IJPSR (2017), Vol. 8, Issue 4 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 19 September, 2016; received in revised form, 25 November, 2016; accepted, 28 November, 2016; published 01 April, 2017

MOLYBDENUM BLUE METHOD FOR THE SPECTROPHOTOMETRIC DETERMINATION OF LEVETIRACETAM- CALCIUM CHANNEL MODULATOR

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Keywords:

Levetiracetam, Molybdenum Blue, Ammonium Molybdate, Spectrophotometry, Calcium Channel Modulator, Antiepileptic Agent

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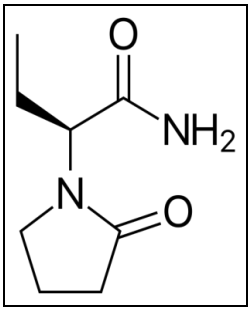
ABSTRACT: A simple, accurate, precise and easy spectrophotometric method for the determination of levetiracetam in pharmaceutical formulations using molybdenum blue method was developed by the authors. Aqueous solution of the drug sample on reaction with ammonium molybdate solution and hydrazine sulphate solution on heating for 5 minutes at a temperature of 60 0 C gave a clear, stable and intense blue colored molybdenum blue complex. This molybdenum blue showed a λ_{max} at 823nm. Beer's law was found to be obeyed in the range 0.02-0.08mg/ml. correlation coefficient was found to be 0.998. Molar abosrptivity was found to be 240.2 lit/mole/cm. LOD and LOQ was found to be 0.12 mg/ml and 0.37mg/ml respectively. The method is important in view of the fact that the excess dosage causes clinical problems and optimum dosage has to be fixed in the use of the drug.

INTRODUCTION: Levetiracetam, marketed under the trade name Keppra among others, is a medication used to treat epilepsy. [1] It is used for partial onset, myoclonic, or tonic-clonic seizures. [2] It is the S-enantiomer of etiracetam.



QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.8(4).1723-26

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8 (4).1723-26

Levetiracetam has potential benefits for other psychiatric and neurologic conditions such as Tourette syndrome, [3] anxiety disorder, [4] and Alzheimer's disease. [5] However, its most serious adverse effects are behavioral, and its benefit-risk ratio in these conditions is not well understood. [6] The most common adverse effects of levetiracetam treatment include CNS effects such as somnolence, decreased energy, headache, dizziness, and coordination difficulties.

These adverse effects are most pronounced in the first month of therapy. About 4% of patients dropped out of pre-approval clinical trials due to these side effects. [7] It also enhances the suicidal thought of the patients who are under treatment with the drug [2]. Hence quantitative determination of levetiracetam in pharmaceutical formulations thus becomes important, since it's over dosage causes ill effects. In literature [8-10] it was found that earlier workers used UV spectroscopy, HPLC, RPHPLC for the determination of levetiracetam.

During the course of study of color reactions between the drug sample and different chromogenic reagents, the authors found that aqueous solution of the drug reacted with ammonium molybdate solution and hydrazine sulphate solution gave intense blue colored, clear and stable molybdenum blue product.

METHODS AND MATERIALS: All the reagents were of Merck AR grade. Double distilled water was used for the preparation of all the solutions.

Preparation of pure drug sample solution (in aqueous media): An adequately weighed quantity of 0.1g of the pure drug sample was transferred into a 250ml beaker, and dissolved in distilled water. The mixture is heated to 600C for half an hour. The resulting solution was cooled to room temperature and filtered. The filtrate was made up to the mark in a 100ml volumetric flask and standardized [14].

Ammonium molybdate solution: An accurately weighed 2.5g of ammonium molybdate was transferred into a 100ml volumetric flask. The substance was dissolved by the addition of 10N sulphuric acid and after complete dissolution, the resulting solution was made up to the mark using 10N sulphuric acid [13].

Hydrazine sulphate aqueous solution: An accurately weighed 0.15g of hydrazine sulphate into a 100ml volumetric flask, was dissolved in double distilled water and after complete dissolution the resulting solution was made up to the mark [13].

Preparation of the pharmaceutical formulation solution: Ten tablets of levetiracetam were ground into a fine powder and from that weighed quantity of 0.1g of the drug sample was transferred into a 250ml beaker and dissolved in 100ml of double distilled water. The mixture was heated to 600c for half an hour. The resulting solution was cooled to room temperature and filtered. The filtrate was made up to the mark in a 100ml volumetric flask.

Instruments used: ELICO LI127 pH meter was used for the determination of pH of samples. JASCO V 750 UV VIS spectrophotometer with matched set of quartz cuvettes (10mm path length) were used for all the absorbance measurements.

Recommended procedure for the determination of λ_{max}: An aliquot of the aqueous solution of the drug sample was transferred into a 50ml volumetric flask. To this 5ml of ammonium molybdate solution and 2 ml of hydrazine sulphate solution were added and mixed well. The resulting solution was made up to the mark using double distilled water. This volumetric flask was heated on a water bath for 5 minutes. An intense blue color was developed. After the predetermined time the flask was cooled to room temperature and the absorption spectra was recorded in the wavelength range of 380-900nm. The intense blue colored product, molybdenum blue, showed a maximum absorbance at 823nm. (**Fig. 1**)

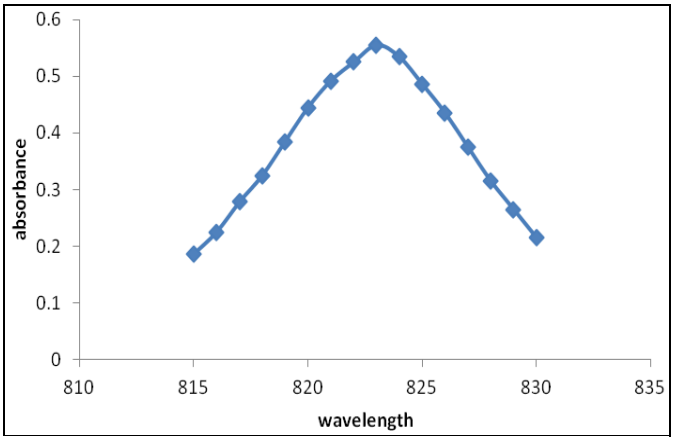


FIG. 1: WAVELENGTH MAXIMUM PLOT OF THE MOLYBDENUM BLUE PRODUCT OBTAINED BY THE REACTION BETWEEN LEVETIRACETAM, AMMONIUM MOLYBDATE AND HYDRAZINE SULPHATE

Recommended procedure for the determination of levetiracetam: For the determination of levetiracetam, a series of solutions of varying concentration solutions of the drug sample were prepared by transferring 1ml, 2ml, 3ml, 4ml 5 ml into 50ml volumetric flasks, to each of which 5ml of ammonium molybdate solution and 2ml of hydrazine sulphate were added. The resulting solution was made up to the mark using double distilled water. These volumetric flasks were heated on a water bath for ten minutes. After the predetermined time, the flasks were cooled to room temperature.

An intense blue colored product was obtained, and for each of the blue coloured solution absorbance

measurements were recorded at 823nm and Beer's law plot was drawn for the same (**Fig. 2).** The concentration of the drug in a solution was determined with the help of the Beer's law plot. (**Fig. 2**)

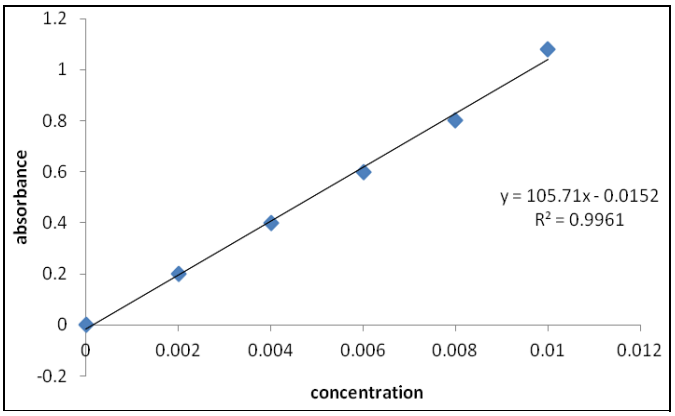


FIG. 2: BEER'S LAW OBEDIENCE PLOT FOR LEVETIRACETAM

RESULTS AND DISCUSSION: Molybdenum blue product is the result for the reaction between the drug sample solution and the reagents specified, showed maximum absorbance at 823 nm (**Fig. 1**). Beer's law was found to be obeyed in the range of 0.02-0.08mg/ml (**Fig. 2**). Molar extinction coefficient for the same was found to 240.2 mole^{-1} lit cm^{-1}. Correlation coefficient in this method was found to be 0.99802, limit of detection was found to be 0.12 mg/ml and limit of quantification was found to be 0.37mg/ml. Relative standard deviation for ten samples was found to be 1.82% which was well within the standard value. The complete spectral data was presented in **Table 1**.

Commercially available tablets of the drug under the trade name keppra were analyzed by the method developed. The result obtained was as accurate as prescribed in standard method. A comparative table for the same is presented in **Table 2**.

TABLE 1: SPECTRAL DATA PARAMETERS

Parameter	Result Obtained
λ_{max}	823 nm
Beers law obidience	0.02-0.08mg/ml
correlation coefficient	0.998
molar absorptivity	240.2 lit/mole/cm
LOD	0.12mg/ml
LOQ	0.37mg/ml
stability of color	24 hours

TABLE 2: COMPARATIVE DATA FOR THE METHOD DEVELOPED BY AUTHORS AND STANDARD METHOD

S. No	Name of the drug	Method proposed by authors	Standard method
1	Keppra 250 mg	99.8	99.9
2	Levecetam 250mg	99.7	99.9

In the present method, the reagents used were found to have no interference with the absorption spectra of the blue colored product. Normally used excipeints such as starch, added flavors were found to have no interference with the absorption measurements. Use of phosphoric acid in the reaction was avoided, as it was reported to interfere in the reaction with molybdenum (VI) [10]. The color reaction between the drug sample solution, ammonium molybdate solution and hydrazine sulphate solution was not observed in acetic acid, sulphuric acid, hydrochloric acid and nitric acid media.

Effect of concentration and volume of reagents: Ammonium molybdate solution: The optimum concentration of ammonium molybdate solution was fixed as 2.5% (W/V) for effective reaction. The optimum concentration of hydrazine sulphate solution was fixed as 0.15% (W/V) for the effective reaction. Addition of 5ml of 2.5% ammonium molybdate solution and 2 ml of hydrizaine sulphate solution was fixed as optimum volumes of the reagents being added to get stable, clear molybdenum blue complex.

CONCLUSIONS: A clear, stable and intense blue colored molybdenum blue complex was the resultant of the reaction between aqueous solutions of the drug levetiracetam with ammonium molybdate and hydrazine sulphate. The molybdenum blue complex showed a λ_{max} at 823 nm, Beer's law obedience in method I was found to be 0.02-0.08mg/ml. The method is important in view of the fact that the excess dosage causes clinical problems and optimum dosage has to be fixed in the use of the drug.

ACKNOWLEDGEMENTS: The authors thank the Principal and management of M V G R College of Engineering, Vizianagaram - 535005 for

providing necessary facilities and for their constant support & encouragement.

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How to cite this article:
Kumar GVSRP, Rao KS, Bharath Y and Avinash MK: Molybdenum blue method for the spectrophotometric determination of levetiracetam- calcium channel modulator. Int J Pharm Sci Res 2017; 8(4): 1723-26.doi: 10.13040/IJPSR.0975-8232.8(4).1723-26.