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ETODOLAC DISSOLUTION IMPROVEMENT BY PREPARATION OF SOLID DISPERSIONS WITH CYCLODEXTRIN COMPLEX'S

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ABSTRACT: Etodolac is an anti-inflammatory drug that is poorly soluble in water. This paper describes an approach to improve the dissolution rate of Etodolac by using solid dispersions (SDs) in hydrophilic polymers. The solid dispersions prepared with a Co-evaporation, kneaded method & Physical Mixture method using different concentrations of α-cyclodextrin (α-CD). The release of Etodolac from various solid dispersions was determined from dissolution studies by use of USP dissolution apparatus. The dissolution study results revealed that there was a considerable increase in solubility of all solid dispersions as compared to pure drug. Prepared solid dispersions were characterized by DSC, PXRD, IR and SEM images were evaluated for drug content, saturation solubility. Physicochemical characterization of solid dispersions suggests a reduction in drug crystallinity following dissolution enhancement. Results indicate that present % DE 30 of drug was improved from 36.01 to 58.57 by the use of Etodolac α-CD-HPMC (1:2:0.3) Kneaded complex.

INTRODUCTION: Etodolac (E) is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of etodolac, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition. Etodolac (E) is a member of the pyrano carboxylic acid group of non-steroidal anti-inflammatory drugs (NSAIDs).

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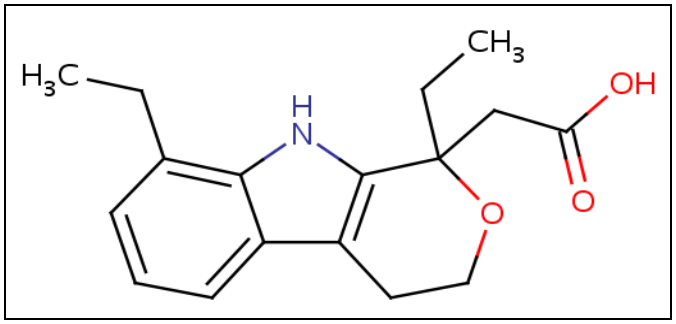
Each tablet and capsule contains 400 mg or 500 mg of etodolac for oral administration. Etodolac is a racemic mixture of [+] S and [-] R-enantiomers. Etodolac is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol. The chemical name is (±) 1, 8 -diethyl-1, 3, 4, 9-tetrahydropyrano-[3, 4-b] indole - 1 - acetic acid. The molecular weight of the base is 287.37. It has a pKa of 4.65 and an n-octanol: water partition coefficient of 11.4 at pH 7.4. The molecular formula for etodolac is $C_{17}H_{21}NO_3$, and it has the following structural formula:

Etodolac is insoluble in water and slightly soluble in simulated gastric fluid. Because of its poor aqueous solubility, Etodolac has limited dissolution

rate and thus delay in onset of action. Being a BCS class II drug, it often shows dissolution rate-limited oral absorption and high variability in pharmacological effects [1].



Therefore, improvement in its solubility and dissolution rate may lead to enhancement in its solubility and dissolution rate may lead to enhancement in bioavailability [2, 3]. Aqueous solubility of any therapeutically active substance is a key property; it governs dissolution, absorption, and thus the *in-vivo* efficacy [4]. To improve the dissolution and bioavailability of poorly water-soluble drugs, various techniques such as hot-melt extrusion [5], common solvent and solvent evaporation [6], cyclodextrin complexation [7], micronization [8], co-grinding [9], solubilization, salt formation, complexation with polymers [10], change in physical form, use of prodrug and drug derivatization, addition of surfactants have been employed.

Preparation of solid dispersions is a technique that provides deposition of the drug on the surface of certain materials that can alter the dissolution characteristics of the drug. Deposition of drug on the surface of an inert carrier leads to a reduction in the particle size of the drug, thereby providing a faster dissolution rate. Various hydrophilic materials with high surface area can be utilized for deposition of the drug on their surfaces [11]. Surface modification and solid-dispersion formulations using hydrophilic excipients can significantly alter the dissolution behavior of hydrophobic drug materials. A number of insoluble drugs have been shown to have improved dissolution character when converted to solid dispersion. Solid dispersion technology is a well-known process used to increase the dissolution kinetics and oral absorption of poorly water-soluble drugs using water-soluble inert carriers [12]. The use of hydrophilic polymers as carriers for the dissolution enhancement of poorly water-soluble drug is increasing [13].

MATERIALS AND METHODS: Etodolac was a gift sample provided by Sun Pharmaceuticals, Vadodara, India and all other materials were of pharmacopeia grade and were procured from commercial sources.

Preparation of Solid Dispersions: In each case solid complexes of drug and cyclodextrin were prepared in 1:1, 1:1:0.2, 1:2 & 1:2:0.3ratios by three methods, kneading.co-evaporation, and physical mixture.

Kneading Method: Drug and cyclodextrin with or without auxiliary substances (PEG, PVP, HPMC) were triturated in a mortar with a small volume of water. After wetting the mixture in a mortar, the thick slurry was kneaded for 45 min and then dried at 55 ºC until dry. The dried mass was pulverized, sieved through sieve no.120 and stored in desiccators till further use.

Co-evaporation Method: Drug with or without auxiliary substances (PEG, PVP, HPMC) was dissolved in methanol, stirred the solution. The solvent was removed at reduced pressure in rotary evaporator at 45 ºC for 3 h and dried mass was pulverized, sieved through sieve no. 120 and stored in desiccators until further use.

Physical Mixture: The Physical mixtures were prepared by gently mixing drug, cyclodextrin with or without auxiliary substance (PEG, PVP, and HPMC), in a mortar with pestle for 10 min. These mixtures were passed through a sieve no. 120 and stored in desiccators until further use.

Estimation of Etodolac: A spectrophotometric method based on the measurement of absorbance at 274 nm in water, phosphate buffer pH 7.4 was used in the present study for the estimation of etodolac. The stock solution of etodolac was subsequently diluted to a series of dilutions containing 5, 10, 15 and 20 µg/ml of solution, using 0.2M phosphate buffer of pH 7.4. The absorbance of these solutions was measured in UV-VIS spectrophotometer (ELICO SL - 159) at 274nm against same dilution as blank [18]. The absorbance's relating to different concentrations of etodolac in 0.2M phosphate buffer of pH 7.4 are given in **Table 1, 2, 3**.

The absorbance was plotted against concentration of etodolac, as shown in **Fig. 1**. The present analytical method obeyed Beer's law in the concentration range of 2-10 µg/ml and is suitable for the estimation of Etodolac from different solutions.

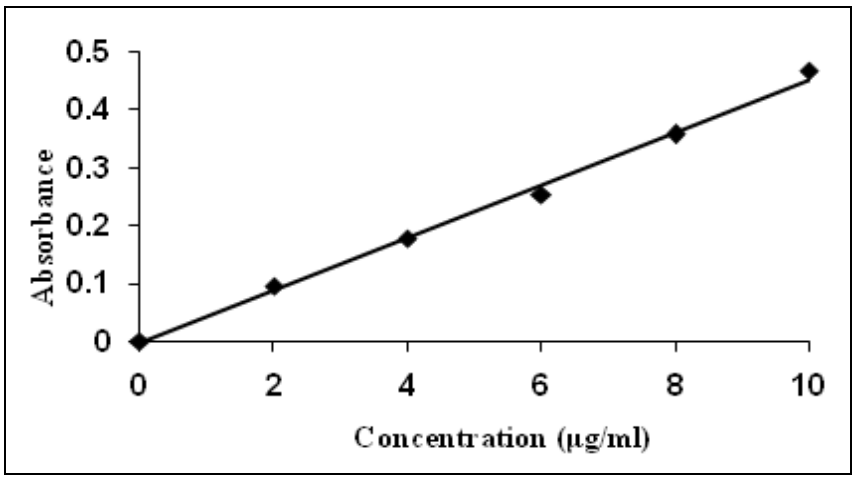


FIG. 1: CALIBRATION CURVE OF ETODOLAC IN 0.2 M PHOSPHATE BUFFER pH 7.4

TABLE 1: COMPOSITION OF VARIOUS SOLID DISPERSIONS PREPARED

S. no.	Composition		
	Drug	Carriers	SD Code
1	Etodolac	α-CD	E- α-CD (1:1)
2	Etodolac	α-CD, PEG	E- α-CD, PEG (1:1:0.2)
3	Etodolac	α-CD, PVP	E- α-CD, PVP (1:1:0.2)
4	Etodolac	α-CD, HPMC	E- α-CD, HPMC (1:1:0.2)
5	Etodolac	α-CD	E- α-CD (1:2)
6	Etodolac	α-CD, PEG	E- α-CD, PEG (1:2:0.3)
7	Etodolac	α-CD, PVP	E- α-CD, PVP (1:2:0.3)
8	Etodolac	α-CD, HPMC	E- α-CD, HPMC (1:2:0.3)

TABLE 2: ABSORBANCES OF VARIOUS CONCENTRATIONS OF ETODOLA IN 0.2M PHOSPHATE BUFFER pH 7.4

Etodolac Concentration (µg/ml)	Absorbance		
	X	SD	RSD
2	0.096	0.0111	0.122
4	0.178	0.0148	0.651
6	0.254	0.0012	0.258
8	0.358	0.0088	0.333
10	0.467	0.0048	0.149

TABLE 3: CALIBRATION CURVE FOR ETODOLAC IN 0.2 M PHOSPHATE BUFFER pH 7.4

S. no.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	2	0.096
3	4	0.178
4	6	0.254
5	8	0.358
6	10	0.467

Phase Solubility Studies: Solubility studies were performed according to the method reported by Higuchi and Connors. Excess drug (25 mg) (etodolac) was added to 15 ml of triple distilled water (pH 6.8) containing various concentrations of α-CD (0-25 mM) taken in a series of 25 ml stoppered conical flasks for etodolac and the mixtures were shaken for 72 h at room temperature (37º ± 0.5 ºC) on a rotary shaker. After 72 h of shaking to achieve equilibrium, 2 ml aliquots were withdrawn at 1-h interval and filtered immediately using 0.45-µ nylon disc filter.

The filtered samples were diluted suitably assayed for the drug content in each case by measuring the absorbance at, at 274 nm in the case of etodolac against blanks prepared in the same concentration of CD in appropriate dissolution fluid used for these drugs so as to cancel any absorbance that may be exhibited by the CD molecules. Shaking was continued until three consecutive estimations are the same in each case. The solubility experiments were conducted in triplicate.

TABLE 4: PHASE SOLUBILITY STUDIES OF ETODOLAC IN WATER

S. no.	Conc. of CD (mM)	Solubility (mM) of Etodolac
		α - CD
1	0	3.6
2	3	4.6
3	6	5.2
4	9	6.1
5	12	7.3
6	15	8.1

Estimation of Etodolacin Solid Dispersions: From each batch, 4 samples of 50 mg were taken and analyzed for Etodolac. 50 mg of dispersion was weighed and transferred into a 100 ml volumetric flask. Methanol was added and mixed the contents thoroughly to dissolve the drug from the dispersion. The solution was then filtered and collected carefully into another 100 ml volumetric flask. The solution was made up to volume with the solvent. The solution was suitably diluted with 0.2 M Phosphate buffer pH 7.4 and observed at 274 nm in water, phosphate buffer pH 7.4. The results are given in **Table 5**.

TABLE 5: DRUG CONTENT OF SOLID INCLUSION COMPLEXES OF ETODOLAC - α -CD, PREPARED BY KNEADING, COEVAPORATION, AND PHYSICAL MIXTURE METHODS

CD Complex	Percent Etodolac Content ($\bar{x}$±s.d.,)		
	Kneading Method	Coevaporation Method	Physical Mixture
E-α CD (1:1)	49.88 ± 0.56 (0.90)	49.89 ± 0.76 (0.70)	49.90 ± 0.90 (0.67)
E-α CD:PEG (1:1:0.2)	45.40 ± 0.27 (0.67)	45.39 ± 0.78 (0.56)	45.29 ± 0.87 (0.55)
E-α CD:PVP (1:1:0.2)	45.46 ± 0.45 (0.56)	44.89 ± 0.88 (0.78)	45.23 ± 0.90 (0.78)
E-α CD:HPMC (1:1:0.2)	45.50 ± 0.71 (0.95)	45.45 ± 0.80 (0.70)	44.90 ± 0.92 (0.87)
E-α CD (1:2)	33.30 ± 0.45 (0.67)	33.28 ± 0.88 (0.59)	33.36 ± 0.90 (0.65)
E-α CD:PEG (1:2:0.3)	30.31 ± 0.29 (0.68)	30.29 ± 0.90 (0.67)	29.94 ± 0.89 (0.54)
E-α CD:PVP (1:2:0.3)	30.30 ± 0.87 (0.56)	30.31 ± 0.45 (0.66)	30.29 ± 0.67 (0.76)
E-α CD:HPMC (1:2:0.3)	30.31 ± 0.90 (0.96)	30.28 ± 0.84 (0.89)	30.28 ± 0.49 (0.58)

X-ray Powder Diffractometry (XRD): The X-Ray Diffractograms of pure drugs (etodolac) exhibited characteristic diffraction pattern indicating their crystalline nature. X-ray diffractograms of pure drugs and their cyclodextrin complexes. X-ray diffraction patterns of pure drug and its cyclodextrin complexes were studied. XRD of etodolac exhibited characteristic diffraction peaks indicating their crystalline nature.

The diffractogram of cyclodextrins exhibited characteristic peaks due to its crystalline nature are shown in **Fig. 20**.

Differential Scanning Calorimetry: The DSC curve of etodolac showed a single sharp exothermic peak at 153.5 ºC corresponding to its melting point αCD, HPMC showed a broad peak associated with loss of water. In the DSC thermograms of etodolac α-CD-HPMC the intensity or height of the exothermic peak at 136.5 ºC respectively was reduced indicating interaction of etodolac with cyclodextrins. The change in symmetry of the peak clearly indicates the formation of a complex.

The exothermic peak of the cyclodextrin complexes of etodolac at 153.5 ºC was markedly reduced indicating the reduction of crystalline nature of the drug and its complexation and amorphization with cyclodextrins are shown in **Fig. 21**.

Fourier-Transform Infrared Spectroscopy (FTIR): The principal IR absorption peaks of etodolac characteristic ketone (C=O) stretching vibration at 1743 cm^{-1}, C-H bending at 1411 cm^{-1}, C-O stretching at 1265.0720 cm^{-1}, C-N vibration at 1313.29 cm^{-1} and aromatic C-H stretching at 744.38 cm^{-1}.

IR absorption peaks of etodolac, HPMC, and its cyclodextrin complexes are shown in **Fig. 22**.

Scanning Electron Microscopy (SEM) Studies: The surface morphology was examined by Scanning electron microscopic studies and the photographs are shown in **Fig. 23**.

SEM is used to study the microscopic aspects of the raw materials like a pure drug, α-CD and the complexation products obtained from different methods of preparation. From SEM analysis it can be seen that pure drug particles appeared with clear surfaces. The samples were fixed on a brass stub using double-sided tape and then gold coated in vacuum by a sputter coater. The pictures were then taken at an excitation voltage of 15 kV. SEM images of etodolac and its cyclodextrin complexes.

In scanning electron microscopy, pure drugs appeared in a crystal form with clear boundaries whereas the images of cyclodextrin complexes are not having any clear boundaries for crystal surfaces and exhibited partial amorphization of the drugs by thorough entrapment into cyclodextrin cavity with loss of little crystallinity.

Dissolution Rate Studies on Solid Dispersions: Dissolution rate of E were studied using a USP XXIII six station dissolution rate test apparatus (Electro Lab). Paddle stirrer at a speed of 50 rpm and temperature of 37º ± 1 ºC were used in each test. Etodolac or solid dispersion of Etodolac equivalent to 20 mg of E was used in each dissolution rate test. Samples of dissolution medium *i.e.*, 0.1 N HCl, (5ml) were withdrawn through a filter (0.45 µ) at different time intervals, suitably diluted, and assayed for E. The dissolution experiments were conducted in triplicate. Dissolution rates of E and its solid dispersions followed first-order kinetics **Table 13, 15, 17**. Dissolution parameters such as T_{50}, DE_{30}, K_1, Percent of Etodolac dissolved in 10 minutes are given in **Table 12, 14, 16.**

RESULTS AND DISCUSSION: The dissolution rate of etodolac (E) from various cyclodextrin solid inclusion complexes were studied in 0.1 N HCl and compared with that of the un-complexed drug. The dissolution data of E-CD complexes are given in **Table 12**, and the dissolution profiles are shown in **Fig. 2, 5, 8, 11, 14, 17**. First-order plots of the etodolac **α**– CD complexes are shown in **Fig. 3, 6, 9, 12, 15, 18**. Hixson-Crowell plots of etodolac **α**–CD complexes are shown in **Fig. 4, 7, 10, 13, 16, 19**. The dissolution of Etodolac from the CD complexes was rapid and higher than that of etodolac as such.

The dissolution data were analyzed as per zero-order and first-order kinetics. The dissolution of etodolac as such and from various cyclodextrin complexes followed first-order kinetics.

The 'r' values were found to be relatively higher in the case of first-order model in all the cases **Tables 13, 15, 17**. From the slope of the first-order linear plots the dissolution rate constant (K_1) values were calculated and are given in **Table 12, 14, 16**. The dissolution efficiency (DE_{30}) values were calculated. The dissolution parameters of etodolac and its cyclodextrin complexes are summarized in **Table 12, 14, 16**. All the dissolution parameters (DP 5min, RDr, 5 min, % dissolved in 10 min., DE_{30}, and K_1) indicated rapid and higher dissolution of etodolac from the CD complexes when compared to un-complexed drug.

Dissolution Profiles of Etodolac and its Solid Dispersions:

TABLE 6: DISSOLUTION PROFILES OF ETODOLAC AND ITS α-CD COMPLEXES PREPARED BY KNEADING METHOD

Time (min)	Percent Etodolac Dissolved (x ± s.d., n=3)				
	E	E: αCD 1:1	E:αCD:PEG 1:1:0.2	E:αCD:PVP 1:1:0.2	E:αCD:HPMC 1:1:0.2
0	0	0	0	0	0
5	32.01 ± 0.95	45.98 ± 0.89	57.93 ± 0.98	65.32 ± 0.90	68.9 ± 0.98
10	37.61 ± 0.92	49.76 ± 0.96	63.49 ± 0.97	70.54 ± 0.91	72.55 ± 0.97
20	40.25 ± 0.91	52.45 ± 0.91	69.52 ± 0.94	71.65 ± 0.94	76.56 ± 0.98
30	44.14 ± 0.96	54.98 ± 0.95	72.34 ± 0.95	74.78 ± 0.95	79.9 ± 0.91
45	46.18 ± 0.91	58.34 ± 0.92	73.78 ± 0.91	77.02 ± 0.93	80.56 ± 0.92
60	48.23 ± 0.96	60.43 ± 0.93	75.23 ± 0.93	78.32 ± 0.95	83.23 ± 0.91
90	49.11 ± 0.93	63.54 ± 0.91	76.34 ± 0.92	79.74 ± 0.98	84.21 ± 0.94
120	49.16 ± 0.89	64.11 ± 0.99	77.22 ± 0.91	80.21 ± 0.96	82.45 ± 0.96

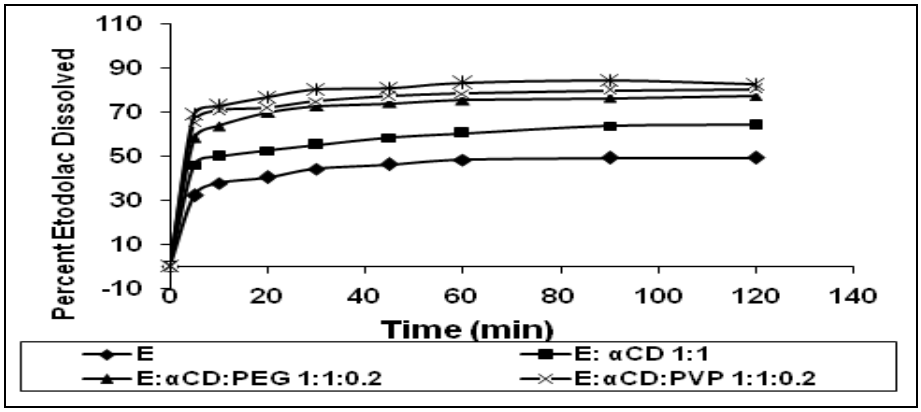


FIG. 2: DISSOLUTION PROFILES OF ETODOLAC AND ITS α-CD COMPLEXES PREPARED BY KNEADING METHOD

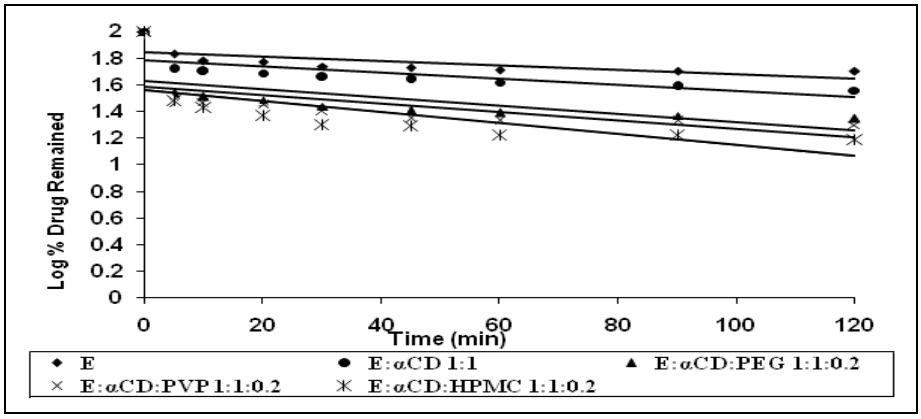


FIG. 3: FIRST ORDER DISSOLUTION PLOTS OF ETODOLAC AND ITS α-CYCLODEXTRIN COMPLEXES PREPARED BY KNEADING METHOD

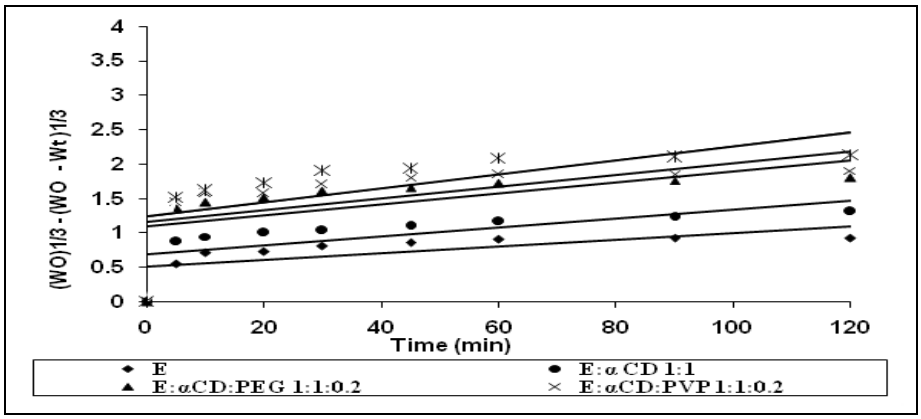


FIG. 4: HIXSON CROWELL PLOTS OF ETODOLAC AND ITS α-CD COMPLEXES PREPARED BY KNEADING METHOD

TABLE 7: DISSOLUTION PROFILES OF ETODOLAC AND ITS α -CD COMPLEXES PREPARED BY KNEADING METHOD

Time (min)	Percent Etodolac Dissolved ($x \pm$ s.d., n =3)				
	E	E: αCD 1:2	E:αCD:PEG 1:2:0.3	E:αCD:PVP 1:2:0.3	E:αCD:HPMC 1:2:0.3
0	0	0	0	0	0
5	32.01 ± 0.95	55.76 ± 0.96	61.69 ± 0.98	69.67 ± 0.98	74.56 ± 0.89
10	37.61 ± 0.92	64.53 ± 0.91	69.34 ± 0.96	72.51 ± 0.97	79.67 ± 0.86
20	40.25 ± 0.91	67.98 ± 0.92	72.34 ± 0.93	74.32 ± 0.96	82.67 ± 0.95
30	44.14 ± 0.96	69.41 ± 0.91	75.67 ± 0.90	77.56 ± 0.95	83.24 ± 0.94
45	46.18 ± 0.91	70.54 ± 0.91	78.23 ± 0.91	81.67 ± 0.92	89.34 ± 0.91
60	48.23 ± 0.96	71.56 ± 0.90	78.65 ± 0.98	84.7 ± 0.90	90.22 ± 0.92
90	49.11 ± 0.93	72.11 ± 0.96	79.27 ± 0.93	88.67 ± 0.90	91.45 ± 0.91
120	49.16 ± 0.89	72.23 ± 0.93	79.78 ± 0.96	89.32 ± 0.89	92.56 ± 0.90

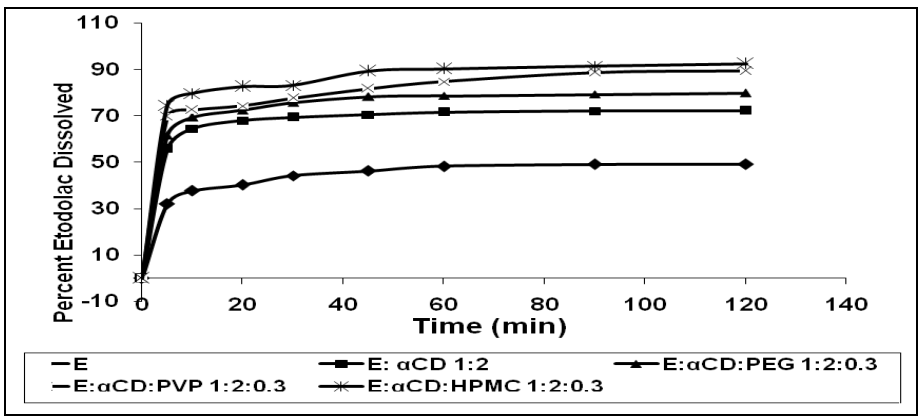


FIG. 5: DISSOLUTION PROFILES OF ETODOLAC AND ITS α-CD COMPLEXES PREPARED BY KNEADING METHOD

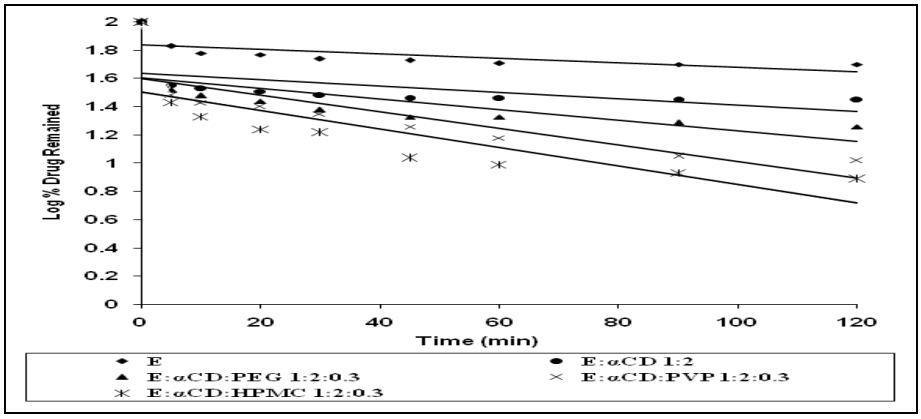


FIG. 6: FIRST ORDER DISSOLUTION PLOTS OF ETODOLAC AND ITS α-CYCLODEXTRIN COMPLEXES PREPARED BY KNEADING METHOD

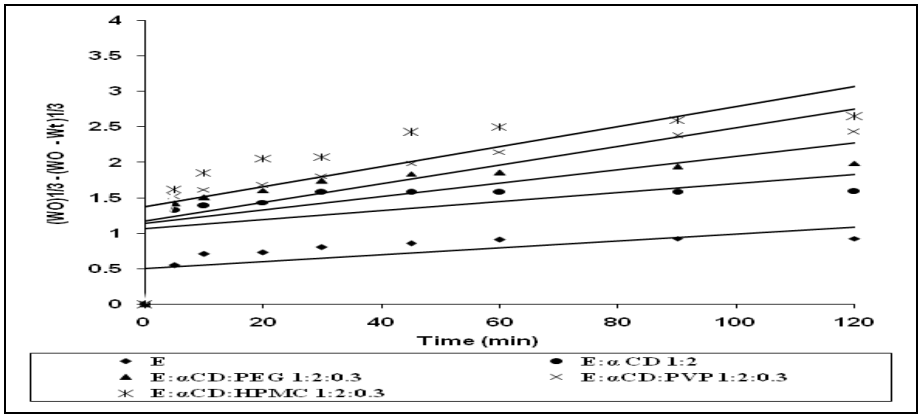


FIG. 7: HIXSON CROWELL PLOTS OF ETODOLAC AND ITS α-CD COMPLEXES PREPARED BY KNEADING METHOD

TABLE 8: DISSOLUTION PROFILES OF ETODOLAC AND ITS α-CD COMPLEXES PREPARED BY COEVAPORATION METHOD

Time (min)	Percent Etodolac Dissolved (x ± s.d., n=3)				
	E	E: αCD 1:1	E:αCD:PEG 1:1:0.2	E:αCD:PVP 1:1:0.2	E:αCD:HPMC 1:1:0.2
0	0	0	0	0	0
5	32.01 ± 0.95	40.62 ± 0.92	48.78 ± 0.91	53.65 ± 0.93	56.24 ± 0.90
10	37.61 ± 0.92	43.45 ± 0.91	51.98 ± 0.98	57.65 ± 0.98	64.65 ± 0.91
20	40.25 ± 0.91	47.46 ± 0.98	59.23 ± 0.96	63.42 ± 0.95	70.54 ± 0.98
30	44.14 ± 0.96	49.56 ± 0.91	60.35 ± 0.92	66.67 ± 0.96	73.65 ± 0.94
45	46.18 ± 0.91	50.76 ± 0.90	63.23 ± 0.92	68.43 ± 0.98	75.54 ± 0.96
60	48.23 ± 0.96	53.34 ± 0.93	66.76 ± 0.91	72.34 ± 0.93	78.32 ± 0.93
90	49.11 ± 0.93	54.56 ± 0.91	69.28 ± 0.97	73.23 ± 0.98	79.12 ± 0.91
120	49.16 ± 0.89	57.45 ± 0.92	70.32 ± 0.98	74.65 ± 0.91	80.11 ± 0.93

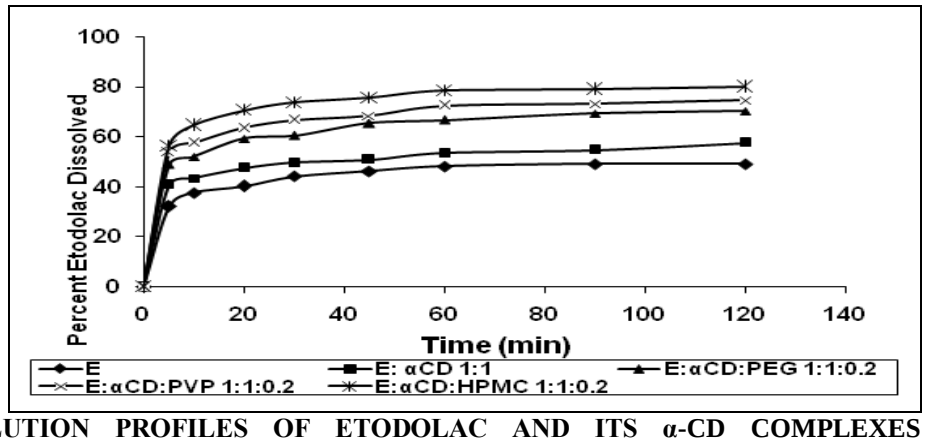


FIG. 8: DISSOLUTION PROFILES OF ETODOLAC AND ITS α-CD COMPLEXES PREPARED BY COEVAPORATION METHOD

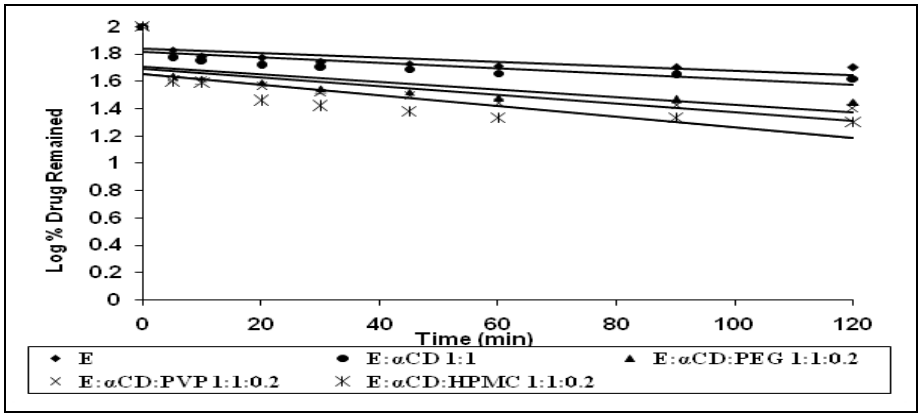


FIG. 9: FIRST ORDER DISSOLUTION PLOTS OF ETODOLAC AND ITS α-CYCLODEXTRIN COMPLEXES PREPARED BY COEVAPORATION METHOD

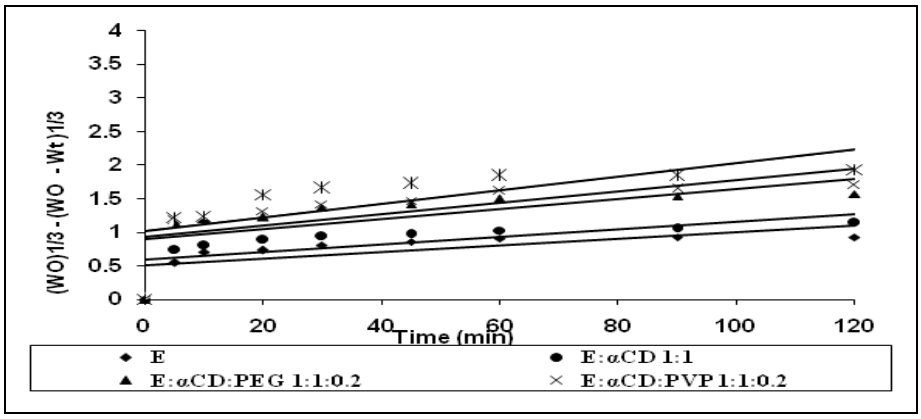


FIG. 10: HIXSON CROWELL PLOTS OF ETODOLAC AND ITS α-CD COMPLEXES PREPARED BY COEVAPORATION METHOD

TABLE 9: DISSOLUTION PROFILES OF ETODOLAC AND ITS α -CD COMPLEXES PREPARED BY COEVAPORATION METHOD

Time (min)	Percent Etodolac Dissolved (x ± s.d., n=3)				
	E	E: αCD 1:2	E:αCD:PEG 1:2:0.3	E:αCD:PVP 1:2:0.3	E:αCD:HPMC 1:2:0.3
0	0	0	0	0	0
5	32.01 ± 0.95	47.35 ± 0.92	53.67 ± 0.90	58.65 ± 0.90	64.65 ± 0.91
10	37.61 ± 0.92	50.32 ± 0.91	59.67 ± 0.91	64.56 ± 0.95	72.43 ± 0.95
20	40.25 ± 0.91	54.33 ± 0.94	62.23 ± 0.92	67.89 ± 0.96	74.65 ± 0.98
30	44.14 ± 0.96	56.26 ± 0.92	66.78 ± 0.93	70.23 ± 0.93	76.87 ± 0.94
45	46.18 ± 0.91	59.34 ± 0.96	69.54 ± 0.98	75.65 ± 0.91	79.32 ± 0.91
60	48.23 ± 0.96	62.32 ± 0.91	72.23 ± 0.94	80.43 ± 0.90	81.23 ± 0.90
90	49.11 ± 0.93	63.65 ± 0.90	73.34 ± 0.93	83.67 ± 0.92	86.46 ± 0.92
120	49.16 ± 0.89	64.23 ± 0.91	75.67 ± 0.92	84.32 ± 0.93	89.22 ± 0.90

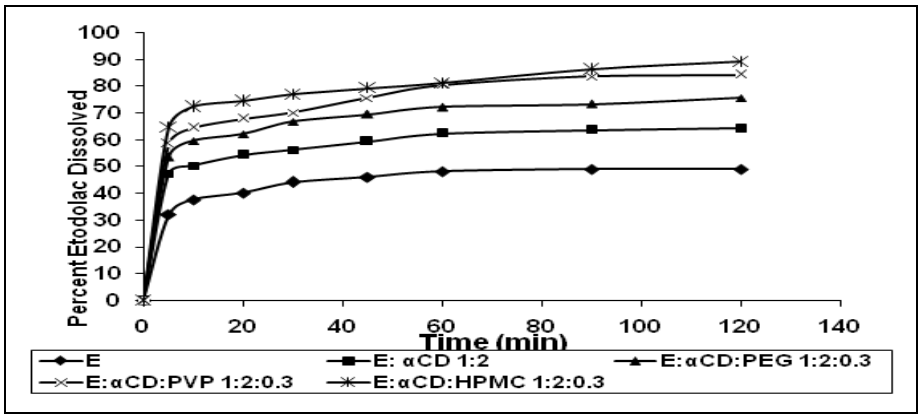


FIG. 11: DISSOLUTION PROFILES OF ETODOLAC AND ITS α-CD COMPLEXES PREPARED BY COEVAPORATION METHOD

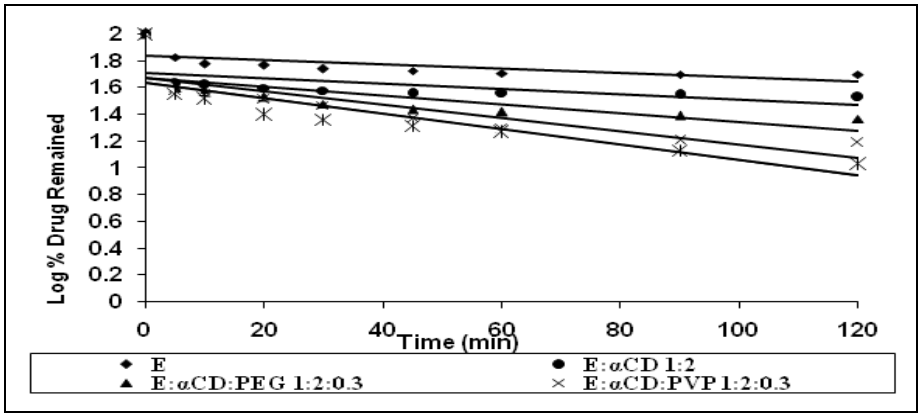


FIG. 12: FIRST ORDER DISSOLUTION PLOTS OF ETODOLAC AND ITS α-CYCLODEXTRIN COMPLEXES PREPARED BY COEVAPORATION METHOD

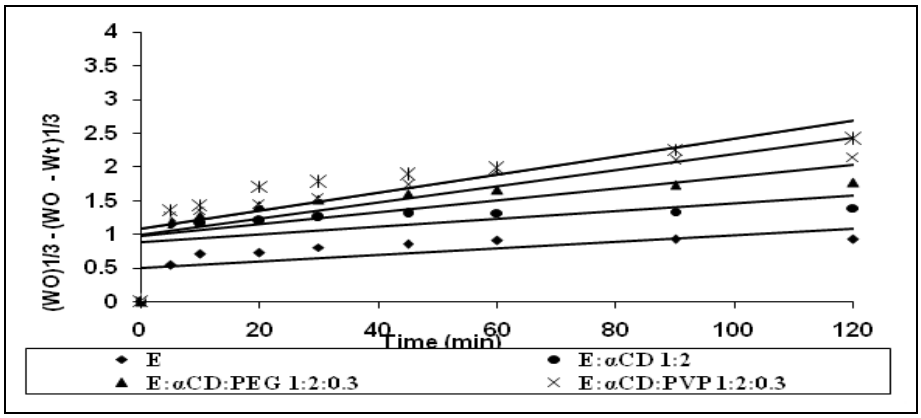


FIG. 13: HIXSON CROWELL PLOTS OF ETODOLAC AND ITS α-CD COMPLEXES PREPARED BY COEVAPORATION METHOD

TABLE 10: DISSOLUTION PROFILES OF ETODOLAC AND ITS A-CD COMPLEXES PREPARED BY PHYSICAL MIXTURE METHOD

Time (min)	Percent Etodolac Dissolved (x ± s.d., n=3)				
	E	E: αCD 1:1	E:αCD:PEG 1:1:0.2	E:αCD:PVP 1:1:0.2	E:αCD:HPMC 1:1:0.2
0	0	0	0	0	0
5	32.01 ± 0.95	35.53 ± 0.91	47.91 ± 0.91	50.12 ± 0.91	54.87 ± 0.96
10	37.61 ± 0.92	41.52 ± 0.96	49.62 ± 0.96	51.92 ± 0.96	56.98 ± 0.90
20	40.25 ± 0.91	44.96 ± 0.95	50.31 ± 0.97	58.49 ± 0.93	58.13 ± 0.91
30	44.14 ± 0.96	46.82 ± 0.97	53.82 ± 0.95	60.92 ± 0.91	68.11 ± 0.96
45	46.18 ± 0.91	47.92 ± 0.86	57.96 ± 0.96	61.41 ± 0.92	70.22 ± 0.92
60	48.23 ± 0.96	50.12 ± 0.89	59.98 ± 0.91	63.98 ± 0.90	72.33 ± 0.93
90	49.11 ± 0.93	51.12 ± 0.96	60.82 ± 0.90	64.92 ± 0.89	73.16 ± 0.98
120	49.16 ± 0.89	53.56 ± 0.91	63.93 ± 0.96	69.16 ± 0.86	74.92 ± 0.93

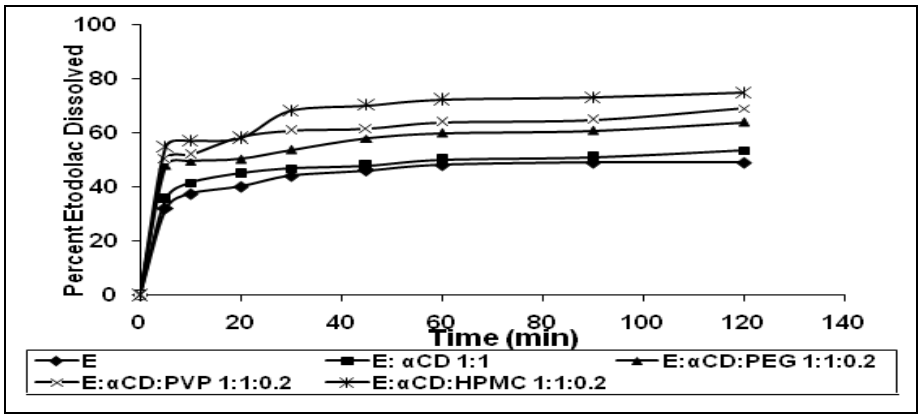


FIG. 14: DISSOLUTION PROFILES OF ETODOLAC AND ITS α-CD COMPLEXES PREPARED BY PHYSICAL MIXTURE METHOD

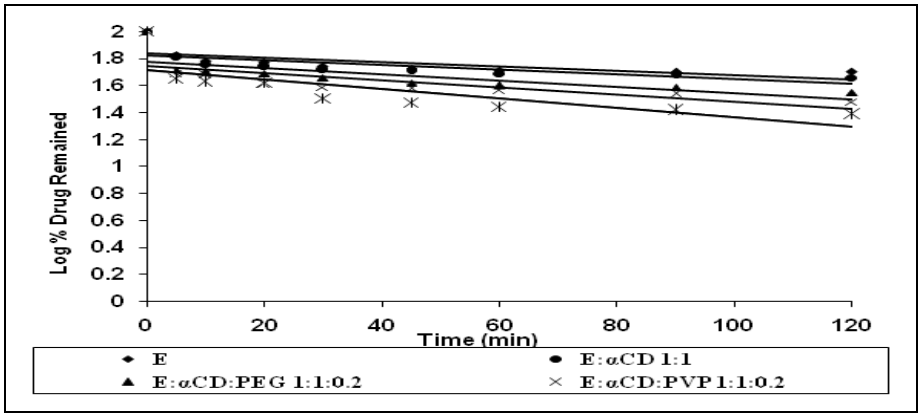


FIG. 15: FIRST ORDER DISSOLUTION PLOTS OF ETODOLAC AND ITS α -CYCLODEXTRIN COMPLEXES PREPARED BY PHYSICAL MIXTURE METHOD

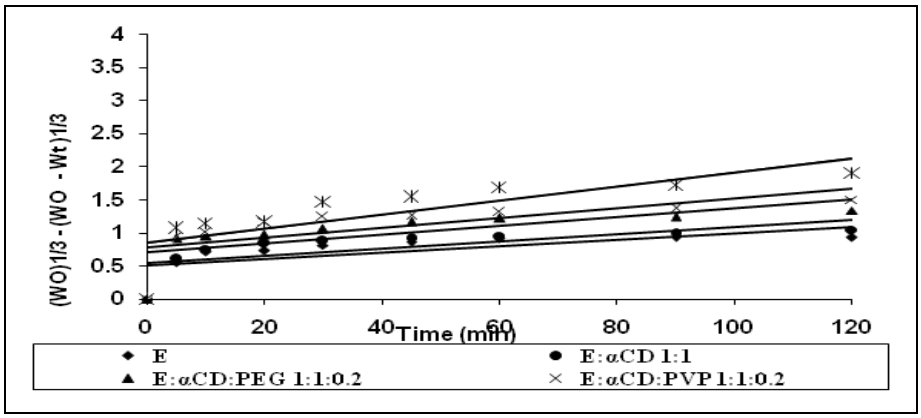


FIG. 16: HIXSON CROWELL PLOTS OF ETODOLAC AND ITS α-CD COMPLEXES PREPARED BY PHYSICAL MIXTURE METHOD

TABLE 11: DISSOLUTION PROFILES OF ETODOLAC AND ITS α -CD COMPLEXES PREPARED BY PHYSICAL MIXTURE METHOD

Time (min)	Percent Etodolac Dissolved (x ± s.d., n=3)				
	E	E: αCD 1:2	E:αCD:PEG 1:2:0.3	E:αCD:PVP 1:2:0.3	E:αCD:HPMC 1:2:0.3
0	0	0	0	0	0
5	32.01±0.95	39.23±0.92	43.92±0.98	52.23±0.98	59.32±0.90
10	37.61±0.92	43.26±0.90	48.89±0.97	54.76±0.91	60.11±0.91
20	40.25±0.91	47.93±0.91	52.66±0.94	56.9±0.92	64.68±0.92
30	44.14±0.96	50.11±0.95	56.77±0.98	64.17±0.91	71.32±0.93
45	46.18±0.91	51.12±0.94	58.93±0.95	66.56±0.90	72.66±0.90
60	48.23±0.96	53.56±0.93	59.15±0.96	69.32±0.92	74.32±0.92
90	49.11±0.93	54.33±0.98	62.16±0.93	71.9±0.96	75.45±0.93
120	49.16±0.89	55.12±0.93	63.44±0.91	74.16±0.93	79.22±0.93

TABLE 12: DISSOLUTION PARAMETERS OF ETODOLAC AND ITS CYCLODEXTRIN COMPLEXES PREPARED BY KNEADING METHOD

S. no.	CD Complex	$DP_{5\ MIN}$	$RD_{r\ 5min}$	%Dissolved in 10 min	DE_{30}	K_1 (min^{-1})	Increase in K_1 (No. of folds)
1	Etodolac	32.01	--	39.61	36.01	0.0037	-
2	E:αCD 1:1	46.92	1.45	49.78	46.62	0.069	18.67
3	E: αCD 1:2	64.38	1.99	65.74	61.13	0.108	29.25
4	E: αCD:PEG 1:1:0.2	65.22	2.02	67.32	62.90	0.113	30.49
5	E: αCD:PEG 1:2:0.3	66.63	2.06	69.32	65.06	0.119	32.37
6	E: αCD:PVP 1:1:0.2	67.89	2.08	70.51	65.16	0.124	33.61
7	E: αCD:PVP 1:2:0.3	69.63	2.15	72.56	67.03	0.131	35.47
8	E: αCD:HPMC 1:1:0.2	69.83	2.16	72.63	68.53	0.132	35.47
9	E: αCD:HPMC 1:2:0.3	72.61	2.25	78.56	73.05	0.144	39.24

TABLE 13: THE CORRELATION COEFFICIENT VALUES IN THE ANALYSIS OF DISSOLUTION DATA OF ETODOLAC CYCLODEXTRIN COMPLEXES PREPARED BY KNEADING METHOD AS PER ZERO ORDER, FIRST ORDER AND HIXSON-CROWELL CUBE ROOT MODELS

S. no.	Cyclodextrin complex	Correlation Coefficient (R^2) value		
		Zero Order	First Order	Hixson Crowell
1	Etodolac	0.803	0.758	0.889
2	E:αCD 1:1	0.890	0.894	0.897
3	E: αCD 1:2	0.825	0.884	0.884
4	E: αCD:PEG 1:1:0.2	0.879	0.892	0.886
5	E: αCD:PEG 1:2:0.3	0.882	0.898	0.891
6	E: αCD:PVP 1:1:0.2	0.885	0.882	0.903
7	E: αCD:PVP 1:2:0.3	0.883	0.902	0.892
8	E: αCD:HPMC 1:1:0.2	0.880	0.902	0.892
9	E: αCD:HPMC 1:2:0.3	0.897	0.933	0.917

TABLE 14: DISSOLITION PARAMETERS OF ETODOLAC AND ITS CYCLODEXTRIN COMPLEXES PREPARED BY COEVAPORATION METHOD

S. no.	Cyclodextrin Complex	$DP_{5\ MIN}$	$RD_{r\ 5min}$	%Dissolved in 10 min	DE_{30}	K_1 (min^{-1})	Increase in K_1 (No. of folds)
1	Etodolac	32.01	--	39.61	36.01	0.0037	-
2	E:αCD 1:1	40.62	1.25	43.45	41.72	0.014	3.08
3	E: αCD 1:2	57.32	1.77	58.23	54.11	0.023	6.26
4	E: αCD:PEG 1:1:0.2	57.98	1.79	59.29	55.40	0.092	24.89
5	E: αCD:PEG 1:2:0.3	59.62	1.84	62.27	59.37	0.099	26.76
6	E: αCD:PVP 1:1:0.2	58.69	1.81	59.89	56.90	0.092	24.89
7	E: αCD:PVP 1:2:0.3	61.66	1.90	64.58	60.51	0.103	28.01
8	E: αCD:HPMC 1:1:0.2	59.87	1.85	60.16	60.85	0.095	25.52
9	E: αCD:HPMC 1:2:0.3	64.63	2.00	66.89	65.20	0.111	29.87

TABLE 15: THE CORRELATION COEFFICIENT (R) VALUES IN THE ANALYSIS OF DISSOLUTION DATA OF ETODOLAC CYCLODEXTRIN COMPLEXES APREPARED BY COEVAPORATION METHODS PER ZERO ORDER, FIRST ORDER AND HIXSON-CROWELL CUBE ROOT MODELS

S. no.	Cyclodextrin complex	Correlation Coefficient (R^2) value		
		Zero Order	First Order	Hixson Crowell
1	Etodolac	0.803	0.803	0.901
2	E:αCD 1:1	0.678	0.722	0.898
3	E: αCD 1:2	0.647	0.877	0.873
4	E: αCD:PEG 1:1:0.2	0.682	0.897	0.890
5	E: αCD:PEG 1:2:0.3	0.663	0.895	0.892
6	E: αCD:PVP 1:1:0.2	0.731	0.891	0.876
7	E: αCD:PVP 1:2:0.3	0.661	0.895	0.894
8	E: αCD:HPMC 1:1:0.2	0.781	0.876	0.873
9	E: αCD:HPMC 1:2:0.3	0.627	0.837	0.887

TABLE 16: DISSOLUTION PARAMETERS OF ETODOLAC AND ITS CYCLODEXTRIN COMPLEXES PREPARED BY PHYSICAL MIXTURE METHOD

S. no.	Cyclodextrin complex	$DP_{5\ MIN}$	$RD_{r\ 5min}$	%Dissolved in 10 min	DE_{30}	K_1 (min^{-1})	Increase in K_1 (No. of folds)
1	Etodolac	32.01	--	37.61	36.01	0.0037	-
2	E:αCD 1:1	35.53	1.06	41.52	39.07	0.055	14.94
3	E: αCD 1:2	43.26	1.29	47.93	46.51	0.066	18.05
4	E: αCD:PEG 1:1:0.2	47.91	1.43	49.62	46.13	0.069	18.67
5	E: αCD:PEG 1:2:0.3	48.92	1.46	52.61	50.15	0.076	20.54
6	E: αCD:PVP 1:1:0.2	50.16	1.50	51.92	50.92	0.074	19.92
7	E: αCD:PVP 1:2:0.3	53.72	1.61	55.99	53.37	0.083	22.41
8	E: αCD:HPMC 1:1:0.2	54.83	1.64	56.99	54.14	0.085	23.06
9	E: αCD:HPMC 1:2:0.3	59.32	1.66	60.16	58.57	0.088	24.01

TABLE 17: THE CORRELATION COEFFICIENT VALUES IN THE ANALYSIS OF DISSOLUTION DATA OF ETODOLAC CYCLODEXTRIN COMPLEXES APREPARED BY PHYSICAL MIXTURE METHOD PER ZERO ORDER, FIRST ORDER AND HIXSON-CROWELL CUBE ROOT MODELS

S. no.	Cyclodextrin complex	Correlation Coefficient (R^2) value		
		Zero Order	First Order	Hixson Crowell
1	Etodolac	0.758	0.803	0.898
2	E:αCD 1:1	0.800	0.947	0.947
3	E: αCD 1:2	0.805	0.922	0.915
4	E: αCD:PEG 1:1:0.2	0.880	0.910	0.884
5	E: αCD:PEG 1:2:0.3	0.895	0.904	0.903
6	E: αCD:PVP 1:1:0.2	0.880	0.879	0.885
7	E: αCD:PVP 1:2:0.3	0.738	0.889	0.889
8	E: αCD:HPMC 1:1:0.2	0.882	0.889	0.912
9	E: αCD:HPMC 1:2:0.3	0.889	0.901	0.920

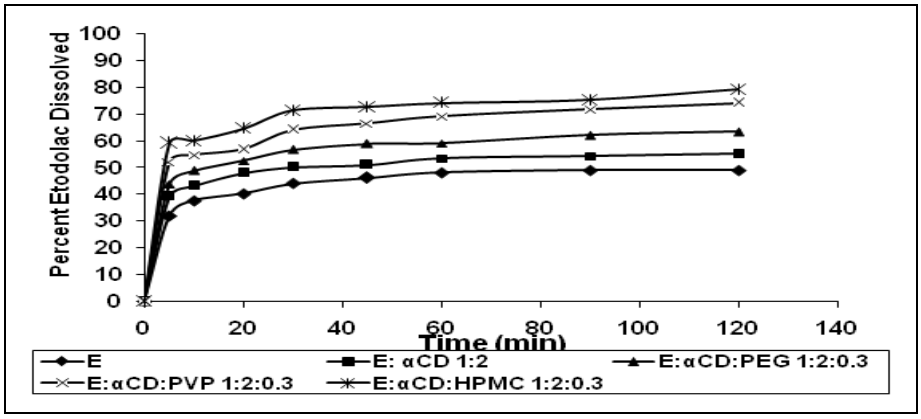


FIG. 17: DISSOLUTION PROFILES OF ETODOLAC AND ITS α-CD COMPLEXES PREPARED BY PHYSICAL MIXTURE METHOD

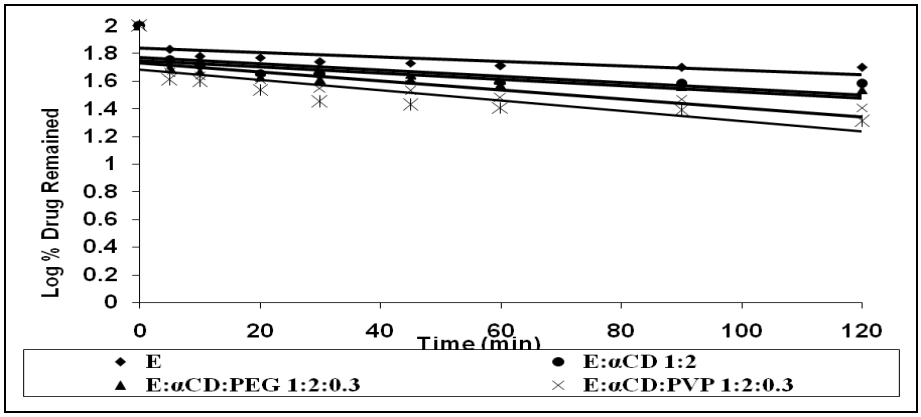


FIG. 18: FIRST ORDER DISSOLUTION PLOTS OF ETODOLAC AND ITS α-CYCLODEXTRIN COMPLEXES PREPARED BY PHYSICAL MIXTURE METHOD

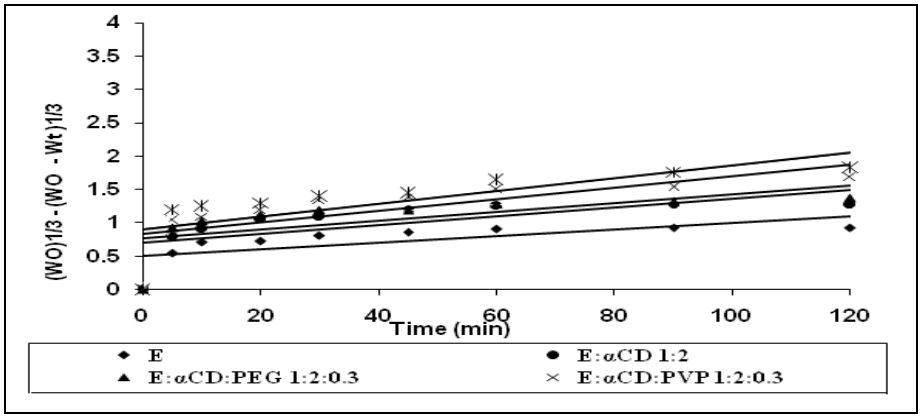


FIG. 19: HIXSON CROWELL PLOTS OF ETODOLAC AND ITS α-CD COMPLEXES PREPARED BY PHYSICAL MIXTURE METHOD

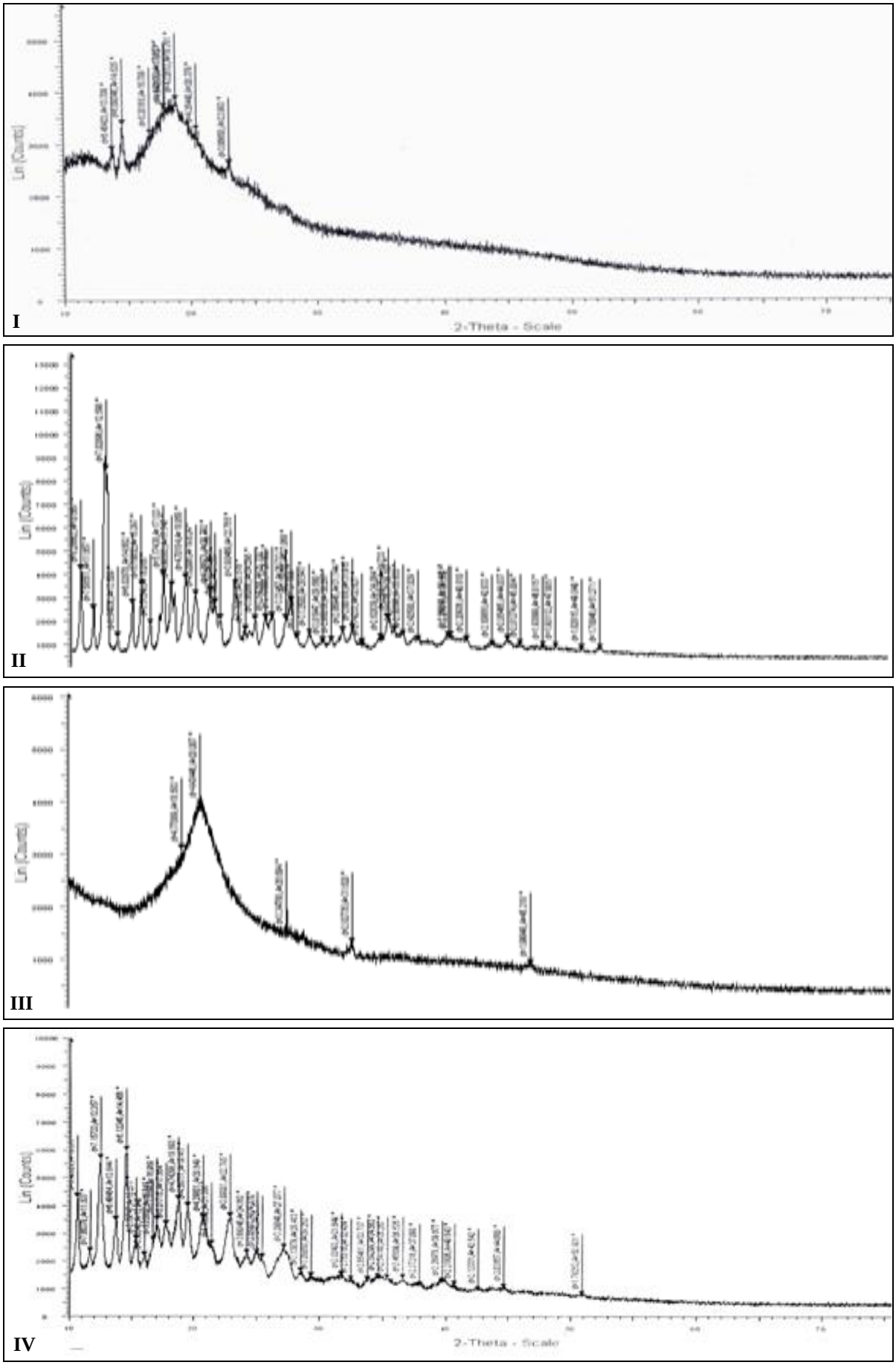


FIG. 20: XRD SPECTRA OF (i) Etodolac (ii) α-CD (iii) HPMC iv) Etodolac: α-CD-HPMC

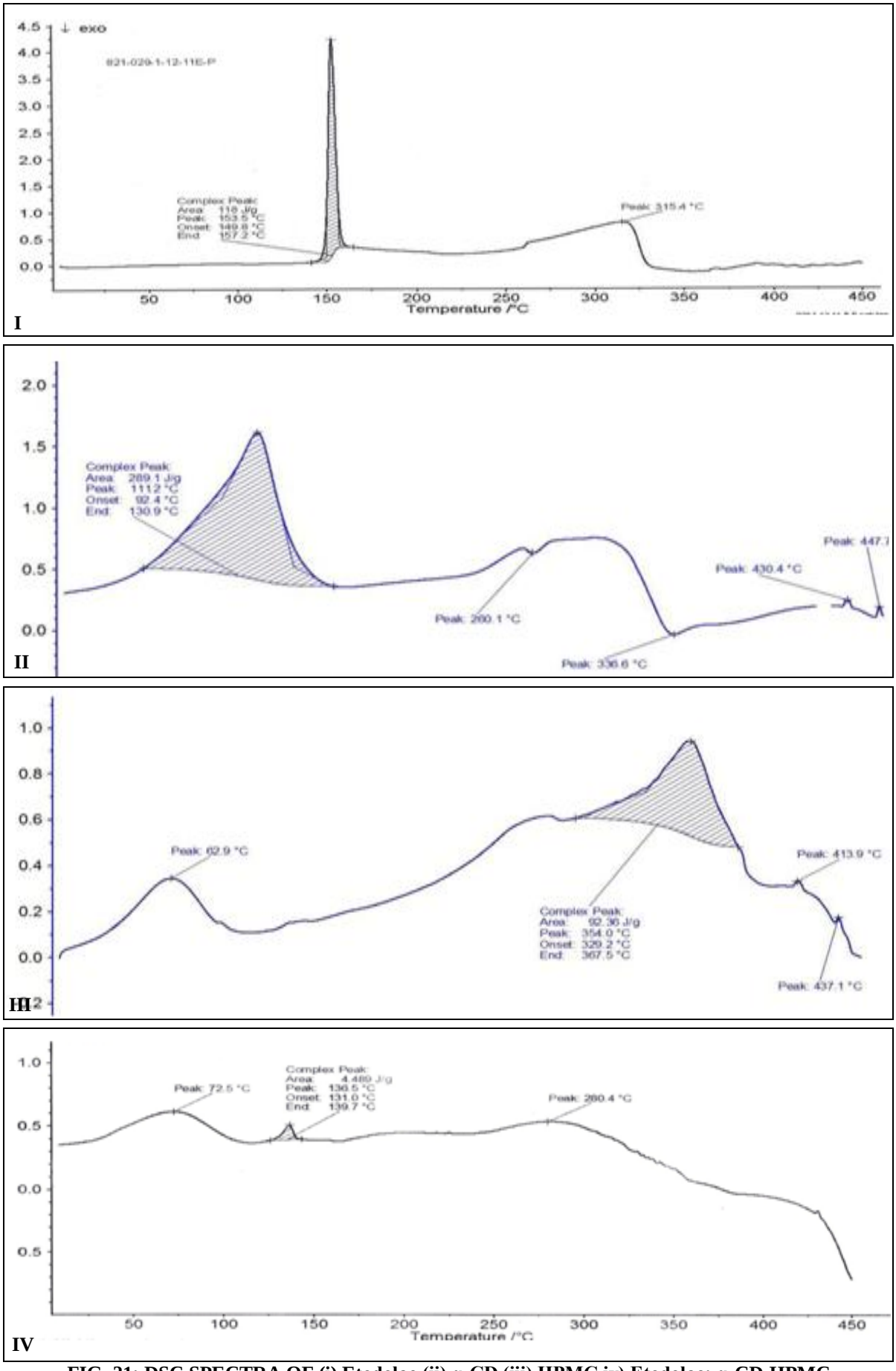


FIG. 21: DSC SPECTRA OF (i) Etodolac (ii) α-CD (iii) HPMC iv) Etodolac: α-CD-HPMC

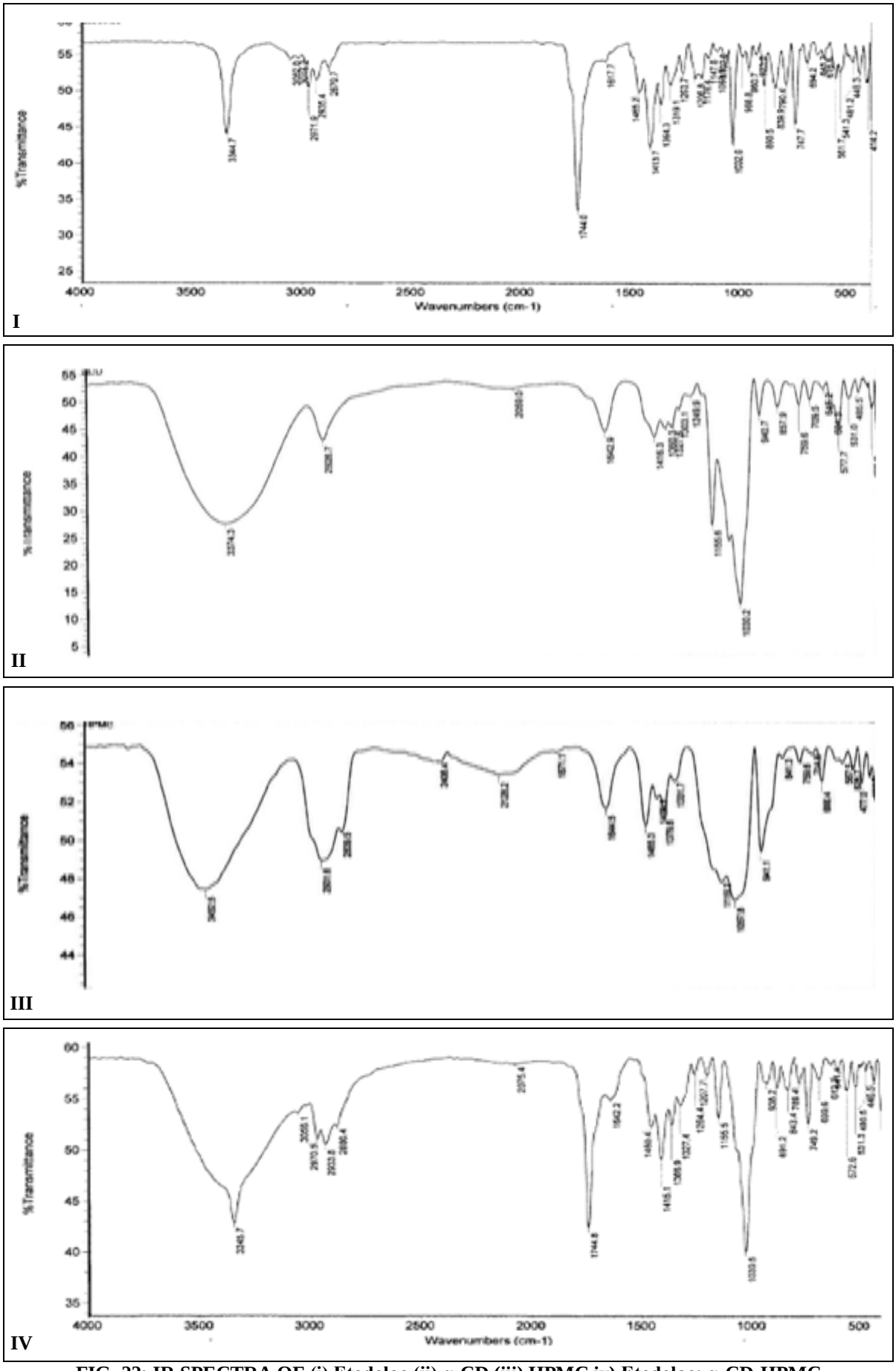


FIG. 22: IR SPECTRA OF (i) Etodolac (ii) α-CD (iii) HPMC iv) Etodolac: α-CD-HPMC

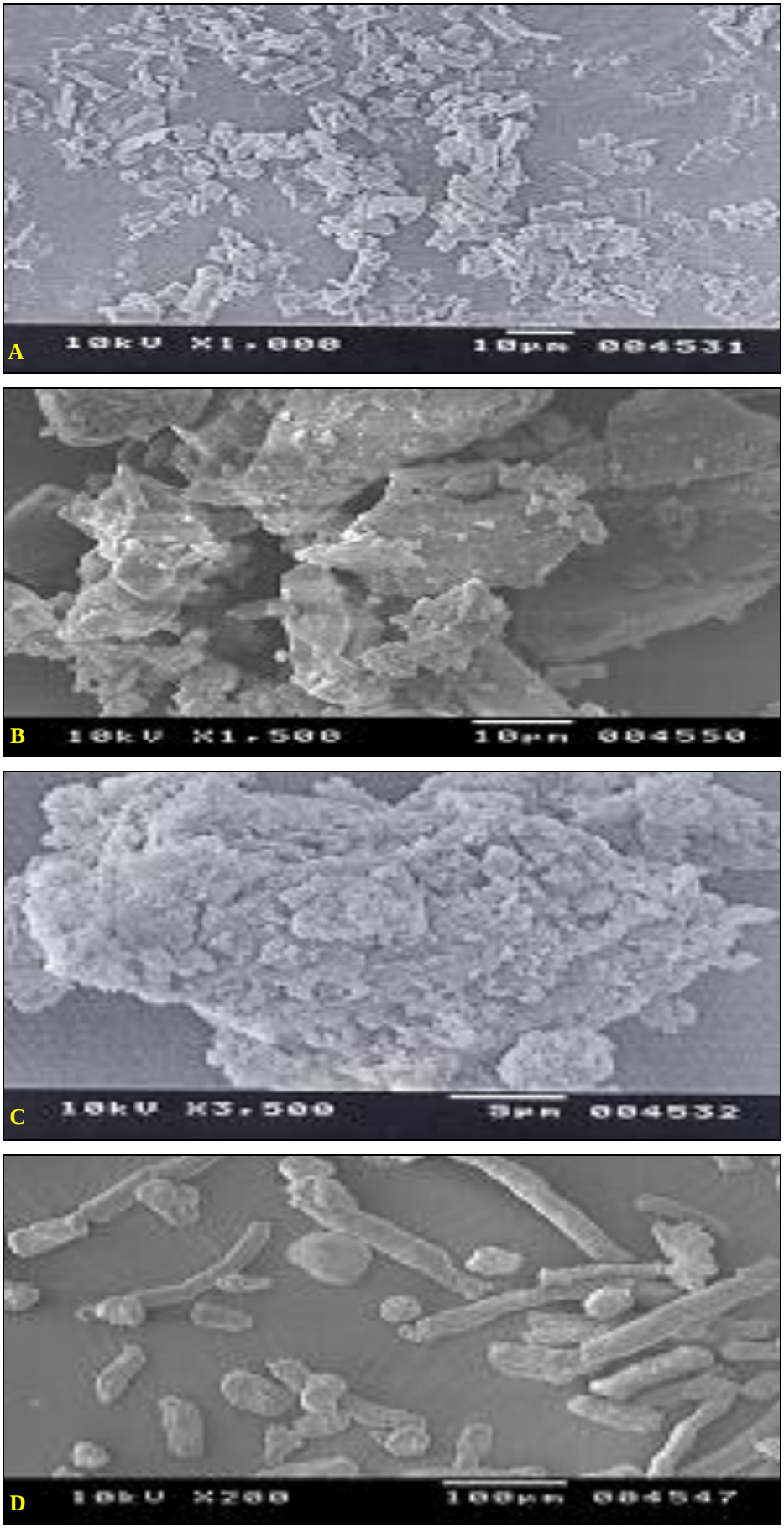


FIG: 23: SEM IMAGES OF (i) Etodolac (ii) α-CD (iii) HPMC iv) Etodolac: α-CD-HPMC

Solid inclusion complexes prepared by the kneading method exhibited higher dissolution rate and DE_{30} values than those prepared by co-evaporation in each case. The higher dissolution rates observed with kneaded complexes may be due to better interaction of drug and CD during the kneading process. In each case, the K_1 and DE_{30} values were increased E: αCD: HPMC 1:2:0.3 solid dispersion gave a 39.24 fold increase in the dissolution rate of Etodolac whereas solid dispersion of Etodolac in alone αCD (E- αCD solid dispersion) gave only 18.67 fold increase. Thus combination of Cyclodextrins with water-soluble carriers PEG, PVP, HPMC resulted in a greater enhancement in the dissolution rate of etodolac.

Dissolution of etodolac from all the solid dispersions followed first-order kinetics with correlation coefficient 'r' above 0.9 **Table 13, 15, 17**. The increasing order of dissolution rates of solid dispersions of etodolac is comparable with solid dispersions of raloxifene-crospovidone [19] atorvastatin-beta cyclodextrin [20] complexation curcumin-cellulose acetate solid dispersion [21]

Mechanism of Increased Dissolution Rate of Cyclodextrin Complexes: The observed increase in the dissolution rate of etodolac from their cyclodextrin complexes is due to the following possible mechanisms:

- Due to the possible reduction in particle size and encapsulation of drug into the cyclodextrin cavity.
- The interactions between the hydrophobic part of the guest and the apolar cavity cause dehydration of the hydrophobic guest molecule and its transfer into the cavity, thereby increasing the affinity toward the water and hence increasing the dissolution.
- The surfactant like properties of CDs can also be postulated to explain the higher dissolution rate of the complexes.
- CDs can also reduce the interfacial tension between the solid particles of drug and the dissolution medium, leading to a greater rate of dissolution.

CONCLUSION: The dissolution rate and dissolution efficiency of etodolac could be enhanced several times by their solid dispersion in cyclodextrins alone and in combination with hydrophilic polymers such as PEG, PVP, HPMC. Cyclodextrin particularly HPMC was found to be good carrier giving solid dispersions with enhanced dissolution rate and efficiency, several times higher than those of pure drug.

Thus, solid dispersion in Cyclodextrin is recommended as an effective and efficient technique for enhancing the dissolution rate, dissolution efficiency of etodolac. Cyclodextrins are inert, safe and non-toxic excipients that are currently used in compressed tablet formulations. These can be used as efficient carriers in solid dispersion techniques to enhance the dissolution rate of insoluble and poorly soluble drugs.

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CONFLICT OF INTEREST: Nil

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