Asian Journal of Chemistry; Vol. 23, No. 10 (2011), 4520-4524

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Individual and Combined Effects of Cyclodextrins, Poloxamer and PVP on the Solubility and Dissolution Rate of BCS Class II Drugs

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(*Received*: 11 December 2010; *Accepted*: 27 June 2011) AJC-10090

The objective of the study is to evaluate the individual main and combined (or interaction) effects of two cyclodextrins (β-cyclodextrins and hydroxy propyl β-cyclodextrins), surfactant (poloxamer 407) and poly(vinyl pyrrolidone) (PVP) on the solubility and dissolution rate of etoricoxib and nimesulide, two BCS class II drugs in a series of 2^3 factorial experiments. The solubility of (i) etoricoxib and (ii) nimesulide each in eight selected fluids containing CDs, poloxamer 407 and PVP as per 2^3 factorial study was determined. The solubility of etoricoxib was markedly enhanced by β-cyclodextrins (2.24 fold), hydroxy propyl β-cyclodextrins (3.14 fold), poloxamer 407 (2.58 fold) and PVP (1.38 fold) individually. β-cyclodextrins in combination with PVP has given highest enhancement (3.44 fold) in the solubility of etoricoxib. Hydroxy propyl β-cyclodextrins in combination with poloxamer 407 and PVP gave respectively 3.74 and 3.39 fold increase in the solubility of etoricoxib. The solubility of nimesulide was also markedly enhanced by β-cyclodextrins (4.12 fold), hydroxy propyl β-cyclodextrins (21.06 fold), poloxamer 407 (5.37 fold) and PVP (24.9 fold) individually. β-Cyclodextrins in combination with poloxamer 407 and PVP gave respectively 5.44 and 26.31 fold increase in the solubility of nimesulide. Hydroxy propyl β-cyclodextrins in combination with poloxamer 407 and PVP gave respectively 5.31 and 26.43 fold increase in the solubility of nimesulide. Poloxamer 407 in combination with PVP has given highest enhancement (28.06 fold) in the solubility of nimesulide. Both the individual and combined effects of cyclodextrins, poloxamer and PVP on the solubility of (i) etoricoxib and (ii) nimesulide were highly significant ($P < 0.01$). Solid inclusion complexes of drug-cyclodextrins (β-cyclodextrins and hydroxy propyl β-cyclodextrins) were prepared with and without poloxamer 407 and PVP by kneading method as per 23-factorial design in each case. ANOVA indicated that the individual main effects of cyclodextrins (β-cyclodextrins and hydroxy propyl-β-cyclodextrins), poloxamer 407 and PVP and their combined effects in enhancing the dissolution rate (K_1) were highly significant ($P < 0.01$) with both (i) etoricoxib and (ii) nimesulide. β-cyclodextrins alone gave a 1.18 fold increase in the dissolution rate of etoricoxib. β-Cyclodextrins in combination with PVP and poloxamer 407 gave respectively 3.0 and 7.4 fold increase in the dissolution rate of etoricoxib. Hydroxy propyl β-cyclodextrins alone gave a 3.55 fold increase and in combination with PVP and poloxamer 407 it gave respectively 57.6 and 23.6 fold increase in the dissolution rate of etoricoxib. β-cyclodextrins alone gave a 9.63 fold increase in the dissolution rate of nimesulide. Where as in combination with PVP and poloxamer 407 it gave respectively 15.51 and 21.78 fold increase in the dissolution rate of nimesulide. Hydroxy propyl β-cyclodextrins alone gave a 10.88 fold increase and in combination with PVP and poloxamer 407 it gave respectively 37.72 and 51.61 fold increase in the dissolution rate of nimesulide. Thus combination of cyclodextrins with poloxamer 407 and PVP has markedly enhanced both the solubility and dissolution rate of etoricoxib and nimesulide.

Key Words: Etoricoxib, Nimesulide, Cyclodextrins, Poloxamer 407, Poly(vinyl pyrrolidone), Solubility.

INTRODUCTION

Etoricoxib and nimesulide, two widely prescribed anti inflammatory and analgesic drugs belong to class-II under BCS and exhibit low and variable oral bioavailability due to their poor aqueous solubility. They are practically insoluble 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 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 solubilizing agent[5-7].

Though cyclodextrin complexation and use of surfactants and poly(vinyl pyrrolidone) (PVP) 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 two cyclodextrins (β-cyclodextrin and HP β-cyclodextrin), surfactant (poloxamer 407) and poly(vinyl pyrrolidone) on the solubility and dissolution rate of (i) etoricoxib (ii) nimesulide were evaluated in a series of 2^3 factorial experiments.

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

Etoricoxib and nimesulide were gift sampls from M/s. Natco Pharma Ltd., Hyderabad. β-Cyclodextrin and hydroxy propyl β-cyclodextrin were gift samples from M/s. Cerestar Inc., USA. Methanol (Qualigens), poly(vinyl pyrrolidone) (PVP-K30) and poloxamer 407 were procured from commercial sources.

Estimation of etoricoxib and nimesulide: UV spectrophotometric methods based on the measurement of absorbance at 289 nm in a phosphate buffer of pH 7.4 and at 397 nm in alkaline borate buffer of pH 8.4 were used for the estimation of etoricoxib and nimesulide respectively. The methods were validated for linearity, accuracy, precision and interference. The methods 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 less than 0.8 and 1.2 % respectively in both the cases. 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 stopped conical flask and the mixtures were shaken for 24 h at room temperature (28 ± 1 ºC) 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 at 289 nm for etoricoxib and at 397 nm for nimesulide. Shaking was continued until two consecutive estimations are the same. The solubility experiments were replicated for four times each (n = 4).

Preparation of drug-cyclodextrin complexes: Solid inclusion complexes of drug-CD were prepared in 1:2 ratio with and without poloxamer 407 (2 %) and poly(vinyl pyrrolidone) (2 %) by kneading method. Etoricoxib or nimesulide, cyclodextrins (β-cyclodextrin or hydroxy propyl β-cyclodextrin), poloxamer 407 and poly(vinyl pyrrolidone) 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 (i) etoricoxib and (ii) nimesulide as such and from cyclodextrin complexes prepared was studied respectively in 900 mL of (i) phosphate buffer of pH 7.4 and (ii) alkaline borate buffer of pH 8.4 using disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature 37 ± 1 ºC was maintained throughout the study. Drug or drug-cyclodextrin complex equivalent to 60 mg of etoricoxib or 50 mg of nimesulide 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 at 289 nm in the case of etoricoxib and at 397 nm in the case of nimesulide. The samples 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 (β-cyclodextrin and hydroxy propyl β-cyclodextrin) (factor A), poloxamer 407 (factor B) and poly(vinyl pyrrolidone) K30 (factor C) on the aqueous solubility of (i) etoricoxib and (ii) nimesulide were evaluated in a series of 2^3-factorial experiments. For this purpose, two levels

TABLE -1
SOLUBILITY OF ETORICOXIB IN VARIOUS FLUIDS AS PER 2^3 – FACTORIAL STUDY

Fluids (Code as per 2^3 – Factorial Experiment)	Solubility (mg/mL) (n = 4) (x ± sd)	Increase in solubility (number of folds)	Significance
Distilled water (1)	0.148 ± 0.003	–	–
Water containing 5 mM β-cyclodextrin (a)	0.303 ± 0.005	2.04	p < 0.01
Water containing 2 % poloxamer (b)	0.381 ± 0.001	2.57	p < 0.01
Water containing 5 mM β-cyclodextrin and 2% Poloxamer (ab)	0.288 ± 0.006	1.94	p < 0.01
Water containing 2 % poly(vinyl pyrrolidone) (c)	0.205 ± 0.005	1.38	p < 0.01
Water containing 5 mM β-cyclodextrin and 2 % poly(vinyl pyrrolidone) (ac)	0.510 ± 0.074	3.44	p < 0.01
Water containing 2 % Poloxamer and 2 % poly(vinyl pyrrolidone) (bc)	0.240 ± 0.016	1.62	p < 0.01
Water containing 5 mM β-cyclodextrin, 2% Poloxamer and 2 % poly(vinyl pyrrolidone) (abc)	0.415 ± 0.005	2.80	p < 0.01
Water containing 5 mM HP β-cyclodextrin (a)	0.465 ± 0.013	3.14	p < 0.01
Water containing 5 mM HP β-cyclodextrin and 2% Poloxamer (ab)	0.553 ± 0.001	3.74	p < 0.01
Water containing 5 mM HP β-cyclodextrin and 2% poly(vinyl pyrrolidone) (ac)	0.503 ± 0.006	3.39	p < 0.01
Water containing 5 mM HP β-cyclodextrin, 2 % Poloxamer and 2 % poly(vinyl pyrrolidone) (abc)	0.353 ± 0.006	2.38	p < 0.01

of cyclodextrins (0, 5 mM), two levels of poloxamer 407 (0, 2 %) and two levels of poly(vinyl pyrrolidone) (0, 2 %) were selected in each case and the corresponding eight treatments involved in the 2^3-factorial study were purified water (1), water containing 5 mM cyclodextrins (β-cyclodextrin or HP β-cyclodextrin) (a); water containing 2 % Poloxamer 407 (b); water containing 5 mM cyclodextrins (β-cyclodextrin or HP β-cyclodextrin) and 2 % Poloxamer 407 (ab); water containing 2 % poly(vinyl pyrrolidone) (c); water containing 5 mM cyclodextrins (β-cyclodextrin or HP β-cyclodextrin) and 2 % poly(vinyl pyrrolidone) (ac); water containing 2 % poloxamer 407 and 2 % poly(vinyl pyrrolidone) (bc) and water containing 5 mM cyclodextrins (β-cyclodextrin or HP β-cyclodextrin) and 2 % of each of poloxamer 407 and poly(vinyl pyrrolidone) (abc) in each case.

The solubility of etoricoxib in the above mentioned eight fluids was determined (n = 4) and the results are given in Table-1. The aqueous solubility of etoricoxib was markedly enhanced by cyclodextrins alone and in combination with poloxamer 407 and poly(vinyl pyrrolidone).

The solubility data were subjected to analysis of variance (ANOVA) to find out the significance of main and combined effects of cyclodextrins (β-cyclodextrin and HP β-cyclodextrin), poloxamer 407 and poly(vinyl pyrrolidone) on the solubility of etoricoxib. The individual and combined effects of β-cyclodextrin, HP β-cyclodextrin, poloxamer 407 and poly(vinyl pyrrolidone) in enhancing the solubility of etoricoxib were highly significant ($P < 0.01$). The solubility of etoricoxib was markedly enhanced by β-cyclodextrin (2.24 fold), HP β-cyclodextrin (3.14 fold), poloxamer 407 (2.58 fold) and poly(vinyl pyrrolidone) (1.38 fold) individually. The order of increasing solubility observed with various β-cyclodextrins and surfactants was HP β-cyclodextrin> poloxamer 407 > β-cyclodextrin > poly(vinyl pyrrolidone). β-cyclodextrin in combination with poly(vinyl pyrrolidone) has given highest enhancement (3.44 fold) in the solubility of etoricoxib. HP β-cyclodextrin in combination with Poloxamer 407 and poly(vinyl pyrrolidone) gave respectively 3.74 and 3.39 fold increase in the solubility of etoricoxib.

The solubility of nimesulide was also markedly enhanced by β-cyclodextrin (4.12 fold), HP β-cyclodextrin (21.06 fold), poloxamer 407 (5.37 fold) and poly(vinyl pyrrolidone) (24.9 fold) individually (Table-2). β-cyclodextrin in combination with poloxamer 407 and poly(vinyl pyrrolidone) gave respectively 5.44 and 26.31 fold increase in the solubility of nimesulide. HP β-cyclodextrin in combination with poloxamer 407 and poly(vinyl pyrrolidone) gave respectively 5.31 and 26.43 fold increase in the solubility of nimesulide. Poloxamer 407 in combination with poly(vinyl pyrrolidone) has given highest enhancement (28.06 fold) in the solubility of nimesulide. Both the individual and combined effects of cyclodextrins, Poloxamer and poly(vinyl pyrrolidone) on the solubility of etoricoxib and nimesulide were highly significant ($P < 0.01$).

To evaluate the individual and combined effects of cyclodextrins (β-cyclodextrin or HP β-cyclodextrin), poloxamer 407 and poly(vinyl pyrrolidone) on the dissolution rate of etoricoxib and nimesulide, solid inclusion complexes of drug-β-cyclodextrin (β-cyclodextrin and HP β-cyclodextrin) were prepared with and without poloxamer 407 and poly-(vinyl pyrrolidone) as per 2^3-factorial design. For this purpose two levels of β-cyclodextrin (0 and 1:2 ratio of drug:β-cyclodextrin) and two levels of each of poloxamer 407 and poly(vinyl pyrrolidone) (0 and 2 %) were selected and the corresponding eight treatments involved in the 2^3-factorial study were etoricoxib or nimesulide pure drug (1); drug-cyclodextrin (β-cyclodextrin or HP β-cyclodextrin) (1:2) inclusion binary complex (a); drug-poloxamer 407 (2 %) binary mixture (b); drug-cyclodextrin (β-cyclodextrin or HP-β-cyclodextrin) (1:2)-poloxamer 407 (2 %) ternary complex (ab); drug-poly(vinyl pyrrolidone) (2 %) binary mixture (c); drug -β-cyclodextrin (β-cyclodextrin or HP β-cyclodextrin) (1:2)-poly(vinyl pyrrolidone) (2 %) ternary complex (ac); drug-poloxamer 407 (2 %)-poly(vinyl pyrrolidone) (2 %) ternary complex (bc) and drug-β-cyclodextrin (β-cyclodextrin or HP β-cyclodextrin) (1:2)-poloxamer 407 (2 %)-poly(vinyl pyrrolidone) (2 %) complex (abc) in each case.

The cyclodextrin complexes were prepared by kneading method. All the solid inclusion complexes of drug-cyclodextrin-poloxamer 407-poly(vinyl pyrrolidone) prepared were found to be fine and free flowing powders. Low coefficient of variation (c.v.) values (< 1 %) in the per cent drug

TABLE-2
SOLUBILITY OF NIMESULIDE IN VARIOUS FLUIDS AS PER 2^3–FACTORIAL STUDY

Fluids (Code as per 2^3 – Factorial Experiment)	Solubility (mg/ mL) (n = 4) (x ± sd)	Increase in solubility (number of folds)	Significance
Distilled water (1)	0.016 ± 0.0005	-	-
Water containing 5 mM β-cyclodextrin (a)	0.066 ± 0.02	4.125	$p < 0.01$
Water containing 2 % poloxamer (b)	0.086 ± 0.002	5.375	$p < 0.01$
Water containing 5 mM β-cyclodextrin and 2 % Poloxamer (ab)	0.087 ± 0.003	5.437	$p < 0.01$
Water containing 5 % poly(vinyl pyrrolidone) (c)	0.399 ± 0.004	24.93	$p < 0.01$
Water containing 5 mM β-cyclodextrin and 5 % poly(vinyl pyrrolidone) (ac)	0.421 ± 0.012	26.31	$p < 0.01$
Water containing 2 % Poloxamer and 5 % poly(vinyl pyrrolidone) (bc)	0.449 ± 0.011	28.06	$p < 0.01$
Water containing 5 mM β-cyclodextrin, 2 % Poloxamer and 5 % poly(vinyl pyrrolidone) (abc)	0.481 ± 0.013	30.06	$p < 0.01$
Water containing 5 mM HP β-cyclodextrin (a)	0.337 ± 0.001	21.06	$p < 0.01$
Water containing 5 mM HP β-cyclodextrin and 2% Poloxamer (ab)	0.085 ± 0.0005	5.312	$p < 0.01$
Water containing 5 mM HP β-cyclodextrin and 5 % poly(vinyl pyrrolidone) (ac)	0.423 ± 0.002	26.43	$p < 0.01$
Water containing 5 mM HP β-cyclodextrin, 2 % Poloxamer and 2 % poly(vinyl pyrrolidone) (abc)	0.518 ± 0.003	32.37	$p < 0.01$

TABLE-3
DISSOLUTION PARAMETERS OF ETORICOXIB –CD COMPLEX SYSTEMS PREPARED AS PER 2^3 FACTORIAL STUDY

Et –CD Complex	Composition	$K_1 \times 10^2$ min^{-1}	Increase in K_1 (No. of folds)	DE_{30} (%)	Increase in DE_{30} (No. of folds)	Significance of K_1
F1	Etoricoxib	1.54	-	18.67	-	-
Fa	Et-β-cyclodextrin (1:2)	1.83	1.18	22.39	1.19	$p < 0.01$
Fb	Et-P 407 (2 %)	2.15	1.39	35.23	1.84	$p < 0.01$
Fab	Et-β-cyclodextrin (1:2)-P 407 (2 %)	11.43	7.4	42.83	2.2	$p < 0.01$
Fc	Et- poly(vinyl pyrrolidone) (2 %)	0.64	0.4	9.92	0.53	$p < 0.01$
Fac	Et-β-cyclodextrin (1:2)- poly(vinyl pyrrolidone) (2 %)	4.73	3	28.81	1.5	$p < 0.01$
Fbc	Et-P407(2 %)-β-cyclodextrin (2 %)	0.99	0.6	17.94	0.9	$p < 0.01$
Fabc	Et-β-cyclodextrin (1:2)-P 407 (2 %) - poly(vinyl pyrrolidone) (2 %)	5.40	3.5	34.60	1.85	$p < 0.01$
Fa	Et-HP β-cyclodextrin (1:2)	5.47	3.55	33.80	1.81	$p < 0.01$
Fab	Et-HP β-cyclodextrin (1:2)- P 407(2 %)	3.64	23.6	48.82	2.6	$p < 0.01$
Fac	Et- HP β-cyclodextrin (1:2)- poly(vinyl pyrrolidone) (2%)	88.83	57.6	54.46	2.91	$p < 0.01$
Fabc	Et- HP β-cyclodextrin (1:2)- P 407 (2 %)- poly(vinyl pyrrolidone) (2 %)	9.71	6.3	48.47	2.5	$p < 0.01$

Et- Etoricoxib, P 407- Poloxamer 407

TABLE-4
DISSOLUTION PARAMETERS OF NIMESULIDE-CD COMPLEX SYSTEMS PREPARED AS PER 2^3 FACTORIAL STUDY

Ni–CD Complex	Composition	$K_1 x 10^2$ min^{-1}	Increase in K_1 (No. of folds)	DE_{30} (%)	Increase in DE_{30} (No. of folds)	Significance of K_1
F1	Nimesulide	1.19	–	6.47	–	–
Fa	NI-β CD (1:2)	11.47	9.64	35.64	5.51	$p < 0.01$
Fb	NI-P 407 (2 %)	9.46	7.95	30.49	4.71	$p < 0.01$
Fab	NI- β CD (1:2)-P 407(2 %)	25.93	21.79	38.57	5.96	$p < 0.01$
Fc	NI-PVP (2 %)	2.04	1.71	16.29	2.52	$p < 0.01$
Fac	NI- β CD (1:2)-PVP (2%)	18.46	15.51	40.21	6.21	$p < 0.01$
Fbc	NI-P 407 (2%)-PVP (2 %)	2.09	1.76	18.92	2.92	$p < 0.01$
Fabc	NI- β CD (1:2)-P 407 (2 %)-PVP (2 %)	38.49	32.35	41.01	6.34	$p < 0.01$
Fa	NI-HP β CD (1:2)	12.95	10.88	34.39	5.32	$p < 0.01$
Fab	NI-HP β CD (1:2)- P 407 (2 %)	61.42	51.61	44.29	6.85	$p < 0.01$
Fac	NI- HP β CD (1:2)- PVP (2 %)	44.89	37.72	42.75	6.61	$p < 0.01$
Fabc	NI- HP β CD (1:2)- P 407 (2 %)-PVP (2 %)	64.79	54.44	44.64	6.89	$p < 0.01$

NI –Nimesulide; CD – Cyclodextrins; P 407 – Poloxamer 407; PVP – Poly(vinyl pyrrolidone).

content indicated uniformity of drug content in each batch of solid inclusion complexes prepared. The dissolution rate of etoricoxib alone and from cyclodextrin complexes was studied in phosphate buffer of pH 7.4. The dissolution of etoricoxib followed first order kinetics with r (correlation coefficient) above 0.91. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[8]. The dissolution parameters are given in Table-3. The dissolution of etoricoxib was rapid and higher in the case of etoricoxib-cyclodextrin binary and ternary complex systems prepared when compared to etoricoxib pure drug as such.

The dissolution rate (K_1) values were subjected to ANOVA to find out the significance of the main and combined effects of cyclodextrins, poloxamer 407 and poly(vinyl pyrrolidone) on the dissolution rate of etoricoxib. ANOVA indicated that the individual main effects of cyclodextrins (β-cyclodextrin and HP β-cyclodextrin), poloxamer 407 and poly(vinyl pyrrolidone) and their combined effects in enhancing the dissolution rate (K_1) were highly significant ($P < 0.01$). β-Cyclodextrin alone gave a 1.18 fold increase in the dissolution rate of etoricoxib. β-Cyclodextrin in combination with poly(vinyl pyrrolidone) and poloxamer 407 gave respectively 3.0 and 7.4 fold increase in the dissolution rate of etoricoxib. HP β-cyclodextrin alone gave a 3.55 fold increase and in combination with poly(vinyl pyrrolidone) and poloxamer 407 it gave respectively 57.6 and 23.6 fold increase in the dissolution rate of etoricoxib.

The dissolution rate of nimesulide alone and from cyclodextrin complexes was studied in alkaline borate buffer of pH 8.4. The dissolution of nimesulide also followed first order kinetics with r (correlation coefficient) above 0.94. The dissolution parameters are given in Table-4. The dissolution of nimesulide was rapid and higher in the case of nimesulide -cyclodextrin binary and ternary complex systems prepared when compared to nimesulide pure drug as such. ANOVA indicated that the individual main effects of cyclodextrins (β-cyclodextrin and HP β-cyclodextrin), poloxamer 407 and poly(vinyl pyrrolidone) and their combined effects in enhancing the dissolution rate (K_1) of nimesulide were highly significant ($p < 0.01$). β-cyclodextrin alone gave a 9.63 fold increase in the dissolution rate of nimesulide. Whereas in combination with poly(vinyl pyrrolidone) and poloxamer 407 it gave

respectively 15.51 and 21.78 fold increase in the dissolution rate of nimesulide. Hydroxy propyl β-cyclodextrin alone gave a 10.88 fold increase and in combination with poly(vinyl pyrrolidone) and Poloxamer 407 it gave respectively 37.72 and 51.61 fold increase in the dissolution rate of nimesulide.

Thus combination of cyclodextrins with poloxamer 407 and poly(vinyl pyrrolidone) has markedly enhanced both the solubility and dissolution rate of etoricoxib and nimesulide, two BCS class II drugs. cyclodextrins (β-cyclodextrin and HP β-cyclodextrin) in combination with poloxamer 407 and poly(vinyl pyrrolidone) gave much higher enhancement in the solubility and dissolution rate of etoricoxib and nimesulide than is possible with them individually. Hence a combination of cyclodextrins with poloxamer 407 and poly(vinyl pyrrolidone) is recommended to enhance the solubility and dissolution rate of these BCS class II drugs.

Conclusion

Both the individual and combined effects of cyclodextrins (β-cyclodextrin and hydroxy propyl β-cyclodextrin), poloxamer 407 and poly(vinyl pyrrolidone) on the solubility and dissolution rate of etoricoxib and nimesulide were highly significant ($P < 0.01$). The cyclodextrins (β-cyclodextrin and HP β-cyclodextrin) in combination with poloxamer 407 and poly(vinyl pyrrolidone) gave much higher enhancement in the solubility and dissolution rate of etoricoxib and nimesulide than is possible with them individually. Hence a combination of cyclodextrins with poloxamer 407 and poly(vinyl pyrrolidone) is recommended to enhance the solubility and dissolution rate of these BCS class II drugs.

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