WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 4, Issue 2, 478-485. Research Article ISSN 2277– 7105

FACTORIAL STUDIES ON FORMULATION DEVELOPMENT OF IRBESARTAN TABLETS EMPLOYING BCD AND KOLLIPHOR HS15

T. Srinivasa Rao[1] and K.P.R. Chowdary*[2]

[1]M. L. College of Pharmacy, Singaraayakonda- 523010, A.P.

[2]A. U. College of Pharmaceutical Sciences, Andhra University, Visakhapatnam – 530 003, A.P.

Article Received on
16 Nov 2014,

Revised on 11 Dec 2014,
Accepted on 05 Jan 2015

***Correspondence for Author**
Dr. K.P.R. Chowdary
A. U. College of Pharmaceutical Sciences, Andhra University, Visakhapatnam – 530 003, A.P.

ABSTRACT

Irbesartan is an effective antihypertensive drug. It belongs to class II under Biopharmaceutical classification system and exhibit low and variable oral bioavailability due to its poor solubility. It is practically insoluble in water and aqueous fluids and its oral absorption is dissolution rate limited. It needs enhancement in solubility and dissolution rate for improvement of its oral bioavailability and therapeutic efficacy. The objective of the present study is to enhance the dissolution rate and formulation development of Irbesartan tablets with fast dissolution characteristics employing βCD and Kolliphor HS15, a non ionic surfactant. The individual and combined effects of βCD (factor A) and Kolliphor HS15 (factor B) on the dissolution rate of Irbesartan from solid inclusion complexes and their tablets were evaluated in a series of 2^2 factorial experiments. The feasibility of formulating Irbesartan - βCD-Kolliphor HS15 inclusion complexes into tablets with fast dissolution rate characteristics was also investigated. The individual and combined effects of βCD and Kolliphor HS15 in enhancing the dissolution rate and dissolution efficiency of Irbesartan from solid inclusion complexes and their tablets were highly significant ($P < 0.01$). The dissolution of Irbesartan was rapid and higher in the case of Irbesartan- βCD and Irbesartan- βCD - Kolliphor HS15 complexes prepared when compared to Irbesartan pure drug. β CD alone gave a 8.26 fold increase and in combination with Kolliphor HS15 it gave 9.94 fold increase in the dissolution rate of (K_1) of Irbesartan. Irbesartan –βCD – Kolliphor HS15 inclusion complexes could be formulated into compressed tablets by wet granulation method and the resulting tablets also gave rapid and higher dissolution of Irbesartan. Irbesartan tablets formulated with βCD and Kolliphor

HS15 individually gave 4.85 and 6.45 fold increase in the dissolution rate and those containing drug - βCD -Kolliphor HS15 complex gave much higher enhancement (22.65 fold) in the dissolution rate when compared to tablets formulated with Irbesartan pure drug. Combination of βCD and Kolliphor HS15 gave much higher enhancement in the dissolution rate of Irbesartan tablets than is possible with them individually. A combination of βCD with Kolliphor HS15 is recommended to enhance the dissolution rate in the formulation development of Irbesartan tablets with fast dissolution rate characteristics.

KEYWORDS: Irbesartan, β Cyclodextrin, Kolliphor HS15, Dissolution Rate, Irbesartan Tablets, Formulation development.

INTRODUCTION

Irbesartan is an effective antihypertensive drug. It belongs to class II under Biopharmaceutical classification system and exhibit low and variable oral bioavailability due to its solubility. It is practically insoluble in water and aqueous fluids and its oral absorption is dissolution rate limited. It needs enhancement in solubility and dissolution rate for improvement of its oral bioavailability and therapeutic efficacy. Several techniques are reported[1] to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs. Complexation[2-5] with βcyclodextrin (βCD) and use of surfactants are two industrially used techniques in the formulation development of insoluble drugs to enhance their solubility and dissolution rate.

The objective of the present study is enhancement of dissolution rate and formulation of Irbesartan tablets with fast dissolution characteristics employing βCD and Kolliphor HS15, a non ionic surfactant. Kolliphor HS15 is reported as non toxic and safe for human and animal use.[6] The study was conducted as a 2^2 factorial experiment. The individual and combined effects of βCD (factor A) and Kolliphor HS15 (factor B) on the dissolution rate of Irbesartan from solid inclusion complexes and their tablets were evaluated in a series of 2^2 factorial experiments. The feasibility of formulating Irbesartan - βCD-Kolliphor HS15 inclusion complexes into tablets with fast dissolution rate characteristics was also investigated.

EXPERIMENTAL

Materials

Irbesartan was obtained from M/s Eisai Pharmatechnology Pvt. Ltd., Visakhapatnam. β-cyclodextrin, Kolliphor HS15, Croscarmellose Sodium, Lactose and PVP K30 were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Methods

Estimation of Irbesartan

Irbesartan was estimated by UV spectrophotometric method and absorbance was measured at 244 nm using 0.1N HCl as solvent. Validation of the method was carried out for accuracy, precision, interference and linearity. The method exhibited linearity in the concentration range 1-10 µg/ml. The accuracy (relative error) and precision (RSD) of the method were found to be 0.95% and 1.55 % respectively. It was observed that the excipients used did not have any interference in the method of analysis.

Preparation of Irbesartan - βCD Complexes

Solid inclusion complexes of Irbesartan – βCD - Kolliphor HS15 were prepared by kneading method. Irbesartan, βCD and KolliphorHS15 were triturated in a dry mortar with a small volume of solvent methanol. The thick slurry formed was kneaded for 45 min and then dried at 55^{o}C until it is dry. **T**he dried mass was powdered and screened through sieve No.120.

Preparation of Irbesartan Tablets Employing βCD Complexes

Irbesartan (100 mg) tablets were prepared as per 2^2 – factorial study by wet granulation method employing Irbesartan- βCD - Kolliphor HS15 inclusion complexes as per the formulae given in Table 2. Drug-CD-Kolliphor HS15 complex systems were initially prepared in each case by kneading method. To the dried complex in the mortar lactose and PVP were added and mixed thoroughly. Water (q.s) was added and mixed thoroughly to form a dough mass. The mass was pressed through mesh No. 12 to obtain wet granules. After drying the wet granules at 60°C for 4 hr, they were passed through mesh No. 16 to break the aggregates. To the dried granules Primojel, talc and magnesium stearate (already screened through sieve No.100) were added and mixed thoroughly in a polyethylene bag. Then the granules were punched into tablets using a 16 station tablet punching machine (M/s. Cadmech) using 9 mm flat and round punches.

Evaluation of Tablets

All the prepared tablets were evaluated for drug content, hardness, friability, disintegration time and dissolution rate. Monsanto hardness tester was used for testing hardness of the tablets prepared. Friability of the tablets was determined in a Roche friabilator. Disintegration time of the tablets was tested in a Thermonic tablet disintegration test machine using water as test fluid.

Dissolution Rate Study

Irbesartan dissolution from βCD - Kolliphor HS15 inclusion complexes and their tablets was studied in 0.1N HCl (900 ml) using LABINDIA 8 station dissolution rate test apparatus. A paddle stirrer at 50 rpm and a temperature of 37 ±1^{o}C were used. Inclusion complex or tablet containing 100 mg of Irbesartan was used in each test. Samples of dissolution media (5 ml) were withdrawn through a filter (0.45 µ) at 5, 10, 20, 30, 40 , 50 and 60 min, suitably diluted and assayed for Irbesartan at 244 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh dissolution fluid and a suitable correction was made for the dug amount lost in samples while calculating the amount and percent drug dissolved at various times. The dissolution experiments were replicated three times each (n=3).

Analysis of results

Dissolution data were analysed as per zero order and first order kinetics to evaluate the dissolution rates. Dissolution efficiency (DE_{15}) values were calculated as per the method of Khan.[7] Dissolution data were also analyzed by Analysis of Variance (ANOVA) of 2^2 factorial study.

RESULTS AND DISCUSSION

The objective of the present study is to enhance the dissolution rate and formulation of Irbesartan tablets with fast dissolution characteristics employing βCD and Kolliphor HS15, a non ionic surfactant. The individual and combined effects of βCD (factor A) and Kolliphor HS15 (factor B) on the dissolution rate of Irbesartan from solid inclusion complexes and their tablets were evaluated in a series of 2^2 factorial experiments. The feasibility of formulating Irbesartan - βCD-Kolliphor HS15 inclusion complexes into tablets with fast dissolution rate characteristics was also investigated.

For 2^2 factorial experiments on dissolution rate, the two levels of βCD (factor A) are 0 and 1:2 ratio of drug: βCD and the two levels of Kolliphor HS15 (factor B) are 0 and 2 %.

Accordingly the four treatments involved are Irbesartan pure drug (1), Irbesartan- βCD (1:2) inclusion complex (a), Irbesartan - Kolliphor HS15 (2%) complex (b) and Irbesartan- βCD (1:2) - Kolliphor HS15 (2%) complex (ab). The complexes were prepared by kneading method.

The prepared solid inclusion complexes were fine and free flowing powders. Low RSD values < 1.25 % in the percent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared.

The dissolution rate of Irbesartan from the βCD complexes prepared was studied in 0.1N HCl. The dissolution of Irbesartan followed first order kinetics with R^2 (coefficient of determination) values greater than 0.946. The dissolution parameters estimated are given in Table 1. All the dissolution parameters indicated rapid and higher dissolution of Irbesartan from the CD complexes when compared to Irbesartan pure drug.

The results of ANOVA indicated that the individual main effects of βCD and Kolliphor HS15 and their combined effects in enhancing the dissolution rate (K_1)and dissolution efficiency (DE_{15}) were highly significant ($P < 0.01$). βCD individually gave a 8.26 fold increase in the dissolution rate of (K_1) of Irbesartan. Whereas when it is combined with Kolliphor HS15 the dissolution rate (K_1) was enhanced by 9.94 fold. Kolliphor HS15 (F_b) individually also gave 7.06 fold increase in the dissolution rate (K_1) of Irbesartan. DE_{15} values were also much higher in the case of βCD – Kolliphor HS15 solid complexes when compared to Irbesartan pure drug.

The Irbesartan - βCD – Kolliphor HS15 solid complexes (1,a,b,ab) were formulated into tablets by wet granulation method as per the formulae given in Table 2. The physical parameters of the tablets prepared are given in Tables 3. Irbesartan content of the tables was within 100± 2% of the labeled claim. Hardness of the tablets was in the range 6.0-7.5 Kg / cm^2. Percentage weight loss was less than 0.85% in the friability test. All the tablets formulated employing inclusion complexes disintegrated rapidly within 2.5 min. The dissolution profiles of the Irbesartan tablets prepared are shown in Fig.1.The dissolution parameters estimated are given in Table 4. Irbesartan dissolution was rapid and higher from the tablets formulated employing drug- βCD- Kolliphor HS15 inclusion complexes when compared to the tablets containing Irbesartan pure drug. The results of ANOVA indicated that the individual as well as combined effects of the two factors involved i.e., βCD (factor

A) and Kolliphor HS15 (factor B) were highly significant (P< 0.01) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{15}) of Irbesartan tablets. Tablets $F_a$and F_b formulated respectively with βCD and Kolliphor HS15 alone gave 4.85 and 6.45 fold increase in the dissolution rate when compared to control tablets F_1 formulated with Irbesartan pure drug. Tablets F_{ab} containing drug - βCD -Kolliphor HS15 complex gave much higher enhancement (22.65fold) in the dissolution rate when compared to control formulation F_1 and also formulations F_a and F_b.

Table 1: Dissolution Parameters of Irbesartan- βCD-Kolliphor HS15 Inclusion Complexes Prepared as per 2^2 Factorial Study.

Irbesartan-CD complexes (Statistical Code as per 2^2 Factorial design)	DE_{15} (%)		$K_1 \times 10^2$ (min^{-1})	
	$\bar{x}$	Increase (no. of folds)	$\bar{x}$	Increase (no. of folds)
Irbesartan (1)	10.15	-	5.31	-
Irbesartan-βCD (a)	63.43	6.25	43.86	8.26
Irbesartan -Kolliphor HS15 (b)	50.54	4.98	37.49	7.06
Irbesartan -βCD- Kolliphor HS15 (ab)	75.62	7.45	52.78	9.94

Table 2: Formulae of Irbesartan Tablets Prepared Employing βCD and Kolliphor HS15 as per 2^2 Factorial Design.

Ingredient (mg/tab)	FORMULATION			
	F_1	F_a	F_b	F_{ab}
Irbesartan	100	100	100	100
β-CD	--	200	--	200
Kolliphor HS15	--	--	5	5
Primojel	15	15	15	15
PVP K30	7	7	7	7
Talc	7	7	7	7
Magnesium stearate	7	7	7	7
Lactose	214	14	209	9
Total weight (mg)	350	350	350	350

Table 3: Hardness, Friability, Disintegration Time and Drug Content of Irbesartan Tablets Formulated employing βCD and Kolliphor HS15.

Formulation (code as per 2^2 Factorial Design)	Hardness (kg/sq.cm)	Friability (%)	Disintegration Time (min.)	Irbesartan content (mg/tablet)
F_1	7.0	0.54	2.5	99.6
F_a	6.5	0.85	2.0	98.8
F_b	6.0	0.35	2.0	100.4
F_{ab}	7.5	0.65	2.5	98.6

Table 4: Dissolution Parameters of Irbesartan Tablets Formulated Employing βCD-Kolliphor HS15as per 2^2 Factorial Design.

Formulation	DE_{30} (%)		K_1 (min^{-1}) ×10^2	
	$(\bar{x})$	Increase in DE_{30} (N0.of folds)	$(\bar{x} \pm s.d.)$	Increase in K_1 (N0.of folds)
F_1	7.40	-	0.23 ± 0.015	-
F_a	24.05	3.25	1.11 ± 0.055	4.85
F_b	34.04	4.60	1.48 ± 0.054	6.45
F_{ab}	46.25	6.25	5.21 ± 0.421	22.65

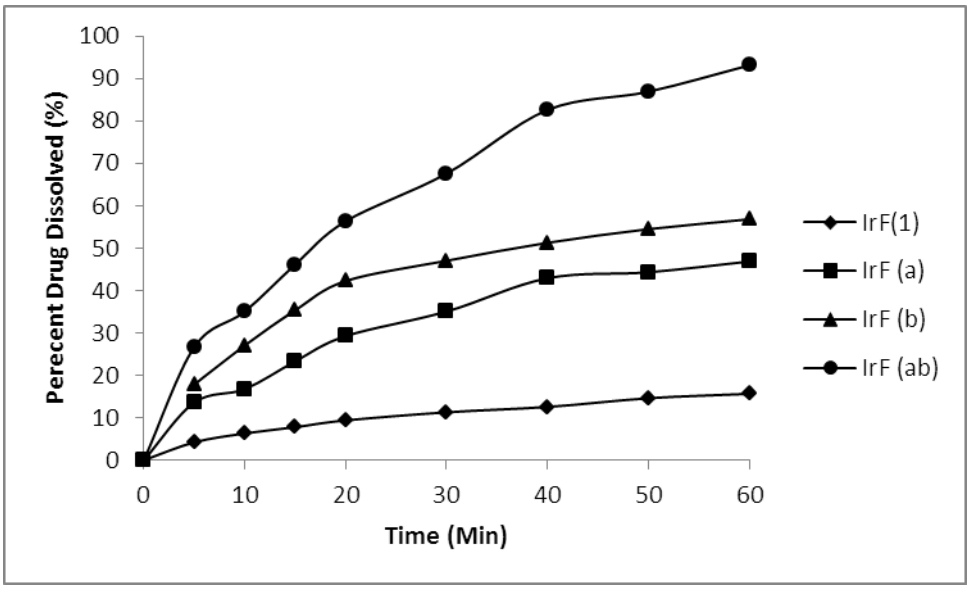

Fig. 1 Dissolution Profiles of Irbesartan Tablets Formulated Employing βCD and Kolliphor HS15 as per 2^2 Factorial Design.

CONCLUSION

Thus combination of βCD and Kolliphor HS15 resulted in a much higher enhancement in the dissolution rate of Irbesartan tablets than is possible with them individually. As such a combination of βCD with Kolliphor HS15 is recommended to enhance the dissolution rate in the formulation development of Irbesartan tablets with fast dissolution rare characteristics.

REFERENCES

1. Chowdary, K. P. R and Madhavi, BLR, Novel Drug Delivery Technologies for Insoluble Drugs, Indian Drugs, 2005; 42(9): 557 – 562.
2. Fromming, K.H. and Szejtli, J. Cyclodextrins in Pharmacy. Kluwer Academic Publications, Dordrecghi, 1994; 20.
3. Duchene, D., Woussidjewe, D. and Dumitriu, S. Polysaccharides in Medical Applications. Marcel Dekker, New York, 1996; 575- 602.

4. Thompson, D.O. Cyclodextrins-Enabling Excipients: Their Present and Future Use In Pharmaceuticals, Crit Rev Therapeutic Drug Carrier System; 1997; 14(1); 1-104.
5. Hedges, A.R. Chemical Review. Industrial applications of cyclodextrins, 1998; 98: 2035-2044.
6. Sherry KU and Ranga Velageti, Solutol HS15 as a Novel Excipient, Pharmaceutical Technology, *Nov* 2010*;* 108-110.
7. Khan, K.A., Journal of Pharmacy and Pharmacology. The concept of dissolution efficiency, 1975; 27: 48-49