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Formulation Development and Optimization of Olmesartan Medoxomil Immediate Release Tablets

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ABSTRACT

Olmesartan Medoxomil blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT1 angiotensin II receptor. ACE inhibitor is used in treatment of hypertension. The objective of the present study was to formulate an immediate release tablet of an antihypertensive drug, Olmesartan Medoxomil. Pre-formulation studies were carried out and results were within the limits. Tablets of Olmesartan Medoxomil were initially prepared by direct compression approach which resulted in poor flowability of the blend. Then the tablets were prepared by wet granulation techniques and the dissolution observed was on lower side. To obtain the desired dissolution pattern various trials had been taken with different excipients. Tablets were evaluated for their weight, hardness, friability, drug content, *in-vitro* dissolution. Similarity and dissimilarity factor were also calculated for Olmesartan Medoxomil with reference tablet. Stability study indicates that the formulation was stable.

Keywords: Olmesartan Medoxomil, Preformulation studies, Solubility study, Multimedia dissolution, Stability study.

INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for systemic effects. In addition oral medication is the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations mainly because of patient acceptance, convenience in administration and cost effective manufacturing process. For many drug substances, conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to patient. [1]

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Immediate release solid oral dosage forms are classified as either having rapid or slow dissolution rates. Immediate release dosage forms are those for which ≥85% of labelled amount dissolves within 30 min. [2]

Aqueous solubility and poor dissolution of insoluble drugs always remains a problem to the pharmaceutical industry. Lipophilic molecules especially those belonging to the biopharmaceutics classification system (BCS) class II and IV, dissolve slowly, poorly and irregularly, and hence poses serious drug delivery challenges like incomplete release from the dosage form, poor bioavailability, etc. [3]

Olmesartan Medoxomil is chemically (5-methyl-2-oxo-2H-1, 3-dioxol-4-yl)methyl-4-(2-hydroxypropan-2-yl)-2-propyl-1-({4- [2- (2H-1, 2, 3, 4-tetrazol-5-yl) phenyl] phenyl}methyl)1H-imidazole-5-carboxylate.

Olmesartan Medoxomil is a prodrug of Olmesartan - a compound that inhibits binding of angiotensin II to the AT1-receptor. Olmesartan Medoxomil is hydrolyzed to

Olmesartan during absorption from the gastrointestinal tract. It is mainly used in the treatment of hypertension. The typical dose of Olmesartan Medoxomil is 20 mg per day in patients who are not volume depleted. Tablet formulation containing 20 mg and 40 mg Olmesartan Medoxomil are available in market. [4]

The objective of the present study was to formulate an immediate release tablet of an antihypertensive drug using different approach. Solubility studies of Olmesartan Medoxomil, pH comparison with reference tablet were performed in line with reformulation study. Precompression and post compression parameters were evaluated.

MATERIALS AND METHODS

Materials

Olmesartan Medoxomil was procured from Glenmark Generic Limited, low substituted Hydroxy Propyl Cellulose LH-11 was purchased from ShinEtsu, Microcrystalline Cellulose was purchased from FMC Biopolymer, Klucel LF was purchased from Hercules, Stearic Acid was purchased from Cognis Speciality Minerals, Magnesium Stearate was purchased from Merck and Opadry white was purchased from Colorcon.

Preparation of Tablets

Olmesartan Medoxomil tablet were prepared by wet granulation method. The different batches designed are as shown in Table 1. Olmesartan Medoxomil, Microcrystalline Cellulose, and Low-Substituted Hydroxypropyl Cellulose were sifted through # 40 Sieves and loaded to RMG. Mixture was mixed for 10 minutes. Binder was prepared by dissolving Klucel-LF in sufficient quantity of Purified Water with continuous stirring to form clear solution.

Klucel binder solution was added in RMG and granulated to achieve end point and granules were dried in suitable drying equipment. Dried granules were sifted through #20 sieve. Sifted granules were loaded in Conta blender. Microcrystalline Cellulose, Low-Substituted Hydroxypropyl Cellulose and Steric acid were sifted through #40 and added in above blender & mixed for 10 minutes. Magnesium stearate was sifted through sieve # 60 and added in above blender and lubricated for 2 minutes. The above blend was compressed with suitable punches and dies. Coating solution was prepared by adding Opadry white in purified water and Coating process was done in suitable coating machine.

Preformulation study

Incompatibility between drugs and excipients can change stability and bioavailability of drugs, thereby, affecting its safety and/or efficacy. Study of drug-excipient compatibility is an important process in the development of a stable solid dosage form. Drug-excipient compatibility testing at an early stage helps in the selection of excipients that increases the probability of developing a stable dosage form.

Drug solubility study

The drug solubility study was carried in water and different buffer solutions such as pH 6.8 and 7.5 phosphate buffer, 0.1 N HCl, 0.01 N HCl and pH 4.5 acetate buffer. The excess amount of drug was added in the buffer solution to make saturated solution.

Sample preparation: 250 mg of active pharmaceutical ingredient was taken in 100 mL flask, which was dissolved and diluted with respective buffers. 2 mL of the solution was pipetted out and diluted up to 20 mL with respective buffer and compared with standard results.

Blend evaluation Parameters

Angle of Repose

The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose was calculated using the following formula

$$\tan \theta = h/r$$

Therefore $\theta = \tan^{-1}(h/r)$

Where, θ = angle of repose, h = height of the cone, r = radius of the cone base

Bulk Density

Apparent bulk density (P_b) was determined by pouring blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density was calculated by using the Following formula [4]

$$P_b = M/V_b$$

Where, P_b = Bulk Density, M = Weight of sample in gm, V_b = Final volume of blend in cm

Tapped Density

It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Tapping was done up to time there is no further movement of volume was noted. The tapped density was calculated by using the following formula [4]

$$P_t = M/V_t$$

Where, P_t = Tapped Density, M = Weight of the sample in gm, V_t = tapped volume of blend in cm

Carr's index or % compressibility

The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) which was calculated as follows: [4]

$$I = P_t - P_b / P_t \times 100$$

Where, I = Carr's index or % Compressibility, P_t = Tapped density, P_b= Bulk density

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It was calculated by the following formula

$$\text{Hausner's ratio} = P_t/P_b$$

Where, P_t = Tapped density, P_b = Bulk density

Evaluation of Tablet Parameters

Compressed tablets were evaluated for following parameters.

Table 1: Formula for Olmesartan Medoxomil tablets

S. No.	Ingredients	Qty./Tablet (mg)					
		F1	F2	F3	F4	F5	F6
1.	Olmesartan Medoxomil	40.00	40.00	40.00	40.00	40.00	40.00
2.	Pregelatinized starch	70.00	70.00	75.00	---	---	---
3.	Silicified MCC	78.00	78.00	278.00	---	---	---
4.	Croscarmellose Sodium	10.00	10.00	15.00	----	----	----
5.	Microcrystalline Cellulose	---	---	----	317.60	265.60	265.60
6.	Low-Substituted Hydroxypropyl Cellulose	---	---	---	14.00	40.00	40.00
7.	Hydroxypropyl Cellulose (Klucel-LF)	---	---	---	10.00	10.00	10.00
8.	Purified Water Ph. Eur	---	---	-----	QS	QS	QS
9.	Microcrystalline Cellulose	---	---	------	20.00	20.00	20.00
10.	Low-Substituted Hydroxypropyl Cellulose	---	---	------	14.00	40.00	40.00
11.	Stearic Acid	---	---	-------	3.50	3.50	3.50
12.	Magnesium Stearate	2.00	2.00	2.00	0.90	0.90	0.90
	Weight of uncoated Tablet	**200.00**	**200.00**	**410.00**	**420.00**	**420.00**	**420.00**
	Coating Formula						
13.	Opadry White YS-1-7040	4.00	4.00	8.20	8.40	8.40	8.40
14.	Purified Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
	Weight of Coated Tablet	**204.00**	**204.00**	**418.20**	**428.40**	**428.40**	**428.40**

Table 2: Preformulation study

S. No.	Sample Name	Stage	Olmesartan related comp. A	Single Max (%)	Total Impurities (%)
1.	Olmesartan Medoxomil	Initial	0.22	0.09	0.42
		55°C	0.16	0.09	0.34
		1M 40°C/75%RH	0.18	0.07	0.36
2.	Olmesartan Medoxomil + Microcrystalline cellulose PH 101	Initial	0.22	0.09	0.43
		55°C	0.19	0.10	0.38
		1M 40°C/75%RH	0.20	0.07	0.37
3.	Olmesartan Medoxomil + Microcrystalline cellulose 102	Initial	0.22	0.09	0.44
		55°C	0.19	0.10	0.38
		1M 40°C/75%RH	0.20	0.07	0.38
4.	Olmesartan Medoxomil + Silicified Microcrystalline Cellulose HD90	Initial	0.24	0.09	0.45
		55°C	0.23	0.12	0.45
		1M 40°C/75%RH	0.24	0.09	0.43
5.	Olmesartan Medoxomil + Croscarmellose Sodium	Initial	0.21	0.09	0.42
		55°C	0.16	0.09	0.34
		1M 40°C/75%RH	0.17	0.07	0.34
6.	Olmesartan Medoxomil + Magnesium Stearate	Initial	0.24	0.09	0.46
		55°C	0.20	0.09	0.38
		1M 40°C/75%RH	0.23	0.07	0.35
7.	Olmesartan Medoxomil + Klucel LF	Initial	0.21	0.09	0.42
		55°C	0.22	0.09	0.40
		1M 40°C/75%RH	0.20	0.07	0.36
8.	Olmesartan Medoxomil + Stearic Acid	Initial	0.22	0.09	0.44
		55°C	0.15	0.09	0.34
		1M 40°C/75%RH	0.19	0.07	0.37
9.	Olmesartan Medoxomil + LHPC-LH11	Initial	0.22	0.09	0.43
		55°C	0.18	0.09	0.36
		1M 40°C/75%RH	0.19	0.07	0.34
10.	Olmesartan Medoxomil Ph. Eur + Opadry white YS-1-7040	Initial	0.23	0.09	0.45
		55°C	0.24	0.11	0.47
		1M 40°C/75%RH	0.21	0.08	0.47
11.	Olmesartan Medoxomil Ph. Eur + Microcrystalline cellulose PH 101+ Microcrystalline cellulose PH 102 + Magnesium Stearate+ LHPC-LH11+ Klucel LF +Steric Acid + Opadry white YS-1-7040	Initial	0.24	0.09	0.46
		55°C	0.27	0.10	0.48
		1 M 40°C/75%RH	0.22	0.07	0.38

Weight variation

Twenty tablets were randomly selected from each formulation and weighed individually to check for weight variation.

Thickness

Thickness was measure by Vernier caliper scale for 10 Tablets.

Hardness: Hardness was determined by using hardness tester. Hardness of three tablets from each batch of different formulation was tested.

Friability

The friability of tablets was determined using Electrolab Friabilator. Olmesartan Medoxomil Tablets were transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes i.e. 100 revolutions. Tablets were dedusted and weighed again. The percentage friability was calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{final}} \times 100$$

% Friability of tablets less than 1% is considered acceptable.

Disintegration Test

One tablet is introduced in to one tube of disintegration apparatus. The assembly is suspended in the beaker containing phosphate buffer pH 6.8 and the apparatus is operated until the tablet disintegrated. [5-6]

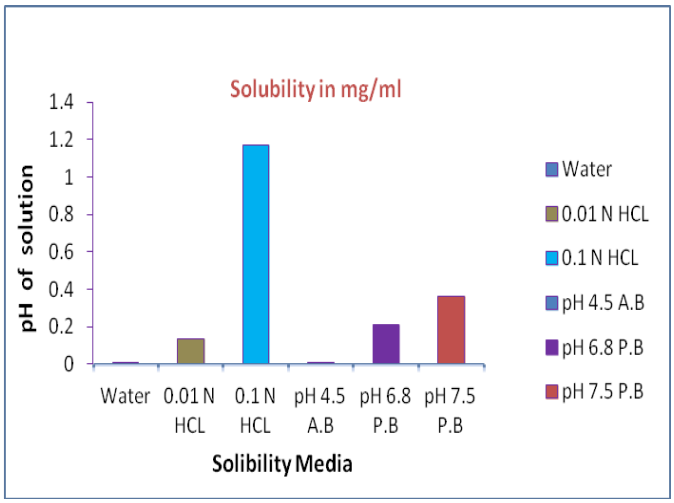

Fig. 1: Solubility in mg/ml

Table 3: Drug solubility study

S. No	Medium	mg/ml
1.	Water	0.0079
2.	0.01 N HCL	0.1336
3.	0.1 N HCL	1.1736
4.	pH 4.5 Acetate Buffer	0.0054
5.	pH 6.8 phosphate Buffer	0.2076
6.	pH 7.5 phosphate Buffer	0.3598

Table 4: Pre compression parameters of different formulations

Formulation	Angle of repose (Degree) ± SD	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio
F4	24.82 ± 0.84	0.40	0.49	18.36	1.22
F5	25.52 ± 0.84	0.38	0.47	19.14	1.20
F6	24.22 ± 0.24	0.39	0.48	18.75	1.23

Table 5: Tablet Parameter

Formulation	Evaluation of Compressed Parameters				
	Avg. Weight Variation ± S.D. (mg)	Thickness ± S.D. (mm)	Hardness ± S.D. (kg/cm2)	Friability (%)	Disintegration Time (Second)
F4	433.70 ± 1.880	4.73 ± 0.050	8.79± 0.530	0.08 ± 0.005	55.00 ± 5.000
F5	421.70 ± 1.330	5.42 ± 0.010	9.90 ± 0.600	0.02 ± 0.005	25.33 ± 4.160
F6	422.70 ± 1.580	5.55 ± 0.020	8.70 ± 0.400	0.01 ± 0.005	46.00 ± 3.600

Hardness challenge study

Final lubricated granules were compressed at a low hardness, high hardness & Optimum hardness, dissolution was performed in 900 ml Phosphate buffer pH 6.8 using USP Type II (paddle) apparatus at 50 rpm for 5 to 45 minutes (37 ± 0.5°C). The absorbance of the samples was measured with suitable dilution using appropriate blank.

Assay

20 tablets were crushed and powder equivalent to 20 mg of Olmesartan Medoxomil and dissolve in 100 ml of Phosphate buffer stirred and filtered and diluted the absorbance of the samples was measured at λ_{max} 257 nm after suitable dilution.

***In-vitro* Dissolution Study**

In vitro dissolution study was carried out in 900 ml Phosphate buffer pH 6.8 using USP Type II (paddle) apparatus at 50 rpm for 45 minutes (37 ± 0.5°C). The absorbance of the samples was measured and with suitable dilution using appropriate blank.

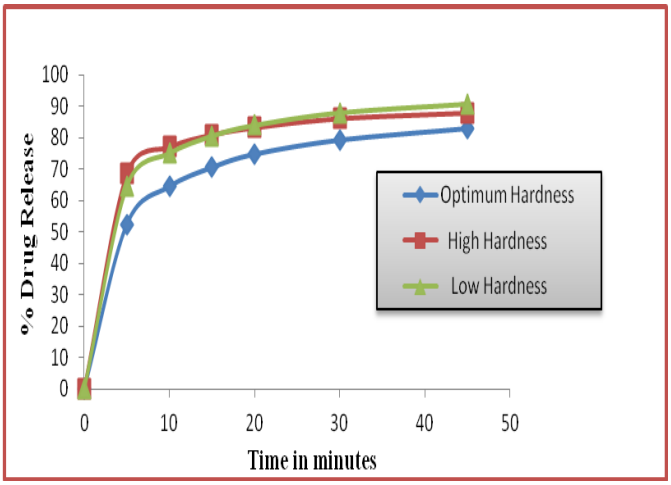

Fig. 2: % Cumulative release for Olmesartan Medoxomil for different Hardness

Table 6: % Cumulative release for Olmesartan Medoxomil for different Hardness

Time	Optimum Hardness	High Hardness	Low Hardness
5	52.50	68.60	64.60
10	64.50	77.10	75.10
15	70.60	81.00	80.60
20	74.80	83.30	84.00
30	79.30	86.20	88.00
45	83.00	88.00	90.80

Table 7: Assay

Formulation	ASSAY (%)
F4	100.10
F5	99.30
F6	99.80

Table 8: Dissolution profiling of Test with innovator in pH 6.8 Phosphate Buffer

Time (Minutes)	% Cumulative release for Olmesartan Medoxomil			
	Reference	F4	F5	F6
0	0.00	0.00	0.00	0.00
10	74.00	62.40	74.4	70.00
15	78.30	67.90	78.9	74.80
20	80.80	73.50	82.7	77.90
30	83.70	74.10	86.9	81.60
45	86.10	76.20	90.10	84.70
60	87.20	77.40	91.70	86.10

Multimedia Dissolution

In vitro multimedia dissolution study was carried out in 900 ml Phosphate buffer pH 6.8, 0.1 N HCl and pH 4.5 Acetate Buffer using USP Type II (paddle) apparatus at 50 rpm for 45 minutes (37 ± 0.5°C).

pH of Tablets

Tablet was crushed in mortar pestle and was added in 100 ml glass beaker. 50 ml of distilled water was added and stirred for 10 minutes and pH was observed.

Stability Studies

The formulated tablet containing final formula "F6" was selected for stability studies. The tablets were stored in 40°C/75% RH in Alu-Alu Blister for 3 months and 30°C/75% RH in Alu-Alu Blister for 6 months.

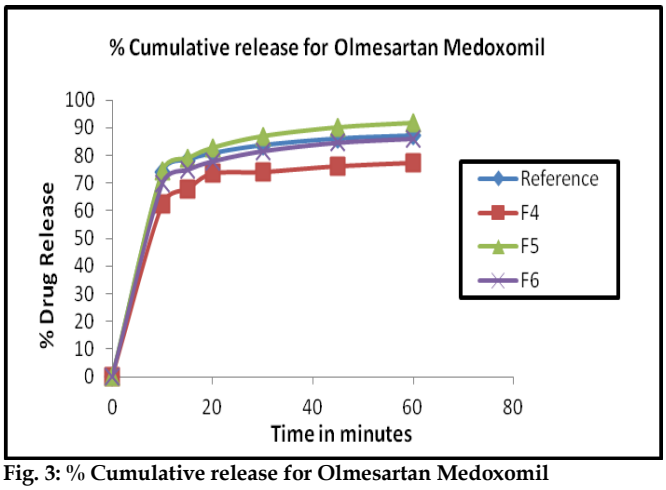

Fig. 3: % Cumulative release for Olmesartan Medoxomil

Table 9: Multimedia Dissolution

Time	Olmesartan Medoxomil Tablets 40 mg		Olmesartan Medoxomil Tablets 40 mg		Olmesartan Medoxomil Tablets 40 mg	
	Test	Reference 40 mg Tablets	Test	Reference 40 mg Tablets	Test	Reference 40 mg Tablets
	In 0.1 N HCL		pH 6.8 Phosphate buffer		pH 4.5 Acetate buffer	
0	0.00	0.00	0.00	0.00	0.00	0.00
10	96.30	95.40	70.00	74.00	7.90	8.8
15	96.90	99.00	74.80	78.30	8.80	9.7
20	96.90	100.20	77.90	80.80	9.20	10.1
30	96.90	100.40	81.60	83.70	9.80	10.7
45	97.0	100.20	84.70	86.10	10.40	11.2
F2	**78.22**		**77.19**		**94.58**	

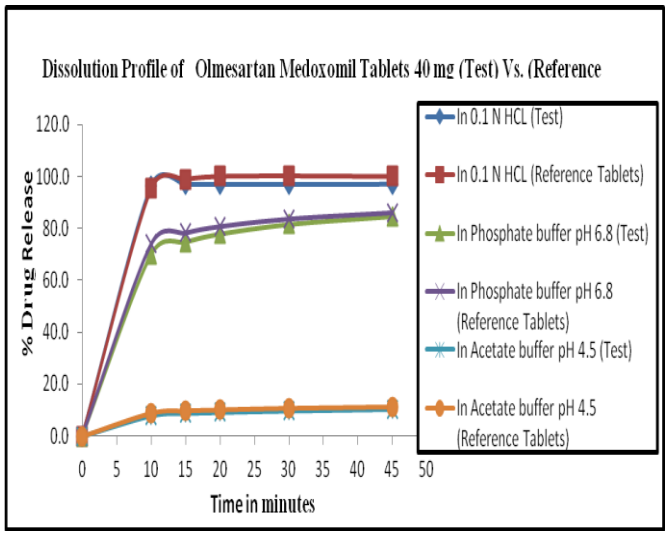

Fig. 4: Dissolution Profile of Olmesartan Medoxomil Tablets 40 mg (Test Vs. Reference)

Table 10: pH of Tablets

S. No	Product Name	pH
1.	Reference Tablets	6.340
2.	Olmesartan Medoxomil tablets 40 mg	5.980

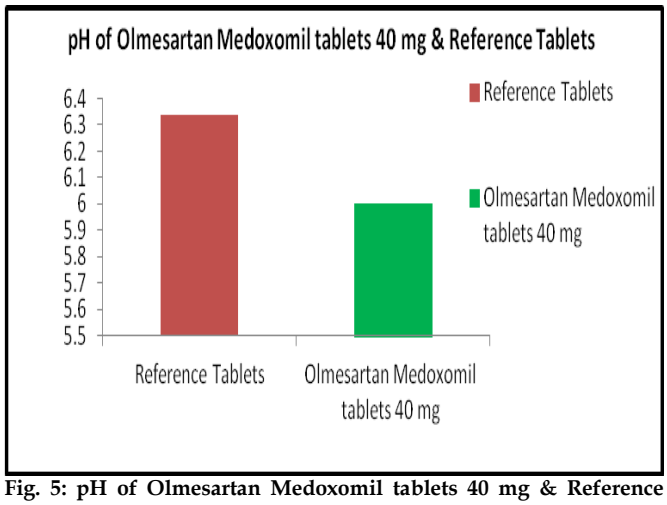

Fig. 5: pH of Olmesartan Medoxomil tablets 40 mg & Reference Tablets

Table 11: Stability Studies

Product Name	Assay	Related substances (%)			% Drug release in 45 minutes			Water by KF
		Olme Related comp A	Single Max	Total Impurities	Avg	Min	Max	
Initial	99.3	0.28	0.09	0.51	90.10	88.40	91.80	4.74
40°C/75% RH 1 M	101.10	0.25	0.08	0.49	85.70	83.40	88.00	4.17
40°C/75% RH 3 M	102.63	0.43	0.07	0.72	90.30	88.80	92.10	5.71
30°C/75% RH 6 M	102.80	0.31	0.10	0.59	85.50	83.80	88.00	5.32

RESULTS AND DISCUSSION

The main objective of the present research work was to develop a stable formulation of Olmesartan tablets in line with reference product. At initial stage, solubility analysis was done to find out solubility of Olmesartan Medoxomil. Drug-excipient compatibility study was performed to evaluate the compatibility of active pharmaceutical ingredient with excipients. Formulation of immediate release tablets of Olmesartan Medoxomil was done by direct Compression, slugging-deslugging and wet Granulation technique but the final formulation was prepared by wet Granulation approach. Formulated blend of Olmesartan Medoxomil was evaluated for blend flow parameters such as bulk density, tapped density, Carr's index and Hausner's Ratio. Post compression parameters were evaluated and found well within the specified limits. Dissolution profile of the tablets was studied by compressing the tablets at low hardness, optimum hardness and high hardness. High hardness dissolution profile was comparatively faster than reference product. To match the dissolution with reference listed tablets optimum hardness tablets dissolution was selected. Optimum hardness tablets were showing similar dissolution

pattern as reference tablets. Multi-media dissolution study was performed on final formulation in Phosphate buffer pH 6.8, 0.1 N HCl and pH 4.5 Acetate Buffer. Results showed that higher dissolution was obtained in 0.1 N HCl medium due to high solubility of Olmesartan Medoxomil in 0.1 N HCl as per solubility study. But as an official media Phosphate buffer pH 6.8, final media of phosphate buffer pH 6.8 was used to match the dissolution with innovator tablets. Accelerated stability study and long term stability study was carried out on final formulation and results were found satisfactory.

In the present study immediate release tablets of Olmesartan Medoxomil were formulated with improved dissolution and less impurity or related substance as compared to marketed preparations. There were no significant changes in their physico-chemical properties, assay, related substances, water content by KF and drug release observed.

REFERENCES

1. Kumar KK, Sampath Kumar K, Satheesh G. Formulation and Evaluation of Clopidogrel Bisulfate Immediate Release Tablets USP 75mg. International Journal of Pharmacy & Technology 2013; 5(2): 5481-5504.
2. Patel HP, Karwa P, Bukka R, Patel NJ. Formulation and Evaluation of Immediate Release Tablets of Zolpidem Tartrate by Direct Compression. International Journal of Pharmaceutical Sciences Review and Research 2011; 7(2):80-85.
3. Panchal DM, Tiwari AK. A Research on Improvisation in Dissolution of Olmesartan Medoxomil by Enhancing its Solubility Using Solid Dispersion Techniques. World Journal of Pharmaceutical Research 2013; 2(5): 1793-1816.
4. Lavande JP, Ade RN, Jaiswal SB, Chandewar AV. Evaluation and Optimization of Olmesartan Medoxomil tablet using Synthetic and Natural superdisintegrants. Int. J. Pure App. Biosci. 2013; 1(5):19-29.
5. Abdul Hasan SA, Jaya LJ. Enhancement of Solubility and Dissolution Rate of Olmesartan Medoxomil by Solid Dispersion Technique. J. Curr. Chem. Pharm. Sc. 2013; 3(2):123-134.
6. Compressed Preparation European Patent Application published in accordance with Art. 153, (4) EPC patent no: EP 2 033 643 A1.
7. Sruthy PN, Anoop KR. Formulation and Evaluation of Olmesartan Medoxomil Floating Tablets. Int J Pharm Pharm Sci. 2013; 5(3): 691-696.
8. Sasidhar RLC, Vidyadhara S, Maheswari GV, Deepti B, Srinivasa Babu P. Solubility and Dissolution Rate Enhancement of Olmesartan Medoxomil by Complexation and Development of Mouth Dissolving Tablets. Advances in Biological Research 2013; 7(2): 32-41.
9. Prudhvi RV, Subhashis D, Maleswari T, Niranjan BM, Bhaskar NB. Preparation, Characterization and Evaluation of Olmesartan Medoxomil-B Cyclodextrin Complexes, Indian Journal of Research in Pharmacy and Biotechnology 2013; 1(3):420-427.

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