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UV-SPECTROPHOTOMETRIC ABSORPTION CORRECTION METHOD FOR THE SIMULTANEOUS ESTIMATION OF METOPROLOL SUCCINATE AND CHLORTHALIDONE IN COMBINED DOSAGE FORM

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ABSTRACT

A new, precise, simple, sensitive, rapid and economical UV- Spectrophotometric absorbance correction method has been developed and validated for simultaneous estimation of Metoprolol succinate (MET) and Chlorthalidone (CHL) in combined dosage form .Methanol was used as solvent. The wavelength selected for absorption correction method were 224nm and 275nm. The method was found to be linear between the range of 10-20µg/ml for MET and 5-25µg/ml for CHL. The mean percentage recovery was found in the range of 96.13% -98.55% and 99.81-101.42% for MET and CHL respectively at three different level of addition. The precision (intraday, inter day) of method were found within limits (RSD< 2.5%). Thus the proposed method was simple, precise, accurate and rapid and it can be successfully applied for simultaneous estimation of metoprolol succinate and chlorthalidone in combined dosage form.

KEYWORDS

Absorbance correction method, Metoprolol succinate and Chlorthalidone.

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INTRODUCTION

Metoprolol succinate, is a beta1-selective (cardio selective) adrenoceptor blocker, for oral administration, available as extended-release tablets. Metoprolol succinate extended-release tablet has been formulated to supply a controlled and predictable release of metoprolol for once-daily administration. The chemical name of MET (±) 1-(isopropyl amino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt). It is a white

crystalline powder with a relative molecular mass of 652.8. It is freely soluble in water and it is soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl-acetate, acetone, diethyl ether. The structure of metoprolol succinate was shown in Figure No.1[1,2,3].

Chlorthalidone may be a long acting thiazide-like diuretic of the sulfamoylbenzamide class that's unproductive of the benzothiadiazine structure. Chlorthalidone is employed within the treatment of high vital sign, edema and congestive coronary failure. The elimination half-life of chlorthalidone is about 40 to 50 hours. IUPAC name of chlorthalidone is 2-chloro-5-(1-hydroxy-3-oxo-2H-isoindol-1-yl) benzene sulfonamide. It is a racemic mixture of 2-chloro-5 (1-hydroxy-3-oxo-1-isoindolinyl) benzene sulfonamide, with the structure of chlorthalidone was shown in the Figure No.2[4,2,3].

According to literature survey few methods like HPLC, UV- Spectrophotometric, HPTLC were available for the simultaneous estimation of metoprolol succinate and chlorthalidone in combined dosage form. Uptill now there was no any method reported by absorbance correction method of quantitative estimation of MET and CHL by UV spectrophotometric method. Hence current study designed to develop new, accurate, simple method of analysis for the simultaneous estimation of MET and CHL in combined dosage form by absorbance correction method (UV - Spectrophotometry)[2,3].

MATERIAL AND METHODS

Material

Metoprolol succinate (working standard), chlorthalidone (working standard), methanol, distilled water.

Marketed formulation

Vinicor D tablet

Instrument used

Digital balance-scale tec,

UV-Visible Spectrophotometer- UV-1900 Shimadzu.

Methods

Accurately weighed quantities (10mg) of MET and CHL in separate 100ml volumetric flask, dissolve them by adding methanol and then volume are made up which gives 100µg/ml. These solutions were used as working standard. Stock solution of MET and CHL were diluted approximately with methanol to obtain concentration of 20µg/ml for MET and 30µg/ml for CHL. The working solution were scanned from 200-400nm to select wavelength for estimation. From overlain spectra wavelength selected for estimation of MET was 224nm and CHL was 275nm were MET shows zero absorbance at 275nm. Absorbance of MET is corrected. Different binary mixture of MET and CHL were then run in entire range from 200-400nm. The drugs obey Beer's law in the concentration range of 10-20µg/ml and 5-25µg/ml for MET and CHL respectively[5,6].

Quantitative estimation of these drugs were calculated using following equation[7].

$A = abc$

$Cx = A1/ab$

$Cx = A1/ax1*b$……. (1)

$A2 = A_{MET} + A_{CHL}$

$A2 = (ay2*cy*b) + (ax2*cy*b)$

$A2 = (ay2*cy) + (ax2*cx)$

$Cy = [A2-(ax2*cx)]/ay2$ …… (2)

Preparation of standard stock solution

An accurately weighed quantity of MET (10mg) and CHL (10mg) were transferred to separate 100ml volumetric flask and then it is dissolved and diluted with methanol to obtain standard solution having concentration 20µg/ml and 25µg/ml.

Preparation of sample solution

Twenty tablet were weighed and powdered. The Powder equivalent to 25mg of MET and 6.25mg of CHL was transferred to 100ml volumetric flask, added with methanol and stirred on magnetic for 60 min. After this the solution was filtered through whatman filter paper and volume is make up to the mark with methanol. The above solution was diluted with methanol to get final concentration of 20µg/ml of MET and 25µg/ml of CHL.

Validation of proposed method

The proposed method was validated according to the International Conference of Harmonization (ICH) guideline[8,9].

Linearity (calibration curve)

The calibration curve were plotted over a concentration range of 10-20µg/ml for MET and 5-25µg/ml for CHL. Accurately measured standard stock solution of each MET (1, 1.2, 1.4, 1.6, 1.8, 2µg/ml) and CHL (0.5, 1, 1.5, 2, 2.5µg/ml) were transferred to a series of 10ml volumetric flask separately. The absorbance of the solutions were measured at 224nm and 275nm. The calibration curve were constructed by plotting absorbance versus concentration and regression equation were calculated.

Precision

Intra-day

Mixed standard solution containing 10, 14, 18µg/ml of MET and 10, 15, 20µg/ml of CHL was analysed three times on the same day. Measure the solution at 224nm (A1) and 275nm (A2). The result were reported in terms of relative standard deviation.

Inter-day

Mixed standard solution containing 10, 14, 18µg/ml MET and 10, 15, 20µg/ml of CHL was analyzed on 3 different days. Measure the solution at 224nm (A1) and 275 nm (A2) and the results were reported in terms of relative standard deviation.

Specificity

Specificity may be a procedure to detect quantitatively the analyte in presence of component which will be expected to be present within the sample matrix. Commonly used excipients in tablet preparation were spiked during a pre weight quantity of drug then absorbance was measured and calculation done to work out quantity of medicine.

Accuracy (Recovery Studies)

The accuracy of the method was determined by calculating recoveries of MET and CHL by the standard addition method. Accuracy is performed at three levels 80, 100 and 120%. Known amount of standard solutions of MET (8, 10, 12ug/ml) and CHL (18, 10, 12µg/ml) were added to a pre-quantified test solution of TAZ (10µg/ml) and CEF (10µg/ml). Absorbance of solution was measured at selected wavelength for MET and CHL. The amount of MET and CHL was calculated at each level by absorbance correction equation method and percentage recoveries were computed.

Limit of detection and limit of quantitation

Limit of detection is that the lowest amount of analyte during a sample which may be detected but not necessarily quantitated as a particular value and limit of quantitation is that the lowest amount of analyte during a sample which may be quantitatively determined with suitable precision and accuracy. The limit of detection (LOD) and therefore the limit of quantification (LOQ) of the drug were derived by calculating the signal-to-noise (S/N) using the following equations designated by International Conference on Harmonization (ICH) guidelines,

$LOD=3.3\sigma/S$

$LOQ=10\sigma/S$

Where, σ = the standard deviation of the response and S = slope of the calibration curve[10,11].

RESULTS AND DISCUSSION

Absorbance correction method

The use of dual wavelength data processing is its ability to calculate the unknown concentration of component of interest in a mixture which containing an interfering component. To discard the effects of an interfering component, two specific wavelengths were chosen.

1. First wavelength λ1 at which minimum absorbance of CHL was observed and there was no interference of MET at this wavelength (275nm).
2. Second wavelength λ2 was the wavelengths absorption maxima of MET and also CHL gives some absorbance at this wavelength (224nm). To remove the interference of CHL to the absorbance at 224.0nm (λ2), another wavelength 275nm (λ1) was found out at which the absorbance of MET was zero. These two selected wavelengths.

Were employed to determine the concentration of MET from the mixture of MET and CHL. The difference in absorbance at these two wavelengths (A224 - A275) cancels out the contribution of absorbance of CHL in mixture.

VALIDATION DATA OF THE PROPOSED METHODS

Linearity

Linear correlation was obtained between absorbance and concentration of MET and CHL in the range of 10-20ug/ml and 5-25µg/ml respectively. The linearity of the calibration curves was validated by the high value of correlation coefficients of regression (Table No.1).

Precision

The low RSD values of inter day (1.25-2.38 and 1.63-2.13%) and intraday (1.93-2.22% and 1.40-1.60%) variations for MET and CHL, respectively reveal that the proposed method is precise (Table No.2).

Accuracy

The recovery experiments were carried out by the standard addition method, the mean recovery obtained was 96.55 ±1.04 and 100.52 ± 0.89 for TAZ and CEF, respectively (Table No.3). The high values which indicate that the method is accurate.

LOD and LOQ

LOD for MET and CHL were found to be 0.85µg/ml and 0.34µg/ml, respectively whereas LOQ for MET and CHL were found to be 2.5µg/ml and 1.03µg/ml, respectively. The data shows that the method is sensitive for the determination of MET and CHL, in the given concentration range.

Assay of the pharmaceutical formulation

The proposed validated methods were successfully applied to determine MET and CHL in their marketed dosage forms. The results obtained for MET and CHL were comparable to the corresponding labeled amounts (Table No.4).

Table No.1: Data of optical characteristics

S.No	Parameters	Observed value	
		Metoprololsuccinate	Chlorthalidone
1	Beer's Law Limit (ug/ml)	10-20µg/ml	5-25µg/ml
2	Correlation coefficient (R^2)	0.9906	0.9992
3	Regression equation	y=0.0343x+0.0044	y=0.0056x+0.005
4	Slope	0.0343	0.0056
5	Intercept	0.0044	0.005

Table No.2: Precision studies

Intra-day

S.No	drug	Sampling time	Conc. Taken	Conc. found	%obtained	SD	%RSD
1	MET	9AM	10	9.8	98	0.00441	1.25
		12PM	14	14.09	100.66	0.01221	1.38
2	CHL	3PM	18	18.17	100.94	0.00997	1.54
		9AM	10	9.88	98.8	0.00058	1.63
		12PM	15	15.11	100.75	0.0017	1.13
		3PM	20	19.81	99.06	0.0013	1.82

Inter-day

S.No	drug	Sampling time	Conc. taken	Conc. found	%obtained	S.D	%RSD
1	MET	Day1	10	9.8	98	0.0079	1.92
		Day2	14	14.27	101.94	0.0111	1.89
2	CHL	Day3	18	18.02	100.14	0.0125	1.93
		Day1	10	9.82	98.9	0.0005	1.40
		Day2	15	15.72	104.79	0.0047	1.60
		Day3	20	19.80	99.01	0.0011	1.54

Table No.3: Recovery studies

Accuracy (recovery studies of metoprolol succinate)

S.No	Drug (level of recovery)	Sample No	Amount present A	Amount added B	Amount Found C	Amount Recovered C-A	% recovered	S.D
1	MET (80%)	1	10	8	16.96	6.96	94.22	1.22
		2	10	8	17.05	7.05	94.72	
		3	10	8	17.38	7.38	96.55	
							Mean 96.11%	
2	MET (100%)	1	10	10	19.25	9.25	96.25	2.11
		2	10	10	19.80	9.8	99	
		3	10	10	20.08	10.08	100.4	
							Mean 98.55%	
3	MET (120%)	1	10	12	21.79	11.79	99.04	2.27
		2	10	12	21.24	11.24	96.54	
		3	10	12	20.42	10.42	92.81	
							Mean 96.13%	

Accuracy (recovery studies of Chlorthalidone)

S.No	Drug (level of recovery)	Sample No	Amount present A	Amount added B	Amount Found C	Amount Recovered C-A	% recovered	S.D
1	CHL (80%)	1	10	8	18.27	8.27	101.05	1.08
		2	10	8	17.83	7.83	99.055	
		3	10	8	17.88	7.88	99.33	
							Mean 99.81%	
2	CHL (100%)	1	10	10	20.08	10.08	100.4	1.47
		2	10	10	20.36	10.36	101.8	
		3	10	10	19.71	9.71	98.85	
							Mean 100.35%	
3	CHL (120%)	1	10	12	22.88	12.88	104.04	2.12
		2	10	12	22.14	12.14	100.63	
		3	10	12	21.91	11.19	99.59	
							Mean 101.42%	

Table No.4: Analysis of Tablet formulation

S.No	Brand	Drug	Labelled Claim (mg/tab)	Amount Found (mg/tab)	% purity
1	Vinicor D	Metoprolol succinate	25	24.66	98.64
2	---	Chlorthalidone	6.25	6.01	96.6

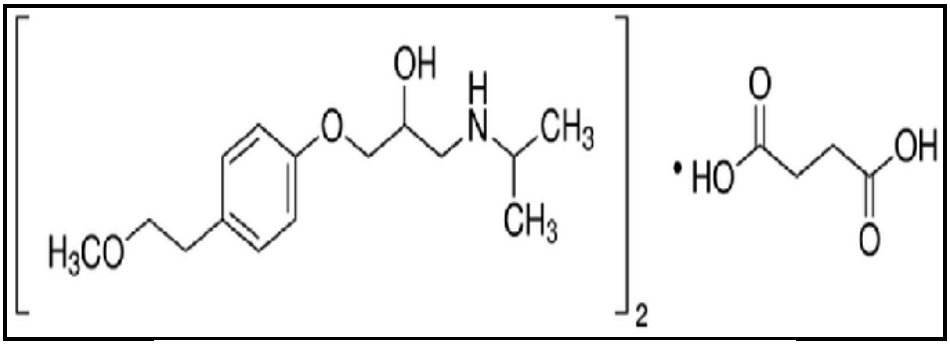


Figure No.1: Structure of Metoprolol succinate

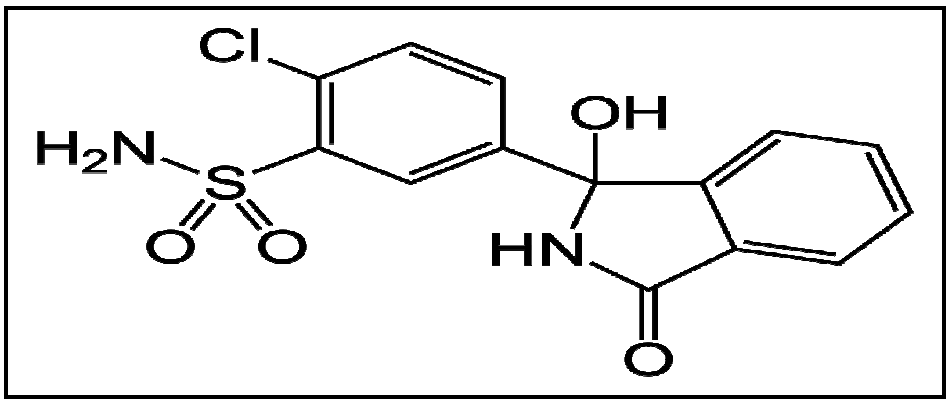
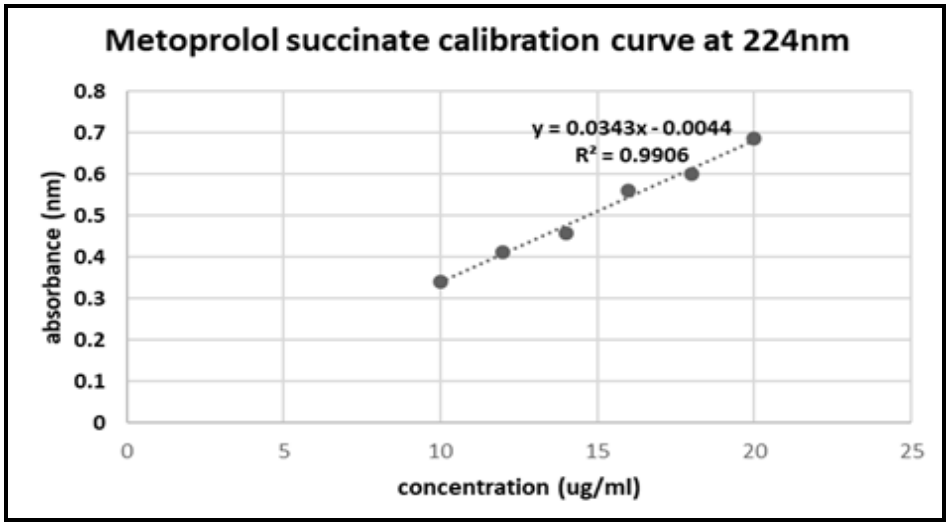
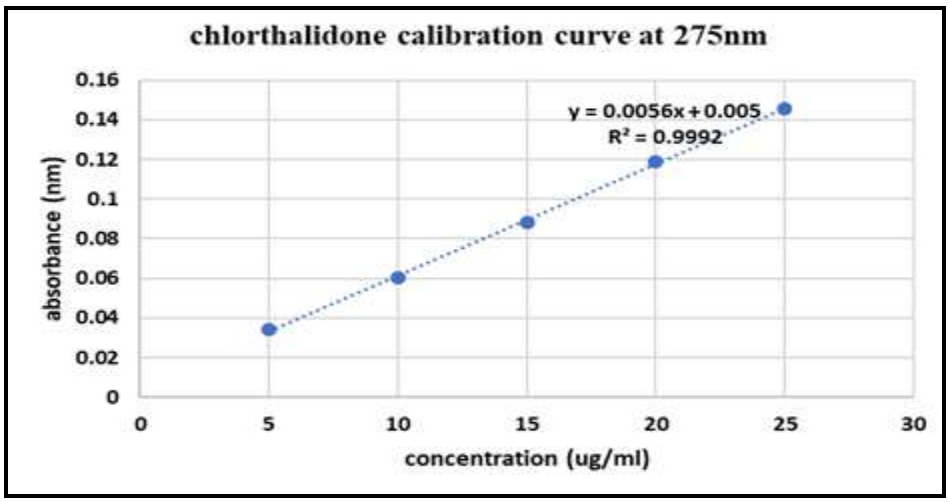


Figure No.2: Structure of Chlorthalidone





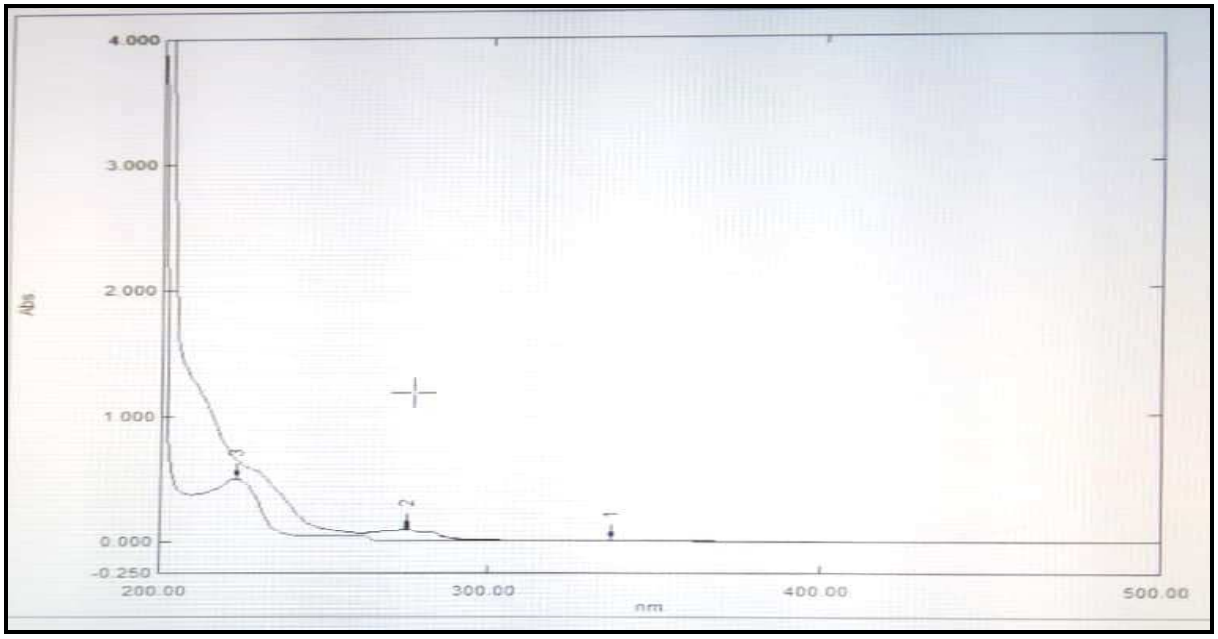


Figure No.3: Overlay Spectra of Metoprolol succinate and Chlorthalidone

CONCLUSION

The results of the analysis of pharmaceutical formulation by the proposed method which Absorbance correction method are highly reproducible and reliable and are in good agreement with the label claim of the drug. The additives usually present in the pharmaceutical formulations of the assayed samples did not interfere with determination of MET and CHL. The methods can be routinely used for the analysis of the MET and CHL in combined dosage form.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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