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Spectrophotometric Method for the Estimation of Meropenem in Pure and in Market Formulation Meronem

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Abstract
Cost effective, sensitive, rapid and simple spectrophotometric method was described for the determination of Meropenem in pure form and in pharmaceutical formulations. The proposed methods were based on the formation of chelating complex between meropenem and gold ion (III). This method was applied for the determination of drug meropenem in pharmaceutical formulation meronem and enabled the determination of the selected drug in microgram quantities The colored species has an absorption maximum at 477 nm for MRP-Au(III) complex and obeys beer's law in the concentration range 15-70 µg/mL of Meropenem. The molar absorptivity was 0.818 $x10^{-3}$ and sandell's sensitivity was $4.6883x10^{-7}$. The slope is 0.0022. The intercept of the equation of the regression line is -0.0009. 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 Meropenem in pharmaceutical formulation.
Keywords: Meropenem, chelating complex, Spectrophotometry.

Introduction

Meropenem (Fig.1) is an ultra-broad spectrum injectable antibiotic used to treat a wide variety of infections, including meningitis and pneumonia. It is a beta-lactam and belongs to the subgroup of carbapenem, similar to imipenem and ertapenem (AHFS 2006).it is highly resistant to degradation by beta-lactamases or cephalosporinases. Resistance generally arises due to mutations in penicillin binding proteins, production of metallo-beta-lactamases, or resistance to diffusion across the bacterial outer membrane (Mosby's Drug Consult 2006). Meropenem acts by interfering with their ability to form cell walls, and therefore the bacteria break up and die (Sean. 1999). Meropenem [Fig.1] (4R, 5S. 6S) – 3 - [(2S, 5S) – 5 – (Dimethyl Carbamoyl) Pyrrolidin -2 yl [Sulfanyl -6 – (1-hydroxy ethyl) – 4 – methyl – 7- Oxo – 1 – azabicyclo hept – 2 ene – 2 carboxylic acid (Zhanel *et al*. 2007). Literature survey reveals that the drugs were determined by using HPLC and some spectrophotometric methods (Chaudhary *et al*. 2010; Ayan *et al*. 2011; Garcia *et al.* 1997; Srinivasa & Saraswathi 2011; Zhao *et al*. 2011; Forsyth et al. 1994; Venkateswara *et al*. 2012). Capillary electrophoresis (Mendeg *et al*. 2005). UV spectrophotometry [Cielecka-Piontek *et al*. 2013; Venkateswararao *et al*. 2013; Judyta et al. 2011). Liquid chromatography-tandem mass spectroscopy (LC–MS–MS) method in peritoneal fluid (Karjagin 2008).

2.Materials & Methods

2.1Apparatus

All spectral characteristics and absorbance measurements were made on double beam Ultraviolet /Visible spectrophotometer (Shimadzu UV-Visible spectrophotometer) with 10 mm matched quartz cells. Infrared spectrum for the produced complex was recorded on Shimadzu Fourier Transform Infrared model FT-IR8000.for pH measurement it's used (Philips, pw 9420 PH meter). Digital accurate balance (Sartorius, BL 210 S)

2.2Reagents and chemicals

Meropenem and pharmaceutical formulation Meronem (Injection powder of meropenem), gold chloride $AuCl_3$ (BDH), hydrochloric acid, sodium hydroxide was purchased from local market.

2.3 Standard solution and working solution preparation

Double distilled water was used as solvent. Stock standard solution of 1000 µg mL^{-1} was prepared by dissolving 0.1g of meropenem in sufficient distilled water and diluted to 100 mL in volumetric flask. Working standard solution of Meropenem (250 µg mL^{-1}) was prepared by dilution of 25 mL stock standard solution with distilled water to100 mL volumetric flask. Stock standard solution was stable for several weeks at room temperature. A100 µg mL^{-1} of gold chloride was prepared by dissolving 0.1541 g of $AuCl_3$ in double distilled water and diluted to 100 mL into a volumetric flask.

2.4 General Procedure & Analytical Curves

2.4.1 Direct Calibration Method

Different aliquots of (0.6 to 2.8 mL) of working standard solution of Meropenem (MRP) (250 µg mL^{-1}) were transferred into a series of 10 mL volumetric flask, to provide final concentration range of 15 – 70 µg mL^{-1}. Then 0.55 mL of 1000 µg Au mL^{-1} was added to each flask. And kept aside for 5 min. then diluted to 10 mL with distilled water .The absorbance of each solution was measured at 477 nm against the reagent blank. The calibration graph was then prepared by plotting the absorbance versus the concentration of MEP. The concentration of the Meronem samples was computed from the regression equation.

2.4.2 Sample Preparation of Drug Meronem

10 vials of Meronem were mixed in a clean agate mortar , A quantity of 0.05 g of fine powder was dissolved in sufficient distilled water with continuous shaking for about 10 min, then transferred into 100 mL volumetric flask, then the volume was made up to the mark with the distilled water.

2.4.3 Standard Additions Method

Aliquots of 0.5 mL the above–prepared Meronem sample solution were pipetted into thirteen of 10 ml calibrated flaks containing 0.600, 0.800, 1.000, 1.200, 1.400, 1.700, 1.800, 2.000, 2.200, 2.400, 2.600, 2.800 mL of 250 µg MRP mL^{-1} then same steps were preceded according to the procedure previously mentioned under direct calibration method.

3. Results & Discussion

3.1Optimization of Conditions on absorption spectrum of the reaction product

3.1.1 Effect of Au (III) concentration:

It was found that the absorbance of MRP-Au(III) complex increases as the concentration of gold (III) ion increases and then deviate towards the Au concentration axis Fig.2. Consequently, the optimum concentration 55 µg Au mL^{-1} was selected to complete formation of chelating complex.

3.1.2 Effect of pH value:

It is evident from Fig.3 that the absorbance increased gradually from pH 1 and reaches to maximum value at pH 3.5 and then the absorbance decreased by increasing pH because of the dissociation of complex, consequently the optimum pH of 3.5 was selected for complete formation of chelating complex.

3.1.3 Reaction time and stability of the chelating complex:

The optimum reaction time was determined by following the absorbance increment at the λ max of the formed complex Fig.4**.** It was found Maximum absorbance was developed at room temperature within 4 minutes of mixing the reactants and the chelating complex MRP-Au(III) was stable for 48 hours.

3.2 Suggested Structure of the Complex

An FTIR spectra of Meropenem and its complex are similar and the main frequencies can be seen in (Fig 5 and 6). The stretching vibrations of the C=O bond in the β-lactam ring were located at 1887cm^{-1} of meropenem while the bands related to the stretching vibrations of the C-N bond in the β-lactam ring were also observed at 1135 cm^{-1}. The range1600-1900 cm^{-1} exhibited distinct bands related to the stretching vibrations of the C=C and C=O bonds. The complexes show these bands at around 1810-1830 and 1100-1110 cm^{-1} ranges respectively. All this suggests that coordination of the ligand occurs through the oxygen and the nitrogen atoms of the lactam ring. The lactam carbonyl and nitrogen bands were substantially shifted toward lower frequencies (30-50 cm^{-1}) relative to the value of the uncomplexed meropenem.

3.3Analytical Validation

Under the experimental conditions described above, the calibration graphs for the MRP-Au(III) constructed by plotting absorbance versus concentration in µg mL^{-1} Conformity with Beer's law was evident in the concentration ranges cited in Table1. Regression equations, intercepts, slopes correlation coefficient, Limit of Detection (LOD) , limit of quantification (LOQ) Sandell's sensitivity and The molar absorptivity for the complex for the calibration data were presented in Table1.The validity of the methods for the assay of MRP was examined by determining the precision and accuracy. These were determined by analyzing five replicates of the drug within the Beer's law limits. Using the recommended procedure previously mentioned under section (2.2.4). The results are given in Table 2. The average percent recoveries obtained were quantitative indicating good accuracy of the method.

3.4 Determination of MRP in Meronem

The proposed method was applied for the detection of MRP in Meronem (powder for injection) vials with stated value of 1000 mg per unit by using direct calibration and standard additions procedures (Fig.8) under optimum conditions. The MRP was determined through measuring the absorbance of the complex results from the reaction of MRP present in the pharmaceutical preparation with gold (III) ion and found to be 991.19 and

987.77 mg / unit with relative error of (-0.88%) and(-1.22%) respectively.
It can also be observed from (Fig.8), that the ratio of the slopes of the direct calibration and standard additions is found to be the same, which indicates that the interferences resulting from drug constituents are insignificant using the proposed procedure. Thus, it is possible to use direct calibration procedure for the determination of MRP in drugs without need the standard additions method which requires more effort, more amount of sample and time-consuming. This is also support the specificity of the proposed method, indicating that the excipients did not interfere with the analysis of MRP.

4 Conclusions

The method that proposed in this work for the quantitation of Meropenem was simple, rapid, accurate and precise. The proposed method is also inexpensive due to use of distilled water for the dilution. Therefore, this method can be used for routine analysis of Meropenem in bulk and pharmaceutical formulations like vial.

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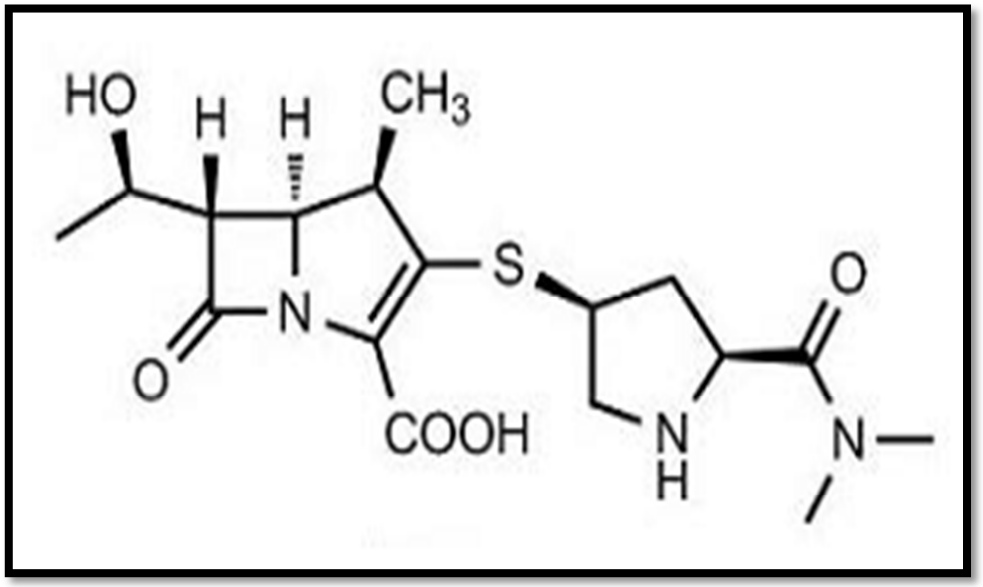

Figure 1: Structure of Meropenem

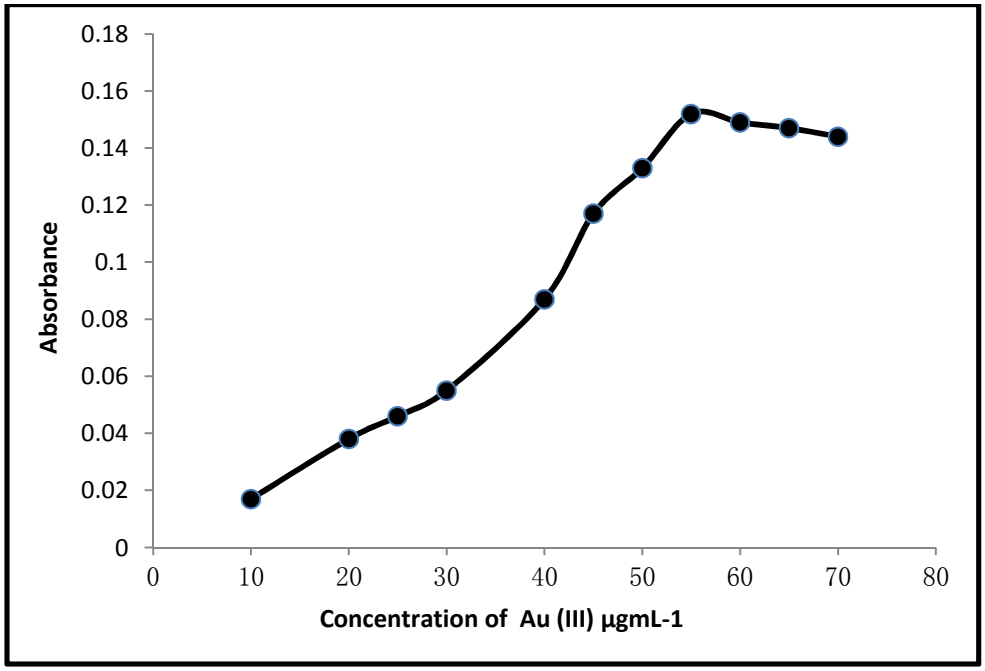

Figure 2: The effect of Au (III) ion concentration on the formation of MRP- Au(III) complex

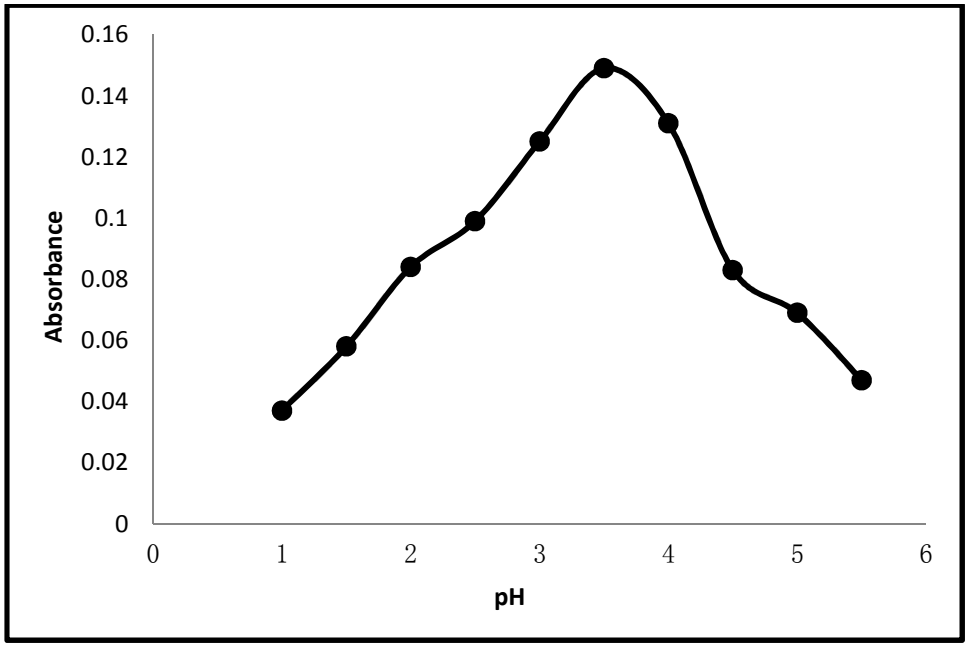

Figure 3: The effect of pH on the formation of MRP-Au(III) complex.

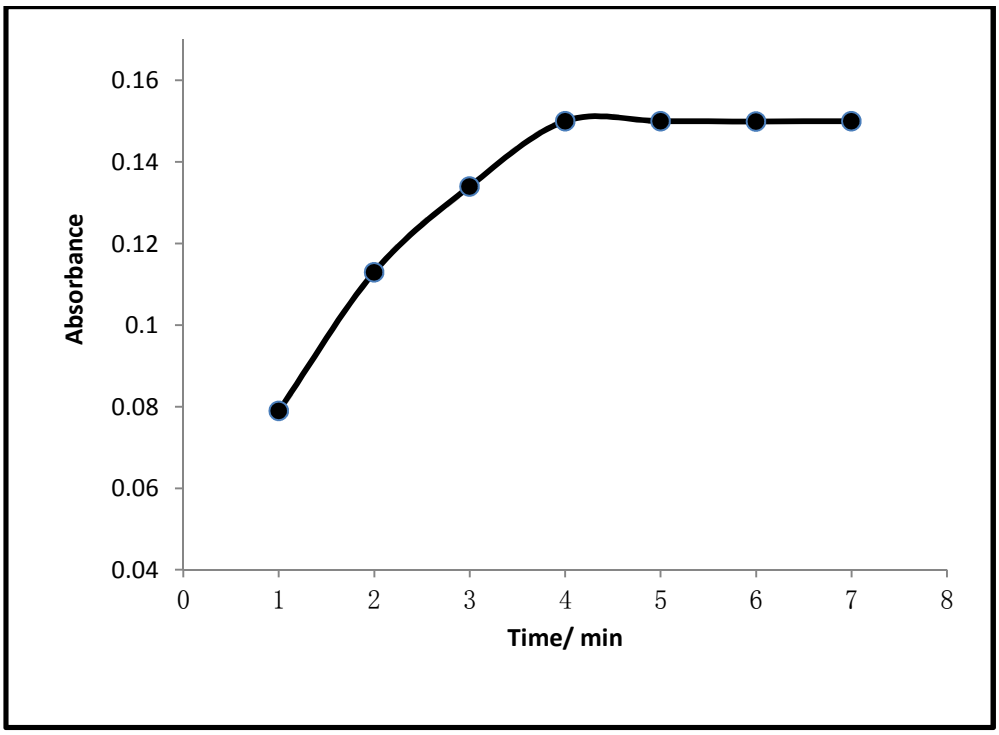

Figure 4: Effect of reaction time on the determination of MRP-Au(III) complex.

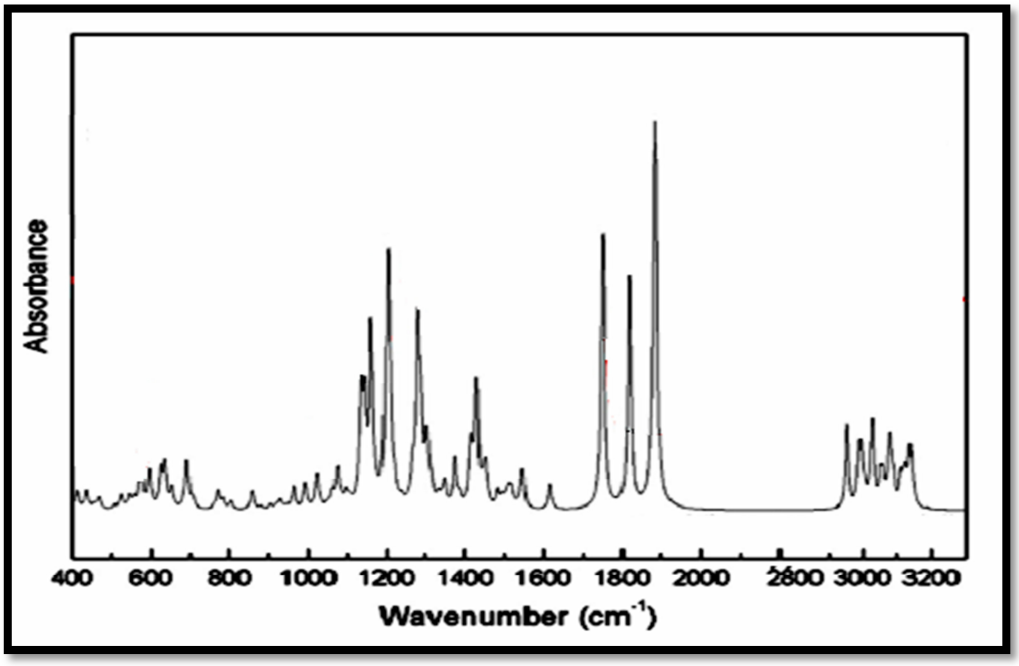

Figure 5: FTIR spectra of meropenem.

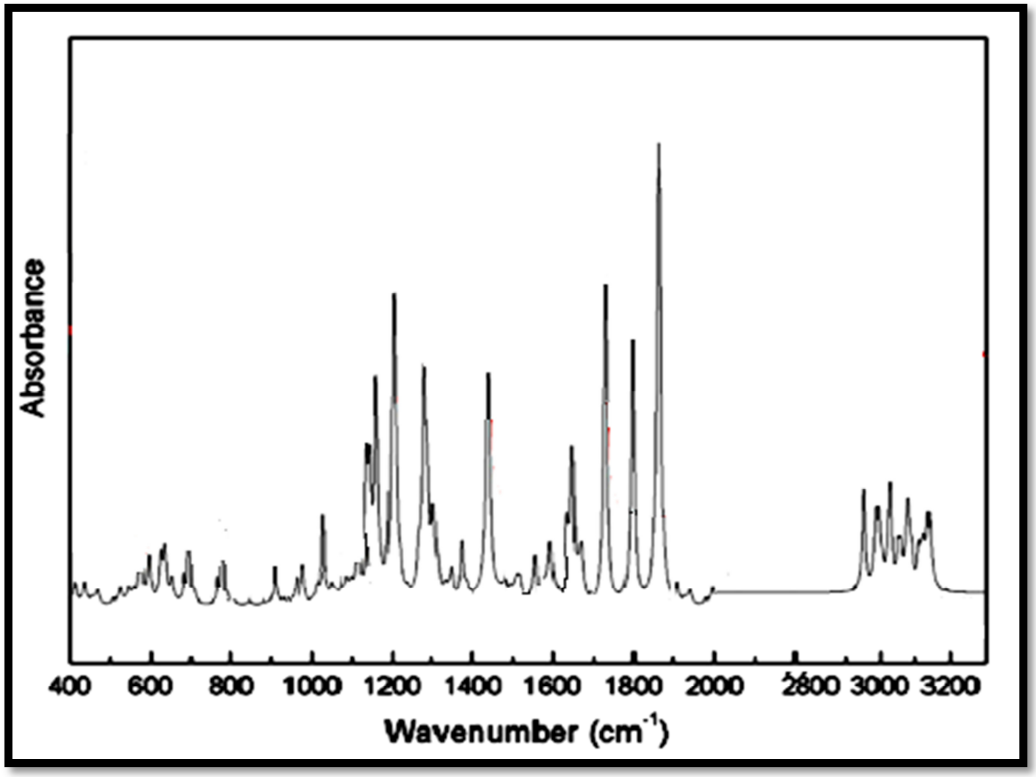

Figure 6: FTIR spectra of MRP-Au(III) complex

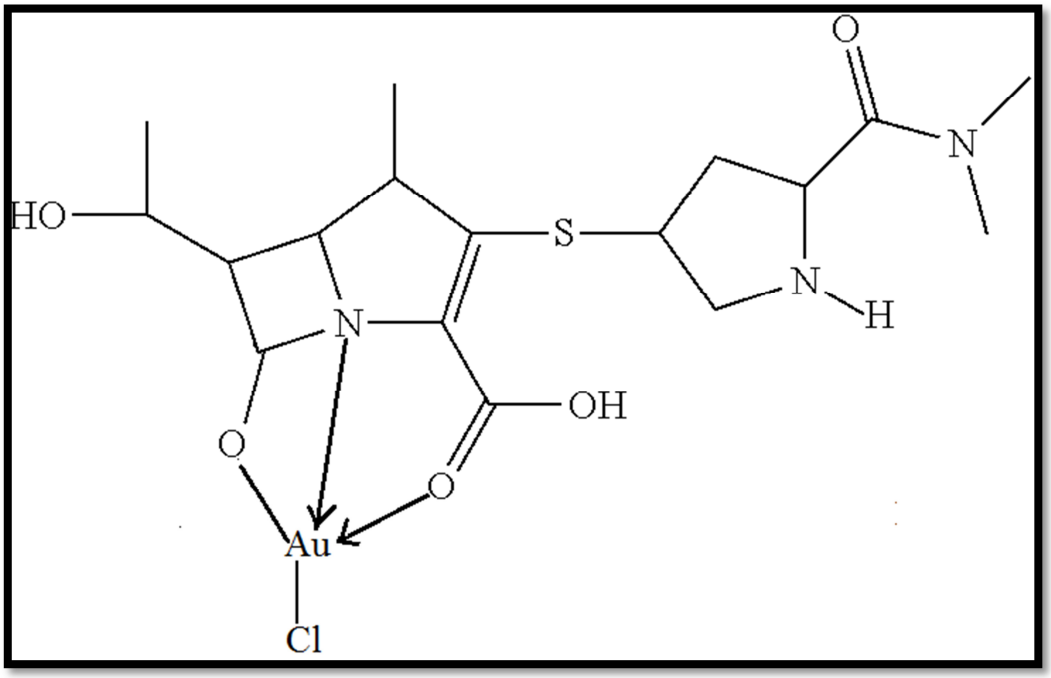

Figure 7: Predicted structure of MRP-Au(III) complex

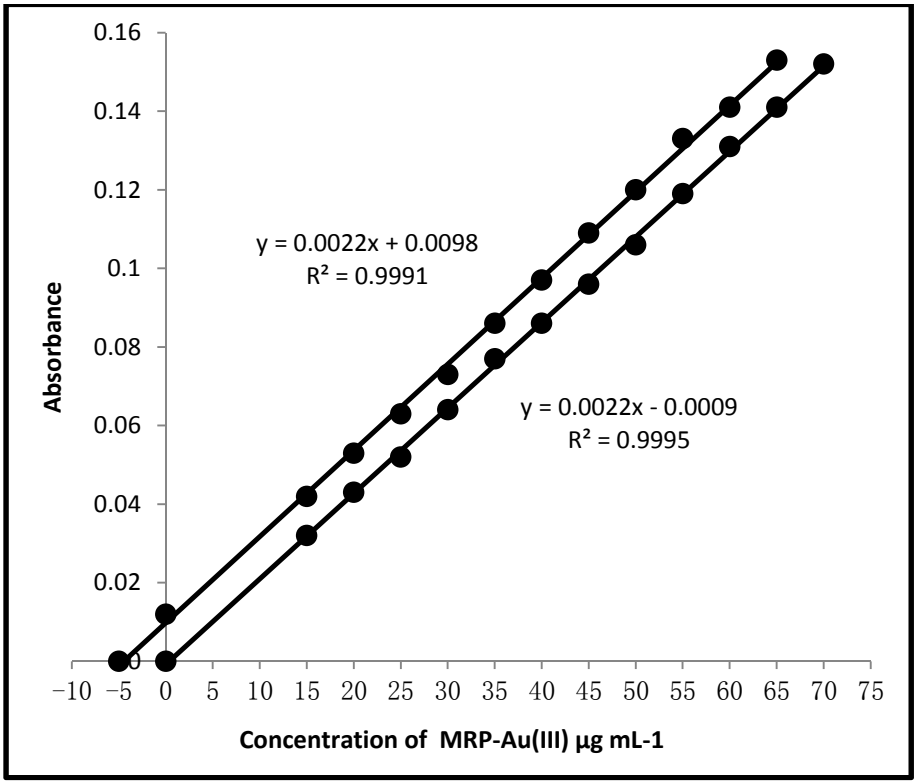

Figure 8: Determination of MRP in pharmaceuticals by using direct and standard additions Procedures

Table 1: Collective performance data for the analysis of meropenem by the proposed method.

Analytical parameters	Values
λmax (nm)	533
Beer's law limits (µg.ml^{-1})	15 – 70
Correlation coefficient (r^2)	0.9995
Regression equation (y=bx+a)	y= 0.0022x + 0.0009
Slope (b)	0.0022
Intercept (a)	0.0009
LOD (µg.ml^{-1})	0.021
LOQ (µg.ml^{-1})	0.37
Molar absorptivity (Ɛ) (L mol^{-1} cm^{-1})	0.818 x10^{3}
Sandell's sensitivity (S) (mg.cm-^{2})	4.6883x10^{-7}

Table 2: The accuracy and precision of the proposed method for the determination MRP in pharmaceutical preparation.

Amount of Levofloxacin taken (µg.mL^{-1})	Amount of Levofloxacin found (µg.mL^{-1})	%Rec.	%$E_{rel.}$	%RSD n = 5	Conf. Limit. for %Rec.±S.D	Mean %$E_{rel.}$
25	25.36	101.44	1.44	1.51	101.47 ± 0.87	1.47
45	45..73	101.62	1.62	1.27		
65	65.88	101.35	1.35	0.93		

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