Research Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

RESEARCH ARTICLE ON OPTIMIZATION OF OLMESARTAN TABLET FORMULATION BY 2^3 FACTORIAL DESIGN

Vaddemukkala Yohan[*1], Muneer Syed[1], D. Srinivasarao[1]

[1*]Department of Pharmaceutics, K.C Reddy Pharmacy College, Jangammguntla palem, Medekonduru, Guntur, Andhra Pradesh, India.

ABSTRACT

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. Olmesartan, 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. Olmesartan tablet formulation by 2^3 factorial designs for selecting the best combinations of diluents, binder and disintegrant giving fast dissolution of the drug Olmesartan.

KEYWORDS

API, Solubility, Dissolution rate, Olmesartan and Anti-hypertensive drug.

Author for Correspondence:

Vaddemukkala Yohan,

Department of Pharmaceutics,

K.C Reddy Pharmacy College,

Jangammguntla palem, Medekonduru,

Guntur, Andhra Pradesh, India.

Email: yohanv333@gmail.com

INTRODUCTION[1,2]

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 and pose challenging problems in their pharmaceutical product development process.

Olmesartan, 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, and 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 Olmesartan tablet formulation by 2^3 factorial designs for selecting the best combinations of diluents, binder and disintegrant giving fast dissolution of the drug Olmesartan. In the 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 Primojel (5%). The two levels of the factor C (diluent) are lactose and DCP (dicalcium phosphate). Eight Olmesartan 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. All the tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as per official methods. The dissolution parameters estimates (K_1 and DE_{30}) were analysed as per ANOVA of 2^3 factorial design to evaluate individual and combined (interaction) effects of the three factors involved and to select the best combinations giving rapid and higher dissolution of Olmesartan, a BCS class II drug.

MATERIALS AND METHOD[3,4]

Olmesartan was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. Polyvinyl phosphate (PVP), Primojel, acacia, lactose, Dicalcium phosphate (DCP), and talc and magnesium stearate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Formulation of Olmesartan Tablets

For formulation of Olmesartan 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 Primojel (5%). The two levels of the factor C (diluent) are lactose and DCP. Eight Olmesartan 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 Olmesartan.

Preparation of Olmesartan tablets

Olmesartan (50 mg) tablets were prepared by wet granulation method as per the formula given in Table No.1. The required quantities of Olmesartan, 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 Olmesartan Tablets Prepared[5]

The tablets were evaluated by physical parameters like Hardness test, Friability, Disintegration Time and Drug Content were done and results tabulated in Table No.2.

Dissolution Rate Study[7]

Dissolution rate of Olmesartan tablets prepared was studied in phosphate buffer of pH 6.8 (900 ml) employing eight station dissolution rate test apparatus (LABINDIA, DISSO 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 Olmesartan at 250 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 is run in triplicate (n=3). The results tabulated in Table No.3.

Analysis of Data[6]

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[1]. Dissolution rate (K_1) and dissolution efficiency (DE_{30}) values were analyzed as per ANOVA of 2^3 factorial experiments. The results tabulated in Table No.5 and 6.

DISCUSSION

Olmesartan, 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. Among the various excipients (additives) added in tablet formulation, the diluent, and binder and disintegrant play a critical role in influencing the dissolution rate and bioavailability of drugs administered as tablet dosage form. The objective of the study is to optimize Olmesartan tablet formulation by 2^3 factorial design for selecting the best combinations of diluent, binder and disintegrant giving fast dissolution of the drug, Olmesartan.

Olmesartan 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 Olmesartan tablets as per 2^3 factorial designs the three factors involved is 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 Olmesartan tablet formulations each containing 50 mg of Olmesartan 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 No.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 Olmesartan tablets prepared are given in Table No.2. The hardness of the tablets was in the range 4.5-5.5 kg/cm^2. Weight loss in the friability test was less than 0.89 % in all the cases. Olmesartan content of the tablets prepared was within 100±3 %. Much variation was observed in the disintegration and dissolution characteristics of the Olmesartan tablets prepared. The disintegration times were in the range 30 sec to 5 min 30 sec with various tablets. Formulations F_1, F_b, F_{ab}, F_c, and F_{bc} disintegrated rapidly within 1 min 20 sec. All the Olmesartan tablets prepared are of good quality and fulfilled the official (I. P 2010) specifications with regard to drug content, hardness, friability and disintegration time. Dissolution rate of Olmesartan tablets prepared was studied in phosphate buffer pH 6.8. The dissolution profiles of the tablets are shown in Figure No.1 and the dissolution parameters are given in Table No.3. Dissolution of Olmesartan from all the tablets prepared followed first order kinetics with coefficient of determination (R^2) values above 0.87. The first 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 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 Primojel and combined effect of Primojel and DCP.

Tablets formulated employing lactose as diluents (F_1,F_a,F_b, F_{ab}) gave higher dissolution rates (K_1) and DE_{30} values when compared to the tablets formulated employing DCP (F_c, F_{ac}, F_{bc}, F_{abc}). The increasing order of dissolution rate (K_1) observed with various formulations was as follows:

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

Among all, formulation F_b (tablets prepared employing lactose, acacia and Primojel), F_1 (tablets prepared employing lactose, acacia and potato starch) and F_a(tablets prepared employing lactose, PVP and potato starch) gave higher dissolution rates and DE_{30} values.

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

Table No.1: Formulae of Olmesartan Tablets Prepared as Per 2^3 Factorial Designs

S.No	Ingredient (mg/ tablet)	F_1	F_a	F_b	F_{ab}	F_c	F_{ac}	F_{bc}	F_{abc}
1	Olmesartan	50	50	50	50	50	50	50	50
2	Acacia	5	-	5	-	5	-	5	-
3	PVP	-	5	-	5	-	5	-	5
4	Potato starch	37.5	37.5	-	-	37.5	37.5	-	-
5	Primojel	-	-	12.5	12.5	-	-	12.5	12.5
6	Lactose	147.5	147.5	172.5	172.5	-	-	-	-
7	DCP	-	-	-	-	147.5	147.5	172.5	172.5
8	Talc	5	5	5	5	5	5	5	5
9	Magnesium stearate	5	5	5	5	5	5	5	5
10	Total weight (mg)	250	250	250	250	250	250	250	250

Table No.2: Physical Parameters of Olmesartan Tablets Prepared as per 2^3 Factorial Designs

S.No	Formulation	Hardness (Kg/cm^2)	Friability (% Wt loss)	Disintegration Time (min-sec)	Drug Content (mg/tablet)
1	F 1	5.0	0.65	1 -10	49.2
2	F a	4.5	0.72	5-30	48.9
3	F b	4.7	0.76	1-10	50.1
4	F ab	5.0	0.83	30	50.4
5	F c	5.0	0.89	1– 19	49.6
6	F ac	4.5	0.69	3 -34	50.5
7	Fbc	5.5	0.85	0- 54	51.2
8	F abc	4.5	0.78	3- 47	51.3

Table No.3: Dissolution Profiles of Olmesartan Tablets Prepared as per 2^3 Factorial Designs

S.No	Time (min)	F_1	F_a	F_b	F_{ab}	F_c	F_{ac}	F_{bc}	F_{abc}
		$\bar{x}$ ±s.d	$\bar{x}$ ± s.d	$\bar{x}$ ± s.d	$\bar{x}$ ± s.d	$\bar{x}$ ± s.d	$\bar{x}$ ± s.d	$\bar{x}$ ±s.d	$\bar{x}$ ± s.d
1	5	23.24 ± 9.52	5.56 ± 0.59	24.37 ± 5.84	6.52 ± 1.96	4.49 ± 0.14	4.49 ± 0.34	5.74 ± 0.32	4.61 ± 0.61
2	10	43.19 ±18.76	30.66 ± 0.91	48.52 ± 7.31	7.48 ± 2.77	7.32 ± 1.45	7.32 ± 0.31	8.65 ± 0.13	8.56 ± 0.29
3	15	57.32 ± 9.39	17.65 ± 1.73	63.38 ± 4.69	9.13 ± 3.18	10.94 ± 2.47	10.94 ± 0.33	17.94 ± 3.64	10.8 ± 50.53
4	20	69.17 ± 3.87	23.89 ± 3.80	80.73 ± 8.81	9.95 ± 3.25	13.25 ± 0.88	13.25 ± 0.18	21.32 ± 4.37	13.91 ± 0.72
5	30	78.78 ± 4.55	34.38 ± 0.25	89.75 ± 8.46	11.65 ± 4.54	17.61 ± 0.80	17.61 ± 0.08	23.07 ± 4.94	15.68 ± 0.27
6	40	86.64 ± 8.70	40.36 ± 0.72	94.54 ± 2.96	14.54 ± 5.32	19.53 ± 0.33	19.53 ± 0.33	25.11 ± 5.37	19.61 ± 0.61
7	50	93.22 ± 6.55	54.96 ± 5.53	98.05 ± 2.40	15.20 ± 4.59	22.12 ± 0.44	22.12 ± 0.23	29.06 ± 1.46	21.44 ± 0.31
8	60	95.84 ± 5.15	59.68 ± 5.68	99.93 ± 0.91	18.14 ± 3.45	23.28 ± 0.49	23.28 ± 0.69	30.36 ± 0.72	22.46 ± 0.43

Table No.4: Dissolution Parameters of Olmesartan Tablets Prepared as per 2^3 Factorial Designs

S.No	Formulation	PD_{10} (%)	T_{50} (min.)	DE_{30} (%)	$K_1 X 10^2$ (min^{-1})
1	F_1	43.19	12	51.05	5.37
2	F_a	10.26	47	27.54	1.38
3	F_b	48.52	10	57.85	7.52
4	F_{ab}	7.48	> 60	37.39	0.92
5	F_c	7.32	> 60	10.04	0.54
6	F_{ac}	5.58	> 60	9.37	0.52
7	F_{bc}	8.65	> 60	14.56	0.74
8	F_{abc}	8.65	> 60	10.13	0.52

Table No.5: ANOVA of Dissolution Rates (K_1) of Olmesartan Tablets Prepared as per 2^3 Factorial Design

S.No	Source of Variance	Degrees of Freedom (DF)	Sum of Squares (SS)	Mean Sum of Squares (MSS)	F- Ratio	Significance
1	Total	23	168.84	7.34	---	---
2	Treatment	7	160.25	22.89	42.7052	
3	Error	16	8.583	0.536	---	
4	F a	1	49.306	49.306	91.98	
5	F b	1	0.601	0.601	1.121	
6	F ab	1	4.335	4.335	8.087	
7	F c	1	56.426	56.426	105.27	
8	Fac	1	45.926	45.926	85.682	
9	Fbc	1	0.2816	0.2816	0.525	
10	Fabc	1	3.375	3.375	6.296	

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

Table No.6: ANOVA of DE_{30} Values of Olmesartan Tablets Prepared as per 2^3 Factorial Designs

S.No	Source of Variance	Degrees of Freedom (DF)	Sum of Squares (SS)	Mean Sum of Squares (MSS)	F – Ratio	Significance
1	Total	23	8651.30	376.143	---	---
2	Treatment	7	8520.94	1217.277	149.4049	
3	Error	16	130.36	8.1475	---	
4	Fa	1	2952.601	2952.601	362.393	
5	Fb	1	4.318	4.318	0.52997	
6	Fab	1	135.75	135.75	16.661	
7	Fc	1	3041.101	3041.101	373.25	
8	Fac	1	2312.806	2312.806	283.86	
9	Fbc	1	17.568	17.568	2.156	
10	Fabc	1	49.651	49.651	6.094	

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

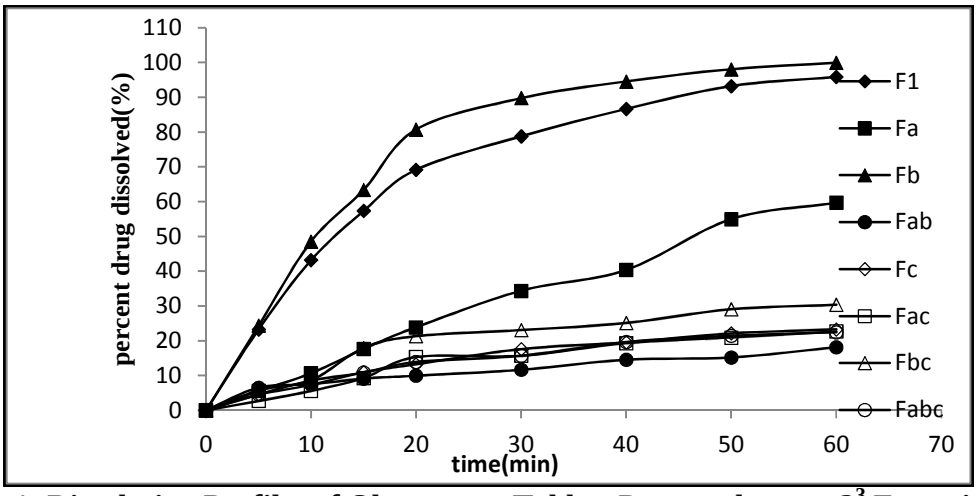

Figure No.1: Dissolution Profiles of Olmesartan Tablets Prepared as per 2^3 Factorial Designs

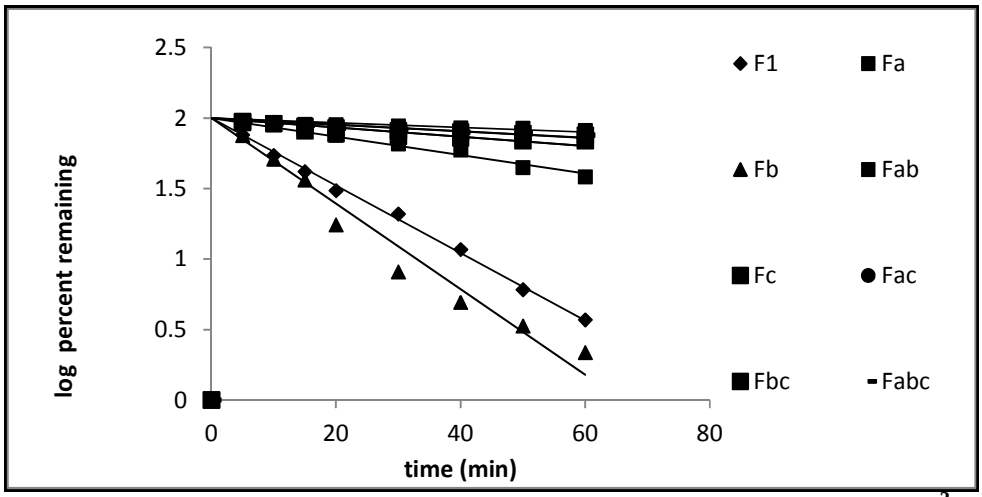

Figure No.2: First Order Dissolution Profiles of Olmesartan Tablets Prepared as per 2^3 Factorial Designs

CONCLUSION

Olmesartan, 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 these excipients in tablet formulation significantly influence dissolution rate and consequently bioavailability of the drug requiring a rational selection of diluents, binder and disintegrant combination. The objective of the study is to optimize Olmesartan tablet formulation by 2^3 factorial design for selecting the best combinations of diluent, binder and disintegrant giving fast dissolution of the drug, Olmesartan.

Olmesartan 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. Eight Olmesartan tablet formulations each containing 50 mg of Olmesartan 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. All the tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as per official methods. From the results obtained the following conclusions are drawn.

Much variations were observed in the disintegration and dissolution characteristics of the Olmesartan tablets prepared employing various combinations of binder (factor A), disintegrant (factor B) and diluent (factor C) as per 2^3 factorial design. 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 Primojel and combined effect of Primojel and DCP.

The disintegration times were in the range 30 sec to 5 min 30 sec with various tablets. Formulations F_1, F_b, F_{ab}, F_c, F_{bc} disintegrated rapidly within 1 min 20 sec.

Tablets formulated employing lactose as diluent gave higher dissolution rates (K_1) and DE_{30} values when compared to the tablets formulated employing DCP.

The increasing order of dissolution rate (K_1) observed with various formulations was as follows:

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

Among all, formulation F_b (tablets prepared employing lactose, acacia and Primojel), F_1 (tablets prepared employing lactose, acacia and potato starch) and F_a(tablets prepared employing lactose, PVP and potato starch) gave higher dissolution rates and DE_{30} values.

Combinations of (i) lactose, acacia and Primojel, (ii) lactose, acacia and potato starch and (iii) lactose, PVP and potato starch are the best combinations of diluent, binder and disintegrant giving rapid and higher dissolution of Olmesartan.

Hence these combinations are recommended for formulation development of Olmesartan tablets giving rapid and higher dissolution of Olmesartan, a BCS class II drug.

ACKNOWLEDGEMENT

Hetero Drugs Ltd., Hyderabad provided all chemicals and our college K.C Reddy Pharmacy College, Jangammguntlapalem, Medekonduru, Guntur, Andhra Pradesh, Indiasupports for doing this project.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Vaddemukkala Yohan *et al.* Research Article on Optimization of Olmesartan Tablet Formulation by 2^3 factorial design, *International Journal of Research in Pharmaceutical and Nano Sciences*, 4(4), 2015, 188 - 195.