Innovare Academic Sciences

International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 7, Issue 1, 2015

Original Article

OPTIMIZATION OF IRBESARTAN TABLET FORMULATION BY 2^3 FACTORIAL DESIGN

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Received: 19 Nov 2014, Revised and Accepted: 23 Dec 2014

ABSTRACT

Irbesartan, 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 Crospovidone and PVP K 30 are tried for enhancing the dissolution rate of irbesartan in its formulation development. The objective of the present study is optimization of irbesartan tablet formulation employing Crospovidone, βCD and PVP K 30 by 2^3 Factorial design. Formulation of irbesartan tablets with NLT 85% dissolution in 15 min employing Crospovidone, βCD and PVP K 30 was optimized by 2^3 Factorial design. Eight irbesartan tablet formulations were prepared using selected combinations of the three Factors as per 2^3 Factorial designs. Irbesartan 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 2^3 Factorial design to find the significance of the individual and combined effects of the three Factors (βCD, Crospovidone and PVP K 30) involved on the dissolution rate of irbesartan tablets formulated.

The individual and combined effects of βCD, Crospovidone and PVP K 30 on the dissolution rate (K1) of irbesartan tablets are highly significant ($P<0.01$). Irbesartan tablet formulation (PFac), disintegrated rapidly with in 1 min and gave very rapid dissolution of irbesartan,100% in 15 min. Higher levels of βCD and lower levels of Crospovidone gave low dissolution rates of irbesartan tablets. The increasing order of dissolution rate (K_1) observed with various formulations was CF_{ac}> CF_a>CF_{ab}>CF_{abc}> CF_1> CF_{bc}> CF_b> CF_c. The polynomial equation describing the relationship between the response i. e. percent drug dissolved in 15 min (Y) and the levels of Crospovidone (X_1),βCD (X_2) and PVP K 30 (X_3) based on the observed results is $Y = 58.57+34.54 (X_1) - 1.89(X_2) – 3.60 (X_1 X_2) -1.82 (X_3) +1.50 (X_1 X_3) + 3.13 (X_2 X_3) - 4.87 (X_1 X_2 X_3)$. Based on the above polynomial equation, the optimized irbesartan tablet formulation with NLT 85% dissolution in 15 min could be formulated employing Crospovidone at 27.70% of drug content, βCD at 1:4 ratio of drug: βCD and PVP K 30 at 1% of drug content. The optimized irbesartan tablet formulation gave 86.18 % dissolution in 15 min fulfilling the target dissolution set. The dissolution profile of the optimized Irbesartan tablet formulation was similar to that of commercial brand (IROVEL-150). Hence the formulation of irbesartan tablets with NLT 85% dissolution in 15 min could be optimized by 2^3 Factorial design.

Keywords: Irbesartan tablets, Optimization, Factorial Design, β Cyclodextrin, Crospovidone, PVP K 30.

INTRODUCTION

About 95% of all potential new 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. Irbesartan, 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 cross povidone and sodium starch glycolate (Crospovidone) are simple industrially useful approaches for enhancing the dissolution rate of poorly soluble drugs in their formulation development. Polyvinyl pyrrolidone (PVP K 30), 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 Crospovidone and PVP K 30 were tried in the present study for enhancing the dissolution rate of irbesartan in its formulation development. Formulation of irbesartan tablets with NLT 85% dissolution in 15 min employing Crospovidone, 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 irbesartan tablet formulation employing Crospovidone, βCD and PVP K 30 by 2^3 Factorial design.

MATERIALS AND METHODS

Materials

Irbesartan was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. Cross povidone, PVP K 30 and β-cyclodextrin was gift samples from M/s. Nalco Pharma Ltd., Hyderabad. Talc and magnesium stearate were procured from commercial sources. IROVEL-150 (uncoated tablets each containing 150mg of Irbesartan manufactured by Sun Pharma Ltd, B. No. BSMO761; Mfg dt.3/2013; Exp. dt. 2/2015). All other materials used were of pharmacopoeial grade.

Methods

Estimation of Irbesartan

An UV Spectrophotometric method based on the measurement of absorbance at 244 nm in 0.1N hydrochloric acid was used for the

estimation of irbesartan. 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 0.9% and 1.55% respectively. No interference by the excipients used in the study was observed.

Formulation of Irbesartan tablets

For optimization of irbesartan tablets as per 2^3 Factorial designs the βCD, Crospovidone and PVP K 30 are considered as the three factors. The two levels of the Factor A (Crospovidone) 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 K 30) are 0% and 2% of drug content. Eight irbesartan tablet formulations employing selected combinations of the three Factors i. e., Crospovidone, βCD and PVP K 30 as per 2^3 Factorial designs were formulated and prepared by direct compression method.

Preparation of Irbesartan tablets

Irbesartan (100 mg) tablets were prepared by direct compression method as per the formula given in table 1. The required quantities of irbesartan, βCD, Crospovidone and PVP K 30 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 9 mm or 12 mm round and flat punches.

Evaluation of tablets

All the irbesartan 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 irbesartan was taken into 100 ml volumetric flask, dissolved in 0.1N Hydrochloric acid and the solution was filtered through Whatman filter paper no.41. The filtrate was collected and suitably diluted with 0.1N hydrochloric acid and assayed for irbesartan at 244 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 irbesartan tablets prepared was studied in 0.1N hydrochloric acid (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 irbesartan at 244 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.

Table 1: Formulae of Irbesartan tablets prepared employing βCD, crospovidone and PVP K 30 as Per 2^3 factorial design

Ingredient (mg/tab)	CF_1	CF_a	CF_b	CF_{ab}	CF_c	CF_{ac}	CF_{bc}	CF_{abc}	OPT
Irbesartan	100	100	100	100	100	100	100	100	100
βCD	100	100	500	500	100	100	500	500	400
Crospovidone	2	30	2	30	2	30	2	30	27.70
PVP K30	-	-	-	-	2	2	2	2	1
Talc	4	4.6	12	12.6	4.08	4.64	12.08	12.64	10.57
Magnesium stearate	4	4.6	12	12.6	4.08	4.64	12.08	12.64	10.57
Total weight (mg)	210	239.2	626	655.2	212.16	241.28	628.16	657.28	549.84

Table 2: Physical Parameters of Irbesartan tablets prepared employing βCD, crospovidone 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)
CF_1	4.5	0.85	8-50	98.6
CF_a	5.0	0.75	1-00	99.4
CF_b	4.5	0.92	6-55	99.5
CF_{ab}	4.5	0.85	3-20	98.2
CF_c	5.0	0.80	8-05	98.4
CF_{ac}	5.0	0.75	1-00	99.3
CF_{bc}	5.0	0.91	2-10	99.5
CF_{abc}	4.5	0.80	1-00	98.5
OPT	5.0	0.90	1-00	99.0

RESULTS AND DISCUSSION

The objective of the present study is to optimize the Irbesartan tablet formulation employing βCD, Crospovidone and PVP K 30 by 2^3 Factorial design to achieve NLT 85% dissolution in 15 min. For optimization of Irbesartan tablets as per 2^3 Factorial design the βCD, Crospovidone and PVP K 30 are considered as three Factors.

The two levels of the Factor A (Crospovidone) 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 K 30) are 0% and 2% of drug content. Eight irbesartan tablet formulations employing selected combinations of the three Factors i. e.,

Crospovidone, βCD and PVP K 30 as per 2^3 Factorial design was prepared. the tablets were prepared by direct compression method as per the formula given in table 1 and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics. The dissolution rate (K1) 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 irbesartan tablets formulated.

Table 3: Dissolution parameters of Irbesartan tablets prepared employing BCD, crospovidone and pvp k 30 as per 2^3 factorial design

Formulation	PD_{15} (%)	T_{50} (min)	T_{90} (min)	DE_{30} (%) ($\bar{x}$ ± sd)	$K_1 X 10^3$ (min^{-1}) ($\bar{x}$ ± s d)
CF_1	33.62	60	>60	29.23±8.25	27±7.31
CF_a	97.18	1.5	9	80.05±0.47	237±1.13
CF_b	21.03	50	>60	17.75±5.18	15.7±7.60
CF_{ab}	89.65	40	60	78.24±0.47	151±1.24
CF_c	10.94	50	>60	11.44±1.23	7.1±2.40
CF_{ac}	100	1	4	91.29±1.28	835.3±3.5
CF_{bc}	30.39	3	20	30.30±1.60	22.6±1.15
CF_{abc}	85.54	10	18	76.89±0.95	127±1.75
OPT	86.18	5	20	73.41±0.97	131±1.05

Table 4: ANOVA of Dissolution rates (K_1) of Irbesartan tablets Prepared using βCD, Crospovidone and PVP K 30 as per 2^3Factorial Design

Source of variation	DF	SS	MSS	F-ratio
Total	23	2149128	93440.36	
Treatment	7	2146544	306649.2	1898.67
Error	16	2584.11	161.5071	
CF_a	1	354804.5	354804.5	2196.83
CF_b	1	187637.9	187637.9	1161.79
CF_{ab}	1	203485.8	203485.8	1259.91
CF_c	1	333680.6	333680.6	2066.04
CF_{ac}	1	298842.5	298842.5	1850.33
CF_{bc}	1	172398.5	172398.5	1067.43
CF_{abc}	1	189730.4	189730.4	1174.75

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

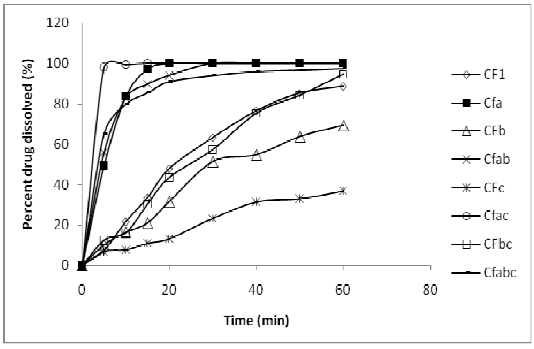

Fig. 1: Dissolution profiles of irbesartan tablets prepared employing βcd,crospovidone and pvp k 30 as per 2^3 factorial design

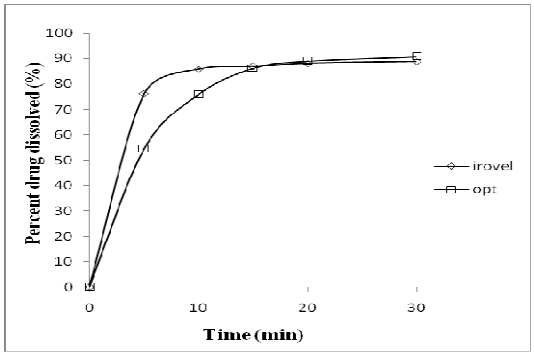

Fig. 2: Dissolution profiles of optimized irbesartan tablet formulation and commercial tablets

The physical parameters of the irbesartan 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. Irbesartan content of the tablets prepared was within 100±3 %. Many variations were observed in the disintegration and dissolution characteristics of the irbesartan tablets prepared. The disintegration times were in the range 1 min to 8 min 50 sec. Irbesartan tablet formulations (CF_a, CF_{ac}, and CF_{abc}) disintegrated rapidly with in 1 min. All other tablets disintegrated rather slowly in about 2-9 min. As βCD level was increased the disintegration time is increased, whereas as Crospovidone concentration is increased the disintegration time is reduced. However, all the irbesartan tablets prepared fulfilled the official (USP 2008) requirements with regard to drug content, hardness, friability and disintegration time specified for uncoated tablets. Dissolution rate of irbesartan tablets prepared was studied in 0.1N hydrochloric acid. The dissolution profiles of the tablets are shown in Fig.1and 2 and the dissolution parameters are given in table 3. Dissolution of irbesartan from all the tablets prepared followed first order kinetics with coefficient of determination (R^2) values above 0.962. 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 dissolution efficiency (DE_{30}) values of the tablets prepared due to formulation variables. ANOVA (Table - 4) of K_1 values indicated that the individual and combined effects of the three Factors, βCD, Crospovidone and PVP K 30 in influencing the dissolution rate of irbesartan tablets are highly significant ($P < 0.01$).

Irbesartan tablet formulation (CF_{ac}) gave very rapid dissolution of irbesartan than others. The tablet formulation (CF_{ac}) gave 100% dissolution in 15 min. Higher levels of βCD and lower levels of Crospovidone gave low dissolution of irbesartan tablets. The increasing order of dissolution rate (K_1) observed with various formulations was CF_{ac}> CF_a>CF_{ab}>CF_{abc}> CF_1> CF_{bc}> CF_b> CF_c.

For optimization, percent drug dissolved in 15 min was taken as response (Y) and level of Crospovidone as (X_1), level of βCD as (X_2)and level of PVP K 30 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 = 58.57+34.54 (X_1) - 1.89(X_2) – 3.60 (X_1 X_2) -1.82 (X_3) +1.50 (X_1 X_3) + 3.13 (X_2 X_3) - 4.87 (X_1 X_2 X_3). Based on the above polynomial equation, the optimized irbesartan tablet formulation with NLT 85% dissolution in 15 min could be formulated employing Crospovidone at 27.70% of drug content, βCD at 1:4 ratio of drug: β CD and PVP K 30 at 1% of drug content. To verify irbesartan tablets was formulated employing the optimized levels of Crospovidone, βCD and PVP K 30. The formulae of the optimized irbesartan tablets is given in Table-1. The optimized irbesartan 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 irbesartan tablets was 5.0 kg/sq. cm. Friability (percent weight loss) was less than 0.92%. Disintegration time of the tablets was 1 min. The optimized irbesartan tablet formulation gave 86.18 % dissolution in 15 min 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 Irbesartan tablets (IROVEL-150) was also studied. The dissolution profiles of optimized Irbesartan 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 similar to the commercial product.

Hence formulation of irbesartan tablets with NLT 85% dissolution in 15 min could be optimized by 2^3 Factorial design.

CONCLUSION

1. The individual and combined effects of βCD, Crospovidone and PVP K 30 on the dissolution rate (K_1) of irbesartan tablets are highly significant ($P<0.01$).

2. Irbesartan tablet formulation (CF_{ac}) disintegrated rapidly with in 1 min and gave very rapid dissolution of irbesartan,100% in 15 min.

3. Higher levels of βCD and lower levels of Crospovidone gave low dissolution rates of irbesartan tablets.

4. The increasing order of dissolution rate (K_1) observed with various formulations was

CF_{ac}> CF_a>CF_{ab}>CF_{abc}> CF_1> CF_{bc}> CF_b> CF_c.

5. The polynomial equation describing the relationship between the response i. e. percent drug dissolved in 15 min (Y) and the levels of Crospovidone (X_1),βCD (X_2) and PVP K 30 (X_3) based on the observed results is Y = 58.57+34.54 (X_1) - 1.89(X_2) - 3.60 (X_1 X_2) - 1.82 (X_3) +1.50 (X_1 X_3) + 3.13 (X_2 X_3) - 4.87 (X_1 X_2 X_3).

6. Based on the above polynomial equation, the optimized irbesartan tablet formulation with NLT 85% dissolution in 15 min could be formulated employing Crospovidone at 27.70% of drug content, βCD at 1:4 ratio of drug: βCD and PVP K 30 at 1% of drug content**.**

7. The optimized irbesartan tablet formulation gave 86.18 % dissolution in 15 min fulfilling the target dissolution set.

8. The dissolution profile of Irbesartan tablet formulation was similar to that of a commercial brand (IROVEL-150).

9. Hence formulation of irbesartan tablets with NLT 85% dissolution in 15 min could be optimized by 2^3 Factorial design.

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