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Research Article

OPTIMIZATION OF βCD AND SUPERDISINTEGRANT LEVELS FOR FORMULATION OF VALSARTAN IR TABLETS BY 2^2 FACTORIAL DESIGN

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Abstract: Valsartan, a widely prescribed anti hypertensive drug belongs to class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It needs enhancement in the dissolution rate in its formulation development. Complexation with β-cyclodextrin (βCD) and use of superdisintegrant (crosspovidone or Primojel) are tried for enhancing the dissolution rate of valsartan tablets. The objective of the present study is to optimize the βCD and superdisintegrant levels for formulation of valsartan IR tablets by 2^2 factorial design to achieve NLT 85% dissolution in 15 min. A total of eight valsartan IR tablet formulations were prepared using selected combinations of the two factors as per 2^2 factorial design. Valsartan tablets were prepared by direct compression method and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics. The dissolution rate (K_1) values were analysed as per ANOVA of 2^2 factorial design to find the significance of the individual and combined effects of the two factors (βCD and superdisintegrant) involved on the dissolution rate of valsartan tablets formulated.The individual and combined effects of βCD and superdisintegrant (crosspovidone or Primojel) on the dissolution rate (K_1) of valsartan tablets are highly significant ($P<0.01$).Valsartan tablets formulated employing superdisintegrant (crosspovidone or Primojel) at a level of 30% of drug content and βCD in 1:1 ratio of drug: βCD (F_a) disintegrated rapidly within 30 seconds and gave very rapid dissolution of valsartan fulfilling the target dissolution of NLT 85% in 15 min. Higher levels of βCD and lower levels of superdisintegrants gave low dissolution rates with both the superdisintegrants. The polynomial equation describing the relationship between the response i.e. percent drug dissolved in 15min (Y) and the levels of superdisintegrant (X_1) and βCD (X_2) based on the observed results is $Y = 42.42+27.795 (X_1) -12.705 (X_2) - 17.09 (X_1 X_2)$ in the case of formulations based on βCD and crosspovidone and $Y = 39.603+24.702 (X_1) -7.652 (X_2) -13.35 (X_1 X_2)$ in the case of formulations based on βCD and Primojel. βCD in 1:1 ratio of drug: βCD and superdisintegrant (crosspovidone or Primojel) at a level of 30% of drug content are the optimized levels for formulation of valsartan IR tablets with dissolution of NLT 85% in 15 min.

Key words: Valsartan tablets, optimization, β-cyclodextrin, superdisintegrants, factorial design

INTRODUCTION

About 95% of all new potential therapeutic drugs (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pH and consequent low dissolution rate. These drugs are classified as class II drugs under BCS with low solubility and high permeability characters. These BCS class II drugs pose challenging problems in their pharmaceutical product development process. Valsartan, a widely prescribed anti hypertensive drug belongs to class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Because of poor aqueous solubility and dissolution rate it poses challenging problems in its tablet formulation development. It needs enhancement in the dissolution rate in its formulation development.

Several techniques[1] such as micronisation, cyclodextrin-complexation, use of surfactants, solubilizers and super disintegrants, solid dispersion in water soluble and water dispersible carriers, microemulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble BCS class II drugs. Among the various approaches cyclodextrin complexation[2, 3] and use of superdisintegrants[4, 5] such as crosspovidone and sodium starch glycolate (Primojel) are simple industrially useful approaches for enhancing the dissolution rate of poorly soluble drugs in their formulation development. In the present study complexation with β-cyclodextrin (βCD) and use of superdisintegrant (crosspovidone or Primojel) are tried for optimizing the formulation of valsartan IR tablets. Valsartan IR tablets with NLT 85% dissolution in 15min are aimed.

Optimization[6] of pharmaceutical formulations involves choosing and combining ingredients that will result in a pharmaceutical product whose attributes conform with certain pre requisite requirements. The choice of nature, qualities and quantities of excipients to be used in a new formulation shall be on a rational basis. The application of optimization techniques in formulation development is relatively new. The optimization process is facilitated by applying factorial designs. The objective of the present study is optimization of βCD and superdisintegrant levels in the formulation development of valsartan IR tablets with NLT 85% dissolution in 15min by 2^2 factorial design.

EXPERIMENTAL

Materials:

Valsartan was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. B-cyclodextrin, Crosspovidone and Primojel were gift samples from M/s Natco Pharma Ltd., Hyderabad. Talc and magnesium stearate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Methods:

Estimation of Valsartan:

An UV Spectrophotometric method based on the measurement of absorbance at 250 nm in 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 0.8% and 1.45% respectively. No interference by the excipients used in the study was observed.

Formulation of Valsartan Tablets:

For optimization of valsartan IR tablets as per 2^2 factorial design the βCD and superdisintegrant (crosspovidone or Primojel) are considered as the two factors. The two levels of the factor A (superdisintegrant) are 2% and 30% of drug content and the two levels of the factor B (βCD) are 1:1 and 1:5 ratio of drug: βCD. Four valsartan IR tablet formulations employing selected combinations of the two factors i.e. superdisintegrant and βCD as per 2^2 factorial design were formulated and prepared by direct compression method. One series of tablets were prepared using crosspovidone and another series of tablets were prepared using Primojel.

Preparation of Valsartan Tablets:

Valsartan (100 mg) tablets were prepared by direct compression method as per the formula given in Table 1.The required quantities of valsartan, βCD and superdisintegrant (crosspovidone or Primojel) as per the formula in each case were blended thoroughly in a closed polyethene bag. Talc and magnesium stearate were the added by passing through mesh no.80 and blended. The blend of ingredients was compressed directly into tablets using an 8- station RIMEK tablet punching machine employing 9mm or 12mm round and flat punches.

Evaluation of Tablets:

All the valsartan tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as follows.

Hardness:

The hardness of prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm^2.

Friability:

The friability of the tablets was measured in a Roche friabilator using the formula

Friability (%) = [(Initial weight- Final weight) / (Initial weight)] x 100

Drug Content:

Weighed tablets (5) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 20 mg of valsartan was taken into 100 ml volumetric flask, dissolved in phosphate buffer of pH 6.8 and the solution was filtered through Whatman filter paper no.41. The filtrate was collected and suitably diluted with phosphate buffer of pH 6.8 and assayed for valsartan at 250 nm.

Disintegration time:

Disintegration time of the tablets was determined using single unit disintegration test apparatus (Make: Paramount) employing water as test fluid.

Dissolution Rate Study:

Dissolution rate of valsartan tablets prepared was studied in phosphate buffer of pH 6.8 (900 ml) employing eight station dissolution rate test apparatus (LABINDIA, DS 8000) using paddle stirrer at 50 rpm and at a temperature of 37°C ± 1°C. One tablet was used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter at different time intervals and assayed for valsartan at 250 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh drug free dissolution fluid and a suitable correction was made for the amount of drug present in the samples withdrawn in calculating percent dissolved at various times. Each dissolution experiment was run in triplicate (n=3).

Analysis of Data:

The dissolution data were analyzed as per zero order and first order kinetic models. Dissolution efficiency (DE_{30}) values were estimated as suggested by Khan[7]. Dissolution rate (K_1) values were analyzed as per ANOVA of 2^2 factorial experiments.

RESULTS AND DISCUSSION

The objective of the present study is to optimize the βCD and superdisintegrant levels for formulation of valsartan IR tablets by 2^2 factorial design to achieve NLT 85% dissolution in 15 min. Superdisintegrant (crosspovidone or Primojel) and βCD are considered as the two factors involved in the2^2 factorial design. The two levels of the factor A (superdisintegrant) are 2% and 30% of drug content and the two levels of factor B (βCD) are 1:1 and 1:5 ratio of drug: βCD. Two superdisintegrants namely crosspovidone and Primojel were used along with βCD. A total of eight valsartan IR tablet formulations were prepared using selected combinations of the two factors as per 2^2 factorial design. One series of tablets were formulated using crosspovidone and another series of tablets were formulated using Primojel. All the tablets were prepared by direct compression method as per the formulae given in Table 1 and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics. The dissolution rate (K_1) values were analysed as per ANOVA of 2^2 factorial design to find the significance of the individual and combined effects of the two factors involved on the dissolution rate of valsartan tablets formulated.

The physical parameters of the valsartan IR tablets prepared are given in Table 2. The hardness of the tablets was in the range 4.5-5.0 kg/cm^2. Weight loss in the friability test was less than 0.92 % in all the cases. Valsartan content of the tablets prepared was within 100±3 %. Much variations were observed in the disintegration and dissolution characteristics of

the valsartan tablets prepared. The disintegration times were in the range 30 sec to 8 min 40 sec. Valsartan tablets (CF_a and PF_a) formulated employing superdisintegrant at 30% of drug content and βCD in 1:1ratio of drug: βCD disintegrated rapidly with in 30 sec in both the cases. All other tablets disintegrated rather slowly in about 5-9 min. As βCD level is increased the disintegration time is increased, whereas as superdisintegrant concentration is increased the disintegration time is reduced. However, all the valsartan tablets prepared fulfilled the official (IP 2010) requirements with regard to drug content, hardness, friability and disintegration time specified for uncoated tablets.

Dissolution rate of valsartan tablets prepared was studied in phosphate buffer pH 6.8. The dissolution profiles of the tablets are shown in Fig.1and 2 and the dissolution parameters are given in Table 3. Dissolution of valsartan from all the tablets prepared followed first order kinetics with coefficient of determination (R^2) values above 0.942. The first order dissolution rate constant (K_1) values were estimated from the slope of the first order linear plots. Much variations were observed in the dissolution rate (K_1) and DE_{30} values of the tablets prepared due to formulation variables. ANOVA (Tables 4 and 5) of K_1 values indicated that the individual and combined effects of the two factors, βCD and superdisintegrant in influencing the dissolution rate of the tablets are highly significant ($P < 0.01$) in both the cases.

Valsartan tablets (CF_a and PF_a) which are prepared employing superdisintegrant at 30% of drug content and βCD in 1:1 ratio of drug: βCD gave very rapid dissolution of valsartan than others. Formulations PF_a and CF_a respectively gave 85.35% and 100% dissolution in 15min. Higher levels of βCD and lower levels of superdisintegrants gave low dissolution of valsartan tablets. The increasing order of dissolution rate (K_1) observed with various formulations was $CF_a > CF_{ab} > CF_b > CF_1$ and $PF_a > PF_{ab} > PF_b > PF_1$. The polynomial equation describing the relationship between the response i.e. percent drug dissolved in 15min (Y) and the levels of superdisintegrant (X_1) and βCD (X_2) based on the observed results is $Y = 42.42+27.795 (X_1) -12.705 (X_2) -17.09 (X_1 X_2)$ in the case of formulations based on βCD and crosspovidone and $Y = 39.603+24.702 (X_1) -7.652 (X_2) -13.35 (X_1 X_2)$ in the case of formulations based on βCD and Primojel.

The results of the study indicated that βCD in 1:1 ratio of drug: βCD and superdisintegrant (crosspovidone or Primojel) at a level of 30% of drug content are the optimized levels for formulation of valsartan IR tablets with dissolution of NLT 85% in 15 min.

Table 1: Formulae of Valsartan Tablets Prepared as Per 2^2 Factorial Design employing βCD and Superdisintegrants

Ingredient (mg/tab)	CF_1	CF_a	CF_b	CF_{ab}	PF_1	PF_a	PF_b	PF_{ab}
Valsartan	100	100	100	100	100	100	100	100
βCD	100	100	500	500	100	100	500	500
Crosspovidone	2	30	2	30	-	-	-	-
Primojel	-	-	-	-	2	30	2	30
Talc	4	4.6	12	12.6	4	4.6	12	12.6
Magnesium stearate	4	4.6	12	12.6	4	4.6	12	12.6
Total weight (mg)	210	239.2	626	655.2	210	239.2	626	655.2

Table 2: Physical Parameters of Valsartan Tablets Prepared as per 2^2 Factorial Design employing βCD and Superdisintegrants

Formulation	Hardness (Kg/cm^2)	Friability (% Wt loss)	Disintegration Time (min-sec)	Drug Content (mg/tablet)
CF_1	4.5	0.75	7-20	98.2
CF_a	4.5	0.65	0-30	99.5
CF_b	5.0	0.92	8-40	99.8
CF_{ab}	5.0	0.82	5-10	98.5
PF_1	4.5	0.73	6-50	98.4
PF_a	5.0	0.68	0-25	99.6
PF_b	5.0	0.91	8-0	99.7
PF_{ab}	4.5	0.80	5-20	98.9

Table 3: Dissolution Parameters of Valsartan Tablets Prepared as per 2^2 Factorial Design employing βCD and Superdisintegrants

Formulation	PD_{15} (%)	DE_{30} (%)	$K_1 X 10^3$ (min^{-1})
CF_1	9.03	8.66	6.16
CF_a	100	91.7	782
CF_b	18.99	19.56	13.90
CF_{ab}	39.82	36.7	32.56
PF_1	9.23	9.26	5.86
PF_a	85.35	65.13	95.73
PF_b	20.64	25.1	15.36
PF_{ab}	43.33	40.86	38.50

Table 4: ANOVA of Dissolution Rates (K_1) of Valsartan Tablets Prepared using βCD and Crosspovidone as per 2^2 Factorial Design

Source of Variation	DF	SS	MSS	F-ratio
Total	11	1315997	119636	
Treatment	3	1315987	438663	350930.4
Error	8	10	1.25	
F_a	1	473423	473423	378738.4
F_b	1	412589	412589	330071.2
F_{ab}	1	429976	429976	343983.2

$F_{0.01(3, 8)} = 7.59$; $F_{0.01(1, 8)} = 11.3$

Table 5: ANOVA of Dissolution Rates (K_1) of Valsartan Tablets Prepared using βCD and Primojel as per 2^2 Factorial Design

Source of variation	DF	SS	MSS	F-ratio
Total	11	15504.5	1409.5	
Treatment	3	14625.6	4875.2	44.373
Error	8	878.94	109.867	
F_a	1	9576.75	9576.75	87.16
F_b	1	1708.85	1708.85	15.55
F_{ab}	1	3340	3340	30.40

$F_{0.01(3, 8)} = 7.59$; $F_{0.01(1, 8)} = 11.3$

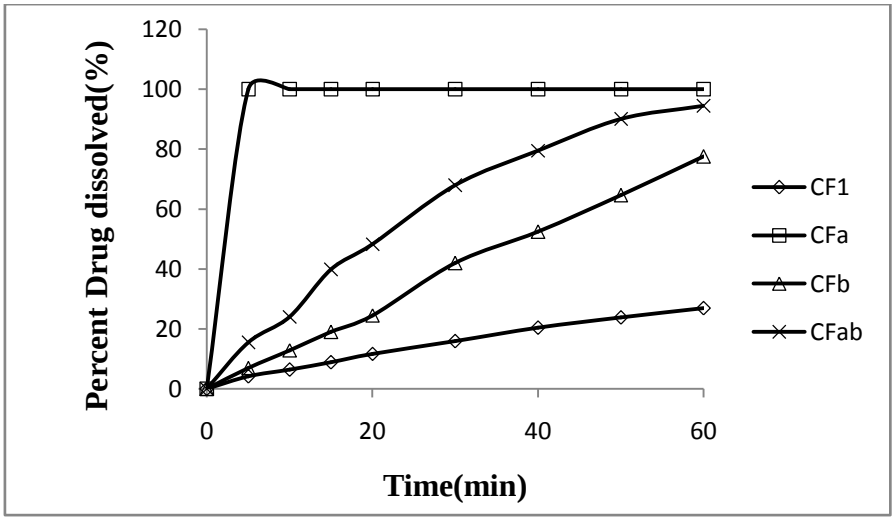

Fig.1: Dissolution Profiles of Valsartan Tablets Prepared employing βCD and Crosspovidone as per 2^2 Factorial Design

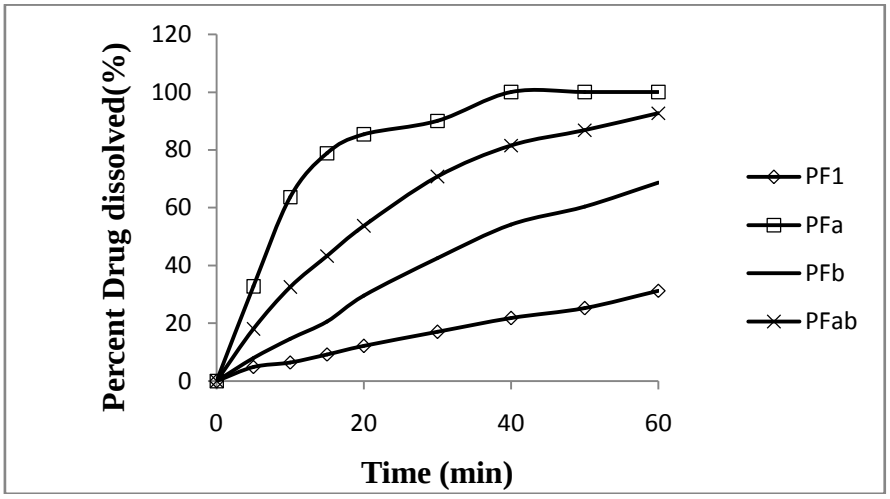

Fig.2: Dissolution Profiles of Valsartan Tablets Prepared employing βCD and Primojel as per 2^2 Factorial Design

CONCLUSIONS

1. The individual and combined effects of βCD and superdisintegrant (crosspovidone or Primojel) on the dissolution rate (K_1) of valsartan tablets are highly significant ($P<0.01$).
2. Valsartan tablets formulated employing superdisintegrant (crosspovidone or Primojel) at a level of 30% of drug content and βCD in 1:1 ratio of drug: βCD (CF_a and PF_a) disintegrated rapidly within 30 seconds and gave very rapid dissolution of valsartan fulfilling the target dissolution of NLT 85% in 15 min.
3. Higher levels of βCD and lower levels of superdisintegrants gave low dissolution rates with both the superdisintegrants.
4. The polynomial equation describing the relationship between the response i.e. percent drug dissolved in 15min (Y) and the levels of superdisintegrant (X_1) and βCD (X_2) based on the observed results is $Y = 42.42+27.795 (X_1) - 12.705 (X_2) -17.09 (X_1 X_2)$ in the case of formulations based on βCD and crosspovidone and $Y = 39.603+24.702 (X_1) -7.652 (X_2) -13.35 (X_1 X_2)$ in the case of formulations based on βCD and Primojel.
5. βCD in 1:1 ratio of drug: βCD and superdisintegrant (crosspovidone or Primojel) at a level of 30% of drug content are the optimized levels for formulation of valsartan IR tablets with dissolution of NLT 85% in 15 min.

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