



# Development and Validation of UV Spectrophotometric Method for Simultaneous Estimation of Olmesartan Medoxomil and Chlorthalidone in Bulk and Tablet

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## ABSTRACT

Based on the fact that no work has been reported so far for a spectrophotometric method for simultaneous estimation of olmesartan medoxomil and chlorthalidone in pharmaceutical dosage form. A precise and selective UV spectrophotometric method has been developed for the simultaneous estimation of olmesartan medoxomil (OLM) and chlorthalidone (CHL) in bulk and tablet dosage form. The spectrophotometric detection was carried out at an absorption maximum of 256 nm and 275 nm using methanol as solvent. Validation of analytical method was performed as per the ICH guidelines Q2A and Q2B. OLM and CHL demonstrated linearity in the concentration range of 5-20  $\mu\text{g mL}^{-1}$  with  $r^2$  of 0.998. The method was found to be linear over the range ( $r^2$  values of 0.997 for OLM and 0.998 for CHL), accurate (recovery; 100.51% for OLM and 99.84% for CHL), and highly precise (% RSD of 0.422 for OLM and 0.882 for CHL in intra-day study, and 0.71 for OLM and 0.934 for CHL in inter-day study, respectively) for analysis of both the drugs in bulk and tablet formulations. This method has been found suitable for estimation of both combination drugs in bulk and tablet formulations.

**Keywords:** chlorthalidone, olmesartan medoxomil, simultaneous estimation, validation, spectrophotometric

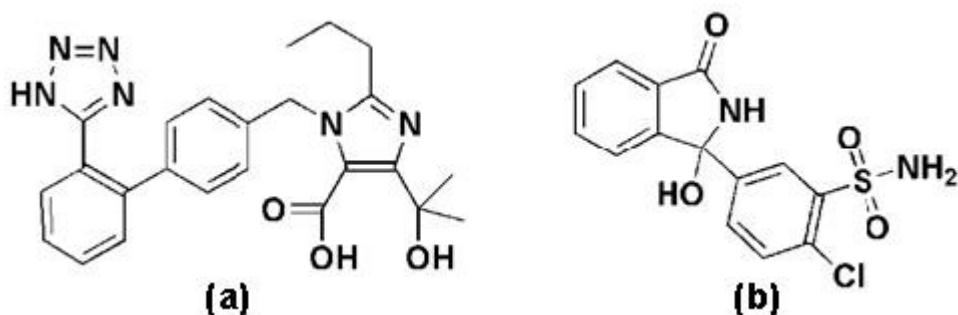
## INTRODUCTION

Olmesartan medoxomil (OLM), chemically is [(5-methyl-2-oxo-1,3-dioxol-4-yl)-methyl-5-(2-hydroxypropan-2-yl)-2-propyl][(4-(2-(2-4-tetrazole-5-yl)phenyl)phenyl)methyl]-imidazole-4-carboxylate (**Figure 1a**). It is an anti-hypertensive drug that blocks the vasoconstrictor effect of angiotensin-II by selectively blocking the binding of angiotensin-II to the angiotensin-1 ( $\text{AT}_1$ ) receptor in vascular smooth muscle [1]. Chlorthalidone (CHL), chemically is 2-chloro-5-[(1-*R,S*)-1-hydroxy-3-oxo-2-dihydro-1H-isoindol-1-yl] benzenesulfonamide (**Figure 1b**). It is a

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**Figure 1.** Structure of drugs (a) Olmesartan Medoxomil (OLM) (b) Chlorthalidone (CHL)

diuretic molecule that inhibits sodium ion transport across the renal tubular epithelium in the cortical diluting segment of the ascending limb of the loop of the henle [2]. The mixture of the two drugs is recommended in case of hypertension with renal failure conditions. OLM and CHL are official in IP and BP and both describes a method for their assay. Literature survey has revealed that many analytical methods are specified for the determination of OLM and CHL as individual and combined dosage form with other combination of drugs, UV-Vis [3], RP-HPLC [4], HPTLC [5], etc. Abdullah *et al.* (2014) [6] reported spectrophotometric determination of chlorthalidone in pharmaceutical formulation using different order methods. A new method was developed for the estimation of telmisartan and CHL using first order derivative spectrophotometry by Parmar & Mehta (2013) [3]. Similarly, Haq *et al.* (2012) [7] has developed method for the simultaneous estimation of atenolol and CHL in bulk and in combined tablet dosage form. Interestingly, few novel spectrophotometric methods for simultaneous determination of metoprolol succinate and OLM in tablet dosage form have also been reported [8-9]. However, no works have been reported so far for a spectrophotometric method for simultaneous estimation of olmesartan medoxomil and chlorthalidone in pharmaceutical dosage form.

The present research involved establishment of method for quantitative determination of OLM and CHL in pharmaceutical dosage form and to identify correctly the critical parameters required for identification. This work highlights a study on the development of a new validated spectrophotometric method for quantitative determination of OLM and CHL in pharmaceutical dosage form. The results were analyzed and validated statistically and by recovery studies.

## MATERIALS AND METHODS

### Apparatus

The spectrophotometric analysis was carried out using double-beam Shimadzu® recording ultraviolet-visible spectrophotometer (Kyoto, Japan) model UV-1800 connected with a computer having spectral bandwidth of 1 nm and wave length accuracy of  $\pm 0.3$  nm

with a pair of 10 mm path length matched quartz cells was used for analytical purpose. All weighings were performed using Shimadzu® electronic balance (Kyoto, Japan) model AUW220D. Sonication was performed Transonic Digital S sonicator, USA.

### Materials

Working standards of olmesartan medoxomil was obtained as gift sample from Ajanta Pharmaceutical Ltd., Mumbai, India and chlorthalidone was provided by Ipca Laboratories Ltd., Mumbai, India. They were used without further purification. Fixed dose combination tablet Biolsar-20 HS® (Unichem Laboratories Ltd.) containing 20 mg olmesartan medoxomil and 12.5 mg chlorthalidone was purchased from a local pharmacy in Nagpur, India. All the chemicals were of analytical grade, purchased from Merck Chemicals Ltd., India. Double distilled water was used as solvent for the experiment.

### Preparation of standard stock solution and sample solution

Sample preparation was done in methanol, taking accurately weighed quantity of 10 mg of OLM and CHL to 100 mL volumetric flasks separately to give stock solutions of final concentration  $100 \mu\text{g mL}^{-1}$ , respectively. The aliquots from stock solution were subsequent transferred into a series of 10 mL volumetric flask and volume was made up by further diluting the above content with methanol to produce a solution of  $10 \mu\text{g/mL}$  of OLM and CHL, respectively.

### Preparation of mixed standard solution

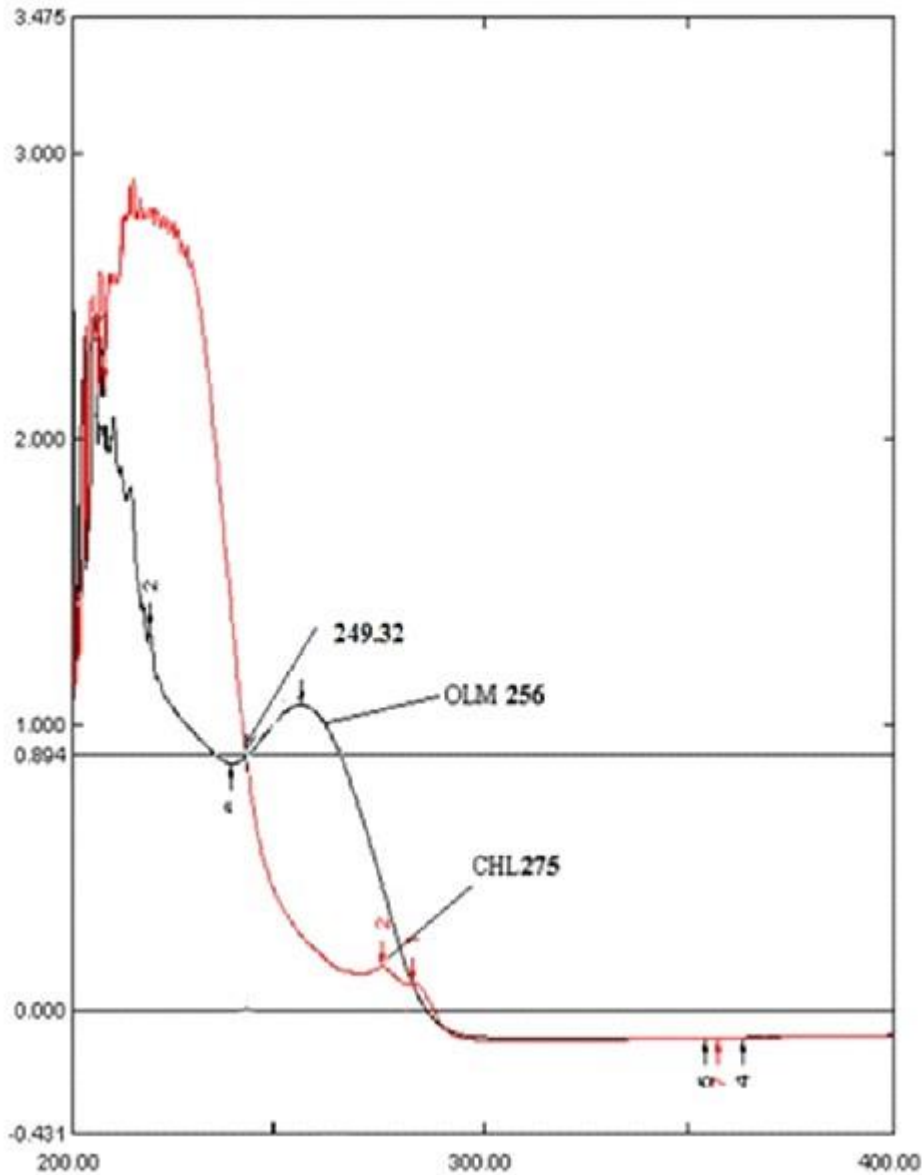
Accurately 20 mg of OLM and 12.5 mg of CHL were weighed into 100 mL volumetric flask and methanol was added. The solution was further sonicated for 20 minutes and then volume was made up to 100 mL with methanol.

### Study and selection of wavelength

The drug solutions of  $10 \mu\text{g mL}^{-1}$  were scanned in the range of 400-200 nm in 1 cm cell against blank using UV-Vis spectrophotometer. The experimentation was performed in triplicate to measure accurate  $\lambda_{\text{max}}$ . The spectrum wavelengths selected for the estimation of drugs were 256 nm as  $\lambda_{\text{max}}$  of OLM and 275 nm as  $\lambda_{\text{max}}$  of CHL (**Figure 2**).

### Study of Beer-Lamberts Law and additivity for olmesartan medoxomil and chlorthalidone

An aliquot portion of stock solutions of OLM and CHL were diluted appropriately with methanol to get a series of concentration between  $4\text{-}20 \mu\text{g mL}^{-1}$  for OLM and  $2.5\text{-}12.5 \mu\text{g mL}^{-1}$  for CHL, respectively. Similarly, aliquot portions of stock solutions were mixed (Std. laboratory mixture) and diluted with methanol to get series of concentration between  $4\text{-}20 \mu\text{g mL}^{-1}$  OLM and  $2.5\text{-}12.5 \mu\text{g mL}^{-1}$  CHL. The absorbance of each solution was measured at 256 nm and 275 nm in 1 cm cell against solvent blank. The absorbance data obtained in the study



**Figure 2.** Overlain UV spectra of OLM and CHL

of Beer-Lambert's Law at 256 nm and 275 nm for OLM and CHL were further used to study additivity on absorbance of OLM and CHL. For calculation of theoretical absorbance of mixture, the corresponding obtained absorbances of drugs at 256 nm and 275 nm were added (absorbance of OLM plus CHL at 256 nm and absorbance of OLM plus CHL at 275 nm). The additive results were further compared with the practical absorbance of mixture, obtained by taking mixture of OLM and CHL.

### Estimation of olmesartan medoxomil and chlorthalidone in bulk drug

For the analysis of drug in bulk, 10 mg of OLM and CHL were accurately weighed and taken in 100 mL volumetric flask and dissolved in methanol by vigorous shaking. Volume was made up to the mark with methanol to get final concentration of about 12.0  $\mu\text{g mL}^{-1}$  OLM and 7.5  $\mu\text{g mL}^{-1}$  CHL. The absorbance of the resulting solutions was measured at 256 nm and 275 nm in 1 cm cell against blank. The amount of each drugs was determined using following simultaneous equation:

$$Cx = \frac{A_2ay_1 - A_1ay_2}{ax_2ay_1 - ax_1 - ay_2}$$

$$Cy = \frac{A_1ax_2 - A_2 - ax_1}{ax_2ay_1 - ax_1ay_2}$$

where,  $Cx$  is concentration of OLM in g/100 mL;  $Cy$  shows the concentration of CHL in g/100 mL;  $ax_1$  describes the absorptivity value of OLM at 256 nm;  $ax_2$  presents the absorptivity value of CHL at 275 nm;  $ay_1$  displays the absorptivity value of OLM at 275 nm;  $ay_2$  represents the absorptivity value of CHL at 256 nm;  $A_1$  signifies the absorbance of laboratory mixture at 256 nm; and,  $A_2$  symbolizes the absorbance of laboratory mixture at 275 nm.

$$\% \text{ estimation} = \frac{C \times d}{W} \times 100$$

where,  $C$  either  $Cx$  or  $Cy$  which represents the concentration of OLM or CHL in g/100 mL;  $d$  describes dilution factor; and,  $W$  shows the weight of drug either OLM or CHL in laboratory mixture.

### Estimation of olmesartan medoxomil and chlorthalidone in tablet formulation

For preparation of sample solution of pharmaceutical mixture twenty tablets (Biosar-20 HS<sup>®</sup>) were weighed and powdered finely. Tablet powder equivalent to 20 mg of OLM and 12.5 mg of CHL was transferred to 100 mL volumetric flask and dissolved in methanol. The solution was ultrasonicated for 30 min and further filtered through 0.45  $\mu\text{m}$  membrane filter. The aliquot portion of filtrate was further diluted to get final concentration of about 20  $\mu\text{g mL}^{-1}$  OLM and 12.5  $\mu\text{g mL}^{-1}$  CHL. The absorbance of sample solutions was measured at 256 nm and 275 nm in 1 cm cell against blank. The content of OLM and CHL in tablet was estimated using the following formulae:

$$\% \text{ label claim} = \frac{C \times d \times W}{Wm \times L}$$

where,  $C$  either  $Cx$  or  $Cy$  which represents the concentration of OLM or CHL in g/100 mL;  $d$  describes dilution factor;  $W$  represents the average weight of tablet;  $Wm$  is the weight of sample taken; and,  $L$  signifies the labeled claim of sample taken.

### Recovery study

Recovery study was carried out by standard addition method. An accurately weighed quantity of preanalyzed tablet powder equivalent to 10 mg of OLM was taken in 100 mL volumetric flask to it standard solution of OLM and CHL were added in different proportion. Then volume was adjusted up to the mark with methanol. Solution was filtered through Whatman filter paper No. 42. The aliquot portions of the filtrate were further diluted to get final concentration. The absorbance of sample solution was measured at 275 nm and 256 nm in 1 cm cell against blank. The content of drug was calculated using same formula as in marketed formulation. The percentage recovery was determined based on the following formula:

$$\% \text{ recovery} = \frac{A}{B + C} \times 100$$

where, *A* is the total amount of drug estimated; *B* describes the amount of drug found on preanalysed basis; and, *C* represents the amount of pure drug added.

### Validation Parameters

Validation of analytical methods, in general, has been extensively covered in the ICH guidelines Q2A and Q2B, in the FDA guidance and by USP. Here validation has been carried out as per ICH guidelines Q2A and Q2B.

### Linearity and range

For linearity, a method was used for the simultaneous determination of two ingredients. Five concentrations were chosen ranging from 50% to 150% of the target analyte concentrations (80, 90, 100, 110, and 120 %) in formulations. All the solutions were prepared by diluting in methanol. Calibration graph was obtained by plotting absorbance versus concentration of standard drugs and regression correlation ( $r^2$ ) was determined.

### Precision

The precision of an analytical method is the closeness of replicate results obtained from analysis of the same homogeneous sample. Precision was determined through the estimate of the relative standard deviation (RSD) values. The studies of ruggedness were carried out to determine inter- and intra-day variability. Intra-day analysis was performed by estimating three concentrations (50%, 75%, and 150%) of standard solution of drugs six times in a single day. For inter-day, analysis was performed employing the similar protocol and recorded on three different days. In addition, the sample solutions were prepared by two different analysts and same procedure was followed as described earlier for analysis in order to determine the precision of the method. The % label claim was calculated as done in marketed formulation estimation.

**Table 1.** Study of Beer-Lambert's Law and additivity study for OLM and CHL

S. No.	Concentration ( $\mu\text{g mL}^{-1}$ )		Absorbance (nm)				Theoretical absorbance of mixture		Practical absorbance of mixture	
	OLM	CHL	OLM		CHL		256 nm	275 nm	256 nm	275 nm
			256 nm	275 nm	256 nm	275 nm				
1.	4	2.5	0.263	0.063	0.094	0.228	0.357	0.291	0.361	0.303
2.	8	5	0.411	0.121	0.176	0.365	0.587	0.486	0.536	0.513
3.	12	7.5	0.549	0.178	0.252	0.511	0.801	0.689	0.767	0.689
4.	16	10	0.703	0.238	0.335	0.671	1.038	0.909	0.903	0.883
5.	20	12.5	0.819	0.293	0.428	0.815	1.247	1.108	1.242	1.108

### Accuracy

The accuracy of an analytical method expresses the closeness of agreement between the value, which is accepted reference value, and the value found. Accuracy studies were done by the standard analysis method. Accuracy is expressed as percentage recovery of the standard spiked to previously analyzed test sample of tablet. Three different concentrations of the standard drug viz. 80%, 100%, and 120% each of the labeled claim were used. The accuracy was reported as % recovery  $\pm$  (% confidence interval) with % relative error on the base of actual and estimated concentrations.

## RESULTS AND DISCUSSION

### Beer-Lamberts Law and additivity values for drugs

The absorbances were recorded skillfully and graphs were plotted between concentration vs absorbance for drugs (**Table 1**) OLM and CHL as well as laboratory mixture for concentration 4-20  $\mu\text{g mL}^{-1}$  and 2.5-12.5  $\mu\text{g mL}^{-1}$ , respectively at selected wavelengths. In laboratory mixture, at 256 nm, the regression equation was found to be  $0.05x + 0.158$ , and at 275 nm, equation was  $0.082x + 0.088$ . In both the cases,  $r^2$  values are 0.998, which indicated desired linearity of the proposed method. The mixture of drugs showed additivity of absorbance at the selected wavelengths. The theoretical absorbance of mixture was found to be nearly equal to practical absorbance of mixture (difference was found to be 0.004-0.135). This represented that the proposed method was sensitive and accurate enough to determine both the drugs in mixture. The results are summarized in **Table 1**.

### Analysis of bulk drug by proposed method

The proposed method was found to be very sensitive for simultaneous determination of OLM and CHL. The method successfully detected both the drugs in microgram concentrations. The drug estimation for OLM was found to be in range of 98.33 to 99.5% and

**Table 2.** Simultaneous estimation of OLM and CHL in bulk

S. No.	Amount of drug sample taken (g)		Absorbance (nm)		% drug estimation	
	OLM	CHL	256 nm	275 nm	256 nm	275 nm
1.	12	7.5	0.769	0.684	98.33	100.00
2.	12	7.5	0.764	0.676	99.10	99.90
3.	12	7.5	0.766	0.678	99.50	99.40
4.	12	7.5	0.765	0.677	99.86	99.20
5.	12	7.5	0.769	0.684	98.56	100.05
				<b>Mean</b>	99.07	99.79
				<b>±S.D.</b>	0.6359	0.3847
				<b>R.S.D.</b>	0.00641	0.00385
				<b>%R.S.D.</b>	0.641	0.3855

S.D. standard deviation; R.S.D. relative standard deviation; %R.S.D. % relative standard deviation

**Table 3.** Simultaneous estimation of OLM and CHL in tablet formulation

S. No.	Wt. of tablet powder (g)	Absorbance		% drug estimation	
		256 nm	275 nm	OLM	CHL
1.	0.1723	1.242	1.108	99.12	99.86
2.	0.1721	1.240	1.106	98.83	100.05
3.	0.1722	1.244	1.103	99.70	99.06
4.	0.1720	1.248	1.110	99.70	99.06
5.	0.1721	1.246	1.105	100.10	99.53
			<b>Mean</b>	99.49	99.51
			<b>±S.D.</b>	0.5081	0.4526
			<b>R.S.D.</b>	0.00510	0.00454
			<b>%R.S.D.</b>	0.510	0.454

S.D. standard deviation; R.S.D. relative standard deviation; %R.S.D. % relative standard deviation

99.2 to 100.05%, respectively. These results represented that the method is precise enough to determine both the components in bulk. The results are demonstrated in [Table 2](#).

### Analysis of marketed formulation by proposed method

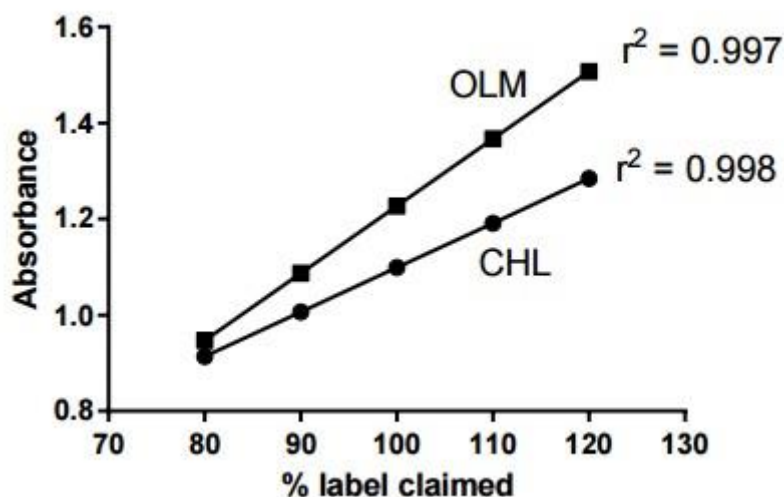
The proposed method was simple, rapid and precise and do not suffer from any interference due to excipients of tablet. Various optical characteristics are shown in the [Table 3](#). The % RSD was found to be 0.51 in case of OLM and 0.454 for CHL, which demonstrated that the method is acceptable (limit; <2%).

### Validation Parameters

#### Linearity and range

The linear regression equation for OLM was  $y = 0.07x + 0.127$  and for CHL, the equation was  $0.074x + 0.074$ . The regression coefficient value of OLM and CHL were found to be 0.997 and 0.998, respectively, which indicated an acceptable degree of linearity ([Figure 3](#)).





**Figure 3.** The plot of linearity and range for OLM and CHL

#### *Accuracy*

The percentage recoveries were calculated from the slope and Y-intercept of the calibration curve. The % recovery for this analytic method for all the three concentration levels ranged 99.04 % to 101.86 % with standard deviation of 1.246 for OLM and 0.7049 for CHL showing that any small change in the drug concentration can be accurately determined with high accuracy. Thus, values of recovery greater than 99.0% indicated that proposed method was accurate for the analysis of the drug. The recovery data for accuracy studies are given in **Table 4**.

#### *Precision*

The % RSD for the intra-day was 0.422 for OLM and for 0.882 for CHL, respectively. For inter-day precision, % RSDs was found to be 0.71 and 0.934. The measured % RSD values for the proposed method was found to be within the acceptance limit of  $\pm 2\%$  which indicated good precision of the developed method. The intra-day and inter-day variability was found to be negligible (**Table 5** and **Table 6**). The results and statistical data for inter-analyst study are given in **Table 7**, where no significant changes were detected. The data indicated displayed brilliant intra-day, inter-day precision and inter-analyst precision results which proved that the proposed method is highly reproducible.

**Table 4.** Results of recovery studies of OLM and CHL

No.	Concentration	Amount of pure drug added ( $\mu\text{g/mL}$ ) (n=6)		Absorbance		% Recovery*	
		OLM	CHL	256 nm	275 nm	OLM	CHL
1	80%	16	10	0.982	0.852	101.86	99.04
2	100%	20	12.5	1.253	1.116	99.40	100.37
3	120%	24	15	1.351	1.247	100.29	100.11
<b>Mean</b>						100.51	99.84
<b><math>\pm</math>SD</b>						1.246	0.7049
<b>RSD</b>						0.0124	0.0070
<b>%RSD</b>						1.239	0.7050

S.D. standard deviation; R.S.D. relative standard deviation; %R.S.D. % relative standard deviation; \*Average of six determinations

**Table 5.** Result and statistical data of intra-day study (3 h interval)

S. No.	Concentration	Absorbance (n = 6)		% Drug estimated*	
		256 nm	275 nm	OLM	CHL
1	50%	1.242	1.106	99.63	98.94
2	75%	1.245	1.108	98.80	99.74
3	150%	1.243	1.109	99.10	100.70
<b>Mean</b>				99.17	99.79
<b><math>\pm</math>S.D.</b>				0.4203	0.8812
<b>R.S.D</b>				0.00421	0.00881
<b>%R.S.D</b>				0.422	0.882

S.D. standard deviation; R.S.D. relative standard deviation; %R.S.D. % relative standard deviation; \*Average of six determinations

## CONCLUSION

In the present investigation, UV method was developed for simultaneous estimation of olmesartan medoxomil and chlorthalidone in bulk and combined dosage form. The method involved solving of simultaneous equation, where 256 nm and 275 nm were selected as detection wavelengths. The developed method was found to be simple, economic, accurate, precise, and reproducible and can be adopted to routine quality control analysis of these two drugs in bulk and pharmaceutical combined dosage forms.

## ACKNOWLEDGEMENT

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**Table 6.** Result and statistical data of inter-day study (3 days)

Day	Concentration	Absorbance (n=6)		% Drug estimated*	
		256 nm	275 nm	OLM	CHL
1	50%	1.243	1.106	99.04	99.68
2	75%	1.246	1.108	99.94	101.17
3	150%	1.244	1.105	98.55	99.45
<b>Mean</b>				99.27	100.01
<b>±S.D.</b>				0.7050	0.9338
<b>R.S.D</b>				0.00710	0.00933
<b>%R.S.D</b>				0.710	0.934

S.D. standard deviation; R.S.D. relative standard deviation; %R.S.D. % relative standard deviation; \*Average of six determinations

**Table 7.** Result and statistical data of analysis performed by two different analysts

S. No.	Concentration	Absorbance (n=6)		% Drug estimated*	
		256 nm	275 nm	OLM	CHL
1	50%	1.243	1.104	99.94	99.68
2	75%	1.245	1.106	98.55	99.94
3	150%	1.242	1.105	99.10	101.45
<b>Mean</b>				99.19	100.35
<b>±S.D.</b>				0.700	0.9557
<b>R.S.D</b>				0.0070	0.00952
<b>%R.S.D</b>				0.70	0.952

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