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Research Article

A FACTORIAL STUDY ON THE EFFECTS OF CYCLODEXTRINS, POLOXAMER 407 AND PVP ON THE SOLUBILITY AND DISSOLUTION RATE OF VALSARTAN

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ABSTRACT

The objective of the study is to evaluate the individual main effects and combined (or interaction) effects of cyclodextrins (βCD and HPβCD), surfactant (Poloxamer 407) and PVP on the solubility and dissolution rate of valsartan in a series of 2^3 factorial experiments. The solubility of valsartan in eight selected fluids containing CDs, Poloxamer 407 and PVP as per 2^3 factorial study was determined. The solubility of valsartan was marginally enhanced by βCD (1.23 fold) and HPβCD (1.378 fold). Whereas PVP gave a moderate enhancement (4.58 fold) and Poloxamer 407 gave markedly higher enhancement (20.58 fold) in the solubility of valsartan. Combination of CDs with Poloxamer 407 and PVP resulted in a much higher enhancement (4.70-15.68 fold) in the solubility of valsartan than the CDs alone. Solid inclusion complexes of valsartan-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 solubility and dissolution rate (K_1) were highly significant ($P < 0.01$). βCD alone and in combination with Poloxamer 407 and PVP gave only a marginal increase (1.37-1.64 fold) in the dissolution rate of valsartan. HPβCD alone and in combination with PVP gave a marked enhancement (5.54-6.62 fold) in the dissolution rate of valsartan. Though Poloxamer 407 has given highest enhancement (20.58 fold) in the solubility of valsartan, it gave only a marginal increase in the dissolution rate, K_1 (1.96 fold) and DE_{30} (1.34 fold). Combination of CDs with PVP has markedly enhanced the solubility and dissolution rate of valsartan, a BCS class II drug than is possible with them individually.

Keywords: Valsartan, Cyclodextrins, Poloxamer 407, PVP, Solubility, Dissolution rate, Factorial Study

INTRODUCTION

Valsartan, a water insoluble anti-hypertensive 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 cyclodextrins (βCD and HPβCD) and surfactant (Poloxamer 407) on the solubility and dissolution rate of valsartan 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.

MATERIALS AND METHODS

Valsartan was a gift sample from M/s. Dr. Reddy's Labs 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 Valsartan

A UV Spectrophotometric method based on the measurement of absorbance at 225 nm in a phosphate buffer of pH 6.8 was used for the estimation of valsartan. 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 0.65% and 1.10% 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 valsartan by measuring absorbance at 225 nm. Shaking was continued until two consecutive estimations are the same. The solubility experiments were replicated for four times each (n=4).

Preparation of Valsartan-CD complexes

Solid inclusion complexes of valsartan-CD were prepared in 1:2 ratio with and without Poloxamer 407 (2%) and PVP (2%) by kneading method. Valsartan, 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 valsartan as such and from CD complexes prepared 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 37±1°C was maintained throughout the study. Valsartan or valsartan-CD complex equivalent to 40 mg of valsartan 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 valsartan at 225 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 HPβCD) (Factor A), Poloxamer 407 (Factor B) and PVP K30 (Factor C) on the aqueous solubility of valsartan 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).

The solubility of valsartan in the above mentioned fluids was determined (n=4) and the results are given in Table-1. 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 valsartan. The results of ANOVA indicated that the individual and combined effects of βCD, HPβCD, Poloxamer 407 and PVP in enhancing the solubility of valsartan were highly significant ($P < 0.01$). The solubility of valsartan was marginally enhanced by βCD (1.23 fold) and HPβCD (1.378 fold). Whereas PVP gave a moderate enhancement (4.58 fold) and Poloxamer 407 gave markedly higher enhancement (20.58 fold) in the solubility of valsartan. The order of increasing solubility observed with various CDs and surfactants was Poloxamer 407 > PVP > HPβCD > βCD. Combination of CDs with Poloxamer 407 and PVP resulted in a much higher enhancement (4.70-15.68 fold) in the solubility of valsartan than the CDs alone.

Table 1: Solubility of valsartan in various fluids as per 2^3 - factorial study

Fluids (Code as per 2^3 - factorial experiment)	Solubility (mg/ml) (n=4) ($\bar{x} \pm sd$)	Increase in solubility (Number of folds)	Significance
Distilled water (1)	0.285 ± 0.0025	-	-
Water containing 5 mM βCD (a)	0.351 ± 0.011	1.23	P < 0.05
Water containing 2% Poloxamer (b)	5.868 ± 0.295	20.58	P < 0.01
Water containing 5 mM βCD and 2% Poloxamer (ab)	2.814 ± 0.036	9.87	P < 0.01
Water containing 2% PVP (c)	1.306 ± 0.027	4.58	P < 0.01
Water containing 5 mM βCD and 2% PVP (ac)	1.919 ± 0.021	6.73	P < 0.01
Water containing 2% Poloxamer and 2% PVP (bc)	2.471 ± 0.062	8.67	P < 0.01
Water containing 5 mM βCD, 2% Poloxamer and 2% PVP (abc)	4.47 ± 0.068	15.68	P < 0.01
Water containing 5 mM HPβCD (a)	0.393 ± 0.005	1.378	P < 0.01
Water containing 5 mM HPβCD and 2% Poloxamer (ab)	3.431 ± 0.048	12.03	P < 0.01
Water containing 5 mM HPβCD and 2% PVP (ac)	1.34 ± 0.022	4.70	P < 0.01
Water containing 5 mM HPβCD, 2% Poloxamer and 2% PVP (abc)	3.749 ± 0.104	13.15	P < 0.01

To evaluate the individual and combined effects of CDs (βCD or HPβCD), Poloxamer 407 and PVP on the dissolution rate of valsartan, solid inclusion complexes of valsartan-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 CD (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 valsartan pure drug (1); valsartan CD (βCD or HPβCD) (1:2) inclusion binary complex (a); valsartan - Poloxamer 407 (2%) binary mixture (b); valsartan-CD (βCD or HPβCD) (1:2) - Poloxamer 407 (2%) ternary complex (ab); valsartan - PVP (2%) binary mixture (c); valsartan-CD (βCD or HPβCD) (1:2) - PVP (2%) ternary complex (ac); valsartan - Poloxamer 407 (2%) - PVP (2%) ternary complex (bc) and valsartan-CD (βCD or HPβCD) (1:2) - Poloxamer 407 (2%) - PVP (2%) complex (abc).

The CD complexes were prepared by kneading method. All the solid inclusion complexes of valsartan-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 valsartan alone and from CD complexes was studied in phosphate buffer of pH 6.8. The dissolution of valsartan followed first order kinetics with r (correlation coefficient) above 0.92. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[8]. The dissolution parameters are given in Table-2. The dissolution of valsartan was rapid and higher in the case of Valsartan-CD binary and ternary complex systems prepared when compared to valsartan pure drug as such.

Table 2: Dissolution parameters of valsartan-CD complex systems prepared as per 2^3 factorial studies

VAL-CD complexes	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	VAL	52.25	4.30	-	19.23	-
F_a	VAL - βCD (1:2)	48.55	4.46	1.037	21.18	1.10
F_b	VAL - P 407 (2%)	71.75	8.43	1.96	25.82	1.34
F_{ab}	VAL - βCD (1:2) - P 407 (2%)	60.85	7.07	1.64	26.14	1.36
F_c	VAL - PVP (2%)	76.50	14.55	3.83	28.48	1.48
F_{ac}	VAL - βCD (1:2) - PVP (2%)	77.53	5.91	1.37	30.06	1.56
F_{bc}	VAL - P 407 (2%) - PVP (2%)	48.75	4.77	1.11	21.59	1.12
F_{abc}	VAL - βCD (1:2) - P 407(2%) - PVP (2%)	63.46	5.42	1.26	24.72	1.29
F_a	VAL - HPβCD (1:2)	72.79	23.84	5.54	27.74	1.44
F_{ab}	VAL - HPβCD (1:2) - P 407 (2%)	63.00	9.95	2.31	25.00	1.30
F_{ac}	VAL - HPβCD (1:2) - PVP (2%)	77.23	28.47	6.62	29.69	1.54
F_{abc}	VAL-HPβCD(1:2) - P 407(2%) - PVP(2%)	78.94	27.87	6.50	29.94	1.56

VAL - Valsartan; 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 valsartan. The results of ANOVA are shown in Tables 3 and 4. 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 and in combination with Poloxamer 407 and PVP gave only a marginal increase (1.37-1.64 fold) in the dissolution rate of valsartan. HPβCD alone and in combination with PVP gave a marked enhancement (5.54-6.62 fold) in the dissolution rate of valsartan. Though Poloxamer 407 has given highest enhancement (20.58 fold) in the solubility of valsartan, it gave only a marginal increase in the dissolution rate, K_1 (1.96 fold) and DE_{30} (1.34 fold).

Table 3: ANOVA of dissolution rate of valsartan 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	248.6618	10.8114	-	-
Treatments	7	243.7286	34.8183	112.9259	P < 0.01
a	1	31.6398	31.6398	102.6168	P < 0.01
b	1	4.6682	4.6682	15.1402	P < 0.01
ab	1	22.6322	22.6322	73.4029	P < 0.01
c	1	15.3613	15.3613	49.8212	P < 0.01
ac	1	17.2280	17.2280	55.8753	P < 0.01
bc	1	108.4083	108.4083	351.5992	P < 0.01
abc	1	43.7908	43.7908	142.0262	P < 0.01
Error	16	4.9332	0.3083	-	-

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

Table 4: ANOVA of dissolution rate of valsartan 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	2165.0321	94.1318	-	-
Treatments	7	2144.8237	306.4034	242.5942	P < 0.01
a	1	1269.1708	1269.1708	1004.8631	P < 0.01
b	1	150.5190	150.5190	119.1730	P < 0.01
ab	1	28.6298	28.6298	22.6676	P < 0.01
c	1	320.5744	320.5744	253.8141	P < 0.01
ac	1	96.7189	96.7189	76.5769	P < 0.01
bc	1	0.1043	0.1043	0.0826	P > 0.05
abc	1	279.1066	279.1066	220.9820	P < 0.01
Error	16	20.2085	1.2630	-	-

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

CONCLUSION

Combination of CDs (βCD and HPβCD) with Poloxamer 407 and PVP resulted in a much higher enhancement (4.70-15.68 fold) in the solubility of valsartan than the CDs alone. Though Poloxamer 407 has given highest enhancement (20.58 fold) in the solubility of valsartan, it gave only a marginal increase in the dissolution rate, K_1 (1.96 fold) and DE_{30} (1.34 fold). Combination of CDs with PVP has markedly enhanced both the solubility and dissolution rate of valsartan, a BCS class II drug. Hence a combination of CDs with PVP is recommended to enhance the solubility and dissolution rate of valsartan.

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