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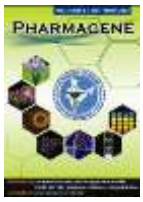

Development and Validation of Zero and First Order Derivative Spectrophotometric Methods For Determination of Oxcarbazepine In Pharmaceutical Dosage Forms

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Abstract : Oxcarbazepine is an antiepileptic drug. It is a 10-keto analogue of carbamazepine with a similar therapeutic profile, but with less adverse effects and less clinical relevant pharmacokinetic drug interactions. This paper describes zero and first order derivative spectrophotometric methods for determination of oxcarbazepine in pharmaceutical preparations. The solutions of the reference drug and pharmaceutical samples were prepared in methanol. Absorbance of oxcarbazepine was measured at 304.5 nm for zero order and at 266.5 nm for first order derivative spectrophotometric methods. Five brands were analysed and showed good results by both the methods. The linearity ranges were found to be 20-80 µg/ml and 10-100 µg/ml for zero and first order derivative spectrophotometric method respectively. The percentage recovery values of oxcarbazepine for both the methods were found between 98.57-101.02%. The precision (intraday, interday and repeatability) of the methods were found to be within limits. The methods developed in this study are accurate, sensitive, precise and reproducible and can be directly and easily applied to the pharmaceutical preparations.

Keywords : Oxcarbazepine, Zero and First order Derivative Spectrophotometric Method.

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INTRODUCTION

Oxcarbazepine (10, 11-dihydro-10-oxo-5H-dibenzo [b,f] aze-pine-5-carboxamide), an antiepileptic drug, is a 10-keto analogue of carbamazepine with a similar therapeutic profile, but with less adverse effects and less clinical relevant pharmacokinetic drug interactions [1-2]. Oxcarbazepine is indicated as first line drug in monotherapy or polytherapy for the treatment of partial seizures with or without secondarily generalized tonic clonic epileptic seizures [3-4]. These actions are thought to be important in the prevention of synaptic neurotransmission and seizure spread in the intact brain [5]. In addition,increased potassium conductance and modulation of high voltage activated calcium channels may contribute to the anticonvulsant effects of the drug [6]. There are LC, GC, voltammetry, HPLC and several other methods for the quantification of oxcarbazepine and its main metabolites 10-hydroxy-10, 11- dihydrocarbamazepine and 10, 11-dihydroxy-trans-10, 11- dihydrocarbamazepine in biological fluids, which are reported.[7-14]. To our knowledge, there is no reported zero and first order derivative spectrophotometry methods for determination of oxcarbazepine in pharmaceutical preparation in literature. Derivative spectrophotometry [15] is an analytical technique of great utility for extracting both qualitative and quantitative information from spectra. In the last year, this

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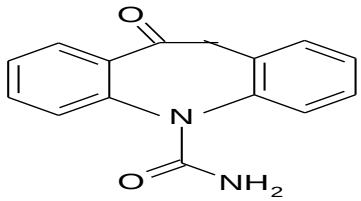
technique has rapidly gained its application in the analysis of pharmaceutical preparations. The developed methods were validated as per ICH guidelines and found to comply with the acceptance criteria [16-17]. Structures of Oxcarbazepine was shown in figure 1.

Figure 1: Chemical structures of the analytes.



MATERIALS AND METHOD

Apparatus

Instrument used was an UV-Visible double beam spectrophotometer, make: SHIMADZU (model UV-1800) with a pair of 1 cm matched quartz cells. All weighing was done on Shimadzu analytical balance (Model AU-220). Calibrated glasswares were used throughout the work.

Reagents and chemicals

Pure drug sample oxcarbazepine was obtained as gift sample from a Alembic pharmaceuticals, Vadodara. Methanol AR was used as solvent.

Preparation of standard stock solution

Accurately weighed quantity of oxcarbazepine 100 mg was transferred to 100 ml volumetric flask, dissolved in little amount of methanol and diluted to the mark with methanol (stock solution: 1000 µg/ml of oxcarbazepine).

Preparation of working standard solution

100 µg/ml of oxcarbazepine solution was prepared by diluting 10 ml of stock solution to 100 ml with methanol.

Preparation of calibration curve

From the working standard solution, appropriate dilutions of oxcarbazepine in the range of 20-80 µg/ml and 10-100 µg/ml were prepared for zero and first order derivative spectrophotometry respectively.

Selection of wavelengths

From the zero and first order spectra of oxcarbazepine (40 µg/ml), the wavelengths 304.5 and 266.5 nm were selected for zero and first order derivative spectrophotometry.

Assay of tablet formulations

Ten tablets were weighed and crushed to obtain a fine powder. An accurately weighed tablet powder equivalent to about 100 mg of oxcarbazepine was transferred to 100 ml volumetric flask and dissolved in 50 ml of methanol. The volume was made up to the mark using methanol as solvent. The resulting solution was filtered through Whatman filter paper and 10 ml of this filtrate was appropriately diluted to get concentration of 100 µg/ml of oxcarbazepine. From this solution, further dilution was made to get the concentration of oxcarbazepine (40 µg/ml). The absorbance was measured at the selected wavelengths and concentrations were determined. The analysis was done in triplicate.

Method validation

Linearity and range

Aliquots of working standard solution of oxcarbazepine were diluted with methanol to get final concentrations in range of 20-80 µg/ml and 10-100 µg/ml for zero and first order derivative spectrophotometry respectively. This calibration range was prepared five times and absorbances were measured at respective wavelengths.

Precision

Precision of the methods was determined by performing interday variation, intraday variation and method repeatability studies. In interday variation, standard solutions of oxcarbazepine was prepared and analyzed on three consecutive days. In intraday variation the absorbance was measured three times in a day. In repeatability study, three concentrations of the drug were analyzed in triplicate.

Recovery studies

To study the accuracy of the proposed method, recovery studies were carried out by standard addition method at three different levels. Known amount of the drug was added to pre-analyzed tablet powder and percentage recoveries were calculated.

Ruggedness

The data for ruggedness were obtained from two different analysts.

RESULTS AND DISCUSSION

Method development and Validation

The derivative wavelength difference ($\Delta\lambda$) depends on the measuring wavelength range and n values (smoothing factor). Generally, the noise decreases by increasing $\Delta\lambda$. Optimal wavelength range should be chosen since the broad peaks become sharper, the ratio of signal/noise elevates and the sensitivity of the method increases by controlling the degree of low pass filtering or smoothing. Therefore, a series of n values (n=1 to 9) were tested in the first order derivative spectra of oxcarbazepine in methanol. Optimum results were obtained in the measuring wavelength range 200-400 nm, n=1 ($\Delta\lambda$=1 nm) for first order derivative spectrophotometric methods.

Figure 2 presents the overlay of UV spectra of oxcarbazepine in methanol with characteristic maxima at 304.5 nm. Figure 3
presents the overlay of first order UV spectra of oxcarbazepine in methanol for different concentrations. As demonstrated in Figure 3, the spectra present characteristic maxima and minima. Wavelength selected for measurement is 266.5 nm.

Figure 2: Overlay of zero order spectra of various concentrations of oxcarbazepine in methanol in methanol

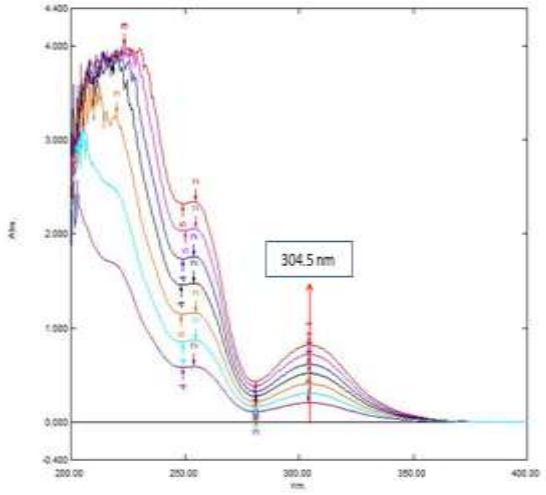
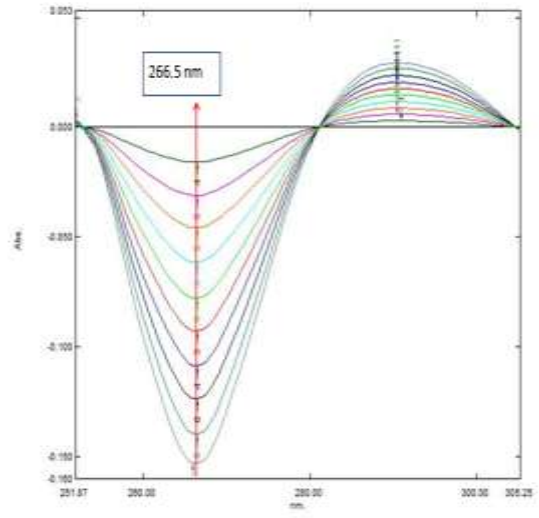


Figure 3: Overlay of first order derivative concentrations of oxcarbazepine in methanol



As no difference was observed between spectra of oxcarbazepine standard and tablet solutions and in the maximum wavelengths of all spectra, it was suggested that the developed methods allowed complete elimination of the background absorption due to the tablet excipients at the chosen wavelengths both in zero and first order derivative spectra of oxcarbazepine (figures 4a and 4b). Optimized method parameters for oxcarbazepine are shown in table 1.

Table 1: Optimized method parameters for Oxcarbazepine

Method parameters	**Optimized parameters**
Solvent	Methanol
Scanning range	200 nm to 400 nm
Scan speed	Medium
Δλ	1 nm
Analytical wavelength for Zero order spectrophotometry	304.5 nm
Analytical wavelengths for First derivative spectrophotometry	266.5 nm
Specificity	Method is specific

Figure 4a: Overlay of zero order spectra of tablet tablet solution of oxcarbazepine (40 µg/ml)and standard solution of oxcarbazepine (80 µg/ml) in methanol

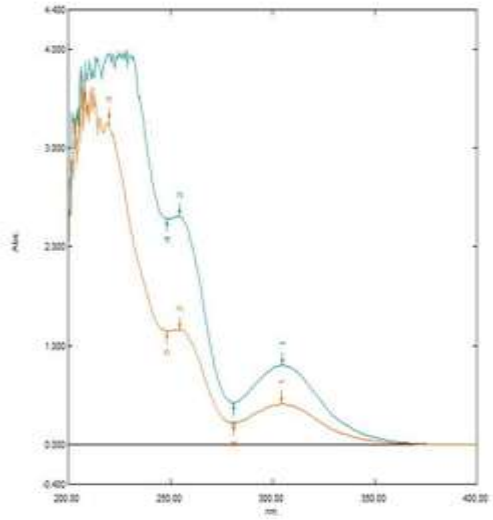
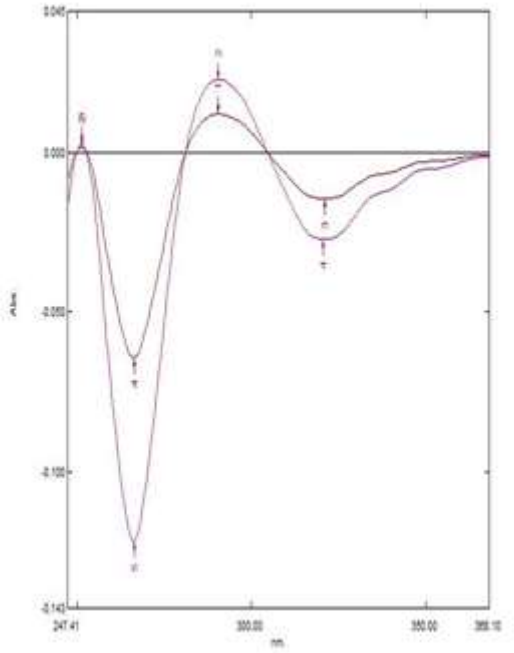


Figure 4b: Overlay of first order derivative spectra tablet solution of oxcarbazepine (40 µg/ml) and solution of oxcarbazepine (80 µg/ml) in methanol



Linearity

The calibration curves of oxcarbazepine were linear in the range of 20-80 µg/ml and 10-100 µg/ml for zero and first order derivative spectrophotometry respectively. The regression equations of calibration curves were

$Y = 0.010264 X + 0.000071$, $R^2 = 0.9999$ for Zero order spectrophotometry and
$Y = 0.001542 X + 0.000267$, $R^2 = 0.9997$ for First order derivative spectrophotometry.

Precision

Relative standard deviation (% R.S.D.) for repeatability was found to be 0.59-0.67% and 0.62-0.94% for zero and first order derivative spectrophotometry respectively. The intraday precision showed % R.S.D. of 0.47-0.87% and 1.05-1.97% for zero and first order derivative spectrophotometry respectively. The inter day precision showed % R.S.D. 0.89-1.95% and 1.85-2.81% for zero and first order derivative spectrophotometry respectively. Results of repeatability, intraday and interday precision of method are illustrated in table 2.

Specificity

Comparison of the zero and first order derivative spectrum of oxcarbazepine in standard and drug formulation solutions show that the wavelength of maximum and minimum absorbance did not change (Figures 4a and 4b). From the results obtained, it is evident that the zero and first order derivative spectrophotometric methods are able to estimate oxcarbazepine in presence of excipients and hence the methods can be considered specific.

Accuracy

The percentage recovery of drug from marketed formulation was determined by standard addition of pure drug at three known concentrations and excellent recoveries were obtained at each level. The percent recoveries for oxcarbazepine at three levels were found to be 100.60±0.0020, 98.85±0.0035, 99.24±0.0045 and 99.87±0.0005, 98.57±0.0005, 101.02±0.0011 for zero and first order derivative spectrophotometry respectively. The results of accuracy study are shown in table 3.

Ruggedness

Relative standard deviation (% R.S.D.) for ruggedness was found to be 0.88-1.74% and 1.15-2.55% for zero and first order derivative spectrophotometry respectively. **in methanol**

Application of the methods in assay of different brands of tablet

The proposed UV methods were applied for the determination of oxcarbazepine in their pharmaceutical formulation (five brands of tablets) and the results are shown in table 4. The high percentage recovery (98.57-101.02 %) values confirm the suitability of the proposed method for the routine determination of these components in combined formulation.

CONCLUSION

The proposed zero and first order derivative spectrophometric methods give accurate and precise results for determination of oxcarbazepine in marketed formulations (tablet) without prior separation and is easily applied for routine analysis. The apparatus and reagents used are easily available. Method validation has been demonstrated by variety of tests for linearity, accuracy, precision, specificity and ruggedness. The proposed methods were successfully applied to determination of this drug in commercial tablets.

Table 2 Complication of obesity

PARAMETERS	ZERO ORDER SPECTROPHOTOMETRY	FIRST DERIVATIVE SPECTROPHOTOMETRY
Linearity range	20-80 µg/ml	10-100 µg/ml
Correlation Coefficient	0.9999	0.9997
Precision	% RSD	
Repeatability	0.59-0.67	0.62-0.94
Intraday	0.47-0.87	1.05-1.97
Interday	0.89-1.95	1.85-2.81
Ruggedness	0.88-1.74	1.15-2.55
% Recovery	98.85-100.60	98.57-101.02

%RSD-Relative Standard Deviation.

Table 3: Recovery study

Amount of Drug Added (µg/ml)	ZERO ORDER SPECTROPHOTOMETRY		FIRST DERIVATIVE SPECTROPHOTOMETRY	
	%Recovery*	SD	%Recovery*	SD
10	100.60	0.0020	99.87	0.0005
20	98.85	0.0035	98.57	0.0005
30	99.24	0.0045	101.02	0.0011

SD- Standard Deviation.

Table 4: Results of assay of oxcarbazepine in different formulations by ZERO ORDER SPECTROPHOTOMETRY and FIRST DERIVATIVE SPECTROPHOTOMETRY.

Brands	Labeled amount Drugs (mg per tab)	Amount of Oxcarbazepine found mg per tab (n = 3)	% Label claim
OXETOL	150	150.66	100.44
SELZIC	150	149.34	99.56
OXRATE	150	147.48	98.32
OXEPTAL	150	150.21	100.14
OXEP	150	149.77	99.85

*Average of three determinations;

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