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OPTIMIZATION OF VALSARTAN TABLET FORMULATION 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. It needs enhancement in the dissolution rate in its formulation development. Complexation with β-cyclodextrin (βCD), use of Primojel and PVP K 30 are tried for enhancing the dissolution rate of valsartan in its formulation development. The objective of the present study is optimization of valsartan tablet formulation employing Primojel, βCD and PVP K 30 by 2^3 factorial design. Formulation of valsartan tablets with NLT 85% dissolution in 10 min employing Primojel, βCD and PVP K 30 was optimized by 2^3 factorial design. Eight valsartan tablet formulations were prepared using selected combinations of the three factors as per 2^3 factorial design. Valsartan tablets were prepared by direct compression method and were evaluated for drug content, hardness, friability, and disintegration time and dissolution rate characteristics. The dissolution rate (K_1) values were analysed as per ANOVA of 2^3 factorial design to find the significance of the individual and combined effects of the three factors (βCD, Primojel and PVP K 30) involved on the dissolution rate of valsartan tablets formulated. ANOVA of K_1 values indicated that the individual and combined effects of the three factors, βCD, Primojel and PVP K 30 in influencing the dissolution rate of valsartan tablets are highly significant ($P < 0.01$).

Valsartan tablet formulations PF_a and PF_{ac} disintegrated rapidly with in 1min and gave very rapid dissolution of valsartan, 100% in 10 min. Higher levels of βCD and lower levels of Primojel gave low dissolution rates of valsartan tablets. The increasing order of dissolution rate (K_1) observed with various formulations was $PF_a = PF_{ac} > PF_{ab} > PF_{abc} > PF_{bc} > PF_b > PF_c > PF_1$. The polynomial equation describing the relationship between the response i.e. percent

drug dissolved in 10min (Y) and the levels of Primojel (X_1) , βCD (X_2) and PVP K 30 (X_3) based on the observed results is $Y = 56.146 + 37.478(X_1) + 1.676(X_2) – 5.288(X_1 X_2) + 1.563(X_3) - 2.942(X_1 X_3) – 1.123(X_2 X_3) - 0258(X_1 X_2 X_3)$. Based on the above polynomial equation, the optimized valsartan tablet formulation with NLT 85% dissolution in 10 min could be formulated employing Primojel at 26.77% of drug content, βCD at 1:3 ratio of drug: βCD and PVP K 30 at 1% of drug content. The optimized valsartan tablet formulation gave 87.23% dissolution in 10min fulfilling the target dissolution set. The dissolution profile of the optimized valsartan tablet formulation was similar to that of a commercial brand (Valent 40). Hence 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, Primojel, PVP K 30, 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. Polyvinylpyrrolidone (PVP), a water soluble polymer is also used for enhancing the solubility of poorly soluble drugs in formulation development. Complexation with β-cyclodextrin (βCD) and use of Primojel and PVP K 30

were tried in the present study for enhancing the dissolution rate of valsartan in its formulation development. Formulation of valsartan tablets with NLT 85% dissolution in 10 min employing Primojel, βCD and PVP K 30 was optimized by 2^3 factorial design.

Optimization [6] 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. The objective of the present study is optimization of valsartan tablet formulation employing Primojel, βCD and PVP K 30 by 2^3 factorial design.

EXPERIMENTAL

MATERIALS: Valsartan was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. Primojel, PVP K 30 and β-cyclodextrin were gift samples from M/s Natco Pharma Ltd., Hyderabad. Talc and magnesium stearate were procured from commercial sources. Valent 40 (film coated tablets each containing 40mg of valsartan manufactured by M/s Lupin Ltd, B.No. A305373; Mfg Dt.11/2013; Exp. Dt. 10/2015) were procured from local market. 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 tablets as per 2^3 factorial design the βCD, Primojel and PVP K 30 are considered as the three factors. The two levels of the factor A (Primojel) are 2% and 30% of drug content; the two levels of the factor B (βCD) are 1:1 and 1:5 ratio of drug: βCD and the two levels of factor C (PVP) are 0 and 2% of drug content. Eight valsartan tablet formulations employing selected combinations of the three factors i.e. Primojel , βCD and PVP K 30 as per 2^3 factorial design were formulated and 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 Table 1.The required quantities of valsartan, βCD, Primojel and PVP K 30 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 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 experiments.

RESULTS AND DISCUSSION

The objective of the present study is to optimize the valsartan tablet formulation employing βCD , Primojel and PVP K 30 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, Primojel and PVP K 30 are considered as the three factors. The two levels of the factor A (Primojel) are 2% and 30% of drug content; the two levels of the factor B (βCD) are 1:1 and 1:5 ratio of drug: βCD and the two levels of factor C (PVP) are 0 and 2% of drug content. Eight valsartan tablet formulations employing selected combinations of the three factors i.e. Primojel, βCD and PVP K 30 as per 2^3 factorial design were prepared. 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 2^3 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 0.92% 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 20 sec to 9 min 20 sec.

Valsartan tablet formulations PF_a , PF_{ac}, PF_{abc} disintegrated rapidly with in 1min. All other tablets disintegrated rather slowly in about 1-10 min. As βCD level was increased the disintegration time was increased, whereas as Primojel concentration was increased the disintegration time was 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.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 0.952. The first order dissolution rate constant (K_1) values were estimated from the slope of the first order linear plots. Much variation was observed in the dissolution rate (K_1) and DE_{30} values of the tablets prepared due to formulation variables. ANOVA of K_1 values (Table 4) indicated that the individual and combined effects of the three factors, βCD, Primojel and PVP K 30 in influencing the dissolution rate of valsartan the tablets are highly significant ($P < 0.01$).

Valsartan tablet formulations PF_a and PF_{ac} gave very rapid dissolution of valsartan than others. These tablets (PF_a and PF_{ac}) gave 100% in 10min. Higher levels of βCD and lower levels of Primojel gave low dissolution of valsartan tablets. The increasing order of dissolution rate (K_1) observed with various formulations was $PF_a = PF_{ac} > PF_{ab} > PF_{abc} > PF_{bc} > PF_b > PF_c > PF_1$.

For optimization, percent drug dissolved in 10 min was taken as response (Y) and level of Primojel as (X_1), level of βCD as (X_2) and level of PVP K 30 (X_3). 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 $Y = 56.146 + 37.478(X_1) + 1.676(X_2) – 5.288(X_1 X_2) + 1.563(X_3) - 2.942(X_1 X_3) – 1.123(X_2 X_3) - 0258(X_1 X_2 X_3)$. Based on the above polynomial equation, the optimized valsartan tablet formulation with NLT 85% dissolution in 10 min could be formulated employing Primojel at 26.77% of drug content, βCD at 1:3ratio of drug: βCD and PVP K 30 at 1% of drug content. To verify valsartan tablets were formulated employing the optimized levels of Primojel, βCD and PVP K 30. The formula 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 dissolution parameters are

given in Table 3. The hardness of the optimized valsartan tablets was 5. 0 kg/sq.cm. Friability (percent weight loss) was less than 0.83%. Disintegration time of the tablets was 20 sec. The optimized valsartan tablet formulation gave 87.23% dissolution in 10min fulfilling the target dissolution set. The dissolution results also indicated validity of the optimization technique employed. For comparison the dissolution rate of a commercial brand of valsartan tablets (Valent 40) was also studied. The dissolution profiles of optimized valsartan tablet formulation developed and commercial brand are shown in Fig.2. The dissolution profiles of both the products are similar and hence the optimized formulation was considered as similar to the commercial product. 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 Bcd, Primojel And PVP K 30as Per 2^3 Factorial Design.

Ingredient (mg/tab)	PF_1	PF_a	PF_b	PF_{ab}	PF_c	PF_{ac}	PF_{bc}	PF_{abc}	OPT
Valsartan	80	80	80	80	80	80	80	80	80
βCD	80	80	400	400	80	80	400	400	240
Primojel	1.6	24	1.6	24	1.6	24	1.6	24	21.42
PVP K 30	-	-	-	-	1.6	1.6	1.6	1.6	0.8
Talc	3.2	3.6	9.6	10	3.3	3.7	9.7	10.1	6.8
Magnesium stearate	3.2	3.6	9.6	10	3.3	3.7	9.7	10.1	6.8
Total weight (mg)	168	191.2	500.8	524	169.8	193	502.6	525.8	355.9

Table 2: Physical Parameters of Valsartan Tablets Prepared Employing βCD, Primojel and PVP K 30 as per 2^3 Factorial Design

Formulation	Hardness (Kg/cm^2)	Friability (% Wt loss)	Disintegration Time(min-sec)	Drug Content (mg/tablet)
PF_1	4.5	0.75	9-20	98.2
PF_a	4.5	0.65	0-20	99.5
PF_b	5.0	0.92	6-20	99.8
PF_{ab}	5.0	0.82	3-25	98.5
PF_c	4.5	0.73	9-0	98.4
PF_{ac}	5.0	0.68	0-25	99.6
PF_{bc}	5.0	0.91	1-45	99.7
PF_{abc}	4.5	0.80	1-00	98.9
OPT	5.0	0.83	0-25	98.6

Table 3: Dissolution Parameters of Valsartan Tablets Prepared Employing βCD, Primojel and PVP K 30 as per 2^3 Factorial Design

Formulation	PD_{10} (%)	T_{50} (min)	T_{90} (min)	DE_{30} (%) ($\bar{x} \pm s\ d$)	$K_1 \times 10^2$ (min^{-1}) ($\bar{x} \pm s\ d$)
PF_1	9.09	60	>60	12.99±0.04	0.89±0.57
PF_a	100	0.5	2.5	91.66±0	78.2±0
PF_b	24.75	17.5	47.5	42.74±0.01	2.72±1.35
PF_{ab}	95.54	1	7	88.48±0.25	25.86±0.09
PF_c	19.84	27.5	>60	26.90±0.02	1.75±0.24
PF_{ac}	100	2.5	4	91.66±0	78.2±0
PF_{bc}	32.04	13	44.5	53.29±0.36	6.50±1.20
PF_{abc}	90.01	2	10	85.30±0.04	18.22±0.04
OPT	87.23	2.8	12.5	85.91±0.02	24.54±0.03

Table 4: ANOVA of Dissolution Rates (K_1) of Valsartan Tablets Prepared Employing βCD, Primojel and PVP K 30 as per 2^3 Factorial Design.

Sourceof Variation	DF	SS	MSS	F-ratio
Total	23	39828.21	1731.661	_
Treatment	7	39827.53	5689.647	134219.5
Error	16	0.678	0.0423	_
PF_a	1	13341.56	13341.56	314729.1
PF_b	1	4192.852	4192.852	98909.97
PF_{ab}	1	5301.454	5301.454	125061.9
PF_c	1	3.375	3.375	79.61
PF_{ac}	1	56.549	56.549	1334.0
PF_{bc}	1	8.354	8.354	197.08
PF_{abc}	1	41.817	41.817	986.48

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

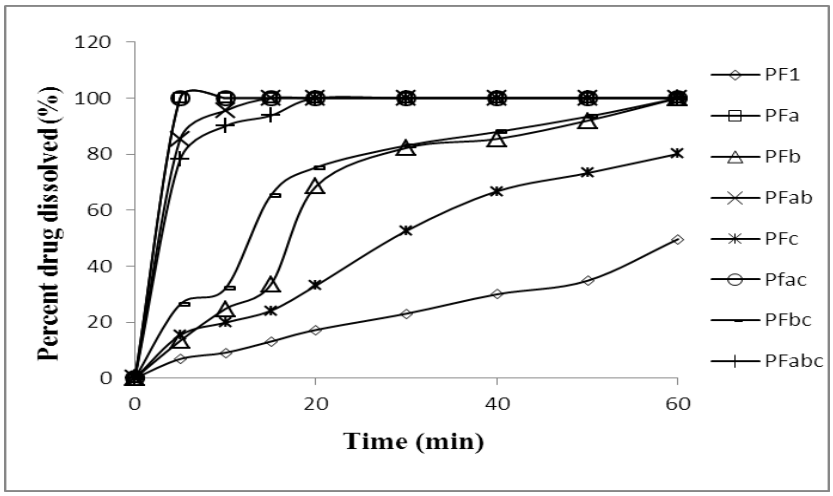

Fig.1: Dissolution Profiles of Valsartan Tablets Prepared Employing βCD, Primojel and PVP K 30 as per 2^3 Factorial Design.

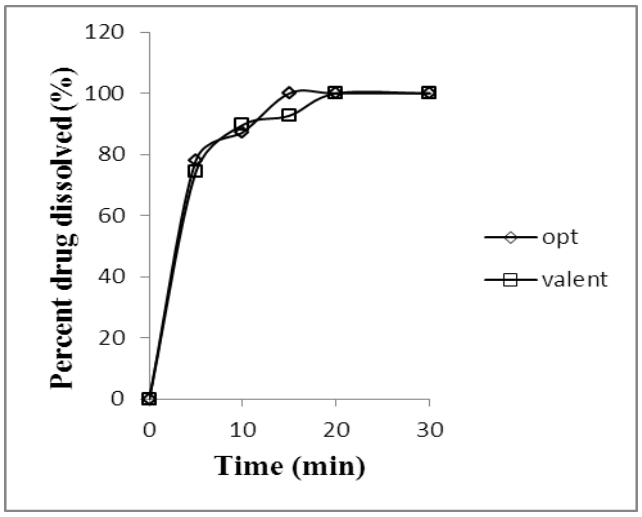

Fig. 2: Dissolution Profiles of Optimized Valsartan Tablet Formulation and Commercial Tablets.

CONCLUSIONS

1. ANOVA of K_1 values indicated that the individual and combined effects of the three factors, βCD, Primojel and PVP K 30 in influencing the dissolution rate of valsartan the tablets are highly significant ($P < 0.01$).
2. Valsartan tablet formulations PF_a and PF_{ac} disintegrated rapidly with in 1min and gave very rapid dissolution of valsartan, 100% in 10 min.
3. Higher levels of βCD and lower levels of Primojel gave low dissolution rates of valsartan tablets.
4. The increasing order of dissolution rate (K_1) observed with various formulations was $PF_a = PF_{ac} > PF_{ab} > PF_{abc} > PF_{bc} > PF_b > PF_c > PF_1$.
5. The polynomial equation describing the relationship between the response i.e. percent drug dissolved in 10min (Y) and the levels of Primojel (X_1) , βCD (X_2) and PVP K 30 (X_3) based on the observed results is $Y = 56.146 + 37.478(X_1) + 1.676(X_2) – 5.288(X_1 X_2) + 1.563(X_3) - 2.942(X_1 X_3) – 1.123(X_2 X_3) - 0258(X_1 X_2 X_3)$.
6. Based on the above polynomial equation, the optimized valsartan tablet formulation with NLT 85% dissolution in 10 min could be formulated employing Primojel at 26.77% of drug content, βCD at 1:3ratio of drug: βCD and PVP K 30 at 1% of drug content.
7. The optimized valsartan tablet formulation gave 87.23% dissolution in 10min fulfilling the target dissolution set.
8. The dissolution profile of the optimized valsartan tablet formulation was similar to that of a commercial brand (Valent 40).

9. Hence formulation of valsartan tablets with NLT 85% dissolution in 10 min could be optimized by 2^3 factorial design.

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