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A Factorial Study to Evaluate the Individual and Combined Effects of β-Cyclodextrin and Tween 80 on the Solubility and Dissolution Rate of Aceclofenac

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The individual and combined effects of β-cyclodextrin and Tween 80 (surfactant) on the solubility and dissolution rate of aceclofenac were evaluated in a 2^2-factorial study. The solubility of aceclofenac in the four selected fluids containing β-cyclodextrin and Tween 80, as per 2^2-factorial study, was determined. The solubility of aceclofenac was markedly enhanced by β-cyclodextrin (1.57 fold), Tween 80 (7.91 fold) individually as well as combinedly (10.5 fold). Both the individual and combined effects were significant ($p < 0.05$). Aceclofenac-β-cyclodextrin complexes with and without Tween 80 were prepared by kneading method and were evaluated for dissolution rate and dissolution efficiency (DE_{15}) as per a 2^2-factorial design. β-Cyclodextrin alone gave marked enhancement in the dissolution rate and DE_{15} of aceclofenac. The main effect of β-cyclodextrin and the combined effect of β-cyclodextrin and Tween 80 in enhancing the dissolution rate were significant ($p < 0.05$). Though Tween 80 has increased the solubility of aceclofenac, it has not significantly enhanced the dissolution rate of aceclofenac.

Key Words: Aceclofenac, β-Cyclodextrin complexation, Solubility, Dissolution rate, Tween 80, Factorial study.

INTRODUCTION

Aceclofenac, a widely prescribed antiinflammatory and analgesic drug belongs to class II under BCS and exhibit 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 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 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 of lipophilic water-insoluble drugs by micellar solubilization. Though β-cyclodextrin complexation and use of surfactants for enhancing the solubility and dissolution rate of poorly soluble drugs have been investigated individually, but 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 and Tween 80, a surfactant on the solubility and dissolution rate of aceclofenac were evaluated in a 2^2-factorial study.

EXPERIMENTAL

Aceclofenac (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 aceclofenae: An UV spectrophotometric method based on the measurement of absorbance at 275 nm in a phosphate buffer of pH 6.8 was used for the estimation of aceclofenac. 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 0.80 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 stoppard 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 aceclofenac by measuring absorbance at 275 nm. Shaking was continued until two consecutive estimations are the same. The solubility experiments were conducted in triplicate.

Preparation of accelofenac-β-cyclodextrin complexes: Solid inclusion complexes of aceclofenac-β-cyclodextrin were prepared in 1:1 ratio with and without Tween 80 (2 %) by kneading method. Aceclofenac, β-cyclodextrin and Tween 80 were triturated in a mortar with a small volume of solvent 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 aceclofenac as such and from β-cyclodextrin complexes was studied in 900 mL of phosphate buffer of pH 6.8 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. Aceclofenac or aceclofenac-β-cyclodextrin complex equivalent to 50 mg of aceclofenac 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 aceclofenac at 275 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid. The dissolution experiments were conducted in triplicate.

RESULTS AND DISCUSSION

The individual main effects and combined (interaction) effects of β-cyclodextrin and Tween 80 on the aqueous solubility of aceclofenac were evaluated in a 2^2-factorial experiment. For this purpose, two levels of β-cyclodextrin (0.5 mM) and two levels of Tween 80 (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 % Tween 80 (b) and water containing 5 mM β-cyclodextrin and 2 % Tween 80 (ab). The solubility of aceclofenac in the above mentioned four fluids was determined (n = 4) and the results are given in Table-1.

TABLE -1
SOLUBILITY OF ACECLOFENAC IN VARIOUS FLUIDS (n = 4)

Fluid	Solubility (mg/100 mL) $\bar{x}$ ± sd	Increase in solubility (No. of folds)
Purified water	5.42 ± 0.184	–
Water containing β-cyclodextrin (5 mM)	8.53 ± 0.311	1.57
Water containing Tween 80 (2 %)	42.90 ± 5.540	7.91
Water containing β-cyclodextrin (5 mM) and Tween 80 (2 %)	57.18 ± 1.310	10.54

The solubility of aceclofenac was markedly enhanced by β-cyclodextrin and Tween 80. A 1.57 and 7.91 fold increase in solubility was observed, respectively with β-cyclodextrin (5 mM) and Tween 80 (2 %). A combination of β-cyclodextrin (5 mM) and Tween 80 (2 %) has given a 10.54 fold increase in the solubility of aceclofenac.

The solubility data were subjected to analysis of variance (ANOVA) to find out the significance of main and combined effects of β-cyclodextrin and Tween 80 on the solubility of aceclofenac. The results of ANOVA are shown in Table-2.

TABLE-2
ANOVA TABLE OF SOLUBILITY DATA

Source of variation	d.f.	s.s.	m.s.s.	F-ratio	$F_{0.05}$
Total	15	7945.42	529.69	–	
Treatment	3	7846.91	2615.63	318.59	3.49
A (β-cyclodextrin)	1	302.32	302.32	36.82	($v_1 = 3$, $v_2 = 12$)
B (Tween 80)	1	7417.94	7419.94	903.52	
AB (Combination)	1	124.93	124.93	15.21	4.75
Error	12	98.51	8.21	–	($v_1 = 1$, $v_2 = 12$)

ANOVA indicated that the individual main effects of β-cyclodextrin and Tween 80 as well as the combined effects are highly significant ($p < 0.01$). A combination of β-cyclodextrin and Tween 80 has resulted in a higher enhancement of solubility of aceclofenac than is possible with them individually. This may be due to better inclusion of drug molecules in cyclodextrin in the presence of Tween 80.

To evaluate the individual and combined effects of β-cyclodextrin and Tween 80 on the dissolution rate of aceclofenac, solid inclusion complexes of aceclofenac-β-cyclodextrin were prepared with and without Tween 80 as per a 2^2-factorial design. For this purpose 2 levels of β-cyclodextrin (0 and 1:1 ratio of drug: cyclodextrin) and two levels of Tween 80 (0 and 2 %) were selected and the corresponding four treatments involved in the 22-factorial study were aceclofenac pure drug (1), aceclofenac-β-cyclodextrin (1:1) inclusion complex (a), aceclofenac-Tween 80 (2 %) blend (b) and aceclofenac β-cyclodextrin (1:1)-Tween 80 (2 %) Ternary complex (ab). The cyclodextrin complexes involved were prepared by kneading method.

All the solid inclusion complexes of aceclofenac-β-cyclodextrin prepared were found to be fine and free flowing powders. Low co-efficient 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 aceclofenac alone and from β-cyclodextrin complexes was studied in phosphate buffer of pH 6.8. The dissolution of aceclofenac followed first order kinetics with r (correlation co-efficient) above 0.91. Dissolution efficiency (DE_{15}) values were calculated as suggested by Khan[5]. The dissolution parameters are given in Table-3.

TABLE-3
DISSOLUTION PARAMETERS OF
ACECLOFENAC-β-CYCLODEXTRIN COMPLEX SYSTEMS

Product	Dissolution parameters ($\bar{x}$ ± sd)	
	DE_{15}	K_1 (min^{-1})
Aceclofenac	20.69 ± 0.32	0.039 ± 0.0052
Aceclofenac β-cyclodextrin (1:1) binary system	84.96 ± 7.71	0.730 ± 0.3800
Aceclofenac-Tween 80 (2 %)	55.99 ± 7.52	0.189 ± 0.2250
Aceclofenac β-cyclodextrin (1:1)-Tween 80 (2 %) ternary system	56.48 ± 7.30	0.110 ± 0.0920

The dissolution of aceclofenac was rapid and higher in the case of aceclofenac-β-cyclodextrin complexes with and without Tween 80 when compared to aceclofenac as such. The DE_{15} was increased from 20.69 % for aceclofenac pure drug to 84.96, 55.99 and 56.48 %, respectively for aceclofenac-β-cyclodextrin, aceclofenac-Tween 80 (2 %) and aceclofenac β-cyclodextrin (1:1)-Tween 80 (2 %) ternary system.

The dissolution parameters (K_1 and DE_{15}) were subjected to ANOVA to findout the significance of the main and combined effects of β-cyclodextrin and Tween 80 on the dissolution rate of aceclofenac. The results of ANOVA are shown in Tables 4 and 5.

ANOVA indicated that the individual main effect of β-cyclodextrin and the combined effects of β-cyclodextrin and Tween 80 in enhancing the dissolution rate ane DE_{15} were significant ($p < 0.05$). Whereas the main effect of Tween 80 was not significant ($p > 0.05$). The results, thus, indicated that β-cyclodextrin alone gave higher enhancement in the dissolution rate and DE_{15} of aceclofenac. Though addition of Tween 80 has increased the solubility of aceclofenac, it has not significantly enhanced the dissolution rate and DE_{15} of aceclofenac.

TABLE-4
ANOVA TABLE OF DISSOLUTION RATE

Source of variation	d.f.	s.s.	m.s.s.	F-ratio	$F_{0.05}$
Total	15	1.8031	0.1200	–	
Treatment	3	1.1850	0.3950	7.74	3.49
A (β-cyclodextrin)	1	0.3773	0.3773	7.39	($v_1 = 3$, $v_2 = 12$)
B (Tween 80)	1	0.0880	0.0880	1.72	
AB (Combination)	1	0.5890	0.5890	11.54	4.75
Error	12	0.6180	0.0510	–	($v_1 = 1$, $v_2 = 12$)

TABLE – 5
ANOVA TABLE OF DE_{15}

Source of variation	d.f.	s.s.	m.s.s.	F-ratio	$F_{0.05}$
Total	15	8821.41	588.09	–	
Treatment	3	8308.29	2769.43	83.92	3.49
A (β-cyclodextrin)	1	4194.18	4194.18	98.08	($v_1 = 3$, $v_2 = 12$)
B (Tween 80)	1	46.54	46.54	1.08	
AB (Combination)	1	65081.10	65081.10	1522.00	4.75
Error	12	513.12	42.76	–	($v_1 = 1$, $v_2 = 12$)

Conclusion

The individual and combined effects of β-cyclodextrin and Tween 80 in enhancing the solubility of aceclofenac were significant ($p < 0.05$). The solubility of aceclofenac was markedly enhanced by β-cyclodextrin (1.57 fold), Tween 80 (7.91 fold) individually as well as combindly (10.5 fold).

β-Cyclodextrin alone gave higher enhancement in the dissolution rate and DE_{15} of aceclofenac. The individual main effect of β-cyclodextrin and the combined effect of β-cyclodextrin and Tween 80 in enhancing the dissolution rate and DE_{15} were significant ($p < 0.05$). Whereas the main effect of Tween 80 was not significant ($p > 0.05$).

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