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Studies On Dissolution Rate Enhancement Of Etodolac In Solid Dispersions By Beta Cyclodextrin Complexes

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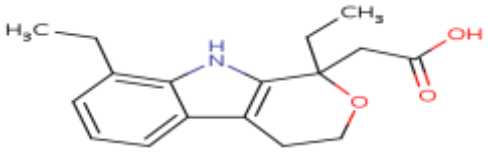
Abstract:
Etodolac is an anti-inflammatory drug that is poorly soluble in water. This paper describes an approach to improve the dissolution rate of Etodolac by using solid dispersions (SDs) in hydrophilic polymers. The solid dispersions were prepared with a Co-evaporation, kneading & Physical Mixture methods using different concentrations of β -cyclodextrin (β-CD). The release of Etodolac from various solid dispersions was determined from dissolution studies by use of USP dissolution apparatus II (paddle method). The dissolution study results revealed that there was a considerable increase in solubility and dissolution of all solid dispersions as compared to pure drug. Prepared Solid dispersions were characterized by differential scanning calorimetry (DSC), powder x-ray diffractometry (PXRD), and infrared spectroscopy (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 82.49 by the use of Etodolac β-CD-HPMC (1:2:0.3) Kneaded complex.

Keywords: Etodolac Solid; dispersions; hydrophilic polymers.

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 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. Therefore, improvement in its solubility and dissolution rate may lead to enhancement in its solubility and dissolution rate may lead to enhancement in bioavailability[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. Chiou[11] and Serajuadin[12] used the solid-dispersion technique for dissolution enhancement of poorly water soluble drugs. 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[13]. 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[14]. The use of hydrophilic polymers as carriers for the dissolution enhancement of poorly water soluble drug is increasing[15,16]. Various hydrophilic carriers such as polyethylene glycol have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs[17]

MATERIALS AND METHODS

Etodolac was a gift sample provided by Sun Pharmaceuticals, Vadodara, India and all other materials were of pharmacopoeia 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 & 1:2:0.3 ratios 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 minutes and then dried at 55^0 C until dry. The dried mass was pulverized, sieved through sieve no.120 and stored in desiccators till further use.

Coevaporation Method

Drug with or without auxiliary substances (PEG, PVP, HPMC) were dissolved in methanol, stirred the solution. The solvent was removed at reduced pressure in rotary evaporator at 45^0 C for 3 hours and dried mass was pulverized, sieved through sieve no.120 and stored in desiccators till 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 minutes. These mixtures were passed through a sieve no.120 and stored in desiccators till further use.

TABLE.1. COMPOSITION OF VARIOUS SOLID DISPERSIONS PREPARED

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

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 □g/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.2. The absorbance was plotted against concentration of etodolac as shown in Fig1.The present analytical method obeyed Beer's law in the concentration range of 2-10□g/ml and is suitable for the estimation of Etodolac from different solutions.

TABLE 2: CALIBRATION CURVE FOR ETODOLAC IN 0.2 M PHOSPHATE

BUFFER PH 7.4 PADDLE 50 rpm, λ_{max} = 274 nm.

Sl. 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

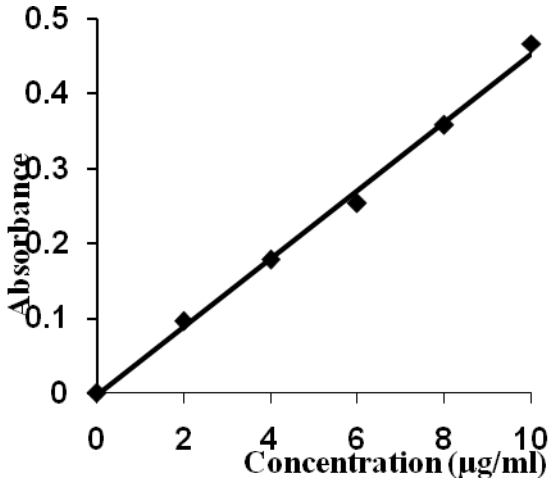


Fig. 1. Calibration Curve of Etodolac in 0.2 M phosphate buffer pH 7.4 Phase Solubility Studies

Solubility studies were performed according to the method reported by Higuchi and Connors[1]. Excess drug (25 mg) etodolac) was added to 15 ml of triple distilled water (pH 6.8) containing various concentrations of β – CD (0-25 mM), taken in a series of 25 ml stoppered conical flasks separately for etodolac and the mixtures were shaken for 72 hours at room temperature (37^0 ± 0.5^0 C) on a rotary shaker. After 72 hours of shaking to achieve equilibrium, 2 ml aliquots were withdrawn at 1-hour 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 274 nm for 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 3: Phase Solubility Studies of Etodolac in Water

Sl. No.	Conc. Of CD (mM)	Solubility (mM) of Etodolac
		β – CD
1	0	3.6
2	3	5.3
3	6	6.5
4	9	7.5
5	12	8.8
6	15	9.9

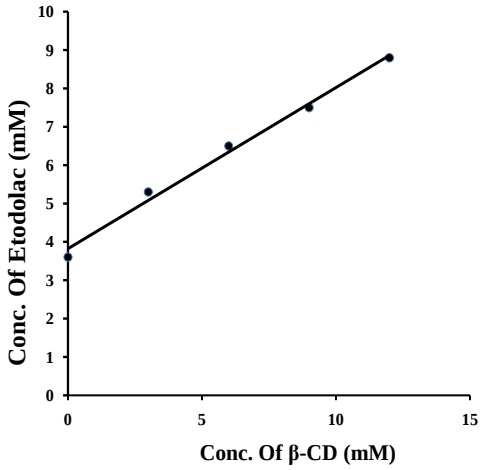


Fig.2.Phase Solubility Diagram of Etodolac with β-CD in water

Estimation of Etodolac in 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 at274 nm in water, phosphate buffer pH 7.4. The results are given in Table 4

Table .4. Drug Content of Solid Inclusion Complexes of Etodolac Prepared By Kneading ,Coevaporation and Physical Mixture Methods

CD Complex	Percent Etodolac Content ($\bar{x}$±s.d.,)		
	Kneading Method	Coevaporation Method	PhysicalMixture
E-β CD (1:1)	49.89±0.88(0.58)	50.09±0.67(0.78)	50.45±0.56(0.90)
E-β CD:PEG (1:1:0.2)	45.40±0.89(0.67)	45.44±0.39(0.70)	44.95±0.86(0.67)
E-β CD:PVP (1:1:0.2)	45.55±0.89(0.89)	44.97±0.88(0.59)	45.35±0.54(0.89)
E-βCD:HPMC (1:1:0.2)	45.35±0.43(0.78)	45.20±0.78(0.45)	45.57±0.56(0.75)
E-β CD (1:2)	33.30±0.65(0.84)	33.31±0.62(0.60)	33.38±0.66(0.76)
E-β CD:PEG (1:2:0.3)	30.26±0.45(0.67)	30.28±0.79(0.70)	30.40±0.67(0.54)
E-βCD:PVP (1:2:0.3)	30.23±0.73(0.90)	30.34±0.80(0.78)	30.31±0.45(0.77)
E-β CD:HPMC (1:2:0.3)	30.37±0.66(0.56)	30.39±0.36(0.90)	30.33±0.89(0.76)

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 the pure drugs and their cyclodextrin complexes are shown in Fig.23.X-ray diffraction patterns of pure drug

and its cyclodextrin complexes were studied.XRD of etodolac exhibited characterestic diffraction peaks indicating their crystalline nature. The diffractogram of cyclodextrins exhibited characterestic peaks due to its crystalline nature are shown.

Differential scanning calorimetry

The DSC curve of etodolac showed a single sharp exothermic peak at 153.5^0 C corresponding to its melting point., βCD,HPMC showed a broad peaks associated with loss of water. In the DSC thermograms of etodolac β-CD-HPMC intensity or height of the exothermic peaks at 139.5^0C respectively were 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 153.5^0 C was markedly reduced indicating the reduction of crystalline nature of drug and its complexation and amorphization with cyclodextrins are shown in Fig.22

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-1and aromatic C-H stretching at 744.38 cm-1. IR absorption peaks of etodolac, HPMC, and its cyclodextrin complexes are shown in Fig.21

Scanning electron microscopy (SEM) studies

The surface morphology was examined by Scanning electron microscope. SEM is used to study the microscopic aspects of the raw materials like pure drug, β -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 vaccum by a sputter coater. The pictures were then taken at an excitation voltage of 15 kV. SEM images of etodolac and its cyclodextrin complexes are shown in Fig.24.

Dissolution Rate Studies on Solid Dispersions

Dissolution rate of E were studied using an USP XXIII six station dissolution rate test apparatus (Electro Lab). Paddle stirrer at a speed of 50 rpm and temperature of $37^0 \pm 1^0$C 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)

Dissolution Profiles of etodolac and its Solid Dispersions

TABLE 5. Dissolution Profiles of Etodolac and its β-CD Complexes Prepared By Kneading Method

TIME (min)	Percent Etodolac Dissolved ($\bar{x}$±s.d., n =3)				
	E	E: βCD 1:1	E:βCD:PEG 1:1:0.2	E:βCD:PVP 1:1:0.2	E:βCD:HPMC 1:1:0.2
0	0	0	0	0	0
5	32.01±0.95	45.67±0.98	60.65±0.91	66.29±0.90	70.32±0.93
10	37.61±0.92	50.67±0.91	69.61±0.94	74.59±0.94	81.65±0.95
20	40.25±0.91	52.81±0.92	75.39±0.95	79.67±0.97	86.39±0.94
30	44.14±0.96	54.67±0.93	79.43±0.92	88.62±0.98	94.56±0.95
45	46.18±0.91	57.32±0.91	80.23±0.93	89.32±0.92	97.32±0.91
60	48.23±0.96	58.65±0.98	83.20±0.93	90.21±0.90	95.45±0.92
90	49.11±0.93	60.43±0.97	86.43±0.90	92.38±0.91	97.32±0.90
120	49.16±0.89	62.54±0.92	90.11±0.91	94.56±0.90	98.19±0.98

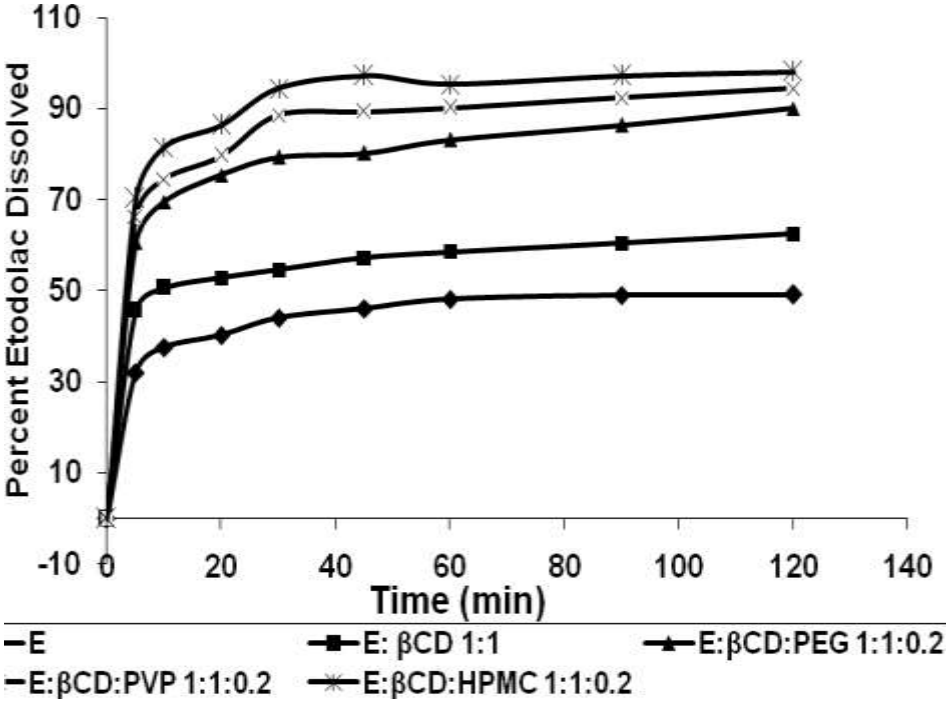


Fig.3.DissolutionProfiles of Etodolac and its β-CD Complexes Prepared by Kneading Method

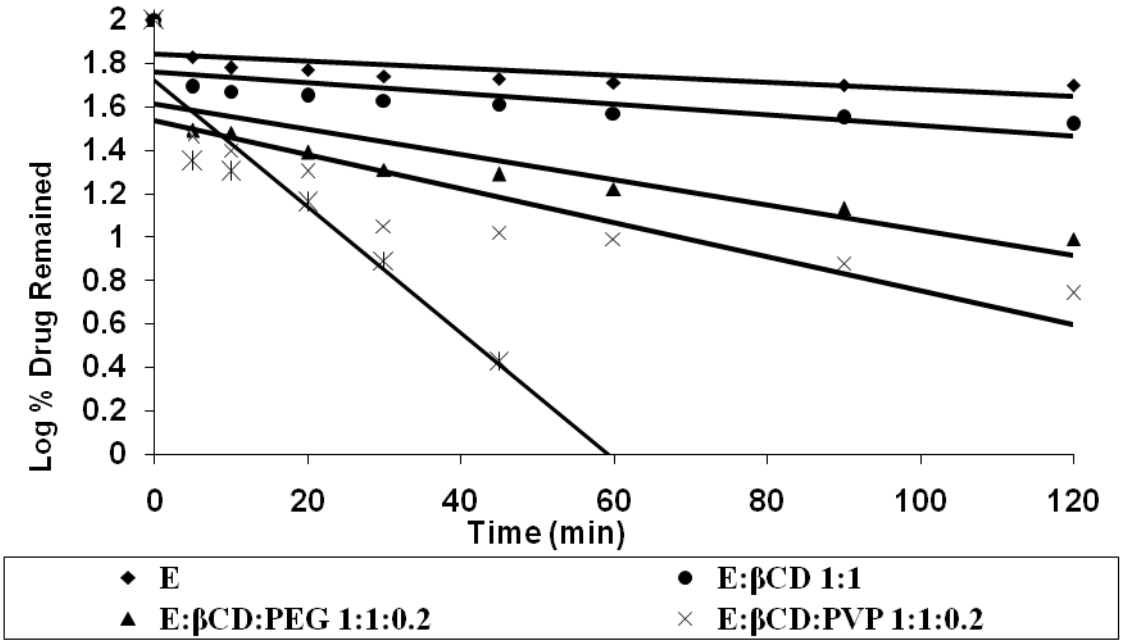


Fig.4. First Order Dissolution Plots of Etodolac and its β-Cyclodextrin Complexes Prepared by Kneading Method

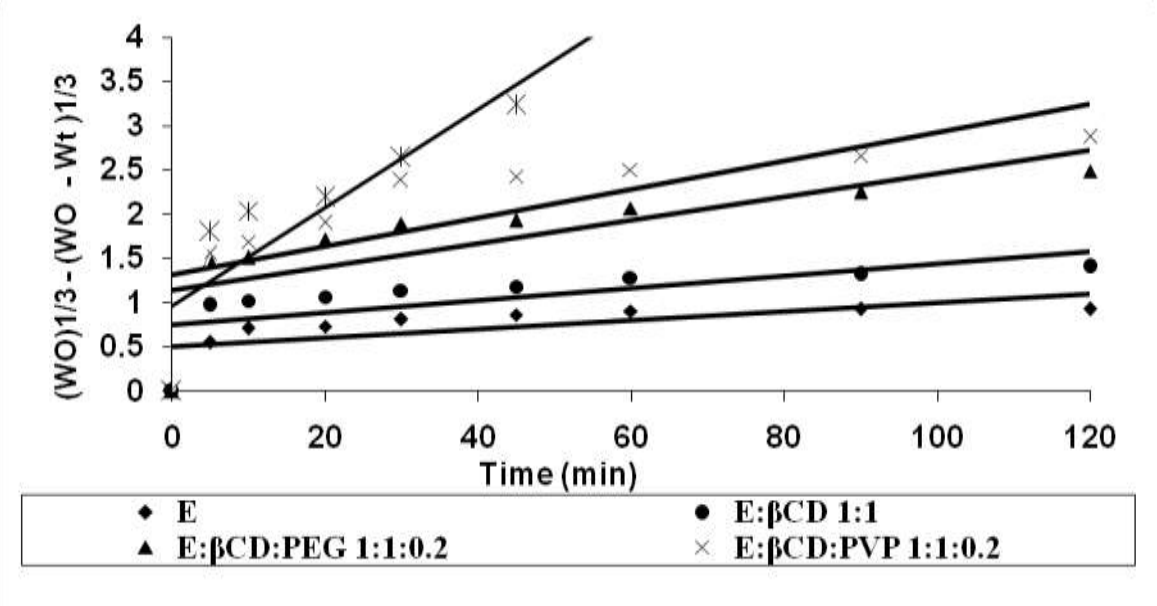


Fig.5. Hixson Crowell Plots of Etodolac and its β-CD complexes Prepared by Kneading Method

Table.6. Dissolution profiles of etodolac and its β-cd complexes prepared by kneading method

TIME (min)	Percent Etodolac Dissolved($\bar{x}$±s.d., n=3)				
	E	E: βCD 1:2	E:βCD:PEG 1:2:0.3	E:βCD:PVP 1:2:0.3	E:βCD:HPMC 1:2:0.3
0	0	0	0	0	0
5	32.01±0.95	59.34±0.92	68.92±0.91	75.67±0.90	80.44±0.91
10	37.61±0.92	65.34±0.91	75.34±0.92	82.13±0.91	86.71±0.95
20	40.25±0.91	69.32±0.98	81.42±0.92	85.39±0.94	92.12±0.94
30	44.14±0.96	72.90±0.90	87.78±0.93	90.22±0.95	97.31±0.98
45	46.18±0.91	75.64±0.94	89.6±0.95	92.43±0.90	100.03±0.96
60	48.23±0.96	77.23±0.90	92.13±0.98	95.45±0.91	-
90	49.11±0.93	78.11±0.98	94.32±0.97	97.11±0.97	-
120	49.16±0.89	79.54±0.96	95.23±0.98	98.34±0.98	-

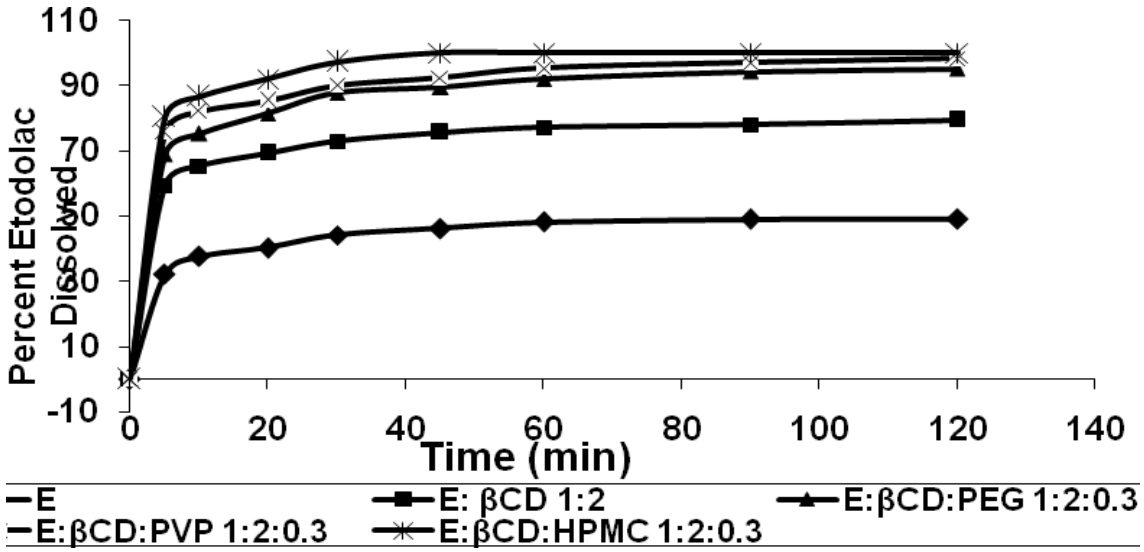


Fig. 6.Dissolution Profiles of Etodolac and its β-CD Complexes Prepared by Kneading Method

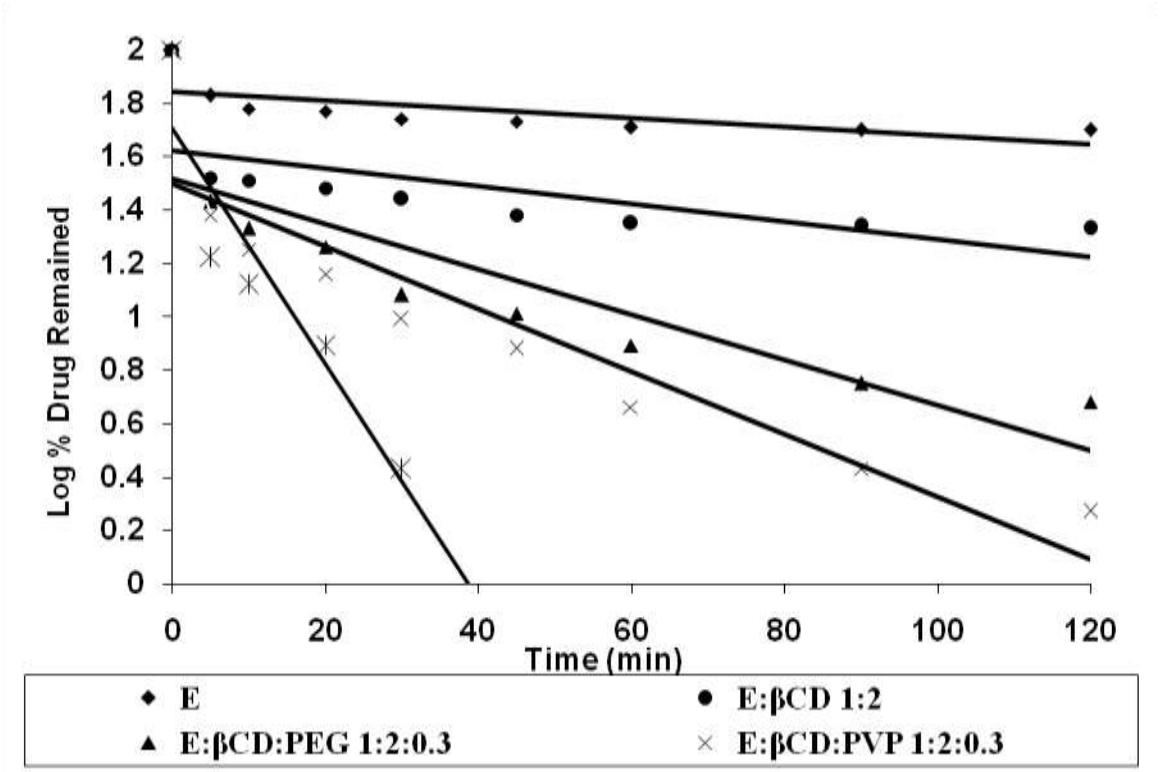


Fig. 7.First Order Dissolution Plots of Etodolac and its β-Cyclodextrin Complexes Prepared by Kneading Method

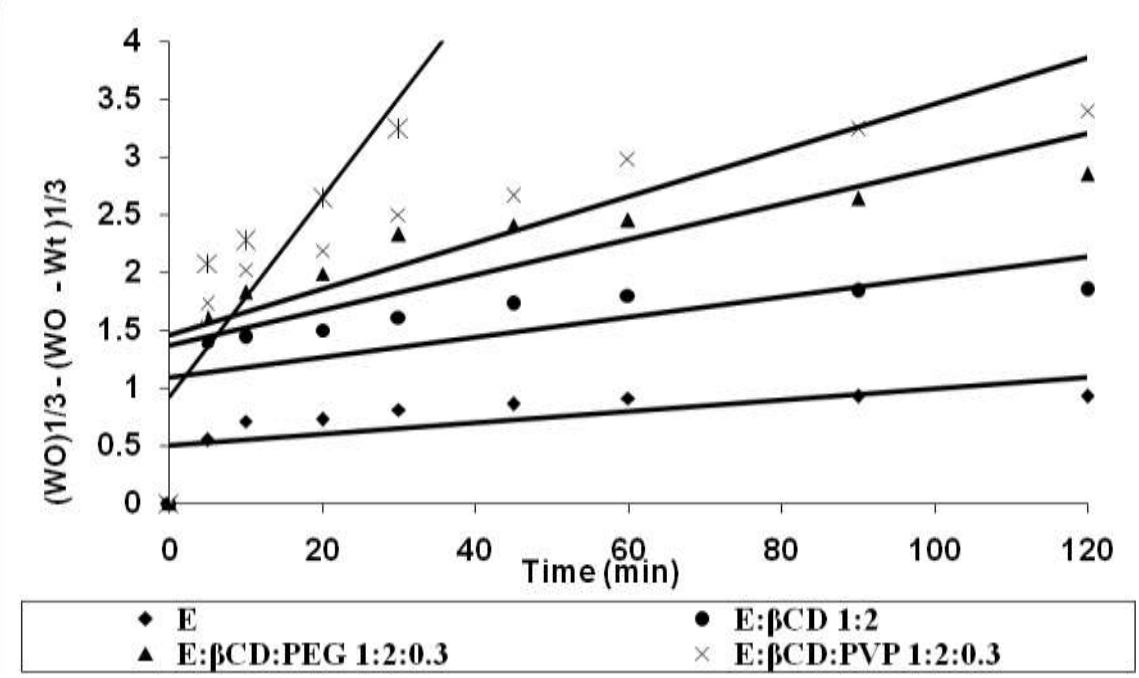


Fig. 8. Hixson Crowell Plots of Etodolac and its β-CD complexes Prepared by Kneading Method

Table 7:DissolutionProfiles of Etodolac and its β-CD Complexes Prepared by Co evaporation Method

TIME (min)	Percent Etodolac Dissolved ($\bar{x}$±s.d., n=3)				
	E	E: βCD 1:1	E:βCD:PEG 1:1:0.2	E:βCD:PVP 1:1:0.2	E:βCD:HPMC 1:1:0.2
0	0	0	0	0	0
5	32.01±0.95	39.65±0.89	50.12±0.92	58.67±0.98	62.34±0.98
10	37.61±0.92	42.67±0.96	59.17±0.96	62.81±0.96	66.59±0.97
20	40.25±0.91	46.56±0.91	62.67±0.95	67.85±0.93	68.09±0.94
30	44.14±0.96	50.23±0.90	68.89±0.94	71.95±0.91	73.86±0.92
45	46.18±0.91	53.45±0.90	69.65±0.98	75.06±0.93	78.67±0.90
60	48.23±0.96	58.65±0.94	71.23±0.96	76.90±0.92	80.12±0.91
90	49.11±0.93	59.21±0.98	72.43±0.93	76.23±0.91	81.55±0.93
120	49.16±0.89	60.33±0.95	73.12±0.91	77.45±0.92	89.22±0.91

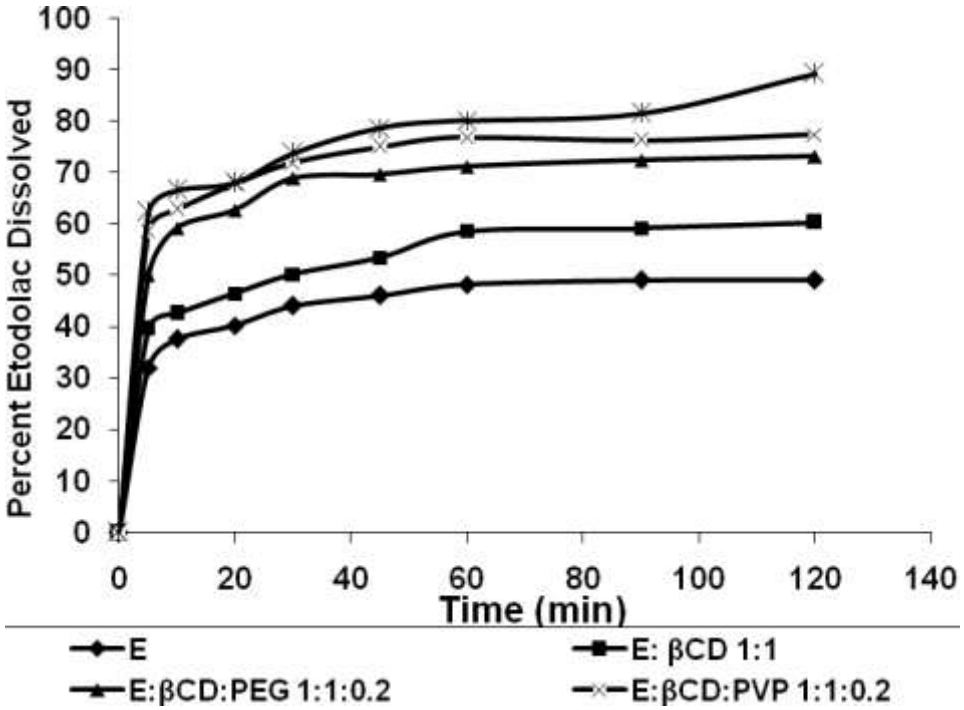


Fig. 9.Dissolution Profiles of Etodolac and its β-CD Complexes Prepared by Coevaporation Method

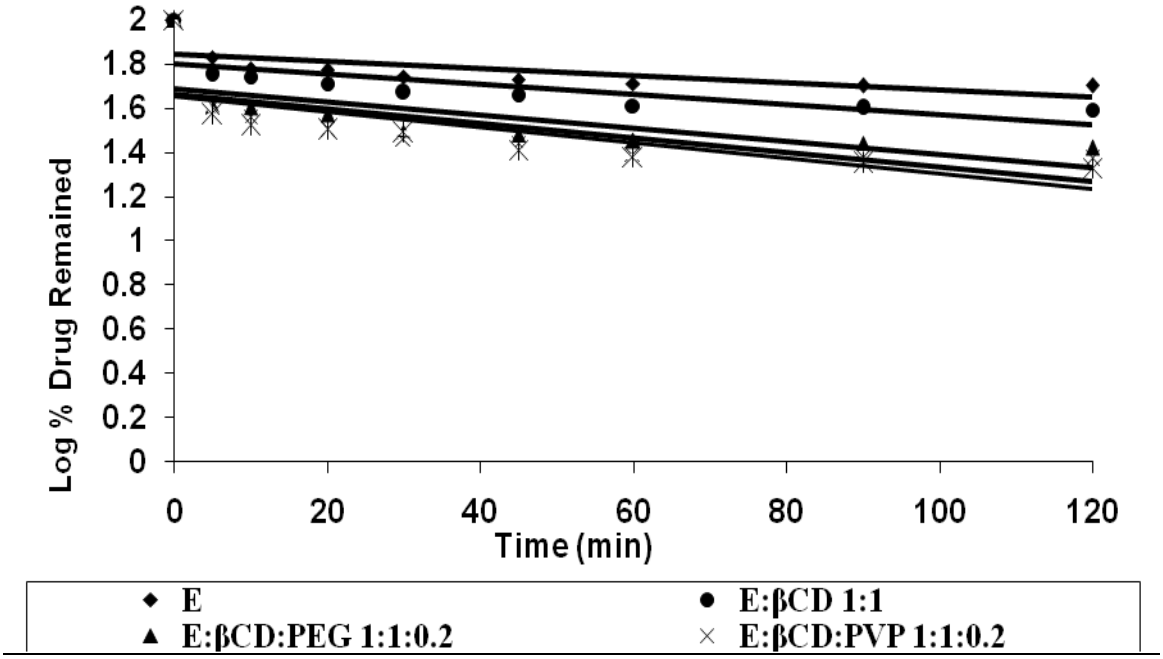


Fig. 10.First Order Dissolution Plots of Etodolac and its β-Cyclodextrin Complexes Prepared by Coevaporation Method

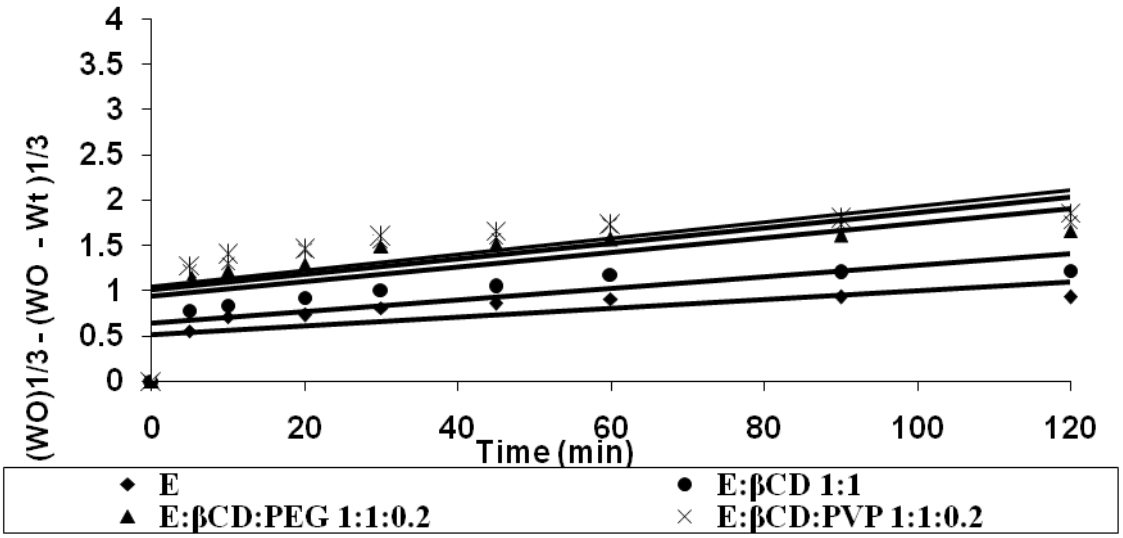


Fig. 11. Hixson Crowell Plots of Etodolac and its β-CD complexes Prepared by Coevaporation Method

Table 8: Dissolution Profiles of Etodolac and its β-CD Complexes Prepared by Coevaporation Method

TIME (min)	Percent Etodolac Dissolved ($\bar{x}$±s.d., n=3)				
	E	E: βCD 1:2	E:βCD:PEG 1:2:0.3	E:βCD:PVP 1:2:0.3	E:βCD:HPMC 1:2:0.3
0	0	0	0	0	0
5	32.01±0.95	50.56±0.96	58.89±0.98	63.45±0.98	70.43±0.93
10	37.61±0.92	54.67±0.95	61.45±0.94	69.45±0.94	71.65±0.96
20	40.25±0.91	56.76±0.90	64.56±0.95	70.81±0.95	74.87±0.91
30	44.14±0.96	57.89±0.91	68.89±0.96	72.61±0.91	75.83±0.94
45	46.18±0.91	60.01±0.91	70.54±0.93	75.34±0.92	83.45±0.97
60	48.23±0.96	66.12±0.92	73.56±0.98	77.69±0.95	88.62±0.98
90	49.11±0.93	69.43±0.95	74.67±0.96	79.54±0.97	89.21±0.90
120	49.16±0.89	69.45±0.98	77.23±0.97	82.31±0.98	89.22±0.91

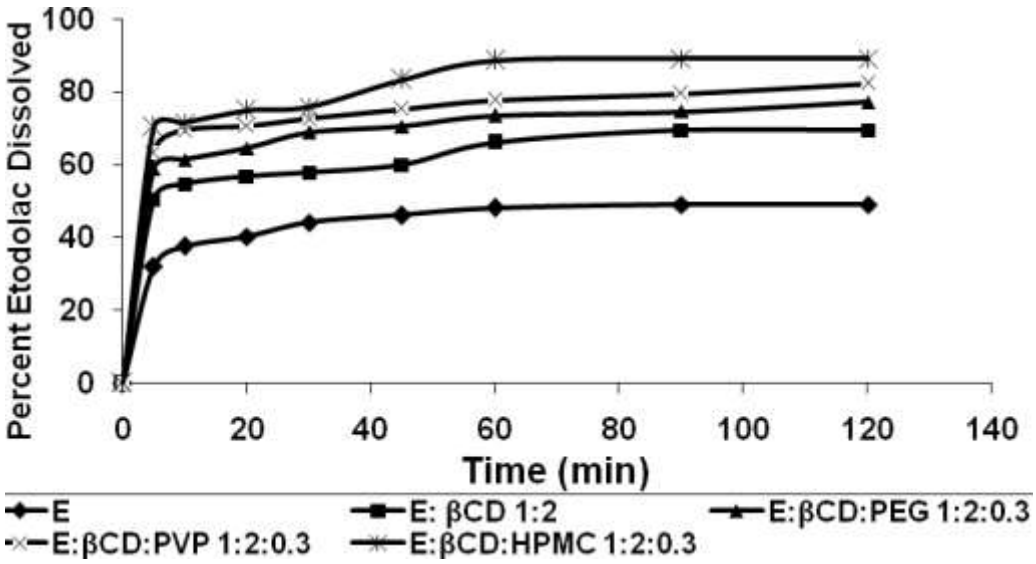


Fig.12. Dissolution Profiles of Etodolac and its β-CD Complexes Prepared by Coevaporation Method

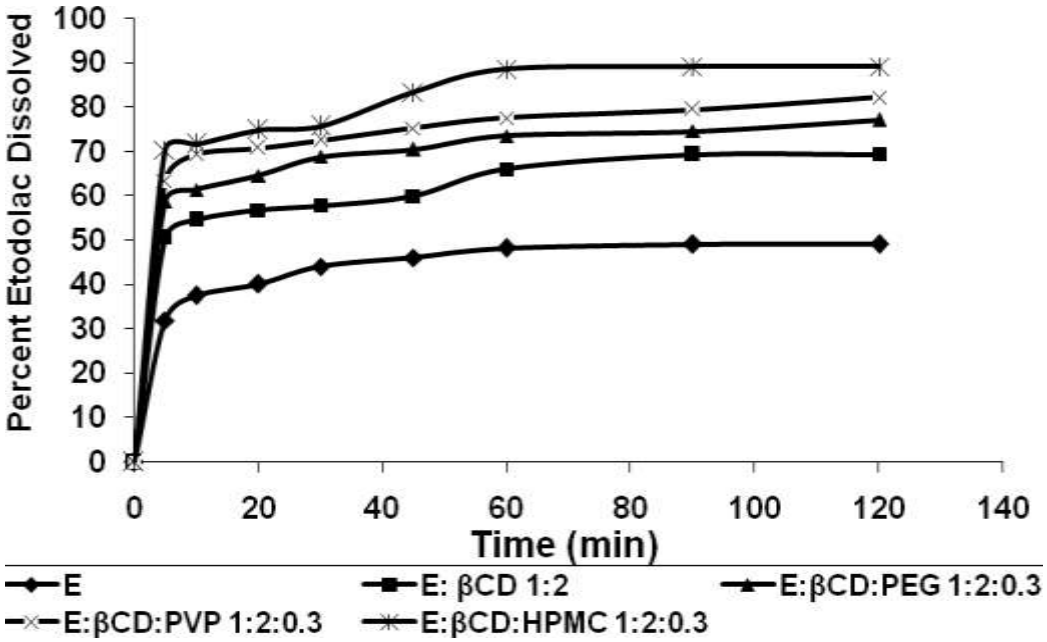


Fig. 13.First Order Dissolution Plots of Etodolac and its β-Cyclodextrin Complexes Prepared by Coevaporation Method

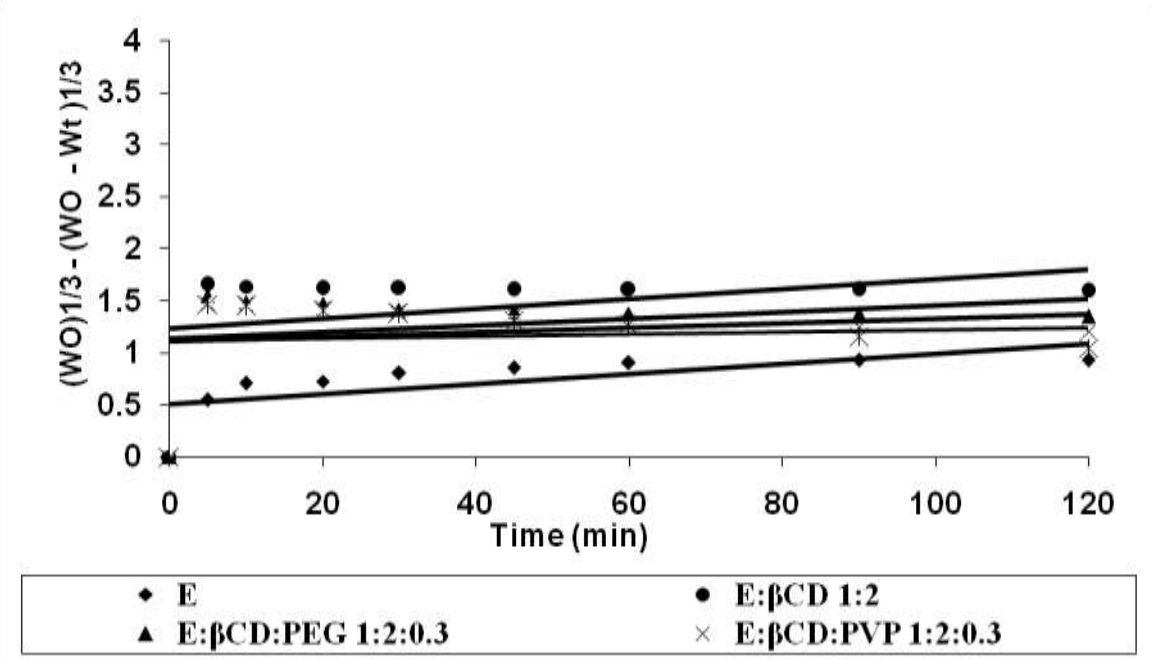


Fig.14.Hixson Crowell Plots of Etodolac and its β-CD complexes Prepared by Coevaporation Method

Table.9:DissolutionProfiles of Etodolac and its β-CD Complexes Prepared by Physical Mixture Method

TIME (min)	Percent Etodolac Dissolved ($\bar{x}$±s.d., n=3)				
	E	E: βCD 1:1	E:βCD:PEG 1:1:0.2	E:βCD:PVP 1:1:0.2	E:βCD:HPMC 1:1:0.2
0	0	0	0	0	0
5	32.01±0.95	34.35±0.98	40.16±0.94	48.61±0.98	53.12±0.98
10	37.61±0.92	39.22±0.91	45.23±0.95	52.12±0.97	60.16±0.97
20	40.25±0.91	44.280.90	50.64±0.98	55.27±0.94	61.67±0.94
30	44.14±0.96	45.34±0.92	55.62±0.97	60.16±0.91	64.13±0.91
45	46.18±0.91	47.93±0.93	58.22±0.91	62.96±0.95	69.47±0.92
60	48.23±0.96	51.34±0.94	60.22±0.92	63.11±0.94	72.12±0.93
90	49.11±0.93	53.21±0.95	63.12±0.93	64.63±0.94	73.63±0.94
120	49.16±0.89	54.65±0.91	66.48±0.95	70.23±0.90	75.38±0.90

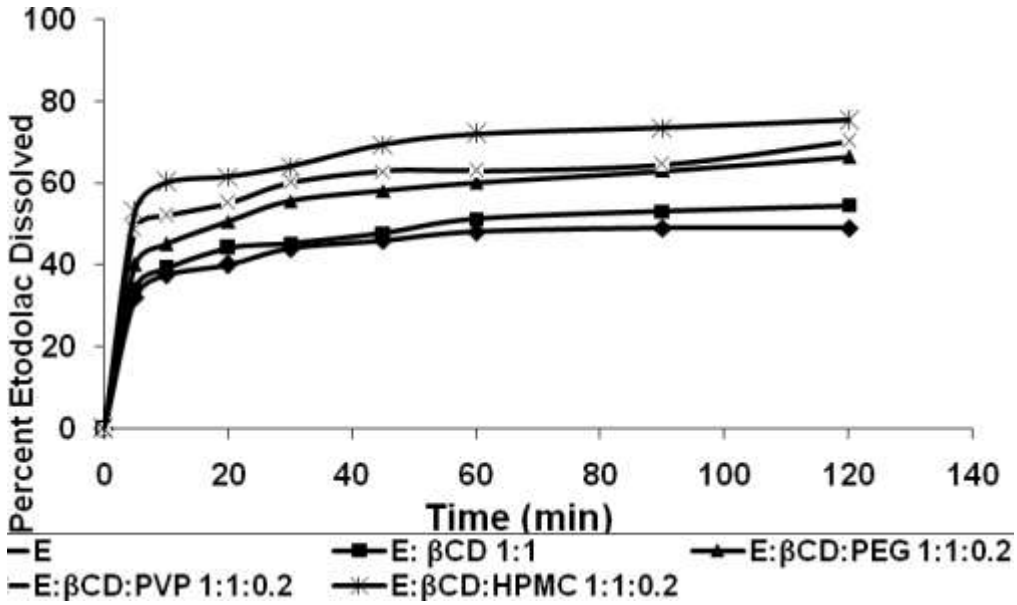


Fig.15.Dissolution Profiles of Etodolac and its β-CD Complexes Prepared by Physical Mixture Method

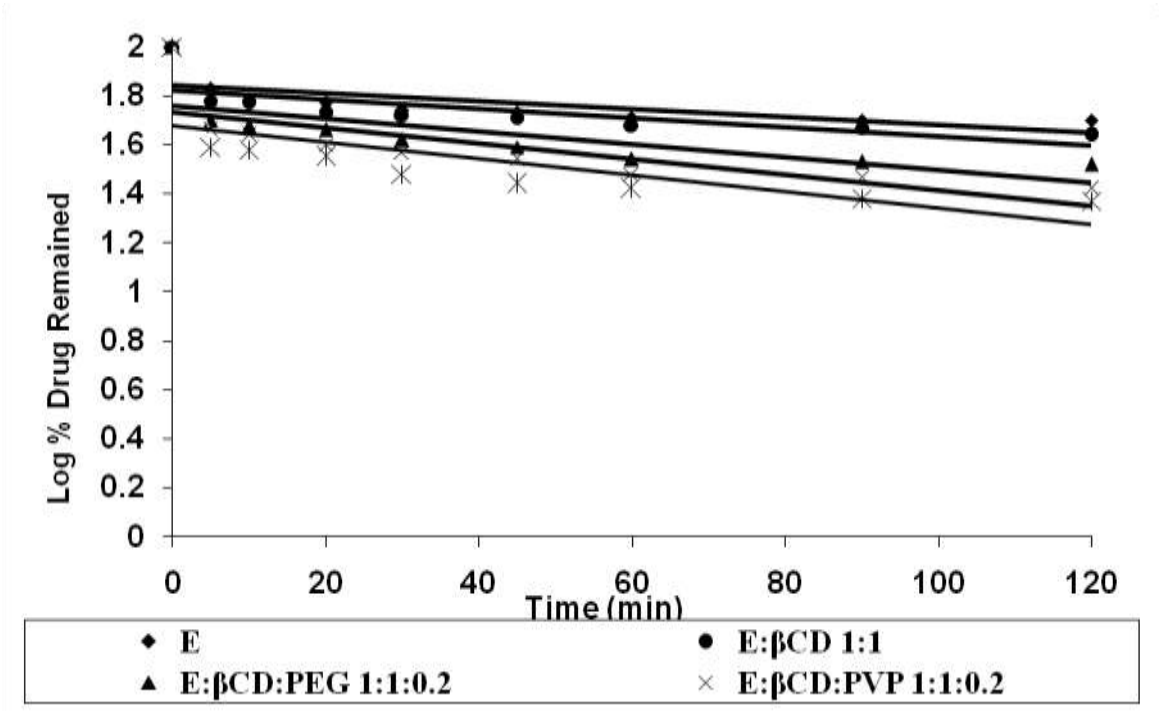


Fig. 16.First Order Dissolution Plots of Etodolac and its β-Cyclodextrin Complexes Prepared by Physical Mixture Method

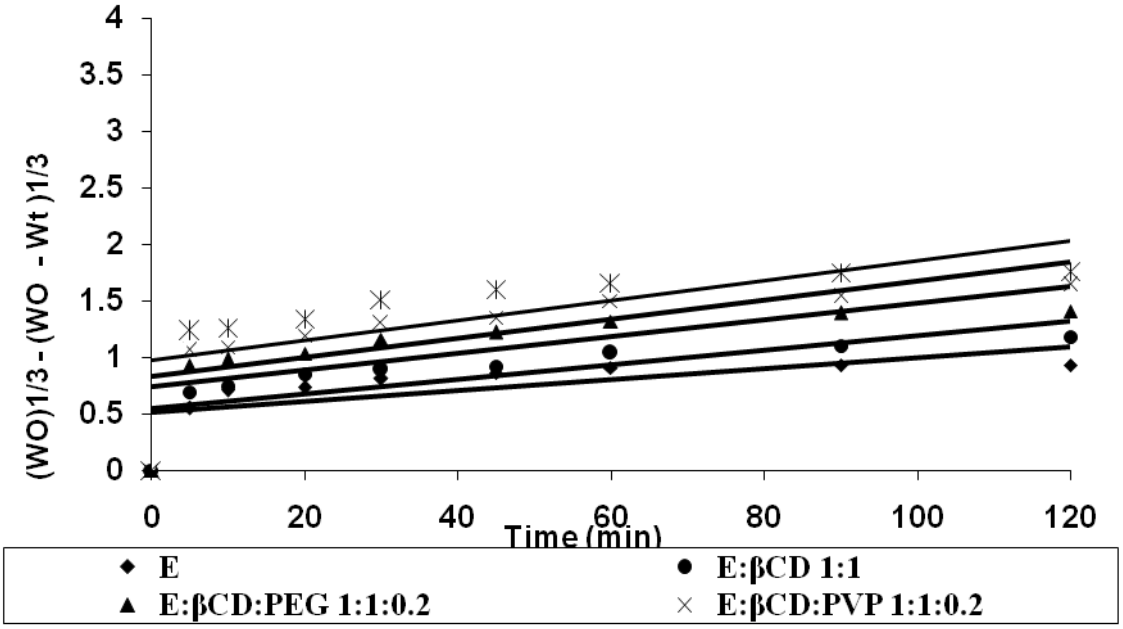


Fig.17. Hixson Crowell Plots of Etodolac and its β-CD complexes Prepared by Physical Mixture Method

Table .10. Dissolution Profiles of Etodolac and its β-CD Complexes Prepared by Physical Mixture Method

TIME (min)	Percent Etodolac Dissolved ($\bar{x}$±s.d., n=3)				
	E	E: βCD 1:2	E:βCD:PEG 1:2:0.3	E:βCD:PVP 1:2:0.3	E:βCD:HPMC 1:2:0.3
0	0	0	0	0	0
5	32.01±0.95	42.62±0.98	48.29±0.91	51.12±0.92	58.12±0.98
10	37.61±0.92	48.39±0.91	52.29±0.94	58.91±0.91	60.12±0.97
20	40.25±0.91	56.63±0.92	59.98±0.98	62.31±0.90	66.86±0.94
30	44.14±0.96	57.61±0.94	62.32±0.96	65.69±0.89	69.34±0.98
45	46.18±0.91	57.92±0.92	68.61±0.96	68.24±0.96	70.16±0.92
60	48.23±0.96	63.61±0.90	69.44±0.95	71.16±0.91	71.12±0.91
90	49.11±0.93	64.44±0.91	69.98±0.91	72.33±0.96	71.88±0.90
120	49.16±0.89	66.53±0.94	70.99±0.98	76.67±0.93	72.23±0.91

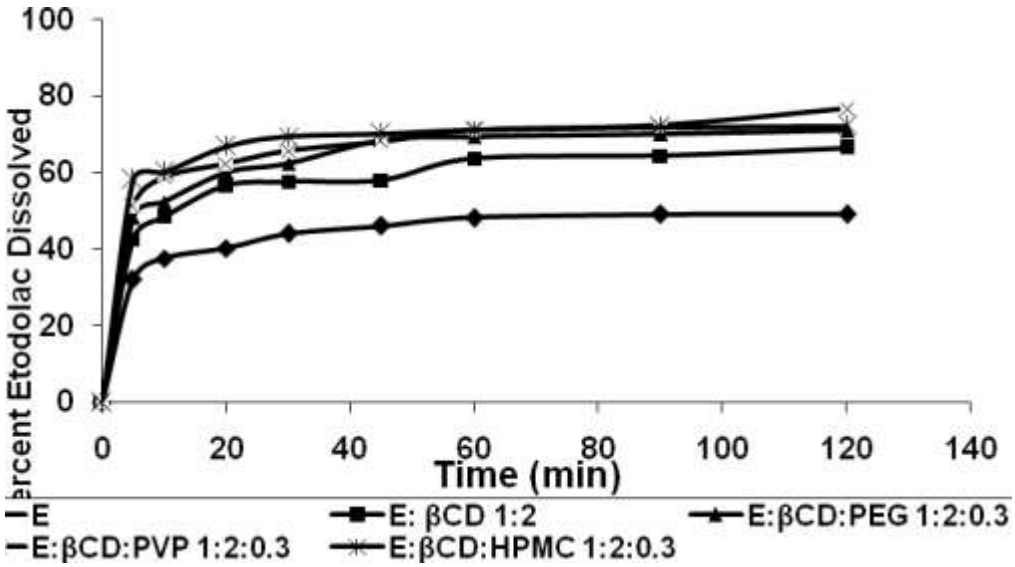


Fig.18.DissolutionProfiles of Etodolac and its β-CD Complexes Prepared by Physical Mixture Method

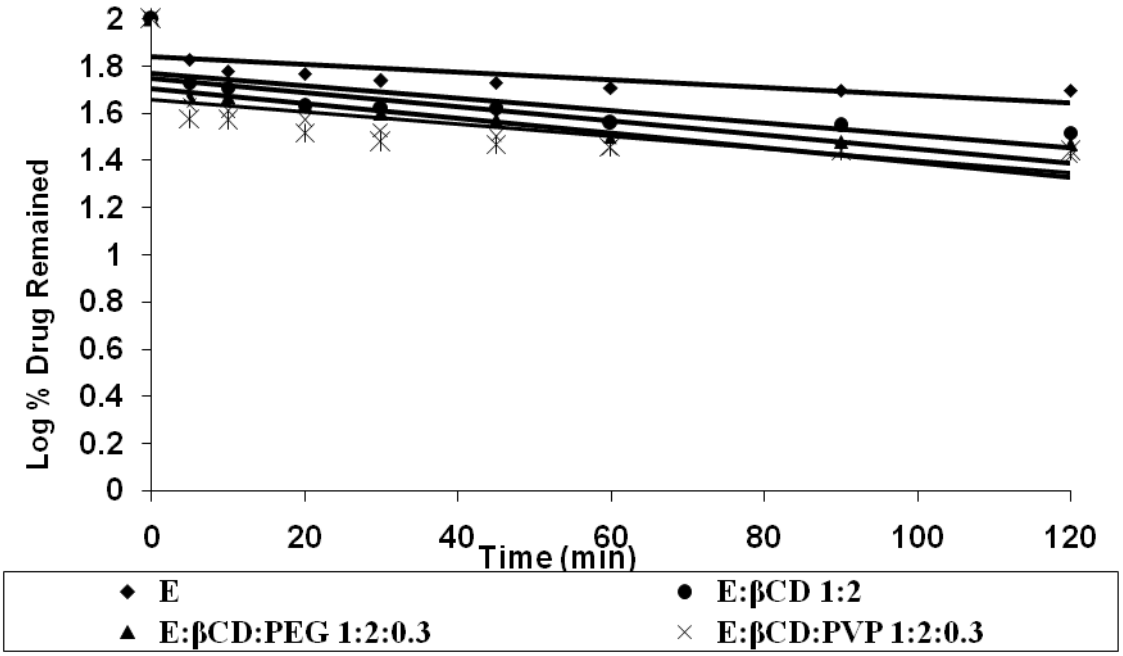


Fig.19. First Order Dissolution Plots of Etodolac and its β-Cyclodextrin Complexes Prepared by Physical Mixture Method

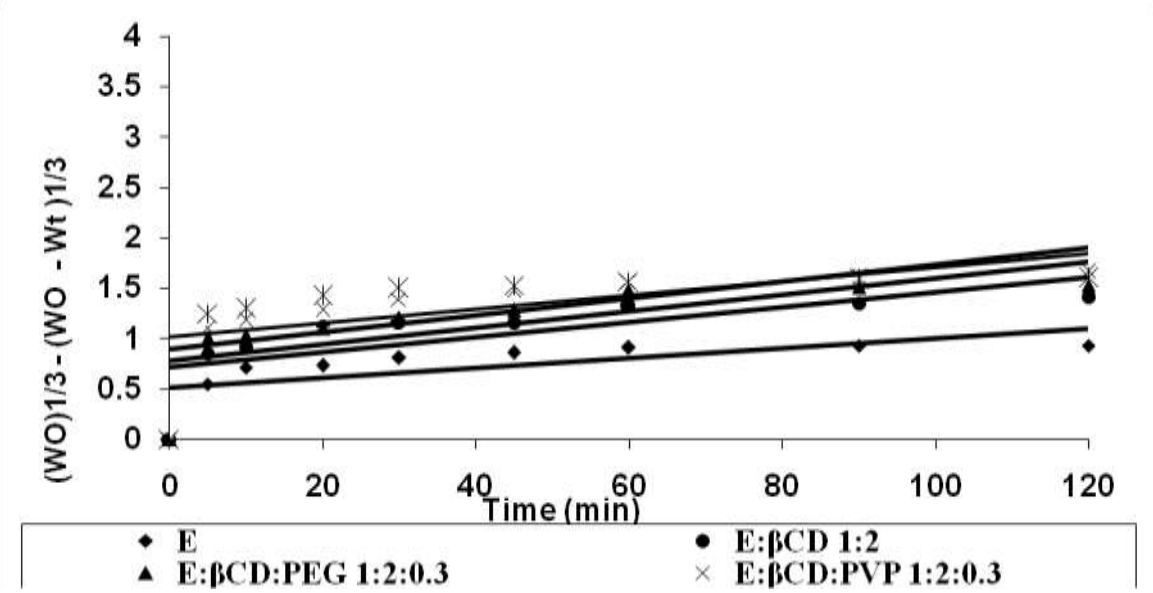


Fig.20. Hixson Crowell Plots of Etodolac and its β-CD complexes Prepared by Physical Mixture Method

Table. 11: Dissolution Parameters of Etodolac and its Cyclodextrin Complexes Prepared by Kneading Method

Sl. 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:βCD 1:1	50.62	1.56	52.87	49.37	0.076	20.54
3	E:βCD 1:2	66.32	2.05	67.55	63.09	0.113	30.45
4	E:βCD:PEG 1:1:0.2	68.59	2.12	69.62	67.15	0.119	32.37
5	E:βCD:PEG 1:2:0.3	72.74	2.25	78.32	73.44	0.154	41.70
6	E:βCD:PVP 1:1:0.2	70.72	2.19	74.52	71.71	0.138	37.34
7	E:βCD:PVP 1:2:0.3	75.62	2.34	82.11	76.57	0.172	46.68
8	E:βCD:HPMC 1:1:0.2	77.35	2.62	82.63	77.30	0.161	43.57
9	E:βCD:HPMC 1:2:0.3	83.41	2.58	86.74	82.49	0.202	56.29

Table.12: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

Sl No.	Cyclodextrin Complex	Correlation Coefficient (R^2) value		
		Zero Order	First Order	Hixson Crowell
1	Etodolac	0.803	0.758	0.889
2	E:βCD 1:1	0.883	0.891	0.886
3	E:βCD 1:2	0.873	0.875	0.877
4	E:βCD:PEG 1:1:0.2	0.872	0.874	0.874
5	E:βCD:PEG 1:2:0.3	0.896	0.926	0.913
6	E:βCD:PVP 1:1:0.2	0.887	0.907	0.900
7	E:βCD:PVP 1:2:0.3	0.899	0.935	0.924
8	E:βCD:HPMC 1:1:0.2	0.893	0.896	0.914
9	E:βCD:HPMC 1:2:0.3	0.882	0.913	0.901

Table. 13:Dissolition Parameters of Etodolac and its Cyclodextrin Complexes Prepared by Coevaporation Method

Sl. 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:βCD 1:1	42.65	1.32	44.82	43.22	0.019	5.22
3	E:βCD 1:2	53.54	1.65	55.64	51.80	0.036	9.81
4	E:βCD:PEG 1:1:0.2	59.11	1.83	60.12	57.18	0.040	11.02
5	E:βCD:PEG 1:2:0.3	64.58	1.99	68.85	63.34	0.119	32.36
6	E:βCD:PVP 1:1:0.2	60.12	1.86	63.12	60.18	0.050	13.51
7	E:βCD:PVP 1:2:0.3	69.45	2.15	70.89	66.20	0.101	27.38
8	E:βCD:HPMC 1:1:0.2	62.32	1.93	66.52	61.03	0.142	38.59
9	E:βCD:HPMC 1:2:0.3	70.41	2.18	71.65	67.20	0.097	26.14

TABLE. 14: The Correlation Coefficient (R) Values in the Analysis of Dissolution Data of Etodolac Cyclodextrin Complexes a prepared by Coevaporation Methods Per Zero Order, First Order and Hixson-Crowell Cube Root Models

Sl No.	Cyclodextrin Complex	Correlation Coefficient (R^2) value		
		Zero Order	First Order	Hixson Crowell
1	Etodolac	0.803	0.803	0.901
2	E:βCD 1:1	0.678	0.722	0.898
3	E:βCD 1:2	0.726	0.890	0.895
4	E:βCD:PEG 1:1:0.2	0.701	0.841	0.910
5	E:βCD:PEG 1:2:0.3	0.677	0.911	0.902
6	E:βCD:PVP 1:1:0.2	0.707	0.803	0.898
7	E:βCD:PVP 1:2:0.3	0.656	0.815	0.879
8	E:βCD:HPMC 1:1:0.2	0.705	0.774	0.914
9	E:βCD:HPMC 1:2:0.3	0.616	0.824	0.876

TABLE.15:Dissolution Parameters of Etodolac and its Cyclodextrin Complexes prepared by Physical Mixture Method

Sl. 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:βCD 1:1	38.35	1.15	40.22	39.55	0.053	14.91
3	E:βCD 1:2	45.62	1.36	48.39	48.17	0.0668	18.05
4	E:βCD:PEG 1:1:0.2	49.19	1.47	51.26	48.45	0.074	19.92
5	E:βCD:PEG 1:2:0.3	52.29	1.56	53.16	50.56	0.076	20.54
6	E:βCD:PVP 1:1:0.2	54.16	1.62	55.63	53.23	0.083	22.41
7	E:βCD:PVP 1:2:0.3	56.12	1.68	58.91	55.79	0.089	24.27
8	E:βCD:HPMC 1:1:0.2	60.38	1.81	61.66	57.42	0.0967	26.14
9	E:βCD:HPMC 1:2:0.3	61.12	1.83	62.61	59.68	0.099	26.76

TABLE.16: The Correlation Coefficient ® Values in the Analysis of Dissolution Data of Etodolac Cyclodextrin Complexes prepared by Physical Mixture Method Per Zero Order, First Order And Hixson-Crowell Cube Root Models

Sl No.	Cyclodextrin Complex	Correlation Coefficient (R^2) value		
		Zero Order	First Order	Hixson Crowell
1	Etodolac	0.758	0.803	0.898
2	E:βCD 1:1	0.783	0.885	0.889
3	E:βCD 1:2	0.805	0.898	0.896
4	E:βCD:PEG 1:1:0.2	0.883	0.892	0.888
5	E:βCD:PEG 1:2:0.3	0.873	0.866	0.874
6	E:βCD:PVP 1:1:0.2	0.877	0.889	0.877
7	E:βCD:PVP 1:2:0.3	0.886	0.898	0.891
8	E:βCD:HPMC 1:1:0.2	0.874	0.876	0.876
9	E:βCD:HPMC 1:2:0.3	0.876	0.876	0.879

RESULTS AND DISCUSSION

The dissolution rate of etodolac (E) from various cyclodextrin solid inclusion complexes was studied in 0.1 N HCl and compared with that of un-complexed drug. The dissolution data of E-CD complexes are given in Table.12, and the dissolution profiles are shown in Figs. 2,5,8,11,14,17.,First order plots of the etodolac β–CD complexes are shown in fig. 3,6,9,12,15,18.. Hixson-Crowell plots of etodolac β–CD complexes are shown in fig. 4, 7, 10, 13, 16, 19.The dissolution of Etodolac from the β–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 (Table 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 Tables 12, 14, 16.All the dissolution parameters (DP 5min, RDr, 5min, % 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.

Solid inclusion complexes prepared by kneading method exhibited higher dissolution rate and DE_{30} values than those prepared by coevaporation 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: β-CD:HPMC 1:2:0.3 solid dispersion gave a 56.29 fold increase in the dissolution rate of Etodolac whereas solid dispersion of Etodolac in alone β-CD (E- β-CD solid dispersion) gave only 20.54 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 are comparable with solid dispersions of raloxifene-crosspovidone[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:

(i) Due to the possible reduction in particle size and encapsulation of drug into the cyclodextrin cavity.

(ii) The interactions between the hydrophobic part of the guest and the apolar cavity causes dehydration of the hydrophobic guest molecule and its transfer into the cavity, thereby increasing the affinity toward water and hence increasing the dissolution.

(iii)The surfactant like properties of CDs can also be postulated to explain the higher dissolution rate of the complexes.

(iv)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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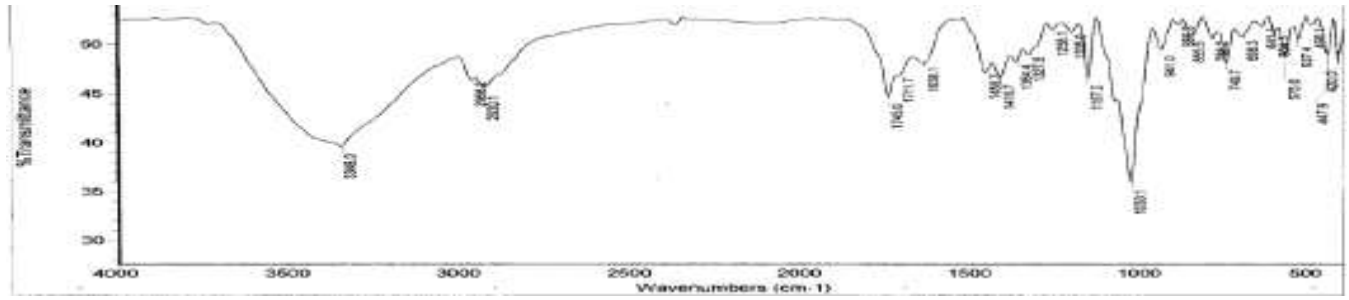
(i)

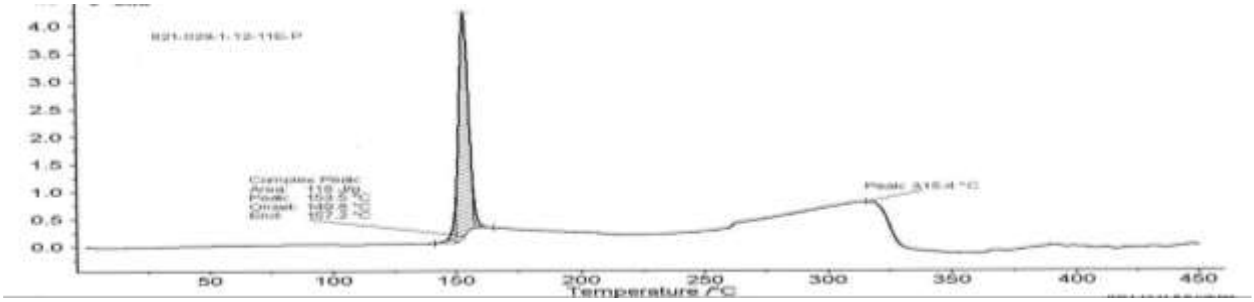
(ii)

(iii)



(iv)

Fig :21. IR Spectra of (i) Etodolac (ii) β-CD (iii) HPMC (iv) Etodolac :β-CD HPMC



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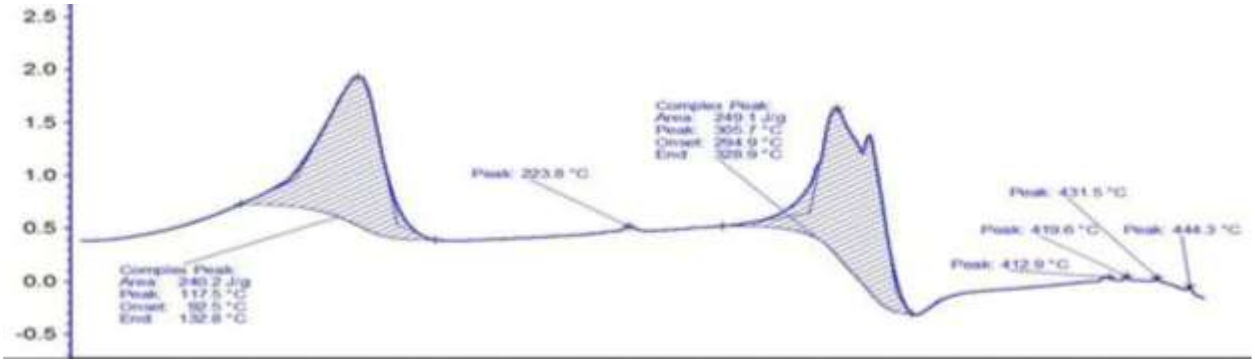

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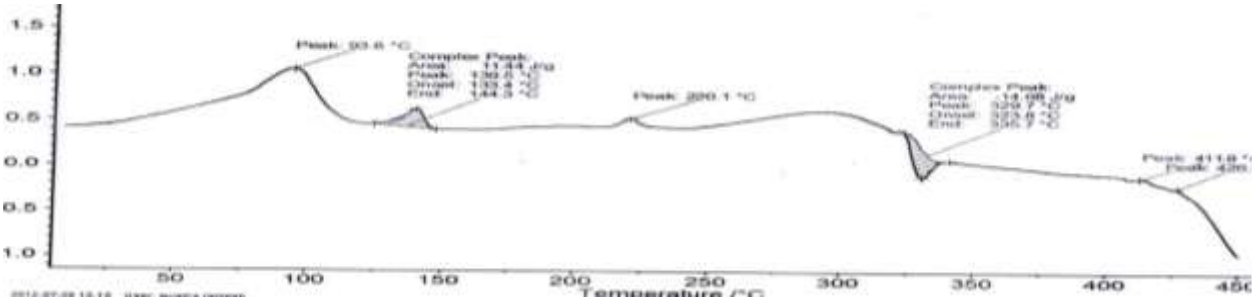

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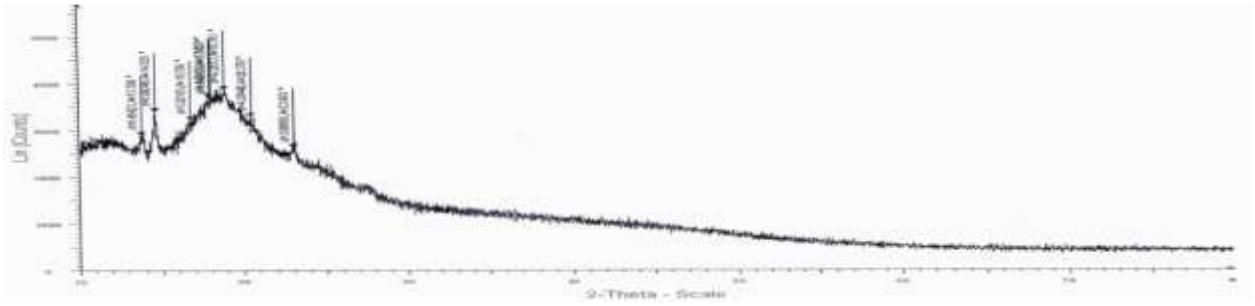
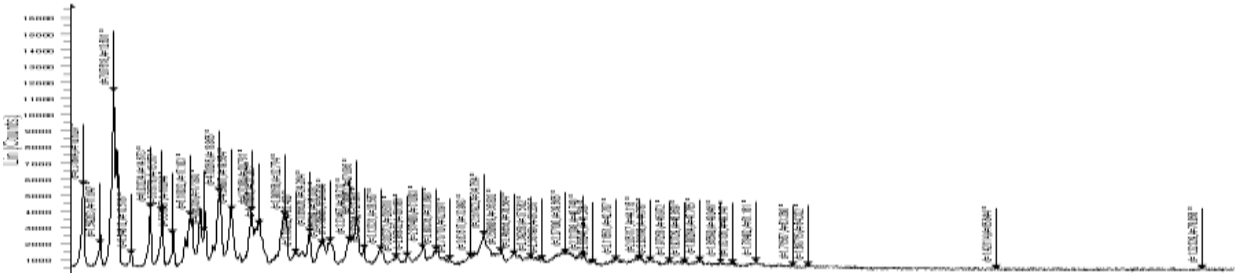
Fig : 22.DSC Spectra of (i) Etodolac (ii) β-CD (iii) HPMC iv) Etodolac: βCD-HPMC



(i)



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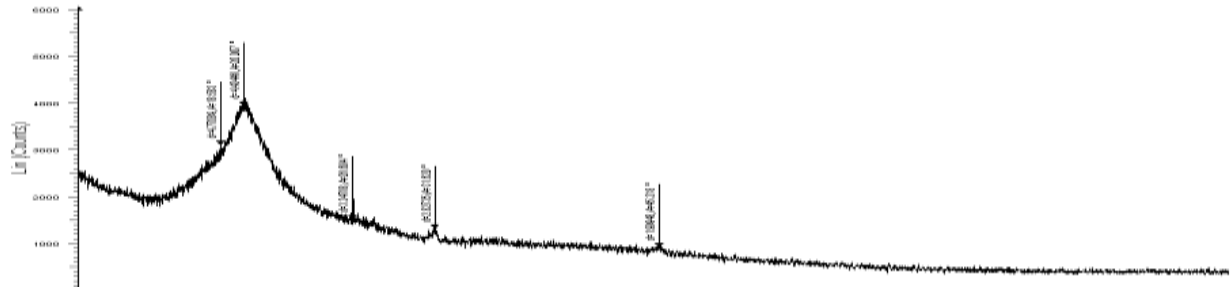

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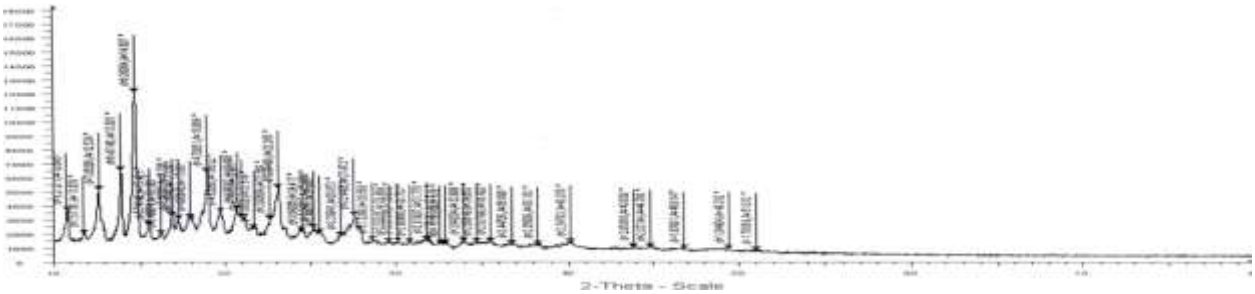

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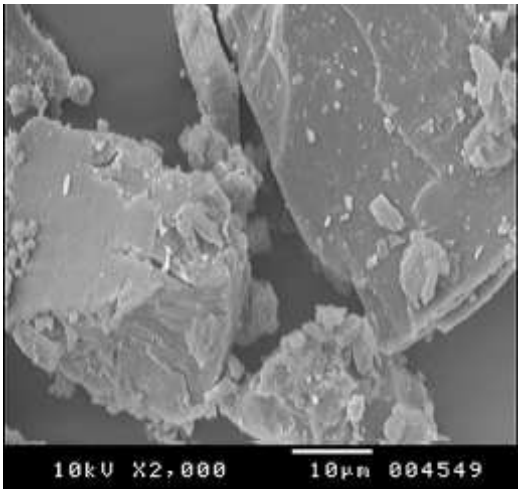
Fig : 23.XRD Spectra of (i) Etodolac (ii) β-CD (iii) HPMC iv) Etodolac :β-CD-HPMC

(i)



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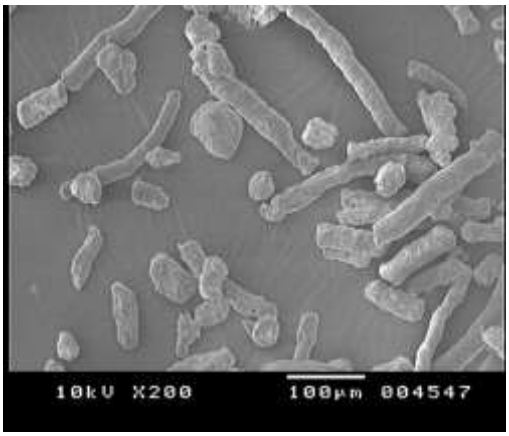

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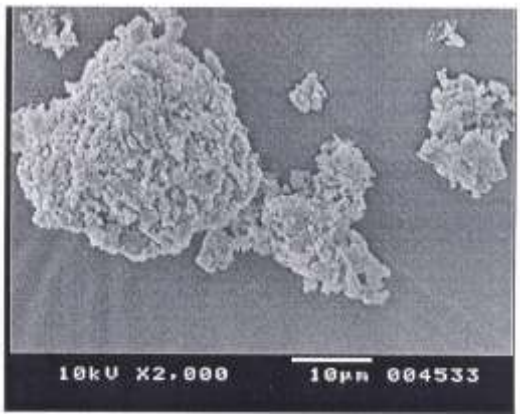

(iv)

Fig : 24.Sem Images of (i) Etodolac (ii) β-CD (iii) HPMC iv) Etodolac :β-CD-HPMC