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Carbamazepine Cocrystals by Solvent Evaporation Technique: Formulation and Characterization Studies

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ABSTRACT

Carbamazepine; an antiepileptic drug, exists in various polymorphic forms out of which Form III is extensively studied as a model form for cocrystallization. The main focus of the present study was to cocrystallize Carbamazepine form III with Itaconic acid as a coformer by solvent evaporation technique using Acetone (Class III) as the solvent medium for drug and coformer interaction at molecular level. The obtained Carbamazepine cocrystals were evaluated for parameters like Visual morphology, differential scanning calorimetry, infrared spectroscopy, x-ray diffractometry, contact angle, drug content uniformity, flow properties and *in vitro* drug release testing. A comparison of the cocrystal characteristics was made with a physical mixture of Carbamazepine with itaconic acid inorder to confirm an interaction at a molecular level between the drug and coformer. The obtained carbamazepine cocrystals showed distinct difference in its morphological characteristics as compared to plain drug. Additionally, the cocrystals showed presence of additional peaks in differential scanning calorimetry thermograph as well as bandshifts in the infrared spectrum. The X-Ray diffractogram of cocrystals was found to show a shift towards left thus confirming a change in the crystal lattice. *In vitro* drug release testing of cocrystals showed an increase in drug release when compared to drug release from physical mixture and plain drug when tested in 1% Sodium lauryl sulphate. Hence Solvent evaporation technique was found to be successful in producing cocrystals of Carbamazepine polymorph III with Itaconic acid as a coformer.

Keywords: Carbamazepine, Itaconic acid, solvent evaporation, coformer, cocrystal, polymorph

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INTRODUCTION

Drug cocrystallization as a part of crystal engineering has been explored extensively in an attempt to tailormake drug features like water-solubility, dissolution rate, morphology, stability etc[1] .Cocrystallization of drugs with dicarboxylic acids as coformers has been studied because of their ability to form homosynthons and heterosynthons with functional groups containing acidic hydrogen present in the drug[2].

Carbamazepine, first generation anticonvulsant has been considered as a model drug for cocrystallization because of presence of a carboxamide synthon in its crystal structure. [3]Furthermore; its low water solubility and existence in four polymorphic forms makes it a drug of choice. A detailed study of inherent crystal packing in carbamazepine drug has shown formation of cyclic dimeric association involving its carboxamide unit acting both as a hydrogen bond donor and acceptor. The proposed strategy by which acids form cocrystals with Carbamazepine drug is replacement of the carboxamide dimer with an amide-carboxylic acid dimer. [4]The probability of different intermolecular associations between the carboxamide group of carbamazepine and acidic group of coformer aids in modification of crystal packing in the drug thus changing its physicochemical properties. Several coformers like Nicotinamide, 4-Amino benzoic acid, succinic acid, salicylic acid, fumaric acid etc have been explored for Carbamazepine drug cocrystals in various stoichiometric ratios. [5]A range of cocrystallization techniques like neat grinding, solvent-assisted grinding, solvent evaporation, slow-cooling crystallization, solvent/non-solvent diffusion, vapour diffusion, sublimation, super-critical fluid technology etc have been explored to formulate cocrystals[6]. Amongst these; solvent evaporation has been recommended because it provides interaction between the drug and the coformer at molecular level. Moreover the lower probability of exposure of the coformer to a renewed surface of the drug for interaction during neat grinding and solvent-assisted grinding decreases the tendency of the drug to interact with the coformer leading to hydrogen bonding and finally formation of a cocrystal[7].

The main objective of the present research work was to formulate cocrystals of Carbamazepine using Itaconic acid as the coformer and solvent evaporation as the technique of cocrystallization. The changes in the inherent crystal lattice of the drug was confirmed by techniques like differential scanning calorimetry, infrared spectroscopy, x-ray diffractometry studies and contact angle measurement studies. The effect of cocrystallization on pharmaceutical parameters like drug release and flow properties was also evaluated.

MATERIALS AND METHODS

Carbamazepine IP (Polymorph III) was gifted by Bajaj Healthcare Ltd, Masjid Bunder, Mumbai, India. Itaconic acid was purchased from Sigma Aldrich, Mumbai, India. Acetone solvent was purchased from Merck and Co, Mumbai, India. All other chemicals used were of analytical grade.

Formulation of Carbamazepine cocrystals

236.39 mg of Carbamazepine IP(Form III) and 130.1 mg of Itaconic acid used as a coformer were dissolved in 50 ml of acetone by stirring. Stirring was continued till a clear solution was obtained. The solution was covered with an Aluminium foil and the solvent from the clear solution was allowed to be evaporated by piercing 5-6 fine holes in the foil. The entire process was carried out at room temperature with constant stirring. The process was continued till a solid cocrystalline product was obtained. The product was dried in oven at 60°C for 5 minutes till all the traces of acetone were removed.The obtained product was evaluated for various parameters. [8]

Preparation of Physical Mixture of Carbamazepine and Itaconic acid

Carbamazepine drug and itaconic acid were weighed and physically mixed in a ratio of 1:1. Care was taken to prevent any reaction induction while manual mixing. The obtained physical mixture was used as a reference to confirm the presence of hydrogen bonding between the drug and coformer in cocrystals .

Evaluation of Cocrystals

Visual Morphology

The visual appearance of plain Carbamazepine, Itaconic acid and the obtained cocrystals were studied and compared using Canon Powershot A480 Digital camera.

***In vitro* drug release studies**

Standard Plot of Carbamazepine in 1% Sodium lauryl sulphate(SLS)

100 mg of Carbamazepine was dissolved in 100 ml of 1 % SLS to give a 1000 ppm solution. 3 ml of the 1000 ppm solution was then diluted to 100 ml using 1% SLS to give a 30 ppm solution. The 30 ppm solution was utilized to prepare various dilutions of 3, 6, 9, 12, 15, 18, 21, 24, 27 and 30 ppm respectively. The absorbance of the various dilutions was measured at 287 nm using Shimadzu 1650 PC UV Spectrophotometer using 1% SLS as a blank. The standard equation and R^2 value were calculated. The equation was utilized to calculate the percent drug release.

***In vitro* release testing of Carbamazepine from the cocrystals**

The *in vitro* release of Carbamazepine from cocrystals was evaluated using USP Dissolution

Apparatus II(Paddle Type). For this, an amount of cocrystalline powder (155.1 mg) equivalent to 100 mg Carbamazepine drug was weighed and filled in hard gelatin capsules size 000. The hard gelatin capsules were clamped in sinkers and the sinkers were added to 900 ml of 1% Sodium lauryl sulphate(SLS). Dissolution was carried out at 75 rpm at 37°C. Aliquots of 10 ml were removed at 5, 10, 15, 30, 45 and 60 minutes and filtered using 0.45 micron filter. Sink conditions were maintained by replacing 10 ml of 1% SLS. The absorbance of the aliquots was measured after single dilution using Shimadzu 1650 PC UV Spectrophotometer at an absorption maxima of 287 nm using 1% SLS as blank. The procedure was repeated for physical mixture of Carbamazepine and itaconic acid and 100 mg of plain drug. The standard equation obtained by plotting a standard curve of the drug in 1% SLS was used for calculating the drug release.[9]

Differential Scanning Calorimetry(DSC) studies

3-5 mg of the Cocrystal powder and physical mixture of Carbamazepine drug and Itaconic acid coformer were placed in empty aluminium pans. The pans were covered with lid and crimped using DSC crimper. The crimped pans were heated against blank crimped pans at the rate of 10°C/minute from 30°C to 300°C under 17 ml/min of nitrogen flow using Pyris-6 Perkin Elmer Differential scanning calorimeter to obtain the endothermic peaks. The endothermic peaks obtained were compared to endotherms of plain drug and coformer.[10]

X-Ray Diffraction studies (XRD)

X-Ray diffractometry studies of carbamazepine drug and carbamazepine cocrystals was conducted using Bruker D8 ADVANCE XRD Analyzer. About 1.5 gms of each sample was placed in the sample holder and the sample holder was placed on the rotating sample stage. The sample was placed in the horizontal position and the X-Ray tube and the detector both were moved simultaneously over the angular range 2 theta. The obtained X-Ray diffractograms were compared and evaluated for changes in signal position.[11]

Contact Angle measurement studies

The enhancement in wetting by cocrystallization of carbamazepine was measured using Contact angle measurement. Flat compacts of carbamazepine drug and its cocrystal were prepared and the contact angle was measured using G10 Contact Angle meter (Kruss, Germany). Sessile drop method was used for the same. A drop of water was dropped from a syringe on the compacts and the angle made by the static water drop with the flat surface of compact was measured immediately.[12]

Infrared Spectroscopy studies

The characteristic peaks for Carbamazepine drug, itaconic acid, cocrystal and physical mixture

of the drug and coformer were measured using Shimadzu MIRACLE IRAffinity-1 FTIR spectrophotometer. The scanning was done from 400 to 4000 cm-1 taking air as the blank measurement. [13]

Flow Property Evaluation

Several flow properties like Tap density, Bulk density, Angle of repose, Carr's index and Hausner's ratio for carbamazepine cocrystals were measured.[14]

Bulk Density

1 gram of the cocrystal sample was weighed and placed in 10 ml measuring cylinder. The volume occupied by the sample was measured in ml. Bulk density for cocrystals was calculated by formula :

$\rho_B = M_{cc}/V_B$

where :

ρ_B = Bulk density of cocrystal

M_{cc} = Mass of cocrystal

V_B = Bulk volume of cocrystal

Tap Density

1 gram of the cocrystal sample was weighed and placed in 10 ml measuring cylinder. The cylinder was tapped for 50 times and the volume was measured in ml.

$\rho_T = M_{cc}/V_T$

ρ_T = Tapped density of cocrystal

M_{cc} = Mass of cocrystal

V_T = Tapped volume of cocrystal

Angle of Repose

The angle of repose of the cocrystal sample was measured by Fixed Funnel Method. 3.36 grams of cocrystal sample was loaded in a broad-mouthed funnel and a cone of 2 cm height was formed. The radius of the circumference formed by the base of cone was measured. The angle of repose was calculated by the formula :

$\Theta = \tan^{-1} (h/r)$

where

Θ = Angle of repose

h= height of the cone formed by powder heap

r = radius of circumference formed by the cone of powder heap

Percent Compressibility index (Carr's Index)

Carr's index of the cocrystals was calculated by the formula :

$CI(\%) = (\rho_T - \rho_B)/\rho_T * 100$

where

CI(%)=Percent Compressibility index

ρ_T = Tapped density of cocrystal

ρ_B = Bulk density of cocrystal

Hausner's Ratio(H.R.)

The Hausner's ratio for the cocrystals was calculated using the formula :

H.R. : ρ_T/ρ_B

Where

H.R. = Hausner's Ratio

ρ_T = Tapped density of cocrystal

ρ_B = Bulk density of cocrystal

Drug Content Uniformity

An amount of Carbamazepine cocrystals containing Carbamazepine drug equivalent to 100 mg was weighed and dissolved in 100 ml 95 % ethanol to give a drug concentration of 1000 ppm solution. 1 ml of resulting solution was diluted to 100 ml with ethanol to give a 10 ppm solution. The absorbance of the resulting solution was measured at 285 nm using Shimadzu 1650-PC UV spectrophotometer. The carbamazepine content of cocrystals was calculated taking 490 as the value of A(1%, 1cm) at an absorption maxima of 285 nm.[15]

RESULTS AND DISCUSSION

Visual Morphology studies

Distinct difference was observed in the morphological features of cocrystals of Carbamazepine as compared to features of plain drug and coformer.[Figure 1(a-c)] Plain itaconic acid was observed to be transparent pale white cubic crystals in nature. Fine bright white powder of Carbamazepine drug was observed whereas Cocrystalline carbamazepine was found to be lemon yellow flaky powder. This indicates that the drug and the coformer have reacted stoichiometrically resulting into a product with morphological characteristics different from the drug and the coformer.

a b c

Figure 1: (a) Plain itaconic acid (b) Plain Carbamazepine (c) Carbamazepine cocrystals

***In vitro* drug release studies**

Standard Plot of Carbamazepine in 1% Sodium lauryl sulphate(SLS)

The standard plot obtained by measuring the absorbance of various dilutions of stock solution of 30 ppm is as given in Figure: 2. A standard equation of y=0.0211x+0.007 and an R^2 value of 0.9993 was obtained.

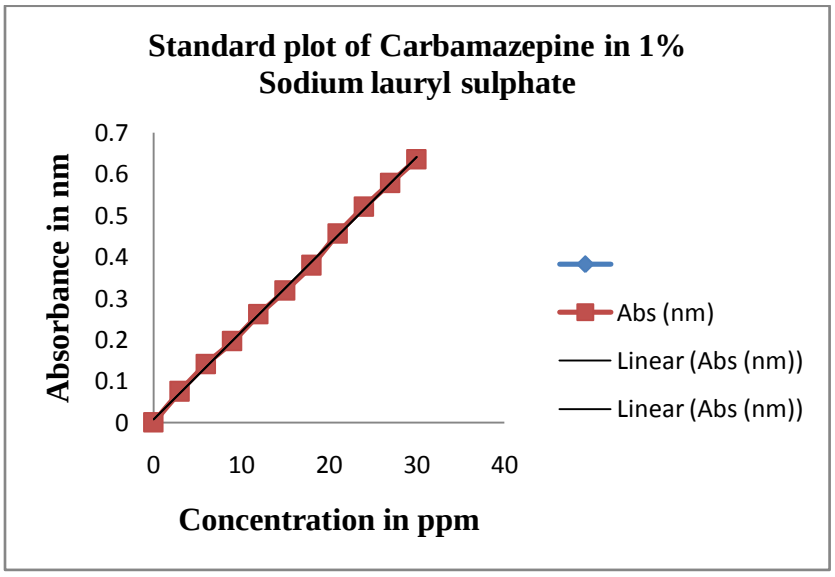


Figure:2 Standard Plot of Carbamazepine in 1% Sodium lauryl sulphate

***In vitro* release testing of Carbamazepine from cocrystals**

A distinct enhancement in Carbamazepine release was obtained on *in vitro* drug release testing of cocrystals as compared to its physical mixture with Itaconic acid and plain Carbamazepine. (Figure:3) The increase in drug release can be attributed to formation of hydrogen bonding between amide functional group and carboxylic acid functional group of Itaconic acid. The presence of Itaconic acid in association with Carbamazepine leads to an enhancement in polarity of hydrophobic carbamazepine thus increasing its dissolution in aqueous media.[16]

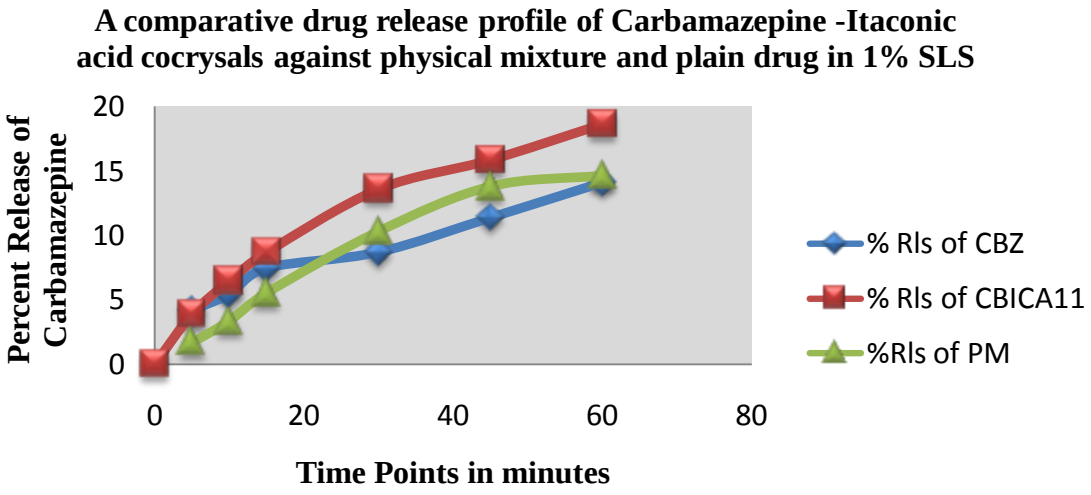


Figure:3 Comparative drug release profile of Carbamazepine and Itaconic acid cocrystals, physical mixture and plain Carbamazepine.

Differential Scanning Calorimetry(DSC) studies

A distinct difference in the DSC endotherm of Carbamazepine cocrystals was observed as compared to endotherm of its physical mixture with coformer, plain drug and coformer. [Figure:4(a-d)]. A new major peak at 141.99°C and a new minor peak at 96.21°C were observed in the thermogram of cocrystal. No melting peak was observed for Itaconic acid thus indicating the physicochemical interaction between itaconic acid and carbamazepine to give cocrystal with lower melting peak. Physical mixture of Carbamazepine and Itaconic acid showed presence of two major peaks one at 195.22°C (close to 193°C i.e. melting temperature of Carbamazepine) and one at 160.60°C (close to melting temperature of Itaconic acid) thus indicating the absence of formation of any new compound(No chemical interaction between Carbamazepine and Itaconic acid).

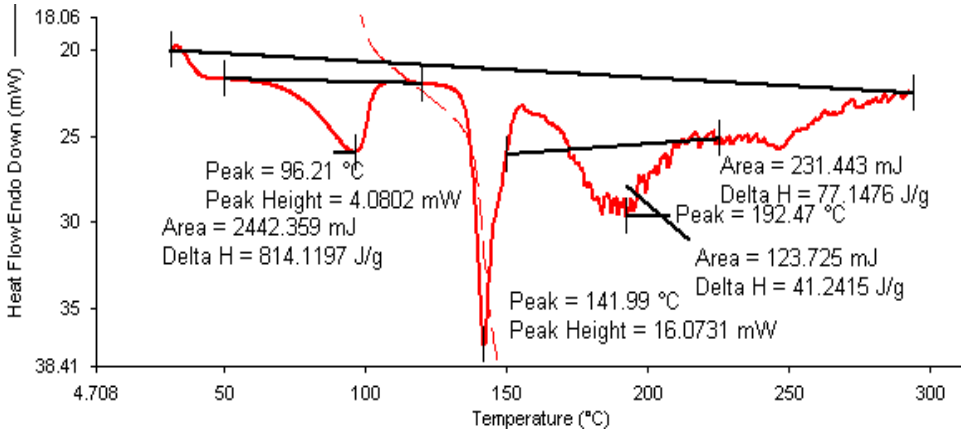


Figure 4a: Differential Scanning calorimetry thermogram of Carbamazepine cocrystal

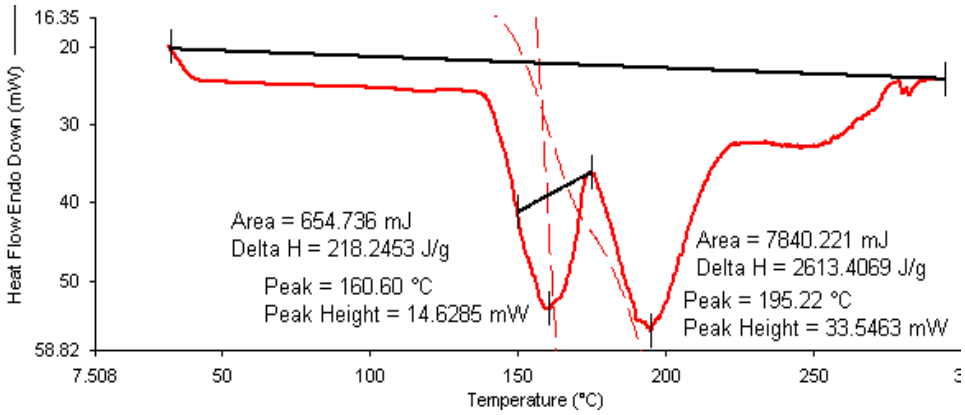


Figure 4b: Differential Scanning calorimetry thermogram of Carbamazepine and itaconic acid physical mixture

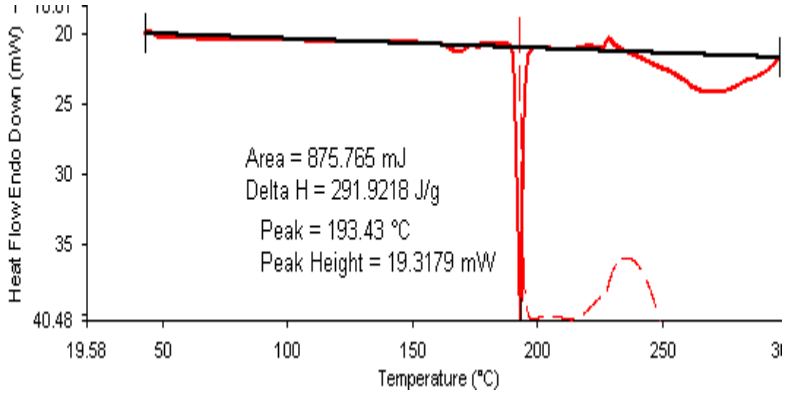


Figure 4c: Differential Scanning calorimetry thermogram of Carbamazepine drug

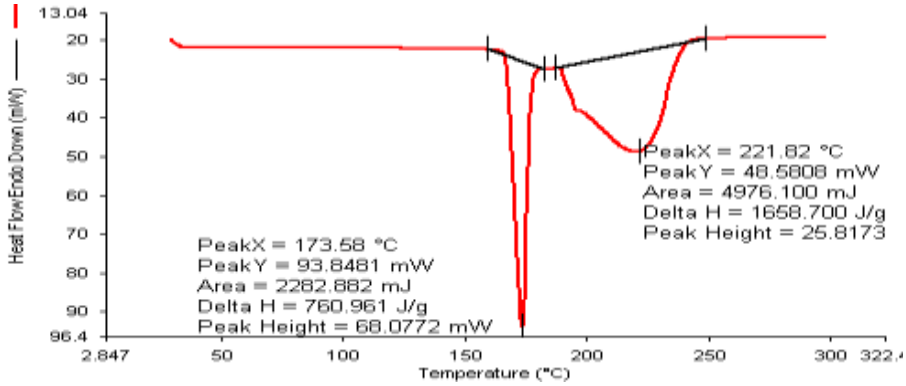


Figure 4d: Differential Scanning calorimetry thermogram of itaconic acid

Infrared Spectroscopy studies

The infrared spectroscopy of carbamazepine polymorph III cocrystals showed distinct shifts in the inherent bands for Carbamazepine drug. Presence of additional bands at wavenumbers other than those for Carbamazepine drug and the coformer were observed thus indicating the formation of a new cocrystalline compound.[Figure 5(a-d)] The characteristic band for –NH valence vibration at 3462 cm^{-1} was found to be elongated and shifted at 3477 cm^{-1}. The –COR

vibration band at 1670 cm^{-1} was found to be strong and shifted at 1685 cm^{-1}. The band range of 1605 to 1593 cm^{-1} characteristic for –C=C- and -C=O vibration and –NH deformation observed in Carbamazepine drug spectrum as a band at 1598 cm^{-1} was found to be absent in the spectrum for cocrystal. A weak band at 850 cm^{-1} characteristic for plain drug spectrum was found to be replaced by two bands at 883 cm^{-1} and 800 cm^{-1}. The spectrum of physical mixture was found to show all the characteristic bands of carbamazepine drug and showed no presence of additional bands or changes in the band strength thus indicating absence of any physicochemical interaction between drug and coformer. [17]

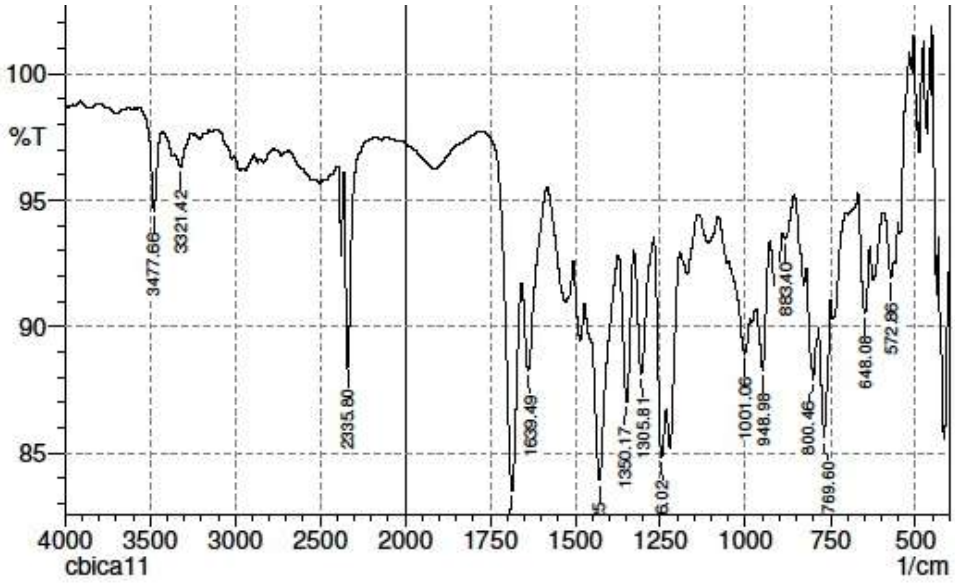


Figure 5a Infrared spectrum of Carbamazepine cocrystal

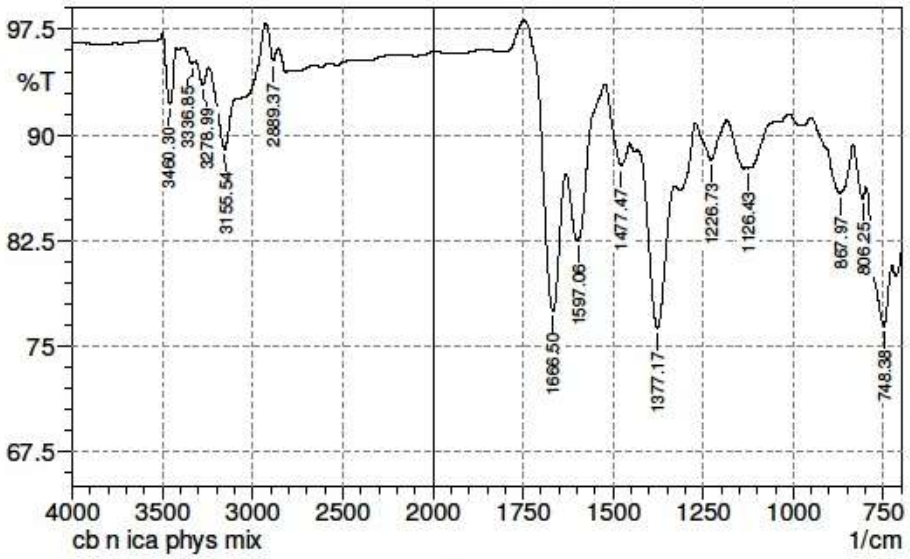


Figure 5b Infrared spectrum of physical mixture of Carbamazepine with itaconic acid

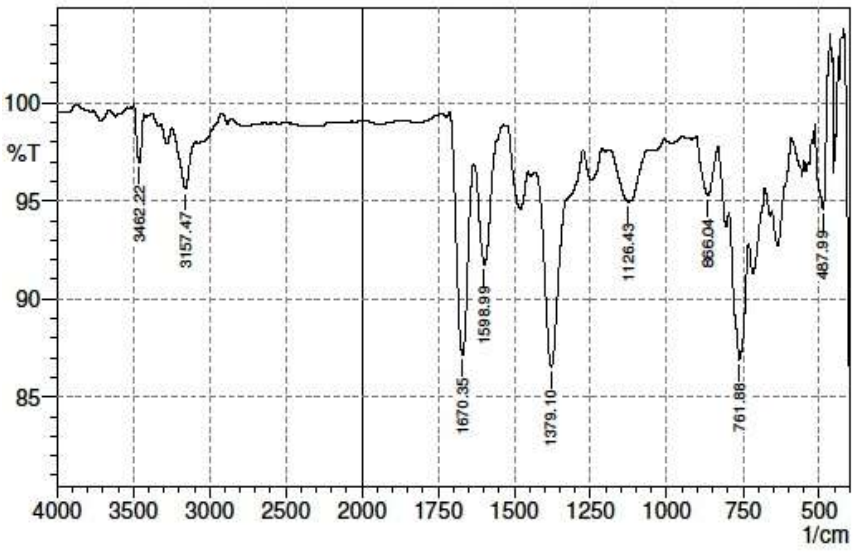


Figure 5c Infrared spectrum of Carbamazepine polymorph III

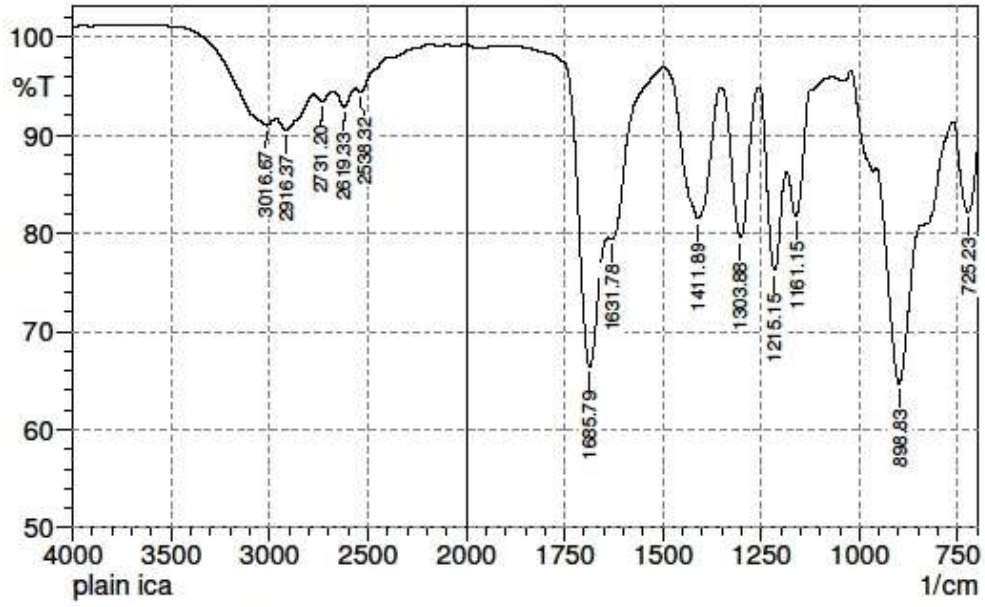


Figure 5d Infrared spectrum of Itaconic acid

X-Ray Diffraction Studies

The X-Ray diffractometry studies of Carbamazepine cocrystals showed presence of several additional diffraction signals at 2 °Θ values of 4.5, 9.5, 13.5, 15.5,18, 22.5, 27, 28.5, 30.5 and 41.5 as compared to that of plain drug which showed signals at 2 °Θ values of 12.5, 14.9, 15.2,15.8, 24.5, 27.2, 27.5 and 32[Figure6(a-c)]. The X-Ray diffractogram of the cocrystal was found to show signal shifts towards left as compared to the diffractogram of plain Carbamazepine indicating changes in interatomic distance of the drug and hence the drug crystal lattice.[18]

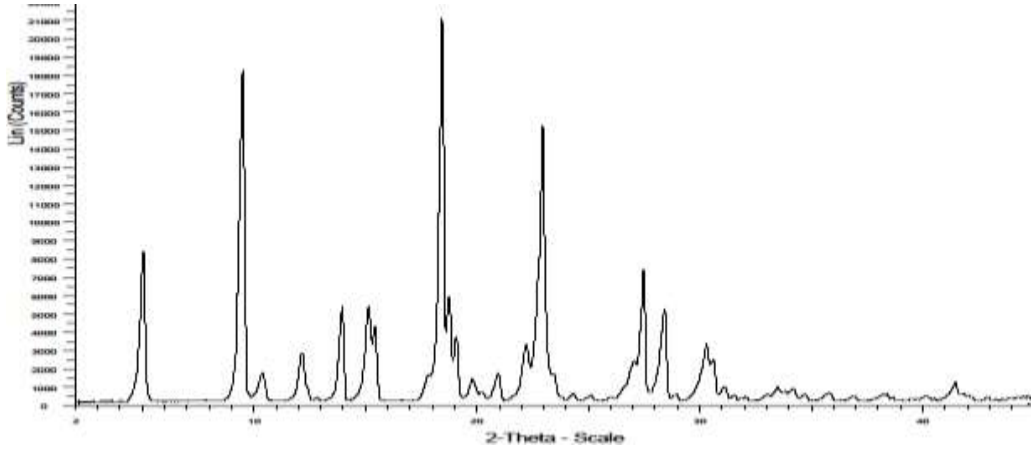


Figure 6a-X-Ray diffractogram of Carbamazepine cocrystal with itaconic acid

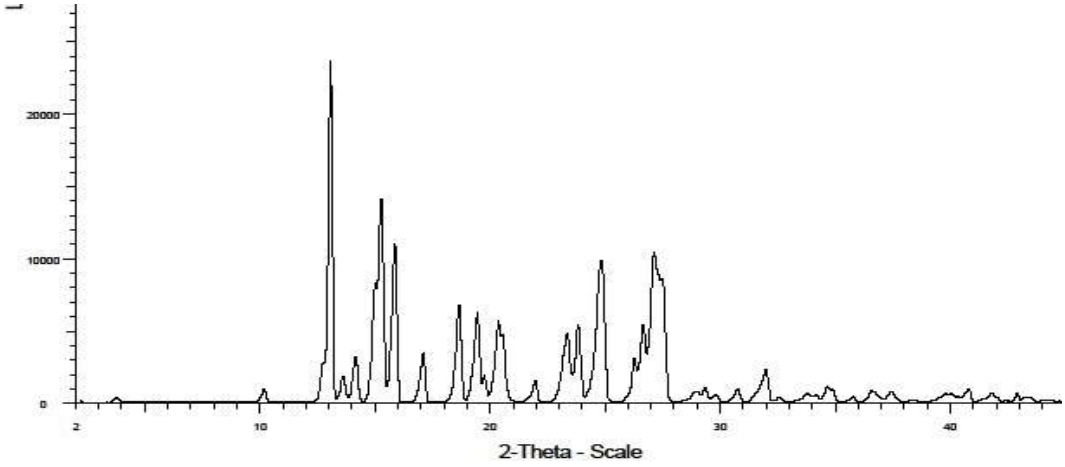
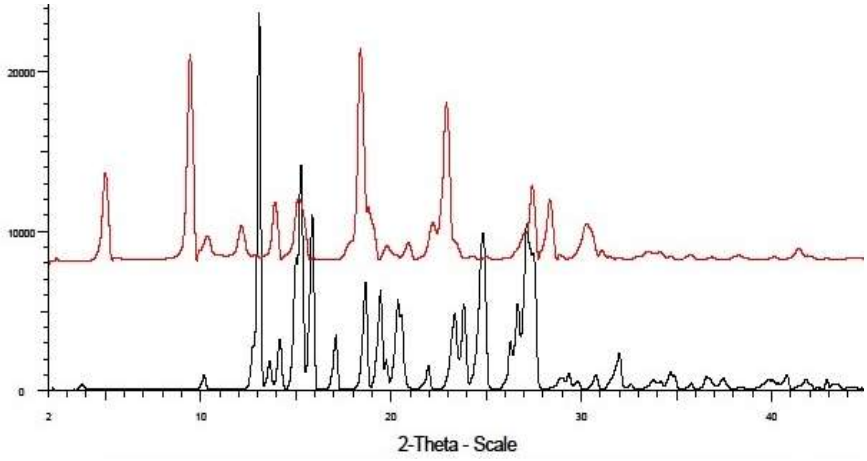


Figure 6b-X-Ray diffractogram of Carbamazepine



Fiure 6c : Overlay of X-ray diffractogram of Carbamazepine cocrystal and plain drug

Contact Angle Measurement studies

Cocrystals were found to show a lowered contact angle i.e. 42° as compared to plain Carbamazepine i.e. 51°. A lowered contact angle of the cocrystals indicates the increased wetting property of cocrystal as compared to drug due to decreased hydrophobicity of drug by presence

of a water-soluble hydrophilic coformer in association with the drug.

Flow Property Evaluation studies

The cocrystals were found to show flow properties as indicated in Table 1.

Table 1: Flow Properties of Carbamazepine cocrystals

Flow Property	Observation made	Flow characteristics
Bulk Volume (ml)	4.3	
Bulk Density (g/ml)	0.233	
Tapped Volume(ml)	2.3	
Tapped Density (g/ml)	0.435	
Angle of Repose(degrees)	40	Passable
Percent Compressibility Index (%CI)	46.44	Very poor
Hausner's Ratio(HR)	1.867	Poor

Drug Content Uniformity studies

The content uniformity for carbamazepine cocrystals was found to be 88.75±1 percent.

CONCLUSION

The technique of solvent evaporation was found to be successful in formulating cocrystals of Carbamazepine polymorph III with itaconic acid. The cocrystals were found to possess morphological and physicochemical attributes different from plain drug. A comparison of drug release profile and other crystal-related data (Infrared spectroscopy, differential scanning calorimetry and x-ray diffractometry) of cocrystal with that of physical mixture of drug and coformer confirmed the changes in hydrophobicity and crystal structure of the drug by cocrystallization.

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