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ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF NIMESULIDE BY CYCLODEXTRINS, POLOXAMER AND PVP

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ABSTRACT

The objective of the study is to evaluate the effects of two cyclodextrins (βCD and HPβCD), surfactant (Poloxamer 407) and PVP on the solubility and dissolution rate of nimesulide in a series of 2^3 factorial experiments. The solubility of nimesulide in eight selected fluids containing CDs, Poloxamer 407 and PVP as per 2^3 factorial study was determined in each case. The solubility of nimesulide was markedly enhanced by βCD (4.12 fold), HPβCD (21.06 fold), Poloxamer 407 (5.37 fold) and PVP (24.9 fold) individually. βCD in combination with Poloxamer 407 and PVP gave respectively 5.44 and 26.31 fold increase in the solubility of nimesulide. HPβCD 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 nimesulide were highly significant ($P < 0.01$). Solid inclusion complexes of nimesulide-CDs (βCD and HPβCD) were prepared with and without Poloxamer 407 and PVP by kneading method as per 2^3-factorial design. ANOVA indicated that the individual main effects of CDs (βCD and HPβCD), Poloxamer 407 and PVP and their combined effects in enhancing the dissolution rate (K_1) were highly significant ($P < 0.01$). βCD alone gave a 9.63 fold increase in the dissolution rate of nimesulide. βCD in combination with PVP and Poloxamer 407 gave respectively 15.51 and 21.78 fold increase in the dissolution rate of nimesulide. HPβCD 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. Combination of CDs with Poloxamer 407 and PVP has markedly enhanced both the solubility and dissolution rate of nimesulide, a BCS class II drug.

Key words: Nimesulide, Cyclodextrins, Poloxamer 407, PVP, Solubility, Dissolution rate, Factorial study.

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INTRODUCTION

Nimesulide, 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. 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]. 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 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 (βCD and HPβCD), a surfactant (Poloxamer 407) and PVP on the solubility and dissolution rate of nimesulide were evaluated in a 2^3 factorial study.

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

Nimesulide was a gift sample 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 nimesulide

An UV spectrophotometric method based on the measurement of absorbance at 397

nm in an alkaline borate buffer of pH 8.4 was used for the estimation of nimesulide. 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 variance were found to be 0.8% 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 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 nimesulide by measuring absorbance at 397 nm. Shaking was continued until two consecutive estimations are the same. The solubility experiments were replicated for four times each (n = 4).

Preparation of nimesulide-CD complexes

Solid inclusion complexes of nimesulide-CD were prepared in 1 : 2 ratio with and without Poloxamer 407 (2%) and PVP (2%) by kneading method. Nimesulide, CDs (βCD or HPβCD), Poloxamer 407 and PVP 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 nimesulide as such and from CD complexes prepared was studied in 900 mL of 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°C was maintained throughout the study. Nimesulide or nimesulide-CD complex equivalent to 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, suitable diluted and assayed for nimesulide at 397 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 two CDs (βCD and

HP-βCD) (Factor A), Poloxamer 407 (Factor B) and PVP K30 (Factor C) on the aqueous solubility of nimesulide were evaluated in a series of 2^3-factorial experiments. For this purpose, two levels of CDs (0, 5 mM), two levels of Poloxamer 407 (0, 2%) and two levels of PVP (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 CDs (βCD or HPβCD) (a); water containing 2% Poloxamer 407 (b); water containing 5 mM CDs (βCD or HPβCD) and 2% Poloxamer 407 (ab); water containing 2% PVP (c); water containing 5 mM CDs (βCD or HPβCD) and 2% PVP (ac); water containing 2% Poloxamer 407 and 2% PVP (bc) and water containing 5 mM CDs (βCD or HPβCD) and 2% of each of Poloxamer 407 and PVP (abc) in each case.

The solubility of nimesulide in the above mentioned eight fluids was determined (n = 4) and the results are given in Table 1. The aqueous solubility of nimesulide was markedly enhanced by CDs, Poloxamer 407 and PVP alone and in combination.

The solubility data were subjected to Analysis of variance (ANOVA) to find out the significance of main and combined effects of CDs (βCD and HPβCD), Poloxamer 407 and PVP on the solubility of nimesulide. The results of ANOVA are shown in Tables 2 and 3. The individual and combined effects of βCD, HPβCD, Poloxamer 407 and PVP in enhancing the solubility of nimesulide were highly significant ($P < 0.01$). The solubility of nimesulide was markedly enhanced by βCD (4.12 fold), HPβCD (21.06 fold), Poloxamer 407 (5.37 fold) and PVP (24.9 fold) individually. The order of increasing solubility observed with various CDs and surfactants was PVP > HPβCD > Poloxamer 407 > βCD. β-Cyclodextrin in combination with Poloxamer 407 and PVP gave respectively 5.44 and 26.31 fold increase in the solubility of nimesulide. HPβCD 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. . HPβCD and PVP alone and in combination gave markedly higher enhancement in the solubility (21- 26 fold) of nimesulide.

To evaluate the individual and combined effects of CDs (βCD or HPβCD), Poloxamer 407 and PVP on the dissolution rate of nimesulide, solid inclusion complexes of nimesulide -CDs (βCD and HPβCD) were prepared with and without Poloxamer 407 and PVP as per 2^3-factorial design. For this purpose two levels of CDs (0 and 1 : 2 ratio of drug : CD) and two levels of each of Poloxamer 407 and PVP (0 and 2%) were selected and the corresponding eight treatments involved in the 2^3-factorial study were nimesulide pure drug (1); nimesulide- CD (βCD or HPβCD) (1 : 2) inclusion binary complex (a); nimesulide-Poloxamer 407 (2%) binary mixture (b); nimesulide-CD (βCD or HPβCD) (1 : 2) –

Poloxamer 407 (2%) ternary complex (ab); nimesulide – PVP (2%) binary mixture (c); nimesulide -CD (βCD or HPβCD) (1 : 2) – PVP (2%) ternary complex (ac); nimesulide - Poloxamer 407 (2%) – PVP (2%) ternary complex (bc) and nimesulide-CD (βCD or HPβCD) (1 : 2) – Poloxamer 407 (2%) – PVP (2%) complex (abc).

Table 1: 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)
Distilled water (1)	0.016 ± 0.0005	-
Water containing 5 mM βCD (a)	0.066 ± 0.02	4.125
Water containing 2% poloxamer (b)	0.086 ± 0.002	5.375
Water containing 5 mM βCD and 2% poloxamer (ab)	0.087 ± 0.003	5.437
Water containing 2% PVP (c)	0.399 ± 0.004	24.93
Water containing 5 mM βCD and 2% PVP (ac)	0.421 ± 0.012	26.31
Water containing 2% Poloxamer and 2% PVP (bc)	0.449 ± 0.011	28.06
Water containing 5 mM βCD, 2% Poloxamer and 2% PVP (abc)	0.481 ± 0.013	30.06
Water containing 5 mM HPβCD (a)	0.337 ± 0.001	21.06
Water containing 5 mM HPβCD and 2% poloxamer (ab)	0.085 ± 0.0005	5.312
Water containing 5 mM HPβCD and 2% PVP (ac)	0.423 ± 0.002	26.43
Water containing 5 mM HPβCD, 2% poloxamer and 2% PVP (abc)	0.518 ± 0.003	32.37

The CD complexes were prepared by kneading method. All the solid inclusion complexes of nimesulide-CD-Poloxamer 407 - PVP 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 nimesulide alone and from CD complexes was studied in alkaline borate buffer of pH 8.4 The dissolution of nimesulide 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-4. The dissolution of nimesulide was rapid and higher in the case of all nimesulide-CD (βCD or HPβCD) complexes prepared when compared to nimesulide as such.

Table 2: ANOVA of solubility data of nimesulide in various fluids as per 2^3–factorial study (βCD-Poloxamer 407-PVP)

Source of variation	D.F	S.S	M.S.S	F-RATIO	Significance
Total	31	1.148	0.037		
Treatment	7	1.147	0.163	2620.8	P < 0.01
a	1	0.0055	0.0055	88.62	P < 0.01
b	1	0.0202	0.0202	324.01	P < 0.01
ab	1	0.0007	0.0007	11.70	P < 0.01
c	1	1.1186	1.1186	17898.14	P < 0.01
ac	1	0.0000052	0.0000052	0.084	P > 0.05
bc	1	0.00018	0.00018	2.96	P > 0.05
abc	1	0.00172	0.00172	27.61	P < 0.01
Error	24	0.0015	0.0000625		

$F_{0.01\ (7,\ 24)} = 3.50$; $F_{0.05\ (7,\ 24)} = 2.43$; $F_{0.01\ (1,\ 24)} = 7.82$; $F_{0.05\ (1,\ 24)} = 4.26$

Table 3: ANOVA of solubility data of nimesulide in various fluids as per 2^3–Factorial study (HPβCD -Poloxamer 407-PVP)

Source of Variation	D. F.	S. S.	M. S. S.	F-ratio	Significance
Total	31	1.0713	0.0345		
Treatment	7	1.0707	0.1529	6116	P < 0.01
a	1	0.0852	0.0852	3411.38	P < 0.01

Cont…

Source of Variation	D. F.	S. S.	M. S. S.	F-ratio	Significance
b	1	0.0006	0.0006	26.64	P < 0.01
ab	1	0.0380	0.0380	1523.52	P < 0.01
c	1	0.8001	0.8001	32004.5	P < 0.01
ac	1	0.0258	0.0258	1035.12	P < 0.01
bc	1	0.0534	0.0534	2138.58	P < 0.01
abc	1	0.0671	0.0671	2686.44	P < 0.01
Error	24	0.0006	0.000025		

$F_{0.01\ (7,\ 24)} = 3.50$; $F_{0.05\ (7,\ 24)} = 2.43$; $F_{0.01\ (1,\ 24)} = 7.82$; $F_{0.05\ (1,\ 24)} = 4.26$

Table 4: Dissolution parameters of nimesulide-CD complex systems prepared as per 2^3 factorial study

NI–CD Complex	Composition	PD_{10} (%)	$K_1 \times 10^2$ (min^{-1})	Increase in K_1 (No. of folds)	DE_{30} (%)	Increase in DE_{30} (No. of folds)
F_1	NI	6.47	1.19	-	6.47	-
F_a	NI-βCD (1:2)	67.22	11.47	9.64	35.64	5.51
F_b	NI-P 407 (2%)	61.19	9.46	7.95	30.49	4.71
F_{ab}	NI-βCD (1:2)-P 407 (2%)	79.79	25.93	21.79	38.57	5.96
F_c	NI-PVP (2%)	30.52	2.04	1.71	16.29	2.52
F_{ac}	NI-βCD (1:2)-PVP (2%)	84.2	18.46	15.51	40.21	6.21
F_{bc}	NI-P 407 (2%)-PVP (2%)	32.48	2.09	1.76	18.92	2.92
F_{abc}	NI-βCD (1:2)-P407 (2%)-PVP (2%)	86.43	38.49	32.35	41.01	6.34
F_a	NI-HPβCD (1:2)	55.18	12.95	10.88	34.39	5.32
F_{ab}	NI-HPβCD (1:2)-P 407 (2%)	96.07	61.42	51.61	44.29	6.85

Cont…

NI–CD Complex	Composition	PD_{10} (%)	$K_1 \times 10^2$ (min^{-1})	Increase in K_1 (No. of folds)	DE_{30} (%)	Increase in DE_{30} (No. of folds)
F_{ac}	NI-HPβCD (1:2) PVP (2%)	92.33	44.89	37.72	42.75	6.61
F_{abc}	NI-HPβCD (1:2)-P407(2%)-PVP(2%)	97.30	64.79	54.44	44.64	6.89

NI- Nimesulide; CD - Cyclodextrins; P 407- Poloxamer 407; PVP - Poly vinyl pyrrolidone.

The dissolution rate (K_1) values were subjected to ANOVA to find out the significance of the main and combined effects of CDs, Poloxamer 407 and PVP on the dissolution rate of nimesulide. The results of ANOVA are shown in Tables 5 and 6. ANOVA indicated that the individual main effects of CDs (βCD and HPβCD), Poloxamer 407 and PVP and their combined effects in enhancing the dissolution rate (K_1) were highly significant ($P < 0.01$).

Table 5: ANOVA of dissolution rate of nimesulide-CD complex systems prepared as per 2^3–Factorial study (βCD–Poloxamer 407-PVP)

Source of variation	D.F	S.S	M.S.S	F-Ratio	Significance
Total	23	3710.01	161.30		
Treatments	7	3709.58	529.94	19683.19	$P < 0.01$
a	1	2373.38	2373.38	88153.03	$P < 0.01$
b	1	687.36	687.36	25530.42	$P < 0.01$
ab	1	256.51	256.51	9527.62	$P < 0.01$
c	1	63.63	63.63	2363.55	$P < 0.01$
ac	1	254.68	254.68	9459.74	$P < 0.01$
bc	1	2.619	2.619	97.28	$P < 0.01$
abc	1	71.36	71.36	2650.67	$P < 0.01$
Error	16	0.4308	0.0269		

$F_{0.01\,(1,\,16)} = 8.53$; $F_{0.05\,(1,\,16)} = 4.49$; $F_{0.01\,(7,\,16)} = 4.03$; $F_{0.05\,(7,\,16)} = 2.66$

Table 6: ANOVA of dissolution rate of Nimesulide-CD complex systems prepared as per 2^3–Factorial study (HPβCD-Poloxamer 407-PVP)

Source of variation	D.F	S.S	M.S.S	F-Ratio	Significance
Total	23	15932.1160	692.7007	-	-
Treatments	7	15931.7324	2275.9618	94921.3003	P < 0.01
a	1	10744.07	10744.07	448092.64	P < 0.01
b	1	2205.86	2205.86	91997.86	P < 0.01
ab	1	1351.67	1351.67	56372.82	P < 0.01
c	1	310.95	310.95	12968.82	P < 0.01
ac	1	656.17	656.17	27366.24	P < 0.01
bc	1	507.62	507.62	21171.17	P < 0.01
abc	1	155.36	155.36	6479.52	P < 0.01
Error	16	0.3836	0.0240	-	-

$F_{0.01\,(1,\,16)}$ = s 8.53; $F_{0.05\,(1,\,16)}$ = 4.49; $F_{0.01\,(7,\,16)}$ = 4.03; $F_{0.05\,(7,\,16)}$ = 2.66

βCD alone gave a 9.63 fold increase in the dissolution rate of nimesulide. βCD in combination with PVP and Poloxamer 407 gave respectively 15.51 and 21.78 fold increase in the dissolution rate of nimesulide. HPβCD 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. CDs (βCD and HPβCD) in combination with Poloxamer 407 and PVP gave much higher enhancement in the solubility and dissolution rate of nimesulide than is possible with them individually.

Thus the results of the study indicated that combination of CDs with Poloxamer 407 and PVP has markedly enhanced both the solubility and dissolution rate of nimesulide, a BCS Class II drug. Hence a combination of CDs with Poloxamer 407 and PVP is recommended to enhance the solubility and dissolution rate of nimesulide.

CONCLUSION

(i) Both the individual and combined effects of cyclodextrins (βCD and HPβCD), Poloxamer 407 and PVP on the solubility and dissolution rate of nimesulide were highly significant (P < 0.01).

(ii) The solubility of nimesulide was markedly enhanced by βCD (4.12 fold), HPβCD (21.06 fold), Poloxamer 407 (5.37 fold) and PVP (24.9 fold) individually.

(iii) βCD in combination with Poloxamer 407 and PVP gave respectively 5.44 and 26.31 fold increase in the solubility of nimesulide. HPβCD in combination with Poloxamer 407 and PVP gave respectively 5.31 and 26.43 fold increase in the solubility of nimesulide.

(iv) βCD alone gave a 9.63 fold increase in the dissolution rate of nimesulide and in combination with PVP and Poloxamer 407 it gave respectively 15.51 and 21.78 fold increase in the dissolution rate of nimesulide. HPβCD 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.

(v) CDs (βCD and HPβCD) in combination with Poloxamer 407 and PVP gave much higher enhancement in the solubility and dissolution rate of nimesulide than is possible with them individually

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