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A FACTORIAL STUDY ON THE EFFECTS OF CYCLODEXTRINS, POLOXAMER 407 AND PVP ON THE SOLUBILITY AND DISSOLUTION RATE OF ETORICOXIB

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ABSTARCT

The individual main effects and combined (or interaction) effects of cyclodextrins (βCD and HPβCD), surfactant (Poloxamer 407) and PVP on the solubility and dissolution rate of etoricoxib were evaluated in a series of 2^3 factorial experiments. The solubility of etoricoxib in eight selected fluids containing CDs, Poloxamer 407 and PVP as per 2^3 factorial study was determined. The solubility of etoricoxib was markedly enhanced by βCD (2.24 fold), HPβCD (3.14 fold), Poloxamer 407 (2.58 fold) and PVP (1.38 fold) individually. βCD in combination with PVP has given highest enhancement (3.44 fold) in the solubility of etoricoxib. HPβCD in combination with Poloxamer 407 and PVP gave respectively 3.74 and 3.39 fold increase in the solubility of etoricoxib. Both the individual and combined effects were highly significant ($P < 0.01$). Solid inclusion complexes of etoricoxib-CDs (βCD and HP-βCD) were prepared with and without Poloxamer 407 and PVP by kneading method as per 2^3-factorial design. ANOVA indicated that the individual main effects of CDs (βCD and HP-βCD), Poloxamer 407 and PVP and their combined effects in enhancing the dissolution rate (K_1) and DE_{30} were highly significant ($P < 0.01$). βCD alone gave a 1.18 fold increase in the dissolution rate of etoricoxib. βCD in combination with PVP and Poloxamer 407 gave respectively 3.0 and 7.4 fold increase in the dissolution rate of etoricoxib. HPβCD alone gave a 3.55 fold increase and in combination with PVP and Poloxamer 407 it gave respectively 57.6 and 23.6 fold increase in the dissolution rate of etoricoxib. Combination of CDs with either Poloxamer 407 or PVP has markedly enhanced both the solubility and dissolution rate of etoricoxib, a BCS class II drug.

Key words: Etoricoxib, Cyclodextrins, Poloxamer 407, PVP, Solubility, Dissolution rate, Factorial study.

INTRODUCTION

Etoricoxib, a widely prescribed anti inflammatory and analgesic drug belongs to class-II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous

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solubility. It is practically in soluble in water and aqueous fluids. As such its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. Among the various approaches complexation with cyclodextrins has gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably affected[1,2]. Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies[3,4]. Poloxamer 407 is a polyethylene oxide- polypropylene oxide-polyethylene oxide triblock co-polymer of non-ionic nature and is used as a solubilising agent[5-7].

Though cyclodextrin complexation and use of surfactants for enhancing the solubility and dissolution rate of poorly soluble drugs have been investigated individually, no reports are available on their combined use in enhancing the solubility and dissolution rate. In the present investigation the individual main effects and combined (or interaction) effects of cyclodextrins (βCD and HPβCD), surfactant (Poloxamer 407) and PVP on the solubility and dissolution rate of etoricoxib were evaluated in a series of 2^3 factorial experiments.

In factorial experiments the effects of several factors of variation are studied and investigated simultaneously, the treatments being all the combinations of different factors under study. In these experiments an attempt is made to estimate the effects of each of the factors and also the interaction (or combined) effects, i.e, the variation in the effect of one factor as a result to different levels of other factors.

EXPERIMENTAL

Materials and methods

Etoricoxib was a gift sample from M/s. Natco Pharma Ltd., Hyderabad. β-Cyclodextrin and hydroxy propyl β-Cyclodextrin were gift samples from M/s. Cerestar Inc., USA. Methanol (Qualigens), Poly vinyl pyrrolidone (PVP-K30) and Poloxamer 407 were procured from commercial sources.

Estimation of Etoricoxib

An UV Spectrophotometry method based on the measurement of absorbance at 289 nm in a phosphate buffer of pH 7.4 was used for the estimation of etoricoxib. The method

was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 1-10 µg/mL. When a standard drug solution was repeatedly assayed (n = 6), the relative error and coefficient of variation were found to be 0.8% and 1.2% respectively. No interference by the excipients used in the study was observed.

Solubility determination

Excess drug (50mg) was added to 15 mL of each fluid taken in a 25 mL stopped conical flask and the mixtures were shaken for 24 h at room temperature (28 ± 1°C) on Rotary Flask Shaker. After 24 h of shaking, 2 mL aliquots were withdrawn at 2 h interval and filtered immediately using a 0.45 µ disk filter. The filtered samples were diluted suitably and assayed for etoricoxib by measuring absorbance at 289 nm. Shaking was continued until two consecutive estimations are the same. The solubility experiments were replicated for four times each (n = 4).

Preparation of Etoricoxib-CD complexes

Solid inclusion complexes of etoricoxib-CD were prepared in 1 : 2 ratio with and without Poloxamer 407 (2%) by kneading method. Etoricoxib, CDs (βCD or HPβCD) and Poloxamer 407 were triturated in a mortar with a small volume of solvent consisting of a blend of water: methanol (1 : 1). The thick slurry formed was kneaded for 45 min and then dried at 55°C until dry. The dried mass was powdered and sieved to mesh No. 120.

Dissolution rate study

The dissolution rate of etoricoxib as such and from CD complexes prepared was studied in 900 mL of phosphate buffer of pH 7.4 using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature 37 ± 1°C was maintained throughout the study. Etoricoxib or etoricoxib-CD complex equivalent to 60 mg of etoricoxib was used in each test. Samples of dissolution media (5 mL) were withdrawn through a filter (0.45 µ) at different intervals of time, suitable diluted and assayed for etoricoxib at 289 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid. The dissolution experiments were replicated four times each (n = 4).

RESULTS AND DISCUSSION

The individual main effects and combined (interaction) effects of two CDs (βCD and HP-βCD) (Factor A), Poloxamer 407 (Factor B) and PVP K30 (Factor C) on the aqueous solubility of etoricoxib were evaluated in a series of 2^3-factorial experiments. For this

purpose, two levels of CDs (0, 5 mM), two levels of Poloxamer 407 (0, 2%) and two levels of PVP (0, 2%) were selected in each case and the corresponding eight treatments involved in the 2^3-factorial study were purified water (1), water containing 5 mM CDs (βCD or HPβCD) (a); water containing 2% Poloxamer 407 (b); water containing 5 mM CDs (βCD or HPβCD) and 2% Poloxamer 407 (ab); water containing 2% PVP (c); water containing 5 mM CDs (βCD or HPβCD) and 2% PVP (ac); water containing 2% poloxamer 407 and 2% PVP (bc) and water containing 5 mM CDs (βCD or HPβCD) and 2% of each of Poloxamer 407 and PVP (abc).

The solubility of etoricoxib in the above mentioned eight fluids was determined (n = 4) and the results are given in Table 1. The aqueous solubility of etoricoxib was markedly enhanced by CDs alone and in combination with Poloxamer 407 and PVP.

Table 1: Solubility of Etoricoxib in Various Fluids as per 2^3 – Factorial Study

Fluids (Code as per 2^3 –Factorial experiment)	Solubility (mg/mL) (n = 4) (x ± sd)	Increase in solubility (Number of folds)
Distilled water (1)	0.148 ± 0.003	-
Water containing 5 mM βCD (a)	0.303 ± 0.005	2.04
Water containing 2% Poloxamer (b)	0.381 ± 0.001	2.57
Water containing 5 mM βCD and 2% Poloxamer (ab)	0.288 ± 0.006	1.94
Water containing 2% PVP (c)	0.205 ± 0.005	1.38
Water containing 5 mM βCD and 2% PVP (ac)	0.510 ± 0.074	3.44
Water containing 2% Poloxamer and 2% PVP (bc)	0.240 ± 0.016	1.62
Water containing 5 mM βCD, 2% Poloxamer and 2% PVP (abc)	0.415 ± 0.005	2.80
Water containing 5 mM HPβCD (a)	0.465 ± 0.013	3.14
Water containing 5 mM HPβCD and 2% Poloxamer (ab)	0.553 ± 0.001	3.74
Water containing 5 mM HPβCD and 2% PVP (ac)	0.503 ± 0.006	3.39
Water containing 5 mM HPβCD, 2% Poloxamer and 2% PVP (abc)	0.353 ± 0.006	2.38

The solubility data were subjected to Analysis of variance (ANOVA) to find out the significance of main and combined effects of CDs (βCD and HPβCD), Poloxamer 407 and PVP on the solubility of etoricoxib. The results of ANOVA are shown in Table 2 and 3. The individual and combined effects of βCD, HPβCD, Poloxamer 407 and PVP in enhancing the solubility of etoricoxib were highly significant ($P < 0.01$). The solubility of etoricoxib was markedly enhanced by βCD (2.24 fold), HPβCD (3.14 fold), Poloxamer 407 (2.58 fold) and PVP (1.38 fold) individually. The order of increasing solubility observed with various CDs and surfactants was HPβCD > Poloxamer 407 > βCD > PVP. βCD in combination with PVP has given highest enhancement (3.44 fold) in the solubility of etoricoxib. HPβCD in combination with Poloxamer 407 and PVP gave respectively 3.74 and 3.39 fold increase in the solubility of etoricoxib.

Table 2: ANOVA of solubility data of etoricoxib in various fluids as per 2^3 –Factorial study (βCD–Poloxamer 407-PVP)

Source of variation	D. F.	S. S.	M. S. S.	F-ratio	Significance
Total	31	0.422	0.013	-	-
treatments	7	0.393	0.056	51.09	$P < 0.01$
a	1	0.145	0.145	132.27	$P < 0.01$
b	1	0.012	0.012	10.545	$P < 0.01$
ab	1	0.071	0.071	65.28	$P < 0.01$
c	1	0.031	0.031	28.45	$P < 0.01$
ac	1	0.088	0.088	80.36	$P < 0.01$
bc	1	0.038	0.038	34.54	$P < 0.01$
abc	1	0.071	0.071	65.27	$P < 0.01$
Error	24	0.028	0.001	-	-

$F_{0.01\,(7,\,24)} = 3.50$; $F_{0.05\,(7,\,24)} = 2.43$; $F_{0.01\,(1,\,24)} = 7.82$; $F_{0.05\,(1,\,24)} = 4.26$

To evaluate the individual and combined effects of CDs (βCD or HP-βCD), Poloxamer 407 and PVP on the dissolution rate of etoricoxib, solid inclusion complexes of etoricoxib-CDs (βCD and HP-βCD) were prepared with and without Poloxamer 407 and PVP as per 2^3-factorial design. For this purpose two levels of CD (0 and 1 : 2 ratio of drug : CD) and two levels of each of Poloxamer 407 and PVP (0 and 2%) were selected and the corresponding eight treatments involved in the 2^3-factorial study were etoricoxib pure drug

(1); etoricoxib CD (βCD or HP- βCD) (1 : 2) inclusion binary complex (a); etoricoxib - Poloxamer 407 (2%) binary mixture (b); etoricoxib -CD (βCD or HP- βCD) (1 : 2) - Poloxamer 407 (2%) ternary complex (ab); etoricoxib – PVP (2%) binary mixture (c); etoricoxib -CD (βCD or HP-βCD) (1 : 2) – PVP (2%) ternary complex (ac); etoricoxib - Poloxamer 407 (2%) – PVP (2%) ternary complex (bc) and etoricoxib -CD (βCD or HP-βCD) (1 : 2) – Poloxamer 407 (2%) – PVP (2%) complex (abc).

Table 3: ANOVA of solubility data of etoricoxib in various fluids as per 2^3–Factorial study (HPβCD–Poloxamer 407 - PVP)

Source of variation	D. F.	S. S.	M. S. S.	F-ratio	Significance
Total	31	0.611	0.019	-	-
Treatments	7	0.609	0.087	1244.28	$P < 0.01$
a	1	0.406	0.406	5811	$P < 0.01$
b	1	0.021	0.021	308	$P < 0.01$
ab	1	0.053	0.053	765	$P < 0.01$
c	1	0.030	0.030	430	$P < 0.01$
ac	1	0.002	0.002	40	$P < 0.01$
bc	1	0.094	0.094	1348	$P < 0.01$
abc	1	0.0007	0.0007	10	$P < 0.01$
Error	24	0.0018	0.00007	-	-

$F_{0.01\,(7,\,24)} = 3.50$; $F_{0.05\,(7,\,24)} = 2.43$; $F_{0.01\,(1,\,24)} = 7.82$; $F_{0.05\,(1,\,24)} = 4.26$

The CD complexes were prepared by kneading method. All the solid inclusion complexes of etoricoxib-CD-Poloxamer 407-PVP prepared were found to be fine and free flowing powders. Low coefficient of variation (c.v.) values (< 1%) in the percent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared. The dissolution rate of etoricoxib alone and from CD complexes was studied in phosphate buffer of pH 7.4. The dissolution of etoricoxib followed first order kinetics with r (correlation coefficient) above 0.91. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[8]. The dissolution parameters are given in Table 4. The dissolution of etoricoxib was rapid and higher in the case of Etoricoxib – CD binary and ternary complex systems prepared when compared to etoricoxib pure drug as such.

Table 4: Dissolution parameters of etoricoxib –CD complex systems prepared as per 2^3 factorial study

Et –CD Complex	Composition	PD_{10} (%)	K_1x10^2 min^{-1}	Increase in K_1 (No. of folds)	DE_{30} (%)	Increase in DE_{30} (No. of folds)
F1	Et	28.20	1.54	-	18.67	-
Fa	Et-βCD (1 : 2)	31.53	1.83	1.18	22.39	1.19
Fb	Et-P 407 (2%)	59.09	2.15	1.39	35.23	1.84
Fab	Et-βCD (1 : 2) - P407 (2%)	69.30	11.43	7.4	42.83	2.2
Fc	Et-PVP (2%)	15.73	0.64	0.4	9.92	0.53
Fac	Et- βCD (1 : 2) -PVP (2%)	37.20	4.73	3	28.81	1.5
Fbc	Et-P407 (2%)-PVP (2%)	25.90	0.99	0.6	17.94	0.9
Fabc	Et- βCD (1 : 2)-P407 (2%)-PVP (2%)	53.35	5.40	3.5	34.60	1.85
Fa	Et-HPβCD (1 : 2)	57.50	5.47	3.55	33.80	1.81
Fab	Et-HPβCD (1 : 2)- P407 (2%)	84.66	3.64	23.6	48.82	2.6
Fac	Et-HPβCD (1 : 2)-PVP (2%)	99.26	88.83	57.6	54.46	2.91
Fabc	Et-HPβCD (1 : 2)-P407 (2%)-PVP (2%)	85.86	9.71	6.3	48.47	2.5

Et- Etoricoxib; CD- Cyclodextrins; P 407- Poloxamer 407; PVP – Poly vinyl pyrrolidone.

The dissolution parameters (K_1 and DE_{30}) were subjected to ANOVA to find out the significance of the main and combined effects of CDs, Poloxamer 407 and PVP on the dissolution rate of etoricoxib. The results of ANOVA are shown in Tables 5 and 6. ANOVA indicated that the individual main effects of CDs (βCD and HP-βCD), Poloxamer 407 and

PVP and their combined effects in enhancing the dissolution rate (K_1) and DE_{30} were highly significant ($P < 0.01$). βCD alone gave a 1.18 fold increase in the dissolution rate of etoricoxib. βCD in combination with PVP and Poloxamer 407 gave respectively 3.0 and 7.4 fold increase in the dissolution rate of etoricoxib. HPβCD alone gave a 3.55 fold increase and in combination with PVP and Poloxamer 407 it gave respectively 57.6 and 23.6 fold increase in the dissolution rate of etoricoxib.

Table 5: ANOVA of dissolution data of etoricoxib–CD complex systems prepared as per 2^3 –Factorial study (βCD–Poloxamer 407-PVP)

Source of variation	D. F.	S. S.	M. S. S.	F-ratio	Significance
Total	23	272.96	11.867	-	-
treatments	7	272.4	38.91	1111.71	P < 0.01
a	1	122.44	122.44	3498.2	P < 0.01
b	1	47.18	47.18	1348	P < 0.01
ab	1	32.55	32.55	930	P < 0.01
c	1	10.07	10.07	28.77	P < 0.01
ac	1	0.429	0.429	12.25	P < 0.01
bc	1	31.579	31.579	902.2	P < 0.01
abc	1	28.145	28.145	804.14	P < 0.01
Error	16	0.56	0.03	-	-

$F_{0.01\ (1,\ 16)} = 8.53$; $F_{0.05\ (1,\ 16)} = 4.49$; $F_{0.01\ (7,\ 16)} = 4.03$; $F_{0.05\ (7,\ 16)} = 2.66$

Table 6: ANOVA of dissolution data of etoricoxib–CD complex systems prepared as per 2^3–Factorial study (HPβCD–Poloxamer 407-PVP)

Source of variation	D. F.	S. S.	M. S. S.	F-ratio	Significance
Total	23	20524.63	892.37	-	-
Treatments	7	19928.91	2846.98	76.47	P < 0.01
a	1	7246.07	7246.07	194.62	P < 0.01
b	1	703.73	703.73	18.902	P < 0.01
ab	1	766.81	766.81	20.59	P < 0.01

Cont…

Source of variation	D. F.	S. S.	M. S. S.	F-ratio	Significance
c	1	1281	1281	34.40	P < 0.01
ac	1	1467.65	1467.65	39.42	P < 0.01
bc	1	4252.27	4252.27	114.21	P < 0.01
abc	1	4211.38	4211.38	113.11	P < 0.01
Error	16	595.72	37.23		
$F_{0.01(1,16)} = 8.53$; $F_{0.05(1,16)} = 4.49$; $F_{0.01(7,16)} = 4.03$; $F_{0.05\,(7,16)} = 2.66$					

Thus the results of the study indicated that combination of CDs with either Poloxamer 407 or PVP has markedly enhanced both the solubility and dissolution rate of etoricoxib, a BCS class II drug. Hence a combination of CDs with Poloxamer 407 and PVP is recommended to enhance the solubility and dissolution rate of etoricoxib.

CONCLUSIONS

(i) The solubility of etoricoxib was markedly enhanced by βCD (2.24 fold), HPβCD (3.14 fold), Poloxamer 407 (2.58 fold) and PVP (1.38 fold) individually.

(ii) βCD in combination with PVP has given highest enhancement (3.44 fold) in the solubility of etoricoxib. HPβCD in combination with Poloxamer 407 and PVP gave respectively 3.74 and 3.39 fold increase in the solubility of etoricoxib.

(iii) ANOVA indicated that the individual main effects of CDs (βCD and HP-βCD), Poloxamer 407 and PVP and their combined effects in enhancing the solubility and dissolution rate (K_1)and DE_{30} were highly significant ($P < 0.01$).

(iv) βCD alone gave a 1.18 fold increase in the dissolution rate of etoricoxib. βCD in combination with PVP and Poloxamer 407 gave respectively 3.0 and 7.4 fold increase in the dissolution rate of etoricoxib.

(v) HPβCD alone gave a 3.55 fold increase and in combination with PVP and Poloxamer 407 it gave respectively 57.6 and 23.6 fold increase in the dissolution rate of etoricoxib.

(vi) Combination of CDs with either Poloxamer 407 or PVP has markedly enhanced both the solubility and dissolution rate of etoricoxib, a BCS class II drug. Hence a combination of CDs with Poloxamer 407 and PVP is recommended to enhance the solubility and dissolution rate of etoricoxib.

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