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Advances in Bioresearch

ORIGINAL ARTICLE

Application of Micellar Solubilization and Microcrystallization Technique for Solubility Enhancement of Etodolac

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ABSTRACT
Poor water solubility of a drug is one of the major hurdles in formulation development of many drugs. Micellar Solubilization and Microcrystallization has proven as a suitable means to overcome aqueous solubility of BCS class II drugs. Etodolac is one of the drugs having limited aqueous solubility, but the non-steroidal anti-inflammatory drug has proven its importance. The current study aims to improve the poor water solubility of Etodolac by using a Micellar Solubilization and Microcrystallization procedures where the efficiency of surfactant has been tested at cloud point temperature and solvent change method has been adopted for the microcrystallization technique. The techniques were found suitable means for the solubility enhancement of etodolac.
Keywords; *Etodolac, Solubility, Surfactant, Micelle, Solvent change.*

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INTRODUCTION

Solubility, the maximum amount of a substance that can be completely dissolved in a specific solvent, significantly impacts the pharmaceutical industry and is crucial for drug distribution. [1-3] However, issues like slow dissolution, impurities, and crystalline solid heterogeneity can cause discrepancies in reported values. [4, 5]

Solubility is a crucial aspect of drug delivery, with various techniques being explored to improve its solubility, but each method has its own drawbacks. [6,7] The molar solubilization capacity (χ) and micelle water partition coefficient (P) are used to evaluate the solubilization capacity of a molecule by a surfactant. [8-10]

Solubility is a crucial factor in the development of dosage form, with water-loving drugs adsorbing on micelle surfaces [11], with intermediate solubility drugs located at intermediate positions. [12].

Drug microcrystals, ranging from 1-10μm in size, are crystalline crystals made up of 100% drug without carrier material.[13,14] They can be produced through milling, precipitation, and solvent evaporation techniques. Stabilization and solubility are crucial for creating finely dispersed, precipitated drugs in ointments [15].

MATERIAL AND METHODS

Solubility study and Analytical characterization of drug

The etodolac has limited water solubility to 322.28μg per ml of water. [16-17]

Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM), X-Ray powder Diffractometry (XRPD)are the most significant tools used for the analytical characterization of drug sample and further prepared formulations. [18-20]

Solubility Enhancement

Micellar Solubilization [21-23]

Micellar solubilization of Etodolac was achieved by cloud point method, in which the pure drug was solubilized in surfactant solution at room temperature and cloud point temperature. Aqueous Tween 80

surfactant solutions of 1, 5, 10 and 20 %w/v were used as solubilization solvent. The Tween 80 solution (10 ml) was taken in centrifuge tube, heated in a water bath up to cloud point temperature and excess amount of drug was added under continuous stirring, solution was cooled to room temperature and the solubility of drug was estimated. Drug solubility in all the surfactant solutions was also determined at room temperature. Samples were kept under shaking at room temperature using rotary shaker for 24 hours to attain equilibrium. The aliquots of these samples were centrifuged by using Remi centrifuge machine and filtered through a 0.45µm nylon membrane filter (Millipore Millex-HN), and absorbance was taken by using UV- VIS spectrophotometer at λ-max 276 nm after its dilution from 1ml to 100 ml by using water as blank. Solubility studies were performed for all surfactant solutions at room temperature in triplicate**.** Each formulation so prepared is abbreviated as Etodolac Micellar Solubilized formulation (EMS).

Microcrystallization by Solvent change method [24,25]

Drug was simultaneously added into methanol (EMC1) and subjected for sonication till maximum solubility was achieved. Above solution were heated separately to boiling point of that solvent in electrical water bath. The drug solution was poured quickly into water maintained at 20°C under continuous stirring with mechanical stirrer. After 45 minutes of stirring, micro crystals formed and were separated from the solution by 0.4µm filter through filtration assembly. Micro crystals were dried at 50°C for 2 hours**.** The same procedure is repeated for ethanol (EMC2).

Characterization of formulation

The formulations so prepared were characterized for the particle analysis [26-27], production yield, drug content, solubility study. Analytical characterization of prepared formulations is done by using FTIR, DSC, XRD and SEM and the outcomes were compared with the preformulation results.

FT-IR was employed to characterize the possible interactions between the drug and the carrier in the solid state on a FT-IR spectrophotometer by the conventional KBr pellet method. The spectra were scanned over a frequency range 4000-400 cm-1. The characteristic bands of the drug are reported.

DSC Thermal analysis as adopted to study the possibility of any interaction between the drugs and the carriers during preparation of formulation. DSC studies were carried using hermetically sealed aluminum pan and a flow of nitrogen used as purging gas. The required Samples were sealed in flat bottom aluminum pans by using pan crimper before heating under nitrogen flow. An unfilled aluminum pan was used as reference. DSC run at 20°C per min.

SEM has helped to capture the images at different magnification where the sample was mounted on a SEM specimen stub. Sample coated with thin layer of gold under vacuum. Sample stub kept in SEM chamber and operated at 10 kV.

XRPD were recorded using X-ray Diffractometer with Cu as target filter having a voltage/current 40 (kV) /30 (mA) at a scan 6o/min. The sample was analyzed at 2θ angle scan range 10-80o. Preset time was 0.2 sec and acquisition time was1h.

RESULT AND DISCUSSION

Characterization of Drug

Fourier Transform Infrared Spectroscopy (FTIR):

The FTIR spectra of Etodolac (Fig. 1) shows stretching vibration at 1033.88cm-1 (C=O stretch), N-H wagging mode at 748.38cm-1, 1178.51cm-1 (-C-O ether group), CH2 deformation at 1317.38cm-1, 1409.96cm-1 (CH3 asymmetric deformation), 1741.72cm-1 (C=O stretching vibration of the COOH group), 3336.85cm-1 (N-H stretching vibration of secondary amine group), 2972.31cm-1 (aromatic C-H group).

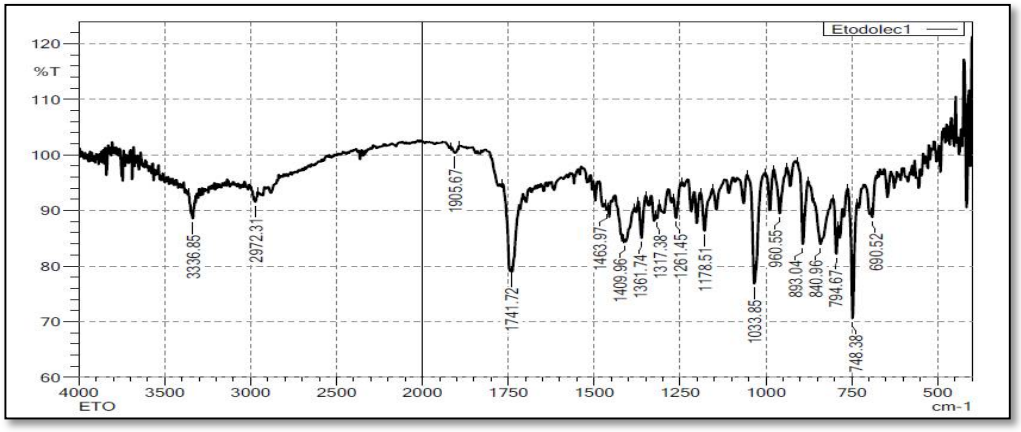

Figure 1: FTIR spectra of Etodolac

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Differential Scanning Calorimetry (DSC):

DSC was used to carry thermal analysis of drug. The DSC curve of Etodolac (Fig. 2) shows a sharp endothermic peak at 156.68oC corresponding to its melting point and indicating crystalline nature of solid. The same thermogram will be used to assess drug excipient compatibility during solubility enhancement processing.

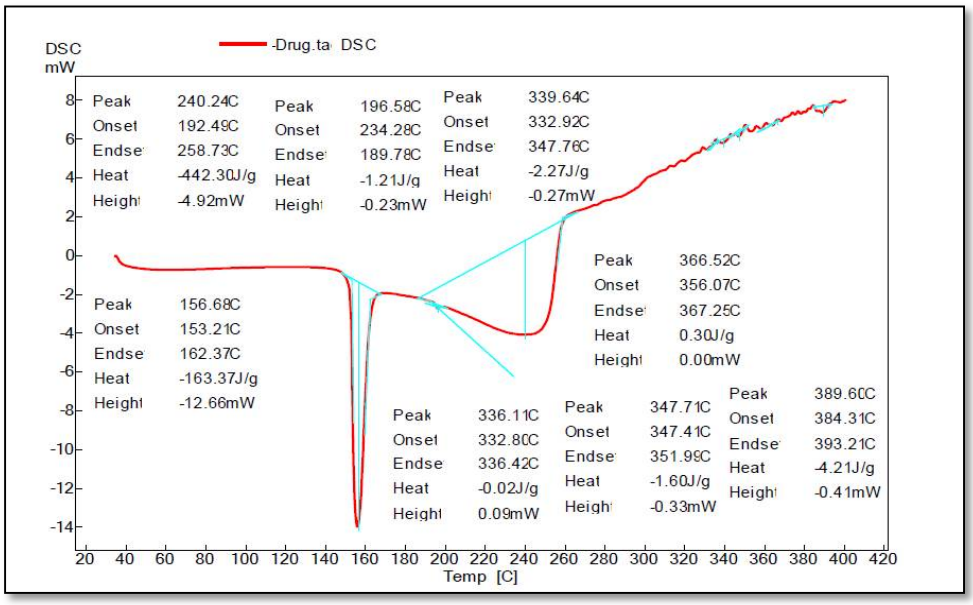
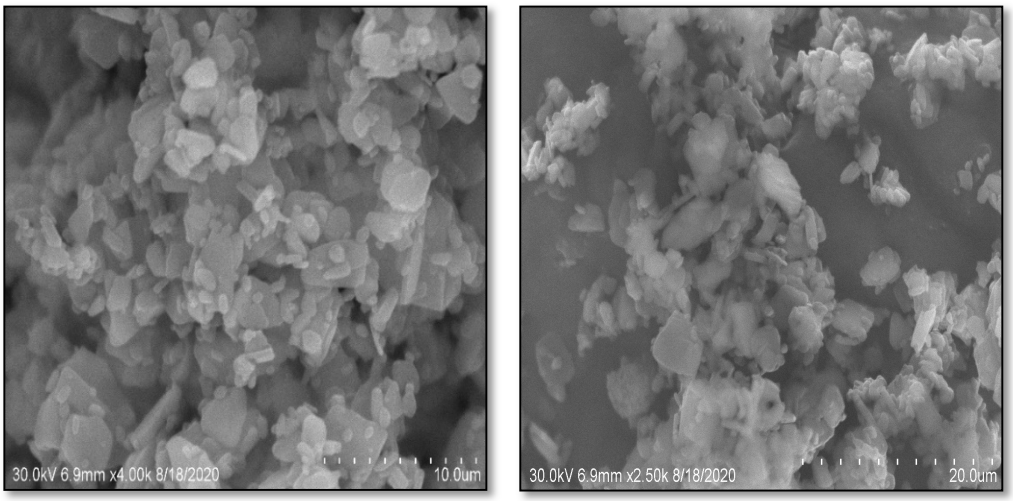


Figure 2: DSC thermogram of etodolac

Scanning Electron Microscopy:

The photomicrographs were taken at various resolutions. SEM analysis of the medication revealed distinct borders with defined shape in a significant proportion. Similarly, irregularly shaped crystals were seen. It validates the crystalline form of drug. The photomicrographs as in figure 3 illustrate crystalline nature of powder drug.



(a) **(b)**

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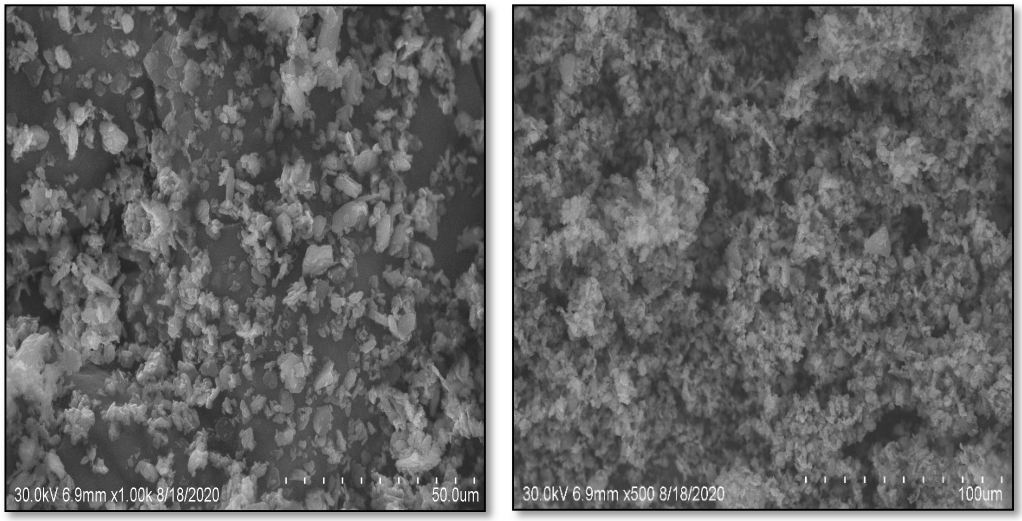

(c) **(d)**

Figure 3: SEM photomicrograph of etodolac at varying resolutions 10µm, (b) 20µm, (c) 50µm and (d) 100µm

X-Ray Powder Diffractometry (X-RD):

Stability and clinical performance of drug are moreover governed by its crystallinity. XRD is a widely accepted tool that helps to predict the crystalline or amorphous nature of drug material. The positions of peak diffraction angle and peak intensities in figure 4 are indicative of crystalline existence and measure of sample crystallinity respectively.

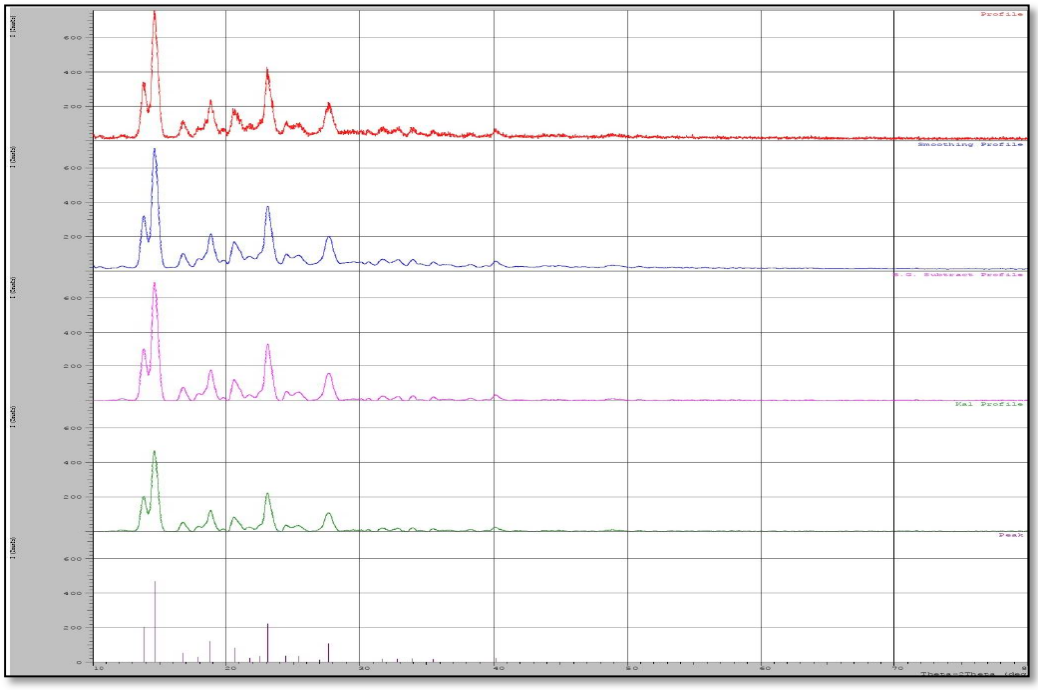

Figure 4: X-ray powder diffraction pattern of etodolac

The diffractogram has shown major characteristic high intensity peak at diffraction angle of 2θ are 13.82, 14.61, 18.80, 23.10 and 27.63 with respective integrated peak intensity counts as 5810, 12827, 3649, 6491 and 3893. More peak intensity is reflection of crystalline nature of the substrate.

Characterization of Solubility Enhancement Approach:

As explained in experimental, the target drug Etodolac was treated with various solubility enhancement techniques where various polymers and processing aids were employed with an objective to enhance solubility of Etodolac and to make it readily soluble in distilled water. The formulations so prepared were evaluated for their rheological characteristics, physical or chemical interactions, quantitative outcomes, and solubility.

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Characterization of Micellar Solubilized formulation

Evaluation of formulation prepared by micellar solubilization technique needs to be concerned with surfactant solution concentration. The fluctuation of surfactant molecule toward aqueous environment is responsible for formation of micelles by self-association. Consequently, balance should to be maintained to utilize maximum efficiency of surfactant for being effective in solubility enhancement.

Micromeritic study

The fundamental and derived properties of formulation's prepared by Micellar Solubilization technique were evaluated to check and confirm their micromeritic behavior. The results obtained are tabulated in table 1. The values of Angle of repose, Hausner's Ratio and Carr's Index are significant than those signifying poor flow behavior.

Table 1: Results for micromeritic study of EMS

Formulation Code	Mean particle Size(µm)	Bulk Density (gm/cm3)	Tapped Density (gm/cm3)	Angle of repose	Hausner's Ratio	Carr's Index
EMS1	91(±0.5)	0.41(±0.04)	0.50(±0.01)	34.4(±1.2)	1.21	21.9
EMS2	164(±0.9)	0.31(±0.04)	0.40(±0.05)	39.5(±0.8)	1.29	29.03
EMS3	176(±0.1)	0.32(±0.02)	0.41(±0.08)	38.8(±2.1)	1.28	28.1
EMS4	151(±0.5)	0.45(±0.01)	0.51(±0.02)	36.3(±1.3)	1.13	13.33

(n=3±SD)

Cloud point study

Tween 80 is a non-ionic surfactant having characteristic miscibility with water. The micelle formation gets affected by means of temperature and solution becomes cloudy. At cloud point, solid experiences incomplete solubility. Generally nonionic surfactants are much more effective at below or near to their cloud point. To prevent depletion of water from non-ionic surfactant and so as to maintain its solubility it was necessary to determine the cloud point temperature which is significant to retard solution from being visibly turbid. The change in concentration of Tween 80 has significant impact on Cloud Point temperature (CPT) which goes on decreasing with increasing concentration of Tween 80 and making it more applicable for the solubility enhancement of solid. The impact of Tween 80 concentration on cloud point temperature is tabulated in table 2.

Table 2: Measurement of cloud point temperature and Solubility

Formulation code	Tween 80 concentration (%w/v)	CPT (oC)	Solubility (µg/ml)	
			At R.T.	At CPT
EMS1	**1**	**92.5(±0.3)**	342.41(±0.28)	371.31(±0.41)
EMS2	5	**88.7(±0.6)**	364.26(±0.67)	394.41(±1.19)
EMS3	10	**85.1(±0.2)**	416.14(±0.73)	478.26(±0.9)
EMS4	20	**83.8(±0.2)**	436.63(±1.42)	504.27(±0.87)

(n=3±SD)

Percent Production Yield and Drug Content

At room temperature and CPT, the percent production yield of all formulations created by micellar solubilization process employing Tween 80 was determined to be greater than 90%. The drug content in all tested combinations was found to be within the acceptable limit of 90-97%. The yield loss is most likely due to material adhering to the walls of processing devices that could not be removed. Table 3 shows the percent production yield and drug content of several micellar solubilized formulations with changing Tween 80 concentrations.

Table 3: Percent Production Yield and Drug content of EMS

Formulation code	Production Yield(%)		Drug Content(%)	
	At R.T.	At CPT		
EMS1	98.24 (± 1.72)	91.61 (± 0.63)	93.12 (±1.72)	89.72(±0.63)
EMS2	96.92 (± 0.95)	92.47 (± 1.85)	96.92 (±0.95)	92.47(±1.85)
EMS3	91.12 (± 0.95)	96.42 (± 1.24)	91.12 (±0.95)	96.42(±1.24)
EMS4	**94.98 (**± 1.04)	**97.51 (**± 0.29)	**94.98 (**±1.04)	**97.5(**±0.29)

(n=3±SD)

Solubility study

Solubilization of Etodolac was influenced by the impact of surfactant concentration on cloud point temperature, with subsequent changes observed at both room and CPT. The solubility values so obtained are tabulated in table 2. It has been observed that the solubility of Etodolac is directly proportional to the surfactant concentration, with Tween 80 concentration significantly influencing it, with a solubility of 504.27 ± 0.87 µg/ml at 20%w/v.

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Fourier Transform Infrared Spectroscopy (FTIR)

As shown in Figure 5, little shifting has been observed in distinctive peaks of drugs. The shifting could be owing to the diluting effect generated by the surfactant excipient in the formulation. Any chemical interaction or bond formation that could result in drug efficacy loss or alteration has not been seen.

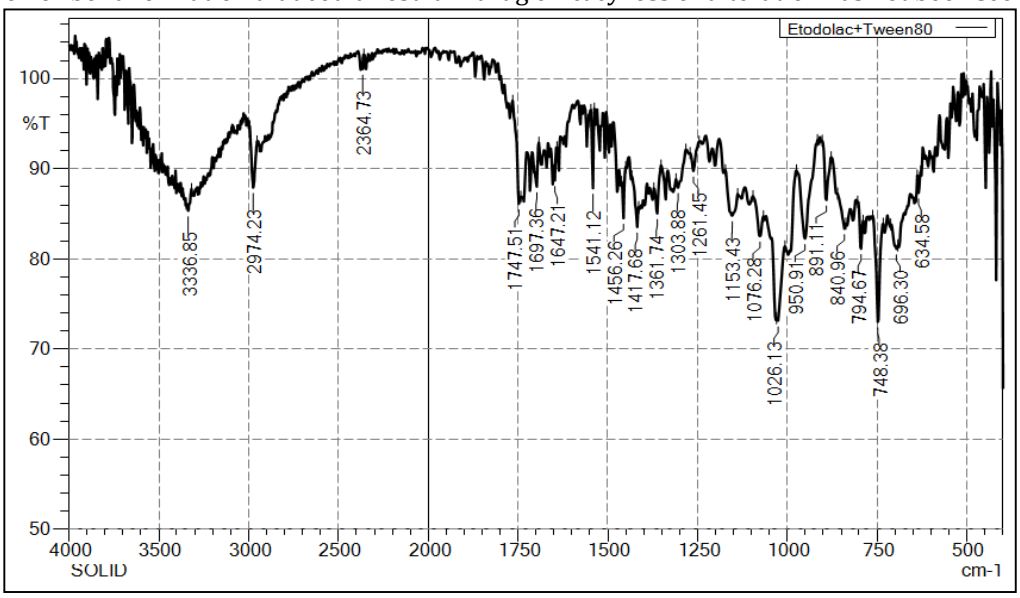

Figure 5: FTIR spectra of micellar solubilized formulationEMS4

Differential Scanning Calorimetry (DSC)

The DSC curve of pure Etodolac shows a sharp endothermic peak at 156.68oC corresponding to its melting point. As observed in figure 6 the presence of peak at 154.59oC suggests that no drug excipient interaction has taken place. The change in intensity of peak indicate that the Etodolac melting level is not shown and this may occur due to the solubilization of low Etodolac due to heat involved at CPT.

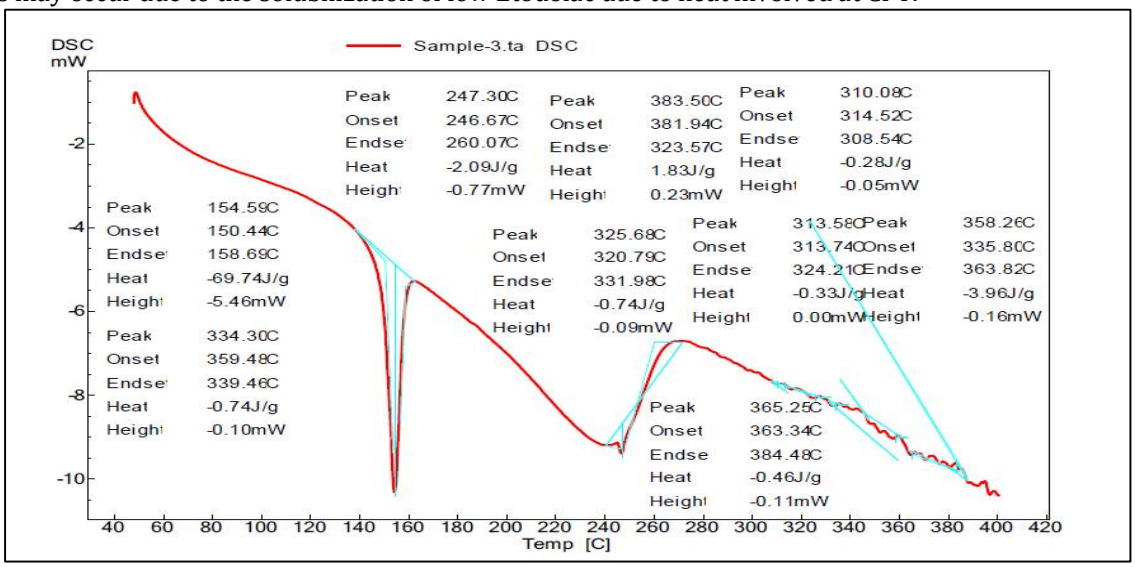

Figure 6: DSC thermogram of micellar solubilized formulation EMS 4

The thermogram shows variation in onset point and end point justifies the thermogram statement. The change in intensity and reduced peak area is the basis to conclude the establishment of amorphization of crystals or partial reduction in crystallinity of drug and that is significant for solubility enhancement of drug in water. The DSC thermogram curve data of micellar solubilized formulation is tabulated in table 4.

Table 4: DSC Thermogram Curve Data for EMS4

Thermogram	Onset Temp.(oC)	Peak Temp.(oC)	End Temp.(oC)
Pure Drug Etodolac	153.21	156.68	162.37
EMS4	150.44	154.59	158.69

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Scanning Electron Microscopy

The SEM micrographs were recorded at different resolutions so as to confirm the physical state and morphology of drug either as crystalline or amorphous. The SEM image of formulation prepared by Micellar Solubilization technique showed porous uniform particle structure (figure 7). The molecular dispersion of drug is signified.

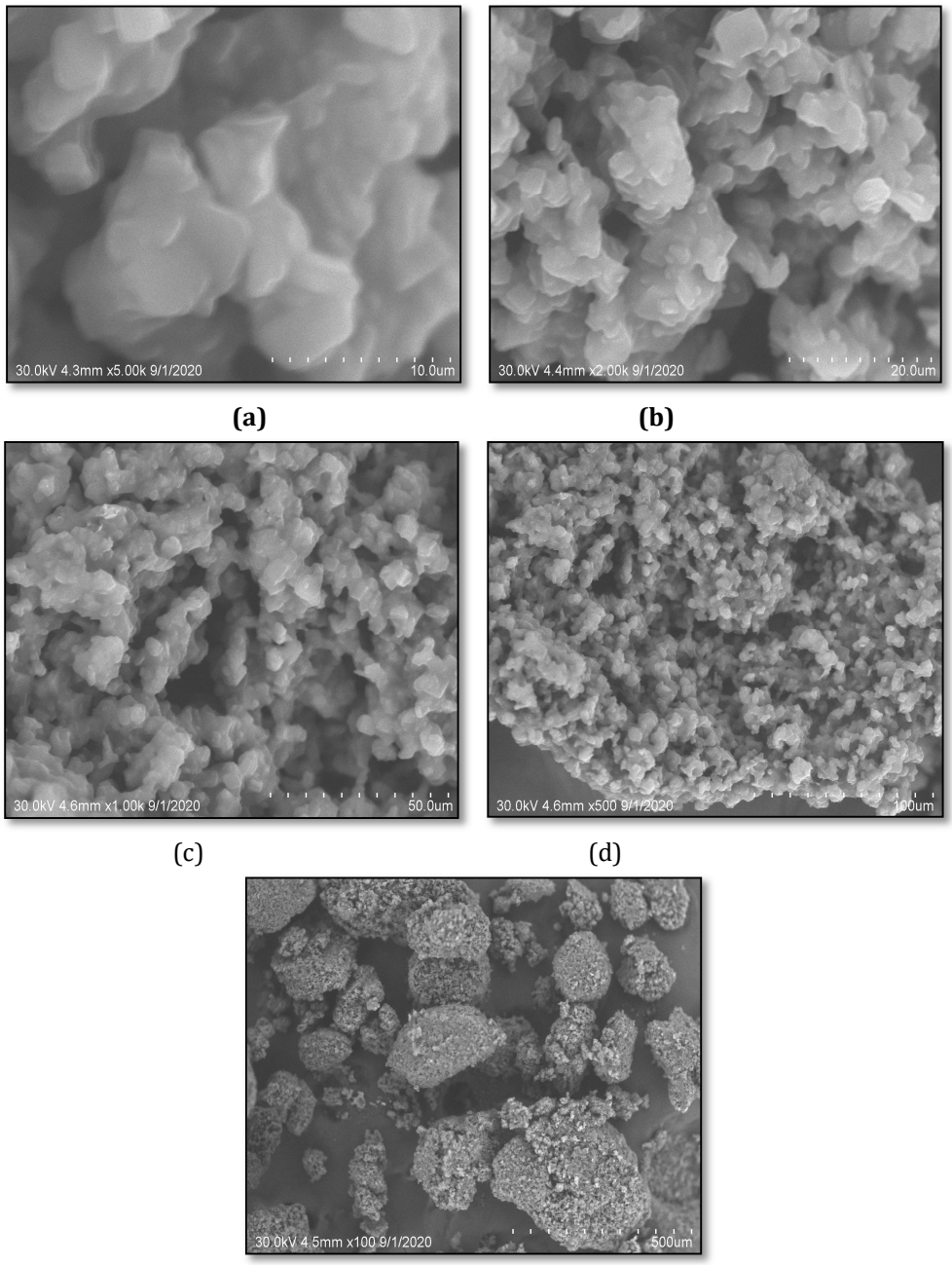

Figure 7: SEM micrographs of micellar solubilized formulation ems 4 captured at various resolutions (a) 10 µm, (b) 20 µm, (c) 50 µm, (d) 100 µm and (e) 500 µm

X-Ray Powder Diffractometry (X-RD)

The X-Ray diffractogram of pure drug has shown 18 peaks out of which major characteristic high intensity peaks at various diffraction angles of 2θ are at 13.82, 14.61, 18.80, 23.10 and 27.63. In Micellar Solubilized Formulations the corresponding peaks (figure 8) diffraction angles of 2θ 14.50, 23.00, 18.72 and 27.48 are less intense than that of the drug but not so significant to characterize as for the amorphous nature. This indicates somewhat distortions in crystalline nature of the drug as process of amorphization. More the intense peak is more the crystallinity.

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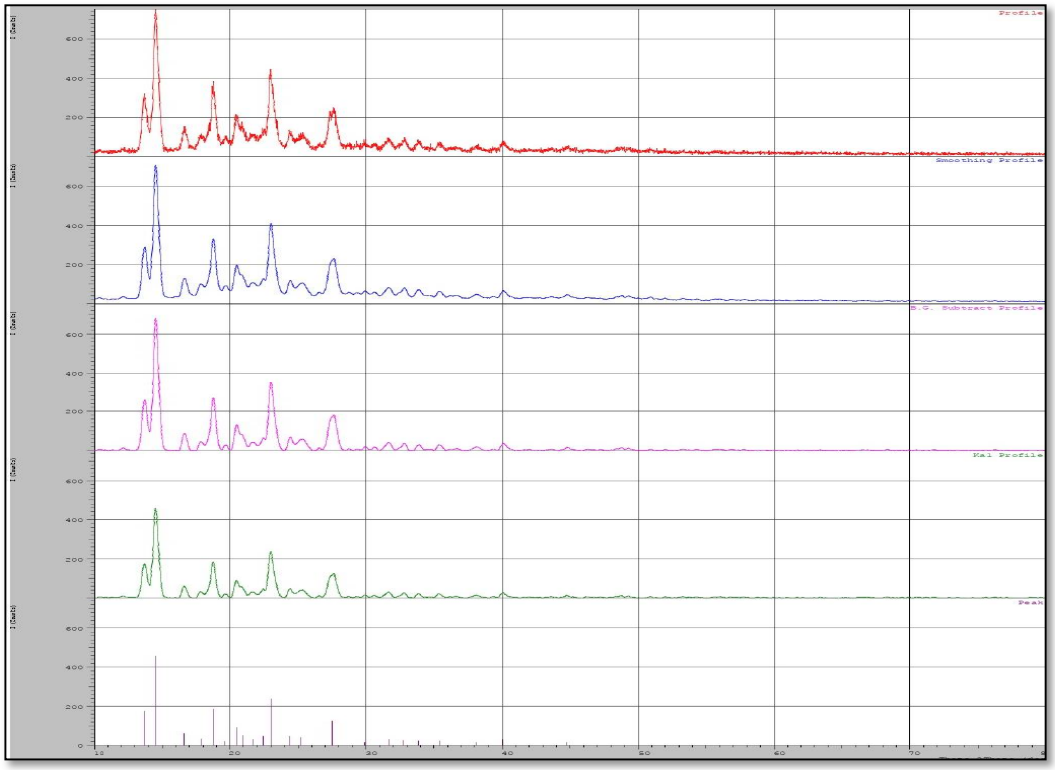

Figure 8: X-Ray diffractogram for micellar solubilized formulation EMS 4

Characterization of Microcrystallized formulation

Crystallinity and crystal characteristics are solvent dependent, and an API's solubility is influenced by the solvent or solvent mixture. Thus, solvent selection is critical in terms of increasing solubility since different solvents can cause variations in solubility with changes in crystal habit. The solvent modification approach produces microcrystals with increased solubility.

Micromeritic study

Morphological and rheological characteristics of solid are reflection of crystal habit and thus it is important to check the fundamental and derived properties of formulation prepared by microcrystallisation technique. The results obtained are tabulated in table 5. The values of Angle of repose, Hausner's Ratio and Carr's Index are significant than those signifying poor flow behavior.

Table 5: Results for Micromeritic study of EMC

Formulation code	Mean particle Size(µm)	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Angle of repose	Hausner Ratio	Carr's Index
EMC1	104(±0.9)	0.35(±0.003)	0.41(±0.02)	39.2(±0.3)	1.17	17.1
EMC2	116(±0.1)	0.32(±0.01)	0.41(±0.03)	36.1(±0.4)	1.28	28.1

n=3±SD

Percent Production Yield and Drug Content:

The percent production yield of both the formulations prepared by microcrystallisation technique using methanol and ethanol was determined and it was found to be more than 89%. The drug content in all the tested combinations was found to be more than 96%. The Percent Production Yield and Drug content of microcrystallized formulation is given in table 6.

Table 6: Percent Production Yield, Drug content and Solubility of EMC

Formulation code	Production Yield(%)	Drug Content (%)	Solubility (µg/ml)
EMC1	88.42(± 2.72)	96.42(±1.24)	392.17(±1.72)
EMC2	93.94(± 1.45)	**97.5**(±0.29)	448.64(±0.85)

n=3±SD

Solubility study

Solubility of Etodolac has been studied pre and post solubility enhancement. The solubility of Etodolac in methanol and ethanol was found to be 392.17µg/ml and 448.64µg/ml respectively.

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Fourier Transform Infrared spectroscopy (FTIR)

As in figure 9 shifting have been observed in FTIR spectra identifying formation of new crystal. –C=0 stretching and C-O stretching is indicative if formation of bond.

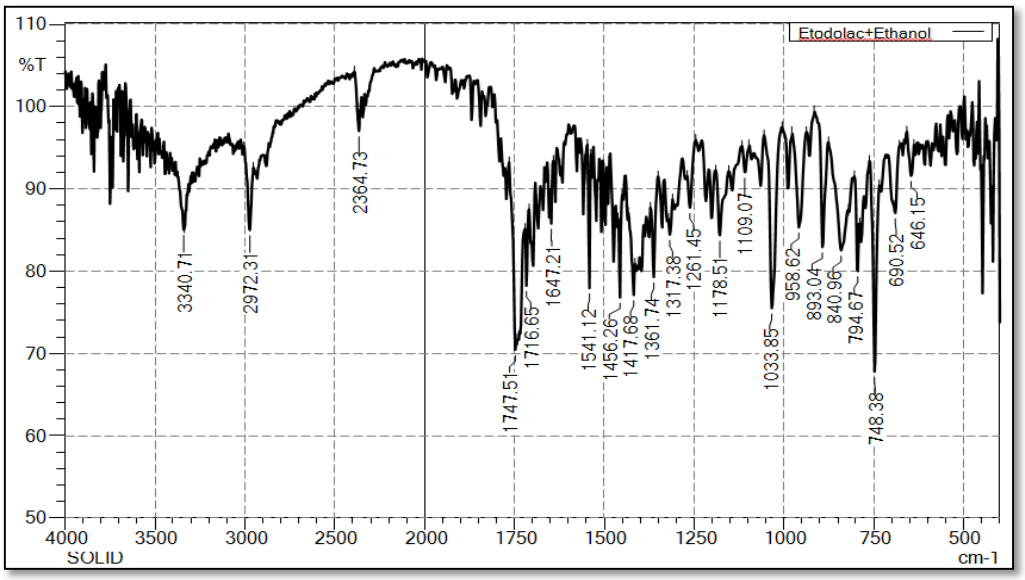

Figure 9: FTIR spectra of microcrystallized formulation EMC 2

Differential Scanning Calorimetry (DSC)

A sharp endothermic peak observed at 156.68oC is the DSC curve of pure Etodolac corresponding to its melting point. As observed in figure 10 the presence of peak at 153.17oC suggests endothermic peak maxima.

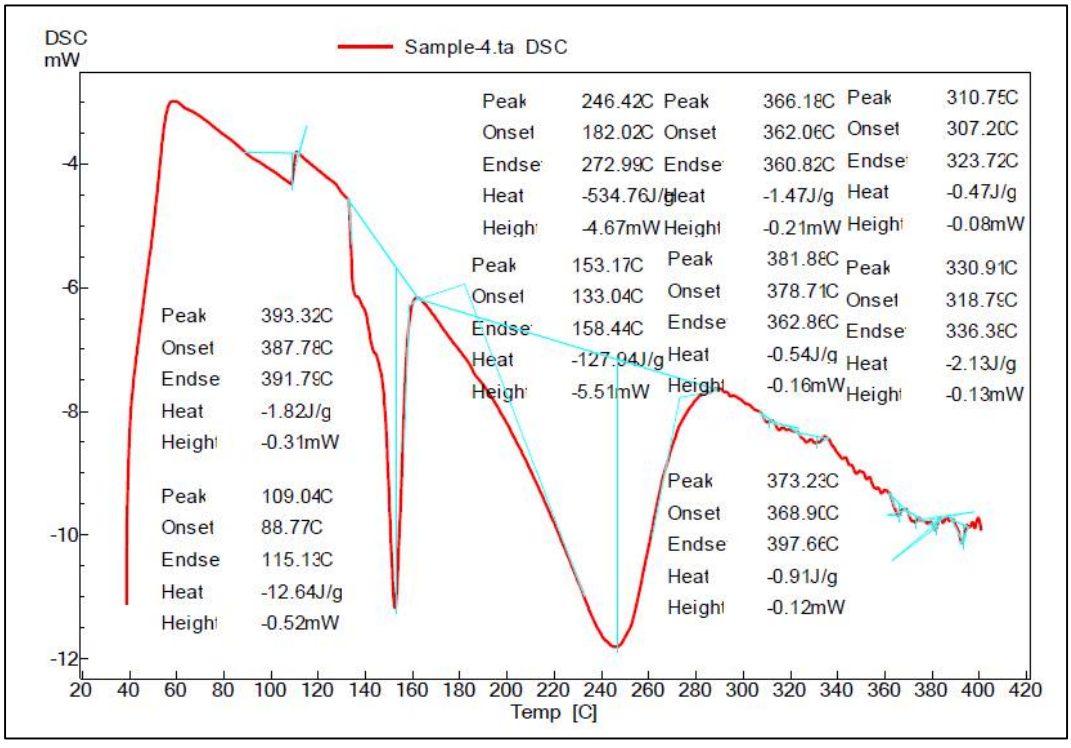

Figure 10: DSC thermogram of microcrystallized formulation EMC 2

Scanning Electron Microscopy

The SEM micrographs were recorded at different resolutions so as to confirm the physical state of drug either as crystalline or amorphous. The SEM image of formulation prepared by microcrystallization technique showed distinct boundary lines to the structure of crystal defining its crystalline appearance (figure 11).

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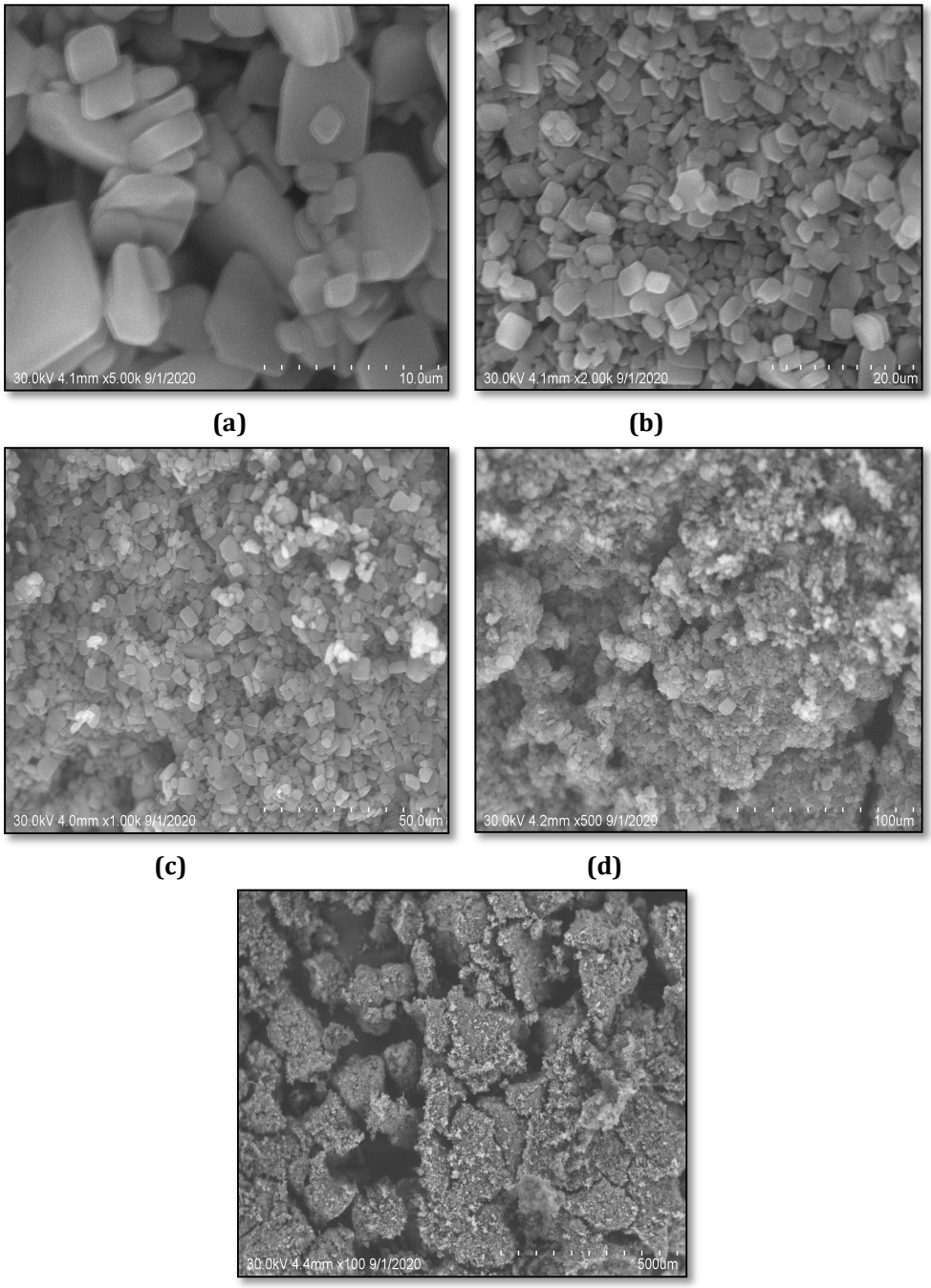

Figure 11: SEM micrographs of microcrystallization formulation EMC 2 captured at various resolutions (a) 10µm, (b) 20 µm, (c) 50 µm, (d) 100 µm and (e) 500 µm

X-Ray Diffraction study

The X-Ray diffractogram of pure drug has shown 18 peaks out of which major high intensity characteristic peaks at various diffraction angles of 2θ are at 13.82, 14.61, 18.80, 23.10 and 27.63. Powder XRD diffractogram of formulation prepared by microcrystal technique showed similar diffraction pattern with some intense sharp peaks as nearly corresponding peaks at 2θ are 14.51, 22.98 and 13.72 as drug has been identified. Figure 12 shows X-Ray diffractogram for microcrystal formulation.

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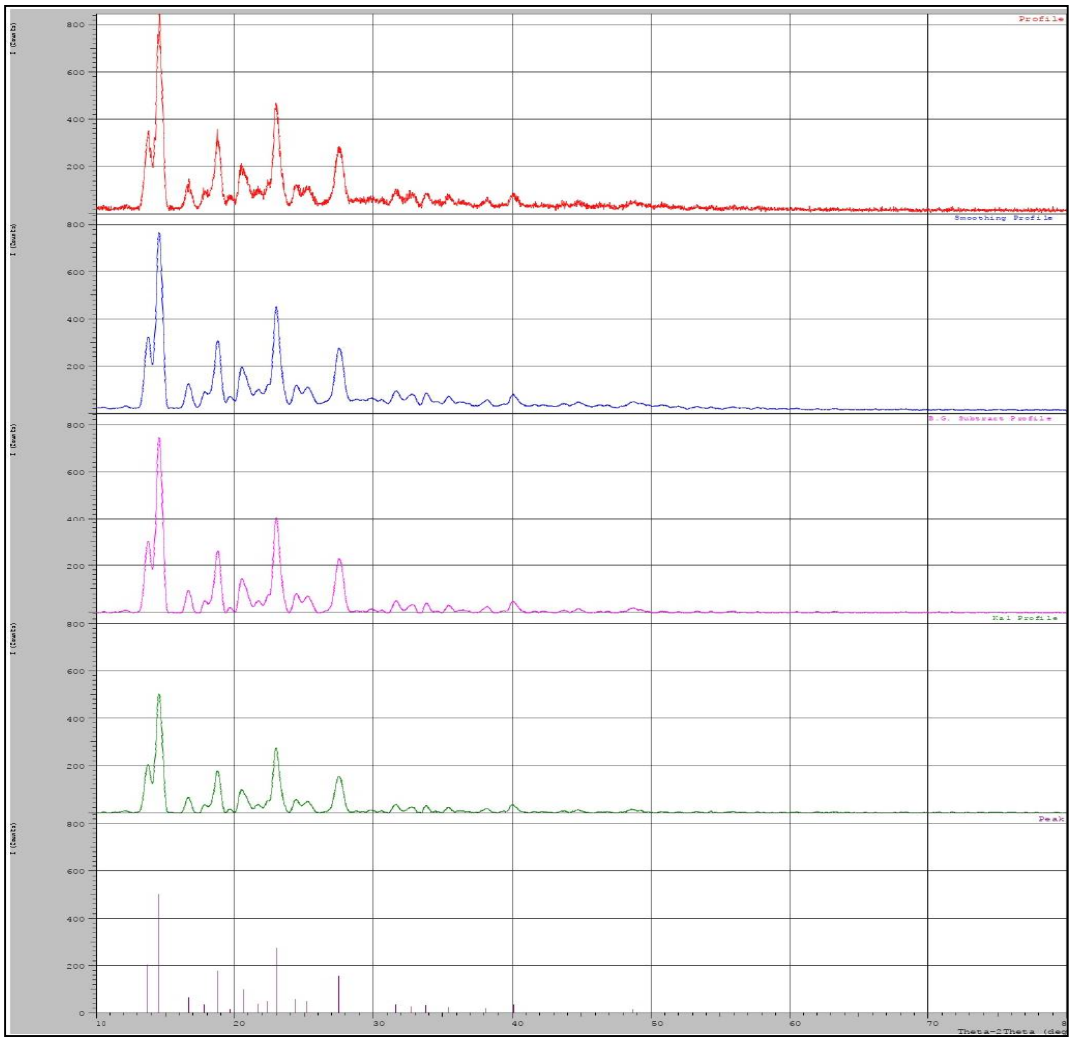

Figure 12: X-Ray diffractogram for microcrystal formulation EMC2

Based on the results obtained from solubility study and characterization by analytical procedures it has been found that both the methods, namely micellar solubilization and microcrystallization method has significantly contributed in the solubility enhancement of Etodolac. Out of the micellar solubilization has edge over the microcrystallization technique.

ACKNOWLEDGMENT: -
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CONFLICT OF INTEREST:- Nil

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