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Research Article

A Novel Simultaneous Estimation Of Ramipril And Olmesartan Medoxomil By First Derivative UV Spectrophotometric Method In Solid Dosage Forms

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ABSTRACT

A new, simple rapid and novel spectrophotometric method has been developed for simultaneous estimation and first order derivatives of Ramipril and Olmesartan Medoxomil. The method involved measurement of absorbance at two wavelength 208nm (RAM) 256 nm (OLM). The Beer's law obeyed the concentration range of 5-50µg/ml for both OLM and RAM 5-50µg/mL for both drugs. The R2 values were found to be 0.996 and 0.994for Olmesartan and Ramipril respectively. Percentage Assay and Recovery were found to be 99.9-99.3% for Olmesartan and Ramipril. The method was validated statistically and by recovery studies. The method shows good linearity, accuracy, and precision, limit of detection and limit of quantification. Both these methods have been successively applied to pharmaceutical formulation and were validated according to ICH guidelines. This method can be successfully employed for the routine simultaneous estimation of OLM and RAM in pharmaceutical dosage forms

INTRODUCTION

Ramipril's chemical name is (2S, 3aS, 6aS) -1[(S)-N-[(S) -1-Carboxy-3-phenylpropyl]alanyl] octahydrocyclopenta[b] pyrrole-2-carboxylic acid, 1-ethyl ester. Ramipril is an angiotensin converting enzyme (ACE) inhibitor. An inactive prodrug, Ramipril is converted to ramiprilat in the liver and is used to treat hypertension and heart failure, to reduce proteinuria and renal disease in patients with nephropathies, and to prevent stroke, myocardial infarction, and cardiac death in high-risk patients. Ramiprilat, the active metabolite, competes with angiotensin I for binding at the angiotensin-converting enzyme, blocking the conversion of angiotensin I to angiotensin II . As angiotensin II is a vasoconstrictor and a negative

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feedback mediator for renin activity, lower concentrations result in a decrease in blood pressure and an increase in plasma rennin. Ramiprilat may also act on kininase II, an enzyme identical to angiotensin-converting enzyme that degrades the vasodilator bradykinin . The chemical structure of Ramipril is shown in Fig 1. The typical dose of Ramipril is 5 mg per day. Literature survey revealed that various analytical methods for quantitative determination of Ramipril in pharmaceutical formulations have been reported in literature like LC-MS (Liquid chromatography-mass spectrophotometry) , Atomic-absorption spectrometry , Capillary electrophoresis , HPLC (High-performance liquid chromatography) Olmesartan Medoxomil chemically name is (5-methyl-2-oxo-2H-1,3-dioxol-4-yl)methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-{[2'-(1H-1,2,3,4-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl}-1H-imidazole-5 carboxylate. Olmesartan belongs to the angiotensin II receptor blocker (ARB) family of drugs, which also includes telmisartan, candesartan, losartan, valsartan, and irbesartan. ARBs selectively bind to angiotensin receptor 1 (AT1) and prevent the protein angiotensin II from binding and exerting its hypertensive effects, which include vasoconstriction, stimulation and synthesis of aldosterone and ADH, cardiac stimulation, and renal reabsorption of sodium, among others. Overall, olmesartan's physiologic effects lead to reduced blood pressure, lower aldosterone levels, reduced cardiac activity, and increased excretion of sodium.

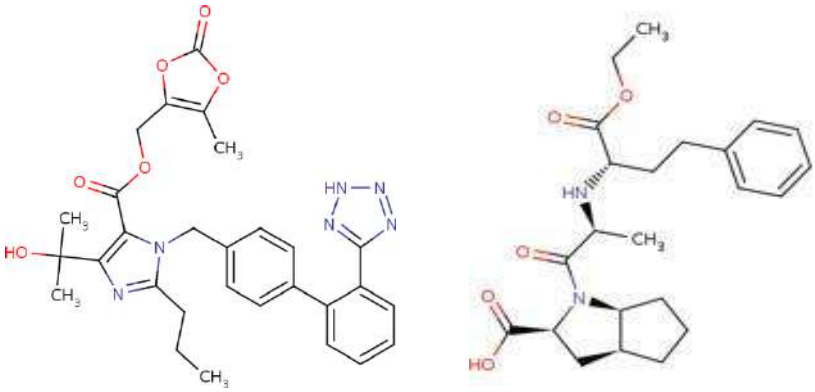


Fig.1.Structure of Ramipril and Omlersartan

MATERIALS AND METHOD:

Pharmaceutically pure sample of Olmesartan Medoxomil were procured from Ajantha Phamaceutical Ltd. Aurangabad and Ramipril were procured from sherya pharmaceutical Ltd. Aurangabad.Both the drugs are used as a standard without further purification. Methanol AR grade (Qualigens, Fine chemicals).was used as solvent for the study. A Shimadzu 1700 UV (Shimadzu, Japan) spectrophotometer with 1 cm matched solution, solution was ultrasonicated. Further dilutions were made to get the concentration of 10µg/ml.

quartz cells, was used for the estimation was used to measure absorbance of the resulting solution

Preparation of Standard stock Solutions: Standard stock solution of RAM and OLM were prepared by separately dissolving accurately weighed quantities (100 mg each) of RAM and OLM in 50 ml methanol and transferred it to 100ml volumetric flask. Volume was made up to mark with methanol to obtain stock solution of 1000 ug/ml concentration. For obtaining clear

Selection of analytical wavelength: The standard solution of RAM (10µg/ml) and OLM (10µg/ml) were scanned separately in the wavelength range

of 200-400 nm and the λ max was found to be 208 nm and 256 nm for RAM and OLM respectively.

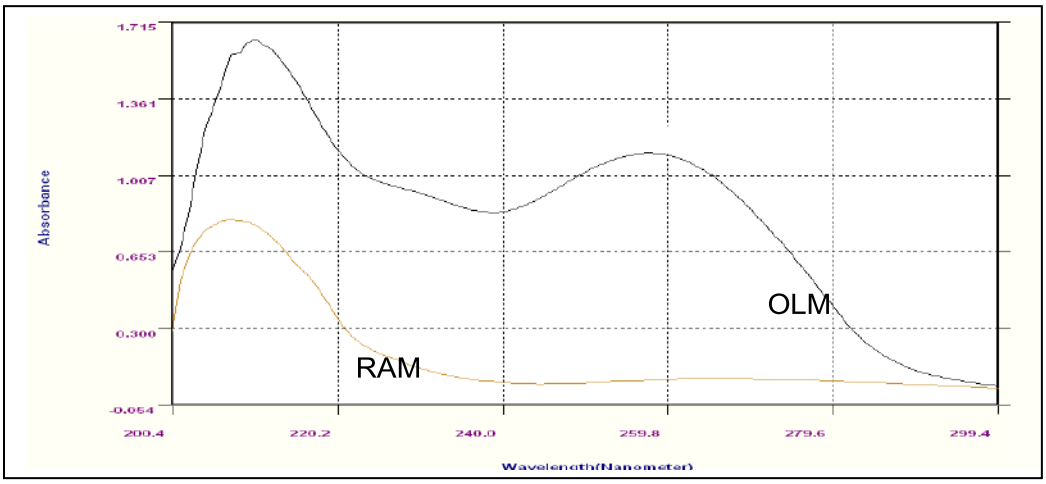


Fig.no. 3 Overlain spectra of RAM & OLM

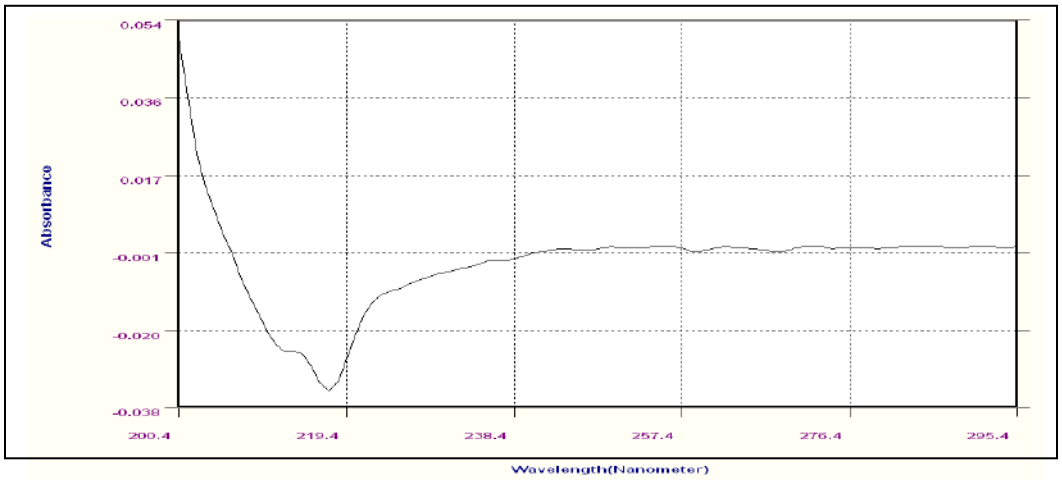


Fig.no.4 derivative spectra of RAM.

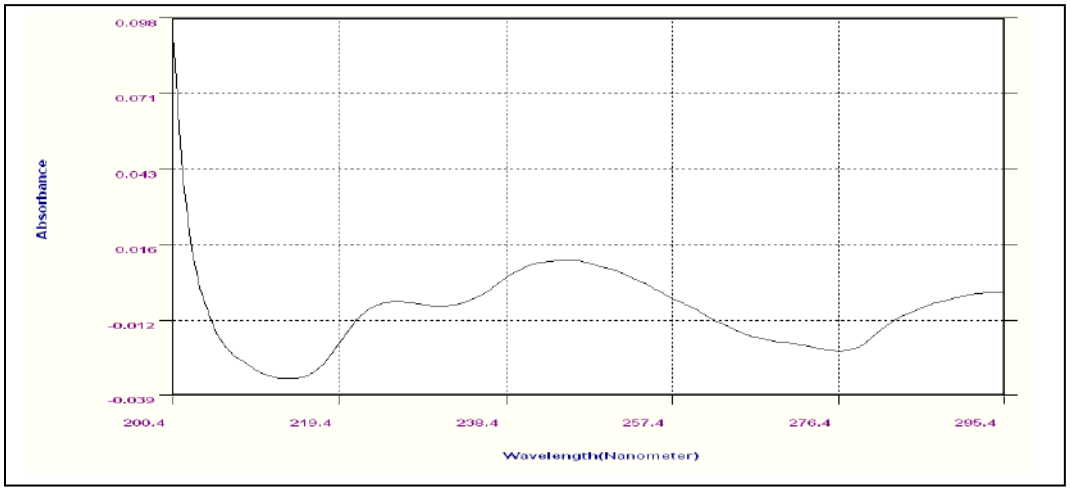


Fig. no. 5 derivative spectra of OLM.

Linearity:

From the standard stock solution of RAM, appropriate aliquots were pipetted out into 10 ml volumetric flasks and dilutions were made with methanol to obtain working standard solutions of concentrations 5, 10, 15, 20, 25, 30, 35 □g/ml. Similarly, from the standard stock solution of OLM subsequents dilution were made with methanol to obtain working standard solutions of concentrations 5, 10, 15, 20, 25, 30, 35 □g/ml. The difference in absorbance (dA/dλ) of RAM and OLM were measured in the first derivative mode of instrument at 237.4 nm and 243.4 nm respectively for RAM and OLM (Table No.4.10) The calibration curve of both the drugs was plotted. (Fig No.4.14 and 4.15) The concentration range over which the drugs followed linearity was chosen as an analytical concentration range that is 5-35 µg/ml for RAM and 5-35 µg/ml for OLM.

Precision:

Assay of method precision (intra-day precision) was evaluated by carrying out three independent assays of test samples of AMB and OLM. The intermediate precision (Intraday precision and inter-day precision) of the method was also evaluated using two different analysts, systems and different days in the same laboratory. The assay values obtained by two analysts were summarized.

Accuracy (Recovery Test):

Accuracy of the method was studied by recovery experiments. The recovery experiments were performed by adding known amounts to tablet. The recovery was performed at three levels, 80, 100 and 120% of RAM & OLM standard concentration. The recovery samples were prepared in before mentioned procedure. Three samples were prepared for each recovery level. The solutions were then analyzed, and the percentage recoveries were calculated from the calibration curve. The recovery values are summarized,

Assay of Tablets:

Twenty tablets were weighed and finely powdered. An accurately weighed portion of the powder equivalent to 20 mg of OLM and 12.5 mg of CLT was transferred to 25 ml ,volumetric flask and sufficient Methanol was added and sonicated for 10 min. The solution was filtered through Whatman filter paper (No. 42). Take 10 mL into 100 mL volumetric flask and then diluted up to volume with Methanol to get stock sample solution. Aliquot of 2.5 mL was pipetted out from above prepared solution and diluted up to 10 mL with Water to get the working sample solution. 6 replicates of these solutions were prepared. The solutions prepared in this manner were then subjected to analysis by developed method. % RSD of Olmesartan medoxomil and Ramipril was calculated.

LOD and LOQ:

The limit of detection (LOD) is the lowest of analyte in a sample which can be detected but not necessarily quantitated as an exact value. The limit of quantification (LOQ) is the lowest amount of an anlyte in a sample which can be quantitatively determined with suitable precision and accuracy. The several approaches are used to determine the detection and quantified limit as per ICH guidelines. This includes the use of standard deviation of response and slope of calibration curve. In the present work LOD and LOQ were determined by using standard deviation of the response and slope approaches and calculate with by using following formula equations .

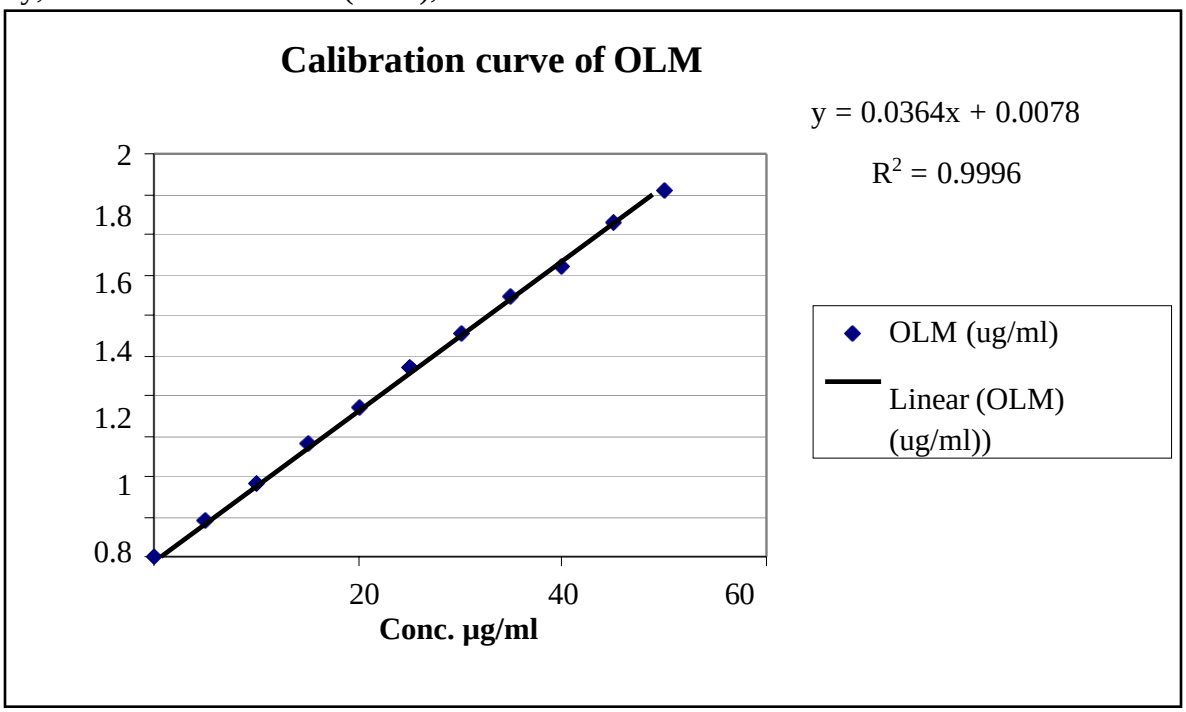
Stability of Drugs in a Selected Solvent:

The stability of the drugs in the selected solvent was determined by measuring the absorbance of the drug solutions(10ug/ml)at different time intervals. The absorbance was measured after every 10 min. The solutions were found to be stable. The stability data is given in Table No.1. and 2 for RAM and OLM respectively. The non-

linear graph between time in mins and absorbance for RAM and OLM.

RESULT AND DISCUSSIONS

The methods were validated with respect to linearity, limit of detection (LOD), limit of quantification (LOQ), precision, accuracy and Robustness.



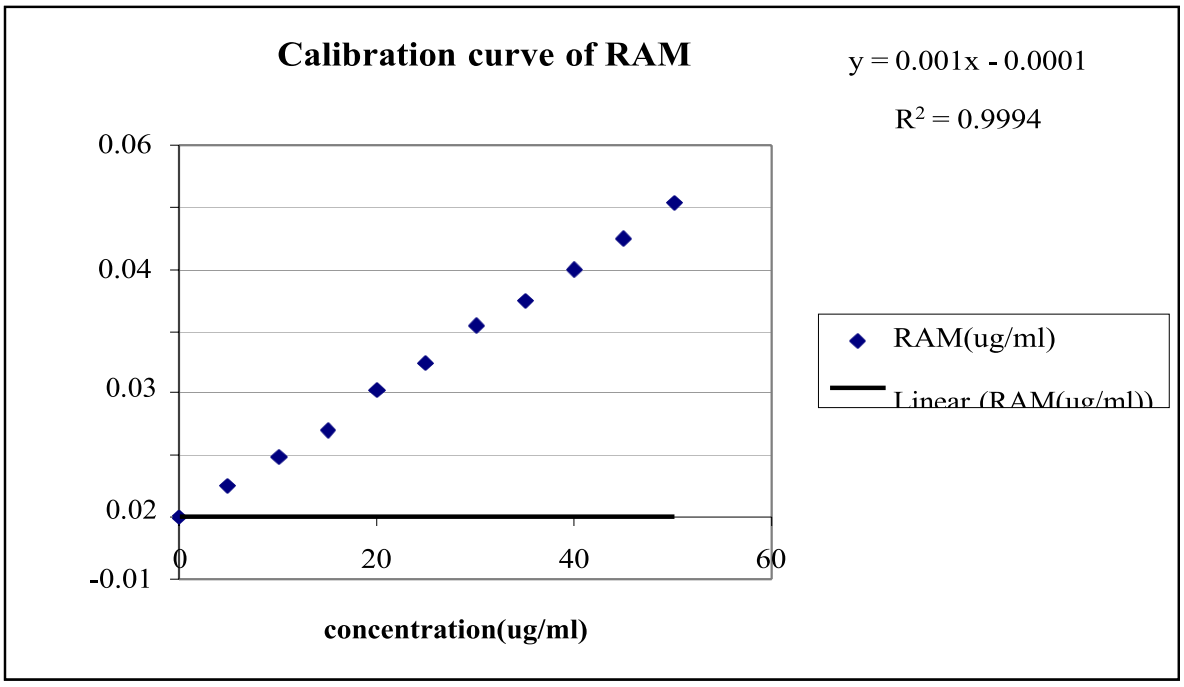


Fig.7 Calibration Curve of RAM

Table 1. Linearity data

Parameters	**Ramipril**	**Olmersartan**
λmax (nm)	208	256
Beers law limits (µg/ml)	5-50 g/ml	5-50 g/ml
Regression line	y = 0.001x - 0.0001	y = 0.001x
Correlation Coefficient(R2)	0.996	0.994
Slope ± S.D	$0.001\pm0.614\times10^{-2}$	0.0364±0.6325×10-3
Intercept ± S.D.	-0.0001±0.0	0.0078±0.4472×10-3
LOD		
LOQ		

Table 2. Determination of Precision for RAM

Sample Number	**Assay of RAM as % of labeled amount**	
	Analyst-I (Intra-day Precision)	**Analyst-II (Interday precision)**
1	99.85	100.10
2	100.10	99.85
3	99.70	99.90
4	99.90	99.95
5	100.15	100.15
6	99.80	99.80
Mean	99.91	99.95
S.D	0.17527	0.2626
R.S.D	0.0017543	0.0026281
C.V.	0.17543	0. 26281

Table 3. Determination of Precision for OLM

Sample Number	**Assay of RAM as % of labeled amount**	
	Analyst-I (Intra-day Precision)	**Analyst-II (Interday precision)**
1	99.10	99.70
2	99.70	99.90
3	99.50	99.75
4	100.10	99.80
5	99.90	99.85
6	99.80	99.95
Mean	99.68	99.82
S.D	0.34882	0.0937
R.S.D	0.003499	0.0009387
C.V.	0.3499	0.09387

Table 4. recovery study for OLM & RAM

Level of % Recovery	***Amount present ((µg/ml))**		**Amount of standard added ((µg/ml))**		**Total amount recovered ((µg/ml))**		**%Recovery**	
	RAM	**OLM**	**RAM**	**OLM**	**RAM**	**OLM**	**RAM**	**OLM**
80	5	20	4	16	8.8972	35.9912	98.8577	99.975
80	5	20	4	16	8.9123	35.9823	99.0255	99.950
80	5	20	4	16	9.0012	36.0013	100.013	100.003
100	5	20	5	20	9.9532	39.967	99.532	99.917

100	5	20	5	20	9.9712	39.9914	99.712	99.978
100	5	20	5	20	10.032	40.001	100.032	100.002
120	5	20	6	24	11.011	43.9701	100.101	99.932
120	5	20	6	24	10.975	44.0023	99.772	100.005
120	5	20	6	24	10.923	43.9872	99.3045	99.970

*Mean of three determinations

Table 5. Statistical Validation of analysis.

Level of % Recovery	%* Mean Recovery		Standard Deviation		Co-efficient ofVariation	
	RAM	OLM	RAM	OLM	RAM	OLM
80	99.2988	99.976	0.6243	0.02626	0.628	0.02627
100	99.7586	99.965	0.253	0.04370	0.25	0.04372
120	99.7258	99.969	0.4001	0.03641	0.4	0.0364

Table 6. Analysis of Formulated Tablet

Sr. No	Label Claim mg/tab		Amount Found mg/tab		%of Label Claim	
	RAM	OLM	RAM	OLM	RAM	OLM
1	5	20	4.99	20.00	100.6	99.85
2	5	20	4.98	20.05	100.2	99.90
3	5	20	5.01	19.97	99.60	99.80
4	5	20	4.97	19.98	99.80	99.85
5	5	20	4.98	19.95	99.90	100.10
6	5	20	5.02	20.00	100.4	100.20

Table 7. Stability Data for RAM

Sr. No.	Time (in min)	Absorbance
1	10	0.2472
2	20	0.2473
3	30	0.2471
4	40	0.2474
5	50	0.2472
6	60	0.2470

Table 8. Stability Data for OLM

Sr. No.	Time (in min)	Absorbance
1	10	0.3520
2	20	0.3522
3	30	0.3521
4	40	0.3522
5	50	0.3520
6	60	0.3521

CONCLUSIONS

The two spectrophotometric methods were developed and validated as per ICH guidelines and suitable for simultaneous estimation of Ramipril and Olmersartan Medoxomil in bulk and tablet dosage forms. The described methods give accurate and precise results for determination of RAM and OLM mixtures in tablets without prior separation and are easily applied for routine analysis. The most striking features of the

Derivative spectroscopic method is its simplicity and rapidity. This method also provides simple and reproducible quantitative analysis without any interference from the excipients. Hence, this method developed was successfully employed in quality control and routine analysis of RAM and OLM containing dosage forms.

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