Asian Journal of Chemistry; Vol. 23, No. 4 (2011), 1453-1455

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Factorial Study to Evaluate the Individual and Combined Effects of Cyclodextrins and Tween 80 on the Solubility and Dissolution Rate of Aceclofenac

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(*Received*: 28 December 2009; *Accepted*: 27 November 2010) AJC-9335

The objective of the study is to evaluate the individual main effects and combined (or interaction) effects of two cyclodextrins [β-cyclodextrin (βCD) and hydroxypropyl-β-cyclodextrin (HPβCD)] and Tween 80, a surfactant on the solubility and dissolution rate of aceclofenac in a series of 2^2 factorial experiments. The solubility of aceclofenac in purified water (1), water containing 5 mM of cyclodextrins (βCD or HPβCD) (a), water containing 2 % Tween 80 (b) and water containing 5 mM of CDs (βCD or HPβCD) and 2 % Tween 80 (ab) were determined as per 22 factorial design. The individual and combined effects of βCD, HPβCD and Tween 80 in enhancing the solubility of aceclofenac were highly significant ($p < 0.01$). The solubility of aceclofenac was markedly enhanced by βCD (1.57 fold), HPβCD (1.47 fold), Tween 80 (7.91 fold) individually as well as combindly by βCD-Tween 80 (10.54 fold) HPβCD-Tween 80 (11.96 fold). Solid inclusion complexes of aceclofenac-cyclodextrins (βCD or HPβCD) were prepared with and without Tween 80 as per 2^2 factorial design by kneading method. The dissolution rate of aceclofenac from the cyclodextrin complexes prepared was studied in phosphate buffer of pH 6.8 (n = 4). Cyclodextrins alone gave higher enhancement in the dissolution rate and DE_{15} of aceclofenac. The individual main effect of cyclodextrins (βCD and HPβCD) and the combined effect of cyclodextrins and Tween 80 in enhancing the dissolution rate and DE_{15} were highly significant ($p < 0.01$). Whereas the main effect of Tween 80 was not significant ($p > 0.05$). Thus, a combination of βCD-Tween 80 and HPβCD-Tween 80 is recommended for enhancing the solubility and dissolution rate of aceclofenac.

Key Words: Aceclofenac, Cyclodextrins, 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 (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 of lipophilic water-insoluble drugs by micellar solubilization. Though 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. The objective of the present study is to evaluate the individual main effects and combined (or interaction) effects of two cyclodextrins [β-cyclodextrin (βCD) and hydroxypropyl-β-cyclodextrin (HPβCD)] and Tween 80, a surfactant on the solubility and dissolution rate of aceclofenac in a series of 2^2 factorial studies.

EXPERIMENTAL

Aceclofenac was a gift sample from M/s. Suyaash Labs, Chennai. β-Cyclodextrin and hydroxy propyl β-cyclodextrin were gift samples from M/s. Cerestar Inc., USA). Methanol (Qualigens) and Tween 80 (BDH) were procured from commercial sources.

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 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 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 replicated four times each (n = 4).

Preparation of accelofenac-CD complexes: Solid inclusion complexes of aceclofenac-CD were prepared in 1:2 ratio with and without Tween 80 (2 %) by kneading method. Aceclofenac, CDs (βCD or HPβCD) and Tween 80 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 aceclofenac as such and form CD 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-CD 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 replicated four times each (n = 4).

RESULTS AND DISCUSSION

The individual main effects and combined (interaction) effects of two cyclodextrins (βCD and HPβCD) and Tween 80 on the aqueous solubility of aceclofenac were evaluated in a series of 2^2-factorial experiments. For this purpose, two levels of cyclodextrins (0, 5 mM) and two levels of Tween 80 (0, 2 %) were selected in each case and the corresponding four treatments involved in the 2^2-factorial study were purified water (1), water containing 5 mM cyclodextrins (βCD or HPβCD) (a); water containing 2 % Tween 80 (b) and water containing 5 mM CDs (βCD or HPβCD) and 2 % Tween 80 (ab). The solubility of aceclofenac in the above mentioned fluids was determined (n = 4) and the results are given in Table-1. The aqueous solubility of aceclofenac was markedly enhanced by CDs alone and in combination with Tween 80.

The solubility data were subjected to analysis of variance (ANOVA) to find out the significance of main and combined effects of cyclodextrins (βCD and HPβCD) and Tween 80 on the solubility of aceclofenac. The results of ANOVA are shown in Tables 2 and 3. The individual and combined effects of βCD, HPβCD and Tween 80 in enhancing the solubility of aceclofenac were highly significant ($p < 0.01$). The solubility of aceclofenac was markedly enhanced by βCD (1.57 fold), HPβCD (1.47 fold), Tween 80 (7.91 fold) individually as well as combindly by βCD-Tween 80 (10.54 fold) HPβCD-Tween 80 (11.96 fold).

TABLE-1
SOLUBILITY OF ACECLOFENAC IN VARIOUS FLUIDS CONTAINING CDs AND TWEEN 80 (n = 4)

Fluid	Solubility (mg/100 mL) ($\bar{x} \pm sd$)	Increase in solubility (No. of folds)
Purified water	5.42 ± 0.184	–
Water containing βCD (5mM)	8.53 ± 0.311	1.57
Water containing HPβCD (5mM)	6.32 ± 0.290	1.47
Water containing Tween 80 (2%)	42.9 ± 5.540	7.91
Water containing βCD (5 mM) and Tween 80 (2 %)	57.18 ± 1.310	10.54
Water containing HPβCD (5 mM) and Tween 80 (2 %)	51.33 ± 3.470	11.96

TABLE-2
ANOVA OF SOLUBILITY DATA (βCD-TWEEN 80)

Source of variation	df	SS	MSS	F-Ratio	Significance
Total	15	7945.42	529.69	–	–
Treatment	3	7846.91	2615.63	318.59	$p < 0.01$
a (βCD)	1	302.32	302.32	36.82	$p < 0.01$
b (Tween 80)	1	7417.94	7419.94	903.52	$p < 0.01$
ab(Combination)	1	124.93	124.93	15.21	$p < 0.01$
Error	12	98.51	8.21	–	–

TABLE-3
ANOVA OF SOLUBILITY DATA (HPβCD-TWEEN 80)

Source of variation	df	SS	MSS	F-Ratio	Significance
Total	15	6477.85	431.85	–	–
Treatment	3	6437.39	2145.79	636.73	$p < 0.01$
a (HPβCD)	1	274.31	274.31	81.39	$p < 0.01$
b (Tween 80)	1	6006.63	6006.63	1782.38	$p < 0.01$
ab(Combination)	1	156.43	156.43	46.41	$p < 0.01$
Error	12	40.46	3.37	–	–

To evaluate the individual and combined effects of cyclodextrins (βCD or HPβCD) and Tween 80 on the dissolution rate of aceclofenac, solid inclusion complexes of aceclofenac-cyclodextrins (βCD or HPβCD) were prepared with and without Tween 80 as per a 2^2-factorial design. For this purpose 2 levels of CD (0 and 1:2 ratio of drug: CD) and two levels of Tween 80 (0 and 2 %) were selected and the corresponding four treatments involved in the 2^2-factorial study were aceclofenac pure drug (1), aceclofenac-CD (βCD or HPβCD) (1:2) inclusion complex (a), aceclofenac-Tween 80 (2 %) blend (b) and aceclofenac CD (βCD or HPβCD) (1:2)-Tween 80 (2 %) ternary complex (ab). The CD complexes were prepared by kneading method. All the solid inclusion complexes of aceclofenac-CD-Tween 80 prepared were found to be fine and free flowing powders. Low co-efficient of variation (c.v.) values (< 1 %) in the per cent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared. The dissolution rate of aceclofenac alone and from CD 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

TABLE-4
DISSOLUTION PARAMETERS OF ACECLOFENAC CYCLODEXTRIN-SURFACTANT SYSTEMS PREPARED

CD-Surfactant system	DE_{15} (%)		K_1 (min^{-1})	
	($\bar{x} \pm sd$)	No. of folds increased	($\bar{x} \pm sd$)	No. of folds increased
Aceclofenac pure drug	20.71 ± 0.32	–	0.039 ± 0.0052	–
Aceclofenac-βCD (1:2) binary system Aceclofenac-	84.96 ± 7.71	4.10	0.73 ± 0.38	18.7
HPβCD (1:2) binary system	76.64 ± 0.59	3.70	0.171 ± 0.013	4.38
Aceclofenac-Tween 80 (2 %) binary system	55.99 ± 7.52	2.70	0.189 ± 0.225	4.84
Aceclofenac-βCD (1:2)-Tween 80 (2 %) Ternary system	56.48 ± 7.30	2.72	0.110 ± 0.092	2.82
Aceclofenac-HPβCD (1:2)-Tween 80 (2 %) Ternary system	67.85 ± 2.69	3.27	0.113 ± 0.012	2.89

(DE_{15}) values were calculated as suggested by Khan[5]. The dissolution parameters are given in Table-4. The dissolution of aceclofenac was rapid and higher in the case of aceclofenac-CD (βCD or HPβCD) complexes with and without Tween 80 when compared to aceclofenac as such.

The dissolution parameters (K_1 and DE_{15}) were subjected to ANOVA to findout the significance of the main and combined effects of CDs and Tween 80 on the dissolution rate of aceclofenac. The results of ANOVA are shown in Tables 5 and 6. ANOVA indicated that the individual main effect of CDs (βCD and HPβCD) and the combined effects of βCD 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 CDs 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-5
ANOVA OF DISSOLUTION RATE OF βCD COMPLEXES

Source of variation	df	SS	MSS	F-Ratio	Significance
Total	15	17495.06	1166.33	–	–
Treatment	3	12849.94	4283.31	11.06	$p < 0.01$
a (βCD)	1	5723.33	5123.33	13.23	$p < 0.01$
b (Tween 80)	1	3280.71	3280.71	8.47	$p < 0.05$
ab(Combination)	1	71134.22	71134.22	183.76	$p < 0.01$
Error	12	4645.12	387.09	–	–

TABLE-6
ANOVA OF DISSOLUTION RATE OF HPβCD COMPLEXES

Source of variation	df	SS	MSS	F-Ratio	Significance
Total	15	393.86	26.25	–	–
Treatment	3	368.84	122.94	59.10	$p < 0.01$
a (HPβCD)	1	256.80	256.80	123.46	$p < 0.01$
b (Tween 80)	1	1.26	1.26	0.60	$p < 0.05$
ab(Combination)	1	110.77	110.77	53.25	$p < 0.01$
Error	12	25.02	2.08	–	–

Conclusion

The individual and combined effects of βCD, HPβCD and Tween 80 in enhancing the solubility of aceclofenac were highly significant ($p < 0.01$). The solubility of aceclofenac was markedly enhanced by βCD (1.57 fold), HPβCD (1.47 fold), Tween 80 (7.91 fold) individually as well as combindly by βCD-Tween 80 (10.54 fold) and HPβCD -Tween 80 (11.96 fold). Cyclodextrins alone gave higher enhancement in the dissolution rate (K_1) and DE_{15} of aceclofenac. The individual main effect of CDs (βCD and HPβCD) and the combined effect of CDs and Tween 80 in enhancing the dissolution rate and DE_{15} were highly significant ($p < 0.01$). Whereas the main effect of Tween 80 was not significant ($p > 0.05$). Thus, a combination of βCD-Tween 80 and HPβCD-Tween 80 is recommended for enhancing the solubility and dissolution rate of aceclofenac.

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