International Research Journal of Pharmacy and Medical Sciences
ISSN (Online): 2581-3277

Formulation Optimization and In Vitro and In Vivo Preclinical Evaluation of Valsartan IR Tablets

N. Tirumalesh[1], K. P. R. Chowdary[2]
[1]Ph.D Research Scholar, Acharya Nagarjuna University, Guntur
[2]Chairman, BOS in Pharmacy, JNTUK, Kakinada and Research Director, Vikas Institute of Pharmaceutical Sciences, Rajahmundry-533102
E-mail: [2]prof.kprchowdary@rediffmail.com

Abstract—*The objective of the present study is optimization of Valsartan tablet formulation employing βCD, Starch 1500, and Soluplus by 2^3 factorial design to achieve NLT 85% dissolution in 10 min and to evaluate the optimized formulations by In Vitro and In Vivo (Preclinical) methods. Eight Valsartan tablet formulations were prepared using selected combinations of the three factors as per 2^3 factorial design. Valsartan tablets were prepared by direct compression method and were evaluated. The individual and combined effects of the three factors βCD, Starch 1500 and Soluplus are highly significant ($P < 0.01$) in influencing the dissolution rate of Valsartan tablets.Valsartan tablet formulations F_b,F_{ab}, F_{bc} and F_{abc} disintegrated rapidly and gave very rapid dissolution of Valsartan, 92.4%, 99.4% ,96.2% and 99.2% in 10 min respectively. The increasing order of dissolution rate (K_1) observed with various formulations was $F_1 < F_c < F_a < F_{ac} < F_b < F_{bc} < F_{ab} < F_{abc}$. The polynomial equation describing the relationship between the response, percent drug dissolved in 10min (Y) and the levels of βCD (X_1) , Starch 1500 (X_2) and Soluplus (X_3) based on the observed results was found to be $Y = 68.625 + 4.375(X_1) + 27.375(X_2) - 2.375(X_1 X_2) + 3.375(X_3) + 0.125(X_1 X_3) - 1.875(X_2 X_3) - 0.625(X_1 X_2 X_3)$ Based on the above equation, the formulation of optimized Valsartan tablets with NLT 85% dissolution in 10 min require βCD at 1:3.5 ratio of drug: βCD, Starch 1500 at 24.37% of drug and βCD content , and Soluplus at 1% of drug and βCD content. The optimized Valsartan tablet formulation gave 85.75% dissolution in 10min fulfilling the target dissolution requirement. The optimized Valsartan IR tablet formulation developed exhibited rapid absorption, higher plasma concentrations and higher bioavailability (123.5%) when compared to Valsartan market product. Hence formulation of Valsartan IR tablets with NLT 85% dissolution in 10 min could be optimized by 2^3 factorial design.*

Keywords— *Formulation Development, Valsartan IR tablets, Optimization, Factorial Design, In Vivo Preclinical evaluation*.

I. INTRODUCTION

Optimization[1] 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. 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. In a few studies[2-8] optimization by factorial designs was employed in the formulation development of BCS Class II drugs.

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. Valsartan, 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[9] 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 and use of superdisintegrants such as Crosspovidone and Sodium starch glycolate, carriers such as Starch 1500 [10-13] are simple industrially useful approaches for enhancing the dissolution rate of poorly soluble drugs in their formulation development. Surfactants such as SLS, Soluplus are also used for enhancing the solubility of poorly soluble drugs in formulation development.

In the present study complexation with β-cyclodextrin (βCD) along with Starch 1500 and Soluplus (a nonionic surfactant) was tried to enhance the dissolution rate of Valsartan IR tablet formulation development. Valsartan IR tablets with NLT 85% dissolution in 10 min was aimed in its formulation development. A 2^3 factorial design employing βCD, Starch 1500 and Soluplus was used for Valsartan IR tablet formulation development to achieve NLT 85% dissolution in 10 min. The objective of the present study is optimization of Valsartan IR tablet formulation employing βCD, Starch 1500, and Soluplus by 2^3 factorial design to achieve NLT 85% dissolution in 10 min and to evaluate the tablets by In vitro and In Vivo (pre-clinical methods)

N. Tirumalesh and K. P. R. Chowdary, "Formulation Optimization and In Vitro and In Vivo Preclinical Evaluation of Valsartan IR Tablets," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 2, Issue 2, pp. 66-70, 2019.

II. EXPERIMENTAL

Materials:

Valsartan was a gift sample from M/s Kekule Pharma Ltd., Hyderabad. β-cyclodextrin, Starch 1500 and Soluplus were gift samples from M/s Natco Pharma Ltd., Hyderabad. Talc and magnesium stearate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Estimation of Valsartan:

An UV Spectrophotometric method based on the measurement of absorbance at 250 nm in 0.1N HCl acid was used for the estimation of Valsartan. 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 0.65% and 1.15% respectively. No interference by the excipients used in the study was observed.

Formulation of Valsartan Tablets:

For optimization of Valsartan tablets as per 2^3 factorial design the βCD, Starch 1500 and Soluplus are considered as the three factors. The two levels of the factor A (βCD) are 1:1 and 1:6 ratio of drug: βCD, the two levels of the factor B (Starch 1500) are 2% and 30% of drug and βCD content, and the two levels of factor C (Soluplus) are 0 and 2% of drug and βCD content. Eight Valsartan tablet formulations employing selected combinations of the three factors i.e. βCD, Starch 1500 and Soluplus as per 2^3 factorial design were formulated and prepared by direct compression method.

Preparation of Valsartan Tablets:

Valsartan (40 mg) tablets were prepared by direct compression method as per the formula given in Table 1. The required quantities of Valsartan, βCD, Starch 1500 and Soluplus 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. The blend of ingredients was then compressed directly into tablets using an 8 - station RIMEK tablet punching machine employing 9mm or 12mm round and flat punches.

Evaluation of Tablets:

All the Valsartan tablets prepared were evaluated for drug content, hardness, friability, and 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 (10) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 40 mg of Valsartan was taken into 100 ml volumetric flask, dissolved in 0.1N HCl acid and the solution was filtered through Whatman filter paper no.41. The filtrate was collected and suitably diluted with 0.1N HCl acid and assayed for Valsartan at 250 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 Valsartan tablets prepared was studied in 0.1N HCl 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 Valsartan at 250nm. 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[14]. Dissolution rate (K_1) values were analyzed as per ANOVA of 2^3 factorial experiments.

Preclinical Pharmacokinteic Evaluation:

In vivo Pharmacokinetic evaluation was done on optimized Valsartan IR Tablets in comparison to its market product in normal healthy rabbits of either sex with a view to evaluate their *in vivo* performance

In vivo Study Protocol:

The following two products were tested for *In vivo* pharmacokinetic evaluation

(i) Valsartan (40mg) tablets (market product)

(ii) Optimized Valsartan IR Tablets (40mg) formulated

As Valsartan studied is safe and for ease of its determination in plasma samples by HPLC, the products are tested in rabbits at human doses after approved by IAEC. Institutional Animal Ethics Committee (No. CPCSEA/CH/ORG/2017 - 025) approved the protocols. The *In vivo* study was conducted as per crossover RBD (n=6). Healthy rabbits weighing 2.0 - 2.5 Kg were used. The washout period was one month. After collecting the blank blood sample, the product in the study was administered orally with 10 ml of water. Blood samples (1.0 ml) were collected from marginal ear vein at different times (0.5, 1, 1.5, 2, 4, 6, 8, and12h) after administration. Samples were collected into heparinized test tubes and were centrifuged for 15 min at

15,000 rpm. The plasma samples were stored under refrigerated conditions at 4 - 8°C prior to assay for drug content on the same day. The plasma concentrations of valsartan were determined by a reported [15] HPLC method after revalidation.

III. Results and Discussion

The objective of the present study is to optimize the Valsartan IR tablet formulation employing βCD , Starch 1500 and Soluplus by 2^3 factorial design to achieve NLT 85% dissolution in 10 min. For optimization of Valsartan tablets as per 2^3 factorial design the βCD, Starch 1500 and Soluplus are considered as the three factors. The two levels of the factor A (βCD) are 1:1 and 1:6 ratio of drug: βCD, the two levels of the factor B (Starch 1500) are 2% and 30% of drug and βCD content, and the two levels of factor C (Soluplus) are 0 and 2% of drug and βCD content. Eight Valsartan tablet formulations employing selected combinations of the three factors i.e. βCD, Starch 1500, and Soluplus as per 2^3 factorial design were prepared. 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 dissolution rate (K_1) values were analyzed 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 Valsartan tablets formulated.

TABLE 1. Formulae of Valsartan IR Tablets Prepared Employing β-CD, Starch 1500 and Soluplus as per 2^3 Factorial Design

Ingredient (mg/ tablet)	Formulation Code								
	F1	F a	F b	F ab	F c	F ac	F bc	F abc	F opt
Valsartan	40	40	40	40	40	40	40	40	40
β-cyclodextrin	40	240	40	240	40	240	40	240	140
Starch 1500	1.6	5.6	24	84	1.6	5.6	24	84	43.87
Soluplus	-	-	-	-	1.6	5.6	1.6	5.6	1.8
Talc	1.6	5.7	2	7.2	1.6	5.8	2.1	7.3	5.0
Magnesium stearate	1.6	5.7	2	7.2	1.6	5.8	2.1	7.3	5.0
Total Weight (mg)	84.8	297	108	378.4	86.4	302.8	109.8	384.2	235.7

F opt: Optimised Formulation to achieve NLT 85% Dissolution in 10 Minutes

TABLE 2. Physical Properties of Valsartan IR Tablets Prepared Employing βCD, Starch 1500 and Soluplus as per 2^3 Factorial Design

Formulation Code	Hardness (Kg/sq.cm)	Friability (% wt Loss)	Disintegration Time (Sec)	Drug Content (%)
F 1	5.5	0.65	95	98.6
F a	4.0	0.70	90	98.2
F b	5.0	0.90	35	99.6
F ab	5.0	0.65	30	100.2
F c	4.5	0.80	85	100.6
F ac	4.5	0.90	90	101.8
F bc	5.0	0.55	22	98.2
F abc	5.5	0.65	30	98.4
F opt	4.5	0.80	20	99.2

The physical parameters of the Valsartan tablets prepared are given in Table 2. The hardness of the tablets was in the range 4.0-5.5 kg/cm^2. Weight loss in the friability test was less than 0.90% in all the cases. Valsartan content of the tablets prepared was within 100±2 %. Much variations were observed in the disintegration and dissolution characteristics of the Valsartan tablets prepared. The disintegration times were in the range 22 to 95 sec. Valsartan tablet formulations F_b, F_{ab}, F_{bc} and F_{abc} disintegrated rapidly within 35 sec. However, all the Valsartan tablets prepared fulfilled the official (IP 2010) requirements with regard to drug content, hardness, friability and disintegration time. Dissolution of Valsartan tablets prepared was studied in 0.1N HCl acid. The dissolution profiles of the tablets are shown in Fig. 1 and the dissolution parameters are given in Table 3.

Dissolution of Valsartan from all the tablets prepared followed first order kinetics with coefficient of determination (R^2) values above 0.920. 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 three factors, βCD, Starch 1500 and Soluplus are highly significant ($P < 0.01$).

Valsartan tablet formulations F_{abc} , $F_{bc,}$ F_{ab} and F_b gave very rapid dissolution of Valsartan than others. These tablets (F_{abc}, F_{bc}, F_{ab} and F_b) gave more than 90% drug release in 10min. Higher levels of βCD and lower levels of Starch 1500 gave low dissolution of Valsartan tablets. The increasing order of dissolution rate (K_1) observed with various formulations was $F_1 < F_c < F_a < F_{ac} < F_b < F_{bc} < F_{ab} < F_{abc}$.

Optimization:

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 polynomial equation describing the relationship between the response, percent drug dissolved in 10min (Y) and the levels of βCD (X_1), Starch 1500 (X_2) and Soluplus (X_3) based on the observed results was found to be $Y = 68.625 + 4.375(X_1) + 27.375(X_2) - 2.375(X_1 X_2) + 3.375(X_3) + 0.125(X_1 X_3) - 1.875(X_2 X_3) - 0.625(X_1 X_2 X_3)$. Based on the

above equation, the formulation of optimized Valsartan tablets with NLT 85% dissolution in 10 min require βCD at 1:3.5 ratio of drug: βCD, Starch 1500 at 24.37% of drug and βCD content, and Soluplus at 1% of drug and βCD content.

TABLE 3. Dissolution Parameters of Valsartan IR Tablets Prepared Employing βCD, Starch 1500 and Soluplus as per 2^3 Factorial Design

Formulation Code	PD_{10} (%) ($\bar{x}$ ± S.D)	T_{50} (min)	DE_{30} (%)	$K_1 \times 10^2$ (min^{-1}) ($\bar{x}$ ± S.D)
F 1	30.2 ± 1.06	20	28.6	3.12 ± 1.43
F a	42.1 ± 1.23	12	45.2	5.52 ± 1.12
F b	92.4 ± 0.24	3.0	81.5	25.40 ± 4.14
F ab	99.4 ± 0.18	2.0	90.4	47.20 ± 1.23
F c	38.9± 0.27	15	37.5	4.25 ± 0.21
F ac	54.2 ± 1.33	9.0	52.5	6.10± 1.23
F bc	96.2 ± 0.46	3.0	85.6	26.20± 1.02
F abc	99.2 ± 0.74	2.0	91.6	169.36 ± 2.0
F opt	85.5 ±1.25	2.0	85.7	48.12± 1.27

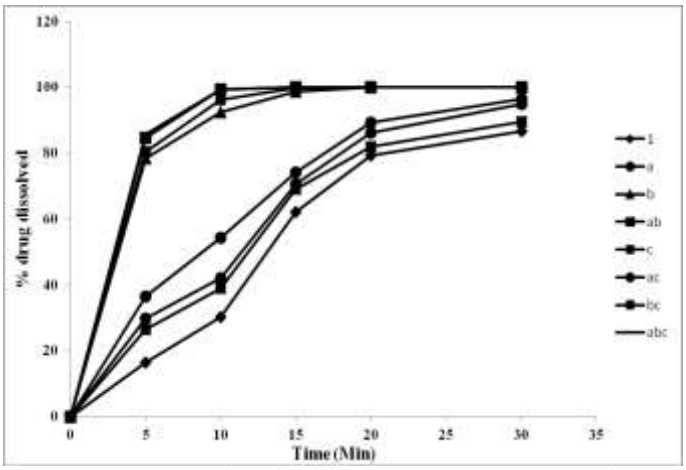

Fig. 1. Dissolution Profiles of Valsartan IR Tablets Prepared using βCD, Starch 1500 and Soluplus as per 2^3 Factorial Design

To verify Valsartan tablets were formulated employing the optimized levels of βCD, Starch 1500 and Soluplus. The formula of the optimized Valsartan tablets is given in Table 1. The optimized Valsartan 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 Valsartan tablets was 4.5 kg/sq.cm. Friability (percent weight loss) was less than 0.80%. Disintegration time of the tablets was 20 sec. The optimized Valsartan tablet formulation gave 85.75% dissolution in 10 min fulfilling the target dissolution requirement. The dissolution results also indicated validity of the optimization technique employed. Hence formulation of Valsartan tablets with NLT 85% dissolution in 10 min could be optimized by 2^3 factorial design.

Preclinical Pharmacokinetic Evaluation:

Plasma concentrations of Valsartan observed following the oral administration of valsartsan IR tablets are shown in Fig. 2. The pharmacokinetic parameters estimated are summarized in Table 4.

The Kel and t1/2 were 0.1784 h-1 and 3.88 h respectively for Valsartan IR tablets (market product) and 0.1644 h-1 and 4.21 h respectively for Optimized Valsartan IR tablets formulated. The t1/2 of Valsartan estimated is in good agreement with the reported[16] value of 3-6 h.

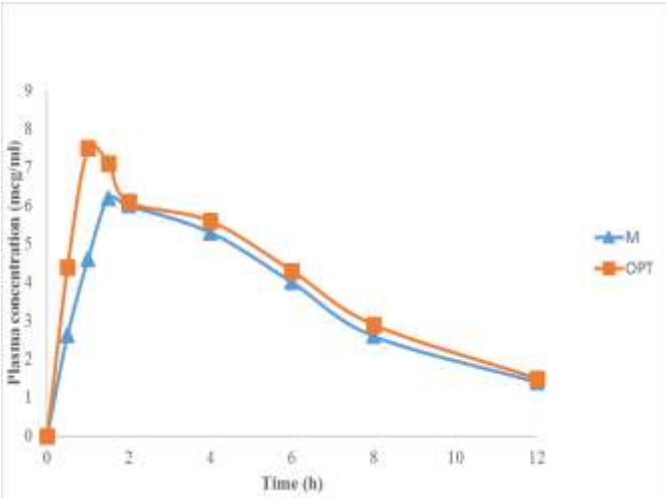

Fig. 2. Plasma concentration Vs Time Profiles of Valsartan IR Tablets Tested

TABLE 4. Pharmacokinetic Parameters of Valsartan IR Tablets Tested

Pharmacokinetic Parameter	Valsartan IR Tablets (Market Product)	Optimized Valsartan IR Tablets Formulated
C_{max} (µg/ml)	6.2±0.25	7.5±0.18
T_{max} (h)	1.5	1.0
Kel (h^{-1})	0.1784	0.1644
t1/2 (h)	3.88	4.21
AUC012 (µg.h/ml)	30.62	38.4
AUC0α (µg.h/ml)	38.46	47.52
Ka (h-1)	1.86	2.42
Rel BA (%)	100	123.5

Valsartan was absorbed rapidly from both IR tablets with an absorption rate constant (Ka) of 1.86 h-1and 2.42 h-1 respectively in the case of market product and optimized formulation developed. A Cmax of 6.2 ± 0.25 µg/ml was observed at 1.5h following oral administration of Valsartan market product. A Cmax of 7.5 ± 0.18 µg/ml was observed at 1.0h following oral administration of optimized Valsartan IR tablets developed. Plasma concentration were later decreased rapidly. Based on (AUC) oα, the relative bioavailability (BA) of optimized Valsartan IR tablets developed was 123.5 %

when compared to Valsartan IR tablets market product (100%).

Thus the optimized Valsartan tablet formulation developed exhibited rapid absorption, higher plasma concentrations and higher bioavailability (123.5%) when compared to Valsartan market product

IV. CONCLUSIONS

1. The individual and combined effects of the three factors, βCD, Starch 1500 and Soluplus are highly significant ($P < 0.01$) in influencing the dissolution rate of Valsartan tablets
2. Valsartan tablet formulations F_{abc}, F_{bc}, F_{ab} and F_b disintegrated rapidly within one minute and gave more than 90% dissolution in 10 minutes.
3. The increasing order of dissolution rate (K_1) observed with various formulations was $F_1 < F_c < F_a < F_{ac} < F_b < F_{bc} < F_{ab} < F_{abc}$.
4. The polynomial equation describing the relationship between the response, percent drug dissolved in 10min (Y) and the levels of βCD (X_1) , Starch 1500 (X_2) and Soluplus (X_3) based on the observed results was found to be $Y = 68.625 + 4.375(X_1) + 27.375(X_2) - 2.375(X_1 X_2) + 3.375(X_3) + 0.125(X_1 X_3) - 1.875(X_2 X_3) - 0.625(X_1 X_2 X_3)$. Based on the above equation, the formulation of optimized Valsartan tablets with NLT 85% dissolution in 10 min require βCD at 1:3.5 ratio of drug: βCD, Starch 1500 at 24.37% of drug and βCD content, and Soluplus at 1% of drug and βCD content.
5. The optimized Valsartan tablet formulation gave 85.75% dissolution in 10min fulfilling the target dissolution requirement.
6. The optimized Valsartan IR tablet formulation developed exhibited rapid absorption, higher plasma concentrations and higher bioavailability (123.5%) when compared to Valsartan market product.
7. Formulation of Valsartan IR tablets with NLT 85% dissolution in 10 min could be optimized by 2^3 factorial design.

REFERENCES

[1] S. Bolton, *Pharmaceutical Statistics*, New York, NY, Marcel Decker Inc, 2nd Edition 1990; 532-570.

[2] K. Ravi Shankar, K. P. R. Chowdary, and A. Sambasiva Rao, "Optimization of Efavirenz tablet formulation employing β CD and soluplus by 2^2 factorial design," *World Journal of Pharmaceutical Research*, vol. 4, issue 6, pp. 2018-2026, 2015.

[3] K. P. R. Chowdary, K. Ravi Shankar, and P. Suneel Kumar, "Optimization of Valsartan tablet formulation by 2^3 factorial design," *Journal of Pharmacy Research*, vol. 8, issue 9, pp. 1321-1325, 2014.

[4] K. P. R. Chowdary, K. Ravi Shankar, and V. V. L. S. P. Sowjanya, "Optimization of Irbesartan tablet formulation by 2^3 factorial design," *Int J Curr Pharm Res*, vol. 7, issue 1, pp. 39-42, 2014.

[5] V. Ramesh, R. Kumar Jat, and K. P. R. Chowdary, "Formulation of Valsartan tablets employing β CD, crospovidone, poloxamer - optimization by 2^3 factorial design," *World Journal of Pharmaceutical Research*, vol. 4, issue 11, pp. 1426-1434, 2015.

[6] V. Ramesh, J. Janardhana Gupta, P. Praveen Srikumar, S. Meenakshi, N. Jyothirmayee, G. Rajeswari, and D. Madhavi "Formulation develpoment and optimization of loratidine tablets employing solid dispersions in MCC pH102 and poloxamer188 as per 2^2 factorial design," *World Journal of Pharmacy and Pharmaceutical Sciences*, vol. 5, issue 4, pp. 1546-1555, 2016.

[7] K. P. R. Chowdary, K. Ravi Shankar, and C. H. Ramesh Babu, "Formulation development of Irbesartan tablets: Selection of diluent-binder-disintegrant combination by 2^3 factorial designs," *Journal of Global Trends In Pharmaceutical Sciences*, vol. 5, issue 1, pp. 1399-1404, 2014.

[8] V. Ramesh, J. Janardhana Gupta, P. Praveen Srikumar, M. Bullebbai, G. Nagesh Babu, and S. K. Noorjahan, "Formulation development and optimization of loratadine tablets employing ßcd, sodium starch glycolate, poloxamer 188 by 23 factorial design," *International Journal of Pharmacy and Pharmaceutical Science Research*, vol. 6, issue 1, pp. 1-5, 2016.

[9] K. P. R. Chowdary and B. L. R. Madhavi, "Novel drug delivery technologies for insoluble drugs," *Indian Drugs*, vol. 42, issue 9, pp. 557-562, 2005.

[10] B. Suribabu, N. Tirumalesh, S. S. Manikiran, and N. Rama Rao, "A factorial study on the enhancement of dissolution rate of nimesulide by solid dispersion," *Journal of Global Trends in Pharmaceutical Sciences*, vol. 5, issue 4, pp. 2008-2011, 2014.

[11] K. P. R. Chowdary, Ch. Chandra Sekhar, P. Suneel Kumar, and S. V. V. Subrahmanyam, "Enhancement of dissolution rate of aceclofenac by solid dispersion in starch 1500 and poloxamer 188," *Journal of Global Trends in Pharmaceutical Sciences*, vol. 4, issue 3, pp. 1168-1173, 2013

[12] K. P. R. Chowdary, V. Sowjanya, B. Suchitra, and M. Subba lakshmi. "A factorial study on the enhancement of dissolution rate of valdecoxib by solid dispersion in combined carriers," *International Research Journal of Pharmaceutical and Applied Sciences*, vol. 3, issue 4, pp. 99-102, 2013.

[13] D. Chowdary, S. Kumar, and G. D. Gupta, "Enhancement of solubility and dissolution of glipizide by solid dispersion (kneading) technique," *Asian J Pharm.*, vol. 3, issue 3, pp. 245-251, 2009.

[14] K. A. Khan, "The concept of dissolution efficiency," *J. Pharm. Pharmacol.*, vol. 27, issue 1, pp. 48-49, 1975.

[15] M. Pérez, G. Ramírez, M. Pérez, and P. Restrepo, "Validation of an analytical method for the determination of Valsartan in human plasma by HPLC/UV with addition standard using Losartan as an internal standard," *Colombia Médica*, vol. 38, issue 1, pp. 13-20, 2007.

[16] A. N. Zaid, R. Cortesi, A. Qaddomi, and S. Khammash, "Formulation and bioequivalence of two Valsartan tablets after a single oral administration," *Sci Pharm*, vol. 79, issue 1, pp. 123-135, 2011.