ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

A Factorial Study on the Effects of β- Cyclodextrin and Poloxamer 407 on the Dissolution Rate of Valsartan from CD Complexes and their Tablets

KPR Chowdary*, K Surya Prakasa Rao

University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam-530003 (AP), India.

ABSTRACT

The objective of the study is to evaluate the individual main and combined (or interaction) effects of β cyclodextrin (βCD) and surfactant (Poloxamer 407) on the dissolution rate of valsartan from CD complexes and from their tablet formulations in a series of 2^2 factorial experiments. Solid inclusion complexes of Drug- βCD were prepared with and without Poloxamer 407 by kneading method as per 2^2-factorial design and were evaluated for dissolution rate and efficiency. ANOVA indicated that the individual main effects of βCD and Poloxamer 407 and their combined effects in enhancing the dissolution rate (K_1) and DE_{30} were highly significant ($P < 0.01$). Poloxamer 407 alone gave higher enhancement in the dissolution rate of Valsartan (1.96 fold) than βCD alone and combination of βCD and Poloxamer 407. The feasibility of formulating valsartan- βCD - Poloxamer 407 solid inclusion complexes into tablets was also evaluated. To evaluate the individual and combined effects of βCD and Poloxamer 407 on the dissolution rate of valsartan tablets, tablets each containing 40 mg of valsartan were formulated employing inclusion complexes of drug- βCD - Poloxamer 407 as per 2^2 factorial design. All the prepared tablets were evaluated for hardness, friability and disintegration time and dissolution rate of valsartan. Valsartan dissolution was rapid and higher from the tablets formulated employing βCD, Poloxamer 407 alone and βCD- Poloxamer 407 inclusion complexes when compared to the tablets containing valsartan alone (plain tablets, F_1). Valsartan tablets formulated employing Poloxamer 407 alone (F_b) gave highest enhancement in the dissolution rate (4.36 fold) and DE_{30} (1.17 fold) of the tablets than those formulated employing βCD alone and combination of βCD and Poloxamer 407. Poloxamer 407 alone gave highest enhancement in the dissolution rate of both valsartan inclusion complexes and valsartan tablets. Drug- βCD- Poloxamer 407 inclusion complexes and their tablets also gave markedly enhanced dissolution rate when compared to those formulated employing βCD alone. Tablets formulated employing valsartan-βCD exhibited poor disintegration and dissolution characteristics. As such Poloxamer 407 alone and in combination with βCD is recommended to enhance the dissolution rate of valsartan tablets.

Key words: Valsartan tablets, β Cyclodextrin, Poloxamer 407, Dissolution rate, Factorial Study.

Corresponding author:

ISSN: 0975-8585

INTRODUCTION

About 95% of the newly developed organic drugs belong to class II under BCS and exhibit low and variable oral bioavailability due to their poor aqueous solubility. They are practically in soluble 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 (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 such as Poloxamer 407 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 dissolution rate from CD complexes and their tablets. In the present investigation the individual main effects and combined (or interaction) effects of β cyclodextrins (βCD) and surfactant (Poloxamer 407) on the dissolution rate of valsartan from CD complexes and their tablet formulations were evaluated in 2^2 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.

MATERIALS AND METHODS

Materials

Valsartan and crosspovidone were gift samples from M/s Dr. Reddy Laboratories, Hyderabad. β- Cyclodextrin was a gift sample from M/s. Cerestar Inc., USA. Methanol (Qualigens) and Poloxamer 407, lactose IP, talc and magnesium stearate 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.

Preparation of Drug-βCD Complexes

Solid inclusion complexes of Drug-βCD were prepared in 1:2 ratio with and without Poloxamer407 (2%) by kneading method. Valsartan, βCD and Poloxamer 407 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^{o}C until dry. The dried mass was powdered and sieved to mesh No. 120.

Preparation of Valsartan- βCD - Poloxamer 407 Tablets

Compressed tablets each containing 40 mg of valsartan were prepared by wet granulation method employing inclusion complexes of drug- βCD - Poloxamer 407 as per 2^2 factorial design. The formulae of valsartan tablets prepared as per 2^2 factorial study are given in Table-2. Lactose was used as filler. Crosspovidone (5%), talc (2%) and magnesium stearate (2%) were incorporated, respectively as disintegrant and lubricants. Purified water was used as granulating fluid in wet granulation method. The tablet granules were compressed into tablets on a 16- station tablet punching machine (M/s Cadmach machineries Pvt. Ltd., Ahmedabad) to a hardness of 5- 6 kg/cm^2.

Evaluation of Tablets

Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time of the tablets prepared was determined using a Thermonic tablet disintegration test machine using water as test fluid.

Dissolution Rate Study

The dissolution rate of valsartan as such and from βCD complexes and their tablets prepared was studied in 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^{o}C was maintained throughout the study. Drug or Drug-βCD complexes or Drug -βCD tablets equivalent to 40 mg of valsartan was used in each test. Samples of dissolution media (5ml) were withdrawn through a filter (0.45µ) at different intervals of time, suitably diluted and assayed at 225 nm for valsartan. The samples of dissolution fluid withdrawn at each time were replaced with fresh fluid. The dissolution experiments were replicated three times each (n=3).

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Analysis of Results

Dissolution data were subjected to analysis of variance (ANOVA) of factorial experiments to find out the significance of the individual main and combined effects of the factors involved i.e., βCD and Poloxamer 407.

RESULTS AND DISCUSSION

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

The βCD complexes were prepared by kneading method. All the solid inclusion complexes of Drug- βCD- Poloxamer 407 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.

Table 1: Dissolution Parameters of Drug- β CD- Poloxamer 407 Complex Systems of Valsartan Prepared as per 2^2 Factorial Study

Complex Systems	$K_1 x 10^2$ (min^{-1})	Increase in K_1 (no.of folds)	DE_{30} (%)	Increase in DE_{30} (no.of folds)	Significance of K_1 and DE_{30}
Val **(1)**	4.3	-	19.23	-	-
Val –βCD (1:2) **(a)**	4.46	1.04	21.18	1.10	P < 0.01
Val -P 407 (2%) **(b)**	8.43	1.96	25.82	1.34	P < 0.01
Val- βCD (1:2)-P407 (2%)**(ab)**	7.07	1.64	26.14	1.36	P < 0.01

Val - Valsartan; β CD -β Cyclodextrin; P 407- Poloxamer407

The dissolution rate of valsartan as such and from βCD complexes prepared was studied in 900 ml of phosphate buffer of pH 6.8. Dissolution followed first order kinetics with r (correlation coefficient) above 0.9402. The first order dissolution rates (K_1) were calculated in each case. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan [8]. The dissolution parameters are summarised in Table 1.

Valsartan dissolution was rapid and higher in the case of Drug – βCD binary and ternary complex systems prepared when compared to pure drug.

The dissolution rate (K_1) and DE_{30} values were subjected to ANOVA to find out the significance of the main and combined effects of βCD and Poloxamer 407 on the dissolution rate and efficiency of valsartan. The results of ANOVA indicated that the individual main effects of βCD and Poloxamer 407 and their combined effects in enhancing the dissolution rate (K_1) and

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DE_{30} were highly significant ($P < 0.01$). Poloxamer 407 alone gave higher enhancement in the dissolution rate of Valsartan (1.96 fold) than βCD alone and combination of βCD and Poloxamer 407.

Table 2: Formulae of Valsartan Tablets Prepared Employing Drug- β CD – Poloxamer 407 as per 2^2 Factorial Study

Ingredient (mg/tablet)	F_1	F_a	F_b	F_{ab}
Valsartan (1)	40.0	-	-	-
Val - βCD (1:2) (a)	-	120.0	-	-
Val - P 407(2%) (b)	-	-	40.8	-
Val - βCD - P 407(2%) (ab)	-	-		122.4
Cross povidone	11.0	11.0	11.0	11.0
Talc	4.4	4.4	4.4	4.4
Magnesium Stearate	4.4	4.4	4.4	4.4
Lactose	160.2	80.2	159.4	77.8
Water as granulating fluid	qs	qs	qs	qs
Total weight	220.0	220.0	220.0	220.0

Table 3: Physical Properties and Dissolution Characteristics of Valsartan Tablets Prepared as per 2^2 Factorial Study

Formulation	Hardness (Kg/Sq. cm)	Friability (% weight loss)	DT (min-sec)	Drug Content (mg/tablet)	Dissolution Rate(K_1) (min^{-1})	DE_{30} (%)
F_1	5.5	0.15	0-40	39.65	0.0151	19.81
F_a	5.0	0.25	12-00	40.05	0.0291	17.20
F_b	5.5	0.16	3-30	39.45	0.0658	22.34
F_{ab}	5.5	0.45	9-12	39.85	0.0525	19.74

The feasibility of formulating valsartan- βCD - Poloxamer 407 solid inclusion complexes into tablets was also evaluated. To evaluate the individual and combined effects of βCD and Poloxamer 407 on the dissolution rate of valsartan tablets, tablets each containing 40 mg of valsartan were formulated employing inclusion complexes of drug- βCD - Poloxamer 407 as per 2^2 factorial design. For this purpose two levels of βCD (0 and 1: 2 ratio of Drug : βCD) and two levels of Poloxamer 407 (0 and 2%) were selected and the corresponding four treatments involved in the formulation of tablets as per 2^2-factorial study were valsartan pure drug (1); Drug- βCD (1:2) inclusion binary complex (a); Drug - Poloxamer 407 (2%) binary mixture (b); Drug- βCD (1:2) – Poloxamer 407 (2%) ternary complex (ab). The formulae of valsartan tablets prepared as per 2^2 factorial study are given in Table-2. All the prepared tablets were evaluated for hardness, friability and disintegration time and dissolution rate of valsartan. The physical properties and dissolution characteristics of the tablets prepared are summarised in Table 3.

All the tablets prepared were found to contain valsartan within 100±5% of the labelled claim. Hardness of the tablets was in the range 5.0- 5.5 Kg/cm^2. Percentage weight loss in the friability test was less than 0.45% in all the cases. Tablets F_1 (plain tablets) and tablets formulated employing Poloxamer 407 alone (F_b) disintegrated rapidly respectively in 40 sec and 3 min 30 sec. Whereas tablets formulated employing βCD alone and in combination with

ISSN: 0975-8585

Poloxamer 407 disintegrated slowly in 9- 12 min. However all tablets formulated fulfilled the official (IP) disintegration time specification of uncoated tablets.

Table 4: Dissolution Parameters of Valsartan Tablets Formulated Employing Drug- β CD – Poloxamer 407 as per 2^2 Factorial Study

Tablets	$K_1 x 10^2$ (min^{-1})	Increase in K_1 (no.of folds)	DE_{30} (%)	Increase in DE_{30} (no.of folds)	Significance of K_1 and DE_{30}
Val (F_1)	1.51	-	19.81	-	-
Val –βCD (1:2) (F_a)	2.91	1.93	17.20	0.86	$P < 0.01$
Val -P 407 (2%) (F_b)	6.58	4.36	23.34	1.17	$P < 0.01$
Val- βCD (1:2)-P407 (2%) (F_{ab})	5.25	3.47	19.74	0.99	$P < 0.01$

Val - Valsartan; β CD -β Cyclodextrin; P 407- Poloxamer407

The dissolution characteristics of the valsartan tablets prepared employing Drug- βCD- Poloxamer 407 inclusion complexes are shown in Table 4. Valsartan dissolution was rapid and higher from the tablets formulated employing βCD, Poloxamer 407 alone and βCD- Poloxamer 407 inclusion complexes when compared to the tablets containing valsartan alone (plain tablets, F_1). The dissolution rate (K_1) and DE_{30} values were subjected to ANOVA to find out the significance of the main and combined effects of βCD and Poloxamer 407 on the dissolution rate and efficiency of valsartan tablets. The results of ANOVA indicated that the individual main effects of βCD and Poloxamer 407 and their combined effects in enhancing the dissolution rate (K_1) and DE_{30} of the tablets were highly significant ($P < 0.01$). Valsartan tablets formulated employing Poloxamer 407 alone (F_b) gave highest enhancement in the dissolution rate (4.36 fold) and DE_{30} (1.17 fold) of the tablets than those formulated employing βCD alone and combination of βCD and Poloxamer 407.

CONCLUSION

Poloxamer 407 alone gave highest enhancement in the dissolution rate of both valsartan inclusion complexes and valsartan tablets. Drug- βCD- Poloxamer 407 inclusion complexes and their tablets also gave markedly enhanced dissolution rate when compared to those formulated employing βCD alone. Tablets formulated employing valsartan- βCD exhibited poor disintegration and dissolution characteristics. As such Poloxamer 407 alone and in combination with βCD are recommended to enhance the dissolution rate of valsartan tablets.

ACKNOWLEDGEMENTS

Authors are thankful to University Grants Commission, New Delhi for providing financial assistance in the form of UGC- JRF to K. Surya Prakasa Rao.

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