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ROLE OF POLYMERIC INTERACTION IN SOLUBILITY ENHANCEMENT OF ETODOLAC BY BALL MILLING AND HOT MELT EXTRUSION TECHNIQUES

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ABSTRACT

The objective of present work was to study the drug-polymeric interaction to improve solubility and hence dissolution rate of poorly soluble drug Etodolac by milling and melt extrusion techniques. During milling high shear generated which increases high interfacial area of drug and polymer promotes amorphous powder formation. However in melt extrusion, high shear mixing of the molten mass cause dispersion of the drug and the polymer at molecular level with drug–polymer interactions promotes amorphizations. Etodolac is weak acid with poor water solubility. The polymers selected for study were Copovidone (Kollidon® VA64) and Eudragit EPO (cationic). Ball mill was used for milling amorphization whereas, single screw Hot Melt Extruder (HME) was used for fusion amorphization. The formulation optimized for drug polymer weight ratio, milling time, Screw speed of (HME) and HME temperature. In-vitro dissolution rate of Etodolac formulation is improved in pH 1.2 buffer solution as compared to that of the pure drug and physical mixtures. The amorphous material was characterized for Crystallinity (DSC and XRD), Drug polymeric interaction study and drug chemical stability (FTIR). Extrusion was found efficient technique for carrier based amorphization as compared to ball mill. Hot melt extruder parameter optimized in order to form uniform molecular level dispersion (Screw speed 50 rpm and temperature 120oC). Extruded product of Etodolac and Eudragit EPO has shown significant.

KEYWORDS: Etodolac, HME, DSC, XRD, FTIR, Amorphizaton.

INTRODUCTION

Oral drug delivery is considered as the simplest and easiest route of drug administration. Oral bioavailability is mainly affected by drug solubility, permeability and first pass metabolism. In fact, most of the new Active Pharmaceutical Ingredients APIs are have low water solubility with low release profiles after oral administration. The biggest challenge in the pharmaceutical industries was to enhance the solubility and the permeability of those drugs as key factors to improve their bioavailability.[1-2] Various techniques have been used to improve the drug water solubility and release profile, and solid dispersions are considered to be the most successful techniques. There are two main solid dispersion manufacturing methods: the melting method, such as hot melt extrusion (HME) and solvent evaporation methods, such as spray drying.[3-6] HME is one of the most commonly used technique to enhance the solubility and oral bioavailability of a poorly soluble drug as a beneficial technique for solid dispersion, which involves simple dispersion of a poorly water soluble API in an inert carrier (polymer), where the drug could exist in amorphous or crystalline state.[7-10] There are many advantages of using HME due to the speed and the continuous manufacturing process. Moreover, as no solvent is required, this is considered to be a green method for enhancement of the solubility and oral bioavailability of poorly soluble drugs.[11-12] Depending on the polymeric carrier, HME can be also used for other purposes such as taste masking, controlling or modifying drug release and stabilizing the active pharmaceutical ingredient. HME takes place within an extruder which has feeder, barrel containing one or more rotating screws, control panel, torque sensors, heating/cooling device and assorted dies as the key components. Extruders consist of four standard sections feeding, conveying/ mixing, extrusion, and post –processing.[13-15]

Etodolac (Fig.1) is a non-steroidal anti-inflammatory agent and inhibitor of prostaglandin synthetize. Etodolac is poorly water soluble, and slightly soluble in simulated gastric fluid. The delayed onset of action is the result of limited dissolution rate due to poor solubility.[16] In vivo therapeutic efficacy of Etodolac is hampered because of its low oral bioavailability and poor onset of action due to low solubility in acidic pH. In order to explore the Etodolac for oral drug delivery system, here is a need to enhance solubility of Etodolac at gastric pH.[16-18] The aim of this study is to investigate solubility enhancement of the BCS class II drug using hot melt extrusion technology.

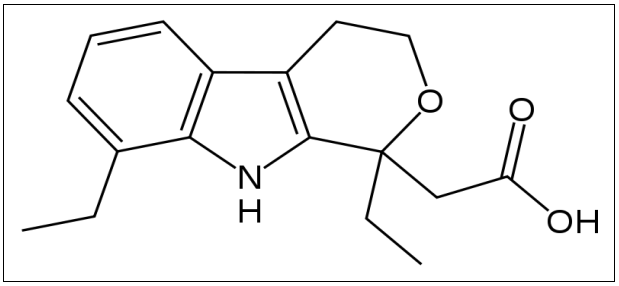


Fig 1: chemical Structure of Etodolac.

MATERIALS AND METHODS

Etodolac was purchased from TCI Chemicals (India) Pvt. Ltd. All other chemicals of analytical grade were used for study.

Instruments Used

A double beam UV-visible spectrometer (UV-530, Jasco) with spectra manager software was used for the analysis. Quartz cells having 3 cm length with 1 cm path length were used for spectral measurement. Weighing balance (Vibra HT, Essae) with internal calibration mode was used for the accurate weighing purpose. Hot Melt Extruder was used for the etodolac solid dispersion. Ball mill was used for milling. Dissolution apparatus was used to determine the dissolution rate of etodolac formulation. Partical size analyser was used to determine the particle size after milling. FTIR, DSC, XRD of drug polymer complex was studied.

Preparation of Etodolac solid Dispersion by Ball Milling

Mixture of the Etodolac and copovidone (kollidone VA64) in 1: 1 ratio (w/w, 10 g: 10 g) was blended in a vertical planetary ball milling prior to extrusion. Each grinding tank (volume of 50 ml) was filled with agate grinding balls (8 mm 4, number: 12), the mass ratio of the ball and the mixture was nearly 1: 1. The effect of time and frequency of the ball milling process on the extrudates were determined. The ball milling frequency was set 20, 30, or 40 Hz and the milling time to 30 min. Then, the milling time was set to 30, 40, and 50 min at milling frequency of 30 Hz. The samples were fed into the extrusion system. The extruder was run at160^{0}C and 120 RPM. The extrudates were milled and sieved after cooling in liquid nitrogen and used for in vitro dissolution testing. The mixture was ball-milled into power under the best operation conditions. The mixture power was manually fed into the extruder under elevated barrel temperature (120^{0}C, 140^{0}C, and 160^{0}C) and screw speed (100, 120, and 140 rpm). The extrudates were collected, cooled under different conditions, milled, and sieved (in the same manner as those prepared through hot-melt extrusion), then kept into a desiccator at

room temperature for future analysis. Same process is followed to prepare Etodolac and Eudrajit (EPO) Solid dispersion.

Preparation of Etodolac solid Dispersion by HME

Extrusion was performed on a process11 twin screw extruder with co-rotating 11 mm screws (length: 44 cm, L/D = 40) and a common screw configuration containing 2 kneading elements (arranged at 30^0,60^0 and 90^0). The Etodolac and copovidone(kollidone VA64)in 1:1 ratio(w/w, 10 g : 10 g) was mixed with mortar and pestle and subsequently fed manually into the hopper of the extruder at barrel temperature 160^0C and screw speed of 120 rpm. The extrudates were solidified in liquid nitrogen and collected, then ground softly in liquid nitrogen with pestle and mortar, passed through an 80 mesh sieve, and kept in a desiccator at room temperature for further analysis. Same procedure is followed to prepare Etodolac and Eudrajit (EPO) solid dispersion.

Evaluation of Etodolac solid dispersions

UV-analysis of Etodolac

A simple, precise, accurate UV-Visible spectrophotometric method of etodolac was developed and validated according to the ICH Q2 (R1) guideline. Seven different calibration standards of etodolac in the range of 1- 20 µg/ml were prepared form stock-I solution by using co-solvent system Methanol and water (50:50) v/v ratio and standard curve graph of etodolac showing absorption vs. concentrations values was plotted using 279 nm as maximum wavelength (λmax) for the detection.

Saturation Solubility Study

Solubility study is assessed out according to the method of Higuchi and Cannors. The saturation solubility of hot melt extrusion and HME process parameters of Etodolac from solid dispersion, physical mixture of polymer as well as Etodolac alone was determined in 1.2 pH medium. Samples are equivalent to 10 mg of drug is taken and to this 10 ml of respective medium is being added in 100 ml capped test tube. The samples were sonicated for 20 min at room temperature and capped glass test tubes were shaken for 48 h at °C, speed 75 rpm using shaking water bath. The solutions in the test tubes were kept for centrifugation for 20 min at 10000 rpm. The supernatant solution was then passed through a whatman Filter Paper (Grade-1) and the amount of the drug dissolved was analysed spectrophotometrically at 279nm.

Particle size analysis

Particle size measurement of the formulation of Etodolac-copovidone (Kollidone VA64) and Etodolac-Eudrajit EPO. The particle size of Etodolac-copovidone (Kollidone VA64) and Etodolac-Eudrajit EPO was determined using Malvern particle size analyser [Mastersizer 3000].

Differential scanning Colorimetory

DSC analysis (DSC-7020 Hitachi) of the etodolac formulation complex are carried out on a samples (1-10 mg) are heated under nitrogen atmosphere on an aluminium pan at a heating rate of 10℃ /min. Over the temperature range 50-200℃. DSC analysis is carried out under nitrogen gas flow of 20 lb/cm2.

Fourier Transformed Infrared (FT-IR) Analysis

Fourier transform infrared spectra of etodolac & its formulation were obtained using FT-IR spectrophotometer (Bruker). The sample panel was cleaned using isopropyl alcohol (IPA) with cotton plug. After the cleaning of panel, samples were sandwiched between panel and the upper arm. For the final graph, the samples were scanned over wave number of 4000–400 cm1.

Powder X-ray diffractometry (PXRD)

The PXRD patterns study of etodolac and its formulation were obtained using X-ray diffractometer (X' Pert PRO PANalytical). Line focus Ni-filtered CuKa1-radiation from an X-ray tube was used. The PXRD patterns of the samples were carried out using graphite crystal monochromator and 40mA current with X'celerator detector. The scanning rate of 1°/min at diffraction angle of 2 theta degree using Cu (as anode) and radiation of wavelength 1.540600 A°.

In-*Vitro* dissolution release

In vitro release studies of etodolac formulation were conducted by using USP eight station dissolution test apparatus (Electrolab).The dissolution medium consisted of phosphate buffer (pH6.8) for the 2 hours. 900 ml of dissolution medium was maintained at 37±0.5 °C, at 100 rpm (paddle method).Aliquots (fractional) of 5 ml were withdrawn at predetermined time intervals and an equivalent amount of fresh solvent at the same temperature was replaced. The samples were analysed by measuring the absorbance at 225 nm.

RESULT AND DISCUSSION

UV-Visible Spectrophotometric method

UV-Visible spectrophotometric method can be made suitable for any compound by developing the calibration curve if an absorption maximum exists. This calibration curve is used to understand the instrumental response to an analyte and predict the concentration of unknown samples. Considering the need of etodolac in quantitative analysis, seven calibration standard curve for etodolac were plotted. Seven different calibration standards viz. 1, 4, 6, 8, 12, 16 and 20 µg/mL were prepared by using Methanol: Water (50:50) v/v ratio. The absorbance of seven different calibration standards at 225 nm was recorded and the graph of concentration vs absorbance was plotted, as shown in Fig. 2. The absorbance values with respective concentration are given in Table 1.

Table 1: Calibration curve data for Etodolac.

Sr. No.	Concentration (µg/ml)	Absorbance
1	1	0.0487
2	4	0.1988
3	6	0.3011
4	8	0.3894
5	12	0.5947
6	16	0.7794
7	20	0.974

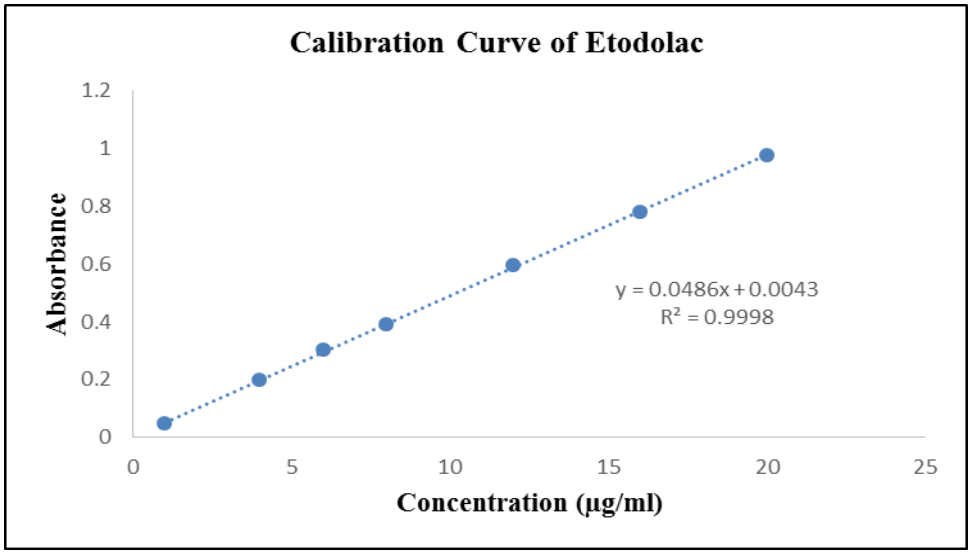


Fig. 2: Calibration curve for Etodolac.

Saturation Solubility study

The solubility of the drug in the presence of concentrated solutions of a polymeric carrier can help determine the mechanism of dissolution from a solid dispersion. To examine the

solubilizing power of drug and physical mixture of polymer, the equilibrium solubility of etodolac in phosphate buffer of pH 1.2 containing polymer was determined and hot melt extrusion technique as compared to ball milling technique. Saturation solubility study exhibited about 30 fold enhancement in solubility of (Etodolac (ETO) - Eudragit (EPO) polymeric complex) formulation at gastric pH in comparison to the plain drug (Fig.3). It was observed that solubility of etodolac was increased to higher level in pH 1.2 medium with Eudragit EPO by Hot melt extrusion technique as compared to ball milling technique.

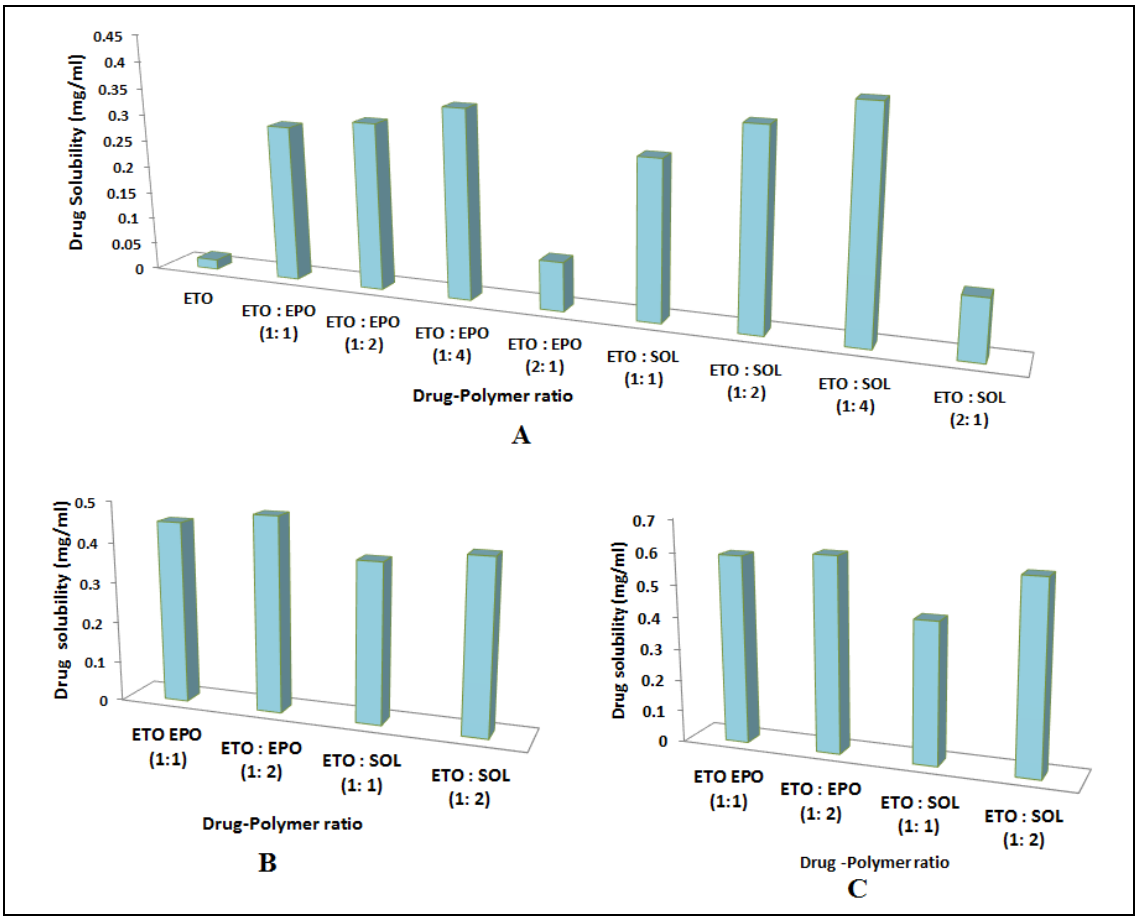


Fig.3. A). Saturation solubility study of drug- polymer physical mixture in gastric pH, B). Saturation solubility study of Ball Mill SD in Gastric pH and C). Saturation solubility study of HME SD in gastric pH.

Particle size analysis

Particle size plays an important role in the formulation to improve solubility. It was observed that particle size consecutively decreases as milling time increases. The particles size 2 & 8 hrs milling cycle of ETO: EPO (1:1) was observed 304 µm and120µm and ETO: Kollidon VA 64 (1:1) 128µm ad 120µm respectively shown in fig.4.

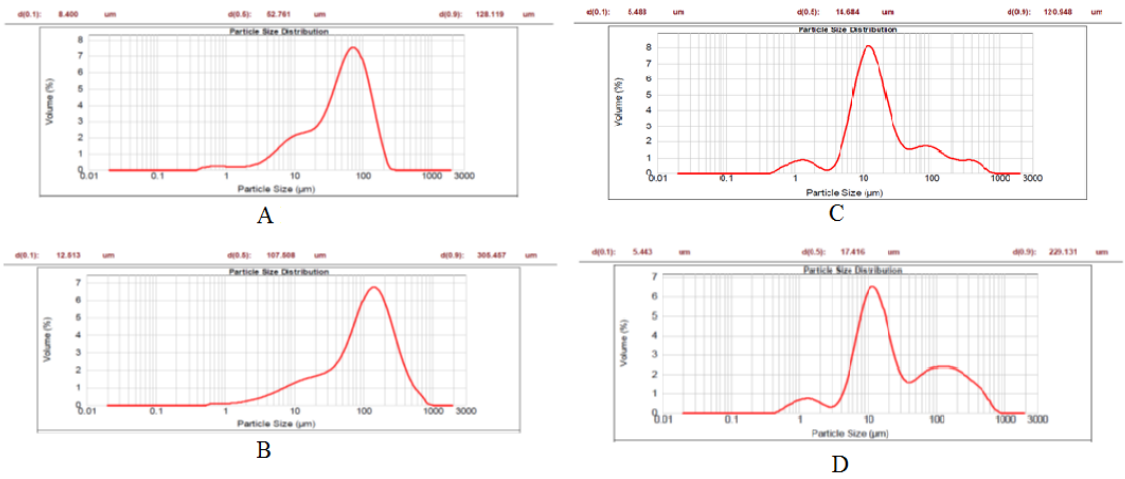
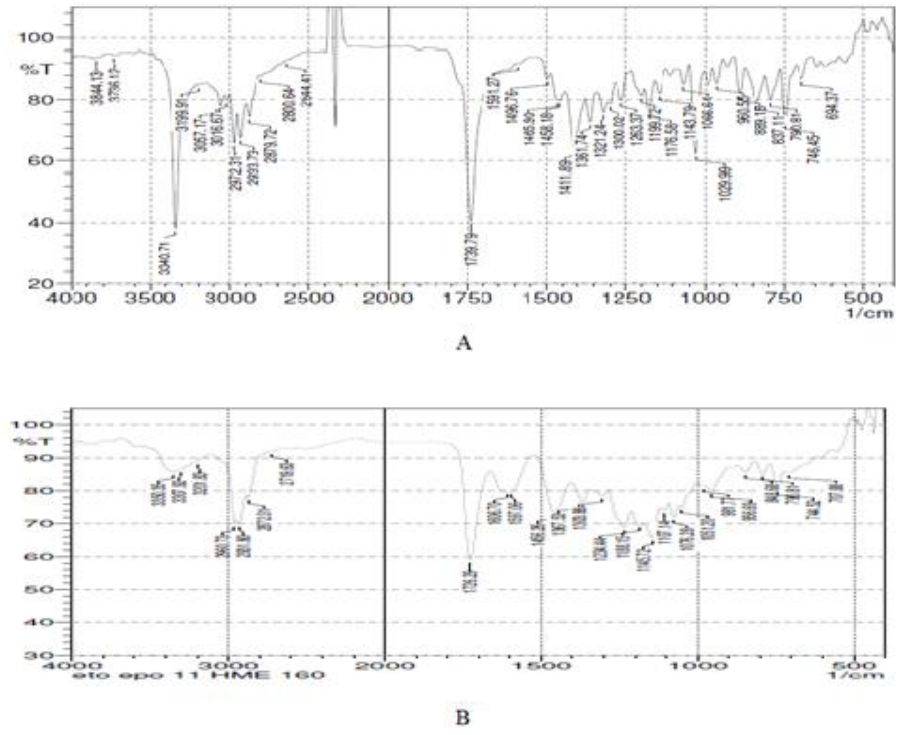


Fig.4. A). Ball Mill [ETO: Kollidon VA 64 1:1] 8hrs, B). Ball Mill [ETO: Kollidon VA 641:1] 2hrs, C). Ball Mill [ETO EPO 1:1] 8hrs & D). Ball Mill [ETO EPO 1:1] 2hrs

FT-IR Analysis.

The IR spectra of Etodolac shows a peak of hydroxyl (-OH) group at about 2972cm-1, which indicates the presence of carboxyl hydroxyl (-OH) group. While in the IR spectra of drug polymer complex (DCP) a broad peak for hydroxyl group appears at (with EPO 2960 cm-1 and with Kollidon VA 64 2969 cm-1 which shows that HME product of ETO EPO has formed polymeric interaction shown in fig.5.



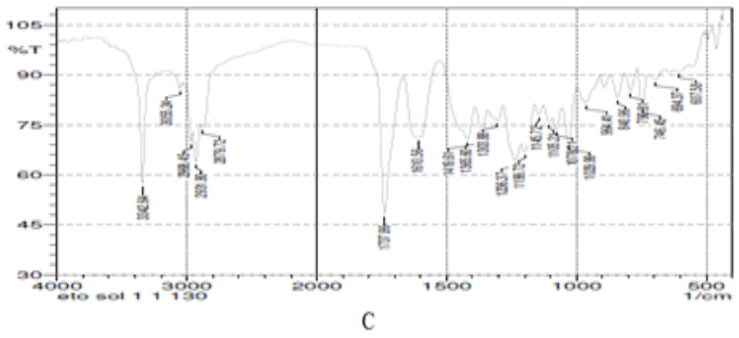


Fig.5. FT-IR spectra of A). ETO, B). ETO EPO HME & C). ETO Kollidon VA 64 HME.

DSC of Etodolac and Polymer Complex

The DSC thermogram of drug showed sharp endothermic peak at 151.02ºC indicating that drug is in pure form in fig.6. Presence of peaks indicates there is no interaction between etodolac and polymer. DSC study also revealed that Etodolac drug with Eudragit EPO and Kollidon VA 64 polymer by processing HME method indicates formation of amorphous product.

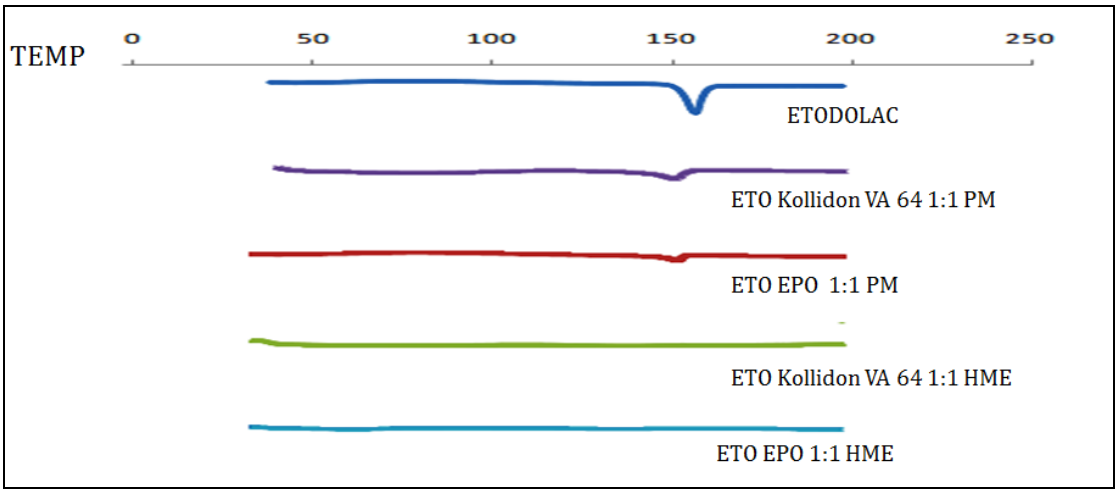


Fig 6: DSC Thermogram of Etodolac & Etodolac with Polymer.

Powder X-ray Diffractometry

In PXRD degree of crystallinity of any material can be determined from peak intensity in spectra, more the peak intensity more the crystalline. Fig. 7 shows XRD spectra of etodolac and etodolac with polymer. XRD study revealed that Etodolac drug with Eudragit EPO by HME method formed amorphous product whereas Etodolac with Kollidon VA 64 formed partial amorphous product.

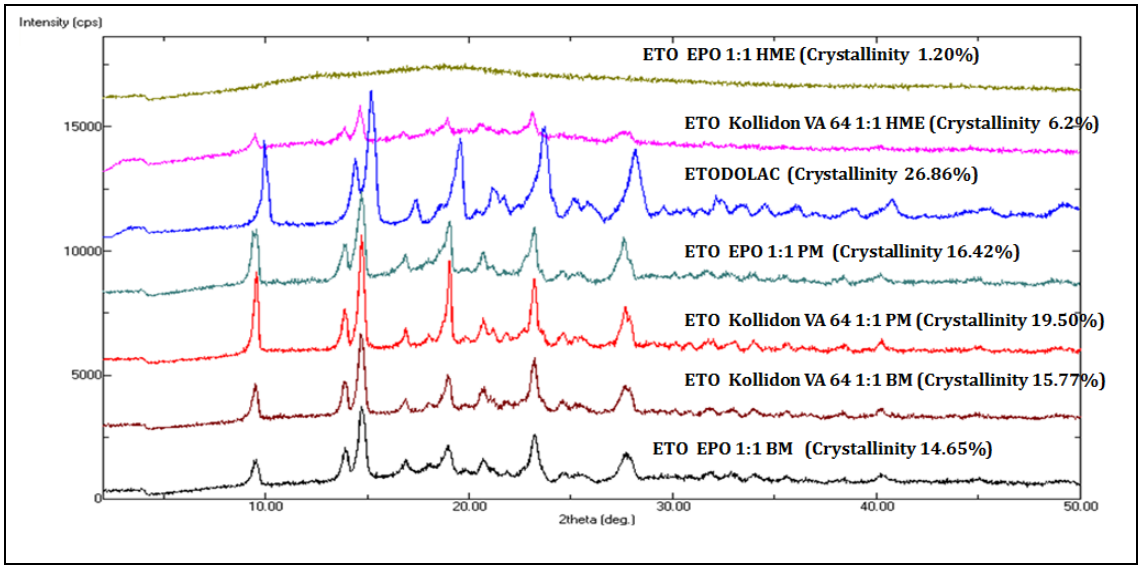


Fig 7: DSC Powder X-ray diffractometry spectra of Etodolac & Etodolac with Polymer.

In-*Vitro* dissolution release

In vitro release studies of etodolac formulation were conducted for a period of 2 hours. ETO-Kollidon VA 64: As the Kollidon VA 64 quantity increases, drug dissolution performance also increases; indicates Kollidon VA 64 improved the solubility of drug mainly by micellar action instead of polymeric interaction. ETO-EPO: at 1:1 ratio has shown admirable enhancement in dissolution indicates polymeric interaction between drug and polymer cause amorphization of drug Milling technique was showed limited performance with both (Eudragit EPO and Kollidon VA 64) as compared to Hot Melt Extrusion technique were shown in fig.8.

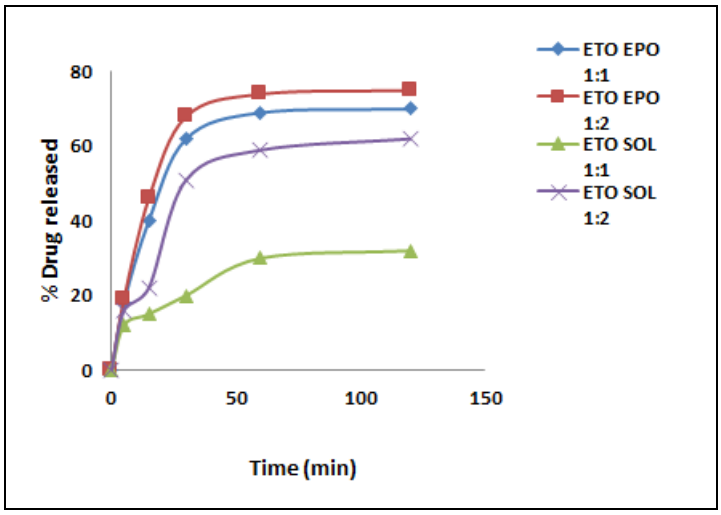


Fig 8: Percent release profile of Etodolac & Etodolac with Polymer.

CONCLUSION

Etodolac polymeric complex were prepared using ball mill and hot melt extrusion techniques with Eudragit EPO and Kollidon VA 64 as a polymers. Solubility of Etodolac was increased to higher level in pH 1.2 medium with Eudragit EPO by Hot melt extrusion technique as compared to ball milling technique. Kollidon VA 64 is polymeric surfactant and improved the drug solubility (limited extent) by micellar activity instead of polymeric interaction. Characterization data confirmed amorphization and polymeric interaction of drug.

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