Original Article

ENHANCEMENT OF THE PHYSICOCHEMICAL PROPERTIES OF POORLY SOLUBLE CABAZITAXEL BY CO-CRYSTALLIZATION TECHNIQUE - IN VITRO STUDIES

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Abstract

To overcome the poor solubility and low bioavailability of Cabazitaxel, co-crystallization technique was attempted. Cabazitaxel co-crystals were prepared with selected co-former citric acid by liquid assisted-grinding method. Characterization was carried out through Fourier Transform infra-red spectroscopy, differential scanning colorimetry and X-ray diffraction. The Fourier-transform infrared spectroscopy results showed that a hydrogen bond was formed between Cabazitaxel and citric acid to yield a co-crystal. Melting point determination and solubility study was carried out to confirm the changes occurred in free drug after co-crystallization with the co-former. The prepared co-crystals were further transformed into immediate release tablets with Croscarmellose sodium as superdisintegrant and menthol as subliming agent. Micrometric properties, pre-compression and post-compression properties were evaluated. Full factorial CCD design was used to optimize the formulation parameters. The optimized batch has shown promising results as per desirability. The optimized batch was kept under stressed conditions and found stable.

Keywords: Cabazitaxel, citric acid, co-crystals, croscarmellose sodium and menthol.

Introduction

The solid-state properties of a drug substance can have a significant influence on the apparent solubility of the drug substance. Since polymorphic forms differ in their internal solid-state structure, a drug substance that exists in various polymorphic forms can have different aqueous solubilities and dissolution rates (Harry G. Brittain et al., 2009). Many problems faced during pharmaceutical product development are mainly due to the drug's physicochemical properties. Drug effectiveness depends on its properties such as solubility, stability, dissolution rate and hygroscopicity etc. Novel solubility enhancements technique including Liquisolid Technique, Spherical Agglomeration, Melt sono-crystallization, The Prodrug Approach, Nanotechnology Approaches were used to increase the solubility of drug. Co-crystal technique is an emerging technique to improvise the solubility and dissolution rate profile of poorly soluble APIs, which can improve bioavailability without any covalent bond modification of active pharmaceutical ingredient (API) along with maintaining a stable crystalline form. Using co-crystallization technique, desired physical and chemical properties of an API can be obtained in comparison to the parent API or its salt (Anand & Nanda, 2022b). The preferred solid form is generally the thermodynamically

most stable crystalline form of the compound (Harry G. Brittain et al., 2009) (FDA, 2007). However, the stable crystal form of the parent compound may exhibit inadequate solubility or dissolution rate resulting in poor oral absorption, particularly for water-insoluble compounds. The taxanes or taxoids are a closely related group of antineoplastic agents that have a unique mechanism of action as inhibitors of mitosis and which are widely used in the therapy of ovarian, breast, lung, esophageal, prostate, bladder and head and neck cancers (Yared & Tkaczuk, 2012). Taxanes are a class of diterpenes (paclitaxel (Taxol: 1992), Cabazitaxel (Taxotere: 1996) and Cabazitaxel (Jevtana: 2010) are microtubule inhibitors and widely used as chemotherapeutic agents for several types of Cancers (Kommineni et al., 2019). Among of them, Cabazitaxel is a such one (Zhang et al., 2016). Cabazitaxel is a semisynthetic analogue of natural toxoids and was developed for its lack of affinity for P-glycoprotein, a drug efflux pump that serves to reduce intracellular concentrations of another drug (Yared & Tkaczuk, 2012). Cabazitaxel works by stopping cancer cells from separating into two new cells. This blocks the growth of the cancer. An additional characteristic of Cabazitaxel is its ability to penetrate the blood–brain barrier in vivo, which is not achievable with other taxanes (Alan W. Partin MD et al., 2021) Cabazitaxel (CTX) is a second- generation taxane derivative, a class of potent anticancer drugs with very low water solubility. CTX is used in patients with resistant prostate cancer unresponsive to the first generation taxane (Parhizkar et al., 2017). Co-crystals are multicomponent system in which one component is Active Pharmaceutical Ingredient (API) and another is called co-former (Fukte S.R. et al, 2014). The citric acid molecule has two distinct hydrogen-bonding functions, namely the hydroxyl and acid groups. The primary objective of this work was to use crystal engineering for improving the solubility and dissolution rate of a Cabazitaxel (CTX). Identifying the therapeutic solubility of CTX co-crystal in a comparative manner for the treatment of prostate cancer is entirely new for drug delivery.

Material

Cabazitaxel (CTX) was obtained as a gift from School of Chemical Sciences and Pharmacy, Central University of Rajasthan, Bandarsindri (Ajmer), Rajasthan, India. All other chemicals were purchased from the M/s Spectrochem ,SDFCL chem (Pvt.) Mumbai,India.

Method

Preparation of Co-crystals of Cabazitaxel

Cabazitaxel co-crystals were prepared by liquid assistant grinding method. Initially, co-former was selected based on the maximum solubility of drug in co-former.

Selection of co-former

One of the challenging tasks in preparation of co-crystals is the selection of suitable solvent. The solvent selected should have adequate solubility of drug and co-former to permit sufficient interaction during crystallization. Various co-formers viz., adipic acid, benzoic acid, cinnamic acid, citric acid, glutaric acid, p- hydroxybenzoic acid, hippuric acid, malonic acid, resorcinol, saccharine sodium, 1-hydroxy-2- napthoic acid, sodium acetate, urea, catechol, ferulic acid, nicotinamide, syringic acid and succinic acid were screened out and one co-former was selected for the preparation of co-crystal (Mulye et al., 2012).

Preparation of co-crystals of Cabazitaxel (CTX)

Liquid assisted grinding method was adopted for the preparation of Cabazitaxel co-crystals. The solvent used for co-crystal formation has a catalytic role in assisting cocrystal formation and should persist for the duration of the grinding process. The liquid component is thought to accelerate reaction kinetics by wetting the solid surface (Karimi-Jafari et al., 2018). Accurately weighed Cabazitaxel (molecular weight: 835.93 g/mol) was mixed with selected co-former in different stoichiometric ratios (1:1, 1:2 & 1:3). It was properly dissolved in ethanol (10 ml) and left for evaporation of solvent. The fine needle shaped crystals were obtained. These were collected into a container and stored properly away from light and moisture till further use (Panzade et al., 2017).

Characterization of Cabazitaxel co-crystal

Determination of Melting point

Melting point of pure Cabazitaxel and co-crystals using digital melting point apparatus. The capillary filled with drug powder was placed in a melting point apparatus and was heated. Melting point of drug powder and co-crystal was noted when it melted in the capillary

Saturation solubility

The solubility was determined by dissolving excess quantity of pure drug and cocrystals in the 10 ml vials containing water. The vials were subjected to agitation on rotary shaker and allowed to stand for equilibrations for 24 hrs. The samples were filtered after 24 hr, diluted with distilled water and analyzed by UV Spectrophotometer at respective wavelength (Anand & Nanda, 2022a).

Fourier transformation infrared spectroscopy (FTIR)

FTIR spectra of the samples were recorded using Alpha Bruker 120602880 (Bruker, Germany). The IR spectra was measured over 4000-400 cm-1 range. KBr pellet method was used. The obtained data was analyzed using OPUS software v.7.2.139.1294 Spectrometer (Bruker, Germany).

Differential scanning calorimetry (DSC)

DSC measurements were carried out in DSC Q10 V9.9 (TA instruments, USA). This was calibrated for heat and temperature with standard of indium. Sample (approx. 2 mg) was placed in sealed non-hermetic aluminium pans and scanned from 30-300 °C at 10 °C rate/min under atmosphere of dry nitrogen (60 ml/min). The resulting data was analyzed with Universal Analysis 2000 Software (TA instruments) (Anand & Nanda, 2022a).

Powder X-ray diffraction (XRD)

Powder XRD was performed at room temperature with an X-ray diffractometer. Monochromatic Cu radiation was obtained with a Ni-filtration and a system of diverging and receiving slides of 1.0º and 0.3 mm, respectively. The diffraction pattern was measured with a voltage of 40 kV and current of 30 mA over a 2θ range of 10-80º using a sampling pitch of 0.02º with a scan speed of 4º/min.

Drug dissolution study

A dissolution study was carried out for Cabazitaxel and prepared co-crystals using USP type I (basket type) dissolution apparatus with 900 ml of 0.1N HCl as the dissolution medium at 37±0.5°. The pure drug and cocrystal equivalent dose of selected drugs was used for the study. Samples were withdrawn at definite time intervals (10 min) for 1 h and each time fresh dissolution medium was added to replace the volume sampled and the samples were quantified using a UV spectrophotometer at respective wavelengths (Panzade et al., 2017).

Preparation of immediate release tablets of Cabazitaxel co-crystals

Immediate release tablets of Cabazitaxel co-crystals were formulated by utilizing the superdisintegrant and subliming agent. Prior to compression, pre-compression parameters were studied.

Evaluation of pre-compression parameters

Prior to compression, powder blends were evaluated for flow and compressibility parameters. Flow properties of powder were determined by angle of repose, Compressibility by Carr's index and Hausner’s ratio.

Angle of repose

Angle of repose formulation blend was determined using the fixed funnel method. Accurately weighed quantity of powder blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the

funnel just touched the apex of the heap of the powder. The powder was allowed to drift through the funnel freely to the bottom. The height and diameter of the powder cone was measured and angle of repose was calculated.

Bulk density and tapped density:

Bulk density and tapped density were determined with the aid of the bulk density apparatus. Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the powder (M) was determined to calculate the bulk density of pure drug and prepared co-crystals.

The measuring cylinder of the apparatus was filled with a known mass of blend and was tapped for a fixed period time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured to calculate the tapped density of pure drug and prepared co-crystals.

Carr's index (%) and Hausner's ratio:

The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of a material because all of these can influence the compressibility index. Thus, Carr's index of the pure drug and co-crystal was measured. Hausner's ratio is a divergent index of powder flow. The Carr's index and Hausner's ratio were calculated for pure drug and co-crystal.

Preparation of immediate release tablets

Direct compression method was used for preparing Cabazitaxel tablets. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablet. An accurately weighed quantity of Cabazitaxel cocrystal equivalent to drug dose and all other ingredients were passed through 60-mesh sieve and mixed in vertical blender for 30 min. The dose of the Cabazitaxel was kept as equivalent to 20 mg (Rao et al., 2015). The resulting blend was directly compressed into tablets. The quantity of all components was constant except superdisintegrant and binder. Round concave tablets of 200 mg in weight and 4 mm in diameter were prepared using Cadmach multi station tablet compression machine.

Optimization of Cabazitaxel co-crystal fast dissolving tablets

A 3^2 full factorial design was used for the preparation of fast dissolving tablets of Cabazitaxel co-crystals. The two independent factors, amount of Crospovidone (X1) and amount of Camphor (X2), were set to three different levels and experimental trials were performed for all nine possible combinations. The dependent responses measured were *in-vitro* disintegration time (Y1) and in-vitro drug release (Y2).

Evaluation of post compression parameters

Prepared co-crystals were also evaluated for post compression parameters viz., thickness, weight variation, hardness, friability, in-vitro disintegration time, drug content, in-vitro dissolution study and stability study.

Thickness and weight variation

The thickness of the tablets was measured using a digital Vernier caliper. Five tablets were randomly taken from each formulation and thickness of each of these tablets was measured. The results are expressed mean±standard deviation (SD). Twenty tablets were selected at random and average weight was determined using an electronic balance (Shimadzu). Tablets were weighed individually and compared with average weight.

Hardness and friability

Five tablets were randomly selected from each batch and hardness of tablets was determined by using Monsanto hardness tester. The mean values and standard deviation for each batch were calculated. The friability of tablets was measured using USP type Roche friabilator. Pre-weighed tablets were placed in plastic chambered friabilator attached to motor revolving at a speed of 25 rpm for 4 min. The tablets were then dedusted, reweighed, and percent weight loss was calculated.

Drug content

Twenty tablets were weighed and powdered. Powder equivalent to a single dose of Cabazitaxel was weighed, dissolved in few ml of Acetonitrile and assayed for drug content at respective wavelength using UV-Visible spectrophotometer (Shimadzu).

***In-vitro* disintegration time**

The digital tablet disintegration test apparatus (Veego) was used to determine in vitro disintegration time (DT) using distilled water at 37±2°. The time in seconds taken by tablet for complete disintegration with no residue remaining in apparatus was recorded as mean±SD.

***In-vitro* drug release study**

The drug release studies were performed using the USP dissolution test apparatus (VDA-6DR USP Stds.,Veego) employing paddle method. The dissolution test was performed using 900 ml of 0.1 N hydrochloric acid at 37±0.5° and paddle speed of 50 rpm. Samples (5 ml) were collected at predetermined time intervals (5 min) and replaced with equal volume of fresh medium. The study was continued for 60 min, samples were then filtered through 0.45 µm membrane filter and analyzed at respective wavelength using UV spectrophotometer (Shimadzu).

Stability study

The optimized formulation was subjected to stability study according to ICH guidelines, at room temperature, 30±2°/60%RH±5% and 40±2°/75% RH±5% condition in stability chamber (HMG, India) for three months. Tablets were analysed for drug release for 90 days at the interval of one month.

Results and Discussion

Selection of co-former

Different co-formers were screened out to select an appropriate co-former which interacts deeply with the selected drug to make a stable and soluble complex. Table 1 represented the various co-formers chosen for preparing co-crystals with Cabazitaxel (CXT), method of preparation and characteristics of final products.

Table 1: Co-former attempts to prepare co-crystals of Cabazitaxel

Drug	**Co-former**	**Method of Preparation**	**Inference**
Cabazitaxel	Adipic acid	Liquid assisted grinding	Stable with low solubility
	Benzoic acid	Liquid assisted grinding	Stable with low solubility
	Cinnamic acid	Liquid assisted grinding	Stable with low solubility
	Citric acid	Liquid assisted grinding	Stable with high solubility
	Glutaric acid	Liquid assisted grinding	Stable with low solubility
	Hippuric acid	Liquid assisted grinding	Stable with low solubility
	Malonic acid	Liquid assisted grinding	Stable with low solubility
	Resorcinol	Liquid assisted grinding	Stable with low solubility
	Saccharine sodium	Liquid assisted grinding	Stable with low solubility

	Sodium acetate	Liquid assisted grinding	Stable with low solubility
	Urea	Liquid assisted grinding	Stable with low solubility
	Ferulic acid	Liquid assisted grinding	Stable with low solubility
	Nicotinamide	Liquid assisted grinding	Stable with low solubility
	Syringic acid	Liquid assisted grinding	Stable with low solubility
	Succinic acid	Liquid assisted grinding	Stable with low solubility

*Citric acid showed high solubility of Cabazitaxel and selected for further study

From the above study, it was observed that Citric acid showed maximum solubility, hence, selected for further study.

Preparation of Cabazitaxel co-crystals

The co-crystals of Cabazitaxel (CXT) were prepared by liquid assisted grinding method and were further characterized for various parameters.

Determination of melting point

Melting point data of different preparations were presented in Table 2. Melting point is one of the most important physicochemical properties of co-crystals and considered as the preliminary test for confirmation of changes occurred in free drug. When the co-crystals were formed the melting point must lie in between the melting points of the two individual molecules, but either below or above the melting point of the drug (Jayasankar et al., 2006). If such results are obtained, it would serve as a confirmation that the co-crystals have formed. It was found that the melting point of preparation was different from the melting points of Cabazitaxel (157°) and the co-former Citric acid (153°) confirming the formation of co-crystals with some chemical interaction between both molecules (Madhuri et al., 2020).

Table 2: Melting point of Cabazitaxel pure drug and co-crystals

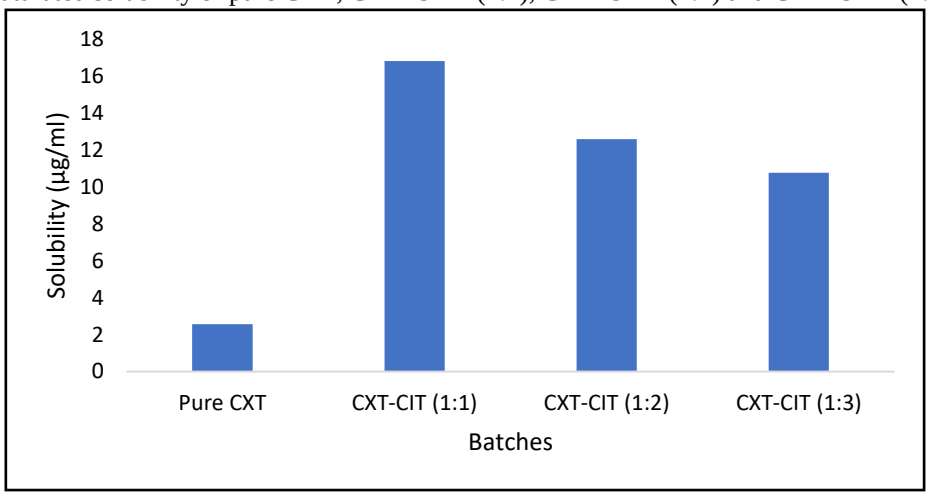
Co-crystal components	**Ratio of drug:Co-former**	**Melting point**
Pure Drug (Cabazitaxel, CXT)	-	157°
Cabazitaxel+Citric acid (CXT+CIT)	1:1	136^{0}
Cabazitaxel+Citric acid (CXT+CIT)	1:2	137^{0}
Cabazitaxel+Citric acid (CXT+CIT)	1:3	137^{0}

Saturation solubility

Solubility study data of different preparations were presented in Figure 1. The preparation comprised of 1:1 drug and co-former ratio showed maximum solubility when compared with pure Cabazitaxel. Although, preparation comprising of drug co-former ratio as 1:2 & 1:3 also showed better solubility enhancement, that was not chosen for further studies due to the fact that the ratio of citric acid and Cabazitaxel led to bulky size, which would

produce problems to formulate and obtain patient acceptance. Thus, 1:1 molar ratio was selected for further studies.

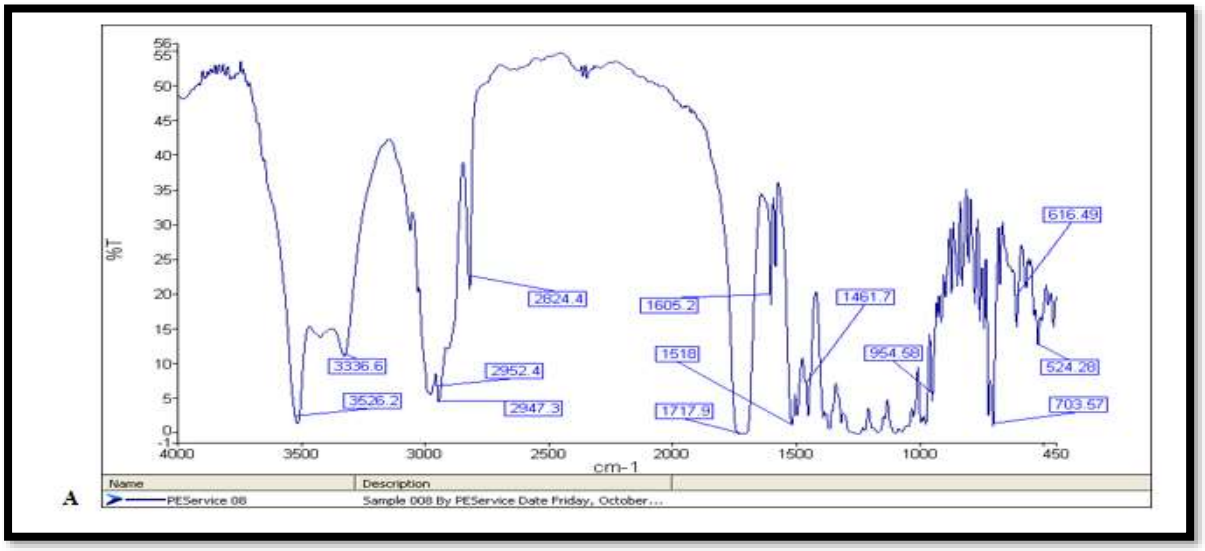
Figure 1: Saturated solubility of pure CXT, CXT–SYA (1:1), CXT–SYA (1:2) and CXT–SYA (1:3) complex

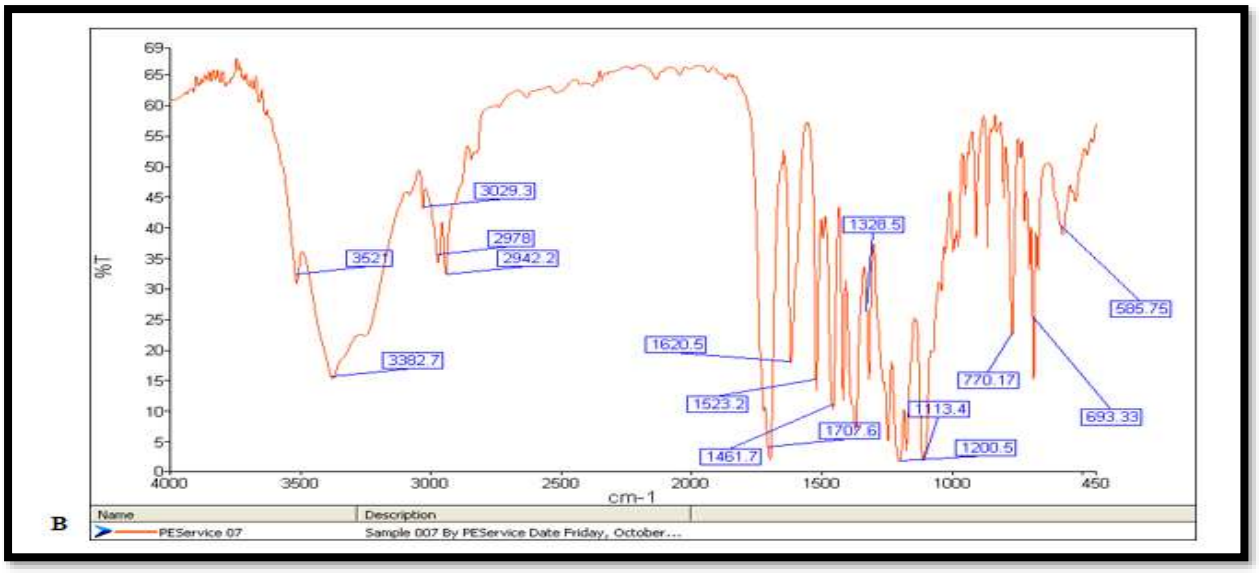


Fourier transformation infrared spectroscopy (FTIR)

FT-IR spectroscopy has been successfully used for exploring the differences in molecular conformations, crystal packing, and hydrogen bonding arrangements for different solid-state forms of an organic compound (Cho et al., 2010). The FT-IR spectra of the CTX–CIT complex and the individual co-formers were shown in Fig. 2. The IR spectrum of CXT had absorption bands at 3626.2 cm^{-1} (NH and OH stretching) (Fig. 2a). The stretching of the carbonyl oxygen (C O) was represented by double peaks at 1461.7 cm^{-1} and 1717.9 cm^{-1} (Fig. 2a) (Shao et al., 2014).

Figure 2: FTIR spectrum of Cabazitaxel (A) and FTIR spectrum of the co-crystal (B)



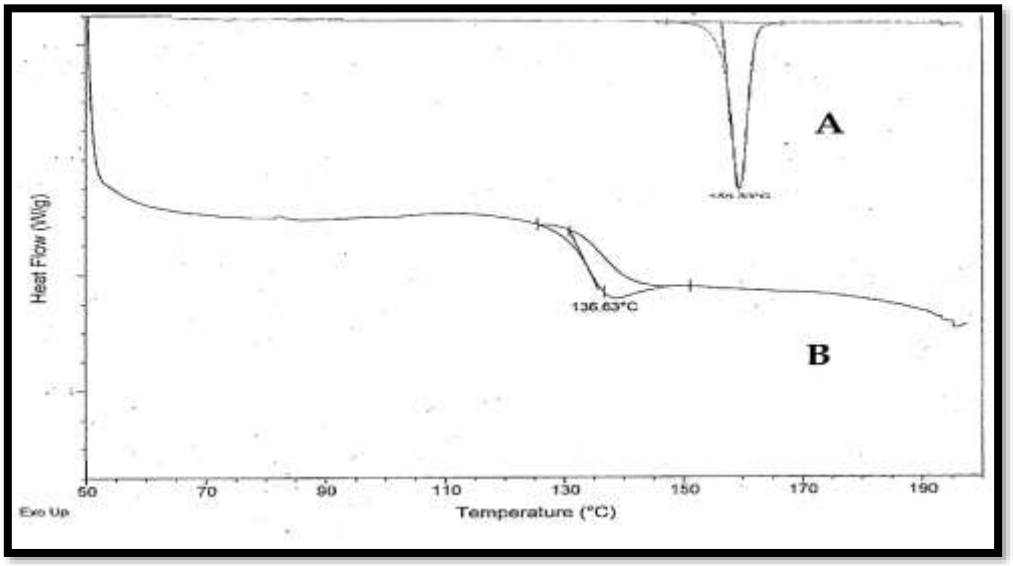


FT-IR revealed evidence of significant intermolecular interactions based on two characteristic shifts toward lower frequencies. In CXT–CIT complexes, an obvious shift of the NH2 and OH stretching took place, and the decrease in CXT was from 3626.2 cm−1 to 3382.7 cm−1 (Fig. 2b). The reason for these shifts of IR bands was predicted due to the involvement of these hydrogens in intermolecular hydrogen boding for the formation. The differences in the peak positions indicated the hydrogen bonding between CXT and CIT, and it implied that the NH, OH and C O groups of CXT and CIT were probably participating in a strong hydrogen bond.

Differential scanning calorimetry (DSC)

The DSC traces and thermal data for CXT, CIT and CXT–CIT complex were presented in Fig. 3. The melting point, as a fundamental physical property for a specific compound, is often determined for the purpose of characterization or purity identification (Mulye et al., 2012). As shown in Fig. 3, CXT showed a melting peak at around 157°C, and CIT demonstrated an endothermic melting peak at 153°C, which were both in agreement with the reported thermal behaviour. In contrast, the complexes exhibited a different melting transition with an endothermic peak at 136.63ºC, which was different from either of the host or guest component. This result might be related to the different existence form between the resultant complex and the individual co-former, which indicated the formation of a new phase. Fig. 3 showed that the pure drug and complexes did not lose weight until reaching their melting points, proving the rid of residual solvent. It indicated the presence of the complex and demonstrated that the new phase seemed to be stable until the melting point.

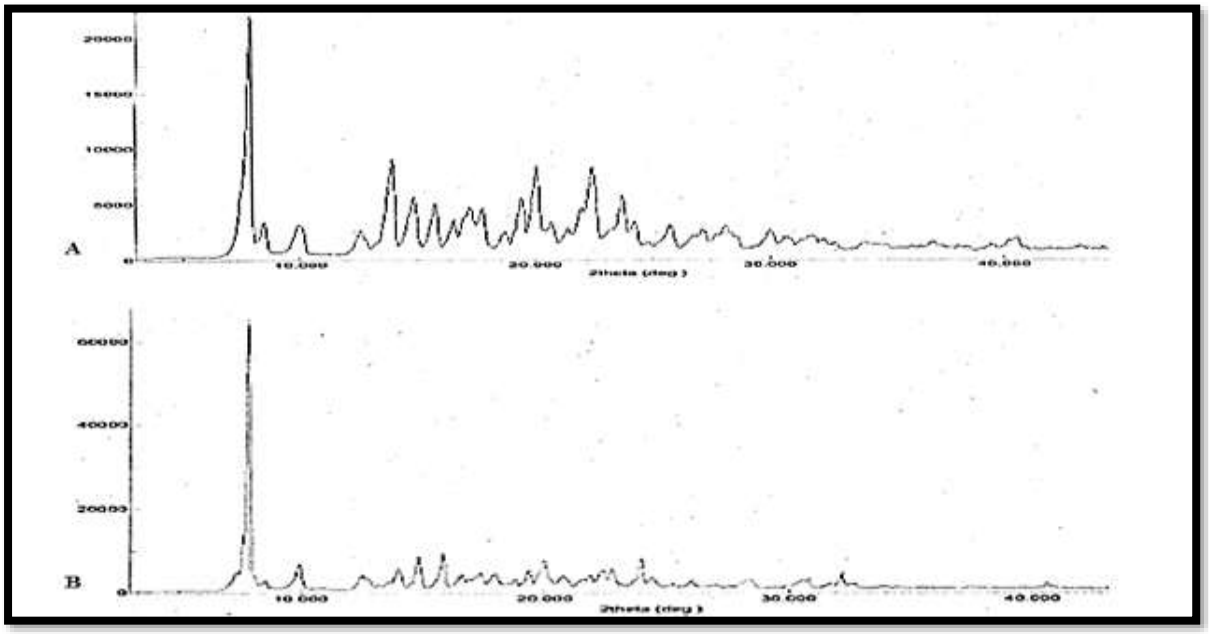
Figure 3: DSC analysis of CXT–CIT complex system



Powder X-ray diffraction (PXRD)

Every compound exhibits distinct peaks in the PXRD pattern and thus the PXRD patterns of API, co-former can be easily differentiated from that of the cocrystals. Results of PXRD were depicted in figure 4.

Figure 4: XRD pattern of pure Cabazitaxel (A) and Co-crystal of Cabazitaxel (B)

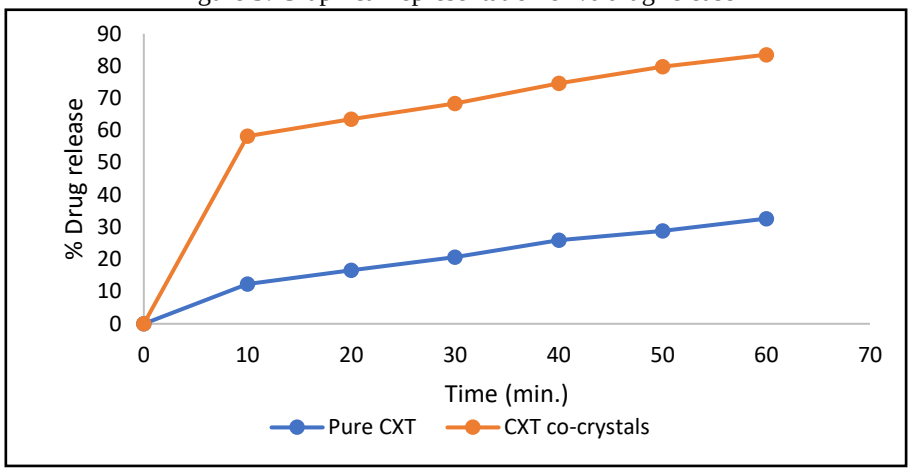


In cocrystal of CXT and CIT, new peak was observed. From the XRD diffraction pattern of all the studied powders, it is clearly vivid that the both the drug and co-crystal have their distinct XRD peaks, which were non-analogous. Moreover, slight shift in parent peak of CXT was observed in cocrystal XRD and these shift in prominent peaks might be due to occurrence of bonding between CXT and CIT.

Drug dissolution study

Drug release profile (n=6) was performed in 0.1N HCl (Figure 5). The cocrystals exhibited enhanced solubility over pure drug in dissolution media. Significant improvement in % Drug Release in dissolution profile of cocrystals was observed in comparison to pure drug.

Figure 5: Graphical representation of % drug release



Preparation of immediate release tablets of Cabazitaxel co-crystals

The prepared Cabazitaxel co-crystals were further converted into immediate release tablet utilizing Croscarmellose sodium as superdisintegrant and Menthol as subliming agent. Direct compression method was used to prepare the tablets.

A 3^2 full factorial design was used to optimize the process parameters.

Optimization of Cabazitaxel co-crystal immediate release tablets

Two independent factors viz., Croscarmellose sodium and Menthol were chosen and their responses on the dependent factors was studied. Analysis of variance (ANOVA) for dependent variables, disintegration time and percent drug release were performed. The coefficients X1(Croscarmellose sodium) and X2 (Menthol) showed significant effect ($p<0.05$) on the selected responses.

Response surface plots

The response surface plots were generated for disintegration time and percent drug release and effect of independent variables, X1 and X2 was studied on the responses (Figure 6,7). The effect of formulation variables on disintegration time (R1) can be described by the model equation

Disintegration Time (sec) = +54.89-6.00*X1 - 17.00*X2

The negative sign for coefficient X1 (Croscarmellose sodium) and X2 (Menthol) indicated that increase in concentration of Croscarmellose sodium (X1) and Camphor (X2), decreased the

disintegration time. A $R^2=1$, indicated a good correlation between independent and dependent variables (Figure 6).

The second parameter, percent drug release (R2) can be described by model equation

% Drug release = +78.26 + 3.11*X1+11.95*X2

The positive sign for coefficient X1 (Croscarmellose sodium) and X2 (Menthol) showed that percent drug release was increased with increase in concentration of X1 and X2 pertaining to the presence of superdisintegrant and subliming agent that cause relaxation of matrix hence, more penetration of fluid in the matrix which leads to faster

disintegration and faster release of drug from the formulation (Figure 7). A R^2=1, indicated a good correlation between independent and dependent variables.

Figure 6: Response surface plot showing the effect of Factor X1 & X2 on distegration time (R1), Model plot (A) and 3D response plot (B)

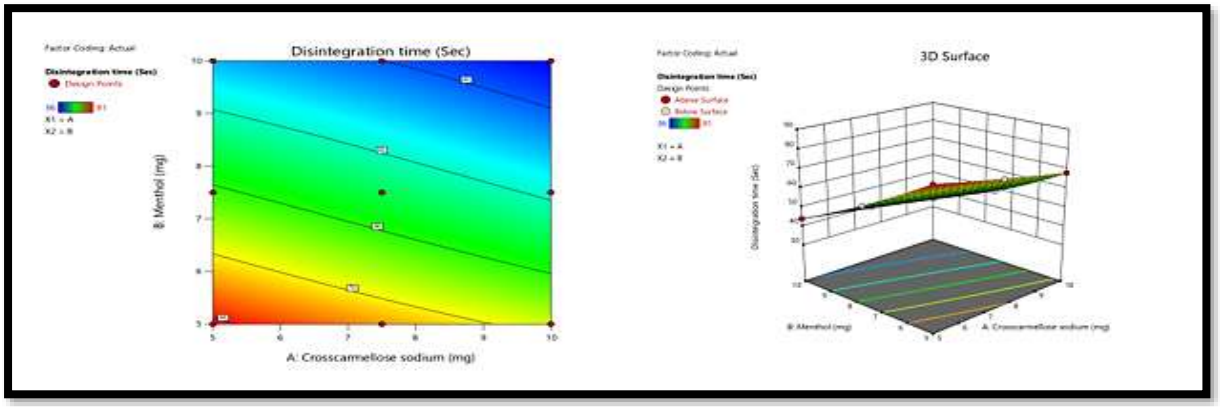
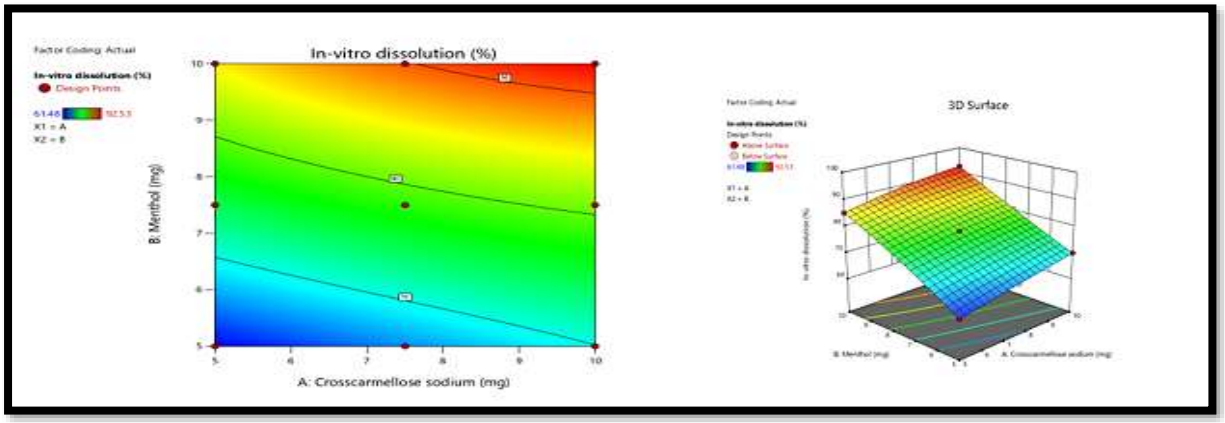


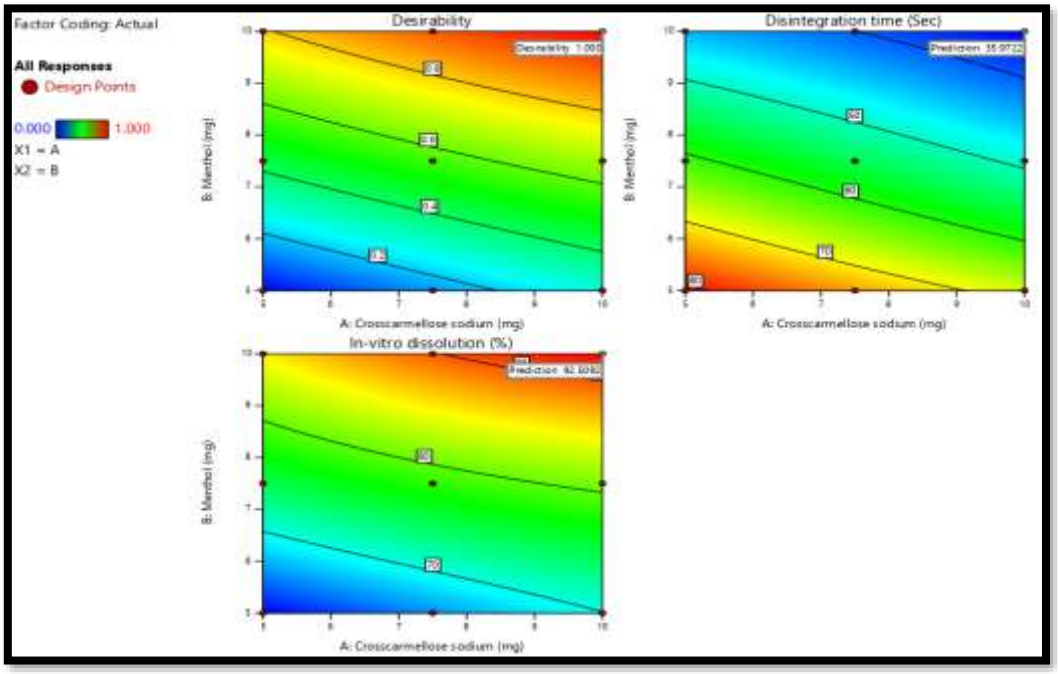
Figure 7: Response surface plot showing the effect of Factor X1 & X2 on in-vitro drug release (R2), Model plot (A) and 3D response plot (B)



Optimization Analysis

Results obtained from factorial design, indicated that the independent factors i.e., Croscarmellose sodium and Menthol have negative effect on Response 1 while it was positive for Response 2. A checkpoint batch was selected on the basis of desirability and a batch comprised of maximum amount of Croscarmellose sodium and Menthol was selected as best batch as it has shown min. disintegration time and maximum drug release. A desirability graph (Figure 8) showing the optimized responses.

Figure 8: Desirability graph showing the optimized parameters



Evaluation of pre-compression parameters

Prior to compression, powder blends were evaluated for flow and compressibility parameters. Flow properties of powder were determined by angle of repose, compressibility by Carr's index and Hausner ratio. Preformulation study results were presented in table 3. All the formulations exhibited good flow properties.

Table 3: Pre-compression parameters of immediate release tablets of Cabazitaxel co-crystals

Parameters	**Pre-compression parameters**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Bulk density (g/cm^2)	0.393± 0.012	0.391± 0.015	0.395± 0.004	0.392± 0.005	0.390± 0.007	0.389± 0.069	0.396± 0.008	0.393± 0.011	0.392± 0.028
Tapped density (g/cm^2)	0.427± 0.005	0.429± 0.002	0.425± 0.014	0.426± 0.008	0.421± 0.003	0.428± 0.022	0.424± 0.015	0.422± 0.009	0.428± 0.011
Hausners's ratio	1.08± 0.009	1.09± 0.027	1.07± 0.013	1.08± 0.016	1.07± 0.009	1.10± 0.006	1.07± 0.014	1.07± 0.011	1.09± 0.013
Carr's index	7.96± 0.006	8.85± 0.012	7.05± 0.013	7.98± 0.005	7.36± 0.013	9.11± 0.009	6.66± 0.018	6.87± 0.007	8.41± 0.015
Angle of repose	28.93± 0.012	31.48± 0.037	30.46± 0.013	29.53± 0.022	30.27± 0.015	28.18± 0.047	27.51± 0.013	29.79± 0.018	25.62± 0.009

Evaluation of post compression parameters

Prepared co-crystals were also evaluated for post compression parameters viz., thickness, weight variation, hardness, friability, in-vitro disintegration time, drug content, in-vitro dissolution study and stability study.

The result of post compression parameters showed that, all the formulated tablets were of uniform weight with acceptable weight variation and thickness. Hardness of all formulations was maintained at 3.4-3.8 kg/cm^2 and friability loss was between 0.70 to 0.88%. The hardness and friability studies revealed that the tablets possessed good mechanical resistance. The immediate release tablets showed drug content between 97.68-99.92% which was within the acceptable limits (Table 4).

From the obtained results, it was observed that the F9 batch was most promising as it exhibited least disintegration time of 36 sec. & maximum drug release of 92.53% which was in agreement with the results of optimization study i.e., 35.97±0.016 sec. and 92.50±0.024%, respectively.

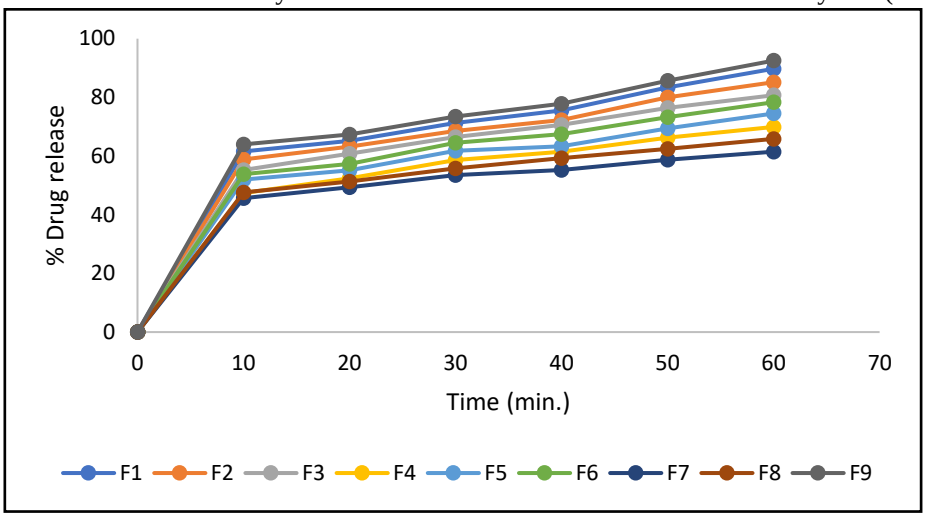
Table 4: Post compression parameters of immediate release tablets of Cabazitaxel co-crystals

Parameters	**Pre-compression parameters**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Weight variation (mg)	200± 0.11	199± 1.5	200± 0.7	201± 1.2	201± 1.3	197± 0.5	202± 0.9	201± 0.11	200± 0.5
Hardness (kg/cm^2)	3.7± 0.03	3.6± 0.11	3.5± 0.06	3.4± 0.12	3.7± 0.11	3.5± 0.14	3.6± 0.13	3.4± 0.15	3.8± 0.11
Thickness (mm)	4.35± 0.3	4.29± 0.6	4.28± 0.5	4.34± 0.7	4.26± 0.13	4.22± 0.8	4.31± 0.6	4.27± 0.5	4.30± 0.9
Friability (%)	0.82± 0.5	0.78± 0.1	0.85± 0.4	0.75± 0.8	0.81± 0.6	0.84± 0.5	0.71± 0.2	0.83± 0.6	0.88± 0.7
Disintegration time (sec.)	40± 0.16	44± 0.15	49± 0.18	68± 0.09	61± 0.42	55± 0.18	81± 0.09	74± 0.15	36± 0.12
Drug content (%)	98.65± 0.11	97.68± 0.15	99.01± 0.5	98.25± 0.5	98.06± 0.21	97.36± 0.13	98.51± 0.08	97.85± 0.17	99.92± 0.12

In-vitro dissolution study

The in-vitro dissolution behavior of developed formulations was studied in 0.1N HCl. The drug release study was carried out for 60 min and depicted in Figure 9. The F9 batch showed maximum drug release (92.50±0.024%). This might be due to greater concentration of superdisintegrant. Depending on the entire evaluation parameters, F9 batch was selected as optimized formulation and subjected for stability study.

Figure 9: In-vitro release study of immediate release tablets of Cabazitaxel co-crystals (F1-F9)



Stability study

The optimized formulation (F9) was subjected to stability study as per ICH guidelines. The optimized formulation did not showed remarkable changes during stressed conditions and found stable at stability conditions.

Conclusion

Cocrystals can be used as an alternative approach based on crystal engineering to enhance specific physicochemical and biopharmaceutical properties of active pharmaceutical ingredients (APIs) when the approaches to salt or polymorph formation do not meet the expected targets. In the present work, co-crystals of Cabazitaxel were prepared with citric acid as a co-former. The co-crystal formation was confirmed by melting point, DSC, FTIR, XRPD and mutually supported each others. Improved dissolution profile was presented by Cabazitaxel co-crystals than the pure drug. The directly compressible immediate release tablets of Cabazitaxel cocrystal with shorter disintegration time, low friability, and greater drug release were developed by 3^2 full factorial design. The formulation F9 was found promising based on the results obtained from factorial design and pre & post-compression parameters. The results indicated that, selected variables showed significant effect on the responses. Thus, Cabazitaxel cocrystals possessing modified physicochemical properties were obtained and successfully formulated as immediate release tablets.

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