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Factorial Study to Evaluate the Individual and Combined Effects of β-Cyclodextrin and Sodium Lauryl Sulfate on the Solubility and Dissolution Rate of Etoricoxib

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The objective of the study is to evaluate the individual main effects and combined (or interaction) effects of β-cyclodextrin and sodium lauryl sulfate, a surfactant on the solubility and dissolution rate of etoricoxib in a series of 2^2 factorial experiments. The solubility of etoricoxib in purified water (1), water containing 5 mM of β-cyclodextrin (a), water containing 2 % sodium lauryl sulfate (b) and water containing 5 mM of β-cyclodextrin and 2 % sodium lauryl sulfate (ab) were determined as per 2^2 factorial design. The individual and combined effects of β-cyclodextrin and sodium lauryl sulfate in enhancing the solubility of etoricoxib were highly significant ($p < 0.01$). The solubility of etoricoxib was markedly enhanced by β-cyclodextrin (2.25 fold), sodium lauryl sulfate (32.16 fold) individually as well as combinedly by β-cyclodextrin and sodium lauryl sulfate (38.82 fold). Solid inclusion complexes of etoricoxib-β-cyclodextrin were prepared with and without sodium lauryl sulfate as per 2^2 factorial design by kneading method. The dissolution rate of etoricoxib from the β-cyclodextrin complexes prepared was studied in phosphate buffer of pH 7.4 (n = 4). The individual main effects of β-cyclodextrin and sodium lauryl sulfate in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) were highly significant ($p < 0.01$). Whereas the combined effect of β-cyclodextrin and sodium lauryl sulfate in enhancing the K_1 and DE_{30} was not significant ($p > 0.05$). A 2.90 and 3.15 fold increase in K_1 and 4.09 and 2.91 fold increase in DE_{30} of etoricoxib was observed, respectively with β-cyclodextrin and sodium lauryl sulfate.

Key Words: Etoricoxib, β-Cyclodextrin, Solubility, Dissolution rate, Sodium lauryl sulfate, Factorial study.

INTRODUCTION

Etoricoxib, a non-steroidal antiinflammatory agent, is a selective inhibitor of COX-2 and is commonly used for osteoarthritis, rheumatoid arthritis, gout and post operative dental pain. It belongs to class II under BCS and exhibits low and variable oral bioavailability due to its poor aqueous solubility. It is practically insoluble in water and aqueous fluids. As such its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution for increasing its oral bioavailibilty. Among the various approaches, complexation with β-cyclodextrin has gained a good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins are cyclic torus-shaped molecules with 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]. Surfactants also increase the solubility of lipophilic water insoluble drugs by micellar solubilisation. Though β-cyclodextrin complexation and the 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. The objective of present study is to evaluate the individual and combined (or interaction) of the effects of β-cyclodextrin and sodium lauryl sulfate, a surfractant on the solubility and dissolution rate of etoricoxib in a series of 2^2 factorial experiments.

EXPERIMENTAL

Etoricoxib was a gift sample from M/s Natco Pharma. Ltd., Hyderabad. β-Cyclodextrin was a gift sample from M/s. Cerestar Inc., (USA). Methanol (Qualigens) and sodium lauryl sulfate (BDH) were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Estimation of etoricoxib: An UV spectrophotometric method based on the measurement of absorbance at 272 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 Beers 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 0.80 and 1.2 %, respectively. No interference by the excipients used in the study was observed.

Solubility determination: Excess drug (50 mg) was added to 15 mL of each fluid taken in a 25 mL stoppered conical flask and the mixtures were shaken for 24 h at room temperature (28 ± 1 ºC) on a 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 272 nm. Shaking was continued until two consecutive estimations are the same. The solubility experiments were replicated four times each (n = 4).

Preparation of etoricoxib-β-cyclodextrin complexes: Solid inclusion complexes of etoricoxib-β-cyclodextrin were prepared in 1:2 ratio with and without sodium lauryl sulfate (2 %) by kneading method. Etoricoxib, β-cyclodextrin and sodium lauryl sulfate 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 ºC 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 β-cyclodextrin complexes was studied in 900 mL of phosphate buffer of pH 7.4 using Disso 2000 (Lab India) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature of 37 ± 1 ºC was maintained throughout the study. Etoricoxib or etoricoxib-β-cyclodextrin complex equivalent to 50 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, suitably diluted and assayed for etoricoxib at 272 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 β-cyclodextrin and sodium lauryl sulfate on the aqueous solubility of etoricoxib were evaluated in a series of 2^2-factorial experiments. For this purpose, two levels of βcyclodextrin (0.5 mM) and two levels of sodium lauryl sulfate (0.2 %) were selected and the corresponding four treatments involved in the 2^2-factorial study were purified water (1), water containing 5 mM β-cyclodextrin (a), water containing 2 % sodium lauryl sulfate (b) and water containing 5 mM of β-cyclodextrin and 2 % sodium lauryl sulfate (ab). The solubility of etoricoxib in the above mentioned fluids was determined (n = 4) and the results are given in Table-1. The aqueous solubility of etoricoxib was markedly enhanced by β-cyclodextrin, sodium lauryl sulfate alone and in combination.

The solubility data were subjected analysis of variants (ANOVA) to find out the significance of the main and combined effects of β-cyclodextrin and sodium lauryl sulfate on the solubility of etoricoxib. The results of ANOVA are shown in Table-2. The individual and combined effects of β-cyclodextrin and sodium lauryl sulfate in enhancing the solubility of etoricoxib were highly significant ($p < 0.01$). The solubility of etoricoxib was markedly enhanced by βcyclodextrin (2.25 fold), sodium lauryl sulfate (32.16 fold) individually as well as combinedly by βcyclodextrin-sodium lauryl sulfate (38.82 fold).

TABLE-1
SOLUBILITY OF ETORICOXIB IN VARIOUS FLUIDS CONTAINING β-CYCLODEXTRIN (βCD) AND SODIUM LAURYL SULFATE (SLS)

Fluid	Solubility (mg/100 mL) (n = 4) ($\bar{x} \pm sd$)	Increase in solubility (No. of folds)
Purified water	0.17 ± 0.013	–
Water containing βCD (5 Mm)	0.38 ± 0.085	2.25
Water containing SLS (2 %)	5.40 ± 0.267	32.16
Water containing βCD (5 mM) and SLS (2 %)	6.52 ± 0.36	38.82

TABLE-2
ANOVA OF SOLUBILITY DATA

Source of variation	d.f.	s.s.	m.s.s.	F-Ratio	Significance
Total	15	13328.34	888.51	–	–
Treatment	3	13267.35	4422.45	870.56	$p < 0.01$
a (βCD)	1	174.30	174.30	34.31	$p < 0.01$
b (SLS)	1	13009.11	13009.11	2560.8	$p < 0.01$
ab (Combination)	1	33.95	83.95	16.52	$p < 0.01$
Error	12	60.99	5.08	–	–

βCD = β-Cyclodextrin; SLS = Sodium lauryl sulfate

To evaluate the individual and combined effects of β-cyclodextrin and sodium lauryl sulfate on the dissolution rate of etoricoxib, solid inclusion complexes of etoricoxib-β-cyclodextrin were prepared with and without sodium lauryl sulfate as per a 2^2-factorial design. For this purpose, two levels of β-cyclodextrin (0 and 1:2 ratio of drug: β-cyclodextrin) and two levels of sodium lauryl sulfate (0.2 %) were selected and the corresponding 4 treatments involved in the 2^2-factorial study were etoricoxib pure drug (1), etoricoxib-β-cyclodextrin (1:2) inclusion complex (a), etoricoxib-sodium lauryl sulfate (2 %) blend (b) and etoricoxib-β-cyclodextrin (1:2)-sodium lauryl sulfate (2 %) ternary system (ab). The β-cyclodextrin complexes were prepared by kneading method. All the solid inclusion complexes of etoricoxib-β-cyclodextrin-sodium lauryl sulfate prepared were found to be fine and free flowing powders. Low coefficient of variation (c.v.) values (< 1 %) in the percentage drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared. The dissolution rate of etoricoxib alone and from β-cyclodextrin 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. The dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[5]. The dissolution parameters are given in Table-3. The dissolution of etoricoxib was rapid and higher in case of etoricoxib-β-cyclodextrin complexes with and without sodium lauryl sulfate when compared to etoricoxib as such.

TABLE-3
DISSOLUTION PARAMETERS OF ETORICOXIB-β-CYCLODEXTRIN-SODIUM LAURYL SULFATE SYSTEMS PREPARED

β-Cyclodextrin-Surfactant system	Dissolution rate $K_1 \times 0^3$ (min^{-1})		Dissolution efficiency DE_{30} (%)	
	($\bar{x} \pm sd$)	Increase in K_1 (No. of folds)	($\bar{x} \pm sd$)	Increase in DE_{30} (No. of folds)
Etoricoxib pure drug	7.76 ± 0.48	–	9.70 ± 1.12	–
Etoricoxib-βCD (1:2) binary system	22.47 ± 3.90	2.9	39.75 ± 5.84	4.09
Etoricoxib-SLS (2 %) binary system	24.50 ± 10.88	3.15	28.27 ± 6.10	2.91

βCD = β-Cyclodextrin; SLS = Sodium lauryl sulfate

Dissolution parameters (K_1 and DE_{30}) were subjected to ANOVA to find out the significance of the main and combined effects of β-cyclodextrin and sodium lauryl sulfate on the dissolution rate and dissolution efficiency of etoricoxib. The results of ANOVA are shown in Tables 4 and 5. ANOVA indicated that the individual main effects of β-cyclodextrin and sodium lauryl sulfate in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) were highly significant ($p < 0.01$). The combined effects of β-cyclodextrin and sodium lauryl sulfate in enhancing K_1 and DE_{30} were not significant ($p > 0.05$). A 2.90 and 3.15 fold increase in K_1 and 4.09 and 2.91 fold increase in DE_{30} of etoricoxib was observed, respectively with β-cyclodextrin and sodium lauryl sulfate.

TABLE-4
ANOVA OF DISSOLUTION RATE DATA

Source of variation	d.f.	s.s.	m.s.s.	F-Ratio	Significance
Total	15	3991.52	972.26	–	–
Treatment	3	2916.80	2913.27	10.85	$p < 0.01$
a (βCD)	1	1284.5	1284.5	14.34	$p < 0.01$
b (SLS)	1	1593.2	1593.2	17.79	$p < 0.01$
ab (Combination)	1	41.08	41.08	0.45	$p > 0.05$
Error	12	1074.71	68	–	–

β-CD = β-Cyclodextrin; SLS = Sodium lauryl sulfate

TABLE-5
ANOVA OF DE_{30} DATA

Source of variation	d.f.	s.s.	m.s.s.	F-ratio	Significance
Total	15	3979.63	265.29	–	–
Treatment	3	3672.27	1224.09	47.79	$p < 0.01$
a (βCD)	1	2750.47	2750.47	107.33	$p < 0.01$
b (SLS)	1	869.95	869.95	33.96	$p < 0.01$
ab (Combination)	1	51.84	51.84	2.02	$p > 0.05$
Error	12	128.75	25.61	–	–

β-CD = β-Cyclodextrin; SLS = Sodium lauryl sulfate

Conclusion

The individual and combined effects of β-cyclodextrin and sodium lauryl sulfate in enhancing the solubility of etoricoxib were highly significant ($p < 0.01$).The solubility of etoricoxib was markedly enhanced by β-cyclodextrin (2.25 fold), sodium lauryl sulfate (32.16 fold) individually as well as combinedly by β-cyclodextrin-sodium lauryl sulfate (38.82 fold). The individual main effects of βcyclodextrin and sodium lauryl sulfate in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) were highly significant ($p < 0.01$). The combined effect of β-cyclodextrin-sodium lauryl sulfate in enhancing the K_1 and DE_{30} was not significant ($p > 0.05$). A 2.90 and 3.15 fold increase in K_1 and 4.09 and 2.91 fold increase in DE_{30} of etoricoxib was observed, respectively with β-cyclodextrin and sodium lauryl sulfate. Thus, a combination of β-cyclodextrin and sodium lauryl sulfate is recommended for enhancing the solubility of etoricoxib. However, for enhancing the dissolution rate they maybe used alone as their combined effect is not significant.

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