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Analytical method development, validation and stability studies of Olmesartan Medoxomil and hydrochlorthiazide in bulk and pharmaceutical dosage form by UV-Spectroscopy

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Abstract
Development of UV method for simultaneous estimation of Olmesartan Medoxomil development was done by Q-Absorbance ratio method and area under curve method and stability indicating studies using methanol as solvent. Most of the studies are not well authenticated and not cross validated by any methodology. Here we have made an attempt to develop a simple, specific, accurate, precise and reproducible method for the simultaneous estimation of Olmesartan Medoxomil (OLM) and Hydrochlorothiazide (HTZ) in combined dosage form by UV spectrophotometric method, the method includes area under curve method (Method I) and Q- absorbance Ratio method (Method II). The wavelengths are 243 nm and 272 nm λ_{max} of both the drugs were prepared for Method I, and for Q-absorbance Ratio method (Method II) 252 nm an iso absorptive wavelength and 272 nm were selected for estimation of Olmesartan Medoxomil and Hydrochlorothiazide respectively and the two drugs are follow Beer's law over the concentration range of 1-6 µg/ml. The % recoveries of the both the drugs were identified to be nearly 100 % representing the accuracy of the proposed methods. LOD and LOQ values of OLM was found to be 0.146, 0.201, 0.136, 0.422, 0.407, 0.486 at different wavelengths 272 nm, 252 nm, 243 nm respectively and LOD and LOQ values of HTZ were found to be 0.135, 0.182, 0.133, 0.410, 0.55, 0.405 at 272 nm, 252 nm, 243 nm respectively. Validation of the proposed methods was preformed out for its accuracy, precision, specificity and ruggedness as per ICH guidelines. The proposed methods successfully validated in routine work for determination of Hydrochlorothiazide and Olmesartan medoxomil in combined dosage form.

Keywords: Hydrochlorothiazide (HTZ), olmesartan medoxomil (OLM), area under curve, q-absorbance ratio method, stability studies

Introduction
Olmesartan Medoxomil was an anti-hypertension drug chemically named as (5-Methyl-2-oxo-1,3-dioxol-4-yl) methyl 5-(2-hydroxypropan-2-yl)-2-propyl-3- [4-[2-(2H-tetrazol-5-yl) phenyl] methyl] imidazole-4-carboxylate. OLM is one of several angiotensin II receptors blocking agents. OLM is an inactive ester prodrug.
Hydrochlorthiazide was a first line diuretic drug. Chemically: 6-Chloro-1, 1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide. It belongs to thiazides class of diuritics, it reduces blood volume by acting on kidneys to reduce sodium reabsorption in the distal convoluted tubule. Thiazides increase the reabsorption of calcium. It was suppose to lower peripheral vascular resistance.

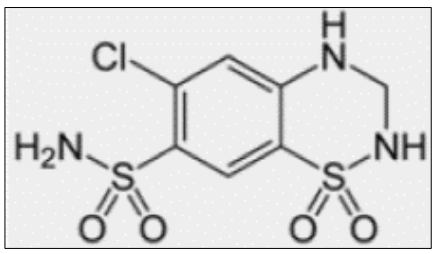

Fig 1: Olmesartan Medoxomil (OLM)

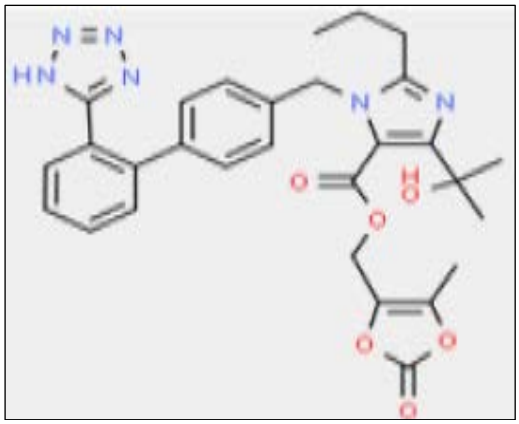

Fig 2: Hydrochlorthiazide (HTZ)

Materials and Methods [1-7]

Chemicals and reagents

Olmesartan Medoxomil and Hydrochlorthiazide procured from the KP laboratories. Commercial pharmaceutical preparation Olmesartan-Hydrochlorthiazide, manufactured by INTAS pharmaceuticals, containing 10mg of Olmesartan and 20mg of Hydroclorthazide was collected from local market, methanol analytical grade was procured from Quietens India Pvt Ltd.

Instrumentation

The proposed methanol was carried on a Shimadzu UV-Visible Spectrophotometer (UV-1800 series). All the products were weighed on Digital balance (Shimadzu), a fast clean Ultra sonicator was used for degassing the solvent.

Selection of Solvents

Methanol was selected as solvent on the basis of the solubility studies for method development.

UV-Spectroscopy

Preparation of Standard Solutions

Weighed 10 mg of OLM and HTZ and placed into a 100 ml volumetric flask separately, added 10 ml of solvent and shake well to dissolve the drug completely to get 100 µg/ml.

Preparation of Sample Solution

20 tablets were taken, crushed to fine powder. Accurately weighed powder sample equivalent to 10 mg of Olmesartan medoxomil and transferred to 100 ml volumetric flask, dissolved in sufficient solvent and filtered through whatmann filter paper.

Determination of λ_{max}

Standard solutions of OLM and HTZ were prepared and scanned in UV- spectrophotometer in the range of 200-400 nm to determine the λ_{max} of each drug λ_{max} of OLM and HCZ were found to be 252 nm and 272 nm respectively.

Method Development [8-12]

Q-Absorbance ratio method: According to Q-absorption ratio method, at two selected wavelengths used the ratio of absorption. One was at iso-absorptive point and other one was at the λmax, the concentrations of the two components were calculated by using the equation.

$C_x = \{(Q_m-Q_y)/ (Q_x-Q_y)\}* (A_1/ax_1)$
$C_y = \{(Q_m-Q_x)/ (Q_y-Q_x)\}* (A_1/ay_1)$

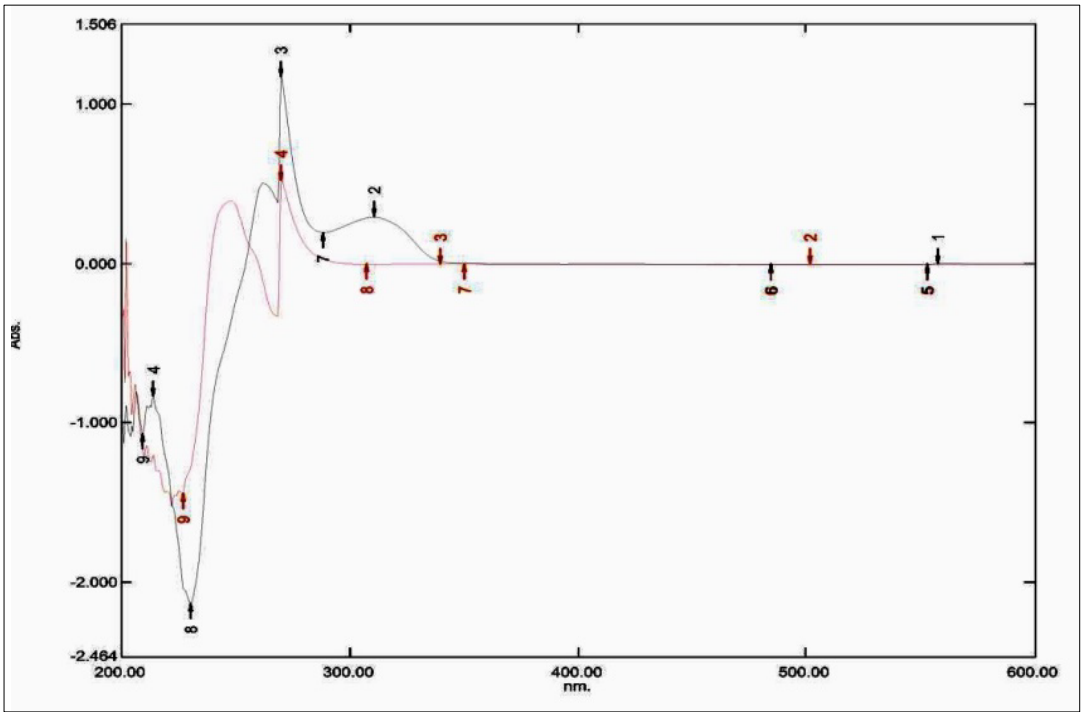

Fig 1: Overlay spectrum of OLM and HTZ

Area Under the Curve Method

OLM and HTZ were scanned between 200-400nm and found 243nm for OLM and 272nm for HTZ as λmax for estimation using area under curve method. Aliquotes of 1-6 µg/ml solutions was prepared using methanol as solvent and measured absorbance of drugs at λmax.

$C^M = X^N_{\lambda1-\lambda2} AUC_{\lambda3-\lambda4} - X^N_{\lambda3-\lambda4} AUC_{\lambda1-\lambda2} / X^N_{\lambda1-\lambda2} = X^M_{\lambda3-\lambda4} - X^N_{\lambda3-\lambda4} X^M_{\lambda1-\lambda2}$
$C^N = X^M_{\lambda1-\lambda2} AUC_{\lambda3-\lambda4} - X^M_{\lambda3-\lambda4} AUC_{\lambda1-\lambda2} / X^N_{\lambda1-\lambda2} = X^M_{\lambda3-\lambda4} - X^N_{\lambda3-\lambda4} X^M_{\lambda1-\lambda2}$

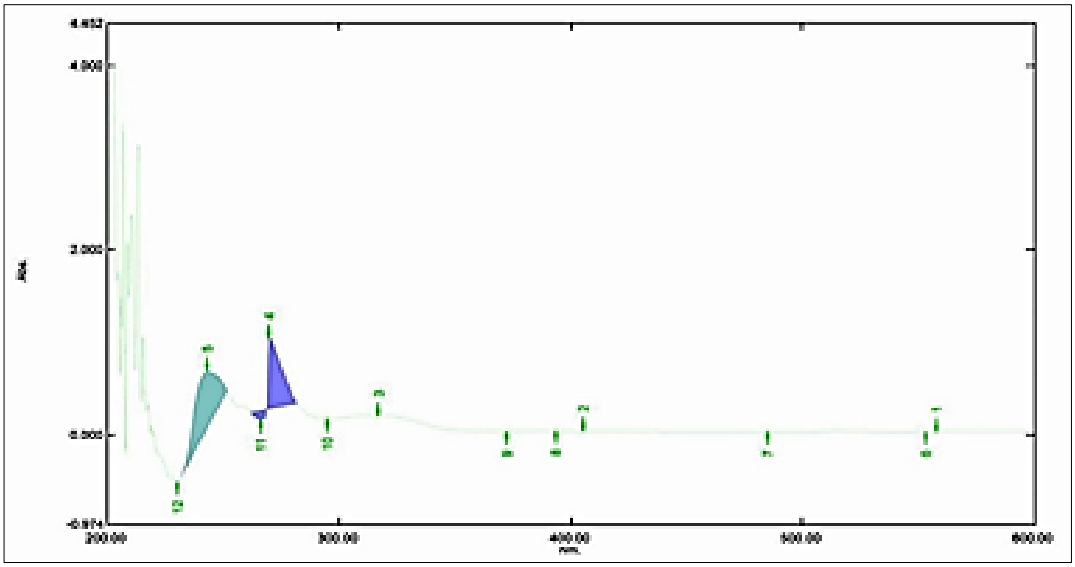

Fig 2: Area under curve of OLM and HTZ

Validation of the Method [13-14]

Validation was performed by UV Spectroscopic method as per International Conference on Harmonization (ICH) guidelines. Different parameters were carried for validation; they are linearity, precision, accuracy, limit of detection (LOD) and limit of quantification (LOQ).

Linearity

The methods were validated as per the guidelines of International conference on Harmonization, calibration curves were plotted with appropriate volumes of working standard solutions for UV and with the range of 1-5 respectively. The linearity was measured by using unweighted data in the least square regression method.

Accuracy and Precision

Accuracy was the percent of analyte recovered from assay by addition known quantity, for the measurement of accuracy data from six determinations over five concentration levels covering the specified ranges were validated. The precision of the product was validated by intermediate precision (inter-day) and repeatability (intra-day) and noted as % RSD for a statistically remarkable number of replicate measurements. The intermediate precision was performed by comparing the assay in three different days and the results were reported as standard deviation and % RSD.

Robustness

Robustness of the method was validated by preparing minute changes in the chromatographic conditions, such as composition mobile phase ratio, flow rate and wavelength.

LOD and LOQ

Limit of quantification and limit of detection were determined by plotting linearity curve for different nominal concentration of OLM and HTZ. The LOD and LOQ values were determined by using the following formula:

$LOD = 3.3 \times \sigma/S$
$LOQ = 10 \times \sigma/S$

Where σ = The standard deviation of the response
S = Slope of calibration curve.

Results and Discussion

Linearity: Different concentration range of 1-6µg/mL of OLM and 1-6µg/mL of HTZ from the stock solutions were prepared. These solutions were scanned in the range of 200-400 nm and the absorbance was noted at the λ_{max} of each drug (272nm for HTZ and 243 nm for OLM.

Table 1: LOD and LOQ of Olmesartan

Parameter	Olmesartan		
	Methods -A		Method-B
	272nm	243nm	252nm
LOD	0.146	0.136	0.201
LOQ	0.422	0.488	0.407

Table 2: LOD and LOQ of Hydrochlorothiazide

Parameter	Hydrochlorothiazide		
	Methods -A		Method-B
	272nm	243nm	252nm
LOD	0.135	0.133	0.182
LOQ	0.410	0.405	0.555

Table 3: Accuracy of Olmesartan

Methods	Amount taken	Amount found	%Recovery
Method A	50	0.139	99.7
	100	0.147	99.8
	150	0.235	100.1
Method B	50	0.142	99.9
	100	0.145	99.9
	150	0.232	100.2

Table 4: Accuracy of Hydrochlorothiazide

Methods	Amount taken	Amount found	%Recovery
Method A	50	0.140	99.5
	100	0.148	99.7
	150	0.230	100.2
Method B	50	0.145	99.4
	100	0.147	100.3
	150	0.235	100.1

Conclusion

The proposed methods successfully validated in present research work for determination of Hydrochlorothiazide and Olmesartan Medoxomil in combined dosage form. The UV

Spectrophotometric methods are simple, fast, sensitive, accurate, precise, less time-consuming and economic. All the parameters were noted within the limits, validation of the proposed methods was performed out for determination of accuracy, precision, specificity and ruggedness as per ICH guidelines. The % recoveries of the both the drugs were identified to be nearly 100% representing the accuracy of the proposed methods. The stability study has been developed for the estimation of Olmesartan and Hydrochlorothiazide. The use of Chemical methods has proved to be a smart strategy to provide both environmental and economic benefits.

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Conflict of Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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