NEW SPECTROPHOTOMETRIC METHOD FOR ANALYSIS OF ERUBULIN IN PHARMACEUTICAL DOSAGE FORMS

NARENDRA DEVANABOYINA*, K.CHAITANYA, K.VENKATESWARAO, N.SRINIVASARAOS.RAVIKUMAR

Department of Pharmaceutical Analysis, Lydia college of pharmacy, ravulapalem-533238, India

Email: narendra.kothapalli@gmail.com

ABSTRACT

A simple, sensitive and economical spectrophotometric method has been developed for the determination of Erubulin in commercial dosage forms.In this method ferric chrloride and Potassium ferricyanide were used for the colour development.The maximum absorbance was found at 410nm against the reagent blank treated similarly.Statistical analysis proves that the proposed method is reproducible and selective for the estimation of eribulin in bulk drug and its tablet dosage form.

KEYWORDS: UV-Spectrophotometer, Erubulin, Potassium ferricyanide **[**K_3 [Fe (CN) $_6$], Ferric chloride **(**$FeCl_3$**)**

INTRODUCTION

Erubulin is an anticancer drug marketed by Eisai Co. under the trade name Halaven. Erubulin mesylate was approved by the U.S. Food and Drug Administration on November 15, 2010, to treat patients with metastatic breast cancer who have received at least two prior chemotherapy regimens for late-stage disease, including both anthracycline- and taxane-based chemotherapies.

Erubulin is also being investigated by Eisai Co. for use in a variety of other solid tumors, including non-small cell lung cancer, prostate cancer and sarcoma. Erubulin has been previously known as E7389 and ER-086526, and also carries the US NCI designation NSC-707389.

Structurally, eribulin is a fully synthetic macrocyclic ketone analogue of the marine sponge natural product halichondrin B,the latter being a potent naturally-occurring mitotic inhibitor with a unique mechanism of action found in the *Halichondria* genus of sponges. Erubulin is a mechanistically-unique dynamics, binding predominantly to a small number of high affinity sites at the plus ends of existing microtubules Erubulin exerts its anticancer effects by triggering apoptosis of cancer cells following prolonged and irreversible mitotic blockade.

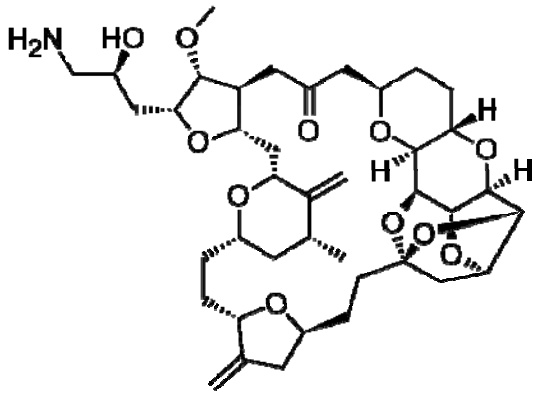


Figure: 01 Structure of Erubulin

IUPAC Name :

2-(3-Amino-2-hydroxypropyl)hexacosahydro-3-methoxy- 26-methyl-20,27-bis(methylene)11,15-18,21-24,28-triepoxy- 7,9-ethano-12,15-methano-9*H*,15*H*-furo(3,2-i)furo(2',3'-5,6) pyrano(4,3-b)(1,4)dioxacyclopentacosin-5-(4*H*)-one

EXPERIMENTAL

All absorbance measurements were made on a 2301 spectrophotometer model with 1 cm matched quartz cells.

2.1 Chemicals and Reagents

All the solutions were freshly prepared.All solvents and other chemicals used through the study were of analytical grade.

2.2 Preparation of Solutions:

2.2.1 Preparation Ferric chloride ($Fecl_3$) solution: Accurately weigh 250mg of ferric chloride ($fecl_3$) and dissolved in 100 ml of distilled water.

2.2.2 Preparation Potassium ferricyanide [K_3 [Fe (CN) $_6$] **solution:** Accurately weigh 100 mg of Potassium ferricyanide **[**K_3 [Fe (CN) $_6$] dissolved in 100ml of distilled water.

2.2.3 Preparation of Standard drug solution:

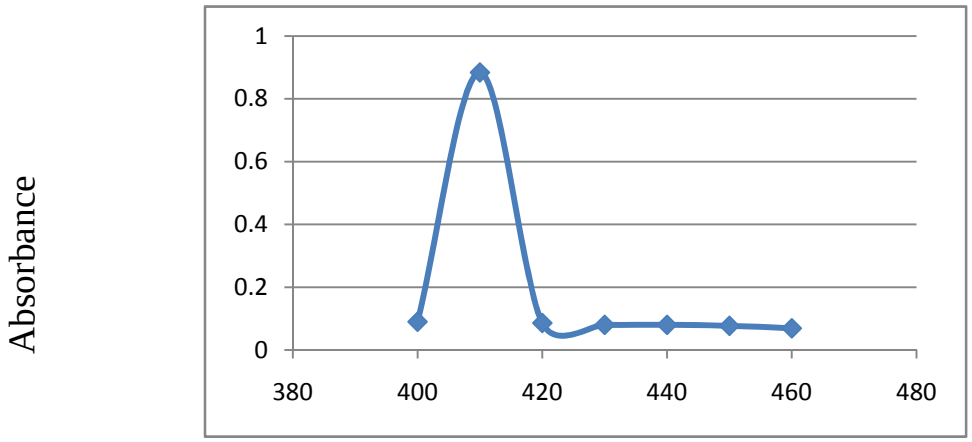
10 mg of Erubulin drug was weighed accurately and dissolved in 10ml of distiiled water, its results in 1000µg/ml of stock solution (I). 1ml of stock solution was pipetted out and makes up to 10ml with distilled water its results in 100µg/ml stock solution (II) further dilutions will be carried out with the stock solution (II).

ASSAY PROCEDURE

Aliquots of standard drug solution of Erubulin (5 µg/ml - 25 µg/ml) were taken in 10 ml test tubes To this 1ml of fecl3 solution was added. Reaction mixture was shaken gently for 2 min. To this mixture, 1.5 ml of Potassium ferricyanide **[**K_3 [Fe (CN) $_6$] solution was added. Shaken well for 2 min. This mixture was incubated for 10minutes. A faint green colour was developed. The final volume of the test tubes was made up to 10ml with distilled water. Absorbance

were measured at 410 nm against a blank solution prepared similarly without drug.Calibration curve was prepared from absorbence values so obtained.

Graph: - 01



Absorption spectrum of Erubulin at 410 nm

Recovery Studies:

To ensure the accuracy and reproducibility of the results obtained, known amounts of pure drug was added to the previously analyzed formulated samples and these samples were reanalyzed by the proposed method and also performed recovery experiments. The Percentage recoveries thus obtained were given in Table 4.

RESULT AND DISCUSSION

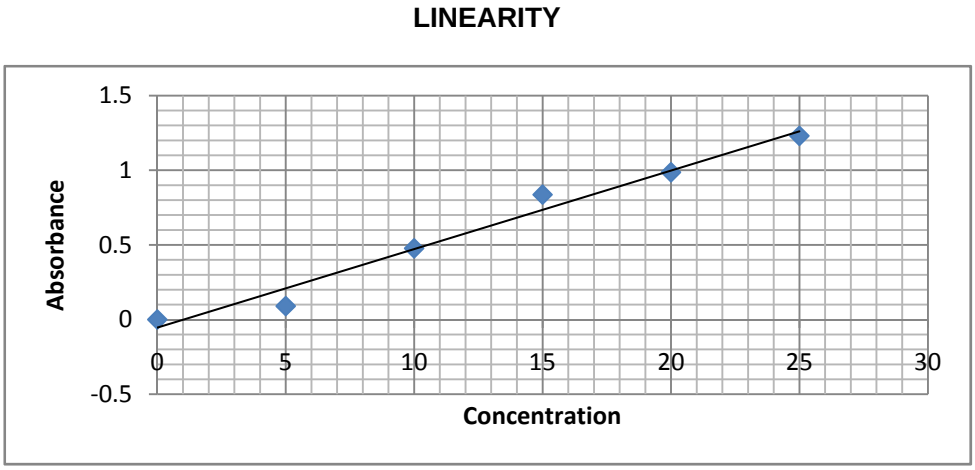
The optimum conditions were established by varying one parameter at a time and keeping the others fixed and observing the effect on absorbance of chromogen for the proposed method.In the present work proposed method have been developed for the estimation of eribulin mesylate from tablet formulations. In this method ferric chrloride and Potassium ferricyanide **[**K_3 [Fe (CN) $_6$] were used for the colour development.The calibration graph of the absobance versus concentration was found to be linear over the range of 5-25 µg/ml for proposed method.Recovery studies were close to 100% that indicates indicating good accuracy of the methods. To evaluate the accuracy and precision of the methods, pure drug solution (within the working limits) was analyzed and being repeated six times. The relative error (%) and relative standard deviation (%) were less than 2.0 and indicate the high accuracy and precision for the proposed methods

Table: - 01

LINEARITY

S.NO	CONCENTRATION	ABSORBANCE	
1	5µg/ml	0.09	Slope:0.049 Intercept:0.054 Cc:0.972
2	10µg/ml	0.477	
3	15µg/ml	0.837	
4	20µg/ml	0.987	
5	25µg/ml	1.231	

Graph: - 02



Calibration curve of Erubulin

Table: - 02

PRECISION

S.No	Concentration	Absorbance	% Relative Standard Deviation
1	15µg/ml	0.814	0.45%
2	15µg/ml	0.824	
3	15µg/ml	0.818	
4	15µg/ml	0.817	
5	15µg/ml	0.818	
6	15µg/ml	0.816	

Table: - 03

RUGGEDNESS

S.No	Concentration	Absorbance	% Relative Standard Deviation
1	15µg/ml	0.865	0.498%
2	15µg/ml	0.867	
3	15µg/ml	0.862	
4	15µg/ml	0.868	
5	15µg/ml	0.874	
6	15µg/ml	0.863	

Table: - 04

RECOVERY

Recovery	Concentration of Sample	Drug Recovery	% Drug Recovery	Average % Recovery
50%	5µg/ml	4.86ppm	97.3	98.2%
100%	10 µg/ml	9.89ppm	98.9	
150%	15 µg/ml	14.76ppm	98.4	

Limit of Detection and Limit of Quantification:

The LOD and LOQ were found to be

LOD	0.6 ppm
LOQ	2 ppm

Conclusion

The Proposed method for the analysis of ERUBULIN in tablets is very simple and rapid. This method was validated for linearity, precision, system suitability, specificity, LOD & LOQ and ruggedness.

ACKNOWLEDGEMENT

With profound sense of gratitude and humbleness we express our sincere thanks to our dedicated supervisor, Faculty members and management of Lydia College of pharmacy, Ravulapalem, East Godavari .Dist, Andhra Pradesh, India

REFERENCE

1. "FDA approves new treatment option for late-stage breast cancer" (Press release). USFDA. 2010-11-15. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm233863.htm. Retrieved November 15, 2010.
2. http://www.clinicaltrials.gov/ct2/results?term=eribulin+OR+E7389
3. Towle MJ, Salvato KA, Budrow J, Wels BF, Kuznetsov G, Aalfs KK, Welsh S, Zheng W, Seletsky BM, Palme MH, Habgood GJ, Singer LA, Dipietro LV, Wang Y, Chen JJ, Quincy DA, Davis A, Yoshimatsu K, Kishi Y, Yu MJ, Littlefield BA (February 2001). "In vitro and in vivo anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B". *Cancer Res.* 61 (3): 1013–21.
4. Yu MJ, Kishi Y, Littlefield BA (2005). "Discovery of E7389, a fully synthetic macrocyclic ketone analogue of halichondrin B". In Newman DJ, Kingston DGI, Cragg, GM. *Anticancer agents from natural products*. Washington, DC: Taylor & Francis.
5. Hirata Y, Uemura D (1986). "Halichondrins - antitumor polyether macrolides from a marine sponge". *Pure Appl. Chem.* 58 (5): 701–710.
6. Bai RL, Paull KD, Herald CL, Malspeis L, Pettit GR, Hamel E (August 1991). "Halichondrin B and homohalichondrin B, marine natural products binding in the vinca domain of tubulin. Discovery of tubulin-based mechanism of action by analysis of differential cytotoxicity data". *J. Biol. Chem.* 266 (24): 15882–9.
7. Jordan MA, Kamath K, Manna T, Okouneva T, Miller HP, Davis C, Littlefield BA, Wilson L (July 2005). "The primary antimitotic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth". *Mol. Cancer Ther.* 4 (7): 1086–95.
8. Okouneva T, Azarenko O, Wilson L, Littlefield BA, Jordan MA (July 2008). "Inhibition of Centromere Dynamics by Eribulin (E7389) during Mitotic Metaphase". *Mol. Cancer Ther.* 7 (7): 2003–11.
9. Kuznetsov G, Towle MJ, Cheng H, Kawamura T, TenDyke K, Liu D, Kishi Y, Yu MJ, Littlefield BA (August 2004). "Induction of morphological and biochemical apoptosis following prolonged mitotic blockage by halichondrin B macrocyclic ketone analog E7389". *Cancer Res.* 64 (16): 5760–6
10. Towle MJ, Salvato KA, Wels BF, Aalfs KK, Zheng W, Seletsky BM, Zhu X, Lewis BM, Kishi Y, Yu MJ, Littlefield BA (January 2011). "Eribulin induces irreversible mitotic blockade: implications of cell-based pharmacodynamics for in vivo efficacy under intermittent dosing conditions". *Cancer Res.* 71 (2): 496–505