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Effects of Cyclodextrins,Tween-80 and PVP on the Solubility and Dissolution Rate of Etoricoxib

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Abstract

Alone and combined effects of cyclodextrins (βCD and HPβCD), surfactant (Tween-80) and PVP on the solubility and dissolution rate of etoricoxib were evaluated in a series of 2^3 factorial design. The complexes of etoricoxib – CDs (βCD and HPβCD) were prepared with and without Tween-80 and PVP by kneading method as per 2^3 factorial designs. The solubility of etoricoxib in eight selected fluids containing CDs, Tween-80 and PVP was determined. The solubility of etoricoxib was markedly enhanced by βCD (2.24 fold), HPβCD (3.14 fold),Tween-80 (2.58 fold) and PVP (1.38 fold) individually. βCD with PVP has given highest enhancement (3.44 fold). HPβCD with Tween 80 and PVP gave 3.74 and 3.39 fold increase in respectively. Alone and combined effects were highly significant ($P<0.01$). ANOVA indicated that the alone CDs (βCD and HPβCD),Tween-80 and PVP and their combined effects in enhancing the dissolution rate(K_1) and DE_{30} were highly significant ($P<0.01$). βCD only gave a 1.18 fold increase in the dissolution rate. βCD with PVP and Tween-80 gave 3.0 and 7.4 fold increase in respectively . HPβCD only gave a 3.55 fold increase and in combination with PVP and Tween-80 it gave respectively 57.6 and 23.6 fold increase in the dissolution rate. Combination of CDs with either Tween-80 or PVP has markedly enhanced both the solubility and dissolution rate of etoricoxib.

Key words: ***Etoricoxib ; Cyclodextrins; Tween-80; PVP; 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 solubility[1]. It has low solubility 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 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 enhanced[2,3]. Cyclodextrins are being increasingly applied in pharmaceutical formulation in recent years due to their approval by various regulatory agencies[4,5].

Though cyclodextrin complexation and use of surfactants for enhancing the solubility and dissolution rate of poorly soluble drugs have been investigated individually, a number of reports are available on their combined use in enhancing the solubility and dissolution rate .However, in the present investigation the individual main effects and combined (or interaction) effects of cyclodextrins (βCD and HPβCD),surfactant (Tween-80) and PVP on the solubility and dissolution rate of etoricoxib were evaluated in a series of 2^3 factorial experiments designed to lower a large number of factors and levels for factors. In these 2^3 experiment, 3 factors with 2 levels was designed.

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, hence by this approach the total number of experiments for all the runs were restricted to 8^6.

EXPERIMETAL

Materials and Methods:

Etoricoxib was a gift sample from M/s Natco pharma Ltd., Hyderabad. β-Cyclodextrin and hydroxyl propyl β-Cyclodextrin were gift samples from M/s. Cerestar Inc.,USA. Methanol (Qualigens), Polyvinyl pyrrolidone (PVP-K30) and Tween-80 were from M/S Cadila Healthcare Limited and M/S ISP Limited respectively. All the solvents and reagents used in this study were procured from Merck, India.

Estimation of Etoricoxib:

An UV spectrophotometry method was developed based on the measurement of absorbance at 289nm in a phosphate buffer of pH 7.4 was used for the estimation of etoricoxib. The method was validated for linearity, accuracy, precision as per ICH Q2B[7] guideline and also validated for interference. The method obeyed Beer's law in the concentration range of 1-10µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variation were found to be 0.95% and 1.6% respectively. No

interference by the excipients used in the study was observed.

Solubility determination:

Excess drug (50mg) was added to 15ml of each fluid taken in a 25 ml stopped conical flask and the mixtures were shaken for 24 h at room temperature (25±1˚C) on Rotary flask Shaker. After 24 h of shaking, 2ml aliquots were withdrawn at 2 h interval and filtered immediately using a 0.45µm disk filter (Durapore, Millipore). 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). Refer table 2.

Preparation of Etoricoxib-CD complexes:

Solid inclusion complexes of etoricoxib-CD were prepared in 1:2 ratio with and without Tween-80(2%) or PVP(2%) by kneading method as enunciated in table 4. Etoricoxib, CDs (βCD or HPβCD), Tween-80 or PVP 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 USP type II paddle at 50 rpm. A temperature of 37±1˚C was maintained throughout the study. Etoricoxib or etoricoxib-CD complex equivalent to 60mg of etoricoxib was used in each test. Samples of dissolution media (5ml) were withdrawn through a filter (0.45µ) at different intervals of time, suitably diluted and assayed for etoricoxib at 289nm.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), Tween-80(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(0.5mM),two levels of Tween-80(0,2%) and two levels of PVP(0,2%) were selected in each case and corresponding eight treatments involved in the 2^3-factorial study were purified water (1),water containing 5nM CDs(βCD or HPβCD)(a);water containing 2% Tween-80 (b);water containing 5mM CDs(βCD or HPβCD) and 2% Tween-80 (ab);water containing 2% PVP (c);water containing 5mM CDs(βCD or HPβCD) and 2% PVP (ac);water containing 2% Tween-80 and 2% PVP (bc) and water containing 5mM CDs (βCD or HPβCD) and 2% of each of Tween-80 and PVP (abc).

The solubility of etoricoxib in the above mentioned eight formulations was determined (n=4) and the results are given table-1.The aqueous solubility of etoricoxib was markedly enhanced by CDs alone and in combination with Tween-80 and PVP.

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), Tween-80 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, Tween-80 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), Tween-80 (2.58 fold) and PVP (1.38 fold) individually.

Table 1 Solubility of etoricoxib in various fluids 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 5mM βCd(a)	0.303±0.005	2.04
Water containing 2% Tween-80(b)	0.381±0.001	2.57
Water containing 5mM βCD and 2% Tween-80 (ab)	0.288±0.006	1.94
Water containing 5% PVP (c)	0.205±0.005	1.38
Water containing 5mM βCD and 5% PVP (ac)	0.510±0.074	3.44
Water containing 2% Tween-80 and 5% PVP (bc)	0.240±0.016	1.62
Water containing 5 mM βCD,2% Tween-80 and 5% PVP(abc)	0.415±0.005	2.80
Water containing 5mM HPβCD(a)	0.465±0.013	3.14
Water containing 5mM HPβCD and 2% tween-80 (ab)	0.553±0.001	3.74
Water containing 5mM HPβCD and 5% PVP(ac)	0.503±0.006	3.39
Water containing 5mM HPβCD,2% Tween-80 and 5% PVP(abc)	0.353±0.006	2.38

Table 2 ANOVA of Solubility Data of Etoricoxib in Various Fliuds as per 23 -Factorial Study (βCD-Tween 80 -PVP)

Source of variation	*D.F*	*S.S*	*M.S.S*	*F-ratio*	*Significance*
Total	31	0.422	0.013		
Treatments	07	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

Table 3 Table 3: ANOVA of solubility Data of Etoricoxib in Various Fluids as per 23-Factorial Study (HPβCD-Tween 80-PVP)

Source of variation	*D.F*	*S.S*	*M.S.S*	*F-ratio*	*Significance*
Total	31	0.0.611	0.019		
Treatments	07	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 order of increasing solubility observed with various CDs and surfactants was HPβCD>Tween-80>βCD>PVP. βCD in combination with PVP has given highest enhancement (3.44 fold) in the solubility of etoricoxib. HPβCD in combination with Tween-80 and PVP gave respectively 3.74 and 3.39 fold increase in the solubility of etoricoxib.

To evaluate the individual and combined effects of CDs (βCD or HPβCD), Tween-80 and PVP on the dissolution rate of etoricoxib, solid inclusion complexes of etoricoxib-CDs(βCD and HPβCD) were prepared with and without Tween-80 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 tween 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 HPβCD) (1:2) inclusion binary complex (a);etoricoxib-Tween-80 (2%) binary mixture (b);etoricoxib –CD (βCD or HPβCD) (1:2)-Tween (2%)ternary complex (ab);etoricoxib-PVP (2%) binary mixture (c);etoricoib-CD (βCD or HPβCD) (1:2)-PVP (2%) ternary complex (ac);etoricoxib-Tween (2%)-PVP(2%) ternary complex (bc) and etoricoxib-CD (βCD or HPβCD) (1:2)-Tween (2%)-PVP complex (abc).

The CD complexes were prepared by kneading method. All the solid inclusion complexes of etoricoxib-CD Tween-80-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 formulated CD complexes was studied in phosphate buffer (pH 7.4) as dissolution medium (n=3) [8,9] as referred in table 3. The dissolution of etoricoxib followed first order kinetics with r^2 (correlation coefficient) above 0.91. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[10.] 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.

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, Tween-80 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 HPβCD), Tween-80 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 Tween-80 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 TWEEN-80 it gave respectively 57.6 and 23.6 fold increase in the dissolution rate of etoricoxib.

Thus the results of the study indicated that combination of CDs with either Tween-80 or PVP has markedly enhanced both the solubility and dissolution rate of etoricoxib, a BCS class II drug. Hence, a combination of CDs with Tween and PVP is recommended to enhance the solubility and dissolution rate of etoricoxib.

Table 4 Dissolution parameters of Etoricoxib –CD Complex System prepared as per 23 Factorial Study

Et-CD Complex	*Composition*	*PD_{10} (%)*	*$K_1 \times 10^2$ 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-Tw(2%)	59.09	2.15	1.39	35.23	**1.84**
Fab	Et-βCD(1:2)-Tw(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(1:2)	37.20	4.73	3	28.81	**1.5**
Fbc	Et-Tw(1:2)-PVP(2%)	25.90	0.99	0.6	17.94	**0.9**
Fabc	Et-βCD(1:2)-Tw(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)-Tw(2%)	84.66	3.64	23.6	48.82	**2.6**
Fac	Et-HPβCD-PVP	99.26	88.83	57.6	54.46	**2.91**
Fabc	Et-HPβCD-Tw-PVP	85.86	9.71	6.3	48.47	**2.5**

Et-Etoricoxib; CD-Cyclodextrins; Tw-Tween-80;PVP-Polyvinyl pyrrolidone

Table 5 ANOVA of Dissolution Data of Etoricoxib-CD complex system Prepared as per 23 –Factorial Study (βCD-Tween 80-PVP)

Source of variation	*D.F*	*S.S*	*M.S.S*	*F-ratio*	*Significance*
Total	23	272.96	11.867		
Treatments	07	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 system prepared as per 2^3-Factorial Study (HPβCD-Tween 80-PVP)

Source of variation	*D.F*	*S.S*	*M.S.S*	*F-ratio*	*Significance*
Total	23	20524.63	892.37		
Treatments	07	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
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

CONCLUSIONS:

1) The solubility of etoricoxib was markedly enhanced by βCD (2.24 fold), HPβCD (3.14 fold), Tween -80(2.58) and PVP (1.38) individually.
2) βCD in combination with PVP has given highest enhancement (3.34 fold) in the solubility of etoricoxib .HPβCD in combination with Tween-80 and PVP gave respectively 3.74 and 3.39 fold increase in the solubility of etoricoxib.
3) ANOVA indicated that the individual main effects o CDs (βCD and HPβCD),Tween-80 and PVP and their combined effects in enhancing the solubility and dissolution rate (K_1) and DE_{30} were highly significant ($P<0.01$).
4) βCD alone gave a 1.18 fold increase in the dissolution rate of etoricoxib.βCD in combination with PVP and Tween-80 gave respectively 3.0 and 7.4 fold increase in the dissolution rate of etoricoxib.
5) HPβCD alone gave a 3.33 fold increase and in combination with PVP and Tween-80 it gave respectively 57.6 and 23.6 fold increase in the dissolution rate of etoricoxib.
6) Combination of CDs with either Tween-80 or PVP has markedly enhanced both the solubility and dissolution rate of etoricoxib,a BCS class II drug. Hence, a combination of CDs with Tween-80 and PVP is recommended to enance the solubility and dissolution rate of Etoricoxib.

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