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DEVELOPMENT AND VALIDATION OF ANALYTICAL METHOD FOR MEROPENEM IN PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

Meropenem is a parenteral carbapenem antibiotic with a very broad spectrum of antibacterial activity against the majority of gram-positive and gram-negative pathogens. In the present work, Two rapid, economical and accurate methods have been developed for the estimation of meropenem in pharmaceutical dosage form. Method A is first order derivative spectroscopy where derivative amplitudes were calculated by considering one minimum (320nm) and one maxima (282nm) of the curve. Method B is area under the curve in which wavelength range 304-299 nm was selected. Linearity was observed in the concentration range 10-50 µg/ml and 5-45 µg/ml for first order derivative spectroscopy and area under the curve respectively the methods ($R^2 = 0.9994$ for method A and $R^2 = 0.9997$ for method B). The % assay for the marketed formulation by first order derivative and area under the curve was found to be 99.97 % and 99.85% respectively. The method was validated with respect to linearity, precision and accuracy studies. Both the methods were found to be simple, precise and accurate and can be employed for routine quality control analysis of meropenem in pharmaceutical dosage form.

INTRODUCTION

Meropenem (Fig. 1), chemically (4R,5S,6S)-3- [[(3S,5S)-5-dimethylcarbamoyl pyrrolidin-3-yl]-Thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3,2,0]hept-2-ene-2-carboxylic acid is a new parenteral carbapenem antibiotic with a very broad spectrum of antibacterial activity against the majority of gram-positive and gram-negative pathogens [1]. It is more active in vitro than imipenem against Enterobacteriaceae and Pseudomonas aeruginosa, but less active against grampositive cocci [2]. Meropenem is more stable to ring opening by human renal dehydropeptidase I (DHP-I) than imipenem and consequently does not require concomitant administration of a DHP- 1 inhibitor. This antibiotic has shown clinical efficacy in the treatment of a wide range of serious infections such as intra-abdominal infections, urinary tract infections and lower respiratory tract infections including patients with cystic fibrosis [3,4]..

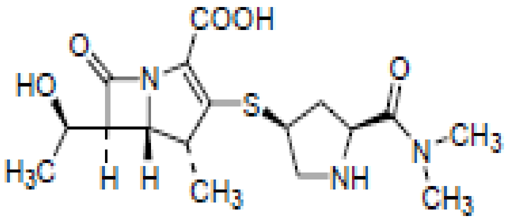


Fig 1: The chemical structure of meropenem

A survey of literature has revealed several analytical methods for the determination of meropenem and its main metabolite (ICI-213689) in biological fluids, including high-performance liquid chromatography (HPLC) [5-8], capillary zone electrophoresis [9,10] and microbiological assay [11]. The literature reports few methods for the quantitation of meropenem in pharmaceutical dosage form. HPLC adopted by the United States Pharmacopoeia [12] was based on the mobile phase containing tetrabutylammonium hydroxide as ion-pairing agent, which shortens column life. Moreover, the mobile phase preparation requires tedious procedures.

Since this antibiotic is widely used in the antimicrobial therapy, it is important to develop and validate analytical methods for its determination in pharmaceutical dosage form. The HPLC method has been highly used in the quality control of drugs because of their sensitivity, Reproducibility and specificity. The UV spectrophotometric (UV) method is very simple, rapid and economical and allows the determination of drugs with sufficient reliability.

The present work reports the spectrophotometric determination of meropenem in pharmaceutical dosage form by first order derivative spectroscopy and area under the curve.

EXPERIMENTAL

Chemicals

Meropenem reference standard was kindly supplied By Alpa Laboratories. Pharmaceutical dosage form (Merotec^{TM}) containing meropenem was obtained commercially and was claimed to contain 250 mg (as anhydrous base) of the drug and 52 mg of the anhydrous sodium carbonate as excipient. Distilled water was used to prepare all solutions for the UV method.

Instrumentation and analytical conditions

A shimadzu model 1700 (Japan) double beam UV/Visible spectrophotometer with spectral width of 2 nm, wavelength accuracy of 0.5 nm and a pair of 10 mm matched quartz cell was used to measure absorbance of all the solutions.

Preparation of the standard Stock solutions

Accurately weighed quantity 100 mg of Meropenem was dissolved in distilled water and the volume was made up to 100 ml to get a stock solution of 1000 µg/mL. Further dilution was made to give stock solution 100µg/ml.

Preparation of the sample solutions

Accurately weighed amount of powder for injection equivalent to 25 mg of meropenem was transferred to 50 ml volumetric flask and dissolved in distilled water (final concentration of 500 µg/ml). Aliquot of this solution were diluted in distilled water at concentration of 15 µg/ml.

METHOD-A

First Order Derivative method

In this method, standard solution(10 µg/ml of meropenem was scanned in the spectrum mode from 400 nm to 200 nm and the absorption spectra thus obtained were derivatized to first order. First order derivative spectra were selected for the analysis of drug. First order derivative spectra of drug showed λmaxima = 282 nm and λminima = 320 nm and amplitude difference was measured for the respective concentration of standard and was plotted against concentration and regression equation was calculated. The concentration range of 10-50µg/ml for meropenem was chosen for the derivative analysis.

METHOD-B

Area under the Curve method

For the selection of analytical wavelength standard solutions (10 µg/ml of meropenem were prepared and series of dilutions of standard solutions of meropenem were prepared by using distilled water and were scanned from 400 to 200 nm. From the spectra of drug obtained after scanning of standard solution of meropenem, area under the curve in the range of 299-394nm was selected for the analysis. The calibration curve was plotted with concentration v/s area under the curve and regression equation was calculated.

Method validation

The methods were validated according to International Conference on Harmonization guidelines for validation of analytical procedures.

Linearity

The calibration curve was obtained with five concentrations of the standard solution (10-50 µg/ml for first derivative method and 5-45 µg/ml for Area under the curve.

Precision

The precision of the assay was determined by repeatability (intra-day) and intermediate precision (Inter-day). Repeatability was evaluated by assaying samples, at same concentration and during the same day. The intermediate precision was studied by comparing the assays on different days (3 days).

Accuracy

The accuracy was determined by recovery of known amounts of meropenem reference standard added to the samples at the beginning of the process. For the UV method, an accurately weighed amount of powder for injection equivalent to 25mg of meropenem was transferred to 50 ml volumetric flask and dissolved in distilled water (final concentration of 500 µg/ml /ml). Aliquots of 25 ml of this solution were transferred into 50 ml volumetric flasks containing11.9, 14.9and 17.8ml of meropenem standard solution (100 µg /ml) and distilled water was added to make up to volume to give a final concentrations of 26.8, 29.8 and 32.7µg/ml. All solutions were prepared in triplicate and assay.

Limit of detection and limit of quantitation

The parameters LOD and LOQ were determined on the basis of response and slope of the regression equation.

RESULTS AND DISCUSSION

Table-1 OPTICAL CHARACTERISTICS OF THE PROPOSED METHODS

PARAMETER	FIRST ORDER DERIVATIVE	AREA UNDER CURVE
Linearity	10-50 µg/ml	5-45 µg/ml
Regression equation (Y = a+ bc)*	$Y = -0.001 + 0.0015c$	$Y = 0.158 + 0.2039c$
slope (b)	0.0015	0.2039

intercept (a)	– 0.001	0.158
% RSD	1.97	1.20
Correlation coefficient	0.9994	0.9997
Limit of detection	1.89	0.73
Limit of quantitation	5.72	2.21

*y= bc+ a where c is the concentration of meropenem in µg/ml and y is absorbance unit

Table-2 Result of marketed formulation analysis

Method	Label claim	% label claim* Mean ± SD	% RSD
Derivative spectroscopy	250 mg	99.97 ± 0.24	0.97
Area under the curve	250 mg	99.85 ± 0.64	0.67

*Average of six determinations

Table-3 Percentage Recovery studies of meropenem

METHOD	Recovery level	% recovery	SD
		Meropenem	
Method A	80 %	98.63	±0.52
	100 %	100	±0.14
	120 %	99.52	±0.39
Method B	80 %	99.16	±0.87
	100 %	99.33	±0.54
	120 %	100.55	±0.63

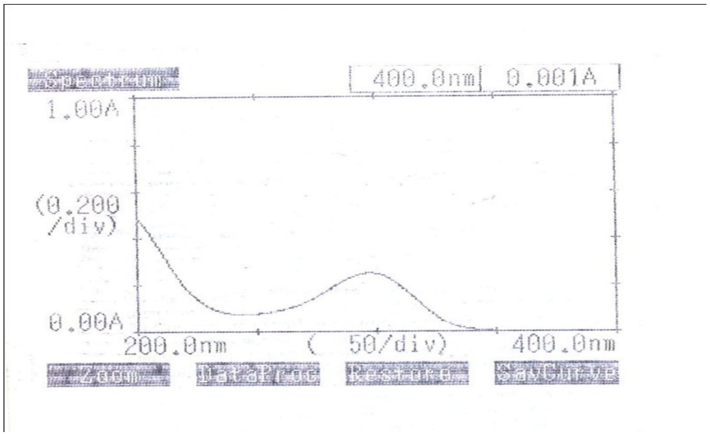


Fig 2: Zero order spectra of meropenem (10µg/ml)

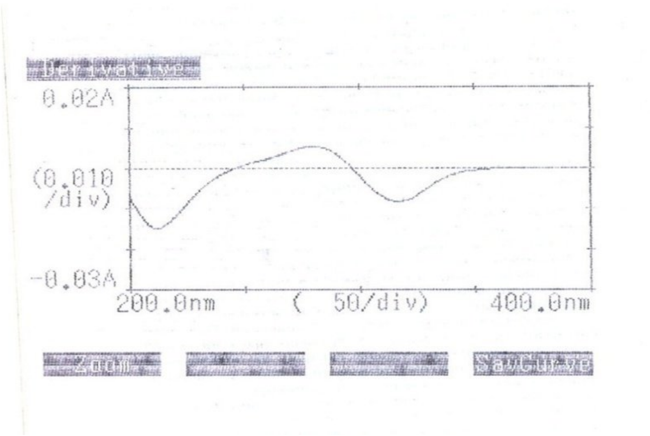
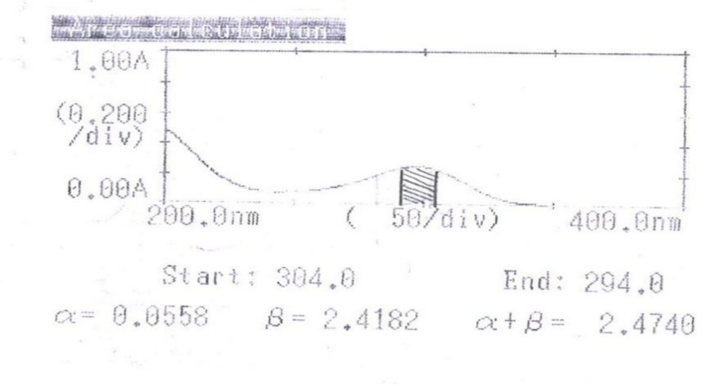


Fig 3: First order derivative spectra of meropenem (10μg/ml)



Start: 304.0 End: 294.0
α= 0.0558 β= 2.4182 α+β= 2.4740

Fig 4: Spectra of meropenem for AUC

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CONCLUSION

The spectrophotometric methods were developed and validated as per ICH guidelines. The standard deviation and % RSD calculated for the proposed methods are within limits, indicating high degree of precision of the methods. The results of the recovery studies performed indicate the methods to be accurate. Hence, it can be concluded that the developed spectrophotometric methods are accurate, precise and can be employed successfully for the estimation of meropenem in pharmaceutical dosage form.

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