Original Article

FORMULATION, CHARACTERIZATION AND EVALUATION OF DOCETAXEL COCRYSTALS FAST RELEASE TABLETS FOR TREATMENT OF CANCER

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Abstract

The current study aims to improve the dissolution and oral bioavailability of a BCS IV drug Docetaxel (DXT) by co-crystallization with a co-former, syringic acid (SYA). A co-crystal of DXT with SYA in different molar ratios were prepared by liquid assisted grinding method. Prepared co-crystals were evaluated for melting point and solubility. Solubility study showed that maximum solubility was achieved with 1:2 molar ratio which was further characterized by FTIR, differential scanning calorimetry (DSC) and powder X-ray diffraction. FT-IR revealed evidence of significant intermolecular interactions based on two characteristic shifts toward lower frequencies pertaining to the complex formation between drug and co-former. The results of DSC and PXRD in were also in full compliance with the reported study. The Docetaxel co-crystals exhibited greater dissolution than the pure drug. The Docetaxel co-crystals were further converted into fast release tablets with superdisintegrant and subliming agent. The formulation parameters were optimized by 3^2 full factorial CCD design. Disintegration time and in-vitro dissolution were taken as dependant variables and effect of superdistigrant and subliming agent was studied. A checkpoint batch comprising of maximum quantity of Crospovidone and Camphor was selected on the basis of desirability, as it has shown minimum disintegration time and maximum drug release. The optimized formulation was kept under stressed condition to check the stability of product and results indicated that it was found stable.

Keywords: Docetaxel, syringic acid, CCD, crospovidone and camphor.

Introduction

Cancer incidence is increasing globally and accounts for about 8.2 million deaths worldwide mainly because of poor tumor targeting and severe dose-related adverse effects to other organs or many other complications associated with the disease (Sohail et al., 2018). In the United States, an estimated 6% of women with breast cancer (BC) are metastatic at diagnosis, with 20% to 30% of early-stage BC patients eventually progressing to metastatic disease. Metastatic BC is a varied disease that can be characterized based on molecular subtype, which also provides prognostic information. The most common subtype is hormone receptor (HR)–positive (either estrogen receptor [ER]–positive or progesterone receptor [PR]– positive), which accounts for approximately 68% of newly diagnosed BCs (Gautam et al., 2022). The taxanes (paclitaxel and docetaxel) represent a novel class of antineoplastic agents that interfere with microtubule function leading to altered mitosis and cellular death. Oral drug delivery is the most convenient way to administer medicine. But oral administration of cancer chemotherapeutic drugs is limited due to an extensive first-pass effect, poor solubility, efflux transport, low

intrinsic permeability of drug limits, bioavailability of drugs and so on. Taxanes share the largest sales volume of around US $3.5 billion of the presently available anticancer drugs. Thus, development of an oral formulation for Docetaxel (DTX) would be a great achievement from the patient's perspective of "chemotherapy at home"(Sohail et al., 2018). The chemotherapeutic drugs are restricted by their poor water solubility. Among of them, docetaxel is a such one (Zhang et al., 2016). Docetaxel (DTX) is belonging to BCS (biopharmaceutics classification system) class IV drugs. However, oral chemotherapy with DTX is also restricted by its active P-glycoprotein (P-gp) efflux and hepatic first-pass metabolism (Cui et al., 2019). Docetaxel is a second-generation taxane derived from the needles of the European yew tree. Early in vitro studies revealed that docetaxel has a wide spectrum of antitumor activity and a number of unique preclinical characteristics compared to other chemotherapeutic agents. Docetaxel is highly effective as monotherapy and combination therapy across a variety of tumor types, including breast, lung, and ovarian, as well as head and neck, gastric, and prostate carcinomas (Herbst & Khuri, 2003). Pharmaceutical research field focuses mainly on either development of newer drug delivery systems or newer solid dosage forms for selected active pharmaceutical ingredient. 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. Biopharmaceutics Classification System (BCS) Class II and IV drugs suffer from poor aqueous solubility and hence low bioavailability. Most of these drugs are hydrophobic and cannot be developed into a pharmaceutical formulation due to their poor aqueous solubility. One of the ways to enhance the aqueous solubility of poorly water-soluble drugs is to use the principles of crystal engineering to formulate cocrystals of these molecules with water-soluble molecules (Sathisaran & Dalvi, 2018), 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, 2022). Syringic acid (SYA) is chemically 4-hydroxy-3,5-dimethoxybenzoic acid with a molecular weight of 198.17 Daltons, melting point 206-209 0C, pKa of 3.93 and log P of 1.04. It is a potential antioxidant used in traditional Chinese medicine. Hepatoprotective effects of SYA are reported in various animal models (Thipparaboina et al., 2016). Cocrystals 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 co-crystals are expected to be more soluble in water than the parent acids, due to the possibility of complex formation in solution and the higher solubility of Syringic acid (Fábián et al., 2011). The primary objective of this work was to use crystal engineering for improving the solubility and dissolution rate of a Docetaxel (DTX). Identifying the therapeutic solubility of DTX cocrystal in a comparative manner for the treatment of prostate cancer is entirely new for drug delivery.

Material and Method

Material

Docetaxel (DTX) 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 Docetaxel

Docetaxel co-crystals were prepared by 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, aerosil-200, nicotinamide, para-amino benzoic acid, anthranilic acid, 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 Docetaxel co-crystals

Liquid assisted grinding method was adopted for the preparation of Docetaxel 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 Docetaxel (molecular weight: 807.8 g/mol) was mixed with selected co-former in different stoichiometric ratios (1:1 and 1:2). 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 Docetaxel co-crystal

Determination of melting point

Melting point of pure Docetaxel and co-crystals using digital melting point apparatus (A.KRÜSS Optronic GmbH, Alsterdorfer Str. 276-27822297 Hamburg) . 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 (Patil et al., 2022)

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 hrs, diluted with distilled water and analyzed by UV Spectrophotometer (Thermo Fisher Scientific,168 Third Avenue, Waltham, MA USA 02451) at respective wavelength (Chen et al., 2021)

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) (Thambiraj et al., 2021)

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) (Waters India Private Limited, TA Instruments Division, Bengaluru, Karnataka) (Patil et al., 2022)

Drug dissolution study

A dissolution study was carried out for Docetaxel 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).

of fast release tablets of Docetaxel co-crystals

Direct compression method was used for preparing Docetaxel tablets. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablet. An accurately weighed quantity of Docetaxel 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 Docetaxel 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 Docetaxel co-crystal fast dissolving tablets

A 3^2 full factorial design was used for the preparation of fast dissolving tablets of Docetaxel co-crystals. The two independent factors, concentration of croscarmellose sodium (X1) and concentration of PVP K-30 (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 percent drug release (Y2).

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.

Pre-compression parameters:

Angle of repose

Angle of repose for Docetaxel and Docetaxel co-crystals was determined using the fixed funnel method. Accurately weighed Docetaxel and co-crystals were 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 (Madhuri et al., 2020).

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 (Basu et al., 2011).

Drug content

Twenty tablets were weighed and powdered. Powder equivalent to a single dose of Docetaxel 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 (Vigo) 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.,Vigo) 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) (Basu et al., 2011).

Stability study

The optimized formulation was subjected to stability study according to ICH guidelines, at 40±2°/75% RH±5% condition in stability chamber (HMG, India) for three months. Tablets were analyzed 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 Docetaxel, method of preparation and characteristics of final products.

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

Drug	Co-former	Method of Preparation	Inference

Docetaxel	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 low 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 high solubility
	Succinic acid	Liquid assisted grinding	Stable with low solubility

*Syringic acid showed high solubility of Docetaxel and selected for further study

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

Preparation of Docetaxel co-crystals

The co-crystals of Docetaxel co-crystals 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 Docetaxel (232°) and the co-former Syringic (205°) confirming the formation of co-crystals with some chemical interaction between both molecules (Madhuri et al., 2020).

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

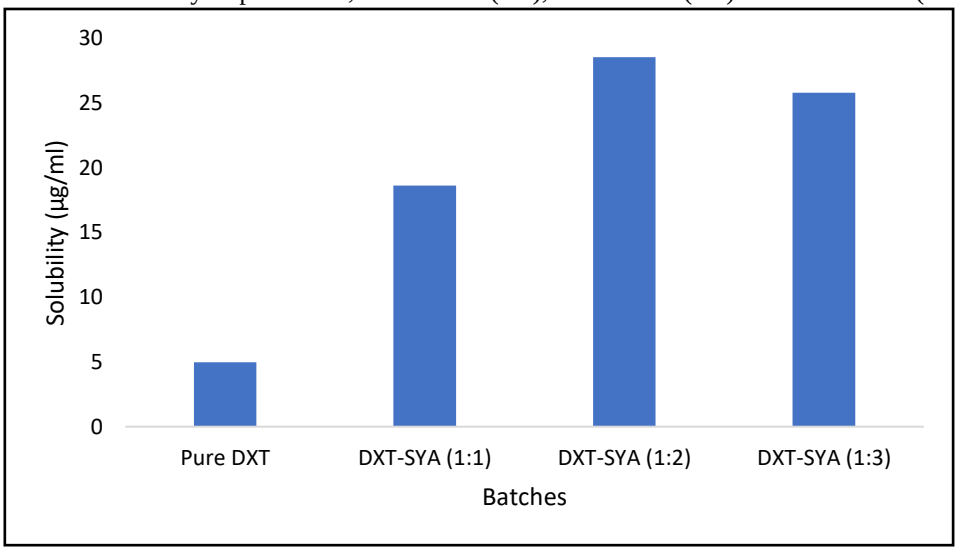
Co-crystal components	**Ratio of drug:Co-former**	**Melting point**
Pure Drug (Docetaxel, DXT)	-	232^0

Docetaxel+Syringic acid (DXT+SYA)	1:1	195^0
Docetaxel+Syringic acid (DXT+SYA)	1:2	196^0
Docetaxel+Syringic acid (DXT+SYA)	1:3	193^0

Saturation solubility

Solubility study data of different preparations were presented in Figure 1. The preparation comprised of 1:2 drug and co-former ratio showed maximum solubility when compared with pure Docetaxel. Although, preparation comprising of drug co-former ratio as 1:3 also showed good solubility enhancement, that was not chosen for further studies due to the fact that the ratio of syringic acid and Docetaxel led to bulky size, which would produce problems to formulate and obtain patient acceptance. Thus, 1:2 molar ratio was selected for further studies.

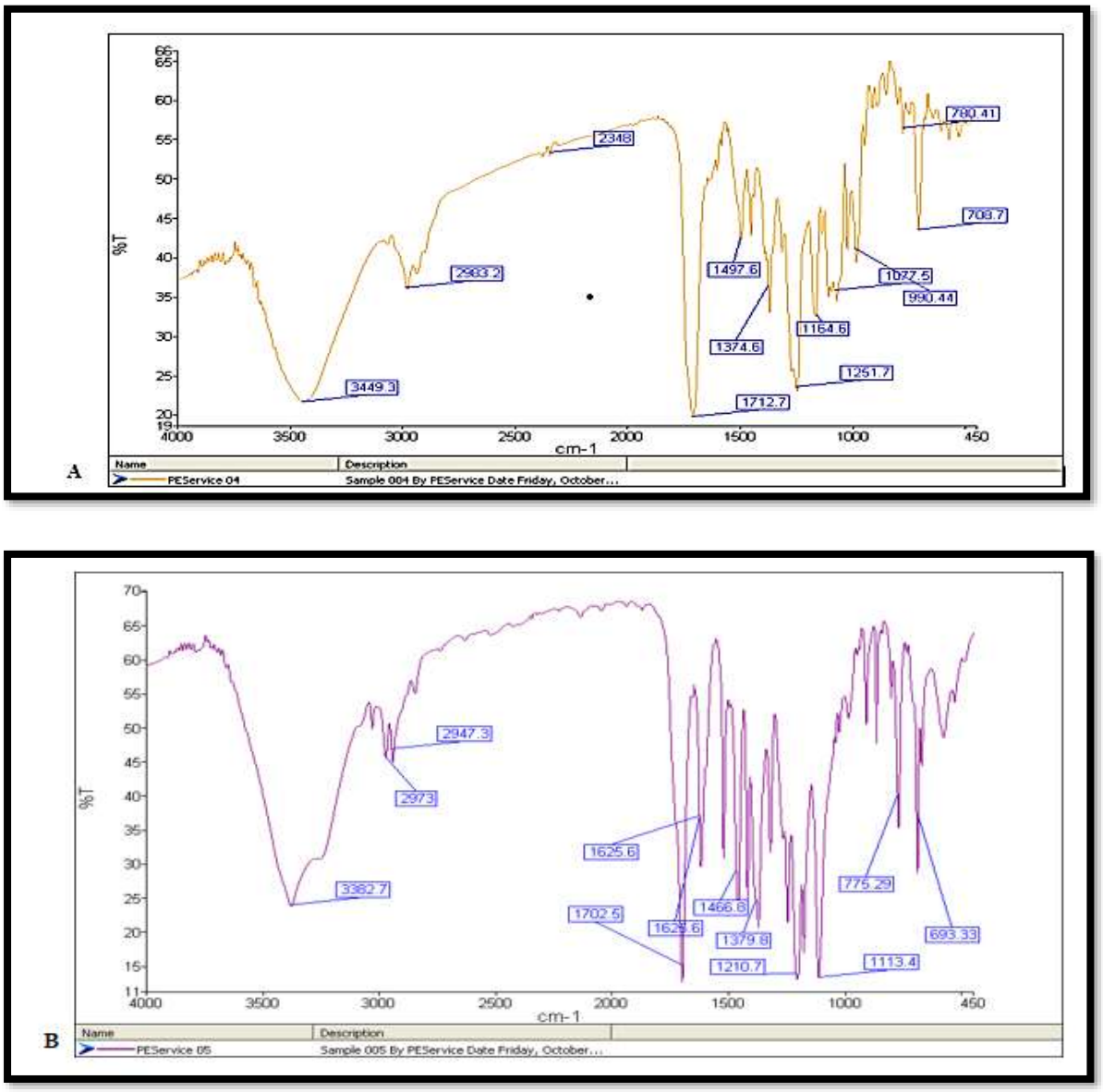
Figure 1: Saturated solubility of pure DTX, DTX–SYA (1:1), DTX–SYA (1:2) and DTX–SYA (1:3) complex



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 DTX–SYA complex and the individual co-formers were shown in Fig. 2. The IR spectrum of DTX had absorption bands at 3349.3 cm^{-1} (NH and OH stretching) (Fig. 2a). The stretching of the carbonyl oxygen (C O) was represented by double peaks at 1447.08 cm^{-1} and 1703.09 cm^{-1} (Fig. 2a).

Figure 2: FTIR spectrum of Docetaxel (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 DTX–SYA complexes, an obvious shift of the NH2 and OH stretching took place, and the decrease in DTX was from 3349.3 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 DTX and SYA, and it implied that the NH, OH and C O groups of DTX and SYA were probably participating in a strong hydrogen bond.

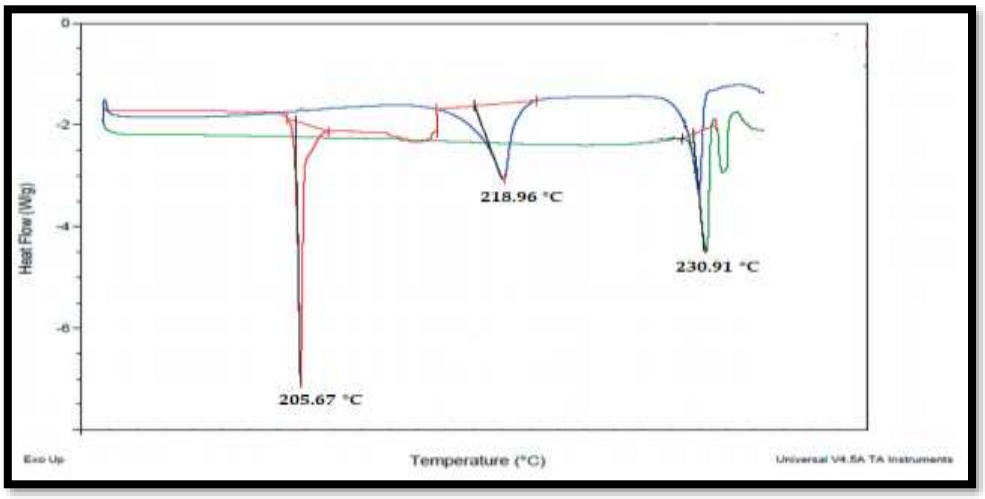
Differential scanning calorimetry (DSC)

The DSC traces and thermal data for DTX, SYA and DTX–SYA 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, DTX showed a melting peak at around 230.91 ^{0}C, and SYA demonstrated an endothermic melting peak at 209 ^{0}C, which were both in agreement with the reported thermal behaviour (Fan et al., 2013; Haneef & Chadha, 2020). In contrast, the complexes

exhibited a different melting transition with an endothermic peak, 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.

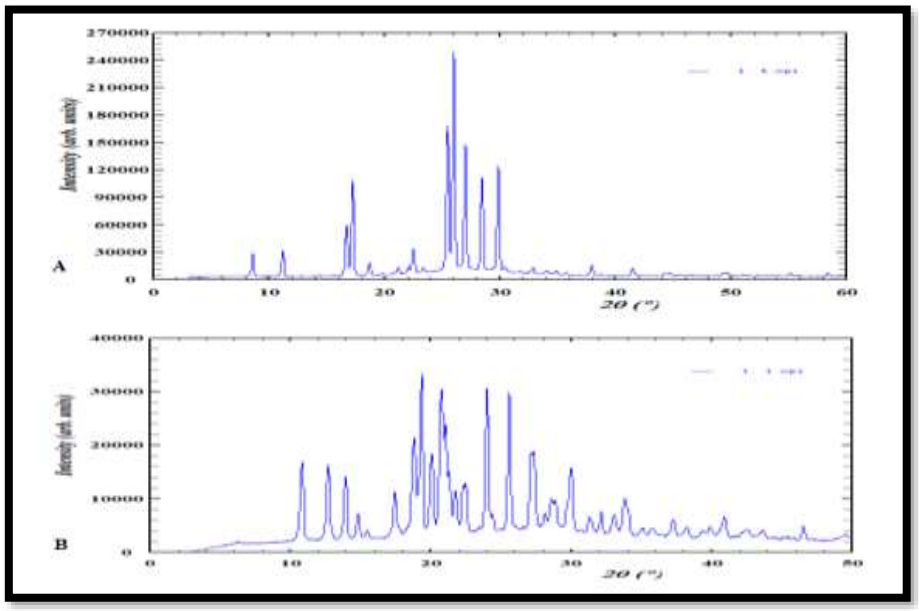
Fig. 3 showed that the pure drug and complexes did not lose weight until reaching their melting points, proving the rid of residual solvent. It indicated the presence of the complex and demonstrated that the new phase seemed to be stable until the melting point.

Figure 3: DSC analysis of DTX–SYA 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 Docetaxel (A) and Co-crystal (B)

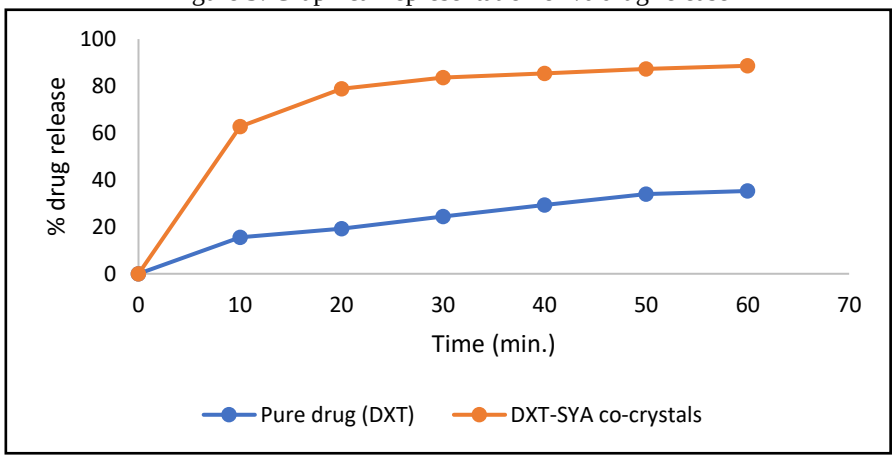


In co-crystal of DXT and SYA, new peak was observed. Moreover, slight shift in parent peak of DXT was observed and these shift in prominent peaks might be due to occurrence of bonding between DXT and SYA.

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 fast release tablets of Docetaxel co-crystals

The prepared Docetaxel co-crystals were further converted into fast release tablet utilizing Crospovidone as superdisintegrant and Camphor 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 Docetaxel co-crystal fast dissolving tablets

Two independent factors viz., Crospovidone and Camphor 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(Crospovidone) and X2 (Camphor) 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) = +52.33-10.00*X1 - 21.50*X2

The negative sign for coefficient X1 and X2 indicated that increase in concentration of Crospovidone (X1) and Camphor (X2), decreased the disintegration time. A R^2=0.9997, indicated a good correlation between independent and dependant variables (Figure 6).

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

% Drug release = + 80.47 + 2.76*X1+10.72*X2

The positive sign for coefficient X1 (Crospovidone) and X2 (Camphor) 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 dependant 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)

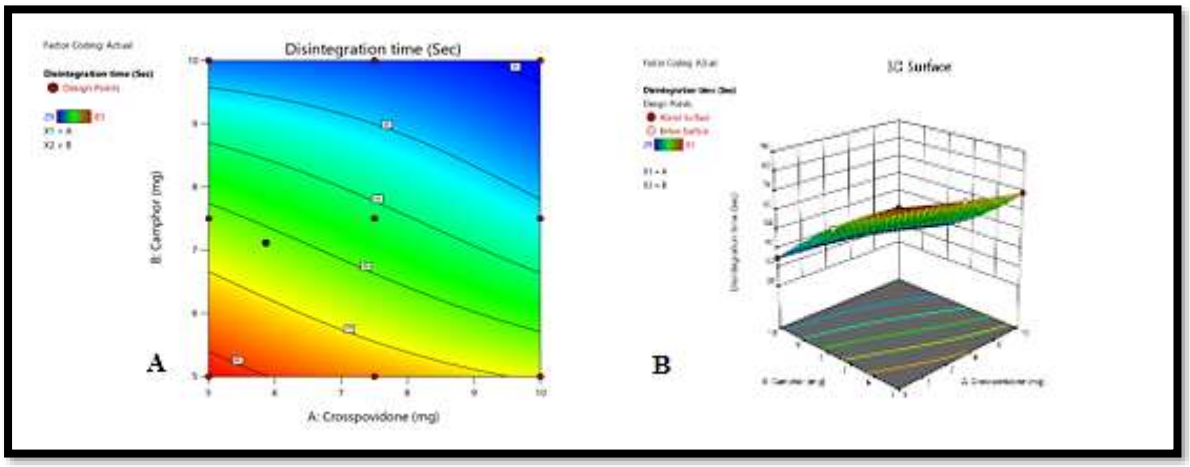
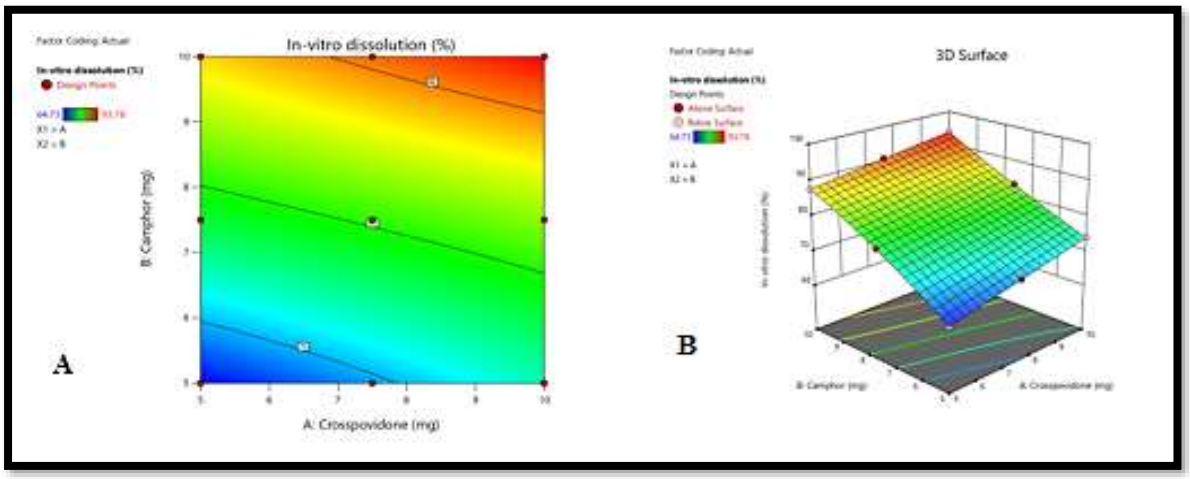


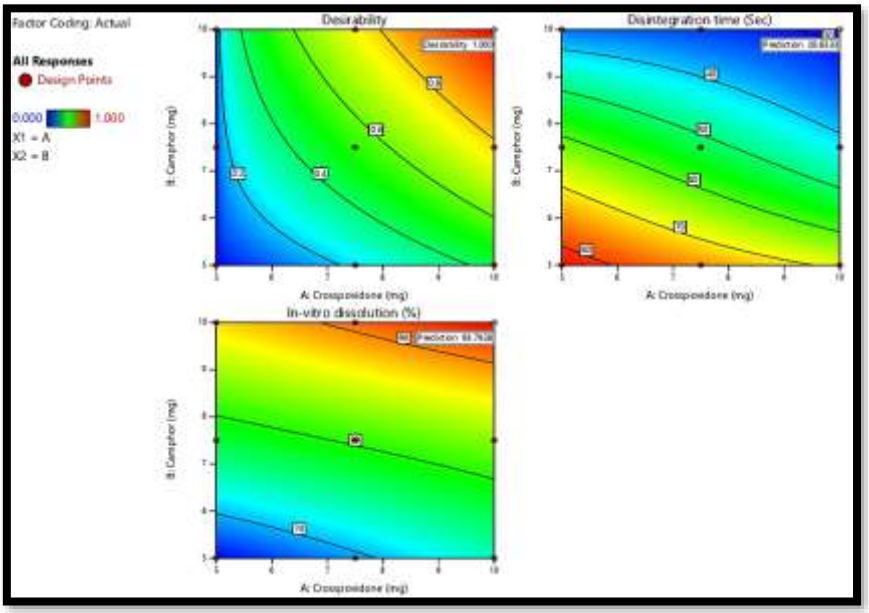
Figure 7: Response surface plot showing the effect of Factor X1 & X2 on in-vitro drug release (R2), Model plot (A) and 3D response plot (B)



Optimization Analysis

Results obtained from factorial design indicated that the independent factors 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 Crospovidone and Camphor 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 fast dissolving tablets of Docetaxel co-crystals

Parameters	**Pre-compression parameters**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Bulk density (g/cm^2)	0.326± 0.005	0.331± 0.012	0.329± 0.006	0.315± 0.017	0.327± 0.008	0.335± 0.096	0.333± 0.062	0.326± 0.015	0.337± 0.039
Tapped density (g/cm^2)	0.395± 0.012	0.401± 0.017	0.405± 0.096	0.411± 0.063	0.408± 0.008	0.403± 0.026	0.413± 0.011	0.407± 0.007	0.412± 0.015
Hausners's ratio	1.21± 0.049	1.21± 0.011	1.23± 0.002	1.30± 0.008	1.24± 0.017	1.20± 0.025	1.24± 0.036	1.24± 0.009	1.22± 0.071
Carr's index	17.46± 0.032	17.45± 0.008	18.76± 0.013	23.35± 0.027	19.85± 0.005	16.87± 0.014	19.37± 0.037	19.90± 0.007	18.20± 0.019
Angle of repose	29.69± 0.009	30.54± 0.065	31.83± 0.011	30.95± 0.028	31.52± 0.048	29.61± 0.064	28.93± 0.015	28.61± 0.027	26.37± 0.013

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 3.2-3.6 kg/cm^2 and friability loss was between 0.69 to 0.85%. The hardness and friability studies revealed that the tablets possessed good mechanical resistance. The fast release tablets showed drug content between 98.27-99.85% 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 (28.83±0.011 sec.) and maximum drug release (93.79±0.048%). The disintegration time was decreased with increasing concentration of superdisintegrant owing to sufficient swelling of tablet required for disintegration and wicking action of superdisintegrant.

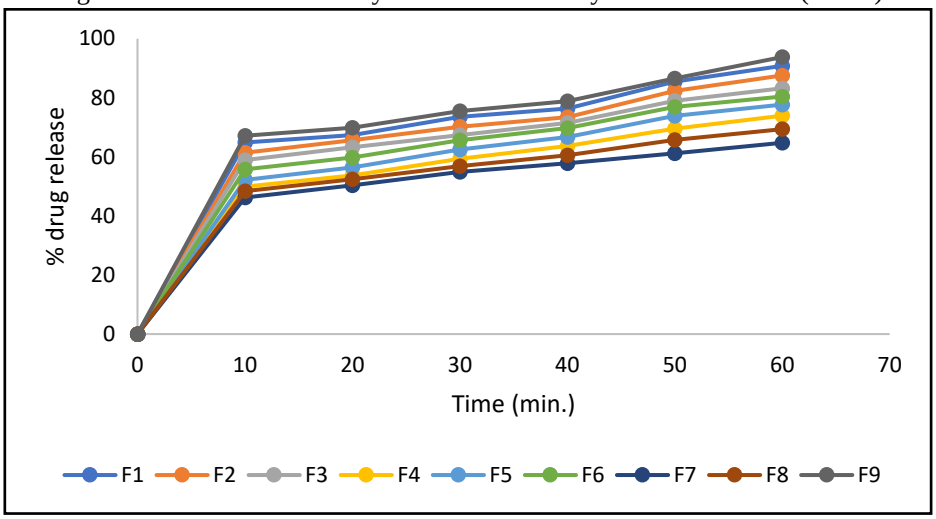
Table 4: Post compression parameters of fast dissolving tablets of Docetaxel co-crystals

Parameters	**Pre-compression parameters**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Weight variation (mg)	200± 0.5	201± 1.2	199± 0.4	202± 1.3	200± 1.1	198± 0.7	201± 0.2	203± 0.5	200± 0.8
Hardness (kg/cm^2)	3.2± 0.02	3.1± 0.13	3.2± 0.05	3.4± 0.13	3.5± 0.11	3.3± 0.12	3.1± 0.09	3.5± 0.12	3.4± 0.15
Thickness (mm)	4.31± 0.5	4.28± 0.7	4.29± 0.3	4.32± 0.6	4.27± 0.2	4.19± 0.5	4.22± 0.1	4.25± 0.8	4.28± 0.6
Friability (%)	0.85± 0.1	0.83± 0.5	0.84± 0.3	0.71± 0.5	0.75± 0.2	0.82± 0.6	0.74± 0.3	0.72± 0.9	0.81± 0.4
Disintegration time (sec.)	32± 0.62	35± 0.59	42± 0.67	69± 0.28	62± 0.74	53± 0.81	83± 0.27	75± 0.35	28.83± 0.011
Drug content (%)	97.82± 0.14	97.69± 0.8	98.27± 0.5	96.59± 0.7	99.01± 0.15	98.78± 0.28	97.45± 0.12	98.91± 0.22	99.85± 0.3

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 (93.79±0.048%). 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 Docetaxel co-crystal tablet batches (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

The cocrystal of Docetaxel was successfully prepared using syringic acid as co-former to improve the solubility and dissolution. Liquid assisted grinding method allowed the formation of cocrystals. The cocrystal formation was confirmed by melting point alterations, DSC changes, shifts in Infra Red bands, changes in 2θ values in XRPD and mutually supported each others. The Docetaxel cocrystals exhibited greater dissolution than the pure drug. The directly compressible fast dissolving tablets of Docetaxel cocrystal with shorter disintegration time, low friability, and greater drug release were developed by 3^2 full factorial design. F9 formulation was found promising based on the evaluation parameters. The result indicated that, selected variables showed significant effect on the responses. Thus, Docetaxel cocrystals possessing modified physicochemical properties were obtained and successfully formulated as fast release tablets.

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