization (Cheney *et al*., 2009, McNamara *et al*., 2006, Variankaval *et al*., 2006). This trend is likely determined by the common plea to enhance the poorly soluble compound (s) bioavailability, accordingly cocrystals exhibiting higher solubility and rapid dissolution are investigated for bioavailability enhancement (Alhalaweh *et al*., 2012, Alhalaweh *et al*., 2013, Sun, 2013).

Among other utilities, the cocrystals have been used to increase poorly soluble drug (s) solubility and bioavailability. Studies involving cocrystal bioavailability (Bak *et al*., 2008; Cheney *et al*., 2009; Hickey *et al*., 2007; Jung *et al*., 2010; Smith *et al*., 2011; Stanton and Bak, 2008; Venczel *et al*., 2012; Weyna *et al*., 2012; Zheng *et al*., 2012) animal models involving dogs or rats have been commonly used. Cocrystals were either given in liquid suspensions with or without added polymers (mostly in rats), or as cocrystal powder with or without additives in capsules (mostly in beagle dogs). These reported studies have clearly demonstrated cocrystals capability of enhancing bioavailability in contrast to poorly soluble API single-component crystal form.

In literature the prevailing method for cocrystals *in vivo* performance is focused on purposely excluding additional formulations so as to relate the "unformulated" cocrystals aq. suspension or filling into capsules 'neat' cocrystal (Childs *et al*., 2013). As reported in two different studies cocrystals of carbamazepine-saccharine (CBZ-SAC) and indomethacine-saccharine (IND-SAC) gave almost 10 and 67fold higher solubility than pure APIs at pH 3, but there *in vivo* performance when given orally in capsule shells resulted in bioavailability comparable to marketed products in tablet forms (Hickey *et al*., 2007; Jung *et al*., 2010). Conversely, in a some cases designing appropriate formulation strategy becomes indispensable with the aim of interpreting improved cocrystal solubility into a therapeutically significant bioavailability improvement as demonstrated by Childs *et al*., where enabling formulation of vanillin cocrystal markedly improved its bioavailability (Childs *et al*., 2013).

For poorly soluble APIs, solubility enhancement is highly desired to ensure their successful development. The

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solubility enhancement increases the drug dissolution rate, which is considered a vital phase in any drug (s) absorption. The use of highly soluble solid form, however, suffers the problem of 'solution mediated phase transformation' (SMPT), where stable solid phase crystallizes upon the dissolution of a more soluble solid form. The occurrence of SMPT negates dissolution rate advantage of soluble forms (Greco and Bogner, 2012). The SMPT is assisted by liquid contact and proceeds in three steps: (i) metastable form dissolution to generate super-saturation (ii) stable form nucleation and (iii) stable form growth. Thus, slowing down or even eliminating one or both of the last two steps in the SMPT process is required to maintain a high dissolution.This can usually be achieved by using polymeric crystallization inhibitors (Raghavan *et al*., 2003; Wang *et al*., 2016).

Carbamezepine (CBZ) is categorised in BCS Class II drug (s), having high intestinal permeability and low water solubility. Its absorption is, therefore, dissolution rate limited. There are reported four anhydrous polymorphs of CBZ and a dihydrate (stable form) in aqueous solution. Different commercial brands of CBZ tablets have a history of bioavailability non-equivalence and clinical failure, which has been attributed to polymorphism (Kobayashi *et al*., 2000; Meyer *et al*., 1998). This is a problem to therapy because CBZ has a narrow therapeutic index, for which a reproducible dissolution rate are indispensable for achieving the desired therapeutic effect while minimizing the risk of toxicity. We recently showed that the use of a soluble cocrystal of CBZ is an attractive approach for addressing this challenge in CBZ delivery using stable tablet formulations (Ullah *et al*., 2015a). In this report, we describe the *in vivo* performance of otherwise highly unstable CBZ-SUC cocrystal in aqueous environment with stable suspension formulations containing crystallization inhibitor (HPMC-AS) with appropriate CBZ solubilizer (Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer®).

MATERIALS AND METHODS

Materials

HPLC grade Methanol and Acetonitrile were purchased from, VWR International Ltd (Leicestershire, England). Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer® were obtained from BASF (Geismar, Germany). HPMC-AS (HF) was obtained from *Shin-Etsu* Chemical Co., Ltd. (Chiyoda, Tokyo, Japan). Carbamazepine was obtained from Sigma Aldrich (St. Louis, MO, USA). Deionized water (double distilled) was used throughout the study.

The preparation of CBZ-SUC 2:1 cocrystal were detailed before (ullah *et al*. 2015b). In brief 4.725g (1.99mM) of CBZ and 1.181g (1mM) of SUC were mixed by hand in a mortar for 30 min with constant dilution of methanol.

METHODS

Optimization of suspension formulations for cocrystal based on in vitro studies

Dissolution experiments (non-sink) were used at ambient conditions with *in situ* Raman spectroscopy to monitor phase change during dissolution experiments to select suitable crystallization inhibitor. Out of three polymers studies HPMC-AS delayed/inhibited the phase conversion of CBZ-SUC for course of time studied (Ullah *et al*. 2017 submitted). In brief impact of three polymers at varying conc on phase stability of cocrystal (CC) were tested in buffer with online monitoring by raman spectroscopy followed by confirmation by off-line methods like FT-IR and PXRD. PVP K-30 & K-90 were unable to kinetically stabilize the CC while HPMC-AS stabilized the CC at 0.025% w/v for the course of time studied. While selection of suitable CBZ solubilizer was based on literature as well as our IDR studies (Ali *et al*. 2010, Ullah *et al*. 2015a). For selecting suitable formulations for *in vivo* studies based on non-sink dissolution experiments, *in vitro* dissolution experiments were executed on heat controllable magnetic stirrer in simulated intestinal fluid (without enzymes), where conc of selected polymers were varied systemically. For all experiments temperature used was 37±1 ℃ with stirring rate of 100rpm. The volume used was 100mL, suitable conc of CC was added to SIF. Around 3mL of Aliquots were taken at stated time points, filtered and quantified by UV-Vis spectrophotometer after appropriate dilutions.

In vivo pharmacokinetic studies

Albino rabbits (1.9-2kg each) were used for PK studies. These studies were carried out according to protocols approved by Pharmacy department research ethical committee at CIIT Abbottabad {ref. no PHM-0023/E, (C/M--4)}. These studies were completed in accordance with Helsinki declaration and Animal scientific procedure act 1986 (UK). PK data for individual formulation was collected in N=4 rabbits. Before dosing rabbits were kept on fasting for 12h with free water excess and 1 week washout period was provided. Post dose blood samples were taken at specified time points i.e, 0,1,2,3,4,6,8,10,12,24,48 and 72h and were initially centrifuged at 3500rpm for 5 min, 200µL of supernatant taken in eppendroft tube was kept at -20 ℃ for further studies. Drug was extracted with acetonitrile (1:1) vortex mixed for about 90 seconds and centrifuged again at 12000rpm for 10 min (Ullah *et al*. 2015a).

STATISTICAL ANALYSIS

CBZ plasma concentration at various time points were calculated for individual rabbit and mean ± SD values were calculated. From plasma concentration-time profiles of individual samples, their peak plasma concentration (C_{max}) and their occurrence time (t_{max}) were read directly

while area under the curve (AUC_{0-72}) was estimated by linear trapezoidal rule. AUC differences in rabbit groups were considered significant at a 'p' value below 0.05 and at 95% confidence interval by applying one way analysis of variance (ANOVA) followed by Tukey's multiple comparison test by using GraphPadPrism5.

RESULTS

Optimization of suspension formulations for cocrystal based on in vitro studies

Suspensions final formulations for *in vivo* studies were optimized by varying the selected polymers (HPMC-AS & Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer®) concentration during *in vitro* studies i.e. In F_1 formulation 0.5% w/v & in F_2 1% w/v HPMC-AS was used, addition of cocrystal to these suspensions improved CBZ conc 3.1 fold and 3.4 fold respectively than CBZ dihydrate owing to the polymer strong crystallization inhibition effect. Therefore 1% w/v HPMC-AS concentration was finalized for final formulation as at 2% w/v HPMC-AS conc didn't further improve the CBZ conc. As shown in fig. 1, the CBZ concentration was directly proportional to added Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer® concentration when used as solubilizer e.g. 1% w/v Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer® addition to kinetically stable F_2 formulation resulted in 4.6fold (F_3) CBZ conc increase than unformulated CBZ-SUC (F_0).This was considerable increase in CBZ concentration *in vitro* caused by kinetic stability of highly soluble cocrystal by crystallization inhibitor polymer aided by appropriate CBZ solubilizer.

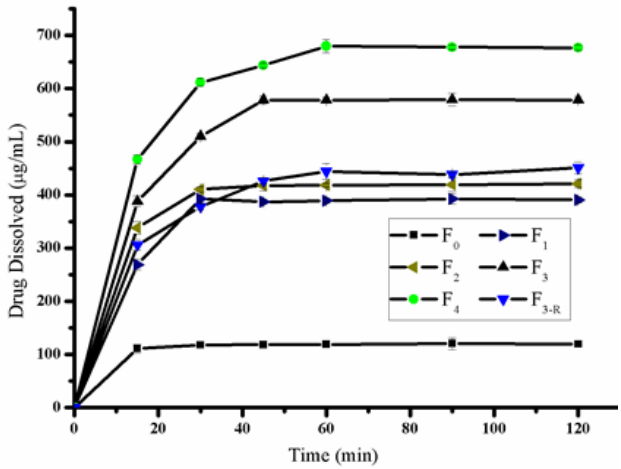

Fig. 1: *In vitro* performance of pure CBZ, cocrystal (F_0) & all experimental suspensions (F_1-F_4), while F_3-R is the CBZ reference formulation of F_3

Further addition of Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer® (2% w/v) in formulation F_4, 5.6fold improvement in solubility of CBZ was observed. Adding more cocrystal to formulation F_3 & F_4 didn't increase CBZ apparent solubility. Thus cocrystal, HPMC-AS 1% w/v and Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer® (both at 1% w/v and 2% w/v) were chosen as final optimized suspension formulations for *in vivo* studies in rabbit models. This suspension (F_4) was sufficiently viscous so influence of further solubilizer was not observed.

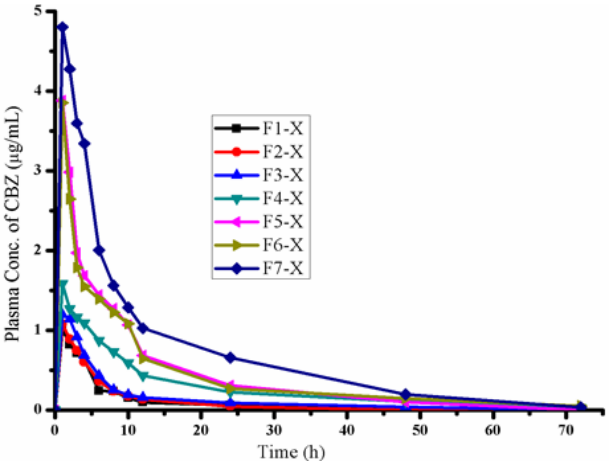

Fig. 2: AUC_{0-72} of CBZ (F_1-X), CC (F_2-X) & all experimental formulations (F_3-X, F_4-X, F_5-X, F_6-X ,F_7-X) (N=4).

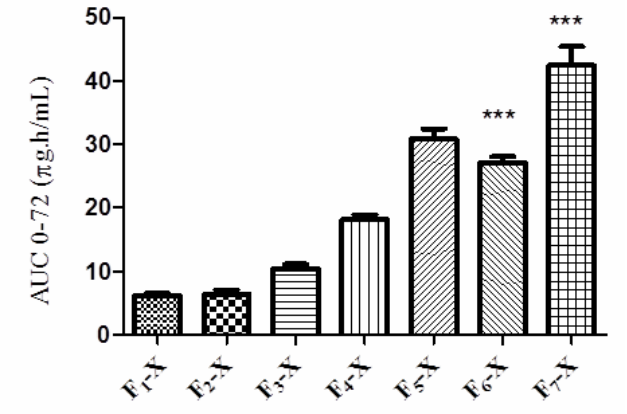

Fig. 3: AUC_{0-72} of all formulations in rabbits N=4. Values are expressed as mean±SEM ($P \mathcal{M} 0.05$; ANOVA,followed by Tukey's post hoc test)

For comparison, suspension of pure CBZ were also prepared having similar composition to F_3 & F_4 coded as F_3-R & F_4-R as shown in fig. 1. Reference formulation F_3-R was 3.5fold more soluble than stable CBZ dihydrate at supersaturated state. This was also significant increase in CBZ conc as a result of CBZ polymorph III supersaturated state, caused by the combination of polymers. Literature studies also ratifies that CBZ (form

Table 1: Composition of suspension formulations for *in vivo* studies in N=4 rabbits

Formulation	Composition (%)			
	CBZ (reference)	CBZ-SUC (cocrystal)	HPMC-AS (crystallization inhibitor)	Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer®(solubilizer)
F_1-X	1	-	-	-
F_2-X	-	1.25*	-	-
F_3-X		1.25*	1	-
F_4-X	1	-	1	1
F_5-X	1	-	1	2
F_6-X	-	1.25*	1	1
F_7-X	-	1.25*	1	2

* Equivalent to 1% CBZ (10 mg.mL^{-1})

Table 2: All PK parameters of CBZ (F_1-X), CC (F_2-X) and all experimental suspension formulations (F_3-X-F_7-X) in albino rabbits N=4, calculated after single CBZ dose (35 mg.kg^{-1})

Parameter	F_1-X	F_2-X	F_3-X	F_4-X	F_5-X	F_6-X	F_7-X
$AUC_{0\rightarrow72}$ (µg.h.mL^{-1})	6.19±0 .7	6.38±1.5	10.45±1.4	18.13±1.6	30.9±3.1	27.3±2	42.4±6
C_{max}(µg.mL^{-1})	1.01±0.18	1.07±0.18	1.43±0.26	1.6±0.15	3.9±0.14	3.9±0.3	4.7±0.42
T_{max}(h)	1.1±0.6	1±0.48	3±0.57	0.5±0.43	0.45±0.65	0.45±0.38	0.40±0.5

III) is 2.92fold soluble than its dehydrate in aq. environment (Murphy *et al*., 2002).

Composition of suspension formulations for in vivo studies

The codes and composition of selected formulation for animal dosing are given in table 1. Uniform suspensions were formulated in mortar and pestle. Initially 1% w/v HPMC-AS was added to phosphate buffer (pH 6.8) and was mixed thoroughly for 5 min, followed by addition of 1% w/v Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer® in formulations F_4-X & F_6-X and 2% w/v Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer® in formulations F_5-X & F_7-X respectively with continuous mixing. Finally the cocrystal (1% w/v) was added to this blended suspension and mixed for 10 min to obtain uniform suspension. The suspensions of formulations F_5-X & F_7-X though viscous but still were pourable. Suitable volume of each suspension was given orally to rabbits based on maximum CBZ dose permissible per kg body wt i.e. 35mg.kg^{-1}. As shown in table 1, F_4-X & F_5-X are CBZ reference formulations of cocrystals F_6-X & F_7-X.

In vivo pK studies

The freshly prepared suspension formulations were orally given to rabbits based on rabbit weight (6.5-7mL). As shown in table 2, $AUC_{0\text{-}72}$ of F_1-X (drug) & F_2-X (cocrystal) was found to be equal. In F_3-X, $AUC_{0\text{-}72}$ improvement was although notifiable but still trivial, indicating HPMC-AS alone wasn't capable of enhancing drug absorption adequately. As given in fig. 2 & table 2, cocrystal formulations F_6-X & F_7-X caused substantial $AUC_{0\text{-}72}$ improvements than unformulated F_2-X where C_{max} was improved significantly from 1.07µg.mL^{-1} to 3.9µg.mL^{-1} & 4.73µg.mL^{-1} respectively. When cocrystal reference i.e. F_4-X & F_5-X formulations were given, cocrystal formulations displayed 1.5fold & 1.37fold AUC enhancement. While observed C_{max} for F_7-X was 4.7µg.mL^{-1} compared to 3.9µg.mL^{-1} of reference F_5-X formulation.

As shown in table 2, $AUC_{0\text{-}72}$ of F_1-X & F_2-X was comparable and no statistically significant difference was observed by applying one way ANOVA followed by Tukey's multiple comparison test ($P \geq 0.05$), this was attributable to immediate dihydrate crystallization due to higher SUC solubility (higher differential solubility of the components) in buffer solution. These results indicated that when highly soluble but extremely unstable CBZ-SUC cocrystal was added to buffer solution, the cocrystal reverted back to its pure components and the aq. environment encouraged the CBZ quick conversion to the lowest soluble but stable dihydrate form. In F_3-X formulation, $AUC_{0\text{-}72}$ difference is still insignificant; indicating crystallization inhibitor alone is not capable to enhance drug absorption. As shown in fig.3, F_6-X formulation caused significant increase in $AUC_{0\text{-}72}$ ($^{***}P \leq 0.05$) than F_2-X, so addition of 1% w/v solubilizer to F_3-X formulation caused 4.3fold increase in bioavailability of CBZ to that of pure cocrystal, while increasing the concentration to 2% w/v the increase in bioavailability was 6.64fold in $AUC_{0\text{-}72}$, and C_{max} was

increased from 1.07μg.mL^{-1} to 4.73μg.mL^{-1}. When reference formulations were given having similar composition to F_6-X and F_7-X, AUC_{0-72} of cocrystal formulation exhibited 1.5fold (**$P \leq 0.05$) and 1.37fold (***$P \leq 0.05$) bioavailability respectively. C_{max} of F_7-X cocrystal formulation was 4.7μg.mL^{-1} as compared to 3.9μg.mL^{-1} of reference formulation.

For all formulations maximum drug concentration (T_{max}) were seen in the first 2h post dose, apart from F_3-X, where T_{max} was delayed till 3h. It was also noted that T_{max} had a direct relation with Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer® concentration in the formulation. In F_7-X T_{max} was at 0.4h in contrast to 1h of F_2-X (cocrystal) owing to high Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer® concentration in the formulation. Also, in F_5-X, T_{max} fell to 0.45h in contrast to 1.1h of F_1-X.

DISCUSSION

All solid state characterization techniques (XRD, FTIR, raman spectrocscopy) and thermal technique (TGA) confirmed cocrystal formation in accordance with all published reference data detailed in our published paper (Ullah *et al*., 2015a). Up till now over 50 CBZ crystal form (s) have been stated and *in vivo* studies of only one CBZ cocrystal (CBZ-SAC) has been detailed so far, where cocrystal in powder form was given orally to beagle dogs in capsule shells, that gave comparable bioavailability to the marketed tablets, hence the cocrystal didn't address the bioavailability concerns of CBZ despite 10fold increase in solubility *in vitro* (Childs *et al*., 2009).

Cocrystal *in vitro* studies confirmed CBZ solubility enhancement by using combination of crystallization inhibitor polymer together with suitable solubilizer in a suspension formulation. Childs *et al*., in their landmark study have reported that only crystallization inhibitor polymer was unable to enhance danazol cocrystals bioavailability lest suitable solubilizer was not added in enabling formulation (Childs *et al*., 2013). Alshahrani *et al*. have reported similar results where HPMC-AS and Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer® blends considerably increased CBZ loading and its release rate in ASD than Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer® alone. Similarly, Poloxamer/407 incorporation in CBZ-Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer® dispersion not simply assisted in its extrusion process but also increased CBZ polymer loading and miscibility and thus enhanced dissolution performance (Djuris *et al*., 2014).
The results of *in vivo studies* suggested that with Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer® addition to kinetically stable HPMC-AS formulation (F_3), CBZ thermodynamic solubility was actually increased, that caused improvements both *in vitro* as well as *in vivo* performance of F_6-X & F_7-X suspension formulations. These findings were very prominent in terms of CBZ absorption in rabbits. This study illustrated that cocrystals demand efficient formulation strategies, if fails to translate the *in vitro* solubility improvements *in vivo* possibly due to 'abrupt' phase change of unstable cocrystal systems due to differential solubilities of individual cocrystal components in aqueous environment.

Similar *in vivo* conclusions have recently been drawn, where CBZ supersaturatable-SMEDDS relative bioavailability was improved 5fold in beagle dogs in contrast to commercial tablets. This bioavailibilty improvement was attributed to the crystallization inhibitor (PVP) incorporation to otherwise unstable SMEDDS that efficiently upheld the super-saturated state by impeding precipitation kinetics (Zhang *et al*., 2011).

Inter subject differences for CBZ were seen to be very prominent in rabbits, as CBZ Log P value is above 2 and drugs having log P value 2 or above, display unpredictable absorption as well as extremely inconsistent bioavailability due to their dissolution rate-limited profile and is usually affected by the fed/fasted states of the patient (Gaikwad *et al*., 2014). No IVIVC was made for developed formulations because of marked variations in the sampling time.

CONCLUSION

CBZ-SUC is a highly soluble but extremely unstable cocrystal in aqueous environment. This solubility advantage has not been fully utilized in formulation approaches owing to the cocrystal rapid conversion to the crystallized drug constituents because of the high super-saturation level attained by the cocrystal than the drug. This study demonstrated that drug super-saturation state may be sustained with appropriate formulation strategy where polymers can provide kinetic stability to cocrystal for course of time for absorption to take place and thus improved bioavailability. In adopted formulation approach the use of crystallization inhibitor polymer (HPMC-AS) together with suitable solubilizer (Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer®) served as a useful approach for improving *in vivo* bioavailability of highly soluble but unstable CBZ-SUC cocrystal. One of the formulation that contained 1% w/v HPMC-AS and 2% w/v Polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer® outperform the unformulated pure cocrystal given in solution as well as the formulation that contained only 1% w/v of HPMC-AS as crystallization inhibitor. Therefore the choice of suitable excipients at appropriate

concentrations is critical for successful formulation performance of a cocrystal.

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