

Experimental design approach for development of cocrystals and immediate release cocrystal tablet of atorvastatin calcium for enhancement of solubility and dissolution

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ABSTRACT: The objective of the present work was to prepare cocrystals of poorly soluble drug Atorvastatin Calcium (AVA) with the aim of increasing its solubility and dissolution properties. Screening of 8 cocrystal formers (CCFs) was performed by Hansen solubility parameter (HSPs) using 4 methods- neat grinding, solvent drop grinding, solvent evaporation and sonocrystallization in equimolar ratio. Solubility of AVA cocrystal (1.9 fold increase) in comparison to plain AVA drug has been demonstrated with solubility experiments. FTIR spectra of AVA cocrystal showed disappearance of O-H group indicating the formation of hydrogen bond synthon between the drug and CCFs. DSC thermogram showed drastic reduction in melting point from 164.6°C to 71.9 °C indicating the reduction in cohesive energy and increase in solubility. XRD pattern showed new crystalline peaks at 2θ values of 9.858°, 15.201°, 22.907°, 25.407°, 29.496°. SEM analysis showed changes in the morphological characteristics as compared to drug and CCFs, indicating different crystalline nature. Experimental design was applied to optimize AVA cocrystal IR tablet for concentration of aerosil (X_1) and MMC 102 (X_2) and were evaluated for drug release (Y_1) and friability (Y_2). It was found that as the concentration of aerosil and MMC 102 increased friability decreased and % drug release increased. A drug release of 98.54±1.163% and friability of 0.515±0.090 % was obtained for optimized batch. *Ex vivo* diffusion study was carried out by isolating rat stomach tissue, exhibiting higher drug release (95.71±0.98 %) than plain AVA and marketed tablet. Thus formulating AVA cocrystal and its subsequent formulation in optimized IR tablet gives a promising opportunity for manufacturing a drug with increased bioavailability.

KEYWORDS: Atorvastatin calcium; co-crystallization; Hansen-solubility parameter; 3^2 factorial design; immediate release tablet; *ex vivo* diffusion.

1. INTRODUCTION

Atorvastatin Calcium (AVA) is a HMG-CoA reductase inhibitor used for the treatment of hyperlipidemia. AVA is a class II drug in Biopharmaceutical classification system (BCS), lipophilic in nature ($\log P = 6.36$) with a reported low oral bioavailability of about 12% [1]. The major challenge with this drug in spite of having a high intestinal permeability at physiologically relevant pH is its poor therapeutic efficiency. This is because of its limited solubility under physiological conditions, which results into variable bioavailability. Many efforts have been made by various research groups to increase the solubility and dissolution rate of AVA by formulating Nanoparticles [2], Nano suspensions [3], liquid solid compacts [4], SEDDS [5], Conjugation with chitosan [6] and different resins [7], coamorphous system [8], Cyclodextrin complexations [9] and solid dispersions using PEG 600 [10], Skimmed milk [11], Microwave assisted [12], Soluplus [13], etc. The weakness of the solid dispersion technique is the instability of amorphous physical form of drug. The enhancement of solubility by this technique generally alters the physical form of the drug. The unstable amorphous form tends to be re-transformed into the crystalline form in storage, so it can change the solubility of the drug [14].

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Co-crystallization is one of the technique which is applied in order to improve various physical and chemical properties of active pharmaceutical ingredient (API) like solubility, dissolution, stability, hygroscopicity, compressibility etc., without affecting the structural integrity. A cocrystal can be defined as a multicomponent complex consisting of API and a cocrystal former (CCF) which remains solid under ambient conditions and are attached via strong supermolecular synthons in a definite stoichiometric ratio [15]. The formation of cocrystal depends on the functional groups present in API and CCF and different non-covalent bonds between them like hydrogen bonds, aromatic-aromatic interactions and van der Waals bonds [16]. AVA offers carbonyl group, amide group and hydroxyl groups indicating its suitability for formation of cocrystals. The carbonyl and amide group can act as hydrogen bond acceptors while hydroxyl groups can act as hydrogen bond donors and can easily participate in hydrogen bonding. However, the cocrystallization approach has not been explored much, except by the research group Wicaksono *et al.* who reported AVA cocrystals with three different CCFs [17-18-19]. In the present study, various other CCFs were explored in accordance with AVA cocrystallization which are not reported yet.

Over the years, cocrystal screening methodology has advanced from being empirically based to a more efficient and rational basis [20]. Cocrystal screening methods can broadly be categorized as solid-based and liquid-based [21]; solid based methods which include neat grinding (co-grinding), hot melt extrusion, twin screw extrusion and liquid based method which include solvent drop grinding, anti-solvent addition, solvent evaporation /solution crystallization, slurry conversion, solvent mediated phase evaporation, supercritical fluid technology, sonocrystallization. While solid-based methods often rely on the stoichiometric ratio of the reactants for cocrystal formation, the liquid-based methods can be either stoichiometric (slow evaporative crystallization, spray drying) [22] or non-stoichiometric (slurry and reaction crystallization [22-23-24]. Furthermore, the prediction of structure and formation of cocrystals using Cambridge structural database and computational methods has also been presented [25-26-27]. In the present study, the concept of miscibility was put to use, which in the solid state, could predict the likelihood of cocrystal formation.

The Hansen solubility parameter (HSP) model is based on the concept of dividing the total cohesive energy into individual components (dispersion, polar and hydrogen bonding) [28]. It proposes that the total force of the various interactions can be divided into partial solubility parameters, i.e. dispersion (δ_d), polar (δ_p) and hydrogen bonding (δ_h). These partial solubility parameters represent the possibility of intermolecular interactions between similar or different molecules. HSPs have been widely used to predict liquid-liquid miscibility, miscibility of polymer blends, surface wettability, and the adsorption of pigments to surfaces [29]. In pharmaceutical sciences, HSPs have been used to predict the miscibility of a drug with excipients/carriers in solid dispersions [30].

Thus in the present study, screening of various CCFs was carried out by investigating total solubility parameter and the objective of enhancing the solubility and dissolution rate of AVA by formulating cocrystal was achieved using different solid and liquid based methods with various CCFs along with subsequent designing of AVA cocrystal in immediate release (IR) tablet formulation.

2. MATERIALS AND METHODS

2.1. Materials

AVA was obtained as a gratis sample from Zydus Research Centre, Ahmedabad. While various CCFs like oxalic acid & Succinic acid (Sisco Research Lab), Nicotinamide, Urea, Avicel PH-102, Lactose & Starch (S. D. fine chem. Ltd), Cinnamic acid, Benzoic acid, Benzamide & Aspartic acid (Samar Chemicals), Aerosil (Evonik Pvt. Ltd.) and all the other chemicals were of high purity being of pharmaceutical grade.

2.1.1. Instrumentation

Instruments used for preparation and characterization of Cocrystals and its immediate release tablet were Digital weighing balance (Elico Pvt. Ltd. India), Digital pH meter (Elico Pvt. Ltd. India), Ultrasonicator (PCI India), USP dissolution apparatus (Electro lab, India), Hot air oven (Bio techniques India), Magnetic stirrer (Remi Instruments Ltd. India), Tablet compression machine (Chamunda Pharma Machinery, Pvt. Ltd. India), Differential scanning calorimeter (Mettler DSC 1 star system, Mettler-Toledo, Switzerland), Scanning electron microscope (ZEISS EVO 18 Germany), Fourier-transform infra-red Spectrometer (IR affinity-1, Shimadzu, Japan), X- ray diffractometer (Bruker Axs, D8 star system, Metter-Toledo, Switzerland), Double beam UV-Visible spectrophotometer (Jasco (V-630), Japan.), Friabilator (Roche friabilator, veegoscientific, India), Hardness tester (Veego Scientific, India), Disintegration apparatus (Campbell Electronics, India).

2.2 Methods

2.2.1 Preformulation studies

The identification of AVA was carried out by melting point determination, FTIR spectrometry and differential scanning calorimetry (DSC). Melting point determination was carried using Thiele tube method [31]. DSC was carried out to study the thermal behaviour of the drug [19]. The analytical method development was carried out using ultraviolet spectroscopic analysis. Calibration of AVA was performed in solvents namely methanol, pH 1.2 hydrochloric acid buffer and pH 6.8 phosphate buffer. A standard stock solution of 1000 ppm was prepared and subsequent dilutions of the solution were prepared from it to determine the λ_{max} . After that calibration curves were plotted using a range of solution concentrations. Various validation parameters like linearity, intraday precision study, interday precision study, robustness, ruggedness were determined in accordance with the ICH guidelines [32].

2.2.2 Selection of CCFs by Hansen solubility parameter [HSPs]

The cohesive energy which holds the material intact, is sum of all the forces like van der Waals interactions, covalent bonds, hydrogen bonds and ionic bonds. It can also be defined as the energy needed to break all the interactions, allowing atoms or molecules to detach and resulting in solid to liquid/gas or liquid to gas transformations. The cohesive energy per unit volume is termed the cohesive energy density (CED). The CED can be used to calculate the solubility parameter (δ) based on regular solution theory restricted to non-polar systems, as follows [16].

$$\delta = (\text{CED})^{0.5} = \left(\frac{\Delta E_v}{V_m} \right)^{0.5} \quad [\text{Eq. 1}]$$

Where (ΔE_v) is the energy of vaporization, and (V_m) is the molar volume. (δ) is measured in units of $(\text{J}/\text{cm}^3)^{0.5}$, $\text{MP}_a^{0.5}$ or $(\text{cal}/\text{cm}^3)^{0.5}$ where one $(\text{cal}/\text{cm}^3)^{0.5}$ is equivalent to $2.0421 \text{ MP}_a^{0.5}$ or $(\text{J}/\text{cm}^3)^{0.5}$.

The total solubility parameter (δ_t), also called the three-dimensional solubility parameter i.e. dispersion (δ_d), polar (δ_p) and hydrogen bonding (δ_h), can be defined as follows:

$$\delta_t = (\delta_d^2 + \delta_p^2 + \delta_h^2)^{0.5} \quad [\text{Eq. 2}]$$

While the partial solubility parameters, (δ_d), (δ_p) and (δ_h) can be calculated using the combined group contribution methods of Van Krevelen-Hoftyzer and Fedors as follows:

$$\delta_d = \frac{\sum_i F_{di}}{\sum_i V_i} \quad [\text{Eq. 3}]$$

$$\delta_p = \frac{(\sum_i F_{pi}^2)^{0.5}}{\sum_i V_i} \quad [\text{Eq. 4}]$$

$$\delta_h = \frac{(\sum_i E_{hi})^{0.5}}{\sum_i V_i} \quad [\text{Eq. 5}]$$

Where (i) is the structural group within the molecule, (F_{di}) is the group contribution to the dispersion forces, (F_{pi}) is the group contribution to the polar forces, (F_{hi}) is the group contribution to the hydrogen bonding energy, and (V_i) is the group contribution to the molar volume.

The difference in total solubility parameter between the drug and the cocrystal former ($\Delta\delta_t$) is used as a tool to predict miscibility, as demonstrated in Eq. (6) [21].

$$\Delta\delta_t = |\delta_{t2} - \delta_{t1}| \quad [\text{Eq. 6}]$$

Where (**t1**) and (**t2**) are cocrystal former and drug respectively. In their work, which included many API/carrier systems, general trend indicating that materials with $\Delta\delta_t < 7 \text{ MP}_a^{0.5}$ are miscible, while systems with $\Delta\delta_t > 7 \text{ MP}_a^{0.5}$ are immiscible. In present study, various CCFS like oxalic acid, succinic acid, nicotinamide, cinnamic acid, benzoic acid, urea, benzamide, aspartic acid were studied and their selection was carried out by HSPs method to investigate their miscibility with AVA.

2.2.3 Preparation of AVA co-crystals

AVA was co-crystallized with different CCFs in stoichiometric ratio of 1:1 i.e. AVA (1 mmol) and CCFs (1 mmol). Four different methods were used; neat grinding, solvent drop grinding, solvent evaporation and sonocrystallization. Briefly for the preparation of co-crystal by neat grinding, the mixture was milled for 40 min in a mortar; for the preparation of co-crystal by solvent-drop grinding, the mixture was milled for 30 min in a mortar with addition of 100 μl methanol. While for the preparation of co-crystal by solvent evaporation, the mixture was added to 10 ml of methanol in a vial and gently heated at 60 °C. The solution was allowed to evaporate slowly; and for the preparation of co-crystal by sonocrystallization, the mixture was added to 10 ml of methanol in a vial and placed in sonication bath for 2 hours. The solution was allowed to evaporate slowly. The products obtained via all these methods were stored at ambient conditions till further evaluation [33].

2.2.4 Characterization of AVA co-crystals

Solubility determination

The solubility of AVA co-crystals prepared by different methods were determined by shake-flask method in pH 6.8 phosphate buffer. For each preparation, a sample of 10 mg equivalent of drug was added to 10 ml of buffer in glass vials with caps. The vials were kept on a glass shaker incubator maintained at 37 ± 0.5 °C for 24 h. The sample was then filtered through whatman filter paper and the filtrate was analysed using a UV spectrophotometer at a predetermined analytical wavelength [34].

Melting point determination

Melting point was determined for plain AVA and CCFs along with AVA cocrystals using different CCFs by Thiele tube method. About 25 mg of the dry sample was placed on a glass slide and formed into a small mound. The open end of capillary tube was pushed into the powder and it was shaken down the tube by tapping the closed end. The filled capillary was attached to the lower end of the thermometer and inserted into main tube of Thiele apparatus. It was heated rapidly with a small flame and then slowly and regularly at the rate of 2 °C per minute. The temperature at which the solid commences to liquefy and at which the solid disappeared was the observed melting point range [31].

Fourier Transform Infrared (FT-IR) Spectroscopy

FT-IR spectrums of AVA cocrystal and CCF were obtained on a FT-IR spectrometer (FTIR- 8001, Shimadzu, Japan) by the KBR pellet method. The drug sample was gently triturated with KBr powder in a weight ratio of 1: 100. The disc was then placed in the sample holder and scanned from 4000 to 500 cm^{-1} . The spectrum of the cocrystal was then compared to that of plain AVA [35].

Differential Scanning Calorimetry (DSC)

DSC thermograms for AVA cocrystals and CCF were obtained using DSC Mettler 10.00 Star system, Mettler-Toledo, Switzerland (Metallurgical Engineering Department, VNIT Nagpur). An accurately weighed sample was run at the scanning rate of 20 °C/min over a temperature range of 100 to 300 °C respectively in aluminium pans under nitrogen atmosphere [36].

X-ray diffraction study

The crystalline behaviour of AVA, CCFs and cocrystals were evaluated with X-ray diffractometry. Diffraction patterns were obtained on Brisker AXS D8 Advance (Sophisticated Analytical Instruments Facility, STIC, Cochin, India.) The X-ray generator was operated at 40 kV tube voltages and 35mA tube current. The scanning angle ranged from 3 to 60° in the step scan mode with step time of 39.8 seconds [37].

Scanning electron microscopy

SEM imaging of AVA, CCFs and cocrystals were performed by a scanning electron microscope (ZEISS EVO 18 Germany – Physics department, RTMNU, Nagpur) using electron beam for surface imaging [19].

Drug content

10 mg equivalent of cocrystal sample was weighed and added to 10 mL methanol in a volumetric flask. The flask was then subjected to sonication for 30 minutes. The solution was then filtered through whatman filter paper, proper dilutions were made and analysed spectrophotometrically at the predetermined analytical wavelength using UV-Visible double beam spectrophotometer [11].

Partition coefficient determination

Cocrystal equivalent to 10 mg of AVA was weighed and taken in a beaker. To this 10 ml of distilled water added and it was stirred well for 20 minutes on a magnetic stirrer. In 60 ml separating funnel, 10 ml of n-octanol was added and the dispersion of cocrystal in water was added to the funnel. The funnel was uniformly agitated for 2 hours and then keep aside for 30 minutes. When two distinct layers were formed, they were separated and the solution was diluted and assay using UV-Spectroscopy by recording absorbance in triplicate. Concentration in both the phases was calculated using calibration equation and the partition coefficient was calculated for the cocrystal [38].

$$\text{Partition coefficient} = C_o / C_w \quad [\text{Eq. 7}]$$

Where C_o - concentration in oil phase, C_w concentration in water phase.

2.2.5 AVA Cocrystal - excipient compatibility study

Cocrystal - excipient compatibility study was carried out by FTIR spectroscopy and DSC, to confirm the stability of AVA cocrystal with other excipients. FTIR spectra and DSC thermograms of AVA cocrystal with IR tablet excipients - aerosil, MCC PH102, lactose and starch were recorded. The spectrums of cocrystal and cocrystal with excipients were matched for appearance or disappearance of any peak while the thermograms were matched for appearance or disappearance of any peak and enthalpy height [38].

2.2.6 Formulation and optimization of AVA cocrystal IR tablet using factorial design

Factorial design was applied to understand the interaction between the formulation variables and their impact on final formulation. IR tablets of AVA cocrystal were prepared by direct compression technique [39]. For this AVA cocrystal and all other excipients according to the formula (Table 1) were weighed accurately and passed through sieve # 22 and mixed for 15 minutes. This blend was evaluated for precompression flow properties like bulk density, tapped density, compressibility index, Hausner ratio and angle of repose [4]. The mixture was then compressed using 10 station rotary tablet compression machine (Chamunda Pharma Machinery Pvt. Ltd.) with 6.0 mm flat round punches with tablet weight 100 mg [40].

A 3^2 full factorial design for two factors and three levels was selected to study the response of independent variables i.e. aerosil (X_1) and amount of MCC 102 (X_2) on the dependent variables - percentage of drug released (Y_1) and percent friability (Y_2) (Table 2). A total of 9 batches were formulated and measured for percentage of drug released and friability. Statistical analysis was carried out and was further validated by Design Expert (Version 8.0.7.1, Stat-Ease Inc., and Minneapolis, MN) to obtain optimized process parameters using ANOVA and polynomial equations [41].

2.2.7 Evaluation of AVA cocrystal IR tablet

AVA cocrystal IR tablets were evaluated for various parameters like hardness, friability, disintegration time, drug content and compared with that of marketed tablet. Hardness of tablets ($n=3$) was estimated by Monsanto hardness tester. Friability was estimated using Roche friabilator (Veego scientific, India). Tablets ($n=6$) from every batch were selected randomly, weighed and placed in the plastic chamber provided in apparatus. Friabilator was operated for 100 revolutions and tablets were collected, de-dusted and reweighed. Percent friability was determined by the difference obtained in two weights. The *in vitro* disintegration test was done in accordance with USP. While the drug content was determined in the same way as described under characterization of AVA cocrystals.

Table 1. Composition of IR-tablet containing AVA cocrystal.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (Cocrystal)	12.65	12.65	12.65	12.65	12.65	12.65	12.65	12.65	12.65
Aerosil	1.10	1.10	1.10	0.80	0.80	1.40	1.40	1.40	0.80
MCC 102	20	16	24	20	16	24	20	16	24
Lactose	29.25	33.25	25.25	29.55	33.55	24.95	28.95	32.95	25.55
Starch	37	37	37	37	37	37	37	37	37
Total weight	100	100	100	100	100	100	100	100	100

Table 2. Experimental design: factors and responses.

Formulation	Types of variable	Variable	Optimization levels used		
			Low (-1)	Medium (0)	High (+1)
Cocrytal IR tablet	Independent	X ₁ (Concentration of aerosil)	0.80	1.10	1.40
		X ₂ (Concentration of MCC 102)	16	20	24
	Dependent	Y ₁ (% Drug Release)		Maximize	
		Y ₂ (% Friability)		Minimize	

In vitro drug release

In vitro drug dissolution study was performed for AVA cocrystal, pure AVA, IR tablet and marketed tablet using USP dissolution apparatus II. Test conditions for dissolution testing were 900 mL of dissolution medium i.e. 6.8 phosphate buffer, with a rotating speed of 75 rpm and temperature 37±0.5 °C. During the study, 5 ml of the aliquots were removed at predetermined time intervals (5, 10, 15, 30, 45, 60, 90, 105 and 120 min) from the dissolution medium which was then replaced with fresh medium. The amount of AVA released in the dissolution medium was determined spectrophotometrically at the predetermined analytical wavelength using UV-Visible double beam spectrophotometer [15].

Ex vivo release profile

Ex vivo drug diffusion study was performed for AVA cocrystal, pure AVA, IR tablet and marketed tablet. For the study, stomach of previously sacrificed male Sprague-Dawley rat was isolated and thoroughly washed with pH 6.8 phosphate saline buffer and mucous and lumen contents were removed. AVA loaded formulations (cocrystal, pure AVA, IR tablet and marketed tablet) were diluted/dispersed and filled in the stomach (equivalent to 10 mg). Both the ends of the tissues were tied properly to avoid any leakage and were placed into beaker containing 50 ml of phosphate saline buffer pH 7.4 as the diffusion medium with the continuous aeration supply under gentle stirring at 37±2 °C. Samples were drawn from the medium at specific time intervals and were evaluated by spectrophotometric analysis [42].

2.2.8 Stability Study

Stability study was performed for optimized IR tablet and AVA cocrystal. The formulations were packed in aluminium foil and placed in stability chambers at 40°C / 75% RH. They were removed at each time point (0, 30, 60, 90 days) and evaluated for appearance, drug content and % drug release in 5 min for cocrystal and appearance, friability test, hardness, disintegration time, drug content and % drug release in 5 min for IR tablet [41].

3. RESULTS AND DISCUSSION

3.1. Preformulation studies

The melting point range by Thiele tube method was found to be 156.2-160.7 °C. The calibration curve of AVA in methanol, pH 1.2 hydrochloric acid buffer and pH 6.8 phosphate buffer along with its regression equation and correlation coefficient is shown in Figure 1. The validation parameters evaluated were as per the ICH guidelines and the linearity range was found to be 5-40 µg/mL. The λ_{max} of AVA was found to be 246 nm [32]. The FT-IR spectrum of AVA showed similar peaks as that of standard spectrum values as shown in Figure 3. The DSC results showed an endothermic peak at 164.6 °C as shown in Figure 4, which complied with the reported range [43].

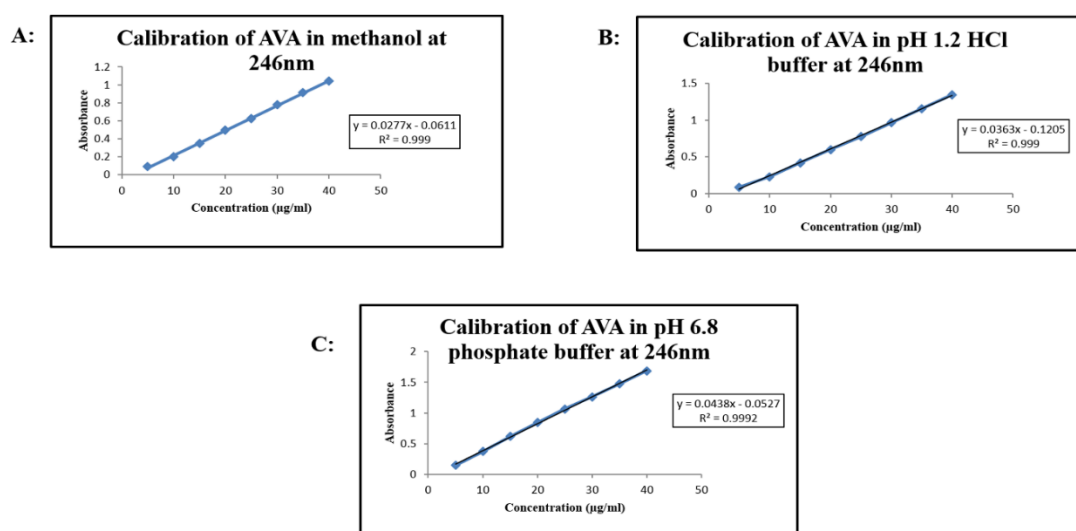


Figure 1. Calibration curve of AVA in (A) Methanol, (B) pH 1.2 HCl buffer, (c) Phosphate buffer pH 6.8.

3.2 Selection of CCFs by Hansen solubility parameter [HSPs]

In present study, selection of CCFs was carried out by HSPs method to investigate the miscibility of AVA and CCFs by using total solubility parameter. In table 3, molar volume and HSPs of AVA was calculated. From these values, miscibility criteria was studied by calculating the total solubility parameter for AVA in accordance with different CCFs (Table 4). From table 4, it was found that the $\Delta\delta_t$ value ($MP_a^{0.5}$) for oxalic acid, succinic acid, nicotinamide, cinnamic acid, benzoic acid, urea, benzamide, aspartic acid was $< 7 MP_a^{0.5}$ [21], hence all CCFs showed miscibility with drug. Thus these CCFs were selected for preparation of cocrystal.

3.3. Preparation of AVA cocrystals

AVA was cocrystallized with different CCFs which showed miscibility as per HSPs method. Four different methods - neat grinding, solvent drop grinding, solvent evaporation and sonocrystallization were used for preparing cocrystals in stoichiometric ratio of 1:1.

3.4. Characterization of AVA cocrystals

3.4.1. Solubility determination

The solubility AVA co-crystals obtained from neat Grinding, solvent drop grinding, solvent evaporation and sonocrystallization method using different CCFs are given in Table 5. It was found that from all CCFs, Cinnamic acid gave the highest enhancement in solubility as compared to the other CCFs from solvent drop grinding method - 575.503 µg/ml i.e. 1.9 fold increase in solubility (Figure 2). This can be attributed to the fact that formation of cocrystal, changes the crystal packing, resulting in reduced crystal energy/or increased solvent affinity [18]. Also in solvent drop grinding method small amount of solvent is used, which acts as a catalyst in co-crystal formation. Moreover, it is one of the most cost-effective method in comparison to other methods, as it uses very less solvent and thus is more environment friendly than the solution based methods [44].

Table 3. Calculation of HSPs and molar volume for AVA.

Group	Frequency	F _{di} (J ^{1/2} cm ^{3/2} mol ⁻¹)	F _{pi} (J ^{1/2} cm ^{3/2} mol ⁻¹)	F _{hi} (J/mol)	V _m ^a (cm ³ /mol)
-CH3	2	840	0	0	67
-CH2-	4	1080	0	0	64.4
=CH-	3	240	0	0	(-3)
>C=	4	280	0	0	(-20)
-OH	2	420	250000	20000	20
-NH-	1	160	44100	3100	4.5
-CO-	1	290	592900	2000	10.8
Phenylene	2	2860	12100	-	32
Phenylene (o, m, p)	1	1270	12100	-	71.6
F	1	220	-	-	22
-COO-	1	390	240100	7000	18
-N<	1	20	640000	5000	(-9)
Ring closure 5 or more atoms	1	190			16
Conjugation in ring for each double bond	2				(-4.4)
Σ		8260	2053400	57100	287.9
$\delta_d = \frac{\sum_i F d_i}{\sum_i V_i}$		823.11 MP _a ^{0.5}			
$\delta_p = \frac{(\sum_i F p_i^2)^{0.5}}{\sum_i V_i}$		24.71 MP _a ^{0.5}			
$\delta_h = \left(\frac{\sum_i E h_i}{\sum_i V_i}\right)^{0.5}$		198.23 MP _a ^{0.5}			
$\delta_t = (\delta_d^2 + \delta_p^2 + \delta_h^2)^{0.5}$		32 MP _a ^{0.5}			

Table 4. Study of miscibility criteria according to total solubility parameter.

Sr.No.	Coformers	δ _t Value (MP _a ^{0.5})	Δδ _t Value (MP _a ^{0.5})
	Atorvastatin	32	
1	Oxalic acid	30.03	1.97
2	Succinic acid	27.00	5
3	Nicotinamide	27.24	4.76
4	Cinnamic acid	25.11	6.89
5	Urea	29.42	2.58
6	Benzoic acid	29.82	2.18
7	Benzamide	27.39	4.61
8	Aspartic acid	29.00	3

Table 5. Cocrystals solubility by different methods.

Sr.No	Coformers (CCFs)	Solubility $\mu\text{g/ml}$ by different methods			
		Neat Grinding	Solvent drop grinding	Solvent Evaporation	Sonocrystallization
1	Oxalic acid	38	11.78	22.69	11.78
2	Succinic acid	329	526.117	161.27	526.117
3	Nicotinamide	484.42	560.531	512.19	560.531
4	Cinnamic acid	495.10	575.503	561.66	565.503
5	Urea	390	426.45	427.7	426.54
6	Benzoic acid	329.52	380.68	395.24	380.68
7	Benzamide	285	363.98	357.58	363.98
8	Aspartic acid	197.15	271.23	427.7	271.23

Furthermore, solvent drop grinding method was selected for formulating AVA cocrystals with cinnamic acid using different molar ratio 1:1, 1:2, 1:3 and 1:4. It was found that solubility of AVA cocrystal with the molar ratio of 1:1 of cinnamic acid gave the highest solubility $575.44 \mu\text{g/ml}$ than 1:2 ($545.32 \pm 0.94 \mu\text{g/ml}$), 1:3 ($567.89 \pm 1.24 \mu\text{g/ml}$) and 1:4 ($456.23 \pm 7.46 \mu\text{g/ml}$). Thus 1:1 molar ratio of drug and cinnamic acid was selected for preparation of optimized AVA cocrystal.

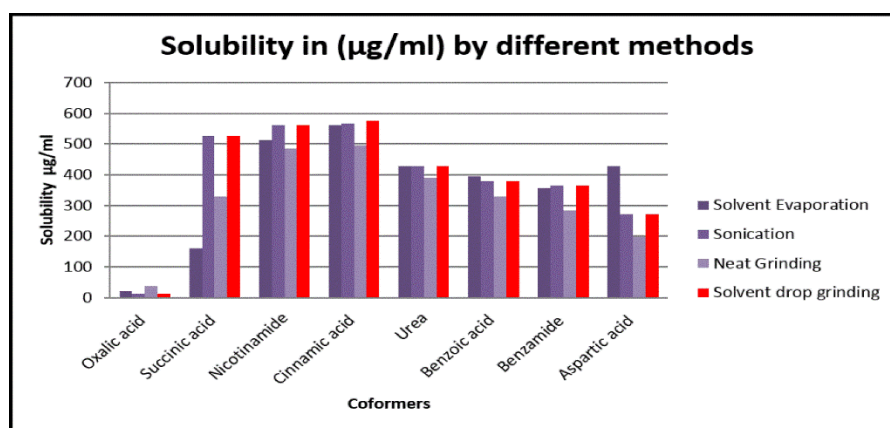


Figure 2. Solubility determination by different methods with various CCFs.

3.4.2. Melting point determination

Melting point was determined for plain AVA and CCFs along with AVA cocrystals using different CCFs by Thiele tube method. It was found that melting point of AVA reduced with all the CCFs as given in Table 6. This drop in melting point can be due to changes in intermolecular interaction between AVA and CCFs.

3.4.3. Fourier Transform Infrared (FT-IR) Spectroscopy

The FT-IR spectrum of AVA exhibited a sharp peak of OH group at 3668.61 cm^{-1} . It showed C-H (alkyl), C=O (carbonyl), N-H (amide), and C-N (amine) group at 2972.31 cm^{-1} , 1651.07 cm^{-1} , 3363.86 cm^{-1} and 1317.07 cm^{-1} respectively. The principal IR absorption peaks of AVA were observed in AVA cinnamic acid cocrystal spectrums. The spectrums of AVA cinnamic acid cocrystal showed disappearance of O-H (hydroxyl) functional group, indicating the formation of hydrogen bond synthons between the AVA and cinnamic acid [45]. Also certain non-significant changes in the absorption peak of C-H (alkyl), C=O (carbonyl), N-H (amide), and C-N (amine) group of AVA from 2972.31 cm^{-1} to 2879.72 cm^{-1} , 1651.07 cm^{-1} to 1670.12 cm^{-1} , 3363.86 cm^{-1} to 3189.02 cm^{-1} and 1317.07 cm^{-1} to 1313.52 cm^{-1} respectively. This depicted successful formulation of cocrystal as shown in Figure 3.

Table 6. Melting point of CCFs and cocrystal.

Sr.No.	Drug/ CCFs	M.P. (°C) CCFs	M.P. (°C) of cocrystals
1	Atorvastatin calcium	159-160	
2	Oxalic acid	102-103	70-75
3	Succinic acid	184-185	95-100
4	Nicotinamide	128-130	110-115
5	Cinnamic acid	133-135	100-110
6	Urea	133-134	120-121
7	Benzoic acid	122-123	80 - 90
8	Benzamide	127- 130	100-101
9	Aspartic acid	270-272	144-145

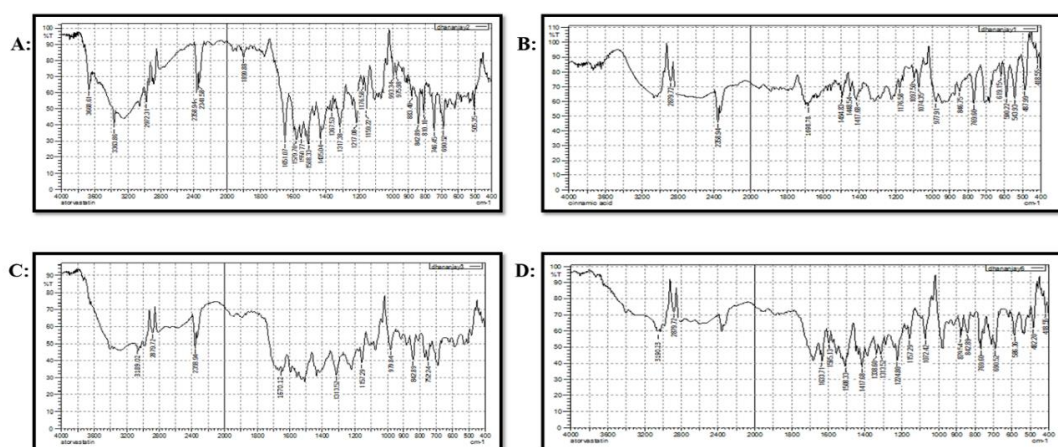


Figure 3. FTIR spectrums of (A) Atorvastatin Calcium (B) Cinnamic acid (C) AVA cocrystal (D) IR cocrystal tablet blend

3.4.4. Differential Scanning Calorimetry (DSC)

AVA displayed a diffused endothermic peak at 164.6°C and thermogram of cinnamic acid exhibited a sharp endothermic peak at 138.3°C. While thermogram of AVA cinnamic acid cocrystal showed an endothermic peak at 71.9°C confirming cocrystal formation by showing characteristic change in the melting behaviour. This drastic reduction in melting point suggests that the cohesive energy of AVA cinnamic acid cocrystal has decreased from that of the plain AVA indicating the increases in solubility of cocrystal as compared to plain drug AVA [46] thus confirming the formation of cocrystal as shown in Figure 4.

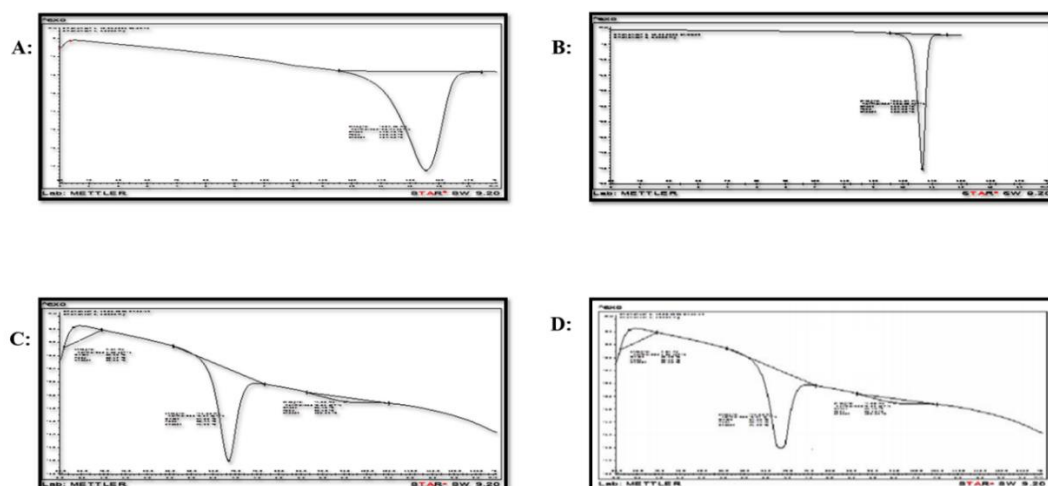


Figure 4. DSC thermograms of (A) Atorvastatin Calcium (B) Cinnamic acid (C) AVA cocrystal (D) IR cocrystal tablet blend

3.4.5. X-ray diffraction study

AVA exhibited many intense sharp diffraction peaks of crystallinity at a diffraction angle of 3.312° , 17.194° , 19.628° , 21.784° , and 22.854° indicating that AVA was present as a crystalline material [43]. The CCF-cinnamic acid showed sharp intense peaks exhibiting its crystalline nature at 2θ value of 9.960° , 18.572° , 21.763° , 22.957° , and 25.464° . While AVA cinnamic acid cocrystal depicted peaks at 9.858° , 15.201° , 22.907° , 25.407° , 29.496° showing a different crystalline nature as compared to AVA as shown in Figure 5.

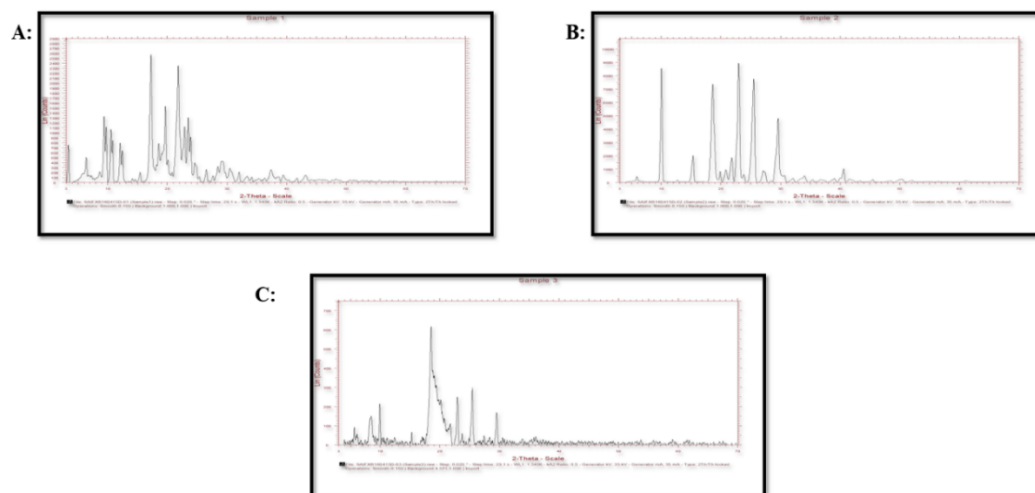


Figure 5. XRD graph of (A) Atorvastatin Calcium (B) Cinnamic acid (C) AVA cocrystal.

3.4.6. Scanning electron microscopy

SEM analysis of plain AVA, cinnamic acid and AVA cinnamic acid co-crystal was performed (Figure 6). Plain AVA exhibited irregular shaped crystals with smooth surface and cinnamic acid exhibited regular shape crystals with smooth surface [43]. While AVA cinnamic acid co-crystals exhibited irregular shape crystals which were different from plain AVA and cinnamic acid which indicates different crystalline nature as compare to the drug and CCFs.

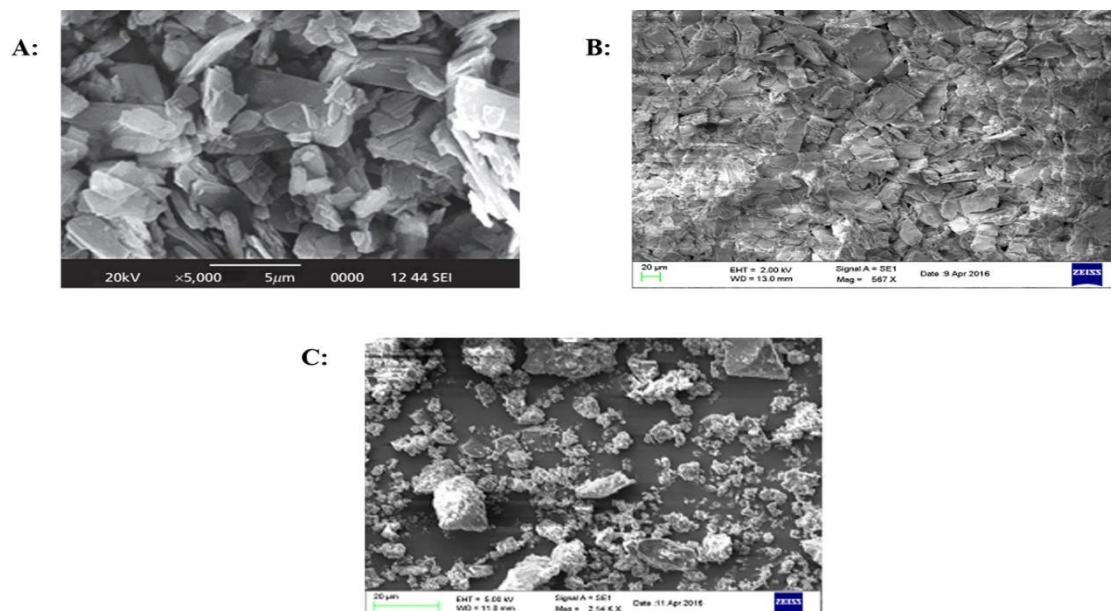


Figure 6. SEM images of (A) Atorvastatin Calcium (B) Cinnamic acid (C) AVA cocrystal.

3.4.7. Drug content and Partition coefficient determination

The percent drug content of AVA in AVA cinnamic acid co-crystal was calculated which was found to be 97.98±0.38 %. While the logP value of AVA cinnamic acid co-crystal was found to be 5.11.

3.5. AVA Cocrystal - excipient compatibility study

3.5.1. FTIR study

FTIR spectrum of AVA cinnamic acid cocrystal along with IR tablet excipients was obtained which showed all the characteristic functional groups as that of the AVA cinnamic acid cocrystal with nonsignificant changes in the absorption peaks of C=O (carbon) and C-N (amine) from 1651.07 cm⁻¹ to 1633.71 cm⁻¹ and 1313.52 cm⁻¹ to 1338.60 cm⁻¹ respectively. These spectral observations thus indicated compatibility between AVA cinnamic acid cocrystal along with IR tablet excipients (Figure 3).

3.5.2. DSC study

DSC thermogram of AVA cinnamic acid cocrystal along with IR tablet excipients was obtained which showed no major shifting of the endothermic peak of cocrystal thus it can be concluded that AVA cinnamic acid cocrystal is compatible with IR tablet excipients (Figure 4).

3.6. Formulation and optimization of AVA cocrystal IR tablet using factorial design

Factorial design was constructed for optimizing the concentration of aerosil (X₁) and MCC 102 (X₂) in AVA cocrystal IR tablet. Initially, flow properties of the powder blend containing AVA cocrystal and other excipients were evaluated. The blend showed good flow properties with angle of repose 29.72°±2.4, Car's compressibility index of 14.67±0.9 % and Hausner's ratio of about 1.17±0.12 [41].

The optimized batch was found by evaluating total of nine batches for percentage of drug released (Y₁) and friability (Y₂). Percent drug release and percent friability values ranged from 89.15±0.274 % to 98.54±1.163% and 0.515±0.090 % to 0.783±0.009 % respectively (Table 7) Wide variation was observed in percent drug release and percent friability on changing the composition of formulation. Batch F6 shows maximum drug release (98.54±1.163%) and minimum friability (0.515±0.090 %) and thus was selected for further processing. All the nine batches formulated were analysed statistically by Design expert software (Version 8.0.7.1, Stat-Ease Inc., and Minneapolis, MN).

Table 7. Optimization of IR cocrystal tablet using 3² Factorial Design.

Batch No	X1 Aerosil (%)	X2 MCC 102 (%)	Y1 %Drug Release	Y2 Friability (%)
F1	1.10	20	92.94±1.051	0.612±0.097
F2	1.10	16	94.82±1.331	0.610±0.083
F3	1.10	24	97.92±0.424	0.611±0.025
F4	0.80	20	96.30±0.430	0.767±0.542
F5	0.80	16	92.35±0.554	0.783±0.009
F6	1.40	24	98.54±1.163	0.515±0.090
F7	1.40	20	92.89±0.335	0.564±0.108
F8	1.40	16	89.15±0.274	0.578±0.083
F9	0.80	24	93.22±0.263	0.764±0.059

The desirability for the optimized batch (F6) was maximum 1. The regression equation of the fitted quadratic model for the two responses obtained as follows [Eq 8-9]:

$$Y_1 = 93.84 - 0.22X_1 + 2.23X_2 + 2.13X_1X_2 \quad [\text{Eq. 8}]$$

$$Y_2 = 0.64 - 0.11X_1 - 0.013X_2 \quad [\text{Eq. 9}]$$

Significant statistical coefficients ($p=0.0219$ for Y_1 and $p=0.0001$ for Y_2) were obtained while the positive coefficient of X_1 & X_2 exhibits that the response is favoured while the negative value shows an inverse relationship between the factor and response. The equations exhibit that concentration of aerosol and MCC have a negative relationship with percent friability and a positive relationship with percent drug release. The software generated a predicted value from the polynomial equation by removing the non-significant terms using ANOVA. The predicted value and experimental value were equated by calculating percentage error (0.52%) which was found to be quite low, proving the validity of generated model (Table 8). A t-test at 95% confidence interval at 2 degrees of freedom was also applied to compare the predicted value and experimental value of responses. No significant difference was recorded between these two values, hence confirming the generated model validity. The 3D figures showed a linear descending pattern for % friability with increasing concentration of aerosol and MCC 102 while an ascending pattern was obtained for % drug release (Figure 7).

Table 8. Experimental and predicted values of the optimized batch.

Formulation	Responses	Predicted	Experimental
IR cocrystal tablet	Drug release (%)	93.84±1.74	98.54±1.163
	Friability (%)	0.64±0.033	0.515±0.090

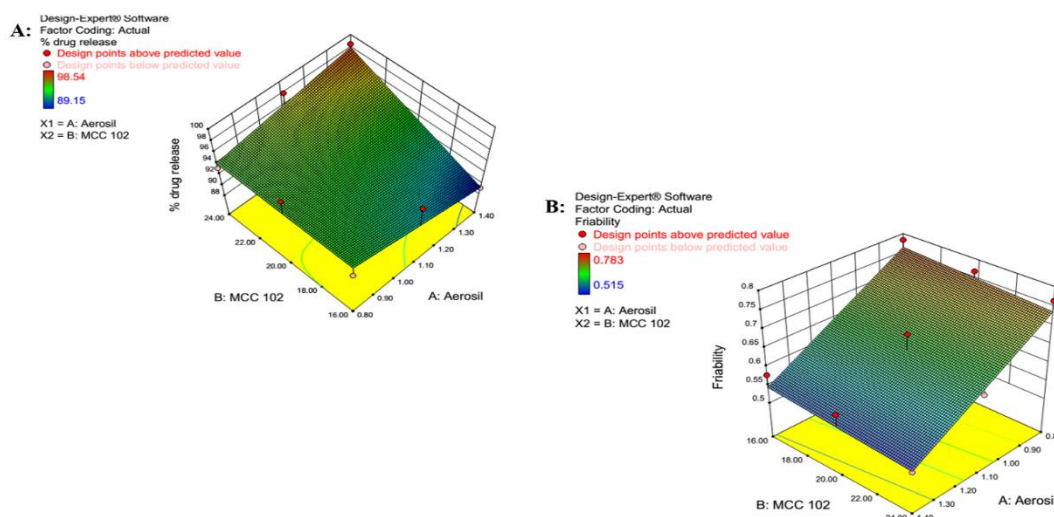


Figure 7. Response surface plot for (A) % Drug release (B) % Friability.

3.7 Evaluation of AVA cocrystal IR tablet

The optimized IR tablet of AVA cocrystal was compared with marketed tablet for various parameters like hardness, friability, disintegration time, drug content. The optimized IR tablet showed % friability of 0.515 ± 0.090 % as compared to 0.442 ± 0.123 % of marketed tablet formulation. The friability was found to be less than 1% indicating the capacity of tablets to handle mechanical stress. While hardness of about 2.9 ± 0.98 kg/cm² was obtained with optimized IR tablet as compared to 3.2 ± 0.023 kg/cm² of marketed tablet, which indicates that the tablets can handle the mechanical stress. Disintegration time of 91 ± 0.56 sec was obtained in comparison to 115 ± 0.034 sec of marketed tablet exhibiting that the tablet can disintegrate and release AVA cocrystal. And a drug content of 98.82 ± 0.33 % was obtained with optimized IR tablet as comparison to 99.18 ± 1.34 % of marketed tablet.

3.7.1. In vitro drug release

In order to determine the quick release of drug in the medium, *in vitro* dissolution studies were carried out for AVA cocrystal, pure AVA, IR tablet and marketed tablet in 900 mL of 6.8 phosphate buffer in a USP dissolution apparatus Type II, with a paddle speed of 75 rpm at temperature of about $37 \pm 0.5^\circ\text{C}$. For AVA cocrystal and AVA cocrystal IR tablet formulations, it was observed that 80.77 ± 0.18 % and 89.03 ± 0.07 % of drug was released within first five minutes of the dissolution study respectively. This clearly indicates that the

conversion of cocrystal into IR tablet increased the drug release. Whereas, the pure AVA and marketed tablet gave $38.04 \pm 0.33\%$ and $56.24 \pm 0.14\%$ of AVA release in the first five minutes, respectively (Table 9). This clearly indicates that the developed cocrystal gave superior dissolution as compared to pure AVA and marketed tablet formulation (Figure 8). From the mathematical treatment of the *in vitro* release data of AVA from cocrystal, IR tablet and marketed tablet, the values of R^2 (regression coefficient) has been obtained and presented in Table 10. From the regression coefficient value it was observed that drug release follows zero order kinetics for AVA cocrystal and IR tablet while pure AVA and marketed tablet followed Higuchi model. The data was further treated as per Korsmeyer's equation and slope (n) values obtained by these equations indicated that the drug released mechanism were quasi fickian diffusion with all the systems.

Table 9. *In vitro* drug release profile.

Sr.No	Time (min)	% Cumulative drug release			
		AVA	AVA Cocrystal	IR Tablet of AVA cocrystal	Marketed tablet
1	5	38.04±5.33	80.77±9.18	89.03±0.07	56.24±2.14
2	15	39.09±5.52	81.70±7.94	89.81±0.24	56.98±2.63
3	30	48.52±8.02	83.78±8.26	90.48±0.45	62.02±0.75
4	45	52.94±6.86	88.45±4.80	92.14±0.71	63.71±0.30
5	60	56.44±5.28	89.92±2.02	94.33±0.51	63.48±3.70
6	75	58.46±0.92	91.73±1.54	95.58±0.31	65.94±2.73
7	90	59.74±1.43	96.82±2.29	96.53±0.26	68.54±3.04
8	105	63.81±0.98	98.10±1.74	97.57±0.10	69.25±4.23
9	120	65.78±0.24	99.28±2.67	98.54±1.16	70.89±5.22

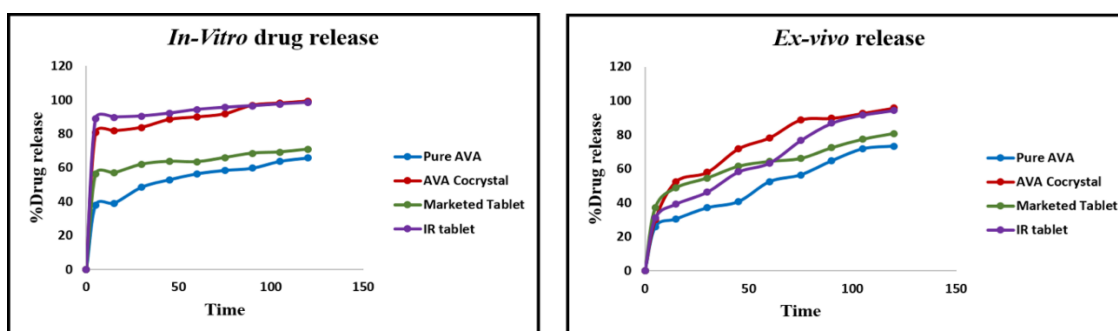


Figure 8. *In vitro* drug release profile and *Ex vivo* diffusion studies of AVA cocrystal IR cocrystal tablet, Pure AVA and Marketed tablet formulation.

3.7.2. *Ex vivo* release profile

To determine the diffusion through the biological membrane, *ex vivo* studies were carried out. After 2 h of diffusion, $95.71 \pm 0.98\%$ of the drug was diffused from AVA cinnamic acid cocrystal and $94.40 \pm 0.99\%$ of the drug was diffused from AVA cocrystal IR-Tablet, while from plain drug suspension and marketed tablet formulation showed $73.24 \pm 0.10\%$ and $80.77 \pm 0.78\%$, respectively (Table 11). This indicates that the amount of the drug diffused through the biological membrane was more when it was given in the form of cocrystal formulations (Figure 8). The augmentation in diffusion rate can be attributed to the reduced energy of the crystal lattice/ or change in the solvent affinity. Conversion of AVA into AVA cocrystal changes the crystal morphology which forms a new surface thus increases its dissolution and diffusion rate [18].

Table 10. Drug release kinetics.

Formulation code	Zero order	First order	Higuchi model	Korsmeyer- Peppas model	
	R ²	R ²	R ²	R ²	N
AVA	0.939	0.969	0.978	0.943	0.186
AVA cocrystal	0.981	0.888	0.952	0.974	0.222
IR tablet	0.986	0.957	0.959	0.845	0.033
Marketed tablet	0.954	0.968	0.969	0.912	0.075

Table 11. Ex vivo diffusion studies.

Sr.No	Time (min)	% Cumulative drug release			
		AVA	AVA Cocrystal	IR Tablet of AVA cocrystal	Marketed tablet
1	5	25.91±0.23	30.17±0.45	31.05±0.20	37.34±1.09
2	15	30.55±0.34	52.52±0.21	39.33±0.76	48.91±0.78
3	30	37.08±0.01	57.93±0.70	46.39±1.09	54.62±0.54
4	45	40.69±0.78	71.73±0.34	58.20±0.04	61.48±0.32
5	60	52.39±0.91	78.26±1.70	63.45±0.65	64.34±1.44
6	75	56.39±0.19	88.72±0.56	76.67±0.17	66.08±0.09
7	90	64.67±0.61	89.67±0.78	86.90±1.01	72.41±0.91
8	105	71.68±1.01	92.59±0.12	91.68±0.76	77.40±0.11
9	120	73.24±0.10	95.71±0.98	94.40±0.99	80.77±0.78

3.8. Stability Study

Stability study was conducted for the optimized AVA cocrystal along with its IR tablet (Table 12). The observations clearly depicted no significant difference in appearance, drug content and % cumulative drug release for AVA cocrystal and friability, disintegration time and % drug release of IR tablet for a period of three months which further ensured the stability of the formulations on storage [41].

Table 12. Stability studies of AVA cocrystal & IR cocrystal tablet.

Formulation	Time Period (days)	Storage condition (40°C/75% RH)		
		Appearance	Drug content (%)	% Cumulative drug release in 5 min
AVA Cocrystal	0	No change	97.98± 0.38	80.77±9.18
	30	No change	97.02±0.13	78.89±3.23
	60	No change	96.89± 1.03	78.12±4.56
	90	No change	96.59±0.47	77.83±1.99
	Time Period (days)	Friability (%)	Disintegration time (Sec)	% Cumulative drug release in 5 min
IR cocrystal tablet (Optimized batch)	0	0.515±0.090	91±0.56	89.03±0.07
	30	0.572±0.231	89±0.33	87.56±1.89
	60	0.594±0.045	84±1.02	86.21±0.99
	90	0.623±0.023	81±0.19	85.89±1.4

4. CONCLUSION

Cocrystals of AVA were successfully designed, formulated and optimized as AVA cocrystal IR tablet using experimental design. AVA cocrystal was formulated with four different methods - neat Grinding, solvent drop grinding, solvent evaporation and sonocrystallization with all the screened CCFs, out of which cinnamic acid gave the highest enhancement in the solubility 575.503 $\mu\text{g/ml}$ with solvent drop grinding method. Solvent drop grinding method was further explored with cinnamic acid in different ratios of 1:1, 1:2, 1:3, 1:4, out of which highest solubility was obtained with 1:1 ratio of AVA and cinnamic acid. Melting point determination and DSC thermograms showed reduced melting point of AVA cinnamic acid cocrystal in comparison with plain AVA, exhibiting the intermolecular interactions and thus confirming the formation of cocrystal. XRD and SEM analysis of AVA cinnamic acid cocrystal showed a different crystalline nature in comparison with AVA and CCFs. While the percent drug content was found to be $97.98 \pm 0.38\%$ and $\log P$ value obtained was 5.11. Optimized AVA cocrystal IR tablet contains aerosil and MCC102 in the ratio 1.40%:24% and showed drug release ($98.54 \pm 1.163\%$), friability ($0.515 \pm 0.090\%$), hardness ($2.9 \pm 0.98 \text{ kg/cm}^2$), disintegration time ($91 \pm 0.56 \text{ sec}$) and drug content ($98.82 \pm 0.33\%$). The *in vitro* dissolution studies for AVA cinnamic acid cocrystal and IR cocrystal tablet showed significantly higher drug release $80.77 \pm 0.18\%$ and $89.03 \pm 0.07\%$ in 5 minutes than pure AVA and marketed tablet. Similarly, *ex vivo* diffusion performance was obtained for AVA cinnamic acid cocrystal and IR cocrystal tablet displayed higher diffusion through biological membrane with drug diffusion of about $95.71 \pm 0.98\%$ and $94.40 \pm 0.99\%$ in 2 hours than pure AVA and marketed tablet. Stability studies depicted no physical or chemical changes over the period of three months. Thus AVA can be successfully designed and formulated as IR tablet with drastically improved solubility and dissolution characteristics.

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