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Evaluation and Formulation of Cocrystals of Efavirenz with Caffeine.

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ABSTRACT

The primary goal of this research is to investigate co-crystallization techniques for engineering pharmaceutical co-crystals of Efavirenz. Cocrystals are a promising strategy for improving the solubility and dissolution of pharmaceuticals that are poorly water soluble. Efavirenz cocrystal with caffeine was created and tested for hardness, thickness, diameter disintegration time, and drug release. Cocrystal optimization was carried out using Central Composite Design. The optimal cocrystal of efavirenz caffeine formula has a 1:1 ratio (F1). The optimized batch had a hardness of 5kg/cm2, a disintegration time of 0.75 minutes, and a drug release rate of 96%. The improved Cocrystal of Efavirenz was compared to the available market formulation, i.e. Efavirenz Immediate Release Tablet. In comparison to the market formulation. In vitro solubility profiles of the improved cocrystal and the commercial formulation were comparable. The drug release rate of the optimized cocrystal formulation was 99.8% in 15 minutes, while the marketed formulation was 101% in 15 minutes. As caffeine, which is employed as a coformer, may reduce the potential negative effects of efavirenz (dizziness, vertigo), when administered alone, this created cocrystal formulation may offer improved outcomes in the treatment of HIV.

Keywords: Cocrystal, Efavirenz, Caffeine, Solubility

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INTRODUCTION

Efavirenz is an antiviral drug that is used to treat and prevent the spread of HIV/AIDS. It belongs to a class of drugs known as non-nucleoside reverse transcriptase inhibitors (NNRTIs), and it works by lowering the level of HIV in the blood. Efavirenz is typically prescribed in combination with other antiretroviral medications [1]. Efavirenz is primarily converted to hydroxylated metabolites by the cytochrome P450 system, with these hydroxylated metabolites then glucuronidated. These metabolites are ineffective against HIV-1. However, it is poorly soluble in water, resulting in limited bioavailability and therapeutic efficacy. To improve its physicochemical features, such as solubility and dissolving behaviour, cocrystals of efavirenz with various conformers have been produced [2].

Cocrystals are a unique technique to modifying the physicochemical properties of active medicinal substances, and their effectiveness in a dosage form can be critical [3]. Cocrystals are a relatively novel method in the pharmaceutical industry that can improve active pharmaceutical ingredient (API) solubility and bioactivity without losing structural integrity [4]. Cocrystals greatly improve the aqueous solubility of medicines that are poorly water soluble [6-8]. Co crystals are made up of two or more molecules joined together by hydrogen bonds [5]. Overall, cocrystals provide a promising way to improving medication characteristics and performance, resulting in better drug formulations, increased bioavailability, and better patient outcomes.

MATERIALS AND METHODS

Materials

Efavirenz, Caffeine, Magnesium Stearate, Aerosil 200, Crosscarmilose sodium Avicell 102 (Microcrystalline cellulose), Lactose.

Method: Dry Grinding Method

Experimental work

Preformulation studies:

Characterization of drug

The pure drug sample is evaluated for its colour, odour and its appearance.

Melting point determination

The melting point of pure drug Efavirenz was determined by melting point apparatus using capillary method.

Calibration of drug by UV Spectroscopy

Calibration curve of Efavirenz in water: methanol (1:1)

Determination of λmax of Efavirenz

The UV method was developed in water: methanol (1:1) solvent. The Efavirenz stock solution (100 µg/ml) was scanned in the 200-400 nm range in order to obtain absorption spectrum.

Standard Solution

The standard stock solution of Efavirenz was prepared in water: methanol (50:50) solvent system. The pure drug Efavirenz about 10 mg was weighed and dissolved in solvent to get the concentration of 100 µg/ml.

Working solution

The two series of working solution were prepared in the linearity range of 2 µg/ml to 10 µg/ml and 5 µg/ml to 25 µg/ml by appropriate dilution of standard stock solution.

Construction of Calibration Curve

Calibration Curve method is essential for determination of absorbance of working solution and the calibration graph is constructed. The maximum absorbance was found to be 244nm.

Saturation Solubility Study

The saturation solubility has been carried out. The amount of drug dissolve in distilled water, 0.1 N HCL and pH6.8 Buffer for 24 hrs in rotary shaker. Appropriate aliquots were then withdrawn and filtered through whatmann filter paper and analyzed spectrophotometrically at 244 nm.

Fourier transfer infrared spectroscopy

FTIR spectrophotometer was used to determine the IR spectra of caffeine. Using dried potassium bromide, baseline correction was performed. 50 mg of KBr and 10 mg of the medication were triturated from originally dried alien in a. A little portion of the triturated sample was stored in the sample container, and the FTIR spectrophotometer was used to scan the sample from 4000 cm to 400 cm. After that, it is compared to official spectra.

Preparation of Efavirenz Cocrystal

Preparation of Efavirenz Cocrystal by using dry grinding method

Solid state grinding is where the materials are mixed, pressed and crushed in a mortar and pestle or mill. The pure drug Efavirenz and coformer Caffeine is mixed in the proportion of 1:1 in the mortar to prepare Efavirenz cocrystals by using caffeine as a conformer. This physical mixture was stored in desiccator and kept for 24 hrs in standard conditions of temperature and humidity. These cocrystals were evaluated for solubility in distilled water,0.1 N HCL solution ,6.8 buffer solution Based on solubility study further solid dispersion were prepared in different proportions.

Evaluation of efavirenz cocrystal by hardness, Disintegration time, in vitro dissolution test

Preparation of Preliminary Trial Batches Efavirenz Caffeine cocrystal tablets

Table 1: Composition of Preliminary Efavirenz-Caffeine Trial Batches based on different composition of binder and disintegrant.

Ingredients	A1 (mg)	A2 (mg)	Drug -coformer ratio
Solid dispersion	200	200	1.1
Aerosil 200	5	5	
Magnesium stearate	5	5	
Avicel 102	150	75	
Croscarmellose sodium	10	20	
Lactose	130	195	

The different compositions Efavirenz-Caffeine cocrystal tablets containing different amount of disintegrant and binder have been formulated and evaluated for hardness, thickness, diameter and weight variation test.

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Preparation of Trial batches Efavirenz Caffiene cocrystal tablet

Table 2: Composition of Efavirenz-Caffeine Cocrystal Trail batches based on different drug conformer ratio

Ingredients	B1(mg)	B2(mg)
Molar ratio of drug and conformer	1:1	1:2
Solid dispersion	200	300
Aerosil 200	5	5
Magnesium stearate	5	5
Avicel 102	75	75
Croscarmellose sodium	20	20
Lactose	195	195

Then trial batches of Efavirenz cocrystal were prepared for the selection of drug- coformer ratio. These batches were evaluated for thickness, Diameter hardness, disintegration time, in vitro dissolution test.

Optimization of Efavirenz Caffeine cocrystal by using Central Composite Design

Table 3: Composition of optimization batches of efavirenz caffeine cocrystal by using Central Composite Design

Batch	Ingredient(mg)					
	Solid dispersion	Aerosil 200	Magnesium-um Sterate	Avicel 102	Croscarmellose sodium	Lactose
F1	200	5	5	75	20	195
F2	200	5	5	75	10	205
F3	200	5	5	55	20	215
F4	200	5	5	55	10	225
F5	200	5	5	65	15	210
F6	200	5	5	65	15	210
F7	200	5	5	65	15	210
F8	200	5	5	65	15	210
F9	200	5	5	65	15	210
F10	200	5	5	51.8	15	224
F11	200	5	5	79	15	195
F12	200	5	5	65	7.9	217
F13	200	5	5	65	22	202

The experienced were designed using Design Expert software Version 121.9

A total 13 experiments were carried out to study the formulation factors on X1 (Avicell 102),

X2 (Crosscarmilose sodium), Y1 (Hardness), Y2 (Dissolution), Y3 (Disintegration)

Comparison of optimized formulation with marketed formulation

The prepared formulation was compared with available Efavirenz (Efcure 200 mg) market formulation. dissolution studies was carried out of the marketed immediate release tablets.

Stability study was carried out for the optimized cocrystal

The stability study of Efavirenz Caffiene cocrystal tablet was carried out for 90 days.The optimized Efavirenz Caffiene Cocrystal tablet evaluated for its appearance ,hardness ,disintegration time .

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RESULTS AND DISCUSSION

Preformulation study

Organoleptic property of drug

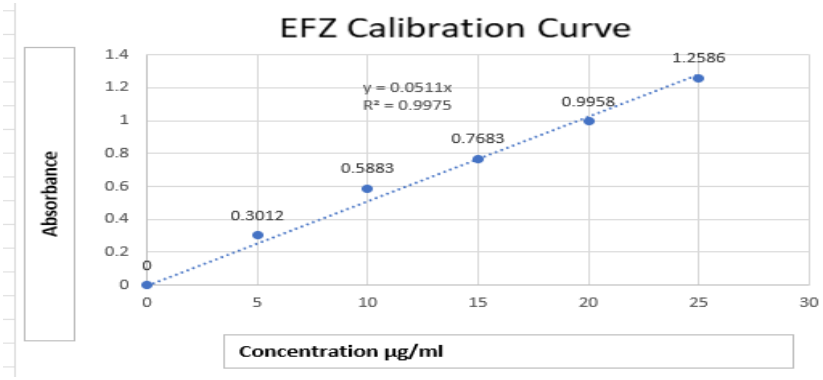
The drug was white amorphous powder which was odurless. The organoleptic properties of pure drug was evaluated and confirmed with the literature.

Melting point determination

The melting point of drug was observed 139℃±0. 057.The reported melting point is 139 ℃ to 141℃.

Calibration curve of drug by UV Spectroscopy.

Figure 1: Calibration curve of Efavirenz in methanol: water (1:1)



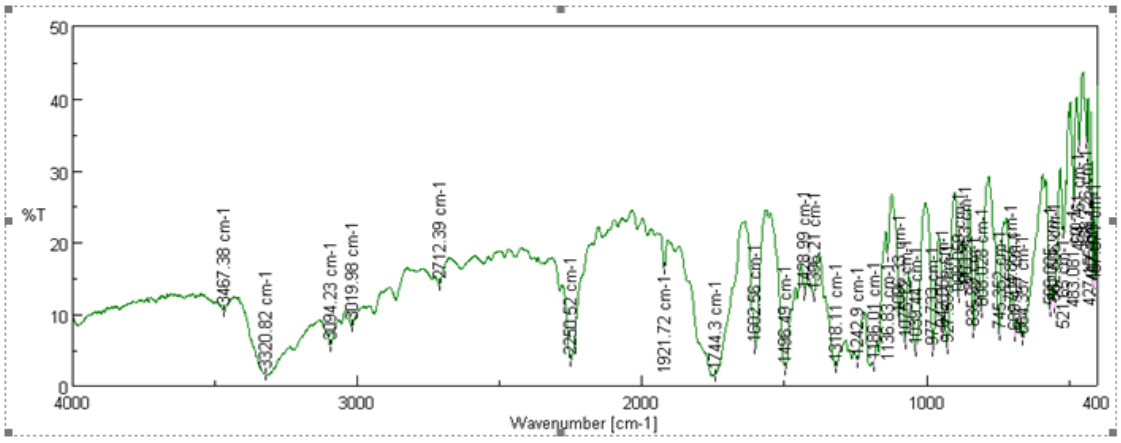
The analytical method (UV)was developed and validated by using Methanol:Water (1:1) as a medium at 244nm.The linear equation was found to be y=0.0511x and R^2 was found to be 0.9975 in concentration 2-10 µg/ml

Determination of saturation solubility

The saturation solubility of drug and in cocrystal form was carried out in distilled water,0.1 N HCL and pH 6.8 buffer. The maximum solubility of drug was observed in distilled water in comparison with the pH 6.8 buffer and 0.1 N HCL.

FTIR studies

Figure 2: FTIR spectra of pure drug (Efavirenz)



The FTIR Spectra of the pure drug was found to be compiled with the standard FTIR Spectra of the drug.

Evaluation of Preliminary trial Batches of Efavirenz -Caffeine cocrystal tablet by different composition of binder (Avicell 102) and disintegrant (Crosscarmilose sodium)

Table 4: Evaluation of preliminary trial batches of Efavirez-Caffiene cocrystal tablet

Parameter	A1 (n=3 Avg ±SD)	A2 (n=3 Avg ±SD)
Thickness(mm)	4.02±0.025	3.07±0.015
Hardness (kg/cm²)	3.06 ±0.01	5±0.577
Disintegration time (min) (n=6Avg ±SD)	276±6.47	33.66 ±6.47

All the trial batches were evaluated for hardness ,disintegration time, in vitro dissolution rate. Batch A2 has shown better results as compared to the A1. Batch A2 has shown 96% within 15 min. and A1 has shown 32% dissolution rate as compared to the A1 .So batch A2 was further taken for optimized.

Evaluation of trial batches of Efavirenz Caffeine cocrystal tablet by different drug conformer ratio.

Table 5: Evaluation of trial batches by different drug coformer ratio Efavirez-Caffiene cocrystal tablet

Parameter (Drug : Coformer)	B1 (1:1) (n=3 Avg ±SD)	B2 (1:2) (n=3 Avg ±SD)
Thickness(mm)	3.07±0.015	3.46±0.0152
Hardness (kg/cm²)	5±0.577	4.6±0.152
Disintegration time (min) (n=6Avg ±SD)	33.66 ±6.47	75.5±8.93

All the trial batches were evaluated for hardness, disintegration time, in vitro dissolution rate. Batch B1 has shown 96% within 15 min. and B2 has shown 45% dissolution rate as compared to the B1 .So batch B1 was further taken for optimized.

Optimization of Efavirenz Caffeine cocrystal tablet by using Central Composite Design

The composition of Efavirenz Caffeine cocrystal tablet finalized as per Batch B1 was further optimized by using Central Composite Design.

Table 6: Responses of Central composite design of Efavirenz caffeine cocrystal tablet.

Batch	Hardness (kg/cm²)	Dissolution (%)	Disintegration (min)
F1	5	96	0.75
F2	4.5	52	1.1
F3	4	58	0.53
F4	2.5	84	0.95
F5	3.6	90	0.7
F6	3.6	90	0.7
F7	3.6	90	0.7
F8	3.6	90	0.7
F9	3.6	90	0.7
F10	2	90	0.5
F11	5.1	85	0.8
F12	3.5	65	1.01
F13	3.6	70	0.85

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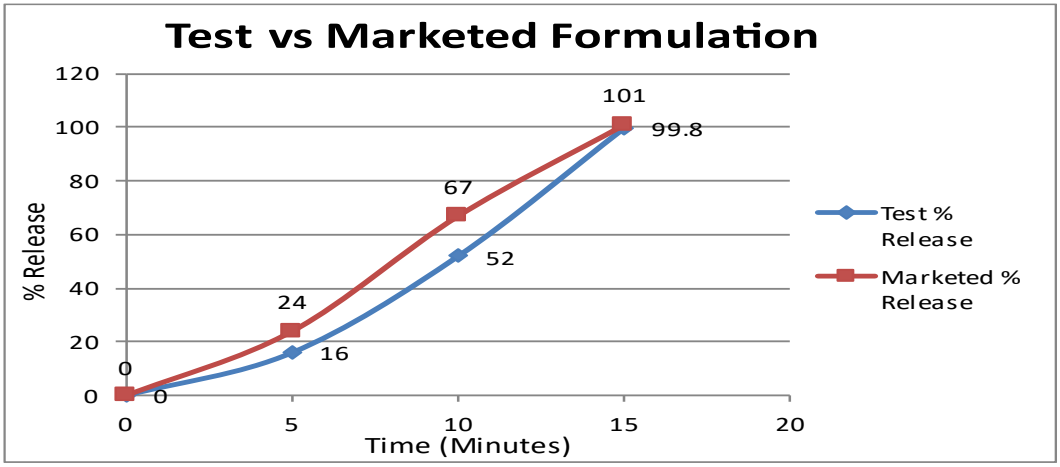
It was observed that for Batch F1 the hardness, disintegration time and in vitro dissolution test was found to be 5 kg/cm² ,0.75 min and 96% drug release respectively. The result has shown better as compared with other batches.

Comparison of optimized Efavirenz Caffeine cocrystal with available marketed formulation

Figure 3: dissolution graph Comparison of optimized batch (F1) with marketed formulation



It is observed that optimized formulation(F1) has shown comparable in vitro dissolution profile in comparison with the marketed formulation (Efcure 200mg). The optimized formulation drug release was found to be 99.8% comparable with the marketed formulation was found to be 101%.

Stability studies of optimized Efavirenz Caffeine Cocrystal

Table 7: Stability studies of optimized Efavirenz Caffeine Cocrystal

Parameter n=3 Avg ±SD	0 days	30 days	60 days	90 days
Appearance	Solid	Solid	Solid	Solid
Hardness (kg/cm²)	4.5 ± 0.12	5 ± 0.23	5 ± 0.22	4 ± 0.19
Disintegration time (sec)	40.83 ±0.080	40.83 ±0.092	40.83 ±0.088	40.83 ±0.079

As per ICH stability studies, it was found that the optimized Efavirenz Caffeine cocrystal tablet was stable for selected formula at accelerated conditions.

CONCLUSION

In the present work it was attempted first time to develop Efavirenz Caffeine cocrystals with the intension of better patient compliance and less or minimized adverse effect of efavirenz (dizziness vertigo) when used alone.

The Efavirenz Caffeine cocrystal were converted into the tablet form and the tablet composition was optimized by using CCD method. This experimentation shows the possibilities of efavirenz caffeine cocrystal for effective and safe use of efavirenz in oral solid dosage form.

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