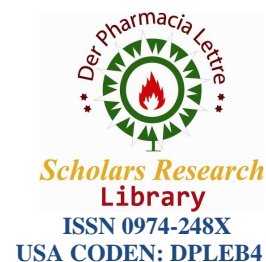




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A Factorial Study on the Effects of HP β Cyclodextrin, Poloxamer 407 and PVP K30 on the Solubility and Dissolution Rate of Pioglitazone

K. P. R. Chowdary* and K. Surya Prakasa Rao

University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam (A.P.) India

ABSTRACT

The objective of the study is to evaluate the individual main effects and combined (or interaction) effects of HP β cyclodextrin (HP β CD), surfactant (Poloxamer 407) and PVP K30 on the solubility and dissolution rate of pioglitazone in a series of 2³ factorial experiments. The solubility of pioglitazone in eight selected fluids containing HP β CD, Poloxamer 407 and PVP K30 as per 2³ factorial study was determined. HP β CD alone gave a marginal increase (2.54 fold) in the solubility of pioglitazone. Combination of HP β CD with Poloxamer 407 and PVP K30 resulted in a higher enhancement in the solubility of pioglitazone, 4.60 fold with HP β CD - Poloxamer 407 and 3.32 fold with HP β CD - PVP K30. Solid inclusion complexes of pioglitazone- HP β CD were prepared with and without Poloxamer 407 and PVP K30 by kneading method as per 2³-factorial design and were evaluated. ANOVA indicated that the individual main effects of HP β CD, Poloxamer 407 and PVP K30 and their combined effects in enhancing the solubility and dissolution rate (K_1) were highly significant ($P < 0.01$). Combination of HP β CD with Poloxamer 407 and PVP K30 also gave significantly higher dissolution rates (K_1) when compared to HP β CD alone. Poloxamer 407 and PVP K30 alone also gave a higher enhancement in the solubility and dissolution rate of pioglitazone. Hence a combination of HP β CD with Poloxamer 407 and PVP K30 or Poloxamer 407 and PVP K30 alone is recommended to enhance the solubility and dissolution rate of pioglitazone, a BCS class II poorly soluble drug.

Key words: Pioglitazone, HP β Cyclodextrin, Poloxamer 407, PVP K30, Solubility, Dissolution rate, Factorial Study.

INTRODUCTION

Pioglitazone, a widely prescribed anti-diabetic 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 HP β -cyclodextrin (HP β CD), surfactant (Poloxamer 407) and PVP K30 on the solubility and dissolution rate of pioglitazone were evaluated in a 2³ factorial study.

MATERIALS AND METHODS

Materials:

Pioglitazone was a gift sample from M/s. Hetero Drugs Ltd., Hyderabad. Hydroxy propyl β -Cyclodextrin was gift sample from M/s. Cerestar Inc., USA. Methanol (Qualigens), Poly vinyl pyrrolidone (PVP K30) and Poloxamer 407 were procured from commercial sources.

Methods:

Estimation of pioglitazone:

A UV Spectrophotometric method based on the measurement of absorbance at 269 nm in 0.1 N hydrochloric acid of pH 1.2 was used for the estimation of pioglitazone. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 1-10 μ g/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.68% and 1.02% 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 \pm 1 $^{\circ}$ 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 pioglitazone by measuring absorbance at 269 nm. Shaking was continued until two consecutive estimations are the same. The solubility experiments were replicated for four times each (n=4).

Preparation of pioglitazone-CD complexes:

Solid inclusion complexes of pioglitazone- HP β CD, Poloxamer 407 and PVP K30 were prepared as per 2³ - factorial study by kneading method. Pioglitazone, HP β CD, 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 $^{\circ}$ C until dry. The dried mass was powdered and sieved to mesh No. 120.

Dissolution rate study:

The dissolution rate of pioglitazone as such and from HP β CD complexes prepared was studied in 900 ml 0.1N hydrochloric acid of pH 1.2 using Disso 2000 (Labindia) 8-station dissolution test

apparatus with a paddle stirrer at 50 rpm. A temperature $37\pm 1^\circ\text{C}$ was maintained throughout the study. Pioglitazone or pioglitazone- HP β CD complex equivalent to 30 mg of pioglitazone was used in each test. Samples of dissolution media (5 ml) were withdrawn through a filter ($0.45\ \mu$) at different intervals of time, suitable diluted and assayed for pioglitazone at 269 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid. The dissolution experiments were replicated three times each ($n=3$).

Analysis of Data:

Solubility, dissolution rate and dissolution efficiency data were analyzed by Analysis of Variance (ANOVA) as per 2^3 factorial study.

RESULTS AND DISCUSSION

The individual main effects and combined (interaction) effects of HP β CD (Factor A), Poloxamer 407 (Factor B) and PVP K30 (Factor C) on the aqueous solubility of pioglitazone were evaluated in a series of 2^3 -factorial experiments. For this purpose, two levels of HP β CD (0, 5 mM), two levels of Poloxamer 407 (0, 2%) and two levels of PVP K30 (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 HP β CD (a); water containing 2% Poloxamer 407 (b); water containing 5 mM HP β CD and 2% Poloxamer 407 (ab); water containing 2% PVP K30 (c); water containing 5 mM HP β CD and 2% PVP K30 (ac); water containing 2% Poloxamer 407 and 2% PVP K30 (bc) and water containing 5 mM HP β CD and 2% of each of Poloxamer 407 and PVP K30 (abc).

The solubility of pioglitazone 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 HP β CD, Poloxamer 407 and PVP K30 on the solubility of pioglitazone. The results of ANOVA indicated that the individual and combined affects of HP β CD, Poloxamer 407 and PVP K30 in enhancing the solubility of pioglitazone were highly significant ($P < 0.01$). The solubility of pioglitazone was marginally enhanced by HP β CD (2.54 fold). Combination of HP β CD with Poloxamer 407 and PVP K30 resulted in a much higher enhancement in the solubility of pioglitazone, 4.60 fold with HP β CD - Poloxamer 407 and 3.32 fold with HP β CD - PVP K30 than with HP β CD alone. Poloxamer 407 and PVP K30 alone gave a moderate enhancement, 4.32 and 9.54 fold respectively in the solubility of pioglitazone.

To evaluate the individual and combined effects of HP β CD, Poloxamer 407 and PVP K30 on the dissolution rate of pioglitazone, solid inclusion complexes of pioglitazone- HP β CD were prepared with and without Poloxamer 407 and PVP K30 as per 2^3 -factorial design. For this purpose two levels of HP β CD (0 and 1:2 ratio of drug : HP β CD) and two levels of each of Poloxamer 407 and PVP K30 (0 and 2%) were selected and the corresponding eight treatments involved in the 2^3 -factorial study were pioglitazone pure drug (1); pioglitazone- HP β CD (1:2) inclusion binary complex (a); pioglitazone - Poloxamer 407 (2%) binary mixture (b); pioglitazone- HP β CD (1:2) - Poloxamer 407 (2%) ternary complex (ab); pioglitazone - PVP K30 (2%) binary mixture (c); pioglitazone- HP β CD (1:2) - PVP K30 (2%) ternary complex (ac); pioglitazone - Poloxamer 407 (2%) - PVP K30 (2%) ternary complex (bc) and pioglitazone-HP β CD (1:2) - Poloxamer 407 (2%) - PVP K30 (2%) complex (abc).

The CD complexes were prepared by kneading method. All the solid inclusion complexes of pioglitazone- HP β CD - Poloxamer 407 /PVP K30 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 pioglitazone alone and from HP β CD complexes was studied in 0.1 N hydrochloric acid of pH 1.2. The dissolution of pioglitazone followed first order kinetics with r (correlation coefficient) above 0.930. Dissolution efficiency (DE₃₀) values were calculated as suggested by Khan⁸. The dissolution parameters are given in Table-2. The dissolution of pioglitazone was rapid and higher in the case of pioglitazone- HP β CD binary and ternary complex systems prepared when compared to pioglitazone pure drug as such. The dissolution profiles are given in figure 1.

Table1: Solubility of Pioglitazone in Various Fluids as per 2³ - Factorial Study

Fluids (Code as per 2 ³ - Factorial Experiment)	Solubility (mg/ml) (n=4) ($\bar{x} \pm \text{sd}$)	Increase in Solubility (Number of Folds)
Distilled water (1)	0.122 \pm 0.08	-
Water containing 5 mM HP β CD (a)	0.310 \pm 0.024	2.54
Water containing 2% Poloxamer (b)	0.527 \pm 0.043	4.32
Water containing 5 mM HP β CD and 2% Poloxamer (ab)	0.562 \pm 0.064	4.60
Water containing 2% PVP (c)	1.165 \pm 0.054	9.54
Water containing 5 mM HP β CD and 2% PVP (ac)	0.405 \pm 0.026	3.32
Water containing 2% Poloxamer and 2% PVP (bc)	1.667 \pm 0.085	13.65
Water containing 5 mM HP β CD, 2% Poloxamer and 2% PVP (abc)	0.616 \pm 0.303	5.04

Table 2: Dissolution Parameters of Pioglitazone- HP β CD – Pol 407 – PVP K30 Complexes Prepared as per 2³ Factorial Study

PIO-CD Complexes	Composition	PD ₁₀ (%)	K ₁ × 10 ² (min ⁻¹)	Increase in K ₁ (no.of folds)	DE ₃₀ (%)	Increase in DE ₃₀ (no.of folds)
F ₁	PIO	23.49	2.25	-	9.20	-
F _a	PIO - HP β CD (1:2)	58.30	5.0	2.23	19.79	2.15
F _b	PIO - P 407 (2%)	80.89	11.16	4.73	24.08	2.62
F _{ab}	PIO - HP β CD (1:2) - P 407 (2%)	70.30	8.37	3.73	21.54	2.34
F _c	PIO - PVP (2%)	81.86	10.01	4.25	21.22	2.31
F _{ac}	PIO - HP β CD (1:2) - PVP (2%)	73.63	7.30	3.25	22.19	2.41
F _{bc}	PIO - P 407 (2%) - PVP (2%)	89.82	10.28	4.36	25.36	2.76
F _{abc}	PIO - HP β CD (1:2) - P 407(2%) - PVP (2%)	73.50	10.23	4.55	23.32	2.53

PIO - Pioglitazone; HP β CD - HP β Cyclodextrin; P 407 - Poloxamer 407; PVP - Poly vinyl pyrrolidone

The dissolution rate (K₁) values were subjected to ANOVA to find out the significance of the main and combined effects of HP β CD, Poloxamer 407 and PVP K30 on the dissolution rate of pioglitazone. ANOVA indicated that the individual main effects of HP β CD, Poloxamer 407 and PVP K30 and their combined effects in enhancing the dissolution rate (K₁) were highly significant (P < 0.01). Pioglitazone – HP β CD complexes alone gave a dissolution rate (K₁) of 0.050 min⁻¹. When HP β CD is combined with Poloxamer 407 and PVP K30 the dissolution rate (K₁) was significantly enhanced to 0.0837 and 0.0730 min⁻¹ respectively with pioglitazone-HP β CD – Poloxamer 407 and pioglitazone- HP β CD – PVP K30 solid inclusion complexes. Poloxamer 407 (F_b) and PVP K30 (F_c) alone and in combination (F_{bc}) also gave higher dissolution rates in the range 0.10 – 0.1116 min⁻¹. DE₃₀ values were also much higher in the case of HP β CD solid complexes when compared to pioglitazone pure drug. Thus Poloxamer 407

and PVP K30 or a combination of HP β CD with Poloxamer 407 and PVP K30 is recommended to enhance the dissolution rate of pioglitazone.

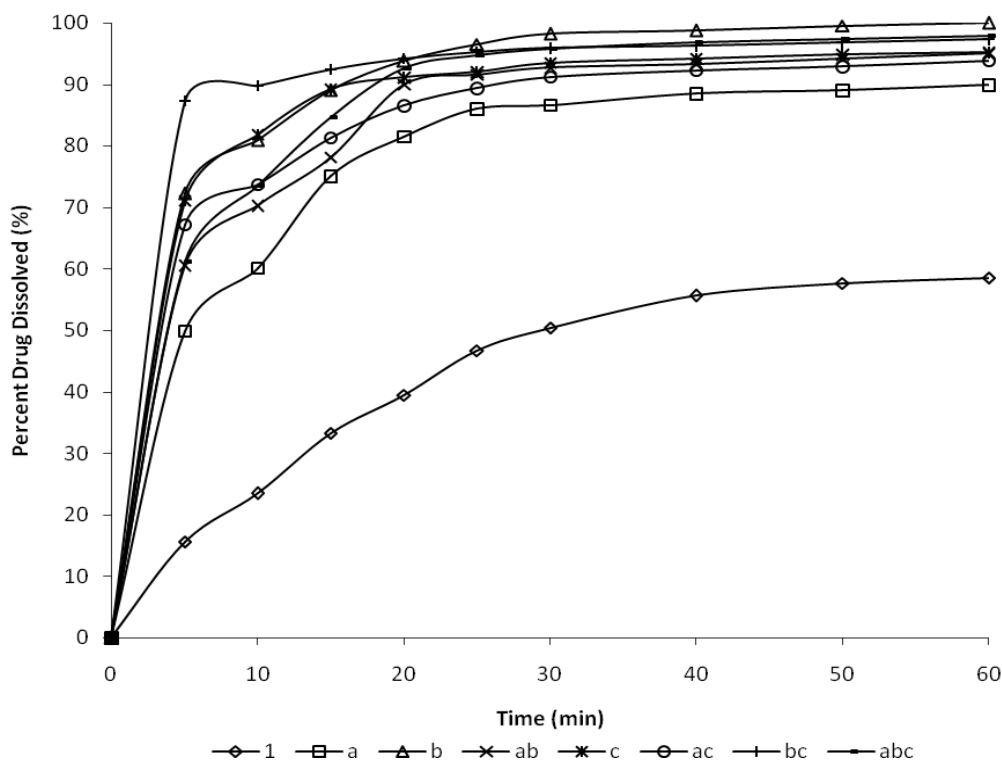


Figure 1: Dissolution Profiles of Pioglitazone – HP β CD Complexes Prepared by Employing HP β CD, Poloxamer 407 and PVP as per 2³ Factorial Design

CONCLUSION

The individual and combined effects of HP β CD, Poloxamer 407 and PVP K30 in enhancing the solubility and dissolution rate of pioglitazone were highly significant ($P < 0.01$). HP β CD alone gave a marginal increase (2.54 fold) in the solubility of pioglitazone. Combination of HP β CD with Poloxamer 407 and PVP K30 resulted in a higher enhancement in the solubility of pioglitazone, 4.60 fold with HP β CD- Poloxamer 407 and 3.32 fold with HP β CD- PVP K30. Combination of HP β CD with Poloxamer 407 and PVP K30 also gave significantly higher dissolution rates (K_1) when compared to HP β CD alone. Poloxamer 407 and PVP K30 alone also gave a higher enhancement in the solubility and dissolution rate of pioglitazone. Hence a combination of HP β CD with Poloxamer 407 and PVP K30 or Poloxamer 407 and PVP K30 alone is recommended to enhance the solubility and dissolution rate of pioglitazone, a poorly soluble BCS class II drug.

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