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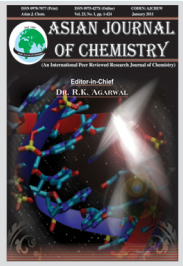

Factorial Study on the Effects of β-Cyclodextrin and Surfactants on the Solubility and Dissolution Rate of Carbamazepine

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Carbamazepine, a widely used anticonvulsant drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. In the present study the individual main effects and combined (or interaction) effects of β-cyclodextrin (βCD) and two surfactants (Tween 80 and sodium lauryl sulphate) on the solubility and dissolution rate of carbamazepine were evaluated in a series of 2^2 factorial experiments. The individual main effects of βCD, Tween 80 and sodium lauryl sulphate (SLS) and combined effect of βCD and SLS in enhancing the solubility of carbamazepine were significant ($p < 0.05$). The solubility of carbamazepine was markedly enhanced by βCD (2.06 folds), Tween 80 (2.72 folds) and SLS (31.76 folds). Combination of βCD and SLS gave a 48.53 fold increase in the solubility of carbamazepine. Carbamazepine-βCD-surfactant binary and ternary systems were prepared by kneading method and were evaluated for dissolution rate and dissolution efficiency (DE_{30}) as per a 2^2 factorial design. The dissolution of carbamazepine was rapid and higher from the binary and ternary systems prepared employing βCD and surfactants when compared to carbamazepine pure drug. β-Cyclodextrin alone gave higher enhancement in K_1 (2.349 folds) and DE_{30} (4.247 folds) of carbamazepine. The individual main effects of βCD and SLS and the combined effect of βCD and SLS in enhancing the K_1 of carbamazepine were significant ($p < 0.05$).

Key Words: Carbamazepine, Solubility, Dissolution rate, Factorial Study, β-Cyclodextrin, Surfactants.

INTRODUCTION

Carbamazepine is a widely used anticonvulsant drug belonging to the chemical class of iminostillbenes. It is used in doses of 100, 200 and 400 mg, 2 or 3 times a day. Carbamazepine belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. 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. In the present study the individual main effects and combined (or interaction) effects of β-cyclodextrin (βCD) and two surfactants (Tween 80 and sodium lauryl sulphate) on the solubility and dissolution rate of carbamazepine were evaluated in a 2^2 factorial study.

EXPERIMENTAL

Carbamazepine was a gift sample from M/s Ranbaxy Research Laboratories, Gurgaon. β-Cyclodextrin was a gift sample from M/s Cerestar Inc., USA. Tween 80 (BDH) and sodium lauryl sulphate (SD Fine Chemie) were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Estimation of carbamazepine: An UV spectrophotometric method based on the measurement of absorbance at 288 nm in purified water was used for the estimation of the carbamazepine. The method obeyed Beer-Lambert's law in the concentration range of 1-10 μm/mL. When the standard drug solution was assayed repeatedly (n = 6), the relative error (accuracy) and coefficient of variation (precision) were found

to be 0.80 and 1.6 %, respectively. No interference from excipients used was observed.

Determination of solubility: The solubility of carbamazepine in the following four selected fluids as per 22 factorial study was determined to evaluate the individual and combined effects of the βCD and surfactants on the solubility of carbabamazepine. The two levels of βCD (factor A) are 0 and 5 mM. The two levels of surfactants (factor B) are 0 and 2 %. Accordingly the four selected fluids as per 2^2-factorial study are purified water (1), water containing βCD (5 mM) (a), water containing 2 % surfactant (Tween 80 or 2 % SLS) (b) and water containing 5 mM of βCD and 2 % surfactant (Tween 80 or SLS) (ab).

Excess drug was added to 15 mL of the selected fluid taken in a 25 mL stoppered conical flask and the mixtures were shaken for 72 h at room temperature (28 ºC) on a rotary flask shaker. After 72 h of shaking to achieve equilibrium, 2 mL of aliquots were withdrawn and filtered immediately using 0.45 µ disc filter. The filtered samples were diluted suitably and assayed for carbamazepine at 288 nm. In each case the solubility determinations were replicate 4 times (n = 4).

Preparation of drug-CD-surfactant systems: To evaluate the individual and combined effects of βCD and surfactants on the dissolution rate of carbamazepine, drug-CD-surfactant systems were prepared employing the following selected combinations of βCD and surfactants as per 2^2 factorial design. The two levels of βCD (factor A) are 0 and 1:2 ratio of drug: βCD, respectively. The two levels of surfactant (factor B) are 0 and 5 %. The selected treatments as per 2^2 factorial design are carbamazepine pure drug (1), carbamazepine - CD (1:2) binary system (a), carbamazepine - surfactant (5 %) binary system (b) and carbamazepine-CD-surfactant ternary system (ab). The binary and ternary systems were prepared by kneading method.

Required quantities of drug, βCD and surfactant were taken in a clean and dry mortar. Kneading fluid consisting of water:alcohol (1:1) was added and mixed to get a thick slurry. The slurry was thoroughly mixed and kneaded for 45 min. Additional quantities of kneading fluid were added to maintain the mixture as thick slurry during the kneading process. After kneading for 45 min the mixture was transferred to a petridish and dried in an oven at 60 ºC. The dried powder was passed through mesh No. 100.

Dissolution rate study: Carbamazepine dissolution from drug-CD-surfactant complex systems was studied using eight station dissolution rate test apparatus (Lab India, Disso 2000) employing a paddle stirrer at 50 rpm and at 37 ± 0.5 ºC. Purified water (900 mL) was used as dissolution fluid. Samples of 5 mL of each were withdrawn at different time intervals over a period of 1 h. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and assayed at 288 nm for carbamazepine using an Elico BL 198 double beam UV-spectrophotometer. All dissolution experiments were repeated four times each (n = 4).

RESULTS AND DISCUSSION

The individual main and combined (interaction) effects of βCD and surfactants (Tween 80 and SLS) on the solubility of carbamazepine were evaluated in a series of 2^2 factorial experiments.

Solubility studies with βCD and surfactants: The results of solubility studies with βCD and surfactants are given in Table-1. The solubility of carbamazepine was markedly enhanced by βCD and surfactants. A 2.06, 2.72 and 31.76 fold increase in the solubility of carbamazepine was observed, respectively with βCD (5 mM) and Tween 80 (2 %) and SLS (2 %). Combination of βCD (5 mM) and Tween 80 (2 %) has given a 4.09 fold increase in the solubility of carbamazepine. Where as the combination of βCD (5 mM) and SLS (2 %) has given a 48.53 fold increase in the solubility of carbamazepine. The solubility data were subjected to analysis of variance (ANOVA) to find out the significance of individual main and combined effects of βCD and the surfactants on the solubility of carbamazepine. The results of ANOVA are given in Tables 2 and 3.

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

Fluid	Solubility (mg/100 mL)	Increase in solubility (No. of folds)
Purified water	12.08 ± 2.85	–
Water containing βCD (5 mM)	24.95 ± 5.37	2.06
Water containing Tween 80 (2 %)	32.91 ± 3.49	2.72
Water containing βCD (5 mM) and Tween 80 (2 %)	49.45 ± 6.00	4.09
Water containing SLS (2 %)	383.74 ± 44.73	31.76
Water containing βCD (5 mM) and SLS (2 %)	586.24 ± 136.61	48.53

TABLE-2
ANOVA OF SOLUBILITY DATA WITH βCD AND TWEEN 80

Source of variation	d.f.	SS	MSS	F-Ratio	Significance
Total	15	2371.87	158.224	–	–
Treatment	3	2084.55	694.85	29.02	($p < 0.01$)
a(βCD)	1	605.03	605.03	25.27	($p < 0.01$)
b(SLS)	1	1407.56	1407.56	58.79	($p < 0.01$)
ab(Combination)	1	71.95	71.95	3.00	($p > 0.05$)
Error	12	287.31	23.94	–	–

TABLE-3
ANOVA OF SOLUBILITY DATA WITH βCD AND SLS

Source of variation	d.f.	SS	MSS	F-Ratio	Significance
Total	15	1015944.70	67729.64	–	–
Treatment	3	954082.98	318027.66	61.69	($p < 0.01$)
a(βCD)	1	45849.51	45849.51	8.89	($p < 0.01$)
b(SLS)	1	872748.32	872748.32	169.29	($p < 0.01$)
ab(Combination)	1	35485.14	35485.14	6.88	($p < 0.01$)
Error	12	61861.72	5155.14	–	–

ANOVA indicated that the individual main effects of βCD, Tween 80 and SLS and the combined (or interaction) effect of βCD and SLS were highly significant ($p < 0.01$), whereas the combined (or interaction) effect of βCD and Tween 80 on the solubility of carbamazepine was not significant ($p > 0.05$).

A combination of βCD and SLS has resulted in a much higher enhancement in the solubility of carbamazepine than is possible with them individually. This may be due to better inclusion of drug molecules in the presence of SLS.

Dissolution rate studies on drug-CD-surfactant systems: All the drug-CD-surfactant binary and ternary systems prepared were found to be fine and free flowing powders. Low coefficient of variation (c.v.) values (< 1 %) in the per cent drug content indicated uniformity of drug content in each case. The dissolution rate of carbamazepine alone and from drug-CD-surfactant systems was studied in purified water. The dissolution of carbamazepine from all binary and ternary systems prepared followed first order kinetics with r (correlation coefficient) above 0.91. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[5]. The dissolution parameters are given in Table-4.

TABLE-4
DISSOLUTION PARAMETERS OF CARBAMAZEPINE-βCD-TWEEN 80 COMPLEX SYSTEMS

Product	Dissolution parameters ($\bar{x} \pm sd$)	
	DE_{30}	K_1 (min^{-1})
Carbamazepine	10.9 ± 1.2	0.0109 ± 0.0009
Carbamazepine βCD (1:2) binary system	46.3 ± 3.7	0.0256 ± 0.0095
Carbamazepine-Tween 80 (5 %)	29.8 ± 2.6	0.0114 ± 0.0006
Carbamazepine βCD (1:2)-Tween 80 (5 %) ternary system	37.9 ± 1.1	0.0232 ± 0.0034
Carbamazepine-SLS (5 %)	25.6 ± 3.5	0.0181 ± 0.0020
Carbamazepine βCD (1:2)-SLS (5 %) ternary system	31.9 ± 3.7	0.0195 ± 0.0030

The dissolution parameters indicated rapid and higher dissolution of carbamazepine from carbamazepine-βCD complexes with and without surfactant when compared to carbamazepine as such. Both K_1 and DE_{30} were markedly higher in the case of binary and ternary systems. βCD alone gave higher enhancement in K_1 and DE_{30} of carbamazepine.

The dissolution rate K_1 was subjected to ANOVA to find out the significance of the main and combined effects of βCD and surfactants on the dissolution rate of carbamazepine. The results of ANOVA are shown in Tables 5 and 6.

ANOVA indicated that the individual main effects of βCD and SLS and combined effects of βCD-SLS in enhancing the dissolution rate were significant ($p < 0.05$). Whereas the individual main effect of Tween 80 and combined effect of βCD-Tween 80 were not significant ($p > 0.05$).

TABLE-5
ANOVA OF $K_1 \times 10^3$ (min^{-1}) VALUES OF βCD- TWEEN 80 SYSTEMS

Source of variation	d.f.	SS	MSS	F-ratio	Significance
Total	15	996.68	66.44	–	–
Treatment	3	682.84	227.61	8.70	($p < 0.05$)
a(βCD)	1	674.18	674.18	25.78	($p < 0.01$)
b(Tween-80)	1	2.002	2.002	0.0765	($p > 0.05$)
ab(Combination)	1	6.656	6.656	0.2545	($p > 0.05$)
Error	12	313.84	26.15	–	–

TABLE-6
ANOVA OF $K_1 \times 10^3$ (min^{-1}) VALUES OF βCD-SLS SYSTEMS

Source of variation	d.f.	SS	MSS	F-Ratio	Significance
Total	15	1130.07	75.338	–	–
Treatment	3	811.49	270.49	10.19	($p < 0.01$)
a(βCD)	1	137.35	137.35	5.175	($p < 0.05$)
b(SLS)	1	391.05	391.05	14.73	($p < 0.01$)
ab(Combination)	1	283.08	283.08	10.66	($p < 0.01$)
Error	12	318.575	26.54	–	–

Conclusion

The individual main effects of β-cyclodextrin (βCD), Tween 80 and sodium lauryl sulphate (SLS) and combined effect of βCD and SLS in enhancing the solubility of carbamazepine were significant ($p < 0.05$). The solubility of carbamazepine was markedly enhanced by βCD (2.06 folds), Tween 80 (2.72 folds) and SLS (31.76 folds). Combination of βCD and SLS gave a 48.53 fold increase in the solubility of carbamazepine. The dissolution of carbamazepine was rapid and higher from the binary and ternary systems prepared employing βCD and surfactants when compared to carbamazepine pure drug. β-Cyclodextrin alone gave higher enhancement in K_1 (2.349 folds) and DE_{30} (4.247 folds) of carbamazepine. The individual main effects of βCD and SLS and the combined effect of βCD and SLS in enhancing the K_1 of carbamazepine were significant ($p < 0.05$).

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