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ORIGINAL ARTICLE

A Green Analytical Spectrophotometric Method Development of Azelnidipine and Olmesartan Medoxomil by Using Mixed Hydrotropic Solubilization

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ABSTRACT
A new UV method was developed for the estimation of Azelnidipine and Olmesartan Medoxomil in tablets using the hydrotropic solubilization method and it was validated as per ICH guidelines. The aim of the present research was to increase the solubility of Azelnidipine and Olmesartan Medoxomil in water by hydrotropic solubilisation. Hydrotopes are surface active, highly water-soluble organic salt, which imparts solubility to insoluble or sparingly soluble organic compounds in water, which is when present at higher concentration. An analytical method was developed for the estimation of Azelnidipine and Olmesartan Medoxomil by spectrophotometry. Solvent 2M sodium acetate and Urea solution was utilized and Identification and quantification was carried out using a UV detector, with working wavelength of 240 nm & 253 nm. Linearity of the drugs was ascertained over the conc range 2-20 mcg/ml (microgram/ml). The accuracy was found within acceptable limit. The developed method is rigid, robust and efficient for the estimation of Azelnidipine and Olmesartan Medoxomil from the tablet dosage form. The effort was made to develop green or eco-friendly analytical method utilising hydrotropic solvent for water insoluble drug.
KEYWORDS: Azelnidipine, Olmesartan Medoxomil, hydrotropic agents, hydrotropic solubilization.

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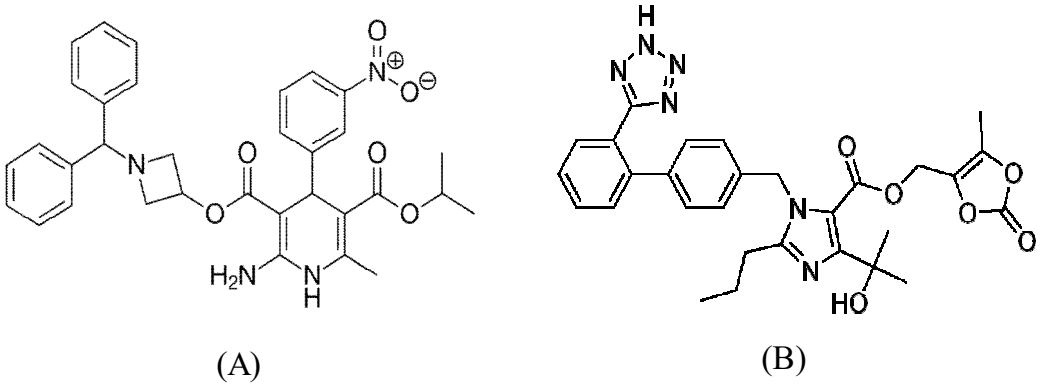
INTRODUCTION

Pharmaceutical products formulated with more than one drug, typically referred to as combination products. These combination products can present daunting challenges to the analytical chemist responsible for the development and validation of analytical methods. The development and validation of analytical methods [Spectrophotometric, High performance liquid chromatography (HPLC) & High-performance thin layer chromatography (HPTLC)] for drug products containing more than one active ingredient. The official test methods that result from these processes are used by quality control laboratories to ensure the identity, purity, potency, and performance of drug products [1]. The number of drugs introduced into the market is increasing every year. These drugs may be either new entities or partial structural modification of the existing ones. Very often there is a time lag from the date of introduction of a drug into the market to the date of its inclusion in pharmacopoeias. This happens because of the possible uncertainties in the continuous and wider usage of these drugs, reports of new toxicities (resulting in their withdrawal from the market), development of patient resistance and introduction of better drugs by competitors. Under these conditions, standards and analytical procedures for these drugs may not be available in the pharmacopoeias. It becomes necessary, therefore to develop newer analytical methods for such drugs.

Azelnidipine (AZEL), (±)- (3)-(1-diphenylmethylazetidin-3-yl)-5- isopropyl-2-amino-1, 4-dihydro-6-methyl-4-(3- nitrophenyl) - 3, 5-pyridinedicarboxylate, is a new dihydropyridine derivative with calcium antagonistic activity [1]. The recommended dosing of AZL is 16 mg per day. Olmesartan medoxomil

(OLME) 2, 3-dihydroxy-2-butenyl4-(1-hydroxy-1-methylethyl)-2-propyl-1-[p-(o-1Htetrazol 5-ylphenyl) benzyl] imidazole-5-carboxylate ,cyclic -2,3 -carbonate. Figure 1 depicted the chemical Structure of AZEL and OLME.



(A) (B)

Figure 1: Structure of (A) AZEL and (B) OLME

MATERIAL AND METHODS

Chemical and Reagents

Azelnidipine was obtained as gift sample from Pure& Cure Health Pvt Ltd, India & Olmesartan Medoxomil was obtained as gift sample from MG Lab, India. Marketed formulation i.e. tab Olmezest-AZ 20 was purchase from local market. All other chemicals and the reagents used were of Anal AR grade.

Instruments

Spectrophotometer: Double beam UV –visible spectrophotometer with 10 mm matched quartz cell, Shimatzu 1800 PC

Calibration Standards

Stock solution

The present study deals with spectrophotometric analysis of Azelnidipine (AZEL) and Olmesartan Medoxomil (OLME) by checking solubility in different hydrotropic agents such as Sodium acetate, ammonium acetate, sodium citrate, sodium gycinate, sodium chloride, and urea. From different hydrotropic agents, Sodium acetate & urea showed best aqueous solubility of AZEL & OLME.

The aliquot portions of stock standard solutions of AZEL & OLME were diluted appropriately with solvent to get a series of concentration between 2-20 (µg/ml**)** of AZEL & OLME. Similarly, aliquot portions of stock standard solutions were mixed and diluted to get series of concentration between 2-20 (µg/ml). The absorbance of each solution was measured at 240 nm & 253 nm in 1 cm cell against solvent blank.

Analysis of Laboratory mixture

In order to see the feasibility of proposed method for simultaneous estimation of AZEL & OLME in pharmaceutical formulations, the method was first tried for the estimation of the drugs in standard laboratory mixture data shown in table 1.

Analysis of marketed formulation

The AZEL & OLME solution were prepare from marketed formulation The solution was filtered through Whatman filter paper no. 41. The absorbance of sample solution was measured at 240 nm and 253 nm in 1 cm cell against blank. data shown in table 1.

Recovery studies

Recovery study was done by standard addition method. Accurately weight the quantity of standard & sample drug. Prepare to it about 50 (µg/ml) of solution. The solution was filtered through Whatman filter paper no. 41. The absorbance of sample solution was measured at 322 nm and 305 nm in 1 cm cell against blank.

Accuracy

Accuracy of an analytical method is the closeness of test results obtained by the method to the true value. It was ascertained on the basis of recovery studies performed by standard addition method. It was ascertained on the basis of recovery studies performed by standard addition method. It was ascertained on the basis of recovery studies performed by standard addition method. Shown in table 4.

Precision

Precision of an analytical method is the degree of agreement among individual results when the method is applied repeatedly to multiple readings of a homogeneous sample. It is expressed as S.D. or R.S.D. of series of measurements. It was ascertained by replicate estimation of the drugs by proposed method.

Ruggedness

The studies of ruggedness were carried out under two different conditions:

Days and Analyst

Intraday

It was performed by using same procedure as under marketed formulation analysis and absorbance recorded at 3 hrs. interval within a day. The % label claim was calculated.

Interday (Different days)

Same procedure was performed as under marketed formulation analysis and absorbance of same sample were recorded on different days.

Different analyst

The sample solutions were prepared by two different analysts and same procedure was followed as described earlier. The % label claim was calculated

Linearity and range

Accurately weighed quantities of formulation equivalent to 80, 90, 100, 110, 120 % of label claim were taken and dilutions were done appropriately to obtain a concentration in the range of 80-120% of the test concentration and absorbance were recorded at 240 nm and 253 nm. AZEL and OLME were found to be linear in 80% - 120% of the test concentration.

Results and Discussion

The physico-chemical characterization of drug molecule is important with regard to its purity, identification in development and validation of analytical method. The various tools used for characterization of drug molecules include melting point, UV spectroscopy, solubility study, etc. The solubility study, melting point analysis, UV spectroscopy of the drug was done.

Quantitative estimation of poorly water-soluble drugs involves use of organic solvents [2]. In the present investigation, hydrotropic solubilization is employed to enhance the aqueous solubility's of poorly water-soluble drugs like Olmesartan Medoxomil & Azelnidipine in tablet dosage forms [3-6]. The solubility of Olmesartan Medoxomil & Azelnidipine was studied in various hydrotropic agents and the one with the best solubility was considered as solvent for developing and validating the UV spectrophotometric method [7]. This method utilizes 2 M Sodium acetate solution & Urea as hydrotropic solubilizing agent.

Beer-Lambert's law Study

AZEL and OLME solution individually follows the Beer-Lambert's law over concentration range 2- 20 (µg/ml) at selected wavelength (Figure 2). The absorbance of OLME and AZEL solution was measured at 240 nm & 253 nm in 1 cm cell against solvent blank.

The mixture of the two drugs also obeys the Beer-Lambert's law over concentration range 2- 20 (µg/ml). Both the drugs showed additivity of absorbance at selected wavelengths. The A (1%, 1cm) values for both the drugs were determined at the selected wavelengths.

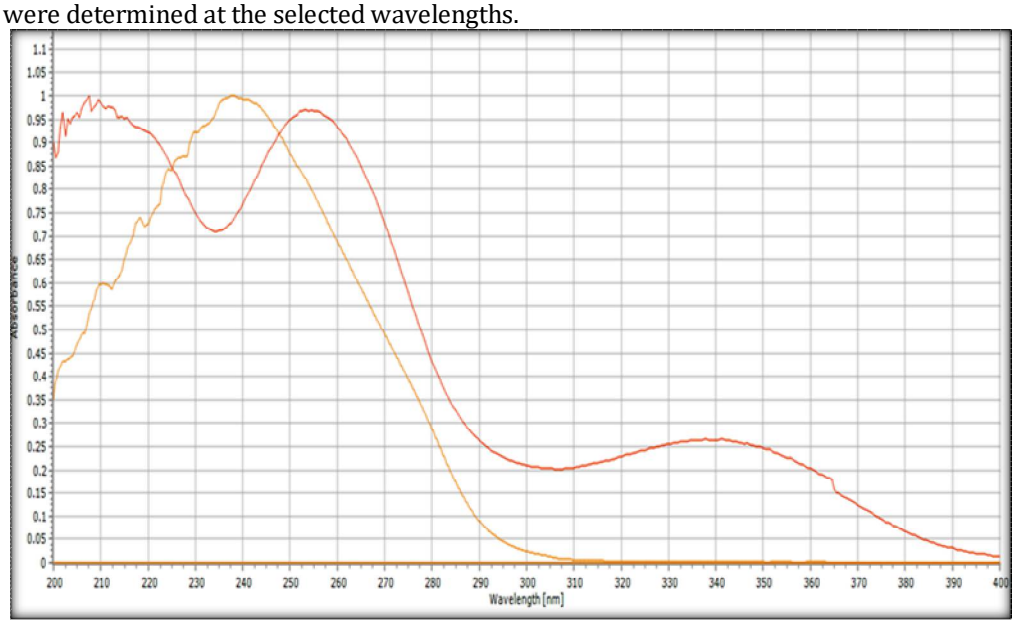


Figure 2: UV Overlain Spectra of OLME & AZEL

The absorbance of OLME and AZEL solution was measured at 240 nm & 253 nm in 1 cm cell against solvent blank. OLME obeyed Beer's law in concentration range of 2-20µg/mL with correlation coefficient

of 0.9998 & regression equation of y = 0.0563x + 0.0101 at 240nm and with correlation coefficient 0.9991& regression equation of y = 0.0495x - 0.0205 at 253nm. AZEL obeyed Beer's law in concentration range of 2-20µg/mL with correlation coefficient of 0.9997 & regression equation of y = 0.0611x - 0.0086 at 240nm and with correlation coefficient 0.999& regression equation of y = 0.0456x - 0.021at 253nm [8-11]. The graphs plotted as concentration Vs absorbance at selected wavelengths are shown in Figure 3 and 4.

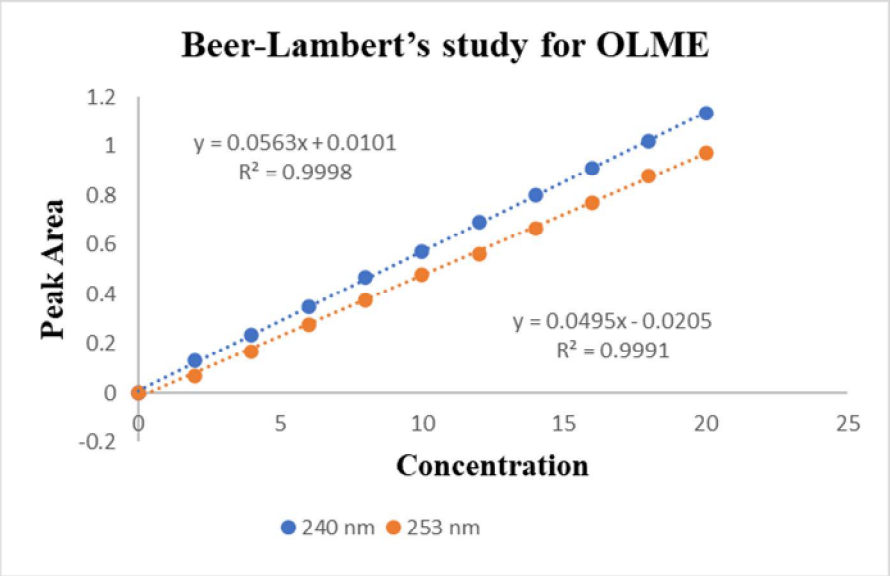


Figure 3: Plot of Beer-Lambert study for OLME at 240 nm & 253nm

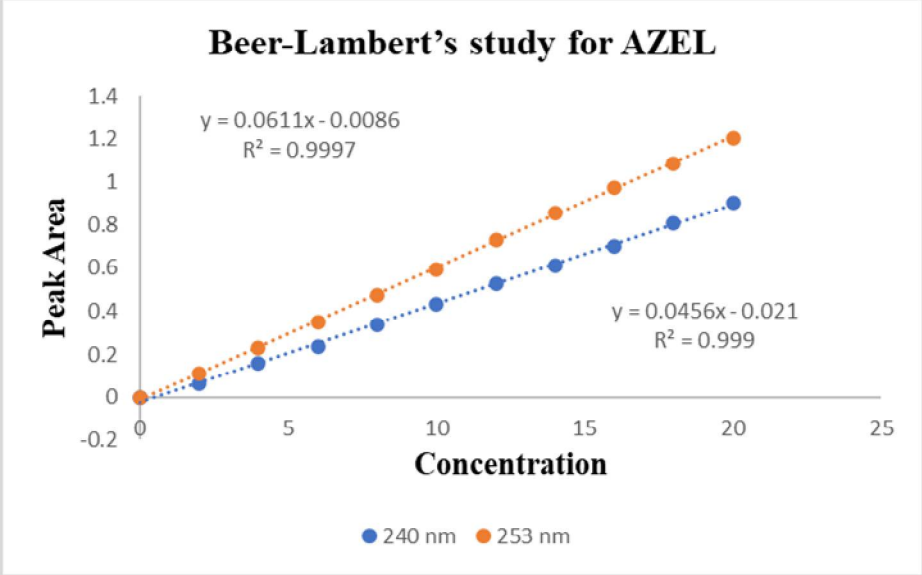


Figure 4: Plot of Beer-Lambert study for AZEL at 240 & 253 nm

The data obtained in the study of Beer – Lambert's law was further used to study additivity on absorbance of OLME & AZEL at 240 nm & 253 nm Mixture of drugs shows additivity of absorbance at selected wavelengths. The mix of both drug obeys the Beer – Lambert's law. Mixture obeyed Beer's law with correlation coefficient of 0.9998 & regression equation of y = 0.1103x - 0.0244 at 253 nm and with correlation coefficient 0.9999 & regression equation of y = 0.1019x - 0.0109 at 240 nm [10, 11]. The graphs plotted as concentration Vs absorbance at selected wavelengths are shown in Figure 5.

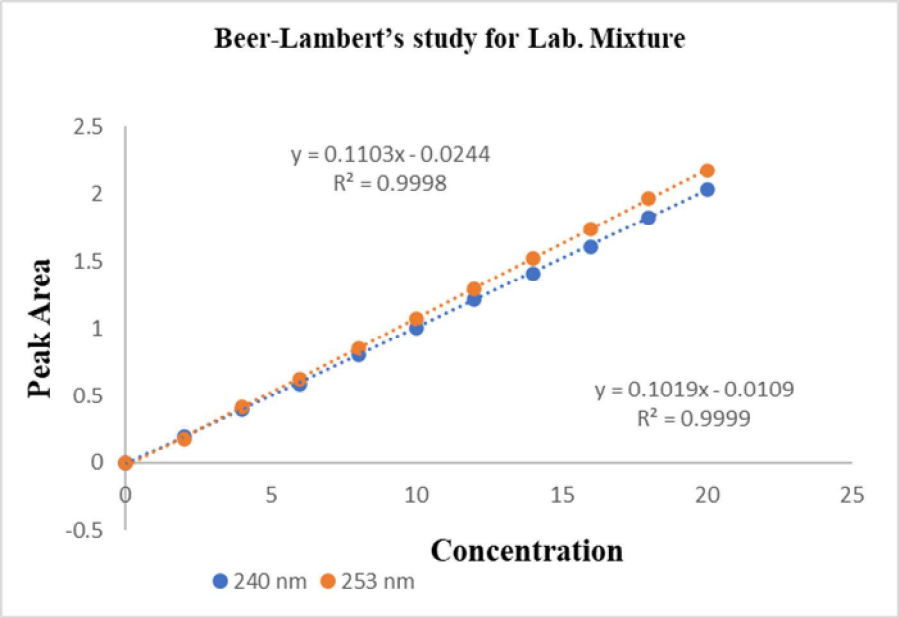


Figure 5: Plot of Beer-Lambert study for Laboratory mixture at 240 & 253 nm

Estimation of the drugs in standard laboratory mixture & marketed formulation

The proposed methods applied for the estimation of the drugs in standard laboratory mixture has yielded very encouraging results and thus it was extended for the estimation of drug in marketed tablet formulation. Recovery studies were performed by adding a known amount of standard drug to preanalysed sample and contents were reanalyzed by proposed methods [12-14]. The summary of this method is shown in the Table 1.

Table 1: Result of estimation of OLME & AZEL in Laboratory mixture& marketed formulation.

Sr.no.	Sample	Statistical data	% Label claim		% Recovery	
			OLME	AZEL	OLME	AZEL
1.	Standard Laboratory mixture	*MEAN*	99.83	100.47	-	-
		S.D.	0.252	1.012	-	-
		C.V.	0.003	0.010	-	-
2.	Marketed formulation Olmezest-AZ 20	Mean	100.20	100.23	100.13	99.87
		S.D.	0.265	0.814	0.208	0.503
		C.V.	0.003	0.008	0.002	0.005

Validation

Validation is normally done to assure the reliability of the proposed method and was performed as per the ICH guidelines for the following criteria.

Accuracy

Accuracy of method is ascertained by recovery studies performed at different levels of concentrations. Mean % recovery was found to be within 98-102%.

Precision

The methods were found to be precise with ±S.D. of 0.695 and 0.506 for the estimation of OLME and AZEL respectively. Result is shown in table 2.

Table 2: Results of Precision studies of OLME and AZEL

Sr.No.	Statistic data	OLME	AZEL
1	Mean	100.34	101.12
2	± S.D.	0.7046	0.5144
3	C.V.	0.695	0.506

Ruggedness

The methods were found to be rugged with no significant changes on test result upon change of analytical conditions like, different time (Intraday), different day (Interday), and Different analyst [15]. Summary of result for ruggedness study is depicted in the table 3 and 4.

Table 3: Summary of result of Ruggedness studies

Parameter	Statistical data	Simultaneous estimation method	
		OLME	AZEL
Interday	Mean	100.07	99.70
	±S.D.	0.153	0.100
	C.V.	0.002	0.001
Intraday	Mean	100.77	99.87
	±S.D.	0.153	0.252
	C.V.	0.002	0.003
Different analyst	Mean	99.43	99.53
	±S.D.	0.3511	0.6027
	C.V.	0.3531	0.6055

Table 4: Result of different analyst study

Sr. No.	% Label claim			
	ANALYST I		ANALYST II	
	OLME	AZEL	OLME	AZEL
01	99.65	99.8	99.6	100.1
02	98.89	99.1	100.8	99.6
03	99.8	99.5	100.9	100.3
Mean	99.45	99.47	100.43	100.00
± S.D.	0.488	0.351	0.723	0.361
C.V.	0.005	0.004	0.007	0.004

Linearity and range

The study of linearity and range was performed as per the USP/ICH recommendation. OLME and AZEL marketed formulation was found to be linear in the range of 80% to 120 % of test [15]. The linearity and range study are shown in figure 5.

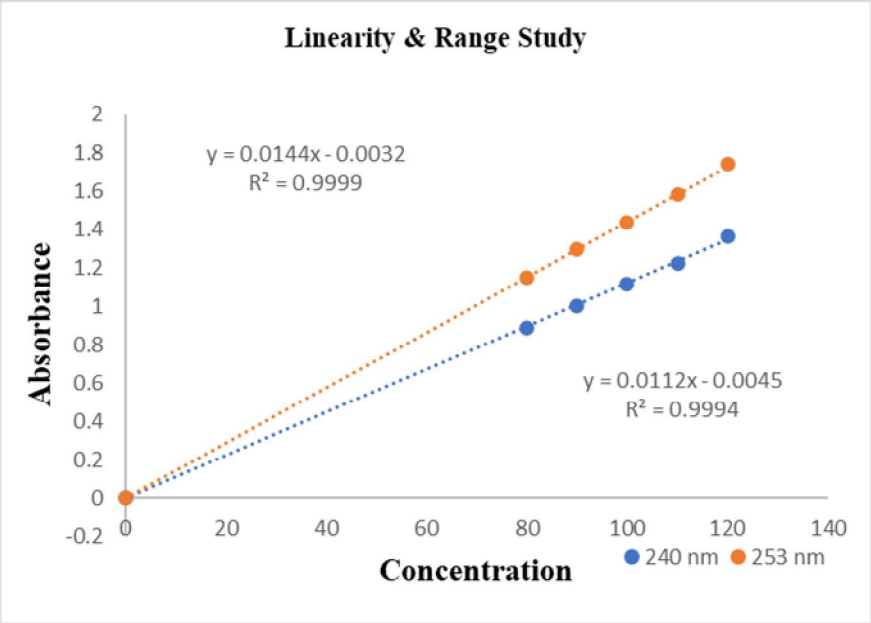


Figure 5: The plot of Linearity and Range Study

CONCLUSION

A validated UV Spectrophotometric method has been developed for the estimation of Azelnidipine and Olmesartan Medoxomil in bulk as well as pharmaceutical dosage form. Quantitative estimation of poorly water-soluble drugs involves use of organic solvents. In the present investigation, hydrotropic solubilization is employed to enhance the aqueous solubility's of poorly water-soluble drugs like Olmesartan Medoxomil & Azelnidipine in tablet dosage forms. The solubility of Olmesartan Medoxomil & Azelnidipine was studied in various hydrotropic agents and the one with the best solubility was considered as solvent for developing and validating the UV spectrophotometric method. This method utilizes 2 M Sodium acetate solution & Urea as hydrotropic solubilizing agent. Accuracy of proposed

method was confirmed by performing accuracy studies that showed the results within the range. Precision of proposed UV method was confirmed by performing intra-day and inter-day precision. Results were well within acceptance criteria that indicate excellent scope of the method for the determination of Olmesartan Medoxomil & Azelnidipine in pharmaceutical dosage forms and bulk. It is concluded that the analytical method was specific, precise, accurate, robust & linear over the concentration range studied. The present analytical method can be used for its intended purpose.

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