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SOLUBILITY ENHANCEMENT OF ETODOLAC USING HOT MELT EXTRUSION

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ABSTRACT
Aqueous solubility of drug has moreover impact on oral bioavailability of that drug. The aim of present work is to enhance solubility of poor water soluble drug through Hot Melt Extrusion technology. The shear and heat so generated in the process are the crucial factor to govern so as to avoid thermal degradation of drug. Etodolac is a poor water soluble nonsteroidal anti-inflammatory agent selected for the study along with Parteck® MXP and Parteck® SI 150 as a polymer. Varying drug: polymer concentration ratio is then processed using twin screw extruders with keen focus on ideal processing parameters. The extrudates were characterized with thermal, microscopic, and spectroscopic analytical methods. The amorphous form of a drug so produced is comparatively more soluble than the crystalline form.

KEYWORDS: Etodolac, Solubility, Hot melt extrusion, Extruder, Extrudate.

INTRODUCTION
Aqueous solubility of drug has major impact on drug absorption.[1,2] The inadequate aqueous solubility creates hindrance in the development process of new drug.[3] To overcome the challenge of inadequate solubility, researchers has used numerous techniques like pH modifications, use of hydrotropes, development of solid dispersions, co solvency, reduction of particle size, chemical modification and complexation to enhance or to modify solubility of drug.[4,5]

However Hot Melt Extrusion (HME) has been emerged as FDA approved solvent free technology for the enhancement of solubility and bioavailability and to control the delivery of an API.[6] The HME process employs heat and pressure to generate homogeneous mixture of BCS class II or Class IV drug and polymer.[7,8] In general the HME technology has goal to uniformly disperse drug in a carrier polymer.[9] As a processing technology, HME is continuously proving its versatility but the temperature sensitive drug may undergo thermal degradation and the same is emerging as a limitation of HME.[10,11] Stable crystalline form may exhibit poor solubility as the water cannot penetrate efficiently. The amorphous form of a drug is comparatively more soluble.[12] These amorphous solid dispersions can be produced via HME.[13,14] The physical properties of a drug are changed during extrusion process and this can be achieved by forcing the drug though die under controlled conditions of temperature and pressure.[15]

Processing temperature regulation[16] and selection of polymeric carrier[17] are the crucial aspect in HME. The ideal processing temperature is selected on the basis of Glass Transition Temperature (Tg), Melting Temperature of drug and carrier (Tm and Tmc) to maintain stability and integrity of drug and polymer.[18,19]

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.[20] Extruders consist of four standard sections feeding, conveying/mixing, extrusion, and post –processing.[21] Etodolac is a non steroidal anti-inflammatory agent and inhibitor of prostaglandin synthetase. 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.[22] The aim of this study is to investigate solubility enhancement of the BCS class II drug using hot melt extrusion technology.

MATERIALS
Etodolac was obtained as gift sample from the IPCA Laboratories Ltd. Mumbai. Parteck® MXP and Parteck® SI 150 were made available by Merck Life Sciences Pvt.

Ltd. Mumbai. All other ingredients were of analytical grade.

METHODS

Hot Melt Extrusion

The damp physical mixture of Etodolac, Parteck® MXP and Parteck® SI 150 were prepared in proportion of 1:1:1 and homogenized. The mass is then extruded with successive steps and events mentioned in literature[23,24] using Twin Screw Thermo Scientific Pharma Mini HME. The continuous thinning, deformation, and elongation processes occurring in a very narrow space between the intermeshing elements facilitate the dissolution of drug molecules and/or their dispersion in a molten carrier.[25] The processing parameters like barrel temperature were subjected to variation as shown in table 1. The extrudates so obtained were allowed to cool at room temperature and stored in tightly closed container. The solid product was finely ground using mortar and then sieved with sieve 80. The fine material is then used for further characterization.

Table 1: Processing parameters in HME.

Formulation Code	Formulation Composition	Temperature (^{o}C)	Screw RPM	Torque Generated (Ncm)
EHME 1	1:1:1	140	30	70-90
EHME 2	1:1:1	150	30	50-60
EHME 3	1:1:1	160	30	43-50
EHME 4	1:1:1	170	30	25-30
EHME 5	1:1:1	180	30	20-25

Characterization of drug and formulation[26-29]

Uv- Vis Scan

Standard Etodolac 05 mg was accurately weighed and transferred to 10 ml volumetric flask. 01 ml methanol was added prior to dilutions with respective solvents i.e. distilled water and 0.1 N HCl. It was dissolved properly and diluted up to mark. This solution was used as working standard solution. The working standard solution so prepared is further diluted to have 05 levels of working concentrations ranging from 10% to 150% using distilled water. The dilutions so prepared were used to measure the absorbance by using UV-VIS spectrophotometry. Calibration curve was drawn by plotting absorbance against concentration of Etodolac.

Differential Scanning Colorimetry

DSC analysis was performed using Mettler DSC 3 by taking 2 to 5mg samples. Samples were sealed in aluminum pan and heated at a rate of 10°C/min over a temperature range under nitrogen with flow rate of 20ml/min. The software used for data analysis was Star E.

NIR Spectroscopy

The near infrared spectra of pure Etodolac samples were recorded by Metrohm XM1100 spectrometer. Samples were examined in the transmission mode. Each spectrum was measured over a frequency range of 400-2500 nm. The software used for the data analysis was Vision. The peaks obtained in the spectra were then compared with corresponding functional groups in the structures of Etodolac.

Percent Production Yield

The Percentage yield of solid dispersions of various combinations was calculated using the weight of final product after drying with respect to the initial total weight of the drug and carrier used for the preparation of solid dispersion.

Percent production yields were calculated as per the formula mentioned below,

$$PY = WO / WT \times 100$$

PY: Percent Production yield; WO: Practical mass (solid dispersions/ complexes); WT: Theoretical mass (carrier + drug).

Drug Content

About 10 mg drug equivalent of solid dispersions (theoretical) were weighed accurately and transferred to 100 ml volumetric flask to which 20 ml methanol was added and sonicated for 15 min. Final volume was made up with methanol to give 100 ppm stock solution. From this stock solution (100 µg/ml), 1 ml was withdrawn and further diluted up to 10 ml with methanol. This solution was used for the assay for drug content by UV spectrophotometer at 250 nm. Concentration of drug in stock solution was calculated by using calibration curve and from which percent drug content in solid dispersions was calculated,

$$\% \text{ Drug Content} = W_A/W_T \times 100$$

W_A: actual drug content; W_T: theoretical drug content.

Solubility Study

Phase solubility studies were carried for drug and extrudates. This study was the basic criteria to identify and judge a formulation of choice, which would enhance the solubility of drug. The following procedure remains same for both the drugs and their extrudates. To perform this study a known excess of the drug (50 mg) alone and the drug equivalent of extrudate were accurately weighed and transferred to a flask containing 25 ml of distilled water. The flask was placed in a shaking incubator having temperature 25^{0}C, rotation 120 rpm, for 96 hours. Aliquots from the flasks were withdrawn and transferred to test tubes and subjected to centrifugation at 2300 rpm for 10 minutes. From the supernatant, 10 µg/ml solution was prepared and analyzed by UV spectrophotometer at 279nm.

RESULTS AND DISCUSSION

The various parameters used for characterization and evaluation of extrudate are discussed below.

UV- Vis Scan of Etodolac

The UV Visible scan of Etodolac shows maximum absorbance peaks at 279 nm and 224 nm in water and 272 and 223 nm in 0.1 N HCl respectively (Fig 1).

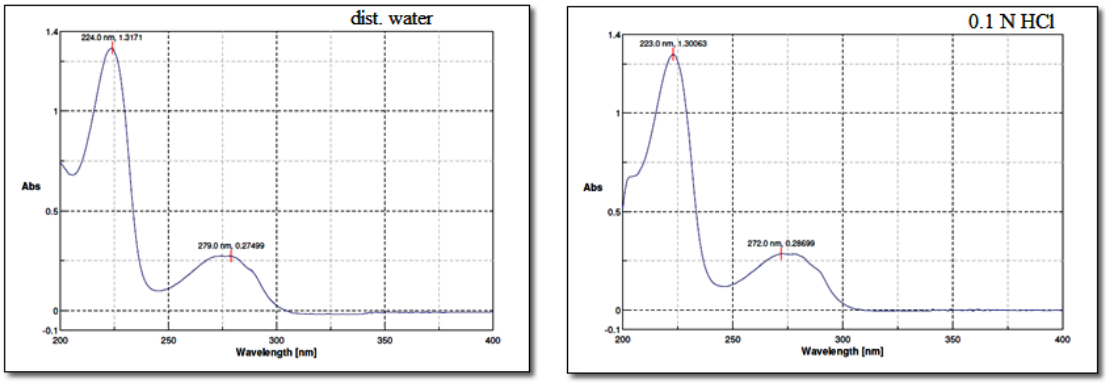

Fig. 1: UV spectra of Etodolac in water and 0.1 N HCl.

As shown in Figure no. 2 and 3, the linearity was observed when concentration is plotted against the absorbance noted on UV Visible spectrophotometer. Each levels absorbance is taken in triplicate. Intercept, slope and regression coefficient were found be -0.0014, 0.1315 and 0.999987 respectively for distilled water and -0.002116304, 0.129934783 and 0.999995 respectively for 0.1 N HCl.

The present analytical method obeyed Beer's law in the concentration range of 0.5 to 7.5 µg/ml and find suitable for the estimation of Etodolac from different solutions.

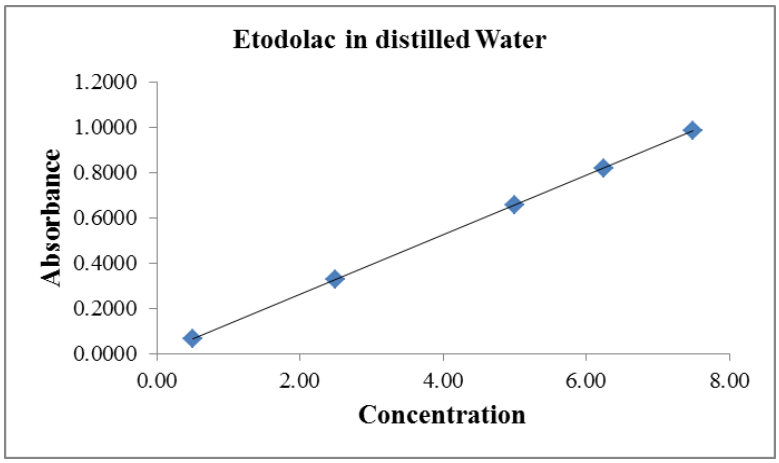

Fig. 2: Calibration curve of Etodolac in distilled water.

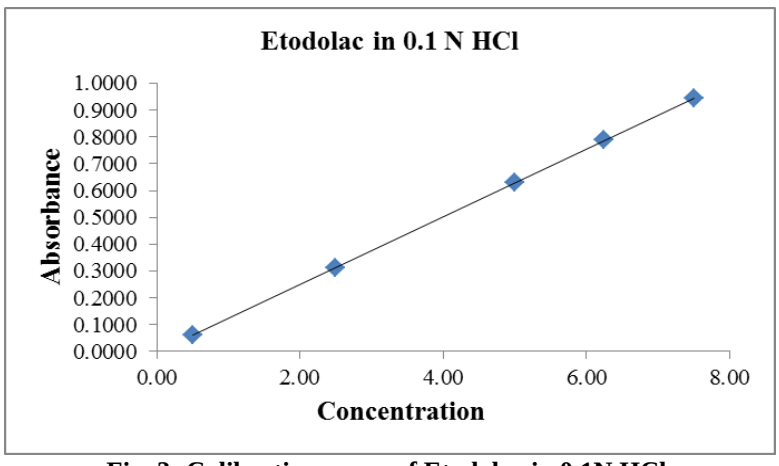

Fig. 3: Calibration curve of Etodolac in 0.1N HCl.

Differential Scanning Colorimetry

DSC of pure drug and extrudates were carried as per specifications mentioned. The sharp peak observed near to the melting point of drug is indication of crystalline nature of the drug. The same peak is absent in further thermogram is indication of breakdown of crystalline nature of the drug with formation of amorphous physical form. The thermoplastic system is characterized by its single glass transition temperature and the DSC thermogram confirms the same with complete amorphization of Etodolac.

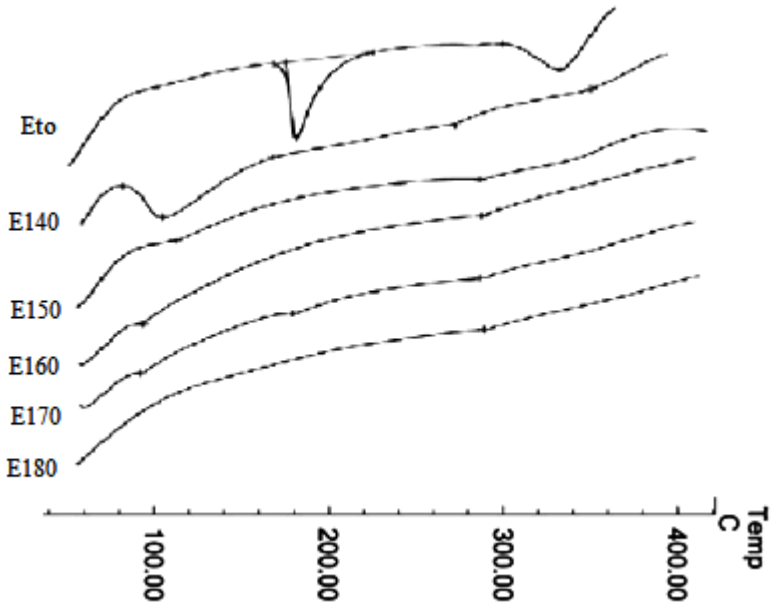

Fig. 4: DSC Spectra for Drug.

NIR spectra

As appeared in figure 5, the blue line and pink line are the spectral characterization of drug and extrudate respectively. The dilution effect observed in spectra is might be due to dilution effect of carrier and processing parameter. Absence of any bond formation or interaction between drug excipient is confirmed as no new band is observed.

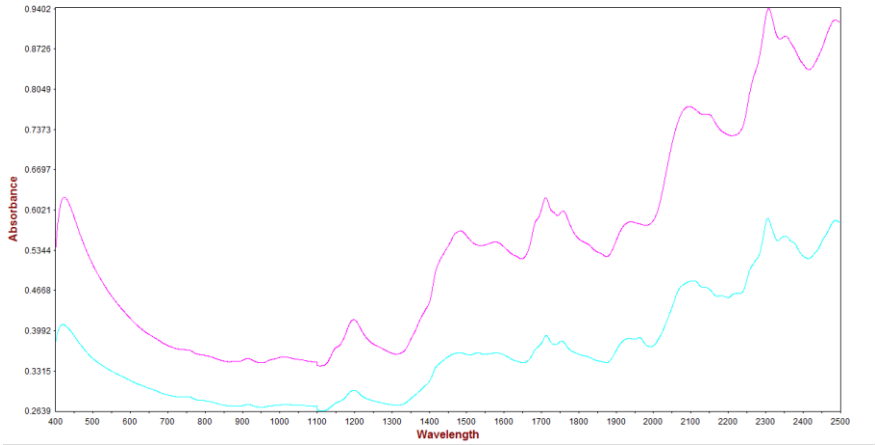

Fig. 5: NIR Spectra for Drug and extrudate.

Percent Production Yield

The percentage yields of extrudates prepared by Hot Melt Extrusion were found to be always in the range of 86 to 87%. Loss in yield was may be due to the product remaining adhered to the screws which could not be retrieved. The production yield of extrudates is shown in figure 6.

Drug Content

The drug content in all the tested combinations was found to be in the range of 92 to 98%, which is on the acceptable limit. The Percent Drug content in extrudates is shown in figure 6.

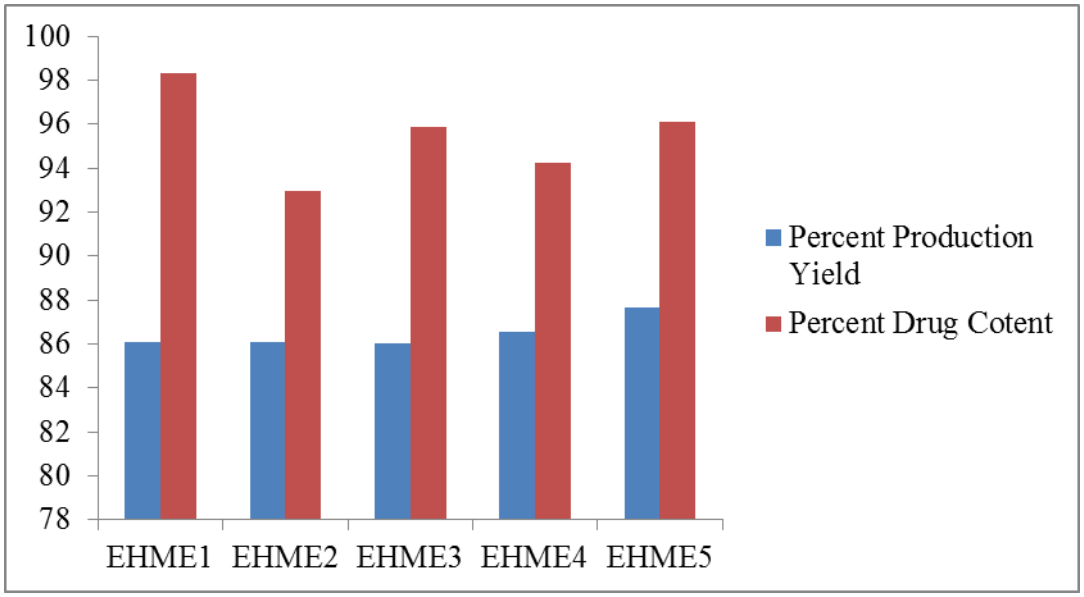

Fig. 6: Percent Production Yield and Percent Drug Content.

Solubility study

To evaluate effect of Hot Melt extrusion and HME process parameters the comparison made between the solubility of pure drug Etodolac and extrudates formed by the process of Hot Melt Extrusion.

The solubility of pure drug in water appears to be poor as only 323.63 µg of drug is soluble per ml of water.

The change in solubility of drug compare to the solubility of drug in water has been observed. The modification in solubility is the reflection of application of enhancement technique. As shown in figure 7 the solubility of all the formulation marked the increase having better solubility compare to the solubility in water.

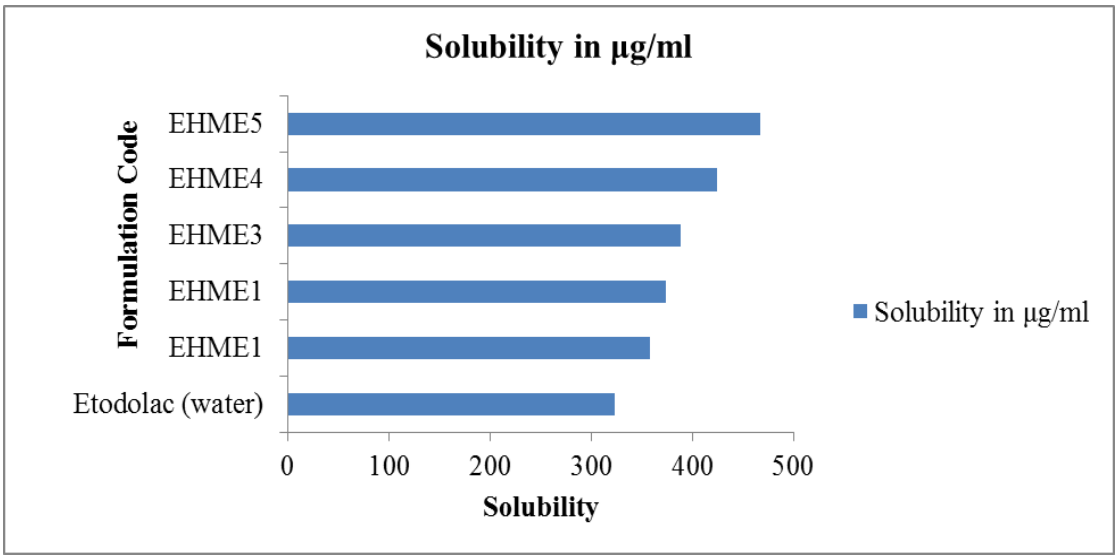

Fig. 7: Phase solubility data of drug and extrudate.

CONCLUSION

The efforts were made to modify the poor water solubility of Etodolac using hot Melt Extrusion Technology. Enhancement on solubility was attributed to trapping of drug inside the carrier matrix and to enhance dispersion with application of temperature. Hot Melt extrusion technology prefers on glass transition temperature thereby limiting thermal degradation of drug with excess heat. Along with the use of novel carriers like Parteck® MXP and Parteck® SI 150, barrel temperature has helped to modify crystalline form to amorphous form and results confirm that the modification in solubility of Etodolac has been achieved. Avenues for improvement remain wide open with rise in temperature but the consideration should be made toward temperature suitability so as to avoid thermal degradation of drug. The solubility study confirms fulfillment of aim and objective of the study.

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CONFLICT OF INTEREST
Nil

LIST OF SYMBOL AND ABBREVIATIONS
nm: nanometer
µg/ml: micrograms per milliliter
mg: miligram
˚C: Degree celcius
$\lambda_{max.}$ wavelength of maximum absorbance
DSC: Differential scanning calorimetry
NIR:Near infrared spectroscopy
%: Percent
Ppm: parts per million

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