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DEVELOPMENT AND EVALUATION OF IRBESARTAN TABLETS: OPTIMIZATION BY 2^2 FACTORIAL DESIGN

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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 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 βCD and Crospovidone by 2^2 factorial design. Formulation of irbesartan tablets with NLT 85% dissolution in 10 min employing βCD and Crospovidone was optimized by 2^2 factorial design. Four irbesartan tablet formulations were prepared using selected combinations of the two factors as per 2^2 factorial design. 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 2^2 factorial design to find the significance of the individual and combined effects of the two factors (βCD and Crospovidone) involved on the dissolution rate of irbesartan tablets formulated. The individual and combined effects of βCD (Factor A) and Crospovidone (Factor B) on the dissolution rate (K_1) of irbesartan tablets are highly significant ($P < 0.01$). Irbesartan tablets (F_b) which are prepared employing βCD in 1:1 ratio of drug: βCD and Crospovidone at 30% of drug content disintegrated rapidly within 20 seconds and gave 92.20% dissolution in

10min. 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 $F_b > F_{ab} > F_1 > F_a$. The polynomial equation describing the relationship between the response i.e. percent drug dissolved in 10min (Y) and the levels of βCD (X_1) and Crospovidone (X_2) based on the observed results is **$Y = 55.83 – 5.56(X_1) + 31.49(X_2) + 0.68 (X_1 X_2)$.** Based on the above polynomial equation, Irbesartan tablet formulation with NLT 85% dissolution in 10 min could be formulated employing βCD at 1:3 ratio of drug: βCD (300 mg per tablet) and Crospovidone at 28.96% of drug content (28.96 mg per tablet). The optimized Irbesartan tablet formulation, Fopt gave 85.45% dissolution in 10min fulfilling the target dissolution set. The results indicated validity of the optimization technique employed and the polynomial equation developed could be used to formulate irbesartan tablets with the desired dissolution rate specification. Hence formulation of irbesartan tablets with the desired dissolution rate specification (85% dissolution in 10 min) could be optimized by 2^2 factorial design.

KEYWORDS: Irbesartan tablets, Optimization, β-cyclodextrin, Crospovidone, 2^2 Factorial Design.

INTRODUCTION

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 superdisintegrant[4,5] such as Crospovidone and sodium starch glycolate (Primojel) 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 are tried in the present study for enhancing the dissolution rate of Irbesartan in its formulation development. The objective of the present study is optimization of Irbesartan

tablet formulation with NLT 85% dissolution in 10 min employing βCD and Crospovidone by 2^2 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.

EXPERIMENTAL

Materials

Irbesartan was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. Crospovidone and β-cyclodextrin were gift samples from M/s Eisai Pharma Technology Pvt. Ltd., Visakhapatnam. Talc and magnesium stearate were procured from commercial sources. 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 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 0.80% and 1.35% respectively. No interference by the excipients used in the study was observed.

Formulation of Irbesartan Tablets

For optimization of Irbesartan tablets as per 2^2 factorial design, the βCD and Crospovidone are considered as the two factors. The two levels of the factor A (βCD) are 1:1 and 1:5 ratio

of drug: βCD and the two levels of the factor B (Crospovidone) are 2% and 30% of drug content. Four Irbesartan tablet formulations employing selected combinations of the two factors i.e. βCD and Crospovidone as per 2^2 factorial design 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 and Crospovidone as per the formula in each case were blended thoroughly in a closed polyethene bag. Talc and magnesium stearate were then added by passing through mesh no.80 and blended. Micromeritic evaluation of the blends was made by determining angle of repose (θ) and compressibility index (CI). The blends of ingredients were then compressed directly into tablets using an 8- station RIMEK tablet punching machine employing 9mm and 12mm 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

Five tablets were weighed and powdered in a glass mortar. 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: Labindia) 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 2^2 factorial experiments.

RESULTS AND DISCUSSION

The objective of the present study is to optimize the Irbesartan tablet formulation employing βCD and Crospovidone by 2^2 factorial design to achieve NLT 85% dissolution in 10 min. For optimization of Irbesartan tablets as per 2^2 factorial design, βCD and Crospovidone are considered as the two factors. The two levels of the factor A (βCD) are 1:1 and 1:5 ratio of drug: βCD and the two levels of the factor B (Crospovidone) are 2% and 30% of drug content. Four Irbesartan tablet formulations were prepared using selected combinations of the two factors as per 2^2 factorial design. The tablets were prepared by direct compression method as per the formulae given in Table 1. The blends of ingredients of various formulations exhibited angle of repose (θ) values in the range $18\text{-}24^0$ and compressibility index values in the range 9-14% indicating good to excellent flow characteristics of the blends suitable for direct compression. 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 2^2 factorial design to find out the significance of the individual and combined effects of the two factors involved on the dissolution rate of irbesartan tablets formulated.

The physical parameters of the irbesartan tablets prepared are given in Table 2. The hardness of the tablets was in the range 5-5.0 kg/cm^2. Weight loss in the friability test was less than 0.85% in all the cases. Irbesartan content of the tablets prepared was within 100±3%. Much variations were observed in the disintegration and dissolution characteristics of the irbesartan tablets prepared. The disintegration times were in the range 20 sec to 8 min 20 sec. Among all, Irbesartan tablets ($F_{b)}$ formulated employing βCD in 1:1ratio of drug: βCD and Crospovidone at 30% of drug content disintegrated rapidly with in 20 sec. As βCD level was increased the disintegration time was increased, whereas as Crospovidone concentration was increased the disintegration time was reduced. However, all the Irbesartan tablets prepared fulfilled the official requirements with regard to drug content, hardness, friability and disintegration time specified for uncoated tablets in IP 2010.

Dissolution rate of Irbesartan tablets prepared was studied in 0.1N hydrochloric acid. The dissolution profiles of the tablets are shown in Fig.1 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 0.926. 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 of K_1 values indicated that the individual and combined effects of the two factors, βCD and Crospovidone in influencing the dissolution rate of irbesartan from the tablets are highly significant ($P < 0.01$).

Irbesartan tablets (F_b) which are prepared employing βCD in 1:1 ratio of drug: βCD and Crospovidone at 30% of drug content gave very rapid dissolution of Irbesartan than others. These tablets (F_b) gave 92.20% dissolution in 10min. 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 $F_b > F_{ab} > F_1 > F_a$.

For optimization, percent drug dissolved in 10 min was taken as response (Y) and level of βCD as (X_1) and level of Crospovidone as (X_2). The polynomial equation describing the relationship between the response, Y and the variables, X_1 and X_2 based on the observed data was found to be $\mathbf{Y = 55.83 - 5.56(X_1) + 31.49(X_2) + 0.68(X_1\ X_2)}$. The coefficients in the polynomial equation indicate the relative magnitude or effect of the factors involved on the response i.e percent drug dissolved. In the above equation the coefficient of (X_2) i.e

crospovidone is much higher than the coefficient of (X_1) i.e βCD indicating that crospovidone has greater influence on percent drug dissolved.

Based on the above polynomial equation, Irbesartan tablet formulation with NLT 85% dissolution in 10 min could be formulated employing βCD at 1:3 ratio of drug: βCD (300mg per tablet) and Crospovidone at 28.964% of drug content (28.96mg per tablet). To verify, optimized Irbesartan tablets (Fopt) were formulated employing the optimized levels of βCD and Crospovidone as per the formula 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 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 0.85%. Disintegration time of the optimized tablets was 15sec. The optimized Irbesartan tablet formulation, Fopt gave 85.45% dissolution in 10 min fulfilling the target dissolution set. These results indicated validity of the optimization technique employed and the polynomial equation developed could be used to formulate irbesartan tablets with the desired dissolution rate specification. Hence formulation of irbesartan tablets with desired dissolution rate specification (85% dissolution in 10 min) could be optimized by 2^2 factorial design.

Table 1: Formulae of Irbesartan Tablets Prepared Employing βCD and Crospovidone as per2^2 Factorial Design and Optimized Formulation.

Ingredient (mg/tab)	F_1	F_a	F_b	F_{ab}	Fopt
Irbesartan	100	100	100	100	100
βCD	100	500	100	500	300
Crospovidone	2	2	30	30	28.96
Talc	4	12	4.5	12	8
Magnesium stearate	4	12	4.5	12	8
Total weight (mg)	210	626	239	654	444.96

Table 2: Physical Parameters of Irbesartan Tablets Prepared as per 2^2 Factorial Design Employing βCD and Crospovidone and Optimized Formulation.

Formulation	Hardness (Kg/cm^2)	Friability (% Wt loss)	Disintegration Time(min-sec)	Drug Content (mg/tablet)
F_1	5.0	0.83	8-20	98.2
F_a	5.5	0.84	6-24	99.3
F_b	5.0	0.82	0-20	98.7
F_{ab}	5.5	0.85	3-45	98.9
Fopt	5.0	0.85	0-15	98.4

Table 3: Dissolution Parameters of Irbesartan Tablets Prepared as per 2^2 Factorial Design Employing βCD and Crospovidone and Optimized Formulation.

Formulation	PD_{10} (%)	T_{50} (min)	T_{90} (min)	DE_{30} (%) ($\bar{x}$ ± s d)	K_1 X 10^2 (min^{-1}) ($\bar{x}$ ± s d)
F_1	30.58	18.0	45	43.9±0.04	2.475±0.62
F_a	18.10	29.5	>60	12.9±0.01	0.985±1.26
F_b	92.20	0.5	8	92.7±0.05	79.725±1.45
F_{ab}	82.45	1.5	15	86.5±0.25	25.286±1.28
Fopt	85.45	1.2	12	89.3±0.56	25.945±0.85

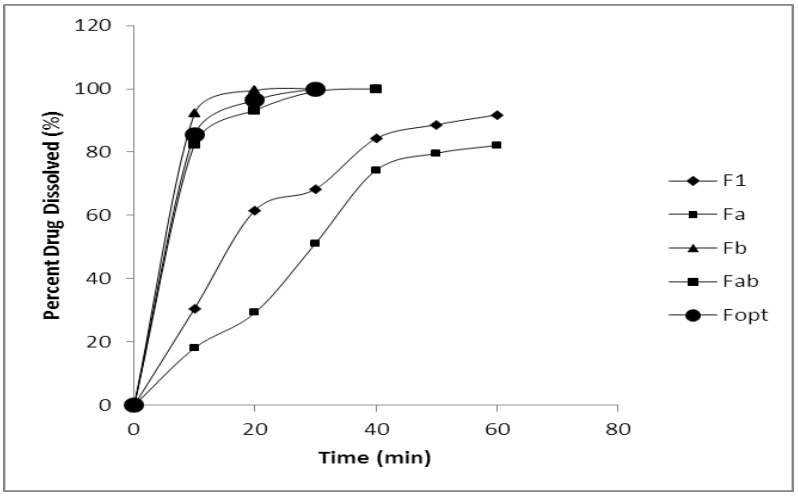

Fig. 1: Dissolution Profiles of Irbesartan Tablets Prepared Employing βCD and Crospovidone as per 2^2 Factorial Design and optimized formulation.

CONCLUSIONS

1. The individual and combined effects of βCD (Factor A) and Crospovidone (Factor B) on the dissolution rate (K_1) of irbesartan tablets are highly significant ($P < 0.01$).
2. Irbesartan tablets (F_b) which are prepared employing βCD in 1:1 ratio of drug: βCD and Crospovidone at 30% of drug content disintegrated rapidly within 20 seconds and gave 92.20% dissolution in 10min.
3. Higher levels of Crospovidone and lower levels of βCD gave higher dissolution rates of Irbesartan tablets.
4. The increasing order of dissolution rate (K_1) observed with various formulations was $F_b > F_{ab} > F_1 > F_a$.
5. The polynomial equation describing the relationship between the response i.e. percent drug dissolved in 10min (Y) and the levels of βCD (X_1) and Crospovidone (X_2) based on the observed results is $\mathbf{Y = 55.83 - 5.56(X_1) + 31.49(X_2) + 0.68(X_1 X_2)}$.

6. Based on the above polynomial equation, Irbesartan tablet formulation with NLT 85% dissolution in 10 min could be formulated employing βCD at 1:3 ratio of drug: βCD (300 mg per tablet) and Crospovidone at 28.96% of drug content (28.96 mg per tablet).
7. The optimized Irbesartan tablet formulation, Fopt gave 85.45% dissolution in 10min fulfilling the target dissolution set.
8. The results indicated validity of the optimization technique employed and the polynomial equation developed could be used to formulate irbesartan tablets with the desired dissolution rate specification. Hence formulation of irbesartan tablets with the desired dissolution rate specification (85% dissolution in 10 min) could be optimized by 2^2 factorial design.

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