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Research Article

A FACTORIAL STUDY ON THE EFFECTS OF β CYCLODEXTRIN AND POLOXAMER 407 ON THE SOLUBILITY AND DISSOLUTION RATE OF PIROXICAM

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ABSTRACT

The objective of the study is to evaluate the individual and combined effects of β cyclodextrin (βCD), surfactant (Poloxamer 407) on the solubility and dissolution rate of piroxicam, a BCS class II drug in a series of 2^2 factorial experiments. The solubility of piroxicam in four selected fluids containing βCD and Poloxamer 407 as per a 2^2 factorial study was determined. The individual and combined effects of βCD and Poloxamer 407 in enhancing the solubility of piroxicam were highly significant ($P < 0.01$). βCD and Poloxamer 407 alone gave an increase of 1.08 and 2.03 fold respectively in the solubility of piroxicam and combinedly they gave 1.97 fold increase in the solubility of piroxicam. Solid inclusion complexes of piroxicam- βCD were prepared with and without Poloxamer 407 by kneading method as per a 2^2-factorial design. The individual main effects of βCD and Poloxamer 407 and their combined effect in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of piroxicam were highly significant ($P < 0.01$). βCD and Poloxamer 407 alone gave respectively 5.51 and 3.34 fold increase in the dissolution rate of piroxicam and combinedly they gave a markedly higher enhancement (20.12 fold) in the dissolution rate of piroxicam. βCD and Poloxamer 407 alone gave respectively 3.26 and 3.08 fold increase in the dissolution efficiency (DE_{30}) of piroxicam and combinedly they gave a markedly higher enhancement (5.55 fold) in the dissolution efficiency (DE_{30}) of piroxicam. Combination of βCD with Poloxamer 407 gave much higher enhancement in the dissolution rate and efficiency (DE_{30}) of piroxicam than is possible with them individually. Hence a combination of βCD and Poloxamer 407 is recommended to enhance the dissolution rate of piroxicam.

Key words: Piroxicam, β Cyclodextrin, Poloxamer 407, Dissolution rate, Factorial Study.

INTRODUCTION

About 95% of the newly developed organic drugs belong to class II under BCS and exhibit low and variable oral bioavailability due to their poor aqueous solubility. They are practically in soluble in water and aqueous fluids. As such their oral absorption is dissolution rate limited and they require enhancement in solubility and dissolution rate

for increasing their 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 such as Poloxamer 407 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 of poorly soluble drugs. The objective of the present investigation is to evaluate the individual main effects and combined (or interaction) effects of β-cyclodextrin (βCD) and surfactant (Poloxamer 407) on the solubility and dissolution rate of piroxicam from CD complexes in a 2^2 factorial experiment. Piroxicam, 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 and needs enhancement in solubility and dissolution rate for increasing its oral bioavailability.

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

Piroxicam 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 Poloxamer 407 were procured from commercial sources.

Estimation of Piroxicam

An UV spectrophotometric method based on the measurement of absorbance at 333 nm in 0.1 N Hydrochloric acid of pH 1.2 was used for the estimation of piroxicam. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 0-10 µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.75% and 1.25% 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°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 piroxicam by measuring absorbance at 333 nm. Shaking was continued until two consecutive estimations are the same. The solubility experiments were replicated four times each (n=4).

Preparation of Piroxicam-CD complexes

Solid inclusion complexes of piroxicam- βCD were prepared in 1:2 ratio with and without Poloxamer 407 (2%) by kneading method. Piroxicam, βCD 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 piroxicam as such and from βCD complexes prepared was studied in 900 ml of 0.1 N hydrochloric acid 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. Piroxicam or piroxicam-CD complex equivalent to 20 mg of piroxicam 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 piroxicam at 333 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid. The dissolution experiments were replicated three times each (n=3).

RESULTS AND DISCUSSION

The individual main effects and combined (interaction) effects of βCD (Factor A) and Poloxamer 407 (Factor B) on the aqueous solubility of piroxicam were evaluated in a 2^2-factorial experiment. For this purpose, two levels of βCD (0, 5mM) and two levels of Poloxamer 407 (0, 2%) were selected in each case and the corresponding four treatments involved in the 2^2-factorial study are purified water (1), water containing 5 mM βCD (a); water containing 2% Poloxamer 407 (b); water containing 5 mM βCD and 2% Poloxamer 407 (ab).

The solubility of piroxicam in the above mentioned four fluids was determined (n=4) and the results are given in Table-1. The aqueous solubility of piroxicam was markedly enhanced by βCD and Poloxamer 407 alone and in combination. The solubility data were subjected to Analysis of variance (ANOVA) to find out the significance of main individual and combined effects of βCD and Poloxamer 407 on the solubility of piroxicam. The results of ANOVA are shown in Table 2. The individual and combined effects of βCD and Poloxamer 407 in enhancing the solubility of piroxicam were highly significant ($P < 0.01$). βCD and Poloxamer 407 alone gave an increase of 1.08 and 2.03 fold respectively in the solubility of piroxicam and combinedly they gave 1.97 fold increase in the solubility of piroxicam.

To evaluate the individual and combined effects of βCD and Poloxamer 407 on the dissolution rate of piroxicam, solid inclusion complexes of piroxicam - βCD were prepared with and without Poloxamer 407 as per a 2^2-factorial design. For this purpose two levels of βCD (0 and 1 : 2 ratio of drug : CD) and two levels of Poloxamer 407 (0 and 2%) were selected and the corresponding four treatments involved in the 2^2-factorial study were piroxicam pure drug (1); piroxicam- βCD (1:2) inclusion binary complex (a); piroxicam - Poloxamer 407 (2%) binary mixture (b); piroxicam- βCD (1:2) – Poloxamer 407 (2%) ternary complex (ab). The CD complexes were prepared by kneading method. All the solid inclusion complexes of piroxicam- βCD - Poloxamer 407 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 piroxicam alone and from βCD complexes prepared was studied in 0.1N hydrochloric acid. The dissolution of piroxicam followed first order kinetics with r (correlation coefficient) above 0.90. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[8]. The dissolution parameters are given in Table-3. The dissolution of piroxicam was rapid and higher in the case of all piroxicam- βCD complexes prepared when compared to piroxicam as such.

The dissolution rate (K_1) values were subjected to ANOVA to find out the significance of the main and combined effects of βCD and Poloxamer 407 on the dissolution rate of piroxicam. The results of ANOVA are shown in Tables 4-5. ANOVA indicated that all the individual main effects of βCD and Poloxamer 407 and their combined effect in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of piroxicam were highly significant ($P < 0.01$).

βCD and Poloxamer 407 alone gave respectively 5.51 and 3.34 fold increase in the dissolution rate of piroxicam and combinedly they gave a markedly higher enhancement (20.12 fold) in the dissolution rate of piroxicam. Similarly βCD and Poloxamer 407 alone gave respectively 3.26 and 3.08 fold increase in the dissolution efficiency (DE_{30}) of piroxicam and combinedly they gave a markedly higher enhancement (5.55 fold) in the dissolution efficiency (DE_{30}) of piroxicam.

Thus the results of the study indicated that combination of βCD with Poloxamer 407 gave much higher enhancement in the dissolution rate and efficiency (DE_{30}) of piroxicam than is possible with them individually. Hence a combination of βCD and Poloxamer 407 is recommended to enhance the dissolution rate of piroxicam, a BCS class II drug.

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

Fluids (Code as per 2^2 – Factorial Experiment)	Solubility (mg/ml) (n=4) (x± sd)	Increase in Solubility (Number of Folds)
Distilled water (1)	0.179±0.004	-
Water containing 5 mM βCD (a)	0.193±0.008	1.08
Water containing 2% Poloxamer (b)	0.364±0.021	2.03
Water containing 5mM βCD and 2% Poloxamer (ab)	0.352±0.037	1.97

Table 2: ANOVA of Solubility Data of Piroxicam in various fluids as per 2^2 – Factorial Study (βCD – Poloxamer 407)

Source of Variation	D.F	S.S	M.S.S	F-Ratio	Significance
Total	15	0.124	0.008	-	-
Treatment	3	0.119	0.040	83.918	P < 0.01
a	1	0.004	0.004	7.869	P < 0.05
b	1	0.118	0.118	250.369	P < 0.01
ab	1	0.008	0.008	16.867	P < 0.01
Error	12	0.006	0.0005	-	-

$F_{0.01\,(1,\,12)} = 9.33$; $F_{0.05\,(1,\,12)} = 4.75$; $F_{0.01\,(3,\,12)} = 5.95$; $F_{0.05\,(3,\,12)} = 3.49$

Table 3: Dissolution Rate and DE_{30} of Piroxicam- βCD – Poloxamer 407 Complex Systems prepared as per 2^2 – Factorial Study

Treatment*	Average K_1 (n=3) (x± sd)	Increase in K_1 (Number of Folds)	Average DE_{30} (n=3) (x± sd)	Increase in DE_{30} (Number of Folds)
1	0.011±0.01	-	3.15±0.04	-
a	0.059±0.17	5.51	10.29±0.01	3.26
b	0.036±0.004	3.34	9.70±0.09	3.08
ab	0.22±0.48	20.12	17.52±0.04	5.55

*1: piroxicam pure drug; a: piroxicam - βCD (1:2) inclusion binary complex;
b: piroxicam - Poloxamer 407 (2%) binary mixture; ab: piroxicam - βCD (1:2) – Poloxamer 407 (2%) ternary complex

Table 4: ANOVA of Dissolution Rate (K_1) of Piroxicam- βCD – Poloxamer 407 Complex Systems prepared as per 2^2 – Factorial Study

Source of Variation	D.F	S.S	M.S.S	F-Ratio	Significance
Total	11	0.079	0.007	-	-
Treatment	3	0.078	0.026	576.297	P < 0.01

a b ab	1 1 1	0.118 0.025 0.068	0.118 0.025 0.068	2602.841 553.472 1503.614	P < 0.01 P < 0.01 P < 0.01
Error	8	0.00036	0.00005	-	-

$F_{0.01\,(1,8)} = 11.26$; $F_{0.05\,(1,8)} = 5.32$; $F_{0.01\,(3,8)} = 7.59$; $F_{0.05\,(3,8)} = 4.07$

Table 5: ANOVA of DE_{30} Data of Piroxicam- βCD – Poloxamer 407 Complex Systems prepared as per 2^2 – Factorial Study

Source of Variation	D.F	S.S	M.S.S	F-Ratio	Significance
Total Treatment	11 3	315.073 310.244	28.643 103.415	- 171.328	- P < 0.01
a b ab	1 1 1	3.566 142.246 203.201	3.566 142.246 203.201	5.908 235.661 336.646	P < 0.05 P < 0.01 P < 0.01
Error	8	4.82884	2.69	-	-

$F_{0.01\,(1,8)} = 11.26$; $F_{0.05\,(1,8)} = 5.32$; $F_{0.01\,(3,8)} = 7.59$; $F_{0.05\,(3,8)} = 4.07$

CONCLUSION

The individual and combined effects of βCD and Poloxamer 407 in enhancing the solubility of piroxicam were highly significant (P < 0.01). βCD and Poloxamer 407 alone gave an increase of 1.08 and 2.03 fold respectively in the solubility of piroxicam and combinedly they gave 1.97 fold increase in the solubility of piroxicam.

The individual main effects of βCD and Poloxamer 407 and their combined effect in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of piroxicam were highly significant (P < 0.01). βCD and Poloxamer 407 alone gave respectively 5.51 and 3.34 fold increase in the dissolution rate of piroxicam and combinedly they gave a markedly higher enhancement (20.12 fold) in the dissolution rate of piroxicam. Combination of βCD with Poloxamer 407 gave much higher enhancement in the dissolution rate and efficiency (DE_{30}) of piroxicam than is possible with them individually. Hence a combination of βCD and Poloxamer 407 is recommended to enhance the dissolution rate of piroxicam.

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