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Derivative spectrophotometric method for simultaneous determination of cilnidipine and olmesartan medoximil in tablet dosage form

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ABSTRACT

This study describes the development and validation for the simultaneously estimation of cilnidipine and olmesartan medoximil in combined tablet dosage form by first order derivative UV spectroscopic method. The quantification was achieved the first order derivative method at 256 nm and 220 nm over the concentration range of 2-10 µg/ml for cilnidipine and 4-20 µg/ml for olmesartan medoximil in a combined tablet formulation. Procedure does not require prior separation of components from the sample. LOD values for CIL and OLM are found to be 0.67 µg/ml and 1.90 µg/ml respectively. LOQ values for CIL and OLM are found to be 2.04 µg/ml and 5.77 µg/ml respectively. The result of analysis has been validated statistically and recovery studies carried out in the range of 80-120 % to confirm the accuracy of the proposed method. The relative standard deviation was found to be < 2.0%. The present result shows that the proposed method can be successfully used for simultaneous determination of the drug content in marketed formulation.

Key words: Validation, Derivative Spectrophotometry, Cilnidipine, Olmesartan Medoximil

INTRODUCTION

Cilnidipine is chemically 1, 4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinecarboxylic acid 2-methoxyethyl(2E)-3-phenyl-propenyl ester. Cilnidipine is a dual blocker of L- type voltage-gated calcium channels in vascular smooth muscle and N-type calcium channel in sympathetic nerve terminals that supply blood vessels^[1] Olmesartan medoximil 2, 3-Dihydroxy-2-Butenyl 4(1-Hydroxy-1-cilhylethyl)-2-Propyl-1-[P-(O-1h-Tetrazol-5-ylphenyl) Benzyl] Imidazole5-Carboxylate, Cyclic 2, 3-Carbonate is indicate for the treatment of hypertension.^[2] It may be used alone or in combination with other antihypertensive agents. OLM is a prodrug that works by blocking the binding of Angiotensin II to the AT1 receptor in vascular muscle.^[3] The review of Literature revealed that various analytical methods involving UV Spectrophotometry, HPLC and HPTLC^[4-12] etc. Have been reported for Cilnidipine and Olmesartan medoximil individual and combination with other drugs but no any analytical method has been reported yet for combination of these two drugs. Therefore the present research work aims to develop a simple, sensitive, accurate and reproducible method for simultaneous estimation of cilnidipine and olmesartan medoximil combined dosage form by spectrophotometric method.

MATERIALS AND METHODS

Instrumentation

A Shimadzu model THERMO Limited, model α double beam UV/Visible spectrophotometer with spectral width of 2 nm. wavelength accuracy of 0.5 nm. All the apparatus and instruments were calibrated and validated as per calibrated as validated as per calibration and validation protocol specified before starting the experimental work.^[13]

Reagents and Materials

API of Cilnidipine was kindly gifted by pure chem. Lab Ankleswar. API of Olmesartan medoxomil was kindly gifted by Cadila pharma Ahmadabad. Olmesartan medoxomil and Cilnidipine combined dosage form (NEXOVAS-O) purchased from local market. All other reagents used were of analytical grade.

Preparation of standard stock Solution

An accurately weighed quantity of CIL 10 mg and OLM 10 mg were transferred to a separate 100 ml volumetric flask and dissolved and diluted to the mark with methanol to obtain standard solution having concentration of CIL 100 $\mu\text{g/ml}$ and OLM 100 $\mu\text{g/ml}$.

Preparation of calibration curves for CIL and OLM

For calibration curve 0.2, 0.4, 0.6, 0.8 and 1.0 ml of cilnidipine solution were taken and made up the volume up to 10 ml with methanol in 10 ml volumetric flask (2-10 $\mu\text{g/ml}$) and for olmesartan medoximil 0.4, 0.8, 1.2, 1.6 and 2.0 ml of olmesartan medoximil solution were taken and made up the volume up to 10 ml with methanol in 10 ml volumetric flask (4-20 $\mu\text{g/ml}$).

Selection of ZCP Values

Standard solution of Cilnidipine and Olmesartan medoximil were scanned separately in the range of 200-400 nm. Convert these spectra into first order derivative spectra. Data was obtained by overlay spectra of both drugs. Data was obtained at 256 nm shows absorbance of cilnidipine at which olmesartan medoximil shows zero absorbance and at 220 nm shows absorbance of olmesartan medoximil at which cilnidipine shows zero absorbance. Which show in figure 1.

Validation of method

The method was validated with respect to linearity, LOD (limit of detection), LOQ (limit of quantification), Precision and accuracy.

Linearity

Linearity of an analytical procedure is its ability to obtain test results which are directly proportional to concentration of analyte in the sample. Calibration curve was plotted over a wide concentration range and the linear response was observed over concentration range for mixture. The calibration curve was constructed by plotting absorbance vs. Concentration.

Precision

Intraday Precision

Three replicates of three mixture concentrations of standard solution of cilnidipine and olmesartan medoximil, total nine determination were analyzed at short interval of time, absorbance were measured and RSD was calculated.

Interday Precision

Three replicates of three mixture concentrations of standard solution of cilnidipine and olmesartan medoximil, total nine determinations were analyzed at three consecutive day and absorbance were measured and RSD was calculated.

Acceptance criteria RSD should be less than 2%.

Limit of Detection and limit of Quantification

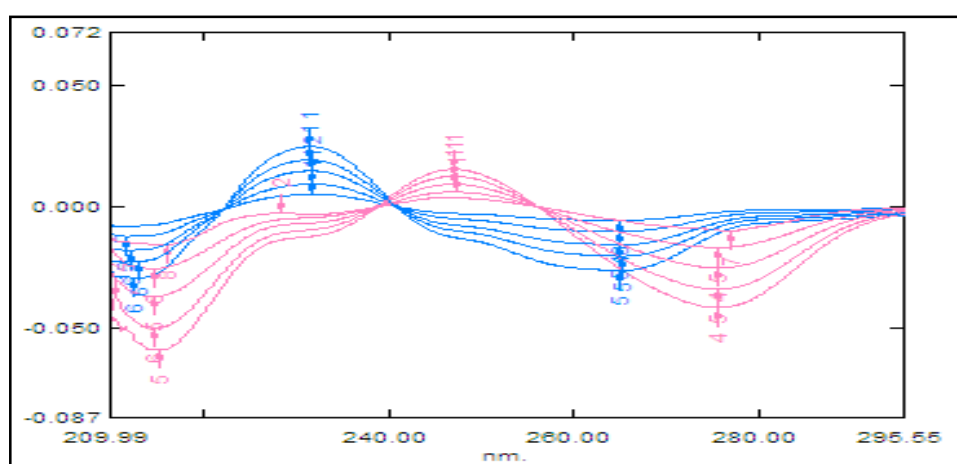
LOD and LOQ were determined by selecting the lowest concentration of calibration curve and six replicates of these target concentration were analyzed. For Cilnidipine six replicates of 4 $\mu\text{g/ml}$ and for Olmesartan medoximil 8 $\mu\text{g/ml}$ were analyzed at 256 and 220 nm respectively.

Accuracy

The accuracy of the method was determined in terms of % recovery of standard. Recovery studies were carried out by addition of standard drug solution at the level of 80%, 100% and 120% to the pre-analyzed sample. In this method the known concentration standard drug was added to the assay sample which is depicted in table 1.

Analysis of tablet dosage form

Twenty tablets were weighed, their mean weight determined and finally powdered. An accurately weighed tablet powder equivalent to 10 mg of CIL and 20 mg OLM was transfer into 100 ml volumetric flask containing 50 ml of diluent, sonicate for 10 minute and volume was made up to the mark with diluent, the resulting solution was filtered using 0.45 μm filter. From filtrate, 1 ml of solution was transferred into 100 ml volumetric flask and volume was made up to mark with diluent to obtain the concentration of 10 $\mu\text{g/ml}$ CIL and 20 $\mu\text{g/ml}$ of OLM. Absorbance of the resulting solution was measured at 256 nm and 220 nm. Result show in table 2

Figure 1 first order derivative spectra of CIL and OLM**Table 1 Recovery studies for the CIL and OLM by First derivative method**

Conc. of Sample taken ($\mu\text{g}/\text{ml}$)	Level	Conc. of Pure API spiked ($\mu\text{g}/\text{mL}$)	Total Conc. ($\mu\text{g}/\text{mL}$)	Mean Total Conc. Found (n=3) ($\mu\text{g}/\text{mL}$)	%Recovery Mean (n=3)	%RSD
CIL 4	80 %	3.2	7.2	7.24248	100.59	0.6
	100 %	4	8	7.9984	99.98	1.4
	120 %	4.8	8.8	8.79384	99.93	1.5
OLM 8	80 %	6.4	14.4	14.39424	99.96	0.5
	100 %	8	16	16.0544	100.34	0.3
	120 %	9.6	17.6	17.57536	99.86	0.4

Table 2 Assay result for CIL and OLM by First derivative method

FORMULATION	Tablet formulation	
	Cilnidipine	Olmesartan medoxomil
Concentration ($\mu\text{g}/\text{mL}$)	10	20
Concentration found ($\mu\text{g}/\text{mL}$) (n=3) \pm SD	10.00567 \pm 0.184	20.00833 \pm 0.551
%Purity	100.0567	100.0417

Table 3 Summary of Validation Parameters for CIL and OLM by First derivative method

PARAMETERS	CIL	OLM
Linearity ($\mu\text{g}/\text{mL}$)	2-10	4-20
%Recovery (%)	99.93 % - 100.59%	99.86% - 100.34 %
Precision((%RSD)		
Repeatability (n=6)	1.44	1.51
Intra-day (n=3)	0.3-0.7%	0.4 – 0.8 %
Inter-day (n=3)	0.8-1.02	1.05-1.18
LOD ($\mu\text{g}/\text{mL}$)	0.67361	1.905256
LOQ ($\mu\text{g}/\text{mL}$)	2.04124	5.773503

RESULTS AND DISCUSSION

In this method, the calibration curve for mixture was found to be linear in the concentration range. The R^2 value for CIL was found to be 0.999. And for OLM was found to be 0.999. The developed method was found to be linear in the concentration range of 2-10 ($\mu\text{g/ml}$) for CIL and 4-20 ($\mu\text{g/ml}$) for OLM. % Recovery of CIL and OLM were found to be 99.93 % - 100.59% and 99.86% - 100.34 % respectively which are within limit (98.0%- 102%) as per ICH guideline. So the developed Method is found to be accurate. The % RSD for CIL was found to be 1.51 and for OLM was found to be 1.44, which is within limit ($< 2\%$). This indicates the developed Method have good repeatability. The % RSD of Intraday precision for CIL was found to be 0.3-0.7 and for OLM was found to be 0.4 – 0.8. The % RSD of Interday precision for CIL was found to be 0.8-1.02 and for OLM was found to be 1.05-1.18, which is within limit ($< 2\%$). So the developed Method is found to be precise. The limit of detection (LOD) for CIL was found to be 0.6 $\mu\text{g/ml}$ and for OLM 1.90 $\mu\text{g/ml}$ the limit of quantification (LOQ) for CIL was found to be 2.04 $\mu\text{g/ml}$ and for OLM 5.77 $\mu\text{g/ml}$. % Assay of CIL and OLM were found to be 100.05 %w/w and 100.04 %w/w respectively which are within limit. So the developed Method can be applied for the simultaneous estimation of CIL and OLM in tablet dosage form. Summary of validation parameters of proposed method is reported in table 3.

CONCLUSION

From the results obtained by applying the suggested procedure, it is obvious that the proposed method is accurate, precise, simple, sensitive, selective and rapid and can be applied successfully in routine analysis for the estimation of CIL and OLM in tablet dosage form.

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