OPTIMIZATION OF IRBESARTAN TABLET FORMULATION EMPLOYING βCD AND CROSPOVIDONE BY 2^2 FACTORIAL DESIGNS

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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 Crospovidone and βCD by 2^2 factorial design. Formulation of irbesartan tablets (i) with NLT 85% dissolution in 15 min and (ii) with NLT 70% dissolution in 15 min employing Crospovidone and βCD in each case 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. Irbesartan tablets formulated employing Crospovidone at a level of 30% of drug content and βCD in 1:1 ratio of drug: βCD (F_a) disintegrated rapidly within 20 seconds and gave very rapid dissolution of irbesartan, 97.18% 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 $F_a > F_{ab} > F_1 > F_b$. The polynomial equation describing the relationship between the response i.e. percent drug dissolved in 15min (Y) and the levels of rospovidone (X_1) and βCD (X_2) based on the observed results is **Y=60.37+33.04 (X_1) − 5.03 (X_2) + 1.265 (X_1 X_2)**. Based on the above polynomial equation, two optimized Irbesartan tablet formulations, One with high dissolution (OPT1) with NLT 85% dissolution in 15 min

could be formulated employing Crospovidone at 24.75% of drug content and βCD at 1:1 ratio of drug:βCD and the other with moderate dissolution (OPT2) with NLT 70% dissolution in 15 min could be formulated employing Crospovidone at 19.07% of drug content and βCD at 1:2 ratio of drug: βCD .The optimized irbesartan tablet formulation,OPT1 gave 88.27% dissolution in 15 min and formulation OPT2 gave 73.48% dissolution in 15 min fulfilling the target dissolution set in each case.The results indicated validity of the optimization technique employed and the polynomial equation developed could be used to formulate Irbesartan tablets with any desired dissolution rate specification. Hence formulation of irbesartan tablets with any desired dissolution rate specification could be optimized by 2^2 factorial design.

KEYWORDS: Irbesartan tablets, Optimization, Factorial Design, β Cyclodextrin, Crospovidone.

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. 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 crospovidone and sodium starch glycolate (Crospovidone) 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 15 min employing Crospovidone and βCD 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. 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) were procured from local market. 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 2^2 factorial designs the βCD and Crospovidone are considered as the two factors. The two levels of the factor A (Crospovidone) 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 irbesartan tablet formulations employing selected combinations of the two factors i.e., Crospovidone and βCD 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 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 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

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).

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 15 min. Crospovidone and βCD are considered as the two factors involved in the 2^2 factorial design. The two levels of the factor A (Crospovidone) 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. 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 and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics.

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 0.93 % 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 20 sec to 8 min 10 sec. Irbesartan tablets (F_a) formulated employing Crospovidone at 30% of drug content and βCD in 1:1ratio of drug: βCD disintegrated rapidly within 20 sec . All other tablets disintegrated rather slowly in about 5-9 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 0.952. The first order dissolution rate constant (K_1) values were estimated from the slope of the first order linear plots. Much variation were observed in the dissolution rate (K_1) and DE_{30} values of the tablets prepared due to formulation variables. Irbesartan tablets (F_a) which are prepared employing Crospovidone at 30% of drug content and βCD in 1:1 ratio of drug: βCD gave very rapid dissolution of irbesartan than others. These tablets (F_a) gave 97.18% dissolution in 15min. 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 $F_a > F_{ab} > F_l > F_b$.

For optimization, percent drug dissolved in 15 min was taken as response (Y) and level of Crospovidone as (X_1) and level of βCD 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 **Y = 60.37+33.04 (X_1) − 5.03 (X_2) + 1.265 (X_1 X_2)**. Based on the above polynomial equation, the following two optimized Irbesartan tablet formulations, one with high dissolution and the other with moderate dissolution were worked out.

1. Irbesartan tablet formulation with NLT 85% dissolution in 15 min could be formulated employing Crospovidone at 24.75% of drug content and βCD at 1:1 ratio of drug: βCD. (OPT 1)
2. Irbesartan tablet formulation with NLT 70% dissolution in 15 min could be formulated employing Crospovidone at 19.07% of drug content and βCD at 1:2 ratio of drug:βCD. (OPT 2)

To verify, optimized irbesartan tablets (OPT1 and OPT2) were formulated employing the optimized levels of Crospovidone and βCD in each case. The formulae of the optimized irbesartan tablets are given in Table1.The optimized irbesartan tablet formulations were prepared by direct compression method and the tablets were evaluated. The physical parameters of the optimized formulations are given in Table2 and the dissolution parameters are given in Table3. The hardness of the optimized irbesartan tablets was 5.0kg/sq.cm. Friability (percent weight loss) was less than 0.92%. Disintegration time of the optimized

tablets was 30sec in the case of OPT1 and 55sec in the case of OPT2. The optimized irbesartan tablet formulation, OPT1 gave 88.27% dissolution in 15 min and formulation OPT2 gave 73.48% dissolution in 15 min fulfilling the target dissolution set in each case. These results indicated validity of the optimization technique employed and the polynomial equation developed could be used to formulate Irbesartan tablets with any desired dissolution rate specification. Hence formulation of irbesartan tablets with any desired dissolution rate specification could be optimized by 2^2 factorial design. . For comparison the dissolution rate of a commercial brand of Irbesartan tablets (IROVEL-150) was also studied. The dissolution profiles of optimized Irbesartan tablet formulations developed and commercial brand are shown in fig.2.The dissolution profiles of optimized formulation OPT1 was similar to that of commercial brand.

Table-1: Formulae of Irbesartan Tablets Prepared Employing βCD and Crospovidone as Per2² Factorial Design and Optimized Formulations.

Ingredient (mg/tab)	CF_1	CF_a	CF_b	CF_{ab}	OPT1	OPT2
Irbesartan	100	100	100	100	100	100
βCD	100	100	500	500	100	200
Crospovidone	2	30	2	30	24.75	19.07
Talc	4	4.6	12	12.6	4.49	6.38
Magnesium stearate	4	4.6	12	12.6	4.49	6.38
Total weight (mg)	210	239.2	626	655.2	233.73	331.83

Table-2: Physical Parameters of Irbesartan Tablets Prepared Employing βCD and Crosspovidone as per 2² Factorial Design and Optimized Formulations.

Formulation	Hardness (Kg/cm²)	Friability (% Wt loss)	Disintegration Time (min-sec)	Drug Content (mg/tablet)
CF_1	5.0	0.78	7-40	98.8
CF_a	5.0	0.67	0-20	99.0
CF_b	4.5	0.93	8-10	98.8
CF_{ab}	4.5	0.88	5-50	98.7
OPT1	5.0	0.69	0-30	98.5
OPT2	5.0	0.80	0-55	98.7

Table 3: Dissolution Parameters of Irbesartan Tablets Prepared Employing βCD and Crosspovidone as per 2² Factorial Design and Optimized Formulations.

Formulation	PD_{15} (%)	T_{50} (min)	DE_{30} (%) ($\bar{x} \pm sd$)	K_1 X 10^3 (min^{-1}) ($\bar{x} \pm sd$)
CF_1	33.62	60	29.23±8.25	27±7.31
CF_a	97.18	1.5	80.05±0.47	237±1.13
CF_b	21.03	50	17.75±5.18	15.7±7.60
CF_{ab}	89.65	40	78.24±0.47	151±1.24

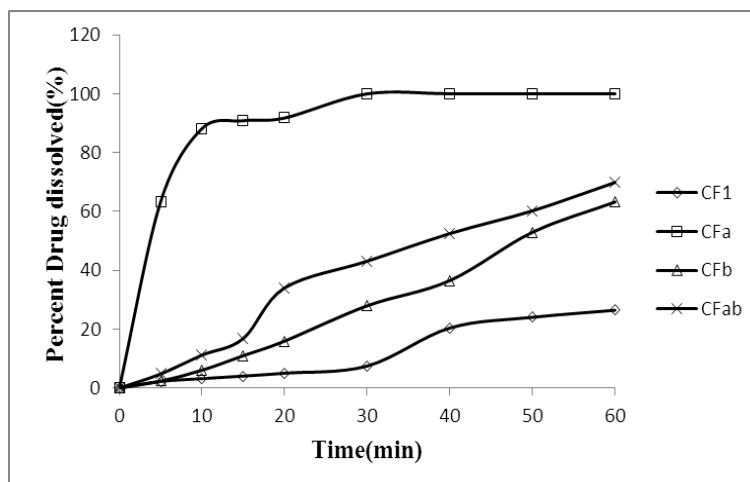| OPT1 | 88.27 | 2.5 | 78.25±0.41 | 148±0.85 |
| OPT2 | 73.48 | 4 | 65.80±0.54 | 84±0.71 |

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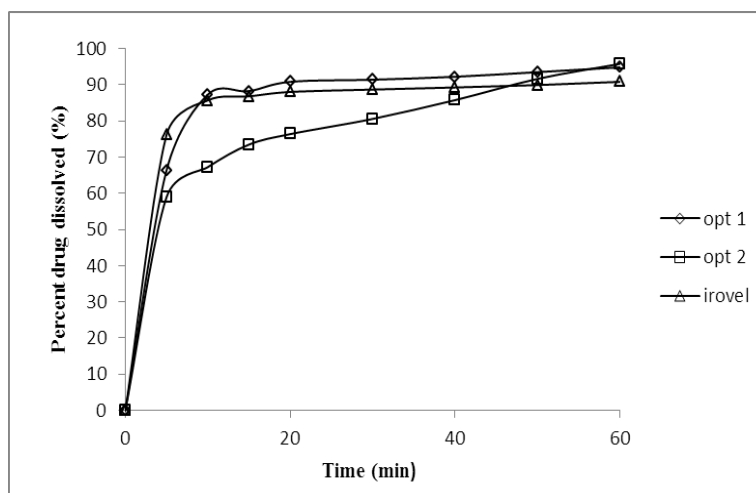

Fig-2. Dissolution Profile of Optimized Irbesartan Tablets Formulation and Commercial Tablets.

CONCLUSIONS

1. Irbesartan tablets formulated employing Crospovidone at a level of 30% of drug content and βCD in 1:1 ratio of drug: βCD (F_a) disintegrated rapidly within 20 seconds and gave very rapid dissolution of irbesartan, 97.18% in 15 min.

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

3. The increasing order of dissolution rate (K_1) observed with various formulations was F_a> F_{ab}> F_1> F_b.

4. The polynomial equation describing the relationship between the response i.e. percent drug dissolved in 15min (Y) and the levels of Crospovidone (X_1) and βCD (X_2) based on the observed results is $Y = 60.37 + 33.04\,(X_1) - 5.03\,(X_2) + 1.265\,(X_1\,X_2)$.

5. Based on the above polynomial equation, two optimized Irbesartan tablet formulations, One with high dissolution (OPT1) with NLT 85% dissolution in 15 min could be formulated employing Crospovidone at 24.75% of drug content and βCD at 1:1 ratio of drug: βCD and the other with moderate dissolution (OPT2) with NLT 70% dissolution in 15 min could be formulated employing Crospovidone at 19.07% of drug content and βCD at 1:2 ratio of drug: βCD.

6. The optimized irbesartan tablet formulation, OPT1 gave 88.27% dissolution in 15 min and formulation OPT2 gave 73.48% dissolution in 15 min fulfilling the target dissolution set in each case.

7. The results indicated validity of the optimization technique employed and the polynomial equation developed could be used to formulate Irbesartan tablets with any desired dissolution rate specification. Hence formulation of irbesartan tablets with any desired dissolution rate specification could be optimized by 2^2 factorial design.

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