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ORIGINAL RESEARCH

Cocrystallization of Etodolac: Prediction of Cocrystallization, Synthesis, Solid State Characterization and *In Vitro* Drug Release

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ABSTRACT

The present investigation deals with determination of Hansen solubility parameters, synthesis and characterization of etodolac co-crystals with various coformers. Various coformers were screened under the study to prepare cocrystals of etodolac for improving its solubility and dissolution. The prepared cocrystals were characterized by saturation solubility study, Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), *in vitro* dissolution studies and stability study. The outcome of study show that the significant improvement in solubility with p-aminobenzoic acid, ferulic acid and salicylic acid. Etodolac:Salicylic acid cocrystal 1:1M were formulated as immediate release tablets. The results reveal that solubility and dissolution of etodolac was improved by cocrystallization and it possesses adequate pharmaceutical stability.

Keywords: Etodolac, Cocrystal, Solubility, Dissolution, Hansen Solubility Parameter

INTRODUCTION

Active pharmaceutical ingredients (API) with poor aqueous solubility are becoming more prevalent in the research and development portfolios of discovery focused pharmaceutical companies (1). Molecules of this type can encounter a number of challenges in pharmaceutical development and may subsequently lead to poor dissolution, poor systemic availability and consequent poor drug efficacy in patients, especially after oral administration. Developments in the field of pharmaceutical sciences have led to the establishment of a number of approaches for addressing the issues of low aqueous solubility. Crystal engineering approaches, which can potentially be applied to a wide range of crystalline materials, offering substitutive and potentially productive and beneficial method for improving the solubility, dissolution rate and subsequent bioavailability of poorly water soluble compounds for pharmaceutical and therapeutic applications (2). The ability to engineer materials with optimum dissolution attributes, whilst maintaining acceptable physicochemical stability provides a strong driver for the utilization of crystal engineering approaches to drug and drug intermediate design. The challenges of low aqueous solubility provide archetypal situation for the utilization of crystal engineering techniques for improving bioavailability, whilst also developing pharmaceutically stable, acceptable and robust dosage forms. This therefore considers the

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potential utility of crystal engineering as an approach for designing efficacious pharmaceutical dosage forms for poorly water soluble drugs. Pharmaceutical cocrystals provides an opportunity for the optimization of key physical and chemical properties of an API whilst retaining its molecular structure, and its physiological activity as there are no making or breaking of the API's covalent bonds. Significant physical, chemical and biological properties of an API such as its aqueous solubility, bioavailability, stability and processability features can be considerably improved upon cocrystallization, thus allowing for optimal drug formulation. Application of the fundamental concepts presented in this paper explains to examine the ability of Hansen solubility parameter to predict the formation of cocrystals systems and pharmaceutical properties of cocrystals, in particular solubility, dissolution, and stability (3). Several research reports of cocrystals show their ability to improve physicochemical including solubility, dissolution, stability, tabletability and pharmacokinetic characteristics especially bioavailability of active pharmaceutical ingredients (4-8). Cocrystal synthesis can work as green technique becoming avenue for pharmaceutical industry (9).

Etodolac, is 2-[(1*RS*)-1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl] acetic acid, (fig.1), is a chiral nonsteroidal anti-inflammatory drug. It is used as analgesic and anti-inflammatory in the treatment of rheumatoid arthritis and osteoarthritis (10). It prohibits the synthesis of inflammatory peripheral prostaglandins by inhibition of the cycloxygenase-2 enzyme. It produces less gastrointestinal toxicity compared to the other NSAIDs (11). Its major site of metabolism is liver where it is converted to inactive metabolites that are primarily eliminated via the renal route (10).

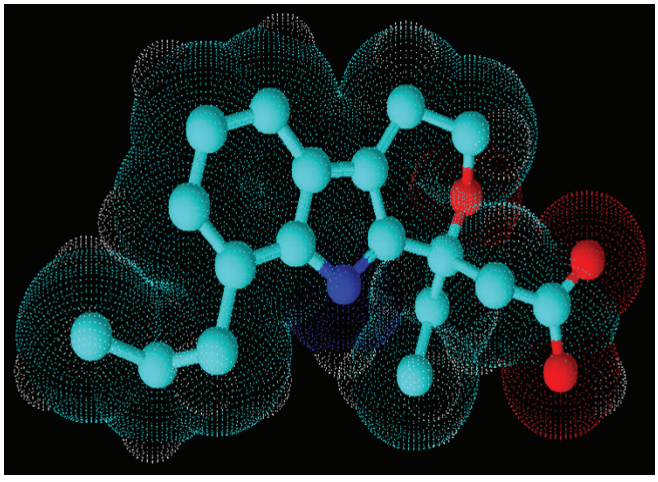


Figure 1. Chemical structure Etodolac

etodolac was selected as it was associated with poor physicochemical characteristics including solubility (12), compressibility and flow properties which could be resolved with the help of crystal engineering i.e. cocrystallization.

The objective of the present study was to check the predictivity of Hansen solubility parameter to formation of multi-component cocrystals systems of etodolac. This could be useful to screen coformers which are having tendency to form cocrystals. In the present study we have screened various coformers based on predictions from Hansen solubility parameter prediction. The corystals with maximum solubility were selected and evaluated by differntial scanning calorimetry, Fourier transform infrared spectroscopy, and powder X-ray diffraction.

1. MATERIALS AND METHODS

2.1 Materials

S-Etodolac was provided by IPCA Lab., Mumbai as gift sample for study. All other chemicals and solvents used under study were of analytical grade and procured from Research Fine Lab, Mumbai.

2.2 Methods

2.2.1 Prediction of Co-crystallization by Hansen Solubility Parameter (HSP)

Solubility parameters for dry chemical components may be obtained by group contribution methods. We have combined Hoftyzer and Van Krevelen method and Fedors group contribution method. In Fedor's method, the chemical structure of etodolac was opened and subsequently the chemical structure was considered as open chain structure (13-14). The solubility parameter components may be calculated from group contributions (F) and molar volume (Vm), using the following equations where δd represents dispersion forces energy, δp represents polar forces energy and δh represents hydrogen bonding energy (15). The representative calculations are given in Table 1.

$$\delta d = (\Sigma Fdi/\Sigma Vm) \text{ ----------Eq.(1)}$$

$$\delta p = ([\Sigma Fpi]^{0.5}/\Sigma Vm) \text{ ----------Eq.(2)}$$

$$\delta h = (\Sigma Fhi/\Sigma Vm)^{0.5} \text{----------Eq.(3)}$$

Table 1. Representative Calculation of Hansen Solubility Parameter of etodolac

Group	Frequency	Fdi ($J^{1/2}cm^{3/2}mol^{-1}$)	Fpi ($J^{1/2}cm^{3/2}mol^{-1}$)	Fhi (J/mol)	Vm[a] (cm^3/mol)
$-CH_3$	2	840	0	0	67
$-CH_2-$	5	1350	0	0	80.5
–COOH	1	530	176400	10000	28.5
–NH–	1	160	44100	3100	4.5
phenyl	1	1270	12100	0	52.4
>CH–	2	160	0	0	-2.0
–O–	1	100	160000	3000	3.8
>C<	1	380	0	0	32
Ring closure	2	0	0	0	-4.4
Conjugation in ring	2	-70	0	0	-19.2
Σ		4720	392600	16100	243.1

The resultant Δδ values of etodolac and selected coformers (Table 2) were compared to predict their solid state miscibility (16).

Table 2. Theoretical prediction of cocrystal formation by Van Kreevalen's method based on miscibility predictions.

Compound	δd	δp	δh	δt	Δδt	REMARK
Etodolac	19.41	2.577	8.13	21.2	---	-----
Salicylic acid	20.1	6.22	15.4	26.07	4.87	MISCIBLE
Benzoic acid	19.62	4.35	10.01	22.45	1.25	MISCIBLE
Malonic acid	18.19	8.13	16.54	25.89	4.69	MISCIBLE
Cinnamic acid	18.6	3.42	8.88	20.89	0.31	MISCIBLE
L-tartaric ecid	20.25	11.4	27.22	35.79	14.59	IMMISCIBLE
p-Aminobenzoic acid	20.78	4.34	13.56	25.19	3.99	MISCIBLE
Hippuric acid	20.41	6.92	10.72	24.07	2.87	MISCIBLE
Ferulic acid	18.37	4.92	14.56	23.95	2.75	MISCIBLE
Maleic acid	17.38	7.07	15.43	24.29	3.09	MISCIBLE
Glutaric acid	17.76	5.64	13.78	23.17	1.92	MISCIBLE
Urea	17.28	15.65	19.55	30.42	9.22	IMMISCIBLE
Ascorbic acid	27	5.64	13.78	23.17	1.97	MISCIBLE

2.2.1 Preparation of cocrystals

Etodolac was cocrystallized with various cocrystals formers (CCF) in the 1:1 Mol stoichiometric ratio using agate mortar and pestle by neat grinding method. The grinding was performed for 20 minutes for each batch (17). The flow properties of cocrystals were determined from angle of repose, Hausner's ratio and Carr's Index.

2.2.2 Melting point determination

The melting point of etodolac, CCFs and cocrystals were determined by Digital melting point apparatus (LAB-TRONICS Ltd) in triplicate.

2.2.3 Differential Scanning Calorimetry (DSC)

Thermal analysis of etodolac and cocrystals was performed by using a differential scanning calorimeter DSC-60A Shimadzu calorimeter. The samples were placed in aluminum pans, sealed hermetically and then these hermetically sealed aluminum pans were heated at a scanning rate of 20°C/min from 50° to 350°C under constant purging dry nitrogen flow (20mL/min). Empty aluminum pan was used as a reference.

2.2.4 Fourier Transfer-Infrared Spectroscopy (FTIR)

Shimadzu FTIR spectrometer Prestige 21 with DRS assembly was used in attenuated total reflectance (ATR) mode for collecting FT-IR spectra of samples. The spectrums were collected over the range of 4000-400cm^{-1} in 45 scans, with a resolution of 5 cm^{-1} for each sample.

2.2.5 Powder X-Ray diffraction Study (PXRD)

In this study, a powder sample of etodolac and cocrystals was exposed to a beam of monochromatic X-ray radiation using a Bruker D8 Discover, which was diffracted and recorded by an X-ray detector. The diffracted data was processed and an X-ray diffraction pattern of powder was plotted.

2.2.6 Solubility Study

Saturation solubility studies etodolac and its cocrystals were performed in according to method reported by Higuchi and Connors (18). For saturation solubility, an excess quantity of cocrystals was added to vials containing 10ml of different solvent media. The vials were then subjected to rotary shaking for 24 hours. After shaking the solutions were filtered through Whatman filter paper No.41 and the filtrate was analyzed by UV spectrophotometer (SICAN 2310, Inkarp Instruments) at 280 nm with appropriate dilutions.

2.2.7 Preparation of Immediate release tablets of etodolac Cocrystals

Immediate release tablet formulation of etodolac cocrystals was prepared by wet granulation method by 2^2 factorial experimental design. The disintegrant cross-carmellose sodium and binder poly vinyl pyrrolidone K30 (PVP-K30) were selected as independent variable. The formulae were as given in Table 3.

Table 3. Formulae for experimental factorial batches

Ingredients	Quantity
Etodolac: Salicylic acid cocrystals	435 mg
Cross carmellose sodium	5%-7%
PVP K30	2.5%-5%
MCC PH-101	q.s
Magnesium stearate	1%
Total weight	520mg

2.2.8 Dissolution study of cocrystals and its formulation

In vitro dissolution study was carried out using a USP type 2 apparatus (USP tablet Dissolution apparatus Veego VDA-6DR) at a rotation speed of 100 rpm. Dissolution medium selected was phosphate buffer pH 6.8 (volume 1000ml, temperature 37°C). After each sampling intervals, sample withdrawn was replaced by same amount of dissolution media kept at same temperature. The sample withdrawn was then immediately filtered and analyzed for sample content by UV spectrophotometer at 280 nm after suitable dilutions.

2.2.9 Stability Study

The immediate release tablets of etodolac-salicylic acid cocrystals were packed in aluminum foil and stored under the following environmental conditions for a period of One month as prescribed by ICH conditions at 5°C ± 30°C and 25° ± 2°C/ RH 60% ± 5%. The tablets were withdrawn at end of 15th and 30th day and evaluated for parameters including color change, assay (drug content), disintegration time, and dissolution study of formulation.

2. RESULTS AND DISCUSSION

The melting point of etodolac (Etd) and cocrystals were as reported in Table 4. It was observed that the melting point lower than the individual API or CCF indicating interaction between them. The Solubility of etodolac was significantly improved by cocrystal formation with salicylic acid, para amino benzoic acid and fumaric acid as compared other CCF under study.

Table 4. Melting Point, Solubility of cocrystals prepared by Neat Grinding

Batch Code	Drug/Coformer	M.P of coformer (^{0}C)	M.P. of cocrystal (by digital melting apparatus)(^{0}C)	Solubility(mg/L)
F1	ETODOLAC (Etd)	145-148	----	676±3.0
NF1	Etd Salicylic acid	157-159	116-118	1566±5.33
NF2	Etd Benzoic acid	122	104-107	155±2
NF3	Etd Malonic acid	134-136	117-118	49.2±3.26
NF4	Etd Cinnamic acid	132-134	112-116	233±2.66
NF5	Etd tartaric Acid	204-206	202-206	215±2.55
NF6	Etd p-ABA	185-188	117-121	3266±1.79
NF7	Etd Hippuric acid	187-190	131-136	204.9±2.90
NF8	Etd Ferulic acid	174	125-133	2186±4.33
NF9	Etd Maleic acid	138-139	90-11	174.1±2.56
NF10	Etd Glutaric acid	94-97	117-118	134.1±4.56
NF11	Etd Urea	133	sticky in nature	-
NF12	Etd Ascorbic acid	95-98	sticky in nature	-

The flow properties of etodolac and its cocrystals were as represented in Table 5. It reveals that there was marked improvement in flow properties of etodolac in cocrystals with salicylic acid as compared to the cocrystals with PABA and ferulic acid.

Table 5. Flow properties of etodolac and its cocrystals

Parameters/Batch	Etodolac	NF1	NF6	NF8
Bulk density (gm/cm^3)	0.315	0.311	0.222	0.323
Tapped density (gm/cm^3)	0.485	0.401	0.321	0.474
Compressibility index (%)	35.05	22.40	30.84	31.85
Hausner's ratio	1.53	1.28	1.44	1.46
Angle of repose (°)	36.33	17.43	33.66	28.59

The melting points of etodolac, NF1-cocrystal, N6-cocrystal and NF8-cocrystal were determined by DSC study and found to be 153.74°C, 119.44°C, 125.44°C, 127.28°C respectively (Fig.2 and 3). From the results of DSC study, the cocrystals formation (i.e. NF1, NF6, NF8 cocrystals) can be confirmed which show characteristic change in the melting behavior. Such peculiar change in melting behaviour confirms the formation of new phase suggesting cocrystal formation. In DSC thermograms the distinct endothermic peaks at temperature other than the melting peak of drug and CCFs and change in heat were observed indicating formation of cocrystal.

The FTIR spectra of API and cocrystals are shown in fig 2 and 4. The carbonyl peak in the region 1680-1760cm^{-1}, -NH stretching region between 3300-3500 cm^{-1}, ether (-O-) peak in the region between 1000 and 1300cm^{-1} of etodolac was retained in all cocrystals spectrums. In most of the cocrystals, distinctive peaks for hydrogen bonding conformation were observed in FT-IR spectrum. The hydrogen bonding in cocrystals by FT-IR spectroscopy is detected by observing a decrease in intensity of C - O-C peak and appearance of low frequency broad C - O-C band. Broad features were observed in the region of 900-1500cm^{-1}, indicating the occurrence of hydrogen bonding. A decrease in N-H stretching frequency indicates that hydrogen is participating in hydrogen bonding. The extent of hydrogen bonding can be determined by extent of decrease in frequency and relative band broadening. The lowering of frequency is the function of degree and strength of hydrogen bonding. The significant changes observed in the region of amine (N-H) and carbonyl(C=O) stretching

indicated formation of new hydrogen bonds.

The crystal structure of the etodolac and cocrystals (NF1, NF6, NF8) was confirmed by X-ray powder diffraction analysis (fig.2 and 5). The comparison of PXRD pattern of etodolac with its cocrystals reveals that there may be formation cocrystal as additional intense peaks were observed in cocrystals. It suggests development of new crystalline phases in cocrystals.

In a saturated solubility study of etodolac cocrystals it was observed that maximum improvement in solubility was observed with CCF in following order p-aminobenzoic acid>ferulic acid> salicylic acid (Table 4). It may be attributed to desirable noncovalent interaction between and API and CCF. Cocrystal with PABA shown discoloration with time while cocrystals with ferulic acid shown overlapping absorption in ultraviolet region with etodolac. Glutaric acid, urea and L-ascorbic acid formed undesirable sticky semisolid material during cocrystallization attempts with etodolac. While with other coformers under study solubility of etodolac was decreased.

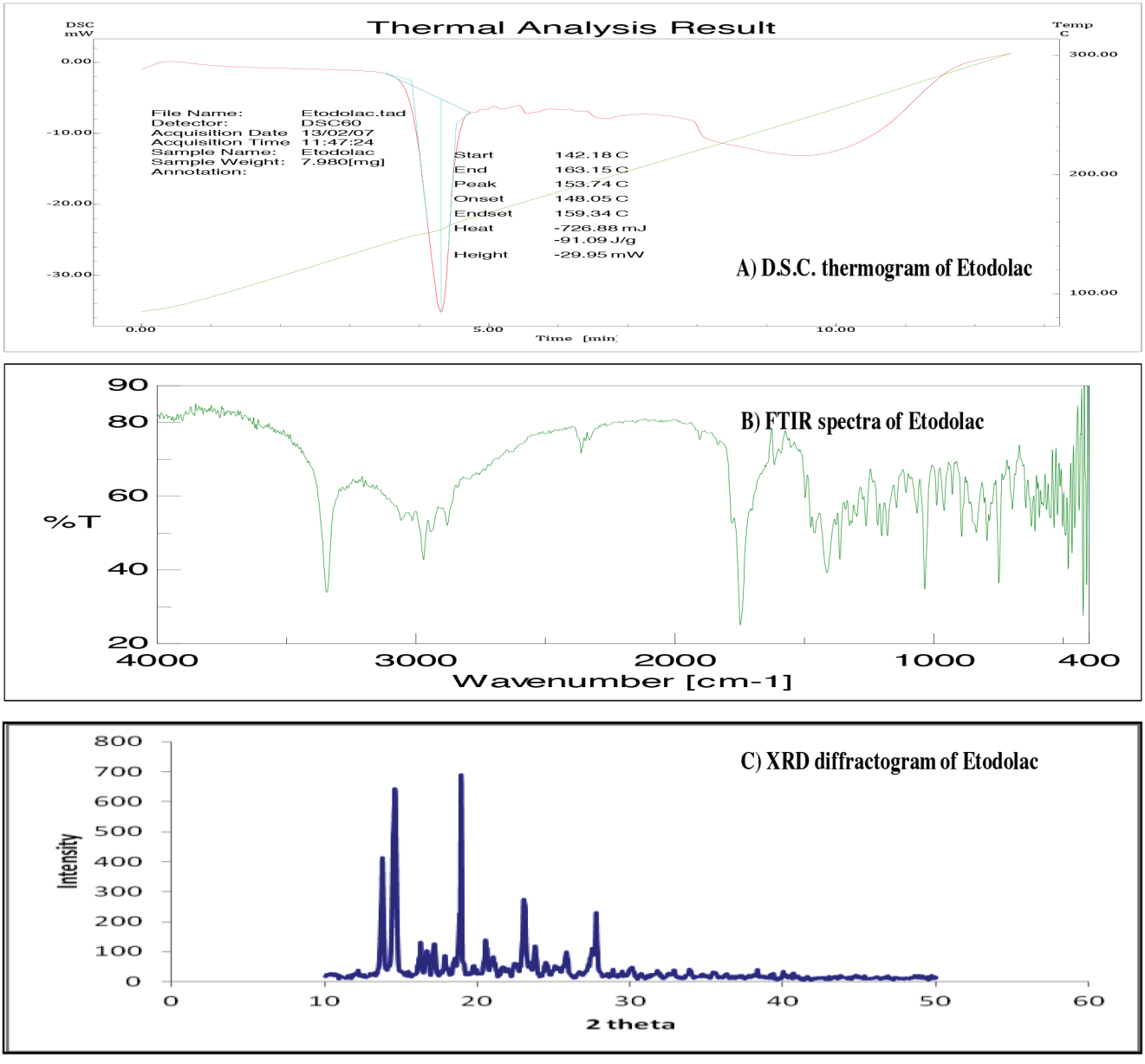
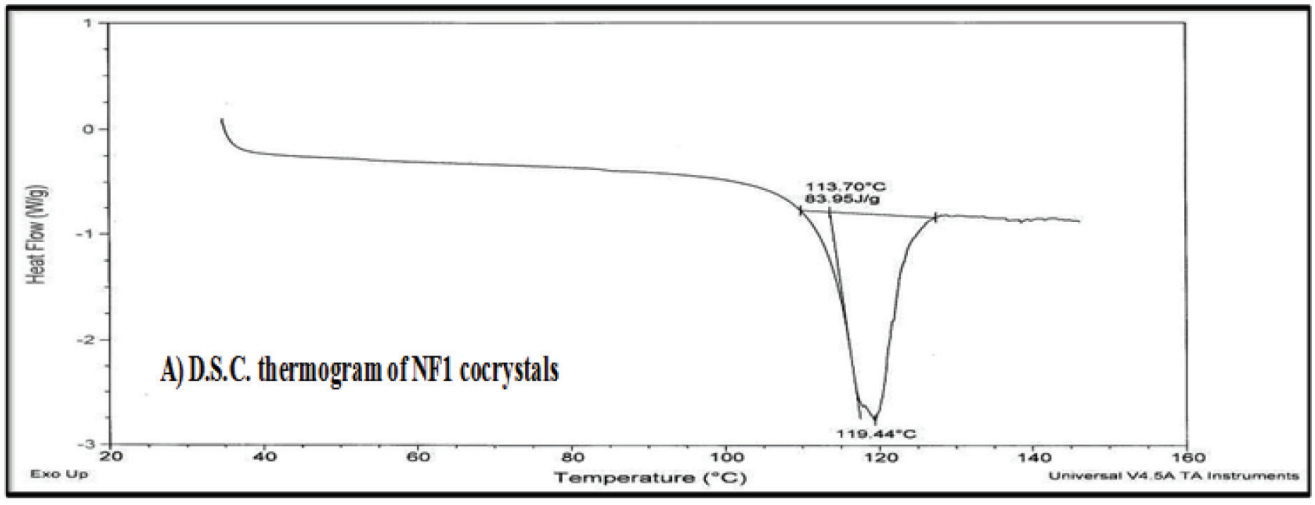
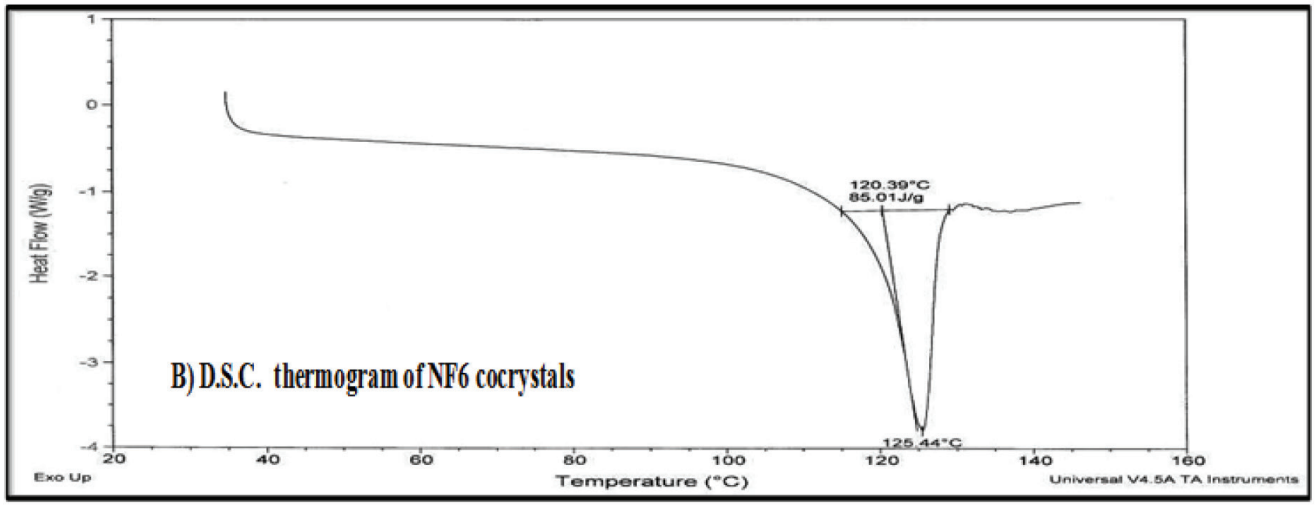


Figure 2. Thermal and spectroscopic study A) DSC thermogram of etodolac B) FTIR spectra of etodolac C) XRD diffractogram of etodolac





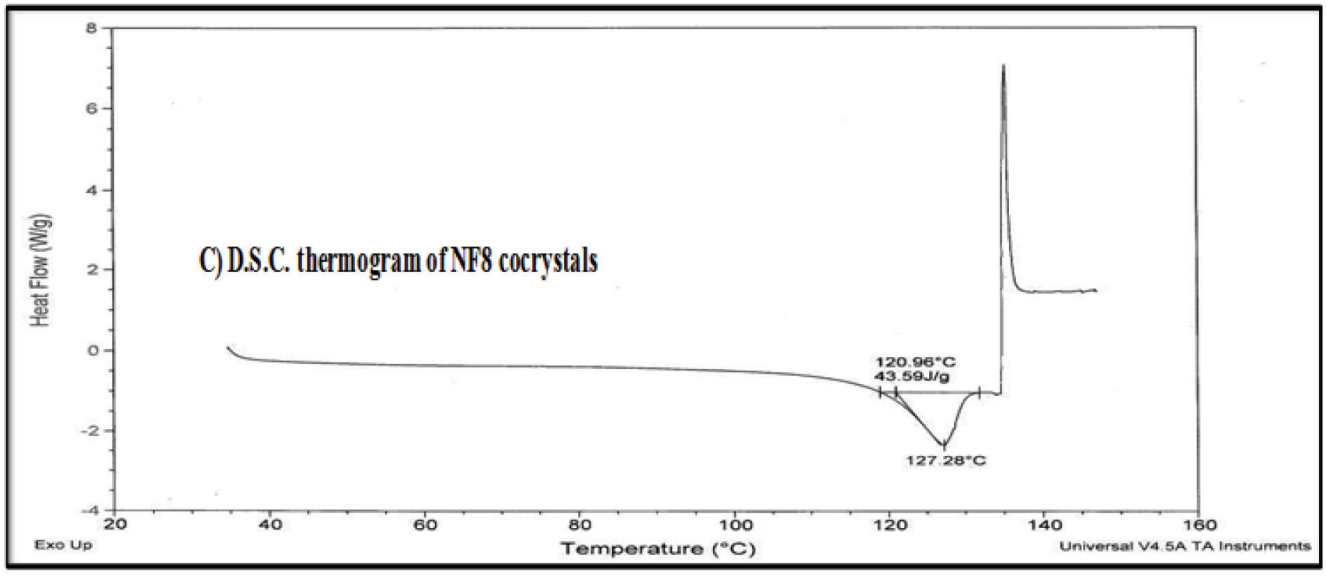


Figure 3. Thermal study (DSC Thermogram) of cocrystals A)NF1 B)NF6 C) NF8

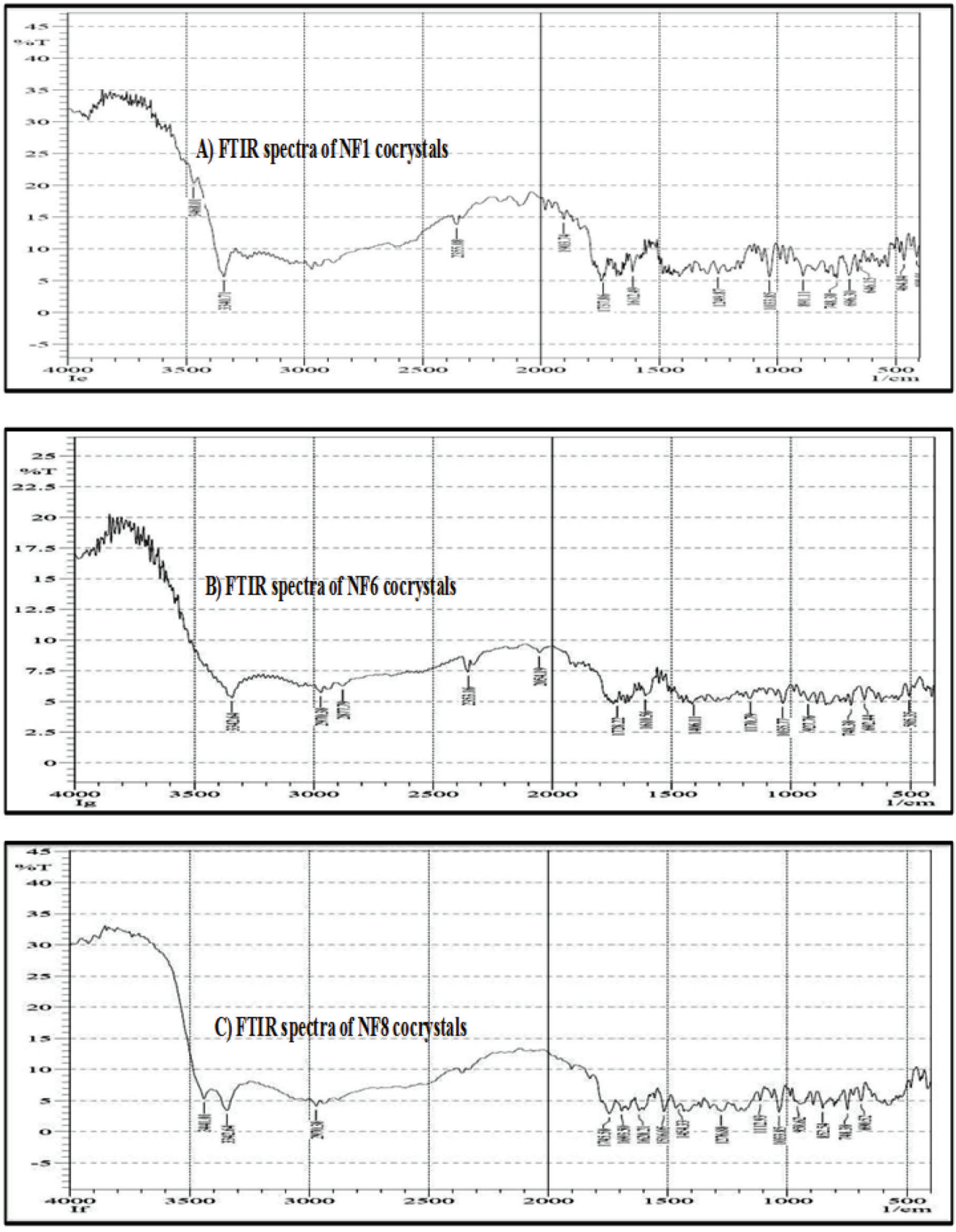


Figure 4. Spectroscopic study (FTIR Spectra) of cocrystal A) NF1 B) NF6 C) NF8

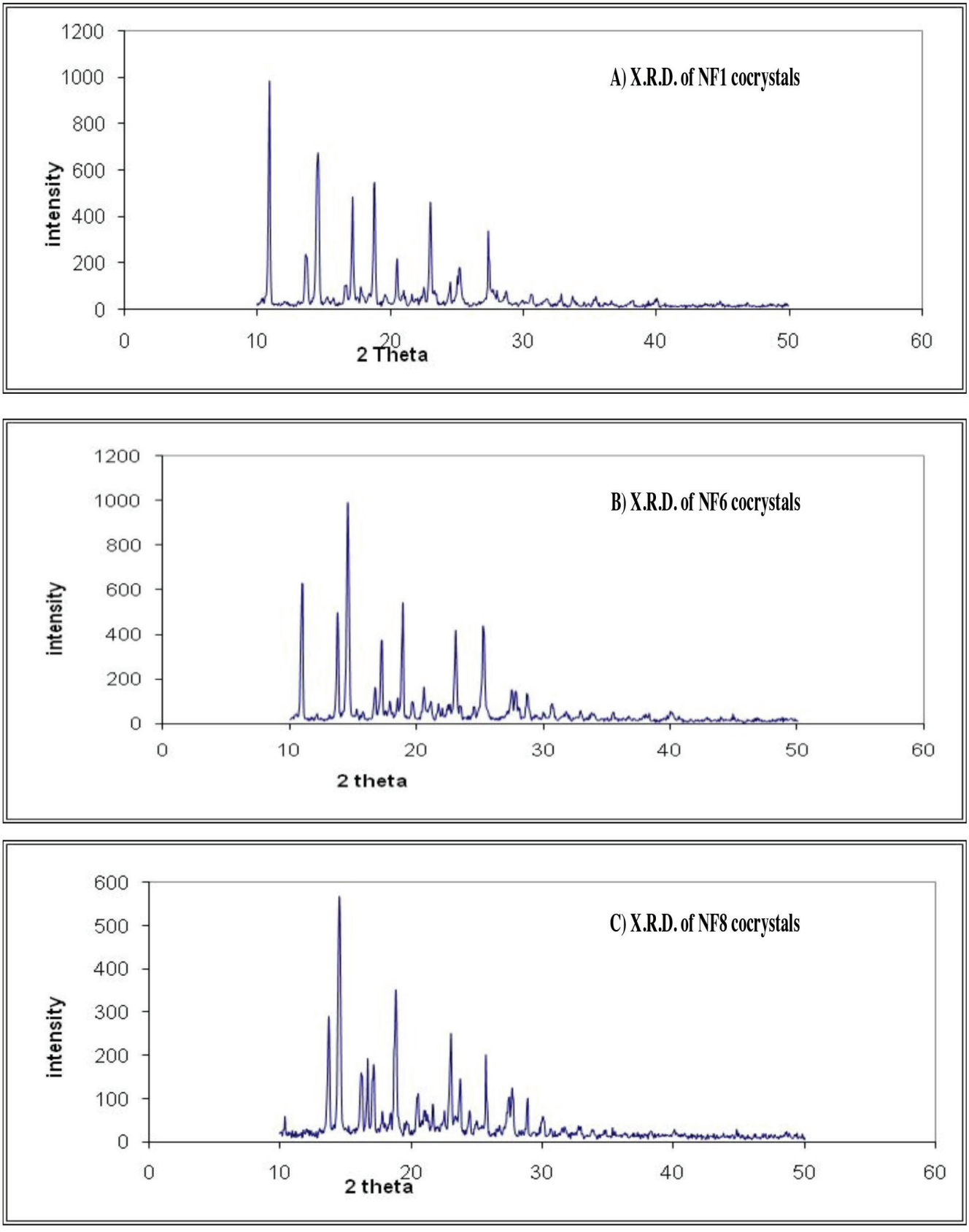


Figure 5. XRD study (diffractogram) of cocrystals A) NF1 B) NF6 C) NF8

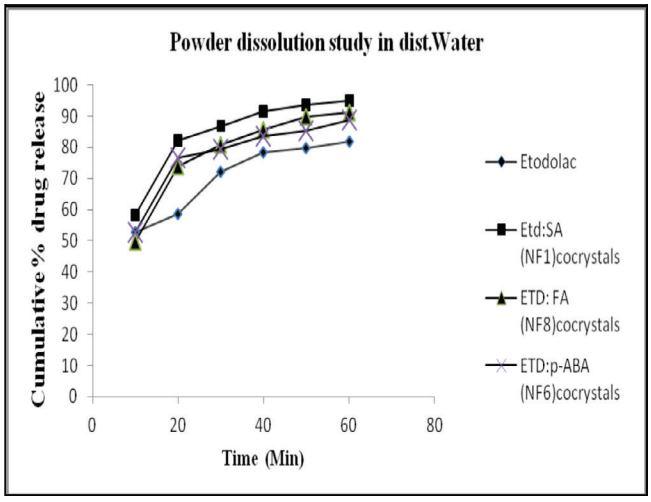


Figure 6. Powder dissolution study of API and cocrystals in dist. Water

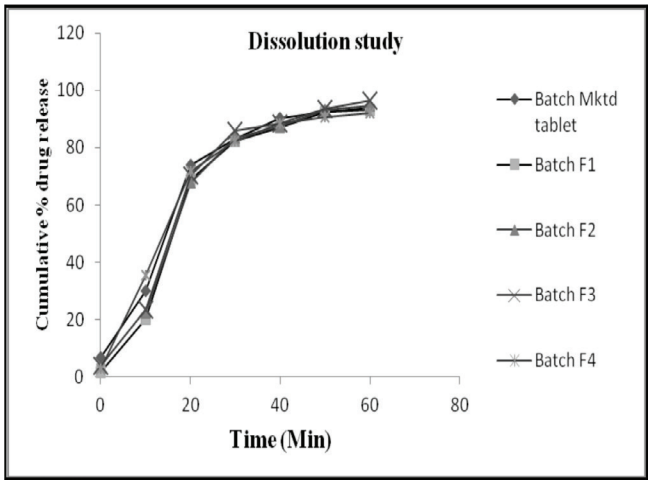


Figure 7. Dissolution study in phosphate buffer pH 6.8

The results of powder dissolution study as shown in fig.6 reveal that dissolution of etodolac was improved by co-crystallization with salicylic acid, ferulic acid and p-aminobenzoic acid. The dissolution of the wet granulation immediate release tablet batches F1 to F4 and marketed tablet showed that almost overlapping dissolution profile (Fig. 7). The Batch -F3 batch was selected as optimized batch as comparatively highest dissolution was obtained as compared to other immediate release tablet batches and found that it was stable under stability study.

3. CONCLUSION

Calculations of Hansen solubility parameters were employed for theoretical predictions of cocrystals of etodolac based on miscibility of API and cocrystal former. It shows limited scope for prediction of cocrystal formation. The neat grinding method of Edotolac cocrystal synthesis resulted in improvement of solubility with PABA, ferulic acid and salicylic acid when they are used as cocrystal formers. It can serve as green method for improving physicochemical characteristics of etodolac.

4. DECLARATION OF INTEREST

All authors approve the final manuscript and declare that there are no conflicts of interests.

5. FUNDING

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Etodolak'ın Ko-kristalizasyonu: Ko-kristalizasyon Tahmini, Ko-kristal Sentezi, Katı Faz Yapı Aydınlatma Çalışmaları ve *In Vitro* İlaç Salımı

ÖZ

Bu araştırma kapsamında, etodolak ko-kristallerinin sentezi ve farklı koformerlerin yapılarının aydınlatılması ile Hansen çözünürlük paratmetrelerinin tayini çalışılmıştır. Etodolak'ın çözünürlüğünün arttırılması ve dissolüsyon özelliğinin iyileştirilmesi amacıyla hazırlanan etodolak ko-kristallerinin farklı koformerleri izlenmiştir. Ko-Kristallerin yapısı; Fourier dönüşümlü infrared spektroskopisi (FTIR), diferansiyal taramalı kalorimetri (DSC) tayini, X-ışını kırınım (PXRD) tayini ile aydınlatılmış, ayrıca çözünürlük ve çözelti doygunluğu çalışmaları, *in vitro* dissolüsyon ve stabilite çalışmaları yapılmıştır. Çalışma sonucunda etodolak'ın, p-amino benzoik asit, ferrulik asit ve salisilik asit ile kokristalleri hazırlandığında çözünürlüğünün arttığı tespit edilmiştir. Etodolak:Salisilik ait 1:1M kokristalinin hızlı ilaç salımı için formüle edilen tablet içeriğinde kullanılması öngörülmüştür. Etodolak ko-kristallerinin yeterli farmasötik stabiliteye sahip oldukları ve etodolak'ın çözünürlük ve dissolüsyon özelliğini arttırdıkları sonucuna ulaşılmıştır.

Anahtar kelimeler: Etodolak, Ko-Kristal, Çözünürlük, Dissolüsyon, Hansen Çözünürlük Parametresi

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