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Factorial Study on the Effects of β-Cyclodextrin and Sodium Lauryl Sulphate on the Solubility and Dissolution Rate of Celecoxib Tablets

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The objective of the study is to evaluate the individual and combined (or interaction) effects of β-cyclodextrin (βCD) and sodium lauryl sulphate (SLS), a surfactant on the solubility and dissolution rate of celecoxib tablets in a 2^2 factorial study. the solubility of celecoxib in the four selected fluids containing βCD and SLS, as per 2^2-factorial study, was determined. The solubility of celecoxib was markedly enhanced by βCD (3.27 fold), SLS (15.84 fold) individually as well as in combined form (28.40 fold). Both the individual and combined effects of βCD and SLS were highly significant ($p < 0.01$). Celecoxib tablets were formulated employing selected combinations of βCD and SLS as per a 2^2 factorial design and were evaluated. The individual main effects of βCD, SLS and their combined effects in enhancing the dissolution rate of celecoxib tablets wer significant ($p < 0.05$). β-Cyclodextrin and SLS alone gave higher enhancement in dissolution rate of celecoxib tablets (2.39-2.46 fold). There was no additional increase in the dissolution rate of celecoxib when a combination of βCD and SLS was used in the tablets.

Key Words: Celecoxib, β-Cyclodextrin, Solubility, Dissolution rate, SLS, Factorial study.

INTRODUCTION

Celecoxib, a widely prescribed antiinflammatory and analgestic drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It is practically in soluble in water and aqueous fluids. As such its oral adsorption is dissolution rate limited and its requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. Among the various aproaches 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]. Surfactants also increase the solubility lipophilic water-insoluble drugs by micellar solubilization. Through 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 β-cyclodextrin (βCD) and sodium lauryl sulphate (SLS), a surfactant on the solubility and dissolution rate of celecoxib tablets were evaluated in a 2^2-factorial study.

EXPERIMENTAL

Celecoxib (gift sample from M/s Suyaash Labs. Chennai), β-cyclodextrin (gift sample from M/s Cerestar Inc., USA) and methanol (Qualigens) were used.

Estimation of celecoxib: An UV spectrophotometric method based on the measurement of absorbance at 254 nm in a phosphate buffer of pH 7.4 was used for the estimation of celecoxib. 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 durg solution was repeatedly assayed (n = 6), the relative error and coefficient of variation were found to be 0.40 and 0.8, 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 celecoxib by measuring absorbance at 254 nm. Shaking was continued until two consecutive estimations are the same. The solubility experiments were replicated four times each (n = 4).

Preparation of celecoxib tablets: Solid inclusion complexes of celecoxib-βCD were prepared in 1:2 ratio with and without SLS (5 %) by kneading method and these complexes were used in the preparation of celecoxib tablets. Celecoxib (50 mg) tablets were formulated employing selected combinations of βCD and SLS as per a 2^2 factorial design. For this purpose 2 levels of βCD (0 and 1:2 ratio of drug: CD) and two levels of SLS (0 and 5 %) were selected and the corresponding four treatments involved in the 2^2-factorial study were tablets of celecoxib pure drug (1), tablets of celecoxib-βCD (1:2) inclusion complex (a), tablets of celecoxib-SLS (5 %) blend (b) and tablets of celecoxib-βCD (1:2)-SLS (5 %) ternary complex (ab). The tablets were prepared by wet granulation method as per the formulae given in Table-1.

TABLE-1
FORMULAE OF CELECOXIB TABLETS PREPARED EMPLOYING β-CD AND SLS AS PER 2^2 FACTORIAL DESIGN

Ingredient (mg/tab)	Formulation			
	F_1	F_a	F_b	F_{ab}
Celecoxib	50	50	50	50
β-CD	–	100	–	100
SLS	–	–	2.5	2.5
Potato starch	31.5	31.5	31.5	31.5
Acacia	4.2	4.2	4.2	4.2
Talc	4.2	4.2	4.2	4.2
Magnesium sterate	4.2	4.2	4.2	4.2
Lactose	115.9	15.9	113.4	13.4
Total weight (mg)	210	210	210	210

Dissolution rate study: The dissolution rate of celecoxib tablets 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 of 37 ± 1 ºC was maintained throughout the study. One celecoxib tablet containing 50 mg of celecoxib 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 celecoxib at 254 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid. The dissolution experiments were replicated 4 times each (n = 4).

RESULTS AND DISCUSSION

The individual main effects and combined (interaction) effects of βCD and SLS on the aqueous solubility of celecoxib were evaluated in a 2^2-factorial experiment. For this purpose, two levels of βCD (0, 5 mM) and two levels of SLS (0, 2 %) were selected and the corresponding four treatments involved in the 2^2-factorial study were purified water (1), water containing 5 mM βCD (a); water containing 2 % SLS (b) and water containing 5 mM βCD and 2 % SLS (ab). The solubility of celecoxib in the above mentioned four fluids was determined (n = 4) and the results are given in Table-2.

TABLE-2
SOLUBILITY OF CELECOXIB IN VARIOUS FUILDS AS PER 2^2 FACTORIAL STUDY (n = 4)

Fluids	Solubility (mg/100 mL) ($\bar{x} \pm sd$)	Increase in solubility (No. of folds)
Purified water	2.30 ± 0.171	–
Water containing β-CD (5 mM)	7.54 ± 0.340	3.27
Water containing SLS (2 %)	36.45 ± 1.316	15.84
Water containing β-CD (5 mM) and SLS (2 %)	65.32 ± 2.14	28.40

The solubility of celecoxib was markedly enhanced by βCD and SLS. A 3.27 and 15.84 fold increase in solubility was observed, respectively with βCD (5 mM) and SLS (2 %). A combination of βCD (5 mM) and SLS (2 %) has given in 28.40 fold increase in the solubility of celecoxib.

The solubility data was were subjected to analysis of Variance (ANOVA) to find out the significance of main and combined effects of βCD and SLS on the solubility of celecoxib. The results of ANOVa are shown in Table-3.

TABLE-3
ANOVA OF SOLUBILITY DATA WITH β-CD AND SLS

Source of variation	df	SS	MSS	F-Ratio	Significance
Total	15	10198.65	679.91	–	–
Treatments	3	10172.75	3390.91	1577.16	$p < 0.01$
a(β-CD)	1	1164.17	1164.17	541.47	$p < 0.01$
b(SLS)	1	8450.2	8450.2	3930.32	$p < 0.01$
ab(combination)	1	558.37	558.37	259.7	$p < 0.01$
Error	12	25.895	2.15	–	–

ANOVa indicated that the individual main effects of βCD and SLS as well as the combined effects were highly significant ($p < 0.01$). A combination of βCD and SLS has resulted in a higher enhancement of solubility of celecoxib than is possible with them individually. This may be due to better inclusion of drug molecules in CD in the presence of SLS.

The evaluate the individual and combined effects of βCD and SLS on the dissolution rate, celecoxib (50 mg) tablets were formulated employing selected combinations of βCD and SLS as per a 2^2 factorial design.

The dissolution rate of celecoxib from the tablets prepared was studied in phosphate buffer of pH 7.4. The dissolution of celecoxib from the tablets followed first order kinetics with correlation co-efficient (r) values above 0.91. The dissolution rates (K_1) are given in Table-4. The dissolution rate of celecoxib from tablets formulated employing βCD, SLS and βCD-SLS systems was higher than that of celecoxib plain tablets.

TABLE-4
DISSOLUTION RATE OF TABLETS FORMULATED EMPLOYING CELECOXIB-β-CD-SLS SYSTEMS

Tablet formuation	Dissolution rate, $K_1 \times 10^3$ (min^{-1}) ($\bar{x} \pm sd$)
F_1 (Celecoxib)	1.739 ± 0.1
F_a (Celecoxib-βCD binary system)	4.272 ± 0.2
F_b (Celecoxib-SLS binary system)	4.151 ± 0.2
F_{ab} (Celecoxib-β-CD-SLS ternary system)	2.027 ± 0.1

The dissolution rate (K_1) values were subjected to ANOVA to find out the significance of the main and combined effects of βCD and SLS on the dissolution rate of celecoxib tablets. The results of ANOVA are shown in Table-5. ANOVA indicated that the individual main effects of βCD, SLS and their combined effects in enhancing the dissolution rate of celecoxib tablets were significant ($p < 0.05$). β-Cyclodextrin and SLS alone gave higher enhancement in the dissolution rate of celecoxib tablets (2.39-2.46 fold). There was no additional increase in the dissolution rate of celecoxib when a combination of βCD and SLS was used in the tablets.

TABLE-5
ANOVA OF $K_1 \times 10^3$ (min^{-1}) VALUES OF TABLETS FORMULATED EMPLOYING CELECOXIB-βCD-SLS SYSTEM

Source of variation	df	SS	MSS	F-Ratio	Significance
Total	15	21.94281	1.462854	–	–
Treatments	3	21.8883	7.296098	1605.994	$p < 0.01$
a(β-CD)	1	0.1681	0.168100	37.00164	$p < 0.01$
b(SLS)	1	0.027889	0.027889	6.138839	$p < 0.05$
ab(combination)	1	21.69231	21.69231	4774.842	$p < 0.01$
Error	12	0.054517	0.004543	–	–

Conclusion

The individual and combined effects of β-cyclodextrin (βCD) and sodium lauryl sulphate (SLS) in enhancing the solubility of celecoxib were highly significant ($p < 0.01$). A 3.27 and 15.84 fold increase in solubility was observed, respectively with βCD (5 mM) and SLS (2 %). A combination of βCD (5 mM) and SLS (2 %) has given a 28.40 fold increase in the solubility of celecoxib. The individual main effects of βCD, SLS and their combined effects in enhancing the dissolution rate of celecoxib tablets were significant ($p < 0.05$). β-Cyclodextrin and SLS alone gave higher enhancement in dissolution rate of celecoxib tablets (2.39-2.46 fold). There was no additional increase in the dissolution rate of celecoxib when a combination of βCD and SLS was used in the tablets.

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