



SPECTROPHOTOMETRIC DETERMINATION OF OXCARBAZEPINE IN PHARMACEUTICAL FORMULATIONS

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ABSTRACT

A simple, rapid, economical and highly sensitive spectrophotometric method is developed for determination of oxcarbazepine (OXC) in pure and in pharmaceutical formulations. The method is based on reaction of OXC with methanolic potassium hydroxide in dimethyl sulfoxide (DMSO) medium to form a colored product, which shows maximum absorption at 430nm. The conditions necessary for the assaying the drug are established. The system is obeying the Beer's law over its concentration range of 1.0-7.02 μgml^{-1} . The calculated molar absorptivity and sandell's sensitivity values are $1.21 \times 10^4 \text{ l mol}^{-1} \text{ cm}^{-1}$ and $0.0208 \mu\text{g/cm}^2$ respectively. The limit of detection (LOD) and limit of quantification (LOQ) of the proposed method are found to be 0.027 and 0.082 $\mu\text{g/ml}$ respectively. The method does not suffer any interference from common tablets excipients up to 40mg. The method is found to be successful for the determination of OXC either in its pure form or in pharmaceutical formulations with good accuracy and precision, and the results are comparable statistically with those determined by the reported method.

Keywords: Oxcarbazepine, Spectrophotometry, Dimethylsulfoxide, Methanolic potassium hydroxide.

INTRODUCTION

Oxcarbazepine (OXC) an antiepileptic drug (AED) has a chemical name 10,11-Dihydro-10-oxo-5H-dibenz (b, f) azepine-5-carboxamide¹, is structurally a derivative of carbamazepine^{2,3}, adding an extra oxygen atom to the benzylcarboxamide group. It was first synthesized in 1966. OXC in humans is known to act as a prodrug to its central nervous system-active metabolite 10-hydroxycarbazepine (MHD)⁴. OXC and MHD are known to exert antiepileptic activity by blockade of voltage-dependent sodium channels in the brain⁵. OXC is used to treat seizures^{6,7}, several types of epilepsy^{3,8,9} and in management of intractable trigeminal neuralgia¹⁰.

Common side effects related to OXC use are appearing to be dosage related and include somnolence, dizziness, vomiting, nausea¹¹ and hyponatremia^{5, 12, 13}. Considering the biological significance of OXC, several quantitative analytical procedures have been reported in the literature for its determination and such methods include, liquid chromatographic methods¹⁴⁻²¹ HPLC²²⁻³³, GC^{34,35}, atmospheric pressure chemical ionization liquid chromatography/mass spectrometry³⁶, HPLC/APCI/MS³⁷, LC-electrospray mass spectrometry³⁸, LC-MS/MS³⁹, micellar electro kinetic chromatography⁴⁰, spectrophotometry⁴¹ and voltammetry⁴². Most of the reported methods^{14-19,22-27,29-40} mainly describe the determination of OXC in biological fluids but only a few methods^{20,41} are describing its determination in pharmaceutical formulations.

In addition some of those methods are requiring expensive equipments, reagents and are also time-consuming. In some cases, the methods are requiring extraction and derivatization procedures due to their relatively low sensitivities. Spectrophotometric method⁴¹ based on its reducing action of ferric ion to ferrous ion which in presence of potassium ferricyanide producing green color is less sensitive. It is involving hazardous chemicals and also requiring heating. Hence considering the biological importance of OXC and also the limitations associated with the reported methods^{14-19,22-27,29-40}, an attempt is made here to develop a simple, rapid, economical and sensitive spectrophotometric method based on the reaction of OXC with methanolic potassium hydroxide in dimethylsulfoxide for its determination either in pure or in dosage form.

MATERIALS AND METHODS

UV-1700 pharماسpec spectrophotometer (Shimadzu, Japan) with 1 cm matched quartz cells was used for absorbance measurements. The standard sample of OXC was obtained from Jubilant Organosys

Ltd. Nanjangud, India. All chemicals used were of analytical grade reagents.

Potassium hydroxide solution (0.05 M)

It was prepared by dissolving 0.7012g of potassium hydroxide in methanol and diluted to 250ml in a volumetric flask.

Standard drug solution

A standard solution of OXC was prepared by dissolving 0.00502g of pure sample of the drug in dimethylsulfoxide and diluted to the mark in a 100 ml volumetric flask with dimethylsulfoxide. The stock solution prepared was having calculated molarity of $1.99 \times 10^{-4} \text{ M}$.

Procedure for the determination of OXC

A known but various volumes, 0.2-1.4ml of $1.99 \times 10^{-4} \text{ M}$ OXC were transferred into series of labeled 10ml volumetric flasks. A measured volume, 0.2ml of methanolic potassium hydroxide solution was added into each flask. The solutions were mixed well and diluted up to the mark with dimethyl sulfoxide. The absorbances of the solutions were measured after 5min at 430 nm against the reagent blank prepared under identical conditions but without the drug.

Procedure for the assay of dosage forms

Commercially available tablets were powdered and the amount equivalent to 150mg of OXC was weighed accurately into a 250ml beaker and the drug was extracted into 100ml acetonitrile. The resulting turbid organic solution was stirred thoroughly with a glass rod and filtered it through a Whatmann number 42 filter paper. The clear filtrate collected in a beaker was evaporated to dryness on a water bath. The residue remained was dissolved in dimethyl sulfoxide and transferred the solution into a 100ml volumetric flask and diluted to the volume with dimethyl sulfoxide. From this solution, an aliquot of 3.5ml was transferred into a 100ml volumetric flask and diluted up to the mark with dimethylsulfoxide. Appropriate aliquots of the tablet extract were subjected to analyses by the method described above.

RESULTS AND DISCUSSION

Literature survey is revealing that sodium methylsulfinyl carbanion or dimsyl ion - a highly reactive reagent prepared either by adding sodium hydride to excess of DMSO⁴³ or by adding sodium methoxide to DMSO⁴⁴ and the anion so produced is considered to be under going addition across the carbonyl group⁴³⁻⁴⁷, in the same way as other anions, there by producing an ion-pair. Literature survey is

also revealing that the hydrolysis of amide groups by potassium t-butoxide in DMSO to amine⁴⁸. Preliminary experiments of the present spectrophotometric method for OXC that contain keto carbonyl group have revealed that, potassium methylsulfinyl carbanion, an anion formed by reaction of potassium methoxide with DMSO must be reacting with OXC either by addition of potassium methylsulfinyl carbanion to keto carbonyl group like

other anions⁴³⁻⁴⁷ there by producing a colored ion-pair or by hydrolysis of amide group of OXC to amine salt by potassiummethoxide in DMSO via colored ion-pair formation. Therefore based on the literature background [43-48] and on the observations of the experimental findings, the following reaction mechanism is given in (Fig. 1).

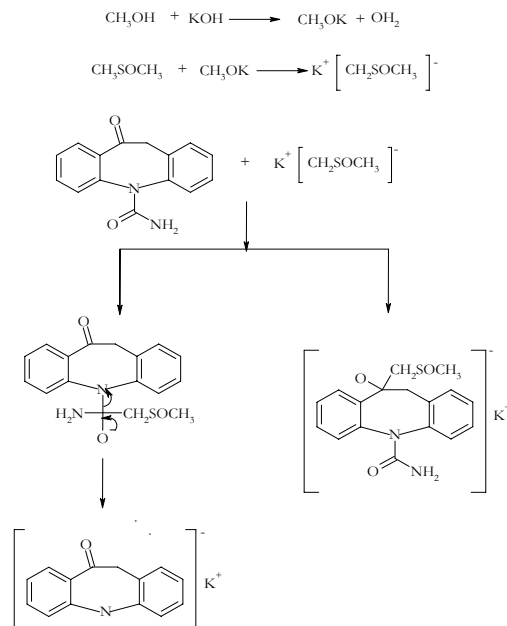


Fig. 1: Reaction mechanism of OXC

The reaction conditions as well as the various experimental parameters that are considered to be affecting the development and stability of the colored product were carefully investigated and optimized for the quantitative determination of OXC in pure and in pharmaceutical formulations. For comparison of the results, OXC was also determined separately by following the reported method⁴¹ for pharmaceutical formulations.

The absorption spectrum obtained from reaction of OXC with methanolic potassium hydroxide in dimethylsulfoxide was showing a maximum absorption at 430 nm and the absorption spectrum is shown in (Fig. 2). The concentration of the OXC can be calculated from regression equation by measuring the absorbance of the solution at 430 nm.

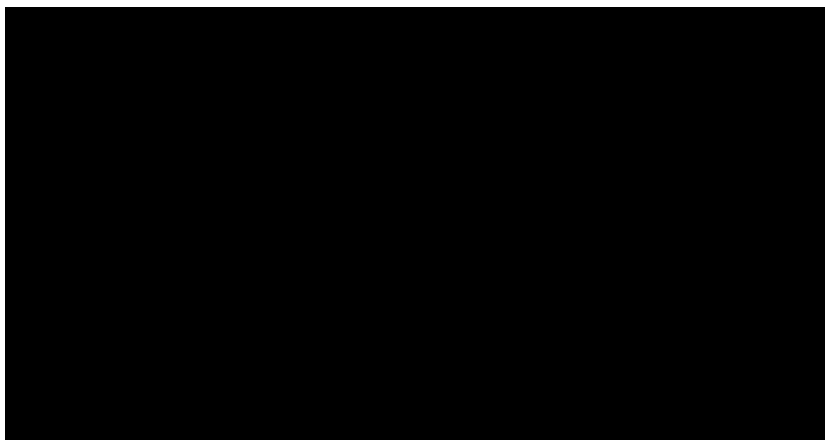


Fig. 2: Absorption spectra of 1=Oxcarbazepine in DMSO, 2=Oxcarbazepine+methanolic KOH +DMSO, 3=Methanolic KOH, 4=DMSO

Optimization of reaction conditions

The effect of different volumes of 0.05 M methanolic potassium hydroxide solution on the color intensity of chromophore at constant concentration of OXC (0.5 ml of 1.99×10^{-4} M) was examined. The results obtained are as shown in (Fig.3) and are revealing that the maximum absorbance was attained with 0.2ml of

0.05M potassium hydroxide solution, after that there appear to be a gradual decrease in absorbance values of the solutions. Therefore, 0.2 ml of 0.05M methanolic potassium hydroxide solution was used throughout the experiment. The effect of time for development of maximum color for the method was examined by mixing 0.5 ml of 1.99×10^{-4} M OXC solution with 0.2 ml of 0.05M methanolic potassium hydroxide solution.

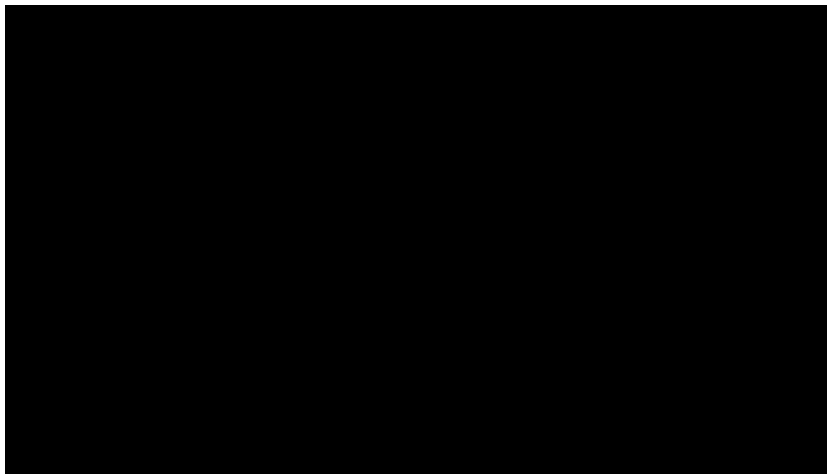


Fig. 3: Effect of different volume of methanolic potassium hydroxide solution

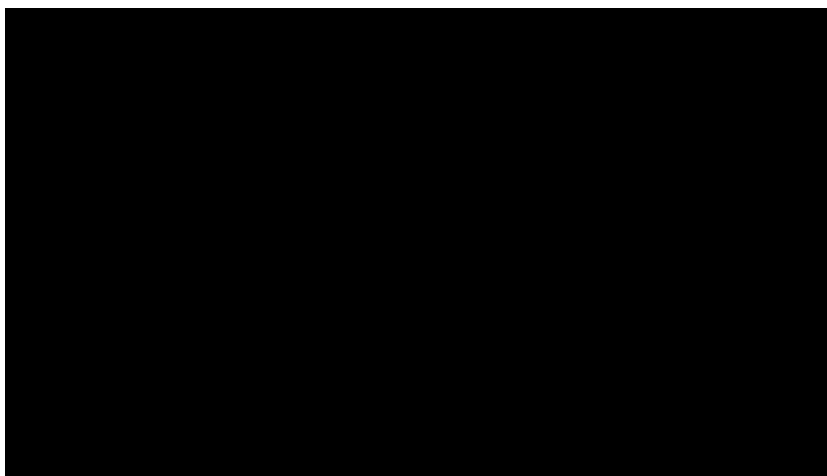


Fig. 4: Effect of different diluents on color

The absorbance of the solution was measured at different intervals of time. The results obtained are indicating that the system is attaining its maximum color intensity in about 5min. and remained almost unchanged for about 120 min. after that, the solution was found to be decreasing its absorbance values very slowly with time but it retained its color for about 3hrs. Therefore the optimum time for completion of the reaction was fixed as 5min. The effect of different diluents on color intensity of chromophore at constant concentration of OXC (0.5ml of $1.99 \times 10^{-4}M$) and methanolic potassium hydroxide (0.2 ml 0.05M) solutions was examined by measuring the absorbance at 430nm against respective diluent blank. The absorbance values obtained with different diluents are shown in (Fig.4). They indicate that the solutions which were diluted with methanol, ethanol and chloroform are found to be having negligible absorbance values but the solutions that were diluted with acetone and acetonitrile were found to be having lower absorbance values than the absorbance value of the solution which was diluted with dimethyl sulfoxide. Therefore DMSO was not only found to be best solvent but it is also involving in color development of OXC. Hence it was employed as a solvent through out the experimental investigations of the drug.

Analytical data

Under the optimized experimental conditions, the standard calibration graph was constructed by following the recommended procedure. A linear correlation was found between the absorbance and the concentration of OXC. Beer's law was obeyed in the range $1.0- 7.03\mu\text{gml}^{-1}$. The regression analysis of Beer's law data using the method of least squares was made to evaluate the slope (m), the intercept (c) and the correlation coefficient(r) for OXC and the values calculated are given in Table 1.

Sensitivity parameters such as molar absorptivity, sandell's sensitivity, and limits of detection and quantification values are calculated as per the current ICH guidelines ⁴⁹, are also compiled in Table1. The limit of detection (LOD) and limit of quantification (LOQ) were calculated according to ICH definitions- $\text{LOD}=3.3\sigma/S$ and $\text{LOQ}=10\sigma/S$ where ' σ ' is the standard deviation of regression line and 'S' is the slope of the calibration curve.

Precision and Accuracy

The precision and accuracy of the developed method was evaluated by performing five replicate determinations of OXC in pure form at three different concentrations ($1.01\mu\text{gml}^{-1}$, $3.01\mu\text{gml}^{-1}$ and $5.02\mu\text{gml}^{-1}$) by recommended procedure. The precision of the proposed method

as expressed by the calculated relative standard deviation (RSD) was found to be 0.79% for OXC ($3.01\mu\text{g ml}^{-1}$) and the corresponding

accuracy as expressed by the calculated relative error was varied between (-1.30 to 1.30%).

Table 1: Optical characteristics and precision data

Parameter	
λ_{Max} (nm)	430
Color stability	2 hrs
Beer's law range ($\mu\text{g ml}^{-1}$)	1 -7.03
Molar absorptivity ($\text{L mol}^{-1} \text{cm}^{-1}$)	1.21×10^4
Sandell's sensitivity ($\mu\text{g cm}^{-2}$ per 0.001A)	0.0208
Regression equation (Y)*	0.1384
Slope (m)	0.0047
Intercept(c)	
Correlation Coefficient(r)	0.9997
RSD (%) (n=5)	0.79
Range of error (%)	± 1.30
Limit of detection ($\mu\text{g ml}^{-1}$)	0.027
Limit of quantification ($\mu\text{g ml}^{-1}$)	0.082

*Y= m X+ c where 'X' is the concentration of the OXC in $\mu\text{g ml}^{-1}$.

Table 2: Determination of oxcarbazepine in presence of excipients

Excipients	Amount of excipients added (mg)	%Recovery \pm %RSD*
Talc	40	101.66 \pm 0.14
Starch	40	100.83 \pm 0.39
NaCl	40	101.66 \pm 0.08
Dextrose	40	100.00 \pm 0.12
Glucose	40	100.83 \pm 0.07
Lactose	40	102.50 \pm 0.11
Magnesium stearate	40	100.00 \pm 0.20
Carboxy methyl cellulose	40	100.00 \pm 0.19

*Average of five determinations, $2.01\mu\text{g ml}^{-1}$ of oxcarbazepine used for measurements.

Interference study

Under the optimized experimental conditions, the effects of additives associated with OXC in its formulations were investigated using the developed method. The results obtained are indicated in Table 2 and are indicating that the method is not suffering any interference from common excipients and other substances added to tablet preparations up to 40mg. The percent of recovery of OXC was found to be ranged from 100 to 101.66%.

Application of the method

The method was applied to the determination of OXC in pure as well as in its pharmaceutical formulations. The results of the assay of tablets are indicated in Table 3 and are found to be highly reproducible as the relative standard deviation was varied between 0.29 - 0.47%. The results obtained by developed method were found to be in good agreement with the reported method⁴¹ and the values claimed on the labels.

Table 3: Determination of oxcarbazepine in pharmaceutical formulations

Pharmaceutical formulations	Labeled amount of drug (mg)	Found \pm %RSD*	
		Developed method	Reported method ⁴¹
Oxep ¹	150	148.12 \pm 0.29	149.50 \pm 0.27
Oxetol ²	150	152.49 \pm 0.47	150.20 \pm 0.21
Oxrate ³	150	150.00 \pm 0.42	149.85 \pm 0.45
Selzic ⁴	150	153.75 \pm 0.36	151.05 \pm 0.50

* Average of five determinations, \$ Marketed by: 1 =Sppl, 2=Sun pharma, 3=Merind, 4=Solus.

CONCLUSION

The developed method is found to be rapid, simple, economical and more sensitive with low values of relative standard deviation. The method is using inexpensive instruments compared to the reported methods¹⁴⁻⁴⁰, further it does not require any expensive reagents and hazardous chemicals⁴¹. The method does not require any stringent experimental conditions, which affect the sensitivity and reliability of the method. The method does not suffer any interference from common tablet excipients and additives upto 40mg. The developed method is offering high sensitivity ($\epsilon=1.21 \times 10^4$), precision (0.79 %) and accuracy (-1.30 to 1.30%). The newly developed method is sensitive enough to enable quantitation of OXC at its lower

concentrations. Hence, the developed method was very effectively employed for routine analysis of OXC in various pharmaceutical formulations.

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