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FORMULATION DEVELOPMENT OF IRBESARTAN TABLETS: SELECTION OF DILUENT- BINDER-DISINTEGRANT COMBINATION BY 2^3 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. Because of poor aqueous solubility and dissolution rate it poses challenging problems in its tablet formulation development. In the case of poorly soluble drugs the excipients in tablet formulation significantly influence dissolution rate and consequently bioavailability of the drug requiring a rational selection of diluent, binder and disintegrant combination. The objective of the study is to optimize irbesartan tablet formulation by 2^3 factorial design for selecting the best combinations of diluent, binder and disintegrant giving fast dissolution of the drug, irbesartan.

Much variations were observed in the disintegration and dissolution characteristics of the irbesartan tablets prepared employing various combinations of binder (factor A), disintegrant (factor B) and diluent (factor C) as per 2^3 factorial design. All the irbesartan tablets formulated disintegrated rapidly within 1 min 25 sec except formulation Fa which disintegrated in 6 min 10 sec.ANOVA of K_1 and DE_{30} values indicated that the individual and combined effects of the three factors in influencing the dissolution rate of tablets are highly significant ($P < 0.01$) except the individual effect of DCP and combined effects of (Primojel – DCP) and (PVP – Primojel – DCP). Among all, formulation F_1 (tablets prepared employing lactose, acacia and potato starch), F_c (tablets prepared employing DCP, acacia and potato starch) and F_b(tablets prepared employing lactose, acacia and Primojel) gave higher dissolution rates and DE_{30} values. The increasing order of dissolution rate (K_1) observed with various formulations was as follows: $F_1 > F_c > F_b > F_{ac} > F_{bc} > F_{ab} > F_{abc} > F_a$. Formulations F_1, F_b, F_c gave 93.07, 93.85 and 92.82 % dissolution in 20 min respectively fulfilling the official dissolution rate test specification.Thus, the results of the present study indicated that combinations of (i) lactose, acacia and potato starch, (ii) DCP, acacia and potato starch and (iii) lactose, acacia and Primojel are the best combinations of diluent, binder and disintegrant and hence these combinations are recommended for formulation of irbesartan tablets giving rapid and higher dissolution of irbesartan, a BCS class II drug.

Key words: Formulation development, Optimization, Irbesartan, Diluent, Binder, Disintegrant, 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. Tablet formulation requires a careful selection of excipients to serve various pharmaceutical purposes. Among the various excipients (additives) added in tablet formulation, the diluent, binder and disintegrant play a critical role in influencing the dissolution rate and bioavailability of drugs administered as tablet dosage form[1]. In the case of poorly soluble drugs these excipients in tablet formulation significantly influence dissolution rate[2-7] and consequently bioavailability of the drug requiring a rational selection of diluents, binder and disintegrant combination. The objective of the study is to optimize irbesartan tablet formulation by 2^3 factorial design for selecting the best combinations of diluent, binder and disintegrant giving fast dissolution of the drug, irbesartan.

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EXPERIMENTAL

Materials:

Irbesartan was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. Lactose, dicalcium phosphate (DCP), polyvinyl pyrrolidone (PVP), potato starch, Primojel, acacia, talc, 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 244nm 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 0.8% and 1.45% respectively. No interference by the excipients used in the study was observed.

Formulation of Irbesartan Tablets:

For formulation of irbesartan tablets as per 2^3 factorial designs the binder, diluent and disintegrant are considered as the three factors. The two levels of the factor A (binder) are acacia and PVP at 2% concentration each and the two levels of the factor B (disintegrant) are potato starch (15%) and Primogel (5%). The two levels of the factor C (diluent) are lactose and DCP. Eight irbesartan tablet formulations employing selected combinations of the three factors i.e., binder, disintegrant and diluent as per 2^3 factorial design were formulated and prepared by wet granulation method and evaluated to find out the significance of individual and combined effects of the binder, disintegrant and diluent and to select the best combinations for formulation of tablets giving fast dissolution of irbesartan.

Preparation of Irbesartan Tablets:

Irbesartan (50 mg) tablets were prepared by wet granulation method as per the formula given in Table 1.The required quantities of irbesartan, lactose, dicalcium phosphate, acacia, PVP, potato starch as per the formula in each case were blended thoroughly in a dry mortar and granulated with water (q.s) as granulating fluid. The wet mass formed was pressed through mesh no.12 to obtain wet granules. The wet granules were dried at 60^0 C for 1hour. The dried granules were passed through mesh no.14 to break the aggregates formed and to obtain discrete granules. Super disintegrant Primojel, talc and magnesium stearate were passed through mesh no.80 and collected on to the bed of tablet granulations prepared and mixed. The tablet granules were blended thoroughly in a closed polyethene bag and compressed in to 250 mg tablets using an 8- station RIMEK tablet punching machine employing 9mm flat punches.

Evaluation of Tablets:

Irbesartan tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as per official methods.

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 acidand 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. Each dissolution experiment was run in triplicate (n=3).

Analysis of Data:

The dissolution data were analysed as per zero order and first order kinetic models. Dissolution efficiency (DE_{30}) values were estimated as suggested by Khan [8]. Dissolution rate (K_1) and dissolution efficiency (DE_{30}) values were analysed as per ANOVA of 2^3 factorial experiments.

RESULTS AND DISCUSSION

Irbesartan tablet formulation was optimized by 2^3 factorial designs for selecting the best combinations of diluent, binder and disintegrant giving fast dissolution of the drug. For formulation of irbesartan tablets as per 2^3 factorial design the three factors involved are binder, diluent and disintegrant. The two levels of the factor A (binder) are acacia and PVP at 2% concentration each and the two levels of the factor B (disintegrant) are potato starch (15%) and Primojel (5%). The two levels of the factor C (diluent) are lactose and DCP. Eight irbesartan tablet formulations each containing 50 mg of irbesartan were prepared employing selected combinations of the three factors i.e., binder, disintegrant and diluent as per 2^3 factorial design. The tablets were prepared by wet granulation method as per the formulae given in Table 1. All the tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as per official methods.

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 0.87 % 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. All the irbesartan tablets formulated disintegrated rapidly within 1 min 25 sec except formulation Fa which disintegrated in 6 min 10 sec. As such all irbesartan tablets formulated employing selected combinations of binder, disintegrant and diluent were of good quality with regard to drug content, hardness, friability and disintegration time.

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 0.905. 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. The results of ANOVA (Tables 4,5) of K_1 and DE_{30} values indicated that the individual and combined effects of the three factors in influencing the dissolution rate of tablets are highly significant ($P < 0.01$) except the individual effect of DCP and combined effects of (Primojel – DCP) and (PVP – Primojel – DCP).

Among all, formulation F_1 (tablets prepared employing lactose, acacia and potato starch), F_c (tablets prepared employing DCP, acacia and potato starch) and F_b(tablets prepared employing lactose, acacia and Primojel) gave higher dissolution rates and DE_{30} values. The increasing order of dissolution rate (K_1) observed with various formulations was as follows:

$F_1 > F_c > F_b > F_{ac} > F_{bc} > F_{ab} > F_{abc} > F_a$

USP 2008 prescribed a dissolution rate test specification of NLT 80% in 20 min for irbesartan tablets. Formulations F_1, F_b, F_c gave 93.07, 93.85 and 92.82 % dissolution in 20 min respectively fulfilling the official dissolution rate test specification.

Thus, combinations of (i) lactose, acacia and potato starch, (ii) DCP, acacia and potato

starch and (iii) lactose, acacia and Primojel are the best combinations of diluent, binder and disintegrant and hence these combinations are recommended for formulation of irbesartan tablets giving rapid and higher dissolution of irbesartan, a BCS class II drug.

CONCLUSIONS

1. Much variations were observed in the disintegration and dissolution characteristics of the irbesartan tablets prepared employing various combinations of binder (factor A), disintegrant (factor B) and diluent (factor C) as per 2^3 factorial design.
2. All the irbesartan tablets formulated disintegrated rapidly within 1 min 25 sec except formulation Fa which disintegrated in 6 min 10 sec.
3. ANOVA of K_1 and DE_{30} values indicated that the individual and combined effects of the three factors in influencing the dissolution rate of tablets are highly significant ($P < 0.01$) except the individual effect of DCP and combined effects of (Primojel – DCP) and (PVP – Primojel – DCP).
4. Among all, formulation F_1 (tablets prepared employing lactose, acacia and potato starch), F_c (tablets prepared employing DCP, acacia and potato starch) and F_b (tablets prepared employing lactose, acacia and Primojel) gave higher dissolution rates and DE_{30} values.
5. The increasing order of dissolution rate (K_1) observed with various formulations was as follows: $F_1 > F_c > F_b > F_{ac} > F_{bc} > F_{ab} > F_{abc} > F_a$
6. Formulations F_1, F_b, F_c gave 93.07, 93.85 and 92.82 % dissolution in 20 min respectively fulfilling the official dissolution rate test specification.
7. Thus, the results of the present study indicated that combinations of (i) lactose, acacia and potato starch, (ii) DCP, acacia and potato starch and (iii) lactose, acacia and Primojel are the best combinations of diluents, binder and disintegrant and hence these combinations are recommended for formulation of irbesartan tablets giving rapid and higher dissolution of irbesartan, a BCS class II drug.

Table 1: Formulae of Irbesartan Tablets Prepared as Per 2^3 Factorial Designs

Ingredient (mg/ tablet)	F_1	F_a	F_b	F_{ab}	F_c	F_{ac}	F_{bc}	F_{abc}
Irbesartan	50	50	50	50	50	50	50	50
Acacia	5	-	5	-	5	-	5	-
PVP	-	5	-	5	-	5	-	5
Potato starch	37.5	37.5	-	-	37.5	37.5	-	-
Primogel	-	-	12.5	12.5	-	-	12.5	12.5
Lactose	147.5	147.5	172.5	172.5	-	-	-	-
DCP	-	-	-	-	147.5	147.5	172.5	172.5
Talc	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5
Total weight (mg)	250	250	250	250	250	250	250	250

Table 2: Physical Parameters of Irbesartan Tablets Prepared as per 2^3 Factorial Design

Formulation	Hardness (Kg/cm^2)	Friability (% Wt loss)	Disintegration Time (min-sec)	Drug Content (mg/tablet)
F 1	5.0	0.66	0 -35	49.8
F a	4.5	0.64	6-10	48.4
F b	4.7	0.71	1-25	50.2
F ab	5.0	0.75	0-40	50.6
F c	5.0	0.69	0– 24	49.3
F ac	4.5	0.87	1 -24	49.5
F bc	4.8	0.79	0- 25	50.7
F abc	4.5	0.85	0- 58	51.3

Table 3: Dissolution Parameters of Irbesartan Tablets Prepared as per 2^3 Factorial Design

Formulation	PD_{20} (%)	T_{50} (min)	DE_{30} (%)	$K_1 X 10^2$ (min^{-1})	Official Dissolution Rate Test Specification
F_1	93.07	4	77.41	19.63	NLT 80% in 20 min (USP 2008)
F_a	25.01	45	17.20	1.74	
F_b	93.85	7	66.57	11.65	
F_{ab}	60.45	17	44.74	7.38	
F_c	92.82	4	76.95	11.72	
F_{ac}	63.56	15	48.64	9.17	
F_{bc}	57.44	19	34.41	7.80	
F_{abc}	29.55	24	28.51	5.87	

Table 4: ANOVA of Dissolution Rates (K_1) of Irbesartan Tablets Prepared as per 2^3 Factorial Design

Source of Variance	Degrees of Freedom (DF)	Sum of Squares (SS)	Mean Sum of Squares (MSS)	F- Ratio
Total	23	690.75	30.03	
Treatment	7	578.88	82.69	11.82
Error	16	111.87	6.99	
F a	1	266.06	266.06	38.06
F b	1	34.29	34.29	4.90
F ab	1	76.07	76.07	10.88
F c	1	12.77	12.77	1.82
Fac	1	117.35	117.35	16.78
Fbc	1	8.91	8.91	1.27
Fabc	1	63.40	63.40	9.07

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

Table 5: ANOVA of DE_{30} Valuesof Irbesartan Tablets Prepared as per 2^3 Factorial Design

Source of Variance	Degrees of Freedom (DF)	Sum of Squares (SS)	Mean Sum of Squares (MSS)	F – Ratio
Total	23	12051.35	523.97	
Treatment	7	11186.40	1598.05	29.56
Error	16	864.95	54.05	
Fa	1	5461.37	5461.37	101.04
Fb	1	646.67	646.67	11.96
Fab	1	1190.60	1190.60	22.02
Fc	1	178.86	178.86	3.30
Fac	1	1024.68	1024.68	18.95
Fbc	1	2634.25	2634.25	48.73
Fabc	1	49.93	49.93	0.92

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

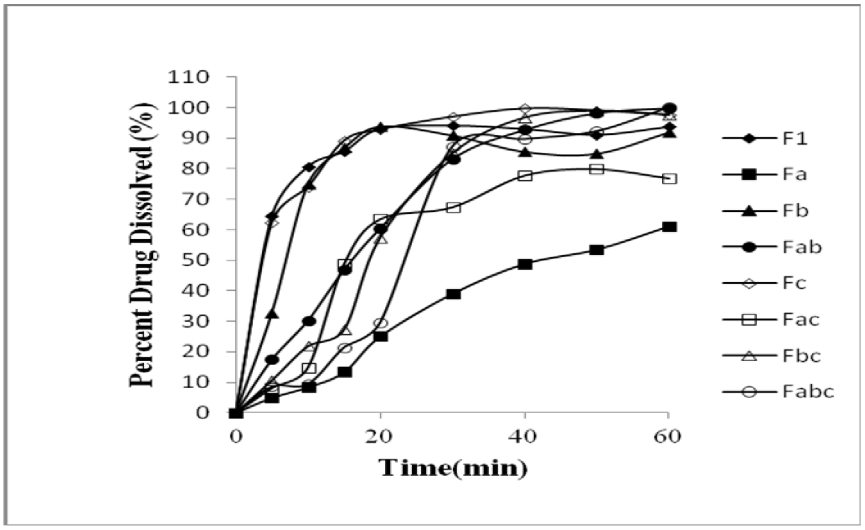

Fig.1: Dissolution Profiles of Irbesartan Tablets Prepared as per 2^3 Factorial Design

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