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# Influence of different solvents on crystal property and solubility characteristics of Carbamazapine

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**Abstract:** Influence of solvents on the crystalline properties and solubility of drugs has received limited attention in the literature. The main objective of this study was to gain an understanding of the influence of different solvents on crystalline modification and subsequently the solubility of carbamazepine immediate release tablet by in vitro dissolution studies. Solubility enhancement was carried out by using different solvents like ethanol, acetone and chloroform. The physical state of the drug was determined using SEM, DSC, PXRD and FTIR. Crystals obtained from ethanol at room temperature shows highest solubility and better release profile.
**Key words:** Crystalline property, Solubility enhancement, immediate release.

## Introduction

Many substances have the ability to crystallize in more than one crystalline form. Although they are chemically identical, there have significant differences in their physicochemical properties. Different crystalline forms of a drug may influence the important pharmaceutical qualities like tableting characteristics, dissolution profile and as well as chemical and physical stability during storage[1]. The crystal habit is an important variable in pharmaceutical manufacturing, where some factors, such as the polarity of crystallization solvent and the presence of impurities in the solvent, affect crystallization[2, 3, 4]. Among them, solvent strongly affects the habit of crystalline materials; however, the role-played by solvent interactions in enhancing or inhibiting crystal growth is still not completely understood [5].

Carbamazepine (CBZ) is a commonly used anticonvulsant drug and belongs to class II of the biopharmaceutical classification system. Compounds ibelonging to class II have high intestinal permeability and low water solubility. Subsequently, the bioavailability of such compounds is limited by their solubility in water. Keeping this in view, crystal modification of CBZ has been undertaken to improve dissolution and bioavailability. It has been recrystallized from selected solvents and solvent system. The newly developed CBZ crystals were characterized by some physicochemical approaches.

## Experimental

### Instruments and Chemicals

Carbamazepine was a gift sample from Nirman Pharma, Vapi, Gujarat, India. All chemicals used in this research work were of analytical grade. Deionized distilled water was used throughout the study.

***Preparation of CBZ crystals***

Crystals were obtained of pure drug from Acetone, Ethanol, and Chloroform. Accurately weighted drug was dissolved in specified solvent. Then they were allowed for air drying. Obtained crystals were passed from sieve 40# and evaluated for different physicochemical parameters.

***Preparation of tablet using prepared crystals***

Conventional immediate release tablet formulation was prepared by direct compression method using the crystals equivalent to 100 mg of CBZ drug, MCC (micro crystalline cellulose) as a diluent, 5% SSG (sodium starch glycolate) as a disintegrating agent, 1% magnesium stearate as a lubricant and 2% talc as a glidant. Accurately weighted material is passed from 40# sieve and mixed thoroughly and compressed by using rotary tablet

machine. Efforts were made to keep the hardness, thickness and compression force constant as to avoid their influence on release profile of drug from tablets.

***Evaluation of prepared crystals***

Prepared crystals were evaluated for following parameters.

1. **Flow property study**

It was carried out by measuring Angle of repose. The angle of repose was determined by the fixed height funnel method and calculated using the following equation. In which *h* is the height of the powder heap and *r* is the radius of the powder heap.

$$\tan\theta = h / r$$

2. **Compression behavior**

It can describe by Carr's index and Hausner's ratio. These parameters were calculated by using tap and bulk density using following equation.

$$\text{Carr's Index} = \left(\frac{TappedDensity - BulkDensity}{TappedDensity}\right)100$$

$$\text{Hausners' Ratio} = \frac{TappedDensity}{BulkDensity}$$

3. **Scanning electron microscopy (SEM)**

Crystal habit and surface features termed as crystal morphology was examined by scanning electron microscope. Crystals were examined with a scanning electron microscope (Philips XL-30 environment) operating at 30 kV. The samples were mounted on a metal stub with double adhesive tape and under pressure of 0.7 torr prior to observation.

4. **Powder X ray diffraction study**

The physical state of CBZ was evaluated by powder X-ray diffraction study. Powder X-ray diffraction patterns of all samples were determined using a defractometer Bruker AXS - D8 from 2θ range 5° to 90°.

5. **Fourier transform infrared spectroscopy study (FTIR)**

FTIR spectra of moisture-free powdered samples of CBZ crystals were obtained using a spectrophotometer (FTIR-8300, Shimadzu Co., Kyoto, Japan) by potassium bromide (KBr) pellet method. The scanning range was 750–4000 $cm^{-1}$, and the resolution was 1 $cm^{-1}$.

6. **Differential Scanning Calorimetry (DSC) study**

DSC scans of all powdered samples were recorded using Shimadzu DSC-60 with TDA trend line software. All samples were weighed (5-8 mg) and heated at a scanning rate of 10 °C/min under dry nitrogen flow (100 mL/min) between 40°C and 250°C. Aluminum pans and lids were used for all samples. Pure water and indium as primary standard were used to calibrate the DSC temperature scale and enthalpic response.

7. **Saturated solubility study**

Solubility studies were performed according to the method reported by Higuchi and Connors[6]. CBZ in amounts that exceeded its solubility, were transferred to screw capped vials containing 10 mL distilled water. The contents were stirred on a vortex mass mixer at room temperature for 24 hrs. This duration was previously tested to be sufficient to reach equilibrium, after which no improvement in solubility was observed. After reaching equilibrium, samples were filtered through a 0.45-µm Whatman filter paper, suitably diluted with distilled water and analyzed for drug content at the 285 nm using a spectrophotometer (Shimazdu-1601, UV–vis spectrophotometer, Shimadzu Corp, Kyoto, Japan). All assays were performed in triplicate.

8. **In vitro dissolution study**

*In vitro* drug-dissolution studies were conducted using the USP Type II apparatus at 75 rpm using distilled water containing 0.1% sodium lauryl sulphate as surfactant at 37 ± 0.5 °C. At specified intervals, 10 ml samples were withdrawn and replaced with fresh medium to keep a constant volume. After appropriate dilution, the sample solutions were analyzed using a UV-visible spectrophotometer at 285 nm. The amount of drug released was determined by reference to a calibration curve.

## Result & discussion

1. **Flow property study**

The result of the flow property study is shown in table I. Results indicated that the pure drug showed excellent flow properties while ethanol and acetone crystals showed the good flow property in comparison to chloroform crystals.

2. **Compression behavior**

Results of the compression behavior are shown in table II. Results showed that pure drug and acetone crystals have poor compressibility while ethanol and chloroform crystals have good compressibility.

Results indicate that pure drug has excellent flow property but poor compressibility where as in case of crystals obtained from different solvents the ethanol crystals have good flow as well as compression property than other two types of crystals.

### 3. Scanning electron microscopy

Photographs of SEM are shown in figure I. The crystal shape of pure drug is irregular aggregates of small size crystals, whereas the crystals obtained from ethanol having rod shape plate like structure. The shape of acetone crystal is hexagonal and the crystals obtained from chloroform are very irregular in shape and agglomerated with each other.

The figures also show a clear difference in size of crystals. The pure drug, ethanol and acetone crystal are almost same in size where as the chloroform crystals are bigger and not uniform in size.

The changes in morphology of CBZ crystals could be due to variations in face dimensions or the appearance or disappearance of some faces. Under certain conditions of crystallization, one set of crystal faces may be induced to grow faster than others, or the growth of another set of faces may be retarded. The change in crystal shape can be also explained on the basis of modified growth rates of crystal faces of different polarity[7].

### 4. Powder X ray diffraction study

XRDP patterns of the treated and untreated samples for diffraction angles in the range of 5°-90° $2\theta$ are depicted in figure II. Pure drug was identical to that of form III reference standard and to that reported by the International Centre for Diffraction Data: the most providing identification is the absence of peaks from 2° to 10° $2\theta$.

The powder diffraction patterns (pdp) of pure CBZ showed characteristic high intensity diffraction peaks at $2\theta$ values of 15.91°, 19.58°, 23.97°, 24.98°, 27.68◦, and 32.05° that matched the known pdp of CBZ form III

The most providing identification in pdp of ethanol crystal is the presence of peaks in between 2° to 10° $2\theta$ at a diffraction angle 6.14°, 7.93°, 8.70°, 9.39° as well as at 12.30°, 13.16°, 14.02°and 19.91° that matched the known pdp of CBZ form I. It also shows the peak at 15.78°, 24.78°, 27.41°, and 32.00° which are characteristic peak of CBZ form III. So, ethanol crystals were mixer of CBZ form I and III.

The acetone crystals show the presence of peaks in between 2° to 10° $2\theta$ at a diffraction angle 5.00°, 8.92° as well as at diffraction angle 13.06°, 19.47° and 24.79° which are characteristics of CBZ form II. It also shows the peak at 15.83°, 24.79°, 27.21°, and 31.99° which are characteristic peak of CBZ form III. So, acetone crystals were mixer of CBZ form II and III.

The powder diffraction patterns (pdp) of chloroform crystals showed characteristic high intensity diffraction peaks at $2\theta$ values of 5.00°, 8.62°, 13.16°, 18.47°, 19.98◦, 24.36° and 28.24° that matched the known pdp of CBZ Form II.

The PDP of pure drug and chloroform crystals is similar to form III. The PDP of ethanol crystals is similar to mixture of form I & III while PDP of acetone crystal is similar to mixture of form II & III. It is reported that solubility of CBZ polymorphs are like CBZ III> CBZ IV> CBZ I> CBZ II that is theoretically and practically CBZ III> CBZ I> CBZ II. Form I is the metastable form of CBZ under ambient conditions. However, on storage form I will tend to convert to the more stable form III. The two forms differ in their solubility evidently due to differences in their free energy. Further the peaks in case of crystals prepared by adding hydrophilic polymer are not much intense, broader and their corresponding $2\theta$ value is decrease for such peaks which indicates the decrease in crystallinity as compare to pure drug.

### 5. Differential scanning calorimetry (DSC) study

Results of the DSC thermograms are shown in figure III. DSC thermograms of CBZ polymorph form I show no transformation and melts between 189 and 193°C. Form II does not melt, but a transformation occurs between 135 and 170°C and the new phase then melts between 188 and 192°C. The large transformation range is due, in part, to higher initiation temperatures for crystals with fewer defects as determined by observing populations of crystals during heating. Form III melts and crystallizes to a new form nearly simultaneously between 162 and 175°C. The new form subsequently melts between 189 and 193°C [8]. Form IV shows melting and partial crystallization to a new form between 178 and 187°C, significantly higher than the transition temperatures of forms II or III. This is followed by further crystallization to produce a material that then melts between 190 and 192°C[9].

DSC trace of pure CBZ shows a polymorphic transition with two endotherms at around 176°C and 194°C. It is well known that CBZ exhibits enantiotropic polymorphism, i.e. there exists a transition temperature below the melting point of either of polymorphs at which both these forms have the same free energy [10]. Above the transition temperature, the higher melting Form I has the lower free energy and is more stable. Below the transition temperature, however, the lower melting Form III is more stable since it has lower free energy. The transition temperature of CBZ enantiotropic forms has been reported to be around 71 ◦C. Hence at room temperature, Form III is the most stable form and is the one possessed by most commercially available CBZ. In case of acetone and ethanol crystal the one more endotherm is around 60°C to 90°C. On heating CBZ dehydrate it loses its water of crystallization and

shows a dehydration endotherm between 50 and 90 °C. The presence of this endotherm was considered as an indication of the dihydrate formation [11, 12].

**6.Fourier Transform Infrared Study (FTIR)**

The FTIR spectra of forms are given in figure IV. The FTIR spectra of CBZ corresponded with those previously reported for Form III by various researchers. Characteristic bands of polymorph III were found at 3466 and 3161 $cm^{-1}$ (–NH valence vibration), 1677 $cm^{-1}$ (–CO–R vibration), 1605 and 1595 $cm^{-1}$ (range of –C=C– and –C=O vibration and –NH deformation). In case of chloroform crstals and pure drug there is a sharp peak at 3500 $cm^{-1}$, the same as in the spectrum of anhydrous CBZ. The IR spectrum from the CBZ dihydrate shows other absorption bands in the regions of 3200–3500 $cm^{-1}$, and there is no sharp peak at 3500 $cm^{-1}$ [13].

**7. Saturated solubility study**

Result of the saturated solubility study is shown in table III. Solubility of CBZ was found to be 4.15 mg/100ml while improvement in solubility was observed with ethanol crystals where as in case of acetone and chloroform crystals solubility decrease slightly.

This difference in solubility can be explained by the different physicochemical properties of the crystals. Saturated solubility study data suggest that the ethanol crystals have a highest solubility than any other type of crystals. This finding is extremely important from a stability aspect. Form I is the metastable form of carbamazepine under ambient conditions. However, on storage form I will tend to convert to the more stable form III. The two forms differ in their solubility evidently due to differences in their free energy.

**8. In vitro dissolution study**

The result of the in vitro dissolution study is shown in table IV. The results showed a marked difference in dissolution behavior of the crystals and pure drug. Results showed that the amount of CBZ dissolved from ethanol crystals was considerably higher than others. The highest dissolution rate was observed for the crystals recrystallized from ethanol and that is 73.86% at 60 min.

The solubility of all the batches ethanol crystals was found to be higher almost double when compared to the pure drug. Since the bioavailability of carbamazepine is limited only by its dissolution rate, even a small increase in dissolution will result in a large increase in its bioavailability.

The results from the dissolution, DSC, and powder X-ray diffraction studies provide an insight into the long-term stability of these dispersions. It can be said that the crystallization conditions and the medium used have major effect on CBZ crystals habit modification under ambient conditions. The crystals showed significant changes in the shape, dissolution rate, XRD patterns and DSC curves. This suggests that the newly developed crystals of CBZ with different solvents exist in different crystalline modification facilitating significantly improved dissolution rate as compared to pure CBZ. There are enough references[14] available in the literature wherein it has been proved that in vitro dissolution data are good predictor of in vivo performance in reality. Therefore, it can be safely concluded that the improvement obtained in the present study in the modified crystals will give better bioavailability and better therapeutic activity clinically. But the stability study at higher temperature and high humidity level may show some physical changes probably due to some phase transitions but retaining the chemical identity. The effect of such changes in reality needs to be explored in actual situations, if any.

**Table I: Results of flow property**

| | **Angle of repose** | **Inference** |
|---|---|---|
| Pure drug | 23.37 | Excellent flow property |
| Ethanol crystals | 34.37 | Good flow property |
| Acetone crystals | 31.60 | Good flow property |
| Chloroform crystals | 40.59 | Poor flow property |

**Table II: Results of compaction behavior**

| | **Carr's index** | **Hausners' ratio** | **Inference** |
|---|---|---|---|
| Pure drug | 11.54 | 1.1304 | Poor compressibility |
| Ethanol crystals | 31.03 | 1.4500 | Good compressibility |
| Acetone crystals | 20.00 | 1.2500 | Poor compressibility |
| Chloroform crystals | 36.84 | 1.5833 | Good compressibility |

**Table III: Results of solubility data**

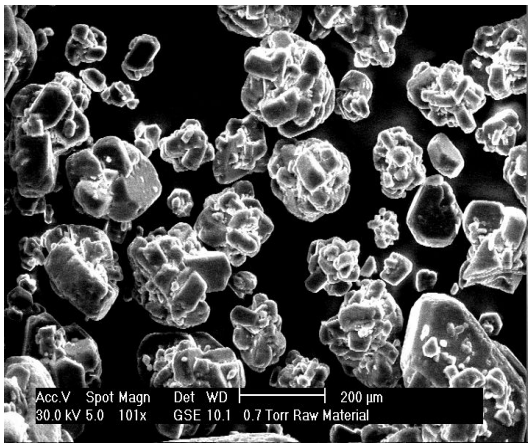
| | **Solubility (mg/100ml)** |
|---|---|
| Pure drug | 4.15 |
| Ethanol crystals | 4.34 |
| Acetone crystals | 4.01 |
| Chloroform crystals | 3.51 |

**Table IV: Results of % Cumulative drug release**

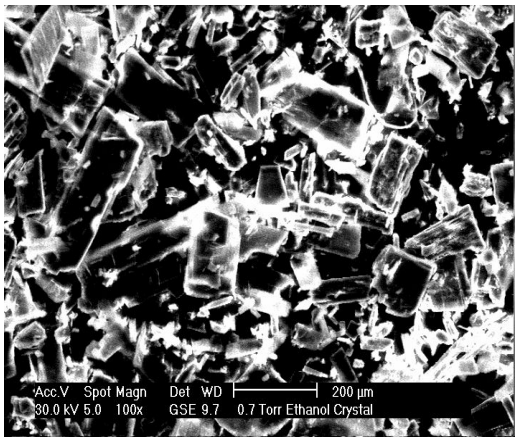
| **Time (min)** | **% Cumulative drug release** | | | |
|---|---|---|---|---|
| | Pure drug | Ethanol crystals | Acetone crystals | Chloroform crystals |
| 0 | 0.00 | 0.00 | 0.00 | 0.00 |
| 10 | 19.50 | 43.91 | 14.68 | 23.51 |
| 20 | 22.51 | 49.82 | 18.72 | 25.86 |
| 30 | 24.54 | 61.67 | 19.99 | 32.53 |
| 40 | 26.91 | 65.34 | 22.54 | 38.37 |
| 50 | 33.59 | 69.23 | 25.60 | 42.01 |
| 60 | 42.69 | 73.86 | 38.60 | 47.02 |

**Figure I: SEM micrograph of different crystals**

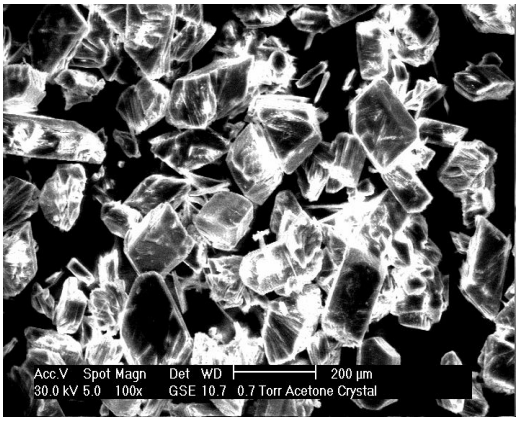
**(A) Pure drug**




**(B) Ethanol crystal**




**(C) Acetone crystals**




**(D) Chloroform crystals**

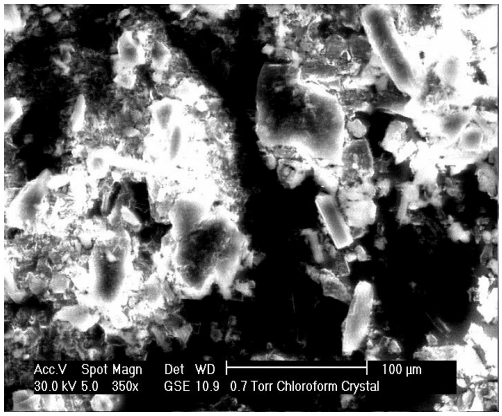
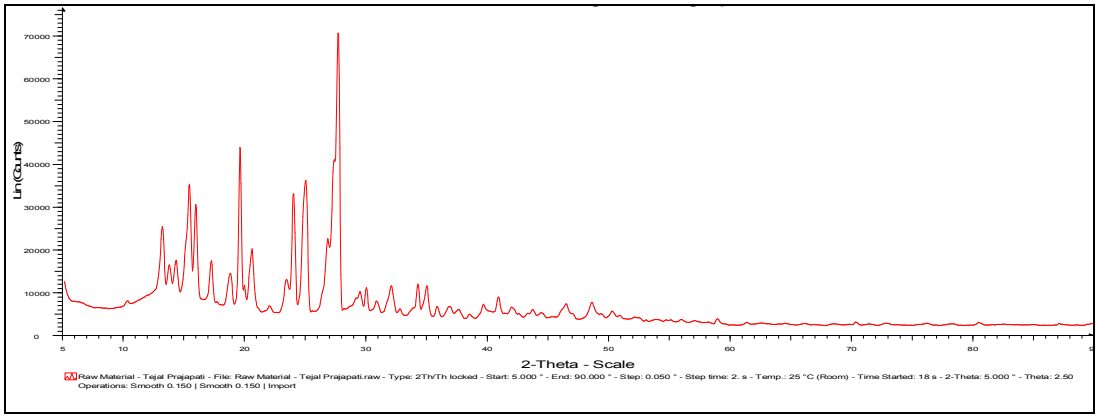
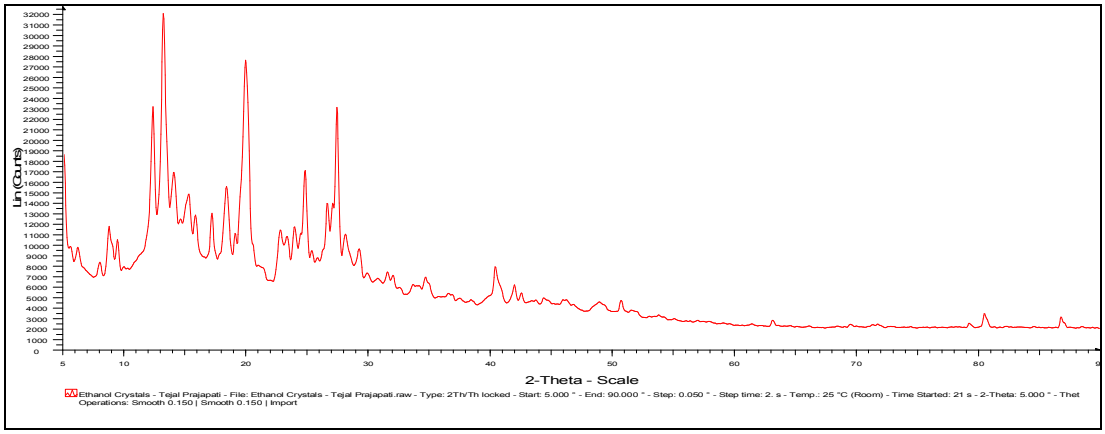


**Figure II: XRD spectras of different crystals (A),(B),(C),(D)**

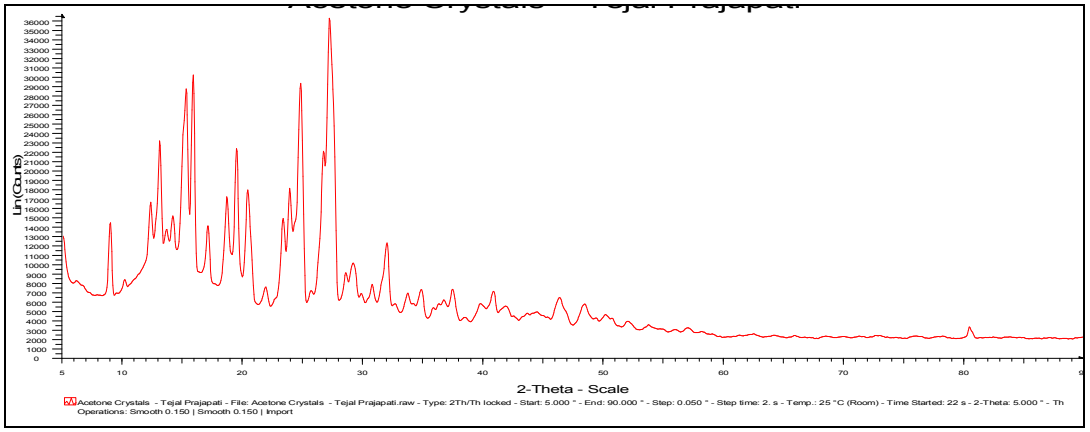
**(A) Pure drug**




**(B) Ethanol crystal**




**(C) Acetone crystal**



**(D) Chloroform crystal**

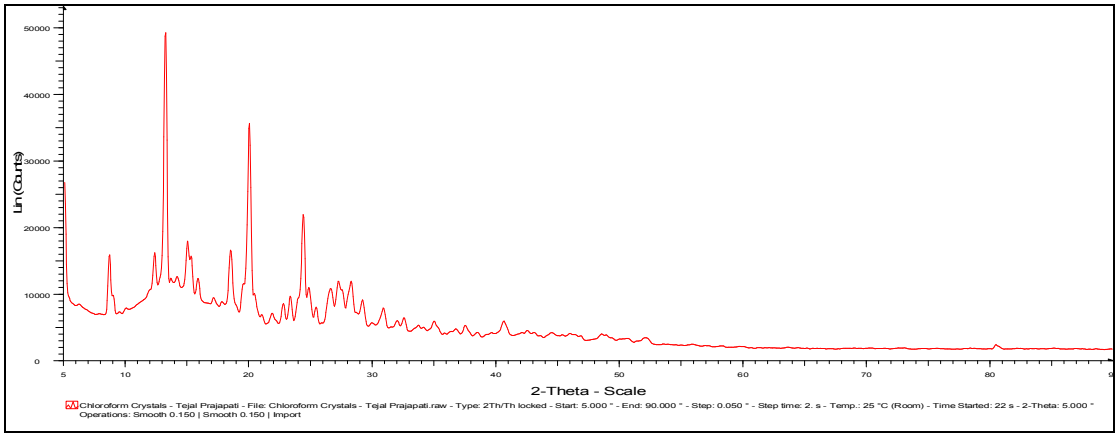
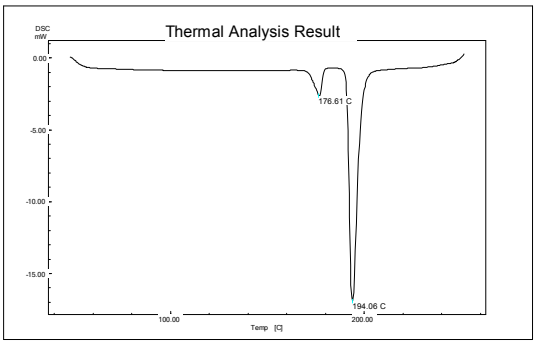
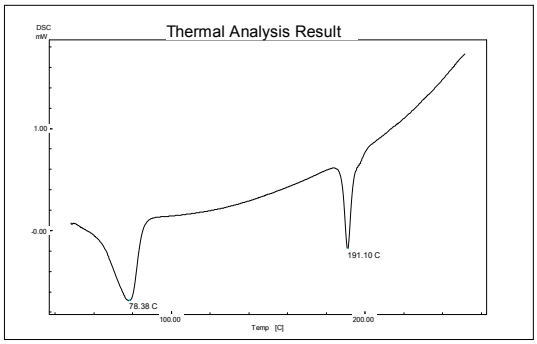



**Figure III: DSC spectras of different crystals**

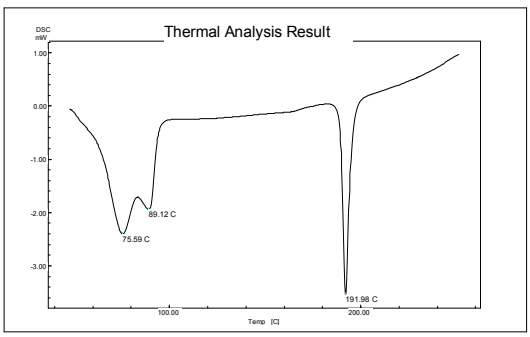
**(A) Pure drug**




**(B) Ethanol crystals**




**(C) Acetone crystals**




**(D) Chloroform crystals**

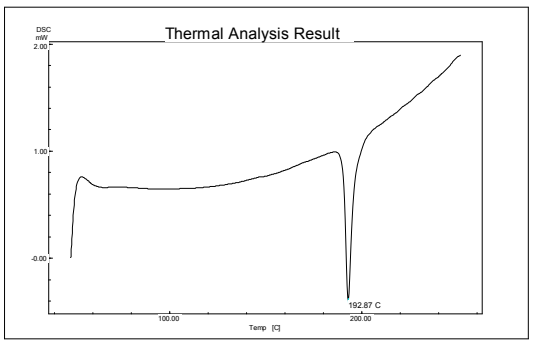
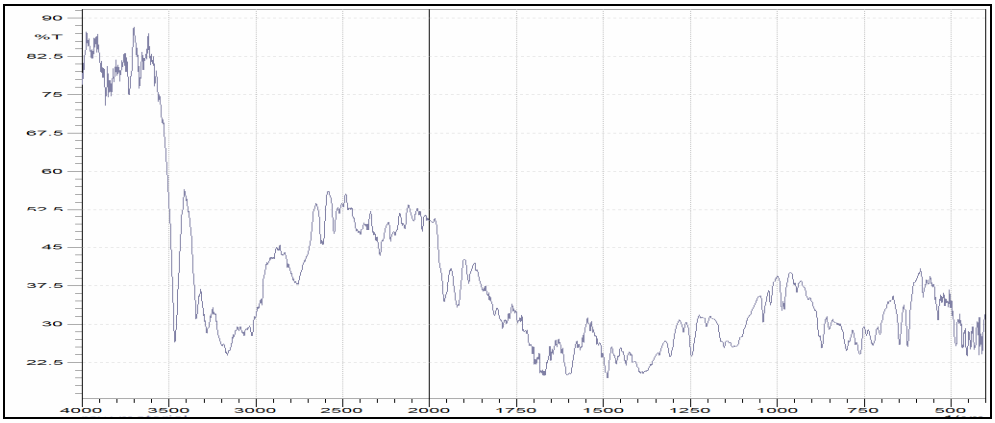
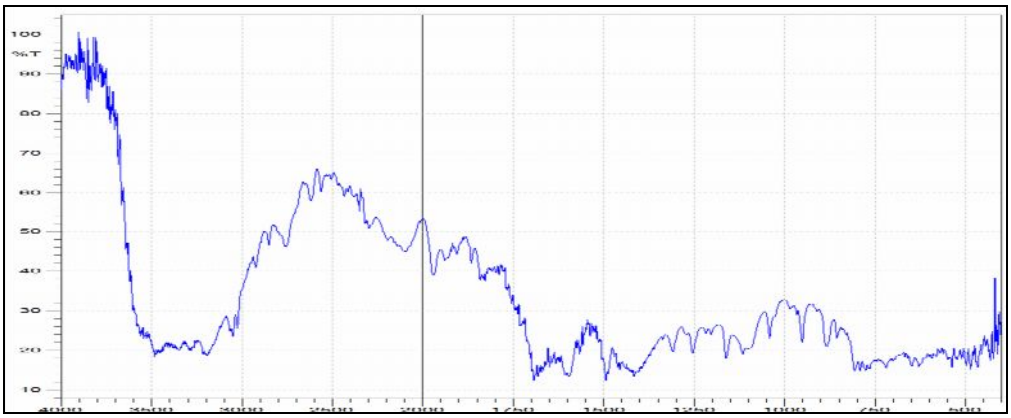


**Figure IV: FTIR spectra of different crystals (A),(B),(C),(D)**

**(A) Pure drug**




**(B) Ethanol crystals**




**(C) Acetone crystals**


**(D) Chloroform crystals**

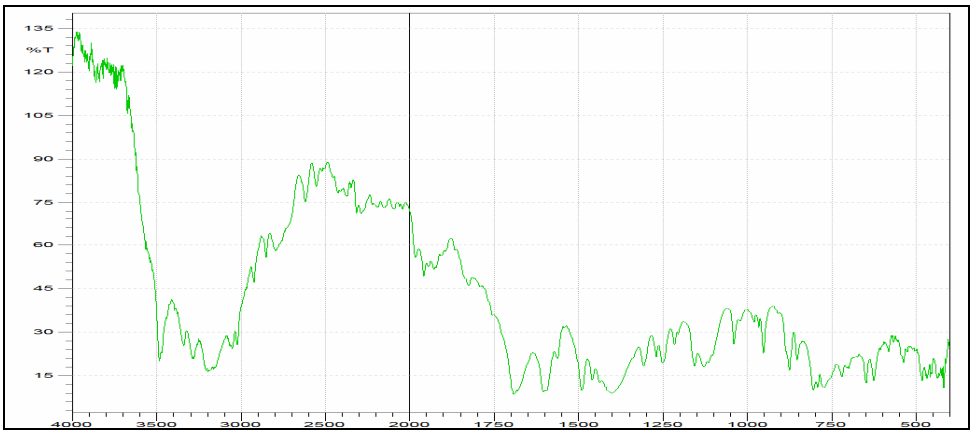



**Figure V: %CDR of different crystals**

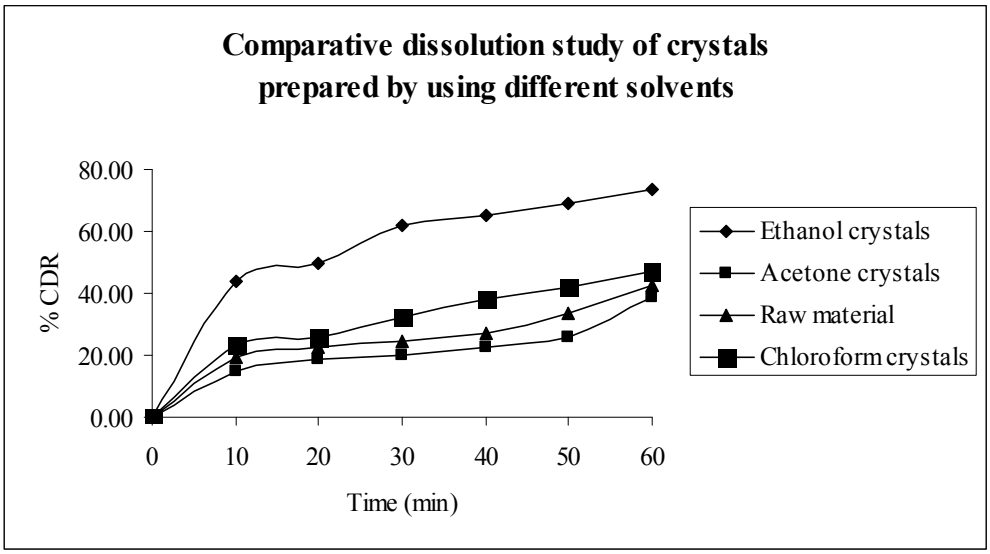
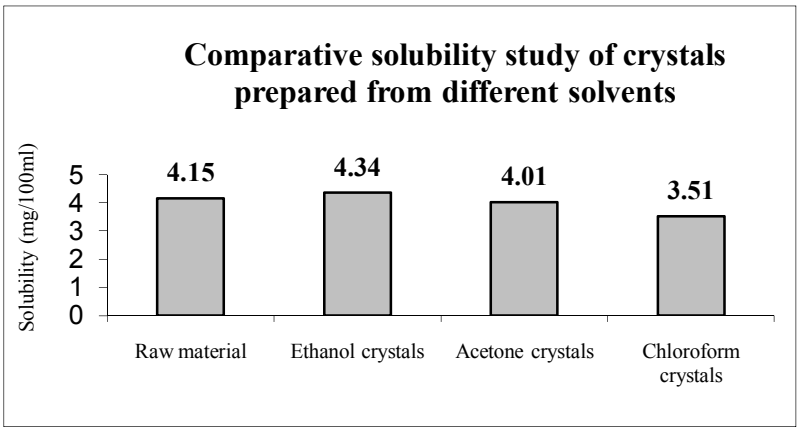



**Figure VI: graph of Comparison of solubility data**



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