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Influence of hydrophilic polymers on crystal property and solubility characteristics of Carbamazapine

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Abstract: Influence of polymers 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 polyethylene glycol 8000, Hydroxy propyl methyl cellulose (HPMC) and poloxamer 407 on the crystalline modification and subsequently the solubility of carbamazepine immediate release tablet by in vitro dissolution studies. Solubility enhancement is carried out by using different hydrophilic additives like HPMC (5cps) and PEG 8000. The physical state of the drug was determined using SEM, DSC, PXRD and FTIR. Crystals obtained from ethanol at room temperature by using PEG 8000 (drug to polymer ratio 1:0.75) and HPMC (drug to polymer ratio 1:0.25) as hydrophilic additive, showed highest solubility and better release profile.
Key words: Crystalline property, Solubility enhancement, Hydrophilic additive

Introduction

Carbamazepine is a commonly used anticonvulsant drug and belongs to class II of the biopharmaceutical classification system. Compounds in this category have high intestinal permeability and low water solubility. Subsequently, the bioavailability of such compounds is limited by their solubility in water[1].

Carbamazepine is known to exist in four different polymorphic forms[2]. An understanding of the polymorphism of carbamazepine and the influence of various excipients on the polymorphic transitions is critical to the development and performance of its solid dosage forms and ultimately its bioavailability. Otsuka et al. showed that hydroxypropylcellulose inhibited the dihydrate formation of carbamazepine[3]. The presence of hydroxypropyl methylcellulose in sustained release carbamazepine tablets was also shown to affect the dissolution of the drug due to its inhibitory effect on dihydrate formation[4]. The solubility of the anhydrous carbamazepine is approximately twice that of its dihydrate[5]. However, the anhydrous form once in contact with water converts to the dihydrate form[6, 7].

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[8]. Therefore the main objective of the present study was to investigate role of PEG 8000 and HPMC on the crystalline & solubility characteristics of carbamazepine.

Materials and methods

Instruments and Chemicals

Carbamazepine was a gift sample from Nirman Pharma, Vapi, Gujarat, India. PEG 8000 and HPMC low viscosity grade (5cps) were purchased

from S. D. fine chemicals Pvt Ltd, Mumbai, India. Other chemicals used in this research work were of analytical grade. Deionized distilled water was used throughout the study.

Experimental method

Preparation of CBZ crystals

Crystals were obtained of drug and polymer in different ratios by dissolving them in ethanol and evaluated for various physicochemical parameters. The hydrophilic polymer was dissolved in above solution. Drug polymer ratio for different batches is given in **table I.**

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.

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

Where,

h: Height of the powder heap

r: Radius of the powder heap

2. Compression behavior

It is described 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

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 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[9]. 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 with reference to a calibration curve.

Results & Discussion

1. Flow property study

The result of the flow property study is shown in table II. Results indicated that the pure drug has excellent flow property while batch H1 prepared with drug:

polymer ratio of 1:0.25 has the good flow property when compared to other batches.

2. Compression behavior

Results of the compression behavior are shown in table III. Results showed that pure drug has poor compressibility where as H1 batch crystals have good compression property. P2 and X3 batch crystals possess poor compression property.

From the results obtained with flow property study and compression behavior**,** it was seen that batch H1 with drug polymer ratio of 1: 0.25 has the good flow property and good compressibility while other batches pure drug, P2 and X3 has excellent flow property but having poor compressibility. So, in terms of flow property and compressibility H1 batch is considered good when compared to others.

3. Scanning electron microscopy (SEM) study

Photographs of the SEM are shown in figure I. Photographs of SEM suggested that the addition of hydrophilic polymers has considerable effect on the shapes and size of CBZ crystals. The crystal shapes of pure drug is irregular aggregates of small size crystals, whereas the crystals obtained after adding HPMC is plate like flaky and somewhat bigger in size. The shape of crystal obtained by adding PEG 8000 and poloxamer 407 are irregular in shape and smaller in size having uniform size distribution.

The changes in morphology of CBZ crystals in case of scanning electron microscopy (SEM) 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[11].

4. Powder X ray diffraction study

X-ray spectra of different batches are shown in figure II. Spectra showed that commercial raw material (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° *2θ*. The powder diffraction patterns (PDP) of pure CBZ showed characteristic high intensity diffraction peaks at 2*θ* 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 H1 batch crystals show the presence of peaks in between 2° to 10° *2θ* at a diffraction angle 6.19°, 8.90° as well as at diffraction angle 12.32°, 13.17°, 18.51° and 24.70° which are characteristics of CBZ form I[12]. It also shows the peak at 15.20°, 27.22°, 27.52°, and 33.66° which are characteristic peak of CBZ form III.

The P2 batch crystals show the presence of peaks in between 2° to 10° *2θ* at a diffraction angle 6.21°, 8.74° as well as at diffraction angle 12.43°, 13.16°, 14.18° 19.18° and 23.34° which are characteristics of CBZ form I. It also shows the peak at 15.31°, 27.27°, 27.52°, and 32.04° which are characteristic peak of CBZ form III.

The X3 batch crystals show the presence of peaks in between 2° to 10° *2θ* at a diffraction angle 6.22°, 8.75° as well as at diffraction angle 12.38°, 13.16°, 14.21° 18.61° and 23.36° which are characteristics of CBZ form I. It also shows the peak at 15.32°, 27.28°, 27.52°, and 30.28° which are characteristic peak of CBZ form III.

Powder X-ray diffraction study showed that pure drug matched the spectra obtained with CBZ form III, while batches H1, P2 & X3 is a mixture of form I & 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 *2θ* 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 form I (Pure Drug) showed 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. 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. 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.

Differential scanning calorimetry results showed that pure CBZ has 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[12]. 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[13]. Hence at room temperature, Form III is the most stable form and is the one possessed by most commercially available CBZ.

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). All the sample except H1 batch crystals and Pure drug there is a sharp peak at 3500 cm^{-1}. 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}.

From figure it was observed that with the use of hydrophilic polymer during crystallization the magnitude of endotherm is decreased and it becomes less sharp and intense. Moreover the melting point of pure drug is 194°C which becomes 190°C, 187.97°C and 186.65°C for H1, P2 and X3 batch crystals respectively. That suggested, drug becomes less crystalline with use of hydrophllic polymers and XRD data also supports this.

Figure IV shows presence of distinct peaks characteristic of crystallinity. The samples of pure drug and of the crystals prepared from ethanol by using various hydrophilic polymer exhibited identical IR spectra which indicated that the altered XRDP spectra for these samples were not associated with changes at the molecular level.

7. Saturated solubility study

Result of the saturated solubility study is shown in table IV. Solubility of CBZ was found to be 4.15 mg/100ml while improvement in solubility was observed with all other types of crystals obtained. In case of H1 and X3 batch crystals solubility is increased up to two fold while P2 batch crystals have increment slightly less than two fold.

Difference in solubility can be explained by the different physicochemical properties of the crystals. Saturated solubility study data suggest that the crystals obtained in presence of hydrophilic polymer have a very much higher solubility than pure drug.

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 V. Above figure shows the comparison of dissolution profiles of pure CBZ and the crystals obtained in presence of hydrophilic polymer. The results showed a marked difference in dissolution behavior of the crystals and pure drug. Results showed that the amount of CBZ dissolved from crystals obtained in presence of hydrophilic polymer was considerably higher than pure drug. The highest dissolution rate was observed for the crystals of batch H1 and X3 and that is 96.46% and 95.64% at 60 min respectively.

The solubility of all the batches H1, P2 & X3 was found to be higher as compared to the pure drug while the solubility of H1 was highest compared to all other batches. The solubility of H1 batch was more than double when compared to the pure drug. The marked enhancement of the dissolution of CBZ crystallized in the presence of hydrophilic polymer can be attributed to the absorption of these polymers by CBZ particles, which increased their wettability and ultimately the dissolution. Since the bioavailability of CBZ is limited only by its dissolution rate, even a small increase in dissolution will result in a large increase in its bioavailability. Based on the results from the dissolution studies it is evident that addition of hydrophilic polymer can significantly improve the dissolution and subsequently the bioavailability of CBZ. This enhancement of solubility may also be due to the modified crystal habit and the presence of polymorphic form of drug which has higher solubility. From amongst three polymer the HPMC 5cps and poloxamer 407 gives better result than PEG 8000. In case of both the polymer the drug release was increase from 42% to around 95%. So, addition of hydrophilic polymer gives positive result to solubility enhancement.

The results from the dissolution, DSC, and powder X-ray diffraction studies provide an insight into the long-term stability of these dispersions. Identification of the factors leading to improved dissolution in solid dispersions can help the formulator to anticipate any stability problems that can occur during the storage of these dispersions. Most importantly, knowledge of the mechanism of enhanced dissolution by these polymeric carriers will help the formulator to choose the formulation with optimum solubility and long term stability. Moreover, polymers such as HPMC and povidone which is commonly as a binder solution can alter the solid state characteristics of the drug during processing. Hence extreme care should be undertaken and the necessary studies performed to detect any solid state transformation when using such systems.

Table I: Preparation of batches with additives

Name of polymer	Batch code	Drug to polymer ratio
HPMC (5cps)	H1	1:0.25
	H2	1:0.50
	H3	1:0.75
	H4	1:1
	H5	1:1.25
PEG 8000	P1	1:0.50
	P2	1:0.75
	P3	1:1
	P4	1:1.25
	P5	1:1.50
Poloxamer 407	X1	1:0.25
	X2	1:0.50
	X3	1:0.75
	X4	1:1
	X5	1:1.25

Table II: Results of flow property

Batch	Angle of repose	Inference
Pure drug	23.37	Excellent flow property
H1 crystals	31.16	Good flow property
P2 crystals	21.80	Excellent flow property
X3 crystals	23.96	Excellent flow property

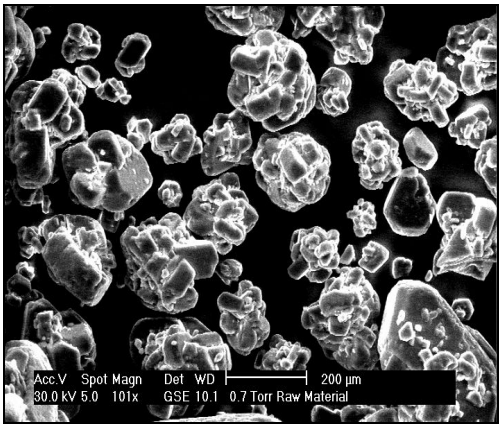
Table III: Results of compaction behavior

Batch	Carr's index	Hausners' ratio	Inference
Pure drug	11.54	1.1304	Poor compressibility
H1 crystals	38.18	1.6176	Good compressibility
P2 crystals	28.26	1.3939	Poor compressibility
X3 crystals	17.14	1.2069	Poor compressibility

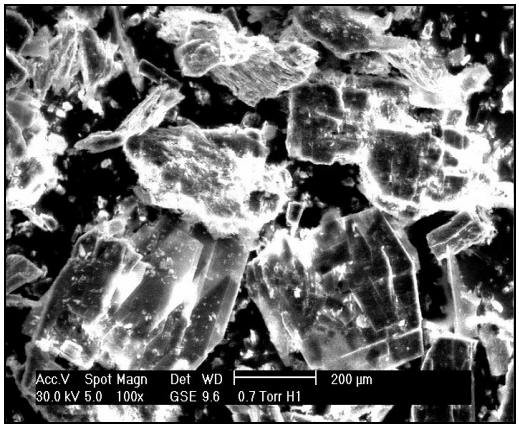
Table IV: Results of saturated solubility studies

Batch	Solubility (mg/100ml)
Pure drug	4.15
H1 crystals	8.95
P2 crystals	7.03
X3 crystals	9.18

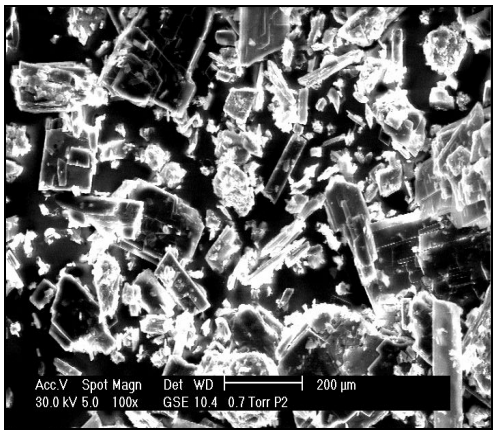
(A) Pure drug



(B) H1 crystals



(C) P2 crystals



(D) X3 crystals

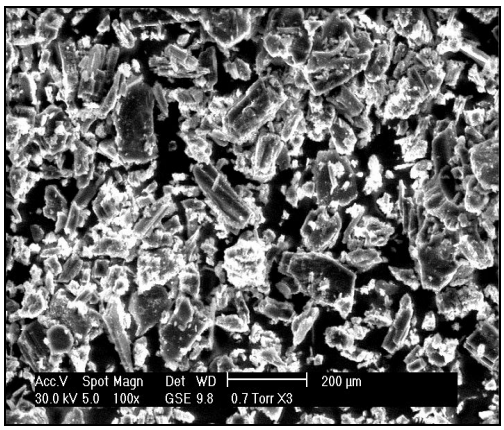
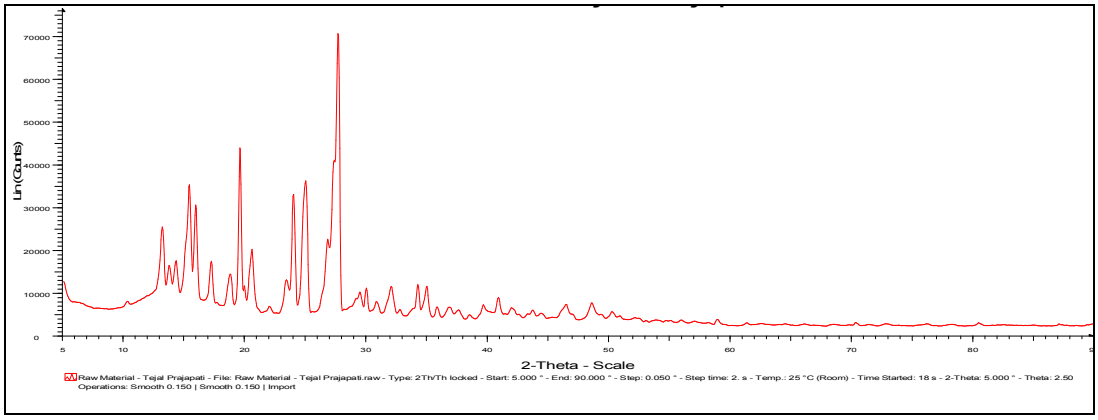
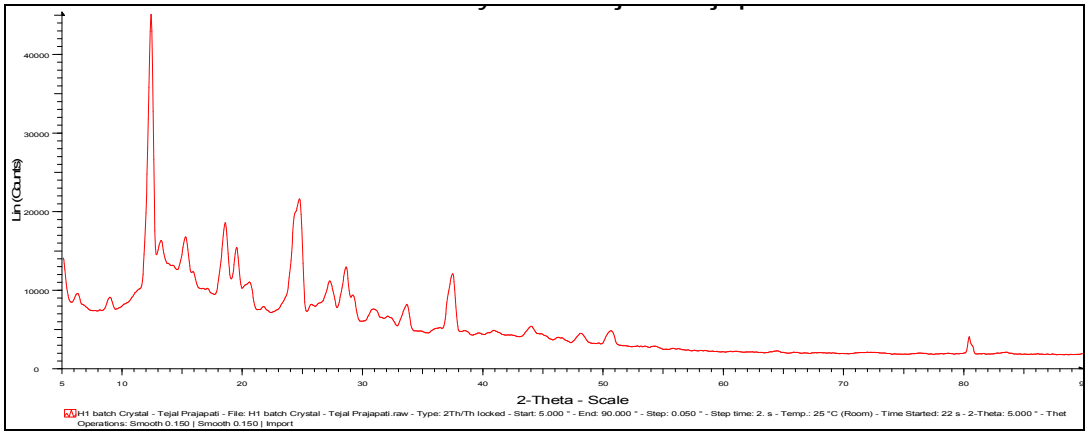


Figure I: SEM micrograph of crystals prepared using hydrophilic polymers

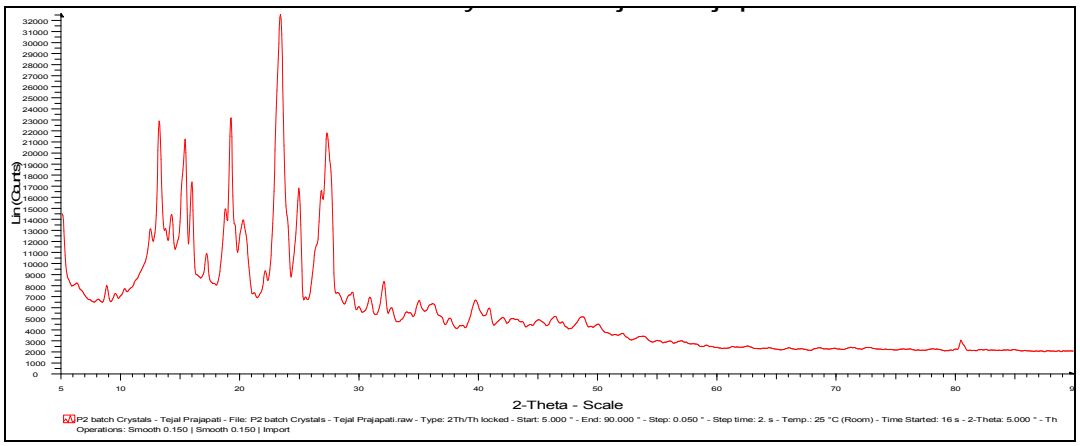
(A) Pure drug



(B) H1 crystals



(C) P2 crystal



(D) X3 crystals

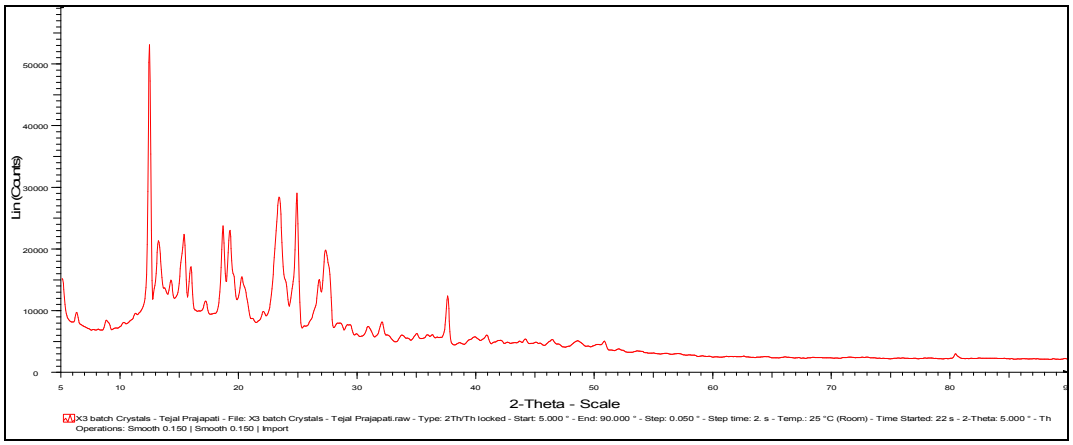
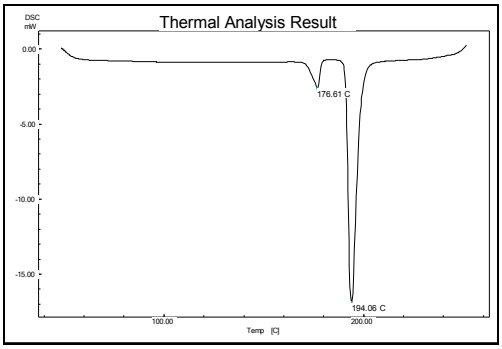
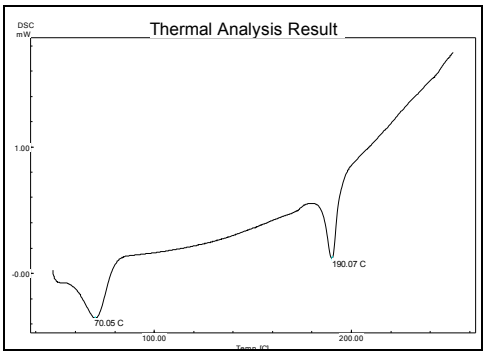


Figure II: X ray spectras of crystals prepared using hydrophilic polymers

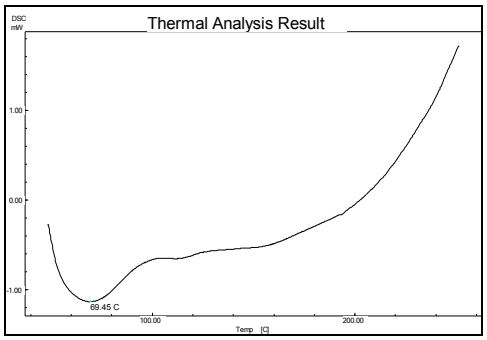
(A) Pure drug



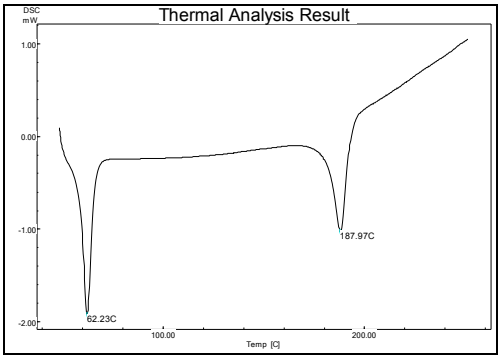
(B) H1 crystals



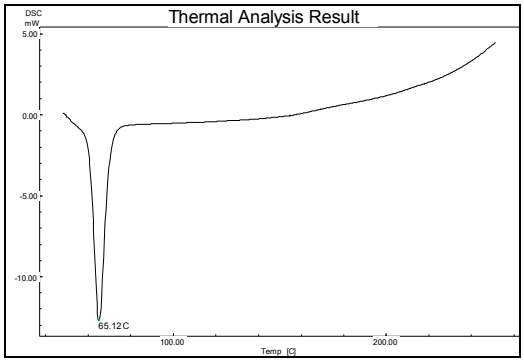
(E) HPMC (5cps)



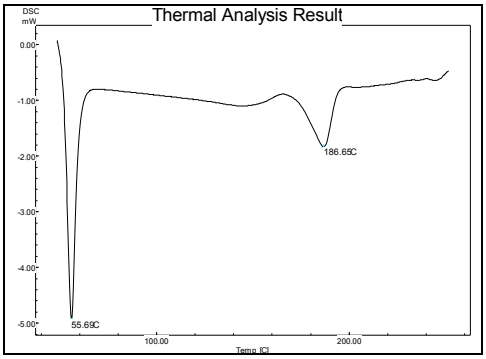
(C) P2 crystals



(F) PEG 8000



(D) X3 crystals



(G) Poloxamer 407

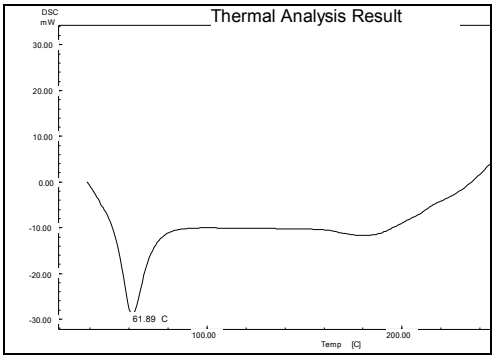
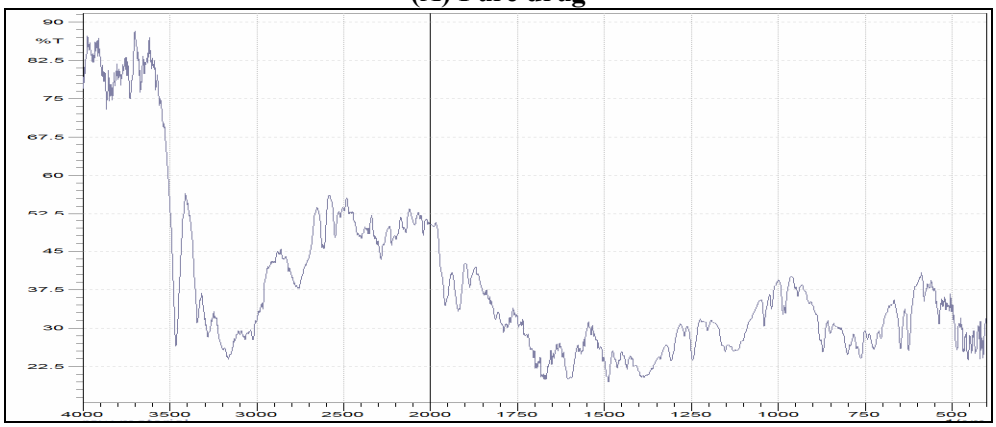
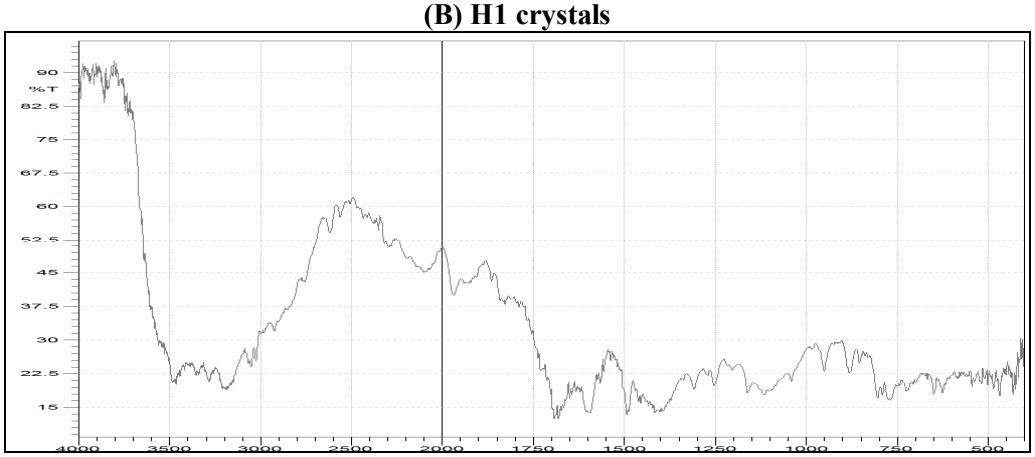


Figure III: DSC spectras of crystals prepared using hydrophilic polymers

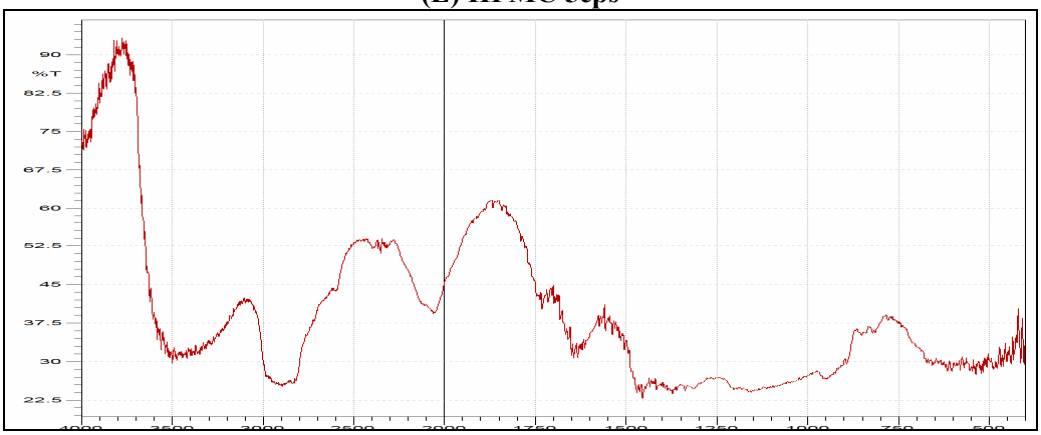
(A) Pure drug



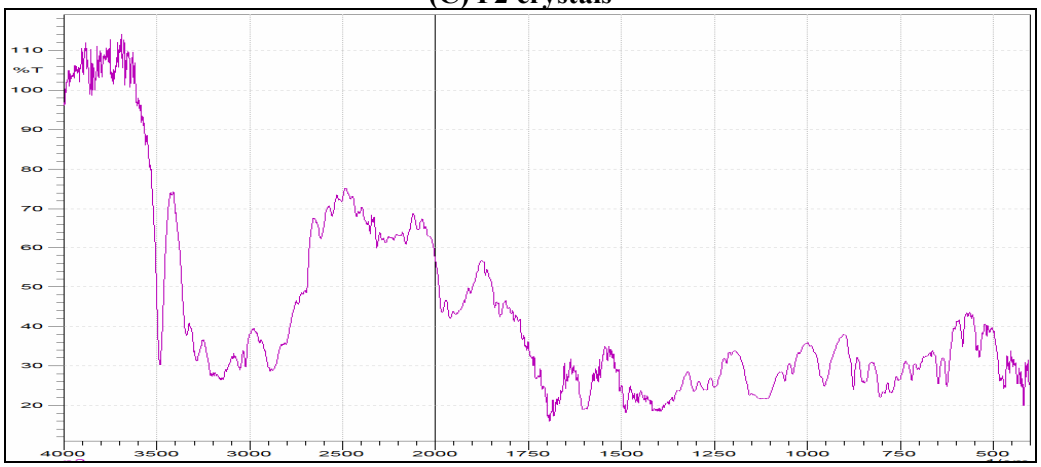
(B) H1 crystals



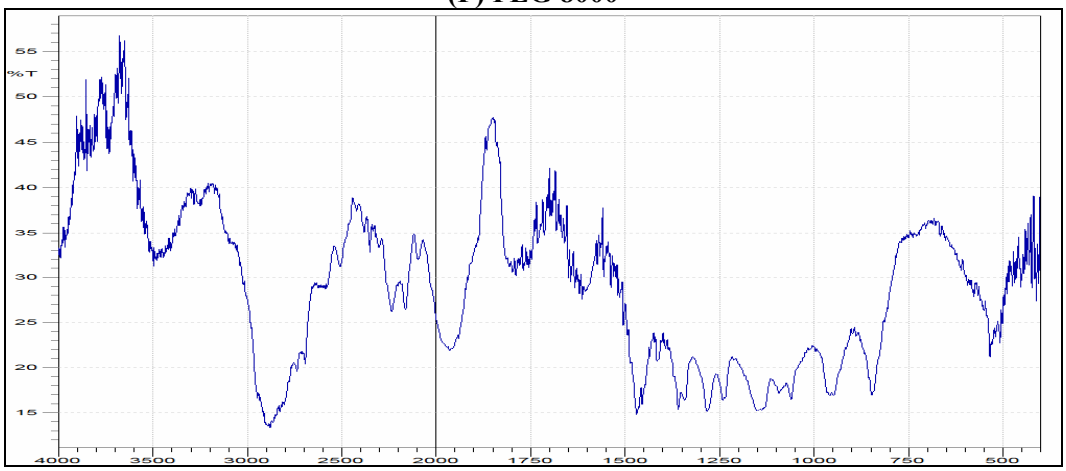
(E) HPMC 5cps



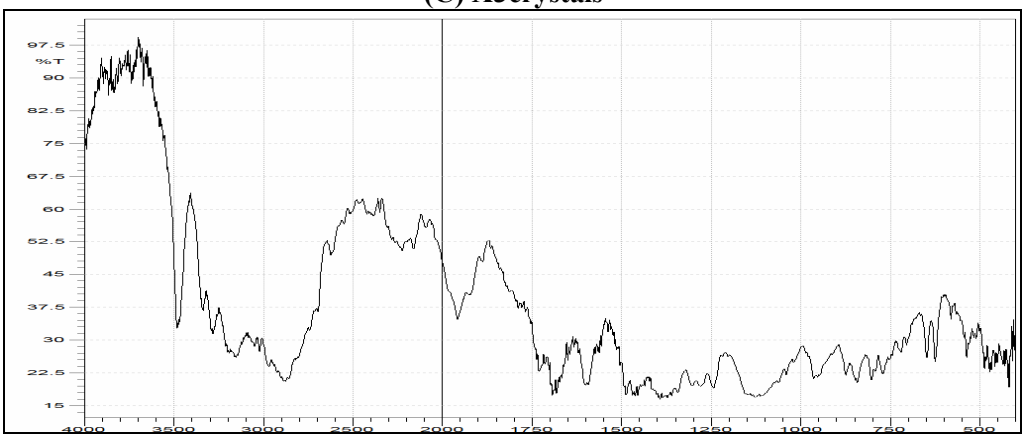
(C) P2 crystals



(F) PEG 8000



(C) X3crystals



(G) Poloxamer 407

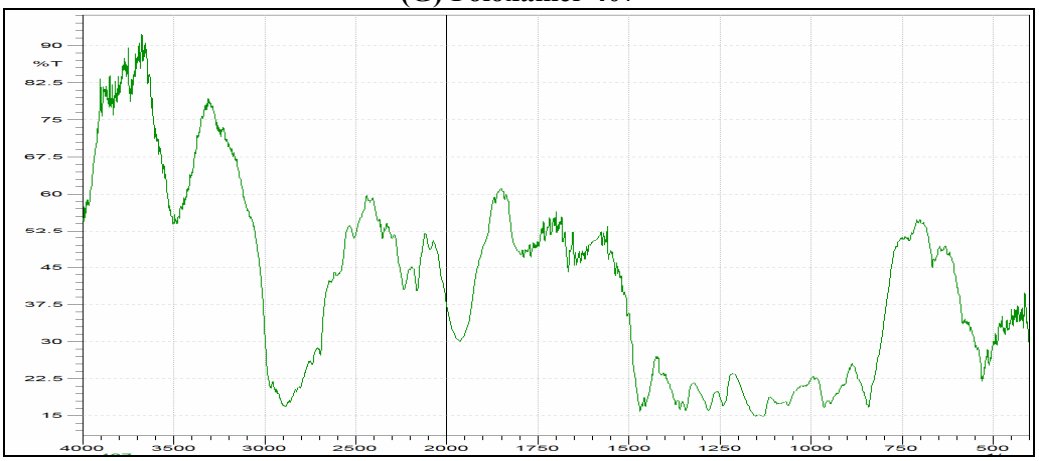


Figure IV: FTIR spectras of crystals prepared using hydrophilic polymers

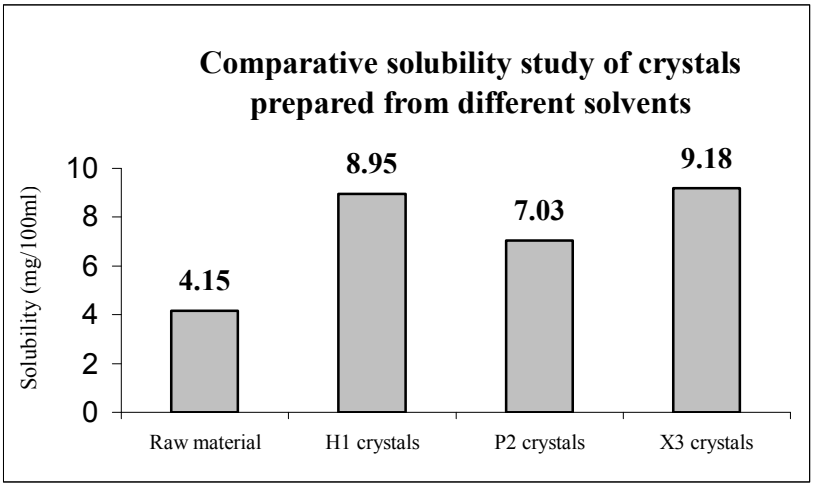


Figure V: Comparison of solubility data of best batches prepared using hydrophilic polymer

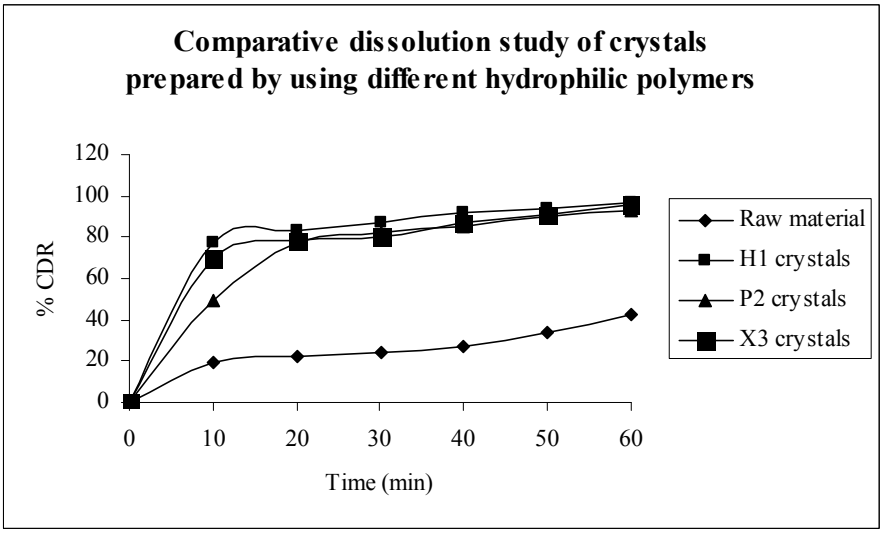


Figure VI: Comparison of best batches prepared using hydrophilic polymers

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