Research Article

A Dissolution Development and Evaluation of Marketed Formulation for Anti Hyper Tensive Drug-Olmesartan Medoxomil

SP. Karuppiah*, K. Anver Basha
Department of Chemistry, Sathyabama University, JPR Nagar, Chennai, India.
***Corresponding author's E-mail:** karu70123@rediffmail.com

Received: 10-02-2017; **Revised:** 06-03-2017; **Accepted:** 20-03-2017.

ABSTRACT

Dissolution method for the release estimation of anti-hypertensive drug Olmesartan Medoxomil was developed by HPLC. The formulated drug product dissolution profile with multimedia dissolution rationale was performed against marketed formulation as per Centre for Drug Evaluation and Research guidelines (CDER). The differential factor (F2) and similarity factor (F1) was evaluated against innovator product available in the market. The chromatographic system equipped with gradient pump, column oven with sample cooler, auto sampler and VWD detector was used for this study. The analyte peak was separated by using column packed with moderately polar Cyano groups (CN, 250X4.6, 5µ).The mobile phase comprised of Buffer: Acetonitrile in the ratio of 40:60 with pump flow rate 1mL/min and UV detection at 225nm.The developed method was validated as per ICH guidelines. The repeatability of the method was established by estimating dissolution for six different sample solution of the same batch. The relative standard deviation for the dissolution values of six determinations of the same batch were 1.63 % which is well within the acceptance criteria of 5.0%.The linearity of the method was determined over the range of 50% to 150% of sample concentrations covering five different levels. The recovery of Olmesartan Medoxomil from 50% to 150% was 98.3% to 99.1% and the percentage RSD was 0.64%.The robustness of the method was studied for 3 chromatographic variables and 3 dissolution condition variables. The stability of the analytical solution was found stable for 24hrs after preparation. The sink condition evaluation of dissolution medium was established and the average amount of active drug substances added shall dissolved in the designed volume of dissolution medium was 90.35% which is well within in the limit of not less than 50%.

Keywords: Dissolution development, Evaluation of marketed formulation, Development and evaluation, Anti-hypertensive drug, Olmesartan Medoxomil.

INTRODUCTION

Olmesartan Medoxomil belongs to the class of medicines called angiotensin II receptor antagonists to treat high blood pressure. It is marketed worldwide by Daiichi Sankyo, Ltd. and in the United States by Daiichi Sankyo, Inc. and Forest Laboratories. The Average Molecular Weight is 558.5851 g/mol and the molecular formula is $C_{29}H_{30}N_6O_6$ which is white to off-white powder soluble in acetone, methanol and practically insoluble in water. The structure is represented in Fig.1. Olmesartan Medoxomil exhibits no potential isomerism. There are no chiral centers for exhibiting enantiomerism and no carbon- carbon double bonds for exhibiting geometrical isomerism.[1-2]

The study on dissolution release indicates that the percentage release of Olmesartan Medoxomil from finished dosage forms. The most of the available literature reveals that there is no stability indicating analytical method available for Olmesartan Medoxomil drug product dissolution development.[3-4]

The aim of the study is to evaluate the percentage release of active substance Olmesartan Medoxomil presents in anti-hypertensive drug formulation. The study reveals the dissolution release pattern of drug substance with the Innovator reference product. The multimedia dissolution profile with 3 different media pH1.2, 4.5 & pH6.8 at various time points (10,20,30 & 45 min) are studied for both innovator as well as our product.[5-12] From the comparative dissolution profile results the difference factor (F1) and the similarity factor (F2) was calculated. The developed method is validated for set of parameters as per ICH guidelines. The developed method is specific, accurate, linear and robust. This method can be used for regular analytical estimation and routine laboratory analysis of drug formulations.[13-16]

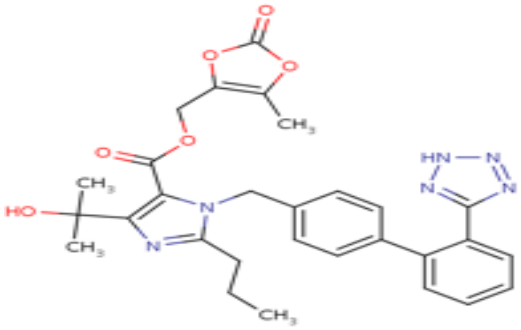

Figure 1: Structure of Olmesartan Medoxomil

MATERIALS AND METHODS

The Olmesartan medoxomil standard was received from M/s Glenmark Generics ltd, Gujarat, India. The solvents and chemicals used for this study received from Qualikems fine chem. Pvt.ltd. Vadodara, India. The

innovator reference product Benicar and local marketed product Olmax were purchased from market. The purified water used for this analysis was collected from Millpore-Milli-Q- system. The chromatographic system equipped with gradient pump, auto injector, VWD detector (Agilent 1260 infinity).The chemstation software was used for integration of data. The Electro lab 8TDL with auto sampler assembly dissolution Tester is used for this dissolution study.

Dissolution Study:

Standard stock solution of Olmesartan Medoxomil working standard was prepared by transferring and an accurately weighed quantity 22.0 mg to 50 mL with diluent to get the final concentration of 440µg/mL. Further dilute 5 ml to 50 mL with dissolution medium (0.1M HCl) to get the final concentration of 44µg/mL. The dissolution parameters are set as per the following; Apparatus II of BP (paddle); Medium 0.1M Hydrochloric acid; Volume 900ml;Time 45 min; RPM 75rpm and Temperature 37° C ± 0.5° C. Place one tablet in to each dissolution vessel and run the apparatus for 45 minutes, collect the sample at time interval 10,20,30 & 45 minutes. The prepared standard and sample solutions were filtered through 0.45µm filter and injected into the chromatograph as per the following chromatographic conditions; Mobile phase Buffer: ACN: 40:60;Pump flow; 1mL/min; Column: Spherisorb Cyano 250 X 4.6,5 µm; Injection volume:20µl and UV detection at 225 nm. The retention time of main peak was observed at RT at 7.5 minutes.

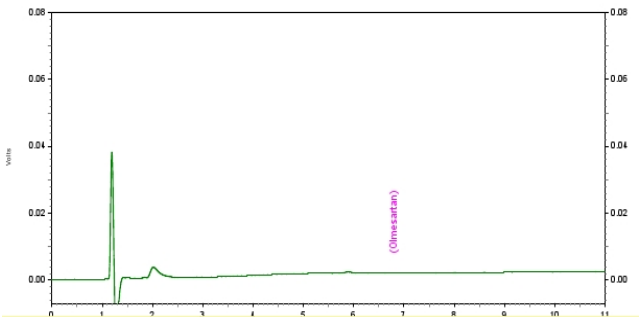

Figure 2: Chromatogram for Placebo Preparation

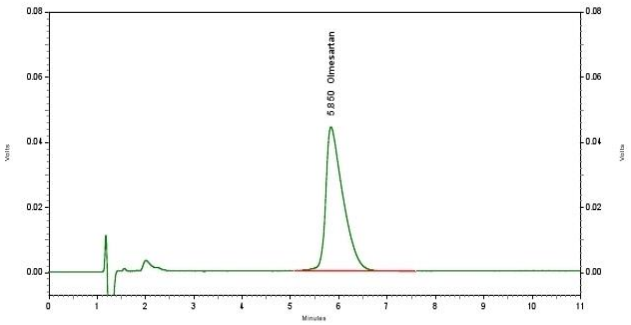

Figure 3: Chromatogram for Standard preparation

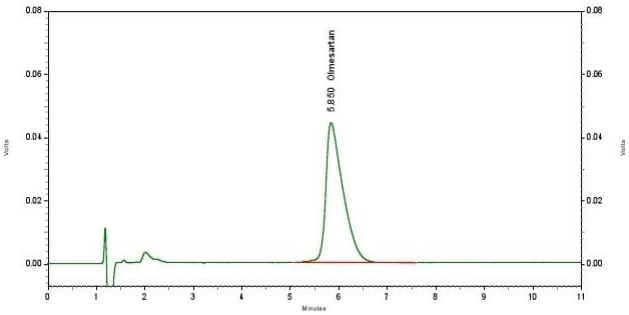

Figure 4: Chromatogram for Sample preparation.

The chromatograms for Placebo,standard and sample preparations were displayed in Fig.2,3 & 4.

Multimedia Dissolution Profile:

The multimedia dissolution profile with pH1.2 (0.1M Hydrochloric acid),pH4.5(Acetate buffer),pH6.8 (Phosphate buffer) were performed for Innovator reference product Benicar 40 mg and marketed formulation Olmax 40 mg tablets. The comparative dissolution profile (CDP) for each medium was calculated against Innovators Benicar. The dissolution profile curves were represented in Fig.5

The standard solution preparation of each medium is different by diluting the stock standard solution with respective medium to get the final concentration of 44µg/mL. The resulting solutions blank (dissolution medium), placebo, standard and sample solutions were injected in to the chromatograph and the results were reported.

Validation of Analytical Method:

The developed dissolution method was validated for the following parameters as per ICH guidelines. The parameters selected were i) Specificity ii) Precision iii) Linearity iv) Recovery v) Robustness vi) Solution Stability and vii) Sink condition Evaluation.

Specificity was performed by spiking Olmesartan Medoxomil working standard with appropriate levels of known weight of Placebo mixture (synthetic mixture of formulation excipients).

Weigh accurately about 330 mg tablet placebo with respect to Olmesartan Medoxomil 40 mg tablets and transferred into dissolution bowl containing 900 ml dissolution medium. Run the instrument as per test conditions, the solution was collected, filtered and injected in to the chromatograph. The specificity was evaluated as interference against Blank, Tablets Placebo, Olmesartan Medoxomil standard, Olmesartan Medoxomil standard spiked with tablets placebo and Olmesartan Medoxomil tablets sample. There should not be any interfering peak in the chromatogram obtained from blank, placebo at the retention time corresponding to Olmesartan Medoxomil.

The precision exercise was carried out fewer than 3 categories, namely system precision, method precision, and intermediate precision.

System suitability parameters and complete operational parameters were studied in this section. HPLC system, comprising accessories like detector, column, pump etc, under given chromatographic condition operates consistently throughout the analysis and can give accurate and precise results, further system suitability was ensured throughout the analysis by injecting the standard at the specified intervals. System precision and Method precision was checked by injecting system suitability standard six times, to ensure the suitability of the analysis for its intended purpose. The % RSD of peak area responses of Olmesartan Medoxomil from six replicate injections of standard solutions should not be more than 2.0.The % RSD from six replicates dissolution sample preparations should not be more than 5.0.

Linearity was established by preparing solutions of the drug, ranging in concentration from below the lowest expected concentration to above the highest concentration during release. Hence the range was covered from 50% to 150 % of the working concentration of 44µg/mL. The linearity range is from 22 µg/mL to 66 µg/mL.

The linear regression coefficient should not be less than 0.999 and not more than 1.000 for Olmesartan Medoxomil. Y-intercept of linearity curve should not be more than 2.0 % of the response of the 100 % working concentration of Olmesartan medoxomil.

The Recovery of the analyte was determined by performing 5 different levels (50%, 75%, 100%, 125% & 150%) by spiking Olmesartan Medoxomil Active pharmaceutical Ingredient (API) with Placebo powder at 22.2µg/mL, 33.32µg/mL, 44.42µg/mL, 55.62µg/mL and 66.72µg/mL respectively. The percentage recovery should be between 95% to 105%.

The robustness of the method was performed for 3 dissolution variables (change in RPM; 73/77rpm, Change in bowl temperature; 36.5/37.5°C,Change in dissolution media volume; 880/920mL) and 3 chromatographic variables (change in flow rate;0.8/1.2mL, Change in column temperature; 23/27°C, Change in mobile phase composition; 380:620/420:580: Buffer:ACN). The percentage RSD from six replicate dissolution sample preparation under each dissolution condition should not be more than 5.0.

The stability in analytical solution was established by injecting standard and sample solution over the period time till 24 hrs. The standard solution was stored under conditions that ensure stability. The stability of the standard was analyzed over a specified period of time by comparing peak area response at different time intervals to that of the initial response. The % RSD of peak area responses of Olmesartan medoxomil obtained at solution stability intervals study calculated together should not be more than 2.0.

The Sink conditions means the drug which goes in to the dissolution medium is not affected by the drug which is not dissolved. In general the dissolution medium volume should be 3 to 5 times the saturation solubility of the drug.

The sink condition evaluation was performed as per the dissolution test method by spiking 133µg/mL of Olmesartan Medoxomil working standard (3X of standard/sample concentration) with 1100 µg/mL of placebo in designed volume of dissolution medium (900mL) at 250 rpm.

Not less than 50% of the amount of active drug substances added shall dissolves in the designed volume of dissolution medium.

RESULTS AND DISCUSSION

The stability indicating Dissolution method was developed for Olmesartan Medoxomil formulated dosage forms by HPLC. The Comparative Dissolution Profile (CDP) was performed with the developed method for Innovators reference Product (Benicar) and marketed formulation (Olmax). The graphical representation was displayed in Fig.5. The multimedia rationale of marketed formulation with pH 1.2, pH 4.5 & pH 6.8 was compared with Innovators reference product and the difference factor (F1), similarity factor (F2) was evaluated. The results were reported in Table.1&2. In order to increase solubility of drug substances, diluent was introduced to prepare standard stock solution (ACN: Water: 80:20).

Hence the drug was poorly soluble in water, the dissolution conditions are optimized to get more release of drug in the medium by altering media volume, paddle rpm and time interval.

The dissolution method was validated as per CDER recommendations and ICH guidelines. The method was found selective and specific since there is no interference observed between peaks of blank, placebo, standard, sample preparations. The method precision was performed by six determinations of assay average value 91.76% and %RSD is 0.79% was listed in Table.3. The method was found linear over the range of 22µg/mL to 66µg/mL and the linear regression R^2 was 0.9999. The results were reported in Table.5

The recovery of spiked Olmesartan medoxomil was studied from 50% to 150% of working concentration and the average recovery 98.48%, RSD 0.64% were listed in Table.5. The robustness variables were studied and listed in Table.6. The analytical solution stability was performed over 24 hrs and found stable. Sink condition was evaluated for dissolution medium. The average percentage release of drug dissolved in the medium for sink condition was found 90.35% which is less than the acceptance criterion of 50% were listed in Table.7

Table 1: CDP for Benicar Vs Olmax in pH 1.2, 4.5 & 6.8 Medium

Time Points	pH 1.2	pH 4.5	pH 6.8	pH 1.2	pH 4.5	pH 6.8
	Benicar			Olmax		
0	0.00	0.00	0.00	0.00	0.00	0.00
10	101.91	13.49	64.41	99.13	20.44	69.45
20	103.74	16.47	72.92	99.45	18.91	77.90
30	102.09	17.39	74.77	101.77	18.53	80.37
45	102.16	18.30	78.46	99.87	18.86	81.30
Sum	**409.90**	**65.66**	**290.56**	**400.22**	**76.73**	**309.01**

Table 2: F1 & F2 values for Each Dissolution Medium

Name of DS Medium	No. of Intervals	F1	F2
pH 1.2(Acidic)	4	2.36	76.30
pH 4.5(Acetate Buffer)	4	7.30	89.39
pH 6.8(Phosphate Buffer)	4	6.35	65.77
Acceptance Criteria		**0-15**	**50-100**

F1-Difference Factor; F2-similarity Factor

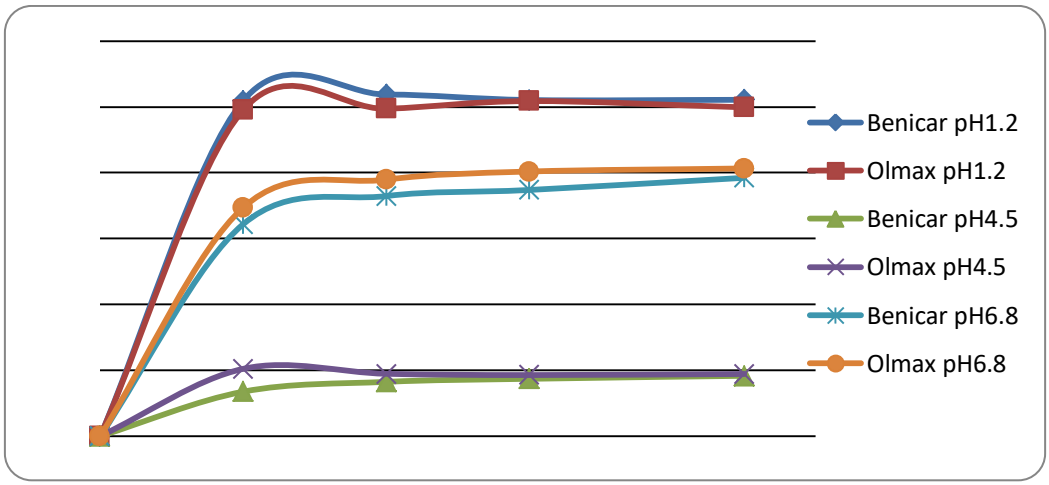

Figure 5: Release pattern of CDP in pH 1.2, 4.5 & 6.8 Medium (Benicar Vs Olmax)

Table 4: Precision Study Data

Bowl Number	% release	Mean	SD	RSD
1	92.72			
2	91.57			
3	90.79	91.76	0.7234	0.79
4	91.17			
5	92.04			
6	92.29			

Table 5: Linearity Study Data

Level %	Concentration (µg/mL)	Regression coefficient	Slope	RSD
50	22.0			
75	33.0			
100	44.0	0.9998	0.3071	0.3924
125	55.0			
150	66.0			

Table 6: Recovery Study Data

Added Amount (µg/mL)	Recovered Amount (µg/mL)	Mean Recovery % (n=3)	SD	RSD
20.60	20.17			
30.17	29.96			
40.67	39.78	99.48	0.6532	0.6633
50.58	49.71			
60.19	59.60			

SD-Standard Deviation; RSD-Related Standard Deviation

Table 7: Robustness Study Data

Chromatographic & Dissolution Variables Release	% Drug	% RSD
Pump Flow 0.8mL	91.29	0.75
Pump Flow 1.2mL	91.19	0.39
Column Temperature 23°C	91.24	0.61
Column Temperature 27°C	91.16	0.46
Mobile phase Ratio 380:620(Buffer : ACN)	91.08	0.48
Mobile phase Ratio 420:580 (Buffer : ACN)	92.10	0.82
Bowl Temperature 36.5°C	96.86	0.87
Bowl Temperature 37.5°C	96.75	0.39
Media Volume 880mL	98.57	0.77
Media Volume 920mL	99.77	1.16
Paddle RPM 73	97.97	2.17
Paddle RPM 77	99.73	1.14

Table 7: Sink Condition Evaluation Data

Bowl Number	% release	Mean	SD	RSD
1	87.25			
2	93.42			
3	87.31	90.35	3.350	3.708
4	93.41			
5	87.26			
6	93.40			

CONCLUSION

The stability indicating dissolution method developed for Olmesartan Medoxomil finished dosage forms by HPLC was more specific, precise, linear, accurate and robust. This method can be used for formulation development research, bioequivalence study, in-vitro dissolution study as well as routine analytical purpose. This method was more reliable for estimation of Comparative Dissolution Profile study with Reference product and marketed formulations.

Acknowledgement: We are very much thankful to the Department of chemistry Sathyabama University, Chennai for their support to complete the project successfully. We do not have any conflicts of interest.

REFERENCES

1. The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals. 15th ed. Cambridge, UK: Royal Society of Chemistry; 2013.
2. Snyder LR, Kirkland JJ, John W.Dolan. Introduction to Modern Liquid Chromatography. 3rd ed. New York; Wiley Inter Science Publication; 2010. p. 199-298.
3. Sagirli O, Önal A, Toker SE, Sensoy D, Simultaneous HPLC Analysis of Olmesartan and Hydrochlorothiazide in Combined Tablets and in vitro Dissolution Studies, Chroma 66, 2007, 213.
4. Bajerski L, Rossi RC, Dias CL, Bergold AM, Froehlich PE, Development and Validation of a Discriminating In Vitro Dissolution Method for a Poorly Soluble Drug, Olmesartan Medoxomil: Comparison Between Commercial Tablets, AAPS PharmSciTech 11, 2010, 637.
5. Asmita Y. Kamble , Mahadeo V. Mahadik , Laxman D. Khatal & Sunil R. Dhaneshwar, Validated HPLC and HPTLC Method for Simultaneous Quantitation of Amlodipine Besylate and Olmesartan Medoxomil in Bulk Drug and Formulation,Analytical Letters, vol.43, issue 2, 2010.
6. Manzoor Ahmed, Rashmi D.R, Satishkumar Shetty A, Anil Kumar S.M, Ravi M.C, Kuppast I.J RP-hplc method development and validation for simultaneous estimation of cilnidipine and olmesartan medoxomil in combined tablet dosage form, WJPPS, Volume.4, Issue 1, 785-795.
7. Shah N , Suhagia B, Shah R, Patel N, Development and validation of a simultaneous HPTLC method for the estimation of olmesartan medoxomil and hydrochlorothiazide in tablet dosage form, IJPS, Vol.69, No.6, 2007.
8. Chintan V. Patel, Amit P. Khandhar, Anandi D. Captain, Kalpesh T. Patel, Validated absorption Factor Spectrophotometric and Reversed-Phase High-Performance Liquid Chromatographic Methods for the Determination of Ramipril and Olmesartan Medoxomil in Pharmaceutical Formulations, EJAC, Vol.2, No.3, 2007.
9. Rote A, Bari P, Spectrophotometric estimation of Olmesartan medoxomil and Hydrochlorothiazide in tablet, IJPS, 72.1, 2010, 111-113.
10. Raveendra Babu Ganduri, Ramprasad Lanka A, Srinivasu Pamidi, Jayachandra R. Peddareddigari, Mustafa Mohammed, New RP-HPLC Method for The Determination of Olmesartan Medoxomil in Tablet Dosage Form, EJAC, Vol.5, No.2, 2010.
11. Celebier M, Altinoz S, Determination of Olmesartan medoxomil in tablets by UV-Vis spectrophotometry,Die pharmazie,Vol.62,No.6, (4), 2007, pp.419-422.
12. Pournima Patil S, Harinath More N, Sachin Pishwikar A, RP HPLC method for simultaneous estimation of amlodipine besylate and olmesartan medoxomil from tablet, IJPPS, Vol.3, Suppl.3, 2007.
13. Chowdry KPR, Devala Rao G, Himabindu G. Validation of analytical methods. Eastern Pharmacist 1999, 42, 39-41.
14. Validation of Compendial Procedure, 1225, United States Pharmacopeia, USP39-NF34, first supplement, 2016.
15. Validation of Analytical Procedures: Text and Methodology Q2 (R1), current step 4 version, November 2005.
16. Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) August 1997.

Source of Support: Nil, **Conflict of Interest:** None.