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FORMULATION DEVELOPMENT OF VALSARTAN TABLETS EMPLOYING β CD, CROSPOVIDONE AND SLS: OPTIMIZATION BY 2^3 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. 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. Complexation with β-cyclodextrin (βCD) and use of Crospovidone and SLS are tried in the present study for enhancing the dissolution rate of Valsartan in its formulation development. The objective of the present study is optimization of Valsartan tablet formulation with NLT 85% dissolution in 10 min employing βCD, Crospovidone and SLS by 2^3 factorial design. Eight valsartan tablet formulations employing selected combinations of the three Factors i.e., βCD, Crospovidone, and SLS as per 2^3 Factorial design were formulated and prepared by direct compression method. All the tablets prepared 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 2^3 Factorial design to find out the significance of the individual and combined effects of the three Factors involved on the dissolution rate of valsartan tablets formulated.

The individual and combined effects of βCD, Crospovidone and SLS on the dissolution rate (K_1) of valsartan tablets are highly significant ($P<0.01$). Valsartan tablet formulations F_b and F_{bc} disintegrated rapidly with in 45 sec and gave very rapid dissolution of valsartan, 100% in

10 min. Higher levels of βCD and lower levels of Crospovidone gave low dissolution rates of valsartan tablets. The increasing order of dissolution rate (K_1) observed with various formulations was $F_{b} = F_{bc} > F_{ab} > F_{abc} > F_a > F_{ac} > F_1 > F_c$.

The polynomial equation describing the relationship between the response i.e. percent drug dissolved in 10 min (Y) and the levels of β CD (X_1) , Crospovidone (X_2) and SLS (X_3) based on the observed results is **$Y = 60.05 + 5.34 (X_1) + 33.88 (X_2) - 8.95 (X_1 X_2) - 3.18 (X_3) - 2.38 (X_1 X_3) + 2.80 (X_2 X_3) + 1.95 (X_1 X_2 X_3)$.** Based on the above polynomial equation, the optimized valsartan tablet formulation with NLT 85% dissolution in 10 min could be formulated employing βCD at 1:3 ratio of drug: β CD, Crospovidone at 26.31% of drug content, and SLS at 1% of drug conten**t.** The optimized valsartan tablet formulation gave 85.86 % dissolution in 10 min fulfilling the target dissolution set. Formulation of valsartan tablets with NLT 85% dissolution in 10 min could be optimized by 2^3 Factorial design

KEYWORDS: Valsartan tablets, Optimization, β-cyclodextrin, Crospovidone, SLS, Factorial Design, Formulation development.

INTRODUCTION

Optimization[1] of pharmaceutical formulations involves choosing and combining ingredients that will result in a formulation whose attributes confirm with certain prerequisite requirements. The choice of the nature and qualities of additives (excipients) to be used in a new formulation shall be on a rational basis. The application of formulation optimization techniques is relatively new to the practice of pharmacy. In general the procedure consists of preparing a series of formulations, varying the concentrations of the formulation ingredients in some systematic manner. These formulations are then evaluated according to one or more attributes, such as hardness, dissolution, appearance, stability, taste and so on. Based on the results of these tests, a particular formulation (or series of formulations) may be predicted to be optimal. The optimization procedure is facilitated by applying factorial designs and by the fitting of an empirical polynomial equation to the experimental results. The predicted optimal formulation has to be prepared and evaluated to confirm its quality.

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[2] 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[3, 4] and use of superdisintegrant[5, 6] such as Crospovidone and sodium starch glycolate (Primojel) and surfactant such as sodium lauryl sulphate (SLS) are simple industrially useful approaches for enhancing the dissolution rate of poorly soluble drugs in their formulation development. Complexation with β-cyclodextrin (βCD) and use of Crospovidone and SLS are tried in the present study for enhancing the dissolution rate of Valsartan in its formulation development. The objective of the present study is optimization of Valsartan tablet formulation with NLT 85% dissolution in 10 min employing βCD, Crospovidone and SLS by 2^3 factorial design.

EXPERIMENTAL

Materials

Valsartan was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. Crospovidone, sodium lauryl sulphate (SLS) and β-cyclodextrin were gift samples from M/s. Eisai Pharma Technology Ltd, Visakhapatnam. 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 0 – 10 µg/ ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.95% and 1.25% respectively. No interference by the excipients used in the study was observed.

Formulation of Valsartan Tablets

For optimization of valsartan tablets as per 2^3 Factorial designs the βCD, Crospovidone and SLS are considered as the three Factors. The two levels of the Factor A (βCD) are 1:1 and 1:5

ratio of drug: βCD, the two levels of the Factor B (Crospovidone) are 2% and 30% of drug content; and the two levels of Factor C (SLS) are 0% and 2% of drug content. Eight valsartan tablet formulations employing selected combinations of the three Factors i.e., βCD, Crospovidone, and SLS as per 2^3 Factorial design were formulated and were prepared by direct compression method.

Preparation of Valsartan Tablets

Valsartan (80 mg) tablets were prepared by direct compression method as per the formula given in Table1. The required quantities of valsartan, βCD , Crospovidone and SLS as per the formula in each case were blended thoroughly in a closed polythene bag. Talc and magnesium stearate were then added by passing through mesh no.80 and blended. The blend of ingredients was then 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 2^3 Factorial experiment.

RESULTS AND DISCUSSION

The objective of the present study is to optimize the valsartan tablet formulation employing βCD, Crospovidone and SLS by 2^3 Factorial design to achieve NLT 85% dissolution in 10 min. For optimization of Valsartan tablets as per 2^3 Factorial design the βCD, Crospovidone and SLS are considered as three Factors. The two levels of the Factor A (βCD) are 1:1 and 1:5 ratio of drug: βCD, the two levels of the Factor B (Crospovidone) are 2% and 30% of drug content; and the two levels of Factor C (SLS) are 0% and 2% of drug content. Eight valsartan tablet formulations employing selected combinations of the three Factors i.e., βCD, Crospovidone, and SLS as per 2^3 Factorial design were formulated and prepared by direct compression method as per the formula given in Table 1. All the tablets prepared 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 2^3 Factorial design to find out the significance of the individual and combined effects of the three factors involved on the dissolution rate of valsartan tablets formulated.

The physical parameters of the valsartan 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 0.94 % in all the cases. Valsartan content of the tablets prepared was within 100±3 %. Many variations were observed in the disintegration and dissolution characteristics of the valsartan tablets prepared. The disintegration times were in the range 25 sec. to 8 min 30 sec. Valsartan

tablet formulations (F_b, F_{bc}, and F_{abc}) disintegrated rapidly with in 1 min. All other tablets disintegrated rather slowly in about 3 min to 8 min 30 sec . As βCD level was increased the disintegration time is increased, whereas as Crospovidone concentration is increased the disintegration time is reduced. However, all the valsartan tablets prepared fulfilled the official 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 of pH 6.8. The dissolution profiles of the tablets are shown in Fig.1 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 0.945. The first order dissolution rate constant (K_1) values were estimated from the slope of the first order linear plots. Many variations were observed in the dissolution rate (K_1) and dissolution efficiency (DE_{30}) values of the tablets prepared due to formulation variables. ANOVA of K_1 values indicated that the individual and combined effects of the three Factors, βCD, Crospovidone and SLS in influencing the dissolution rate of valsartan tablets are highly significant ($P < 0.01$). Valsartan tablet formulations F_b and F_{bc} gave very rapid dissolution of valsartan than others. They gave 100% dissolution in 10 min. Higher levels of βCD and lower levels of Crospovidone gave low dissolution of valsartan tablets. The increasing order of dissolution rate (K_1) observed with various formulations was $F_b = F_{bc} > F_{ab} > F_{abc} > F_a > F_{ac} > F_1 > F_c$.

Optimization

For optimization, percent drug dissolved in 10 min was taken as response (Y) and level of βCD as (X_1), level of Crospovidone as (X_2) and level of SLS as (X3).The polynomial equation describing the relationship between the response ,Y and the variables, X_1 , X_2 and X_3 based on the observed data was found to be **$Y = 60.05 + 5.34 (X_1) + 33.88 (X_2) – 8.95 (X_1 X_2) - 3.18 (X_3) - 2.38 (X_1 X_3) + 2.80 (X_2 X_3) + 1.95 (X_1 X_2 X_3)$** . Based on the above polynomial equation, the optimized valsartan tablet formulation with NLT 85% dissolution in 10 min could be formulated employing βCD at 1:3 ratio of drug: β CD, Crospovidone at 26.31% of drug content, and SLS at 1% of drug content. To verify, valsartan tablets were formulated employing the optimized levels of βCD (240 mg/ tablet), Crospovidone (21.05 mg/tablet) and SLS (0.8 mg/tablet). The formulae of the optimized valsartan tablets is given in Table 1. The optimized valsartan tablet formulation was prepared by direct compression method and the tablets were evaluated. The physical parameters of the optimized formulation

are given in Table 2 and the dissolution parameters are given in Table 3. The hardness of the optimized valsartan tablets was 4.5 kg/sq.cm. Friability (percent weight loss) was less than 0.85%. Disintegration time of the tablets was 40 sec. The optimized valsartan tablet formulation gave 85.86 % dissolution in 10 min fulfilling the target dissolution set. The dissolution results also indicated validity of the optimization technique employed. Hence formulation of valsartan tablets with NLT 85% dissolution in 10 min could be optimized by 2^3 Factorial design.

Table 1: Formulae of Valsartan Tablets Prepared Employing β CD, Crospovidone and SLS as Per 2^3 Factorial Design

Ingredient (mg/tab)	F_1	F_a	F_b	F_{ab}	F_c	F_{ac}	F_{bc}	F_{abc}	Fopt
Valsartan	80	80	80	80	80	80	80	80	80
βCD	80	400	80	400	80	400	80	400	240
Crospovidone	1.6	1.6	24	24	1.6	1.6	24	24	21.05
SLS	-	-	-	-	1.6	1.6	1.6	1.6	0.8
Talc	3.2	9.6	3.6	10	3.3	9.7	3.7	10.1	6.8
Magnesium stearate	3.2	9.6	3.6	10	3.3	9.7	3.7	10.1	6.8
Total weight (mg)	168	500.8	191.2	524	169.8	502.6	193	525.8	355.45

Table 2: Physical Parameters of Valsartan Tablets Prepared Employing βCD, Crospovidone and SLS as per 2^3 Factorial Design

Formulation	Hardness (Kg/cm^2)	Friability (% Wt loss)	Disintegration Time (min-sec)	Drug Content (mg/tablet)
F_1	4.5	0.73	8-30	98.1
F_a	5.0	0.94	6-50	99.4
F_b	4.5	0.65	0-25	99.4
F_{ab}	5.0	0.87	4-10	98.2
F_c	4.5	0.78	8-10	98.4
F_{ac}	5.0	0.90	3-10	99.5
F_{bc}	5.0	0.65	0-45	99.1
F_{abc}	4.5	0.80	1-00	98.4
Fopt	4.5	0.85	0-40	98.2

Table 3: Dissolution Parameters of Valsartan Tablets Prepared Employing βCD, Crosspovidone and SLS as per 2^3 Factorial Design

Formulation	PD_{10} (%)	T_{50} (min)	T_{90} (min)	DE_{30} (%) ($\bar{x} \pm s\ d$)	$K_1 X 10^2$ (min^{-1}) ($\bar{x} \pm s\ d$)
F_1	16.04	35	>60	22.75±0.83	1.64±0.06
F_a	50.69	10	35.5	57.45±1.92	7.44±1.06
F_b	100	0.5	2.5	91.66±0	78.2±0
F_{ab}	91.04	2	4	87.19±1.89	26.8±1.91
F_c	12.63	42.5	>60	15.85±0.14	1.23±0.01

F_{ac}	30.15	17	52	42.04±1.47	4.07±0.15
F_{bc}	100	2.5	4	91.66±0	78.2±0
F_{abc}	89.51	3.5	10	84.25±0.35	20.2±1.36
Fopt	85.86	2.5	12	85.25±0.41	24.25±0.03

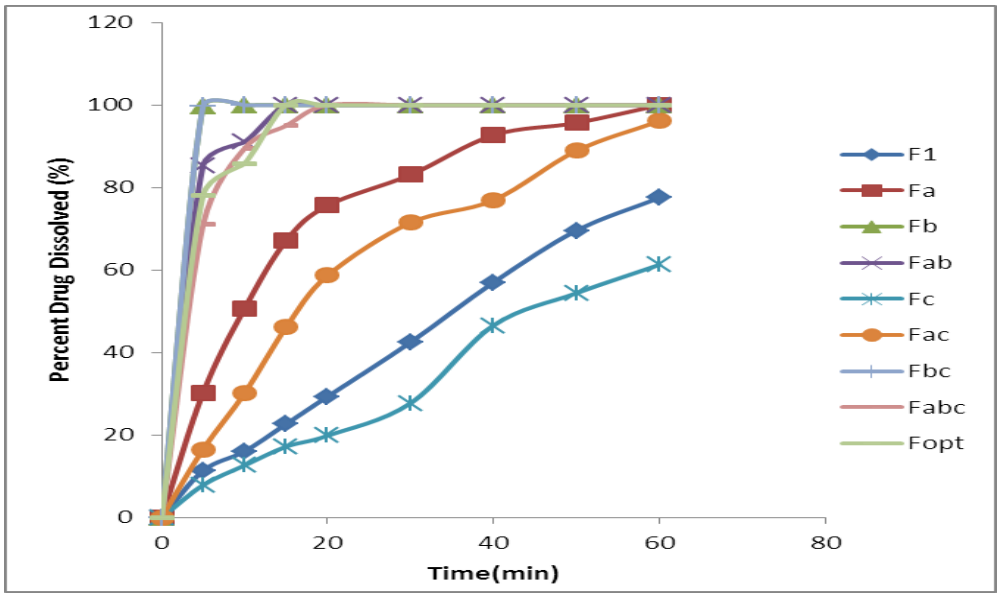

Fig.1: Dissolution Profiles of Valsartan Tablets Prepared Employing βCD, Crospovidone and SLS as per 2^3 Factorial Design

CONCLUSIONS

1. The individual and combined effects of βCD , Crospovidone and SLS on the dissolution rate (K_1) of valsartan tablets are highly significant ($P<0.01$).
2. Valsartan tablet formulations F_b and F_{bc} disintegrated rapidly with in 45 sec and gave very rapid dissolution of valsartan, 100% in 10 min.
3. Higher levels of βCD and lower levels of Crospovidone gave low dissolution rates of valsartan tablets.
4. The increasing order of dissolution rate (K_1) observed with various formulations was

   $F_b = F_{bc} > F_{ab} > F_{abc} > F_a > F_{ac} > F_1 > F_c$.
5. The polynomial equation describing the relationship between the response i.e. percent drug dissolved in 10 min (Y) and the levels of β CD (X_1) , Crospovidone (X_2) and SLS (X_3) based on the observed results is **$Y = 60.05 + 5.34 (X_1) + 33.88 (X_2) – 8.95 (X_1 X_2) - 3.18 (X_3) - 2.38 (X_1 X_3) + 2.80 (X_2 X_3) + 1.95 (X_1 X_2 X_3)$.**
6. Based on the above polynomial equation, the optimized valsartan tablet formulation with NLT 85% dissolution in 10 min could be formulated employing βCD at 1:3 ratio of drug: β CD, Crospovidone at 26.31% of drug content , and SLS at 1% of drug content

7. The optimized valsartan tablet formulation gave 85.86 % dissolution in 10 min fulfilling the target dissolution set.
8. Formulation of valsartan tablets with NLT 85% dissolution in 10 min could be optimized by 2^3 Factorial design.

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