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Enhancement of Dissolution rate of Naproxen by Solid Dispersions with cyclodextrin Complex's

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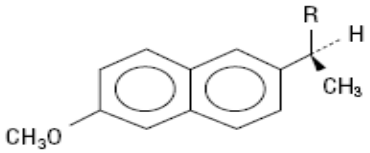
ABSTRACT: Naproxen is an anti-inflammatory drug that is poorly soluble in water. This paper describes an approach to improve the dissolution rate of Naproxen by using solid dispersions (SDs) in hydrophilic polymers The solid dispersions prepared with a Co-evaporation, kneaded method & Physical Mixture method using different concentrations of α-cyclodextrin (α-CD). The release of Naproxen 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 36.34 to75.04 by the use of Naproxen α-CD-HPMC (1:2:0.3) Kneaded complex.

Keywords: Naproxen Solid dispersions, hydrophilic polymers

I. INTRODUCTION

Naproxen is a Proprionic acid derivative related to the Arylacetic acid group of NonSteroidal Anti-Inflammatory drugs [1]..The chemical names for Naproxen and Naproxen Sodium are (S)-6-Methoxy-A-Methyl-2-Naphthaleneacetic Acid and (S)-6-Methoxy-a-Methyl-2-Naphthaleneacetic Acid, Sodium salt, respectively[1,2].. Naproxen and Naproxen Sodium have the following structures, respectively



II. 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[3,4].

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.	Naproxen	α-CD	N- α-CD (1:1)
2.	Naproxen	α-CD ,PEG	N- α-CD,PEG (1:1:0.2)
3.	Naproxen	α-CD ,PVP	N- α-CD ,PVP (1:1:0.2)
4.	Naproxen	α-CD ,HPMC	N- α-CD ,HPMC (1:1:0.2)
5	Naproxen	α-CD	N- α-CD (1:2)
6	Naproxen	α-CD ,PEG	N- α-CD,PEG (1:2:0.3)
7	Naproxen	α-CD ,PVP	N- α-CD ,PVP (1:2:0.3)
8	Naproxen	α-CD ,HPMC	N- α-CD ,HPMC (1:2:0.3)

ESTIMATION OF NAPROXEN IN SOLID DISPERSIONS

100 mg of inclusion complex was taken in a 50 ml volumetric flask. Methanol about 40 ml was added and mixed thoroughly. The contents were repeatedly warmed in a hot bath while mixing to dissolve the drug in the solvent[6,7]. The solution was made up to volume with methanol. The solution was then suitably diluted and assayed for drug content by the specific spectrophotometric method

TABLE 2: Drug Content of Solid Inclusion Complexes of Naproxen □-CD , Prepared by Kneading ,Coevaporation and Physical Mixture Methods

CD Complex	Percent Naproxen Content ($\bar{x} \pm s.d.$,)		
	Kneading Method	Coevaporation Method	PhysicalMixture
N-α CD (1:1)	**49.89±0.71**	**49.79±0.86**	**49.95±0.82**
N-α CD:PEG (1:1:0.2)	**45.84±0.94**	**45.98±0.88**	**45.40±0.89**
N-α CD:PVP (1:1:0.2)	**45.78±0.77**	**44.60±0.78**	**45.88±0.54**
N-α CD:HPMC (1:1:0.2)	**45.37±0.84**	**45.56±0.92**	**44.93±0.94**
N-α CD (1:2)	**33.34±0.78**	**33.38±0.65**	**33.30±0.85**
N-α CD:PEG (1:2:0.3)	**30.59±0.69**	**30.79±0.89**	**29.70±0.77**
N-α CD:PVP (1:2:0.3)	**30.63±0.93**	**30.27±0.73**	**30.39±0.95**
N-α CD:HPMC (1:2:0.3)	**30.27±0.88**	**30.35±0.78**	**30.29±0.38**

X-Ray Powder Diffractometry (Xrd)

The X-Ray diffractograms of pure drug naproxen exhibited characteristic diffraction pattern indicating their crystalline nature. X-ray diffractograms of the pure drugs and their cyclodextrin complexes are shown in Fig.
21

Differential scanning calorimetry

The DSC curve of naproxen showed a single sharp exothermic peak at 158.9^0 C corresponding to its melting point. αCD,HPMC showed a broad peaks associated with loss of water. In the DSC thermograms of naproxen α-CD-HPMC the intensity or height of the exothermic peaks at 153.7^0C respectively were reduced indicating interaction of naproxen with cyclodextrins. The change in symmetry of the peak clearly indicates the formation of a complex. The exothermic peak of the cyclodextrin complexes of naproxen at 153.7^0 C was markedly reduced indicating the reduction of crystalline nature of drug and its complexation and amorphization with cyclodextrins are shown im Fig.20

Fourier-transform infrared spectroscopy (FTIR)

The principal IR absorption peaks of naproxen at 2968 cm^{-1} (Ar-C-H stretch), 2829 cm^{-1} (COOH stretch), 3543 cm^{-1} (OH stretch in COOH), 3092 cm^{-1} (CH stretch in CH_3), 1157 cm^{-1} (C-O-C stretching), 1717 cm^{-1} (C=O stretch in COOH) , 1387 cm^{-1}(CH bending in Ar-CH), 1596 cm-1(C=C stretching) were all observed in the spectra of naproxen and its cyclodextrin complex N-HPβ -CD-HPMC. IR absorption peaks of naproxen , HPMC and its cyclodextrin complexes are shown in Fig.19

Scanning electron microscopy (SEM) studies

The surface morphology was examined by Scanning electron microscopic studies and the photographs are shown in **Fig. 22** .SEM is used to study the microscopic aspects of the raw materials like pure drug, α-CD and the complexation products obtained from different methods of preparation. The pictures were then taken at an excitation voltage of 15 kV. SEM images of naproxen and its cyclodextrin complexes[8,9] .

Dissolution Rate Studies on Solid Dispersions:

Dissolution rate of drug from the CD complexes was studied using USP XXIII – 6 station dissolution rate test apparatus (ElectroLab) with a paddle stirrer at specified rpm and a temperature of $37^0 \pm 1^0$ C with 0.1 N HCl, (pH 1.2) Drug or drug-CD complex equivalent to 100 mg of naproxen was used in each dissolution rate test.

Samples of dissolution medium (5ml) were withdrawn through a filter (0.45 µ) at different time intervals, suitably diluted and assayed for the drug content by measuring absorbance at 272 nm in the case of naproxen[10,11,12].. The dissolution fluid withdrawn at each sampling time was replaced with fresh dissolution fluid in each case. Dissolution experiments were conducted in triplicate in each case.

Dissolution Profiles of Naproxen and its Solid Dispersions

TABLE.3: Dissolution Profiles of Naproxen and its □-CD Complexes Prepared by Kneading Method

	Percent Naproxen Dissolved(*x*s.d., n=3)				
	N	N: αCD 1:1	N:αCD:PEG 1:1:0.2	N:αCD:PVP 1:1:0.2	N:αCD:HPMC 1:1:0.2
0	0	0	0	0	0
5	20.13±0.92	30.32±0.98	34.56±0.90	40.66±0.90	50.32±0.90
10	23.14±0.95	40.63±0.95	42.13±0.91	45.89±0.91	56.83±0.91
20	25.32±0.93	41.83±0.91	45.43±0.94	50.36±0.94	61.42±0.94
30	26.12±0.96	43.16±0.94	46.32±0.98	55.89±0.97	66.34±0.98
45	28.7±0.94	48.32±0.92	51.35±0.97	63.16±0.98	69.53±0.97
60	29.97±0.91	51.64±0.93	57.46±0.94	68.49±0.95	75.13±0.94
90	34.45±0.93	54.36±0.90	61.66±0.95	70.56±0.96	80.93±0.92
120	43.05±0.98	56.83±0.91	66.85±0.91	77.32±0.93	84.16±0.93

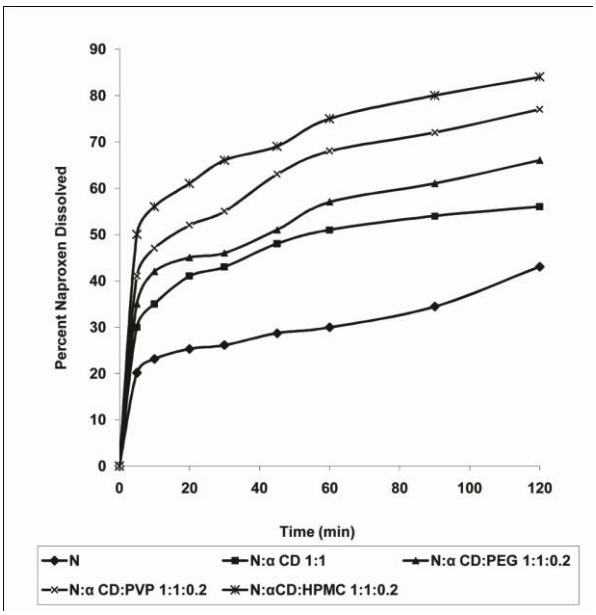


Fig. 1.Dissolution Profiles of Naproxen and its □-CD Complexes Prepared by Kneading Method

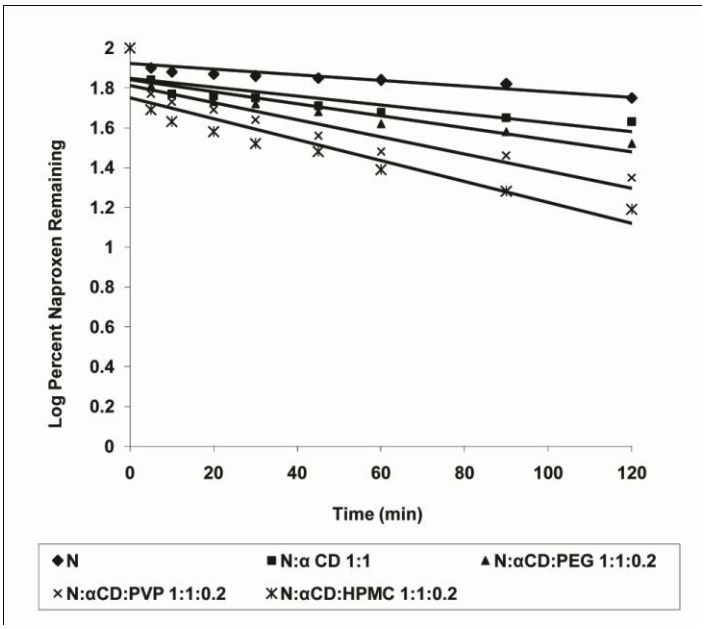


Fig. 2.First Order Dissolution Plots of Naproxen and its □-CD Complexes Prepared by Kneading Method

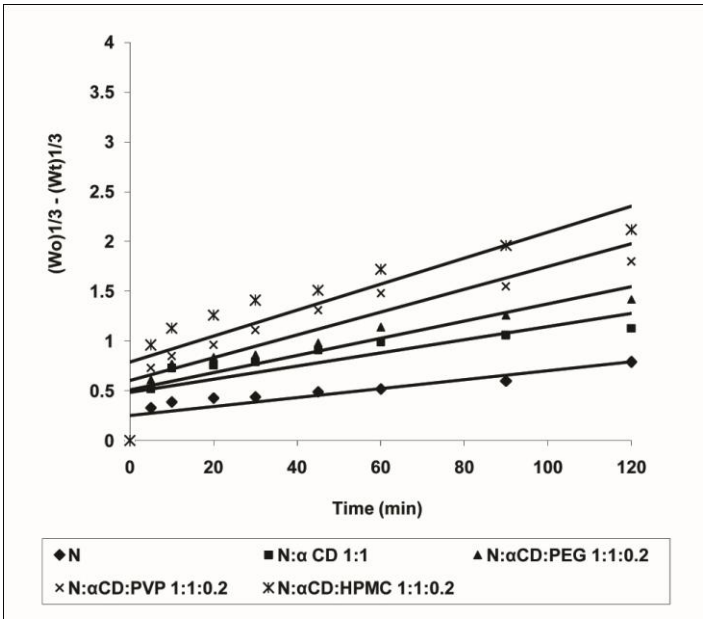


Fig. 3. Hixson Crowell Plots of Naproxen and its □-CD complexes Prepared by Kneading Method

Table.4. Dissolution Profiles of Naproxen and its □- CD prepared by Kneading Method

TIME (min)	Percent Naproxen Dissolved($\bar{x}$± s.d., n=3)				
	N	N: □ CD 1:2	N: □ CD:PEG 1:2:0.3	N:□ CD:PVP 1:2:0.3	N:□ CD:HPMC 1:2:0.3
0	0	0	0	0	0
5	20.13±0.92	53.16±0.89	58.32±0.89	64.16±0.96	70.32±0.68
10	23.14±0.95	62.53±0.95	66.31±0.96	73.56±0.94	79.16±0.87
20	25.32±0.93	66.13±0.97	74.16±0.75	80.62±0.92	86.63±0.86
30	26.12±0.96	73.54±0.93	85.33±0.82	88.68±0.87	92.96±0.98
45	28.7±0.94	80.16±0.95	90.32±0.86	92.16±0.78	96.98±0.91

60	29.97±0.91	83.54±0.93	92.13±0.88	95.32±0.76	98.33±0.90
90	34.45±0.93	85.61±0.98	94.16±0.87	96.13±0.98	99.44±0.88
120	43.05±0.98	88.23±0.92	95.32±0.80	98.15±0.88	99.86±0.97

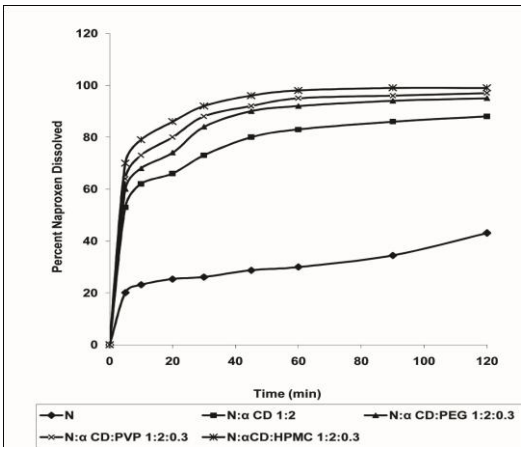


Fig .4 Dissolution Profiles of Naproxen and its □- CD complexes prepared by Kneading Method

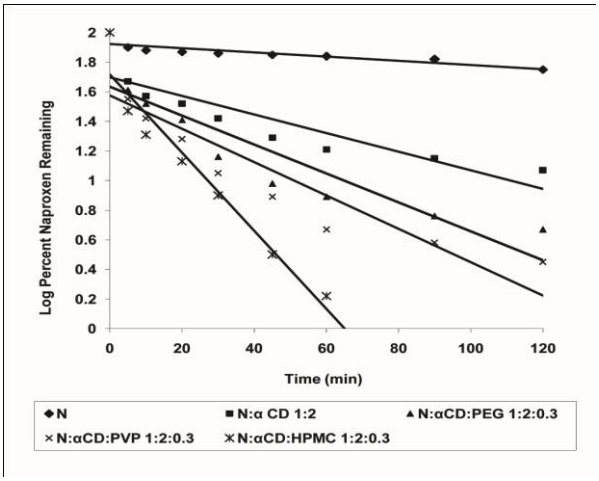


Fig. 5. First Order Dissolution Plots of Naproxen and its □- CD Complexes prepared by Kneading Method

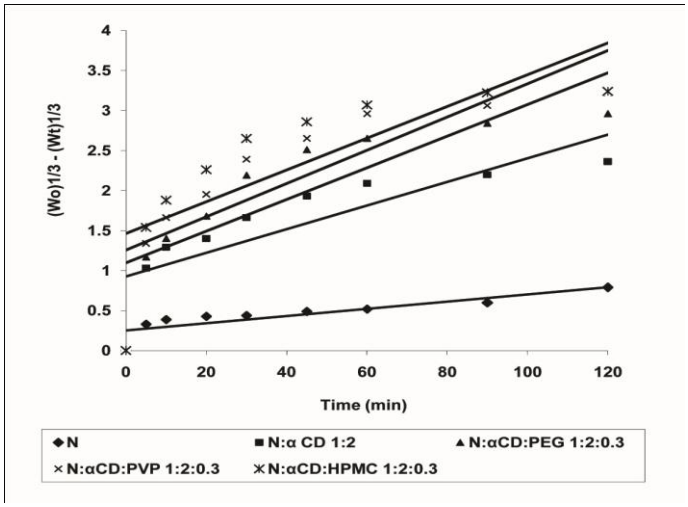


Fig.6. Hixson Crowel Dissolution Plots of Naproxen and its □- CD Complexes prepared by Kneading Method

TABLE 5. Dissolution Profiles of Naproxen and its □-C D Complexes Prepared by Co Evaporation Method

TIME (min)	Percent Naproxen Dissolved ($\bar{x}$± s.d., n=3)				
	N	N: □ CD 1:1	N:□ CD:PEG 1:1:0.2	N:□ CD:PVP 1:1:0.2	N:□ CD:HPMC 1:1:0.2
0	0	0	0	0	0
5	20.13±0.92	26.23±0.92	30.65±0.960	33.65±0.91	37.23±0.93
10	23.14±0.95	37.36±0.93	39.31±0.91	42.98±0.92	45.38±0.94
20	25.32±0.93	39.38±0.95	41.34±0.94	47.63±0.94	52.34±0.92
30	26.12±0.96	40.61±0.94	42.23±0.95	49.98±0.98	56.43±0.91
45	28.7±0.94	44.33±0.98	47.53±0.92	53.61±0.96	59.35±0.98
60	29.97±0.91	49.46±0.97	51.64±0.98	58.94±0.94	65.31±0.97
90	34.45±0.93	51.63±0.91	57.66±0.97	60.65±0.95	70.39±0.96
120	43.05±0.98	54.39±0.92	59.58±0.93	65.23±0.91	73.61±0.91

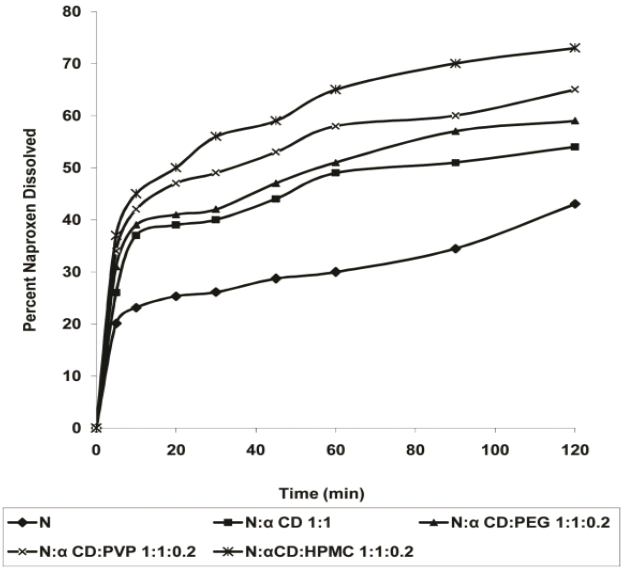


Fig .5.129Dissolution Profiles of Naproxen and its α- Cyclodextrin complexes prepared by Coevaporation Method

Fig.7.DissolutionProfiles of Naproxen and its □-CD Complexes Prepared by Coevaporation Method

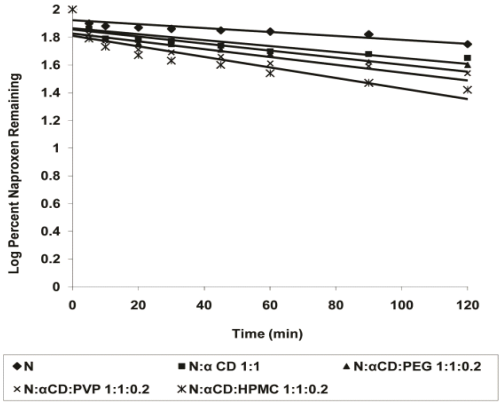


Fig .5.130 First Order Dissolution Plots of Naproxen and its Cyclodextrin complexes prepared by Coevaporation Method

Fig.8. First Order Dissolution Plots of Naproxen and its □-CD Complexes Prepared by Coevaporation Method

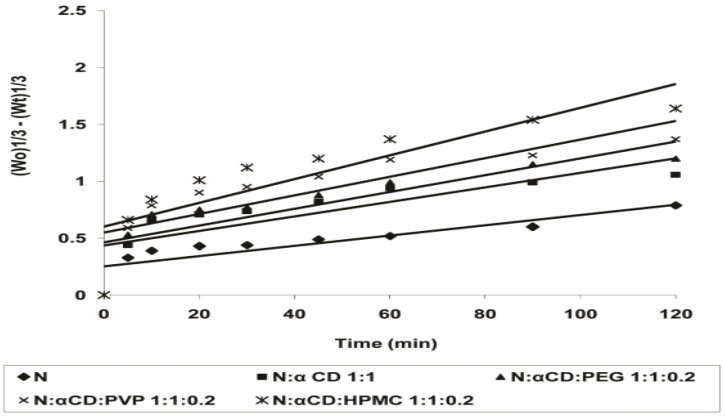


Fig.5.131 Hixson Crowel Dissolution Plots of Naproxen and its Cyclodextrin complexes prepared by Coevaporation Method

Fig.9. Hixson Crowell Plots of Naproxen and its □-CD complexes Prepared by Coevaporation Method

TABLE.6. Dissolution Profiles of Naproxen and its □-CD Complexes Prepared by Co Evaporation Method

TIME (min)	Percent Naproxen Dissolved ($\bar{x}$±s.d.,n =3)				
	N	N:□ CD 1:2	N:□ CD:PEG 1:2:0.3	N:□ CD:PVP 1:2:0.3	N:□ CD:HPMC 1:2:0.3
0	0	0	0	0	0
5	20.13±0.92	44.61±0.98	49.32±0.98	53.61±0.91	58.23±0.90
10	23.14±0.95	52.35±0.96	56.31±0.96	62.65±0.97	66.61±0.94
20	25.32±0.93	56.31±0.92	63.61±0.94	68.26±0.90	70.36±0.96
30	26.12±0.96	62.94±0.94	73.32±0.90	75.86±0.95	77.69±0.93
45	28.7±0.94	70.61±0.91	80.23±0.95	84.61±0.96	80.89±0.92
60	29.97±0.91	73.45±0.90	82.31±0.93	85.13±0.93	85.32±0.94
90	34.45±0.93	75.16±0.92	84.61±0.97	87.31±0.94	86.74±0.95
120	43.05±0.98	78.32±0.97	85.23±0.91	88.57±0.93	86.68±0.90

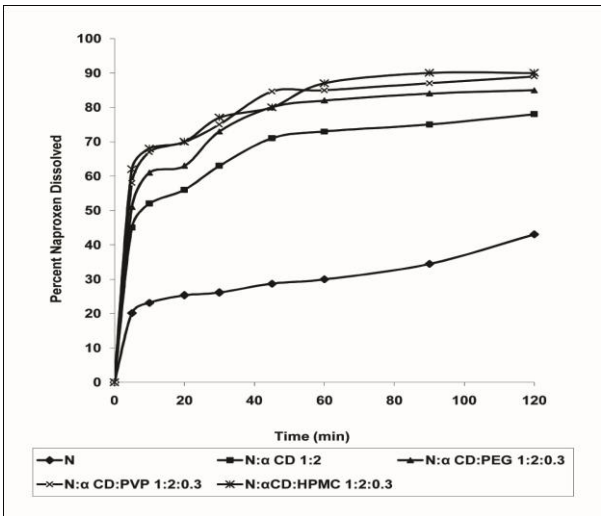


Fig.10. Dissolution Profiles of Naproxen and its □-CD Complexes Prepared by Coevaporation Method

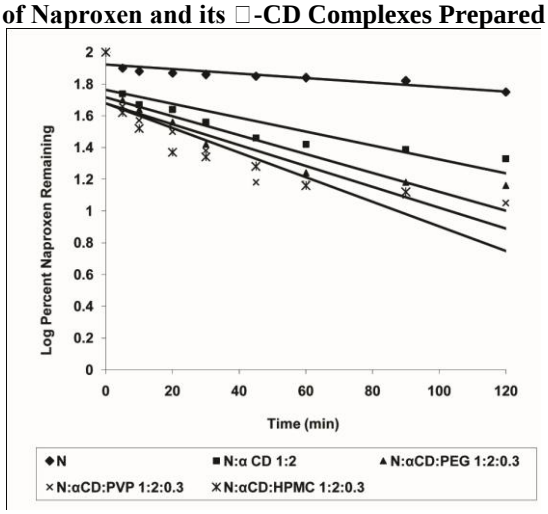
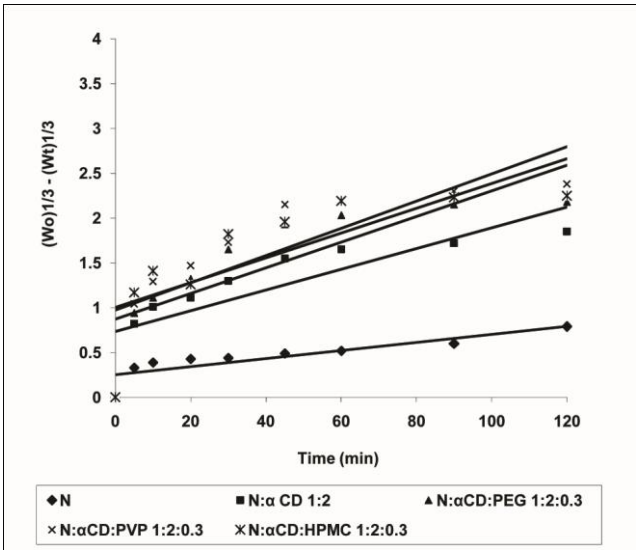


Fig. 11.First Order Dissolution Plots of Naproxen and its □-CD Complexes Prepared by Co Evaporation Method



.Fig.12.Hixson Crowell Plots of Naproxen and its □-CD complexes Prepared by CoevaporationMethod

TABLE :7.Dissolution Profiles of Naproxen and its □-CD Complexes Prepared by Physical Mixture Method

TIME (min)	Percent Naproxen Dissolved ($\bar{x}$± s.d., n =3)				
	N	N: □ CD 1:1	N: □ CD:PEG 1:1:0.2	N:□ CD:PVP 1:1:0.2	N:□ CD:HPMC 1:1:0.2
0	0	0	0	0	0
5	20.13±0.92	22.56±0.98	24.86±0.96	25.56±0.92	28.32±0.97
10	23.14±0.95	30.63±0.89	33.13±0.97	36.88±0.93	40.83±0.95
20	25.32±0.93	32.83±0.92	35.43±0.90	39.33±0.92	42.43±0.94
30	26.12±0.96	35.16±0.91	38.61±0.91	40.36±0.91	44.34±0.95
45	28.7±0.94	37.33±0.95	41.35±0.92	44.16±0.93	48.53±0.96
60	29.97±0.91	39.64±0.92	44.46±0.91	45.49±0.94	51.13±0.95
90	34.45±0.93	42.23±0.90	46.65±0.90	49.93±0.96	55.93±0.97
120	43.05±0.98	44.83±0.89	48.85±0.90	51.23±0.97	58.16±0.98

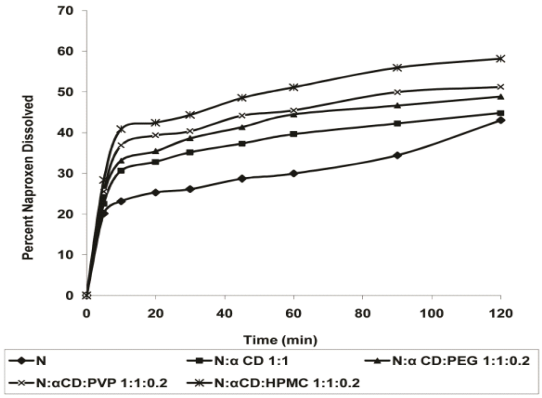


Fig .5.159Dissolution Profiles of Naproxen and it's α- Cyclodextrin complexes prepared by Physical Mixing Method

Fig. 13.Dissolution Profiles of Naproxen and its □-CD Complexes Prepared by Physical mixture Method

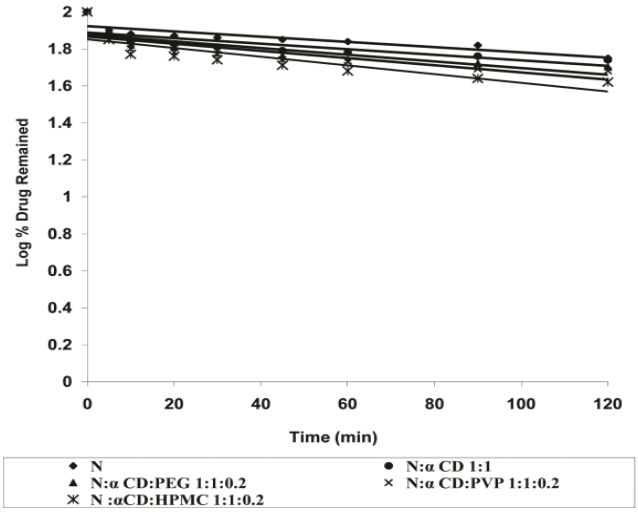


Fig .5.160 First Order Dissolution Plots of Naproxen and it's α- Cyclodextrin complexes prepared by Physical Mixing Method

Fig. 14.First Order Dissolution Plots of Naproxen and its □-CD Complexes Prepared by Physical mixture Method

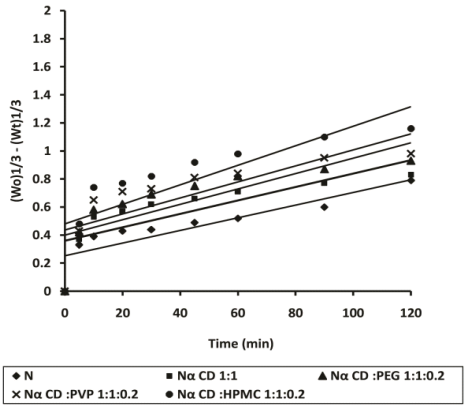


Fig .5.161 Hixson-Crowell Plots of Naproxen and it's α- Cyclodextrin complexes prepared by Physical Mixing Method

Fig. 15. Hixson Crowell Plots of Naproxen and its □-CD complexes Prepared by Physical mixture Method

TABLE 8:Dissolution Profiles of Naproxen and its □-CD Complexes Prepared by Physical Mixture Method

TIME (min)	Percent Naproxen Dissolved ($\bar{x}$± s.d., n =3)				
	N	N: □ CD 1:2	N: □ CD:PEG 1:2:0.3	N:□ CD:PVP 1:2:0.3	N:□ CD:HPMC 1:2:0.3
0	0	0	0	0	0
5	20.13±0.92	30.16±0.93	35.66±0.95	38.16±0.94	43.32±0.94
10	23.14±0.95	38.38±0.90	40.93±0.92	42.56±0.98	48.38±0.92
20	25.32±0.93	42.13±0.89	45.16±0.90	45.62±0.96	51.34±0.91
30	26.12±0.96	44.49±0.91	53.94±0.91	55.68±0.92	58.96±0.91
45	28.7±0.94	47.16±0.83	58.32±0.95	58.23±0.95	61.89±0.90
60	29.97±0.91	53.54±0.92	60.45±0.92	62.91±0.90	66.97±0.89
90	34.45±0.93	56.61±0.97	64.16±0.93	64.16±0.96	69.44±0.88
120	43.05±0.98	60.32±0.93	66.23±0.95	68.75±0.92	73.86±0.89

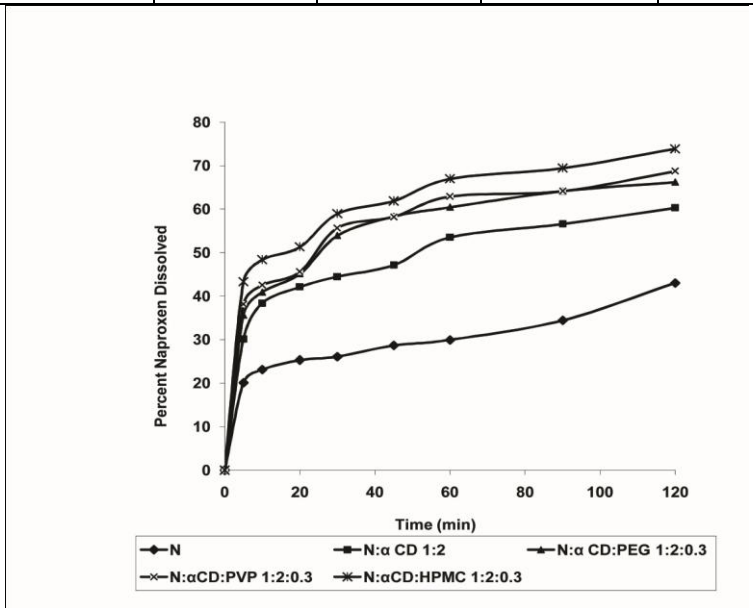


Fig.16.DissolutionProfiles of Naproxen and its □-CD Complexes Prepared by Physical Mixture Method

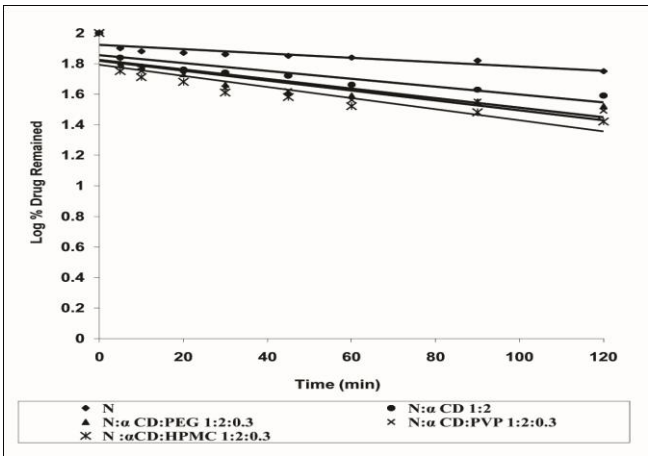


Fig.17. First Order Dissolution Plots of Naproxen and its □-CD Complexes Prepared by Physical Mixture Method

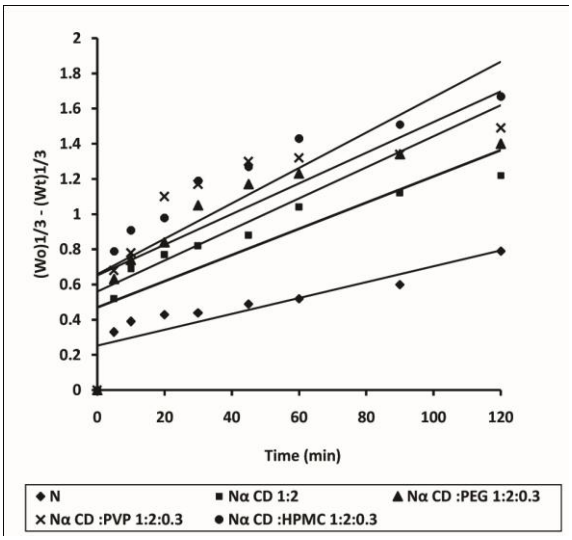


Fig.18. Hixson Crowell Plots of Naproxen and its □-CD complexes Prepared by Physical Mixture Method

TABLE 9: Dissolution Parameters of Naproxen and its □- CD 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	Naproxen	20.13	--	23.14	22.38	0.0038	-
2	N:αCD 1:1	30.32	1.48	40.63	36.34	0.025	6.61
3	N: αCD 1:2	53.16	2.60	62.53	58.79	0.049	13.02
4	N: αCD:PEG 1:1:0.2	34.56	1.69	42.13	39.15	0.028	7.27
5	N: αCD:PEG 1:2:0.3	58.32	2.85	66.31	65.24	0.060	15.99
6	N: αCD:PVP 1:1:0.2	40.66	1.99	45.89	44.35	0.031	8.20
7	N: αCD:PVP 1:2:0.3	64.16	3.14	73.56	70.73	0.075	19.77
8	N:αCD:HPMC 1:1:0.2	50.32	2.46	56.83	54.12	0.042	11.15
9	N: αCD:HPMC 1:2:0.3	70.35	3.44	79.16	75.04	0.091	23.99

TABLE.10.The Correlation Coefficient (**R^2**)Values in the Analysis of Dissolution Data of Naproxen CD 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	Naproxen	0.752	0.796	0.936
2	N:αCD 1:1	0.961	0.975	0.971
3	N: αCD 1:2	0.927	0.955	0.945
4	N: αCD:PEG 1:1:0.2	0.812	0.947	0.947
5	N: αCD:PEG 1:2:0.3	0.807	0.878	0.932
6	N: αCD:PVP 1:1:0.2	0.794	0.926	0.923
7	N: αCD:PVP 1:2:0.3	0.799	0.952	0.942
8	N:αCD:HPMC 1:1:0.2	0.732	0.932	0.927
9	N: αCD:HPMC 1:2:0.3	0.912	0.955	0.938

TABLE. 11. Dissolution Parameters of Naproxen and its □- CD 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	Naproxen	20.13	--	23.14	22.38	0.0038	-
2	N:αCD 1:1	26.23	1.28	37.36	37.33	0.050	13.33
3	N: αCD 1:2	44.61	2.18	52.35	40.93	0.059	15.75
4	N: αCD:PEG 1:1:0.2	30.65	1.50	39.31	44.48	0.064	16.96
5	N: αCD:PEG 1:2:0.3	49.32	2.41	56.31	49.77	0.071	19.83
6	N: αCD:PVP 1:1:0.2	33.65	1.64	42.98	59.69	0.059	15.72
7	N: αCD:PVP 1:2:0.3	53.61	2.62	62.65	62.20	0.105	27.87
8	N:αCD:HPMC 1:1:0.2	37.32	1.82	45.38	65.07	0.110	28.94
9	N: αCD:HPMC 1:2:0.3	58.23	2.85	66.61	68.66	0.128	35.82

TABLE. 12.. The Correlation Coefficient (R^2)Values in the Analysis of Dissolution Data of Naproxen CD Complexes 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	Naproxen	0.752	0.796	0.936
2	N:αCD 1:1	0.863	0.967	0.975
3	N: αCD 1:2	0.849	0.976	0.975
4	N: αCD:PEG 1:1:0.2	0.860	0.933	0.973
5	N: αCD:PEG 1:2:0.3	0.845	0.980	0.972
6	N: αCD:PVP 1:1:0.2	0.823	0.954	0.957
7	N: αCD:PVP 1:2:0.3	0.736	0.881	0.895
8	N:αCD:HPMC 1:1:0.2	0.913	0.992	0.985
9	N: αCD:HPMC 1:2:0.3	0.881	0.960	0.955

TABLE.13.Dissolution Parameters of Naproxen and its □- CD 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	Naproxen	20.13	--	23.14	22.38	0.0038	-
2	N:αCD 1:1	22.56	1.12	30.63	23.22	0.0186	4.92
3	N: αCD 1:2	30.16	1.49	38.39	36.08	0.025	6.58
4	N: αCD:PEG 1:1:0.2	24.86	1.23	33.13	30.67	0.0197	5.19
5	N: αCD:PEG 1:2:0.3	35.66	1.77	40.93	40.22	0.0213	5.62
6	N: αCD:PVP 1:1:0.2	25.56	1.26	36.88	33.32	0.023	6.199
7	N: αCD:PVP 1:2:0.3	38.16	1.89	42.56	41.47	0.022	5.83
8	N:αCD:HPMC 1:1:0.2	28.32	1.40	40.83	34.29	0.026	6.72
9	N: αCD:HPMC 1:2:0.3	**43.32**	**2.15**	**48.38**	**46.25**	**0.024**	**6.26**

TABLE .14. The Correlation Coefficient (R^2) values in the Analysis of Dissolution Data of Naproxen CD 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	Naproxen	**0.752**	**0.796**	**0.936**
2	N:αCD 1:1	**0.803**	**0.859**	**0.968**
3	N: αCD 1:2	**0.835**	**0.852**	**0.896**
4	N: αCD:PEG 1:1:0.2	**0.805**	**0.837**	**0.906**
5	N: αCD:PEG 1:2:0.3	**0.825**	**0.886**	**0.902**

6	N: αCD:PVP 1:1:0.2	**0.852**	**0.878**	**0.898**
7	N: αCD:PVP 1:2:0.3	**0.810**	**0.866**	**0.896**
8	N:αCD:HPMC 1:1:0.2	**0.839**	**0.893**	**0.947**
9	N: αCD:HPMC 1:2:0.3	**0.771**	**0.836**	**0.952**

III. RESULTS AND DISCUSSION

The dissolution rate of Naproxen (N) 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 N-CD complexes are given in Table.1, and the dissolution profiles are shown in **Figs.1,4,7,10,13,16**,First order plots of the Naproxen □– CD complexes are shown in **Fig. 2,5,8,11,14,17**. Hixson-Crowell plots of Naproxen □– CD complexes are shown in **Fig. 3,6,9,12,15,18**.The dissolution of Naproxen from the CD complexes was rapid and higher than that of Naproxen as such. The dissolution data were analyzed as per zero-order and first-order kinetics. The dissolution of Naproxen 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 10,12,14**). From the slope of the first order linear plots the dissolution rate constant (K_1) values were calculated and are given in **Tables 9,11,13**. The dissolution efficiency (DE_{30}) values were calculated. The dissolution parameters of Naproxen and its cyclodextrin complexes are summarized in **Tables 9,11,13** . All the dissolution parameters (DP 5min, RDr, 5min, % dissolved in 10 min., DE_{30} and K_1) indicated rapid and higher dissolution of Naproxen 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 N: αCD:HPMC 1:2:0.3 solid dispersion gave a **23.99 fold** increase in the dissolution rate of Naproxen whereas solid dispersion of Naproxen in alone αCD (N- αCD solid dispersion) gave only 6.61 fold increase. Thus combination of Cyclodextrins with water soluble carriers PEG, PVP, HPMC resulted in a greater enhancement in the dissolution rate of Naproxen.

Dissolution of Naproxen from all the solid dispersions followed first order kinetics with correlation coefficient 'r' above 0.9 (**Tables:10,12,14**) .The increasing order of dissolution rates of solid dispersions of Naproxen are comparable with solid dispersion.

Mechanism of Increased Dissolution Rate of Cyclodextrin Complexes

The observed increase in the dissolution rate of Naproxen from their cyclodextrin complexes is due to the following possible mechanisms[13,14,15]:

- 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 a polar 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.
- 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.

IV. CONCLUSION

The dissolution rate and dissolution efficiency of Naproxen could be enhanced several times by their solid dispersion in cyclodextrin 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[14,15,16].. Thus, solid dispersion in Cyclodextrin is recommended as an effective and efficient technique for enhancing the dissolution rate, dissolution efficiency of Naproxen. Cyclodextrin 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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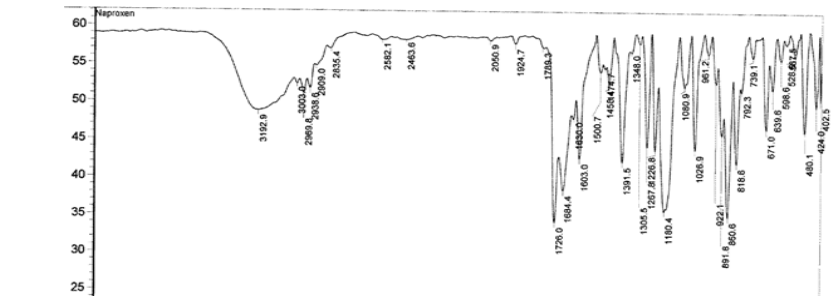

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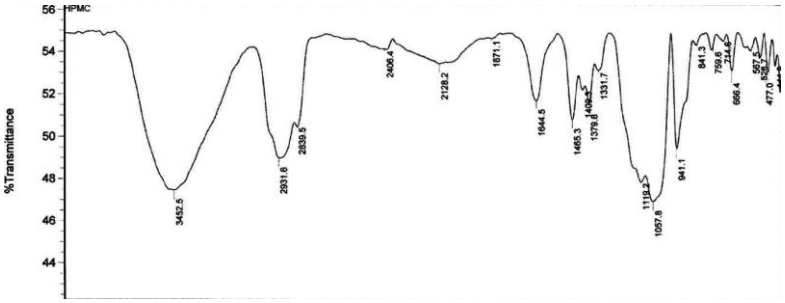

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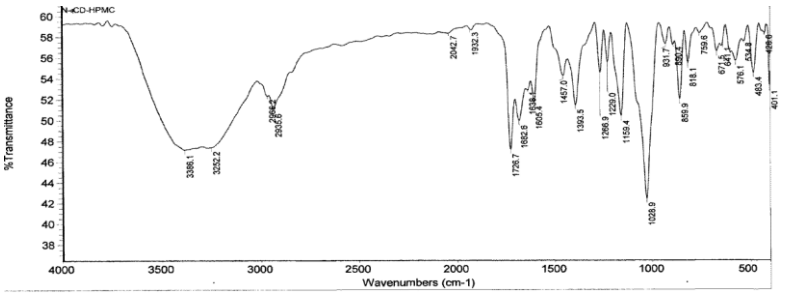

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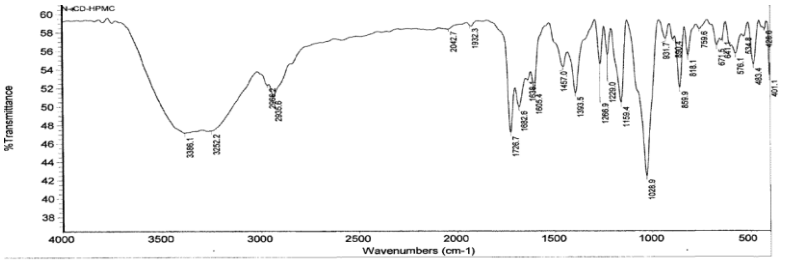

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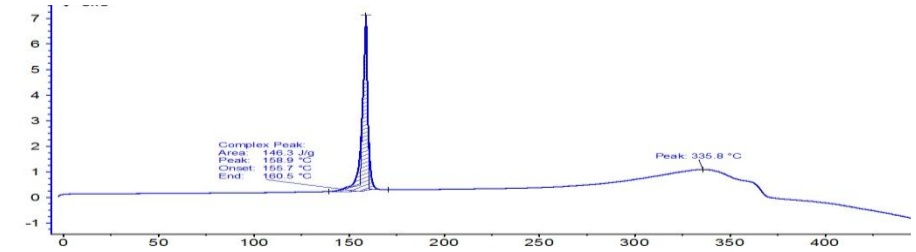
Fig : 19. IR Spectra of (i) Naproxen (ii) α-CD (iii) HPMC (iv) Naproxen :α-CD HPMC



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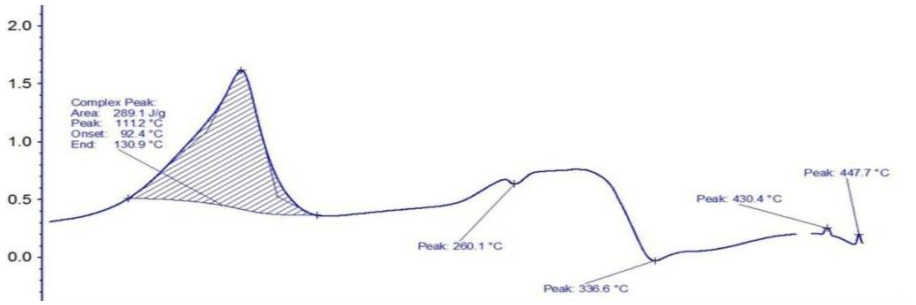

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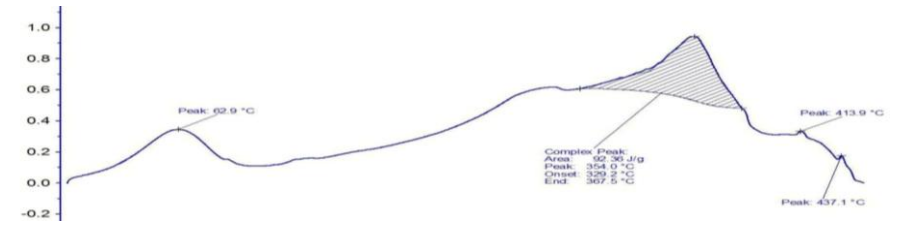

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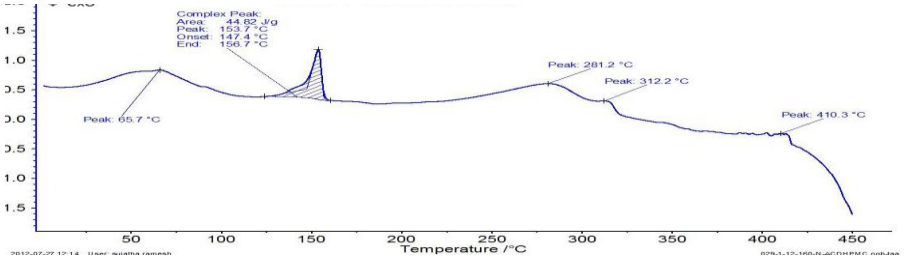

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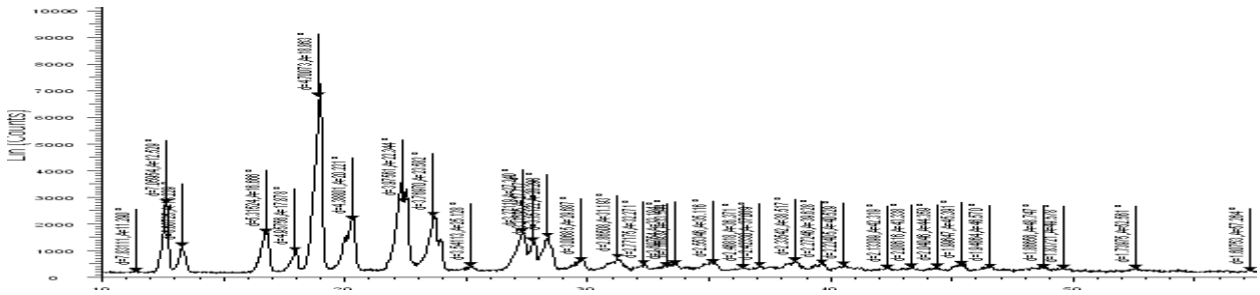
Fig : 20. DSC Spectra of (i) Naproxen (ii) α-CD (iii) HPMC iv) Naproxen: αCD-HPMC



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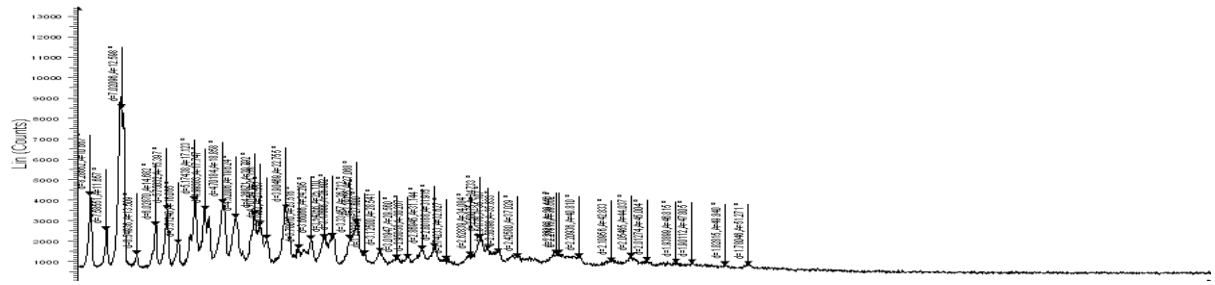

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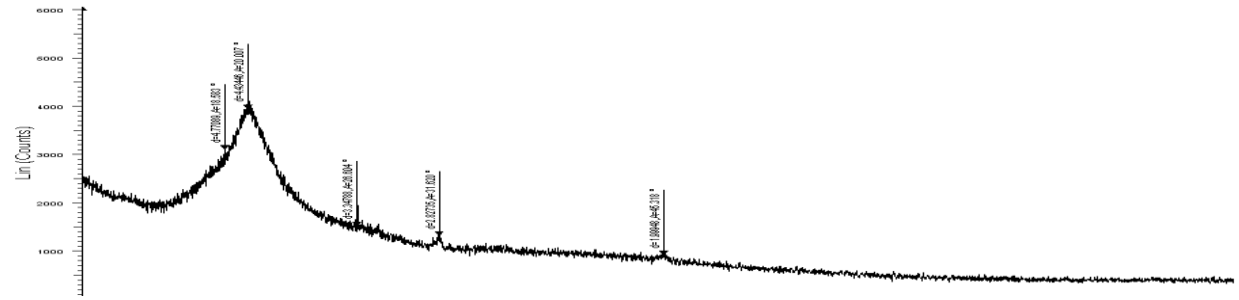

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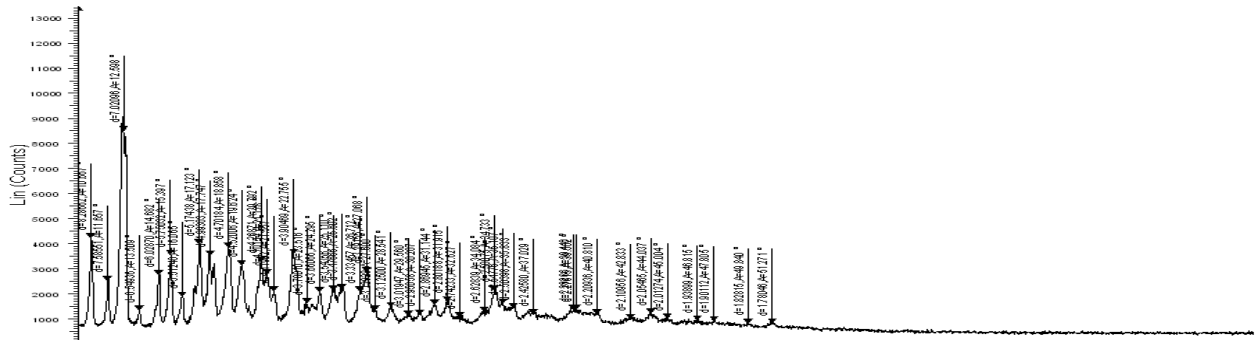

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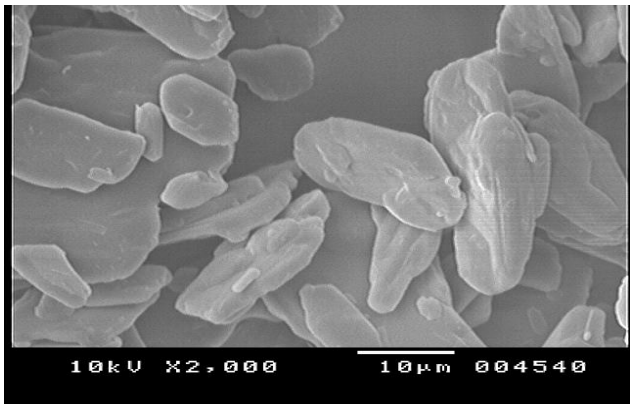
Fig :21. XRD Spectra of (i)Naproxen (ii) α-CD (iii) HPMC iv) Naproxen : αCD-HPMC



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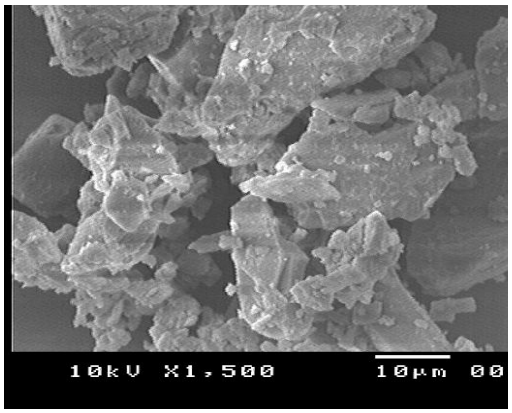

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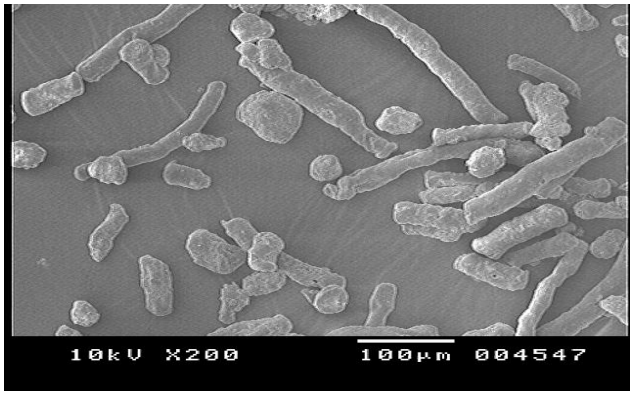

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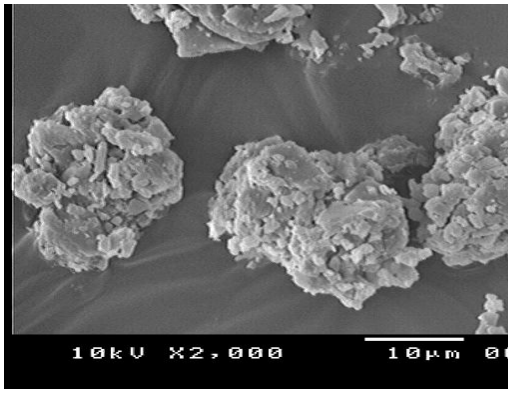

(IV)

Fig : 22.SEM images (i)Naproxen (ii) α-CD (iii) HPMC iv) Naproxen : αCD-HPMC