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NOVAL METHOD DEVELOPMENT FOR THE DETERMINATION OF ERTAPENEM IN BULK AND INJECTION FORMULATIONS BY NIN HYDRIN AND ASCORBIC ACID USING SPECTROPHOTOMETER

Dr. N. Aruna Kumari[1], Polepalle. Tirupalu[2]

[1]Professor of Engineering Chemistry
Visakha Institute of Engineering and Technology
Narava, Visakhapatnam, Andhra Pradesh,(India)
[2]Lecturer in Chemistry,Dept. Of Chemistry
RGUKT Srikakulam,APIIIT (India)

ABSTRACT

A simple and cost effective spectrophotometric method was described for the determination of Ertapenem in pure form and in pharmaceutical formulations. The method is based on the formation of colored chromogen when the drug reacts with Nin Hydrin and Ascorbic acid. This method was applied for the determination of drug contents in pharmaceutical formulations and enabled the determination of the selected drug in microgram quantities (0.5 to 3.0 mL). No interferences were observed from excipients and the validity of the method was tested against reference method. The colored species has an absorption maximum at 563 nm for Ertapenem and obeys beer's law in the concentration range 3-50 µg/mL of Ertapenem. The apparent molar absorptivity was $83x10^{-3}$ and sandell's sensitivity was $7x10^{-4}$. The slope is 0.2200 ± 0.0037, the intercept of the equation of the regression line is 0.0114 ± 0.0067. The optimum experimental parameters for the reaction have been studied and the validity of the described procedure was assessed. Statistical analysis of the results has been carried out revealing high accuracy and good precision. The proposed method was successfully applied for the determination of Ertapenem in pharmaceutical formulations.

Keywords- Ertapenem, Nin Hydrin, Ascorbic acid Chromogen, Molar absorptivity, Sandell's sensitivity, Spectrophotometry.

I.INTRODUCTION

Ertapenem[1] (Fig:1) is a carbapenem antibiotic marketed by Merck as Invanz. It is structurally very similar to meropenem including its stability to dehydropeptidase-1. ERP is a new carbapenem of beta-lactam-type antibiotics with an exceptionally broad spectrum of activity. It is has antimicrobial activity against many Gram-

positive and gram-negative aerobes and anaerobes and is resistant to nearly all beta-lactamases, including extended-spectrum beta-lactamases[2-11].

II.DRUG PROFILE

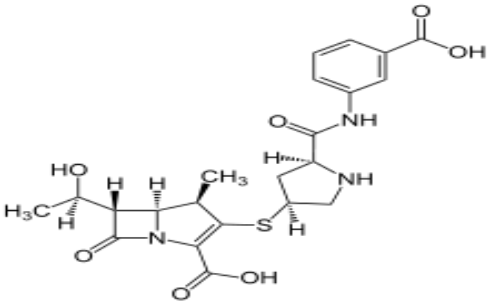
Name	:	Ertapenem (ERP)
Chemical Name	:	(4R,5S,6S)-3-[(3S,5S)-5-[(3-carboxyphenyl)carbamoyl] pyrrolidin-3-yl]sulfanyl-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid
Structure	:	

Fig 1

Molecular formula	:	$C_{22}H_{25}N_3O_7S$
Empirical formula	:	$C_{12}H_{17}N_3O_4S•H_2O$
Molecular weight	:	475.51 g/mol
Color	:	Off-white
p^{Ka}	:	3.37
Solubility	:	Soluble in water and slightly soluble in methanol.
Pharmacodynamic / Chemotherapeutic category	:	Antibacterial Agent

III.LITERATURE SURVEY ON THE ANALYTICAL METHODS FOR ERP

Literature survey revealed that a few analytical methods have been reported for the determination of ERP in pure drug and pharmaceutical dosage forms and in biological samples using UV visible spectroscopy and liquid chromatography.

A very few physico-chemical methods appeared in the literature for determination of ERP in pharmaceutical formulations. The methods so far reported include HPLC[262-273] and MS. Apart from providing better detection and improve peak shape and high resolution; the proposed method demonstrated a low noise and better signal-to-noise ratio during the detection process.

The analytically important functional groups of ERP are not properly exploited for designing suitable spectrophotometric methods for the determination of ERP. Hence there is a need to develop sensitive and flexible visible spectrophotometric methods, which prompted the author to choose ERP for the investigation based on the different chemical reactions. Fourteen methods for UV and one method for HPLC have been developed for ERP. The methods are based on the reactivity of ERP with suitable reagents to produce colored species of reasonable stability having possibility for visible spectrophotometric determination of ERP in its bulk form.

IV.EXPERIMENTAL

4.1 Instruments used

All spectral characteristics and absorbance measurements were made on Perkin Elmer, LAMBDA 25 double beam UV-Visible spectrophotometer with 10 mm matched quartz cells. A systronics digital pH meter 361 was used for pH measurements.

4.2 Preparation of standard drug solution

The stock solution (1mg/mL) of drug was prepared by dissolving 100 mg of ERP in 100 mL of distilled water. A portion of this stock solution was diluted stepwise with the distilled water to obtain the working standard solution of 100 µg/mL in the proposed methods.

4.3 Recommended Procedure

Aliquots of working standard solution (0.5 to 3.0 mL) of ERP were transferred into a series of 25 mL of volumetric flasks, to provide final concentration range of 2 – 12 µg/mL were delivered. To each flask 4.0 mL of pH 5.0 buffer solution 2.5 mL of NH solution (0.1%) and 2.5 mL of AA (0.1%) were added and the flask is heated on a water bath for 15 min. and then cooled in an ice bath and the total volume was made up to the mark with distilled water. The absorbance was measured immediately at 563 nm against a similar reagent blank. The colored species was stable for 1 h. The amount of ERP present in sample solution was calculated from its calibration graph.

Chemistry of the coloured species in the present investigation

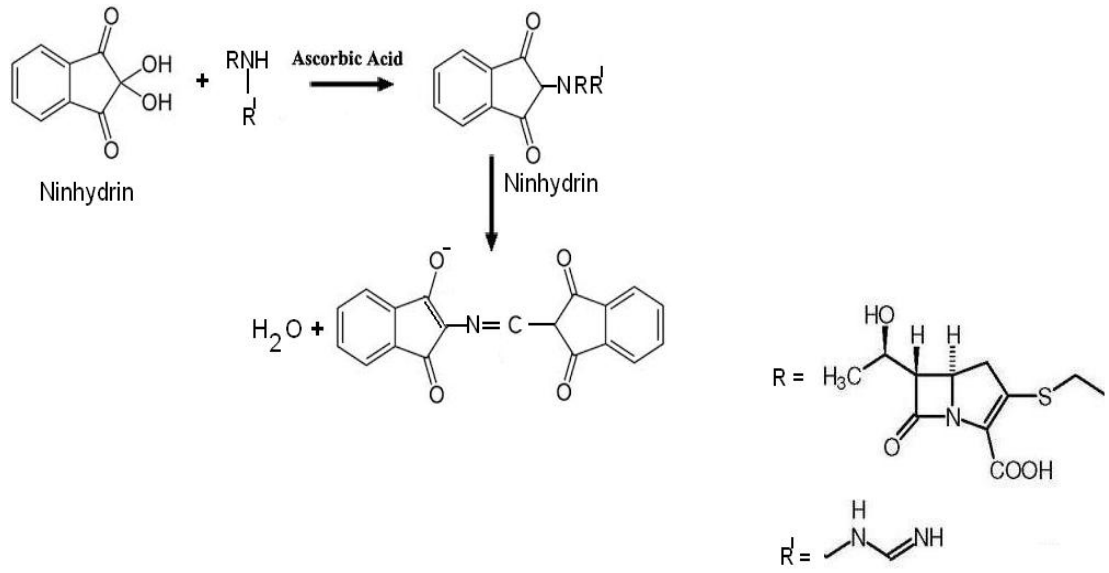
ERP possesses different functional moieties such as

Secondary amine, β-lactum ring in which there is a carboxylic acid, Tertiary nitrogen, Vulnerable oxidising centers, Hetero Sulphur and Double bonds.

An attempt has been made to indicate the nature of coloured species formed in each proposed method for the determination of ERP tentatively based on analogy.

Parameter	Range of study	Optimised condition in procedure	Remarks

Ammonium salts, dilute ammonia solutions, and some amines give a blue colour under certain conditions, apparently because of an intermolecular oxidation and reduction of the ninhydrin in the presence of ascorbic acid (AA). In the present investigation, the selected penems possesses amino group in their moiety, when heated with ninhydrin in the presence of AA forms a blue violet colour product. The reaction pathway can be represented in the following Scheme.



Scheme

The order of addition of the reagents was given in the proposed methods and the parameter fixations were given in Tab. 1

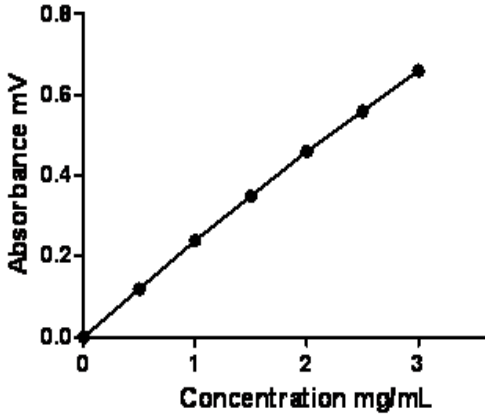
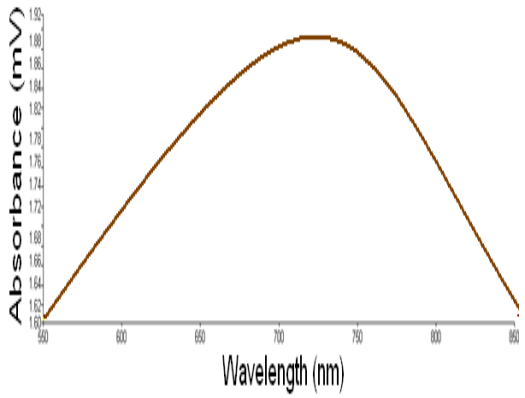
Tab. 1 RESULTS OF METHOD OPTIMISATION FOR ERP – NH & AA

λ_{max} (nm)	400-600	563	
Effect of volume of NH required for Condensation (mL)	0.5-3.0	2.5	Volume of NH above 2.5 mL gave high optical densities in blanks (>2.5), which resulted in deviations from Beers law.
Effect of volume of AA (mL)	0.5-3.0	2.5	To speed up the condensation stage in color development, 2.5 mL of AA was found necessary for maximum color development.
Effect of volume of Buffer (mL)	4.0	4.0	Addition of 4.0 mL of Buffer is necessary for proceeding the reaction
Effect of reaction time (min)	15-30	15	The minimum time required for complete oxidation was found to be 15 min.
Effect of temperature (^{0}C) for Condensation	20-40	32 ± 2 Lab. Temp	At low temperatures (<30^{0}C) the reaction time was found to be more and at high temperatures (>34^{0}C) no added advantage was found.
Stanidng time (min)	1-3	2	A minimum amount of time, i.e., 1 min was necessary for undergoing condensation and beyond 3 min results in low sensitivity.
Stability period after final dilution (min)	5-40	40	The absorbance of the colored product decreases slowly with time after 40 min.

TABLE 2 SHOW THE SPECTRAL VALUES OBTAINED IN THE PROPOSED METHOD - OPTICAL AND REGRESSION CHARACTERSTICS, PRECISION AND ACCURACY OF THE PROPOSED METHODS FOR ERP

PARAMETER	**NH & AA**
λ_{max} nm	563
Beer's law limits, µg/mL	2-12
Molar absorptivity, L/mol.cm	$83x10^{-5}$
Sandell's sensitivity µg/cm^2/0.001 absorbance unit	$7x10^{-2}$
Regression equation (Y = a + bc)	
Slope(b)	0.2200 ± 0.0037
Standard deviation of slope (Sb)	0.009856
Intercept	0.0114 ± 0.0067
r^2	0.9986

Limit of Detection	0.0056	
Limit of Quantification	0.017	
Standard deviation of intercept (Sa)	0.0024	
Standard error of estimation (Se)	0.0121	
Correlation coefficient ®	0.9998	
Relative standard deviation (%)*	0.0414	
% Range of error (Confidence limits)*		
Precision		
0.05 level	0.2231	
0.01 level	0.3196	
Accuracy		
Bulk sample	Amount found (µg)	% error
50	49.96	0.08

FIGURES SHOW THE BEER'S LAW PLOTS FOR THE PROPOSED METHODS FOR ERP	**FIGURE SHOW THE ABSORPTION SPECTRA OF THE PROPOSED METHODS FOR ERP**
 ERP(0.5-3mL)+buffer(4mL)+NH(2.5mL) +AA(2.5mL)	pH 5.0 Buffer, NH (0.1%), AA (0.1%) 

75	74.89	0.14
100	99.74	0.26

V.CONCLUSION

Even though there are very few methods for the determination of ERP, there is not even a single report utilizing spectrophotometric technique. Hence the proposed method is valuable for the determination of ERP. The proposed method exploit the various functional groups in ERP molecule. The contaminants, which do not contain the functional groups chosen in the present investigation, do not interfere in the color development by proposed method. Thus the proposed method is simple, sensitive and selective with reasonable precision and accuracy and constitute better alternatives to the reported ones in the assay of ERP in bulk form and pharmaceutical formulations.

REFERENCES

[1.] Agarwal H,Kaul N; paradar AR,Mahadik KR. Talanta. 2003;61:581-9.

[2.] Connors KA. A Text book of Pharmaceutical Analysis. 3rd ed. Wiley intersciences Inc.Delhi. 1994;233.

[3.] Goodman, L.S. and Gilman, A.G., The Pharmacological Basis of Therapeutics, 9th Edn. By Hardman, J.G., Limbard, L.E., Editors in Chief, McGraw - Hill, 1996.

[4.] Wolff, M.E., Edt, Burger's Medicinal Chemistry, Part IV, 4th Edn., Wiley Interscience, New York, 1981.

[5.] Deorge, R.F., Edt., Wilson and Gisvolds's Text book of Organic and Medicinal and Pharmaceutical Chemistry, 8th Edn., Lippincott Company, 1982.

[6.] Korolkovas, A., Essentials of Medicinal Chemistry, 2nd Edn., Wiley Interscience, New York, 1988.

[7.] Topliss, J.G.. Edt.. Quantitative Structure - activity relationships of Drugs, Vol 19, Academic press, London, 1983.

[8.] William O. Foye, Edt., Principles of Medicinal Chemistry, 3rd Edn., Varghese, Bombay, 1989.

[9.] Melentyeva, G., Antonova, L., Pharmaceutical Chemistry, Mir Publishers, Moscow, 1988.

[10.] L.M. Atherden, Edr, Bentley and Drivers Text Book of Pharmaceutical Chemistry, 8th Edn., Oxford University Press, 1996, 4th Impression.

[11.] Parimoo.Pharmaceutical Analysis, CBS Publishers and Distributors. New Delhi. 2002; 145.