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New spectrophotometric microdetermination of carbapenem antibiotics derivatives in pharmaceutical formulations

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Abstract

A new sensitive spectrophotometric method was developed to determine three carbapenem antibiotics: imipenem, meropenem and ertapenem. The proposed method was based on the formation of the coloured tris(o-phenanthroline)-iron(II) complex (ferroin) [Phen] or Fe (II)-2,2′-bipyridyl complex [Bip] in the reaction of the tested drugs with the corresponding iron (III)-complexes in an acetate pH 4 buffer. The formed coloured complexes showed maximum absorbance at 510 and 520 nm for [Phen] and [Bip], respectively. The reaction conditions, including the pH, reagent concentration, reaction time, temperature and stability of the formed coloured species, were optimized to achieve the highest sensitivity. Linear calibration curves were obtained in the concentration ranges from 0.2 to 10, 0.5 to 10 and 0.5 to 10 $\mu g\,mL^{-1}$ for the aforementioned drugs in the same order. The developed method was successfully applied to determine the investigated carbapenems in their pharmaceutical formulations with average recoveries of 100.8, 99.8 and 99.4% for the Phen method and 98.9, 101.7 and 100.6% for the Bip method for imipenem, meropenem and ertapenem, respectively. A statistical comparison of the results with the reference method showed good concurrence and indicated no significant difference in accuracy or precision.

Keywords: Carbapenem antibiotics; Spectrophotometry; Oxidation reaction; Pharmaceutical analysis

1. Introduction

Carbapenems are β-lactam antibiotics, such as penicillins and cephalosporins, that inhibit bacterial cell wall synthesis by binding to penicillin-binding proteins (PBP) [1,2]. The analogues of carbapenem (imipenem, {(5*R*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-3-({2-[(iminomethyl)amino]ethyl}thio)-7-oxo-1-azabicyclo[3.2.0] hept-2-ene-2-carboxylic acid}), meropenem, ({3-[5-(dimethylcarbamoyl) pyrrolidin-2-yl] sulfanyl-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0] hept-2-ene-2-carboxylic acid), and ertapenem ({(4*R*,5*S*,6*S*)-3-[(3*S*,5*S*)-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}), which are used in treatment, have an exceptionally broad spectrum of antibacterial activity. Since the late 1970s, when thienamycin was discovered, the next analogues of carbapenem have been introduced into

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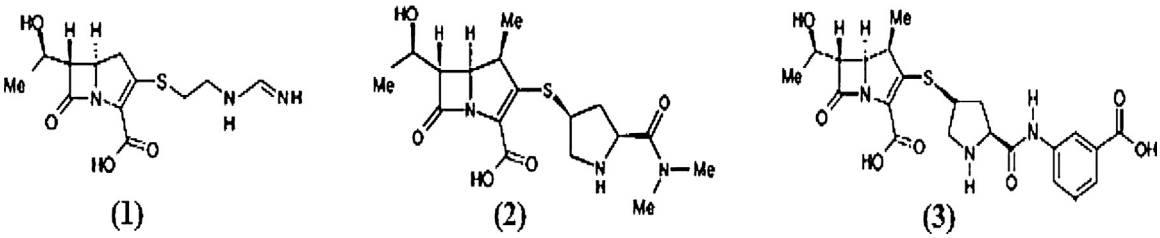

Fig. 1. Chemical structures of imipenem (1), meropenem (2), and ertapenem (3).

therapeutic use, which include imipenem, panipenem, meropenem, ertapenem, biapenem and doripenem. The three carbapenems currently under investigation using the developed method are imipenem, meropenem and ertapenem (Fig. 1).

Several analytical techniques were published for carbapenem analysis [3]. Currently, the most common techniques are chromatographic methods [4–8]. In addition to the chromatographic methods, capillary zone electrophoresis [9,10] and a microbiological assay [11] were also reported. The determination of imipenem and its metabolites in human urine and pharmaceutical formulations using electrochemical methods were reported [12,13]. The electrochemical protocol was performed in phosphate buffer solutions over a pH range of 2.0 to 8.0 using differential pulse polarography, cathodic adsorptive stripping voltammetry, cyclic voltammetry, linear sweep voltammetry and adsorptive stripping voltammetry. The proposed methods have been used for the direct determination of imipenem in spiked human urine and real human-derived urine with good results and should be appropriate for monitoring purposes with a detection limit of 0.28 $\mu g\,L^{-1}$ imipenem.

Spectrophotometric methods were also reported for the determination of carbapenems. Classic UV spectrophotometry has been used to estimate meropenem in powder for injection (wavelength is 298 nm) [14], and first-derivative bivariate procedures have been applied to determine meropenem in the presence of its metabolite (open-ring degradation product) [15]. The UV methods are notably simple, rapid and economical, and they enable drug determination with sufficient reliability.

Drug quality control is a branch of analytical chemistry with a wide impact on public health; thus, the development of reliable, quick and accurate methods for active-ingredient determination is notably important. Spectrophotometric methods are the most commonly used techniques and continue to enjoy wide popularity [16–18]. The common availability of the instrumentation, simplicity of the procedures, and speed, precision and accuracy of the technique make spectrophotometric methods attractive. Redox reactions have been used as the basis to develop simple and sensitive spectrophotometric methods to determine many pharmaceutical compounds [19–21]. In oxidimetric reactions, the most commonly used oxidizing agents is Fe (III), which reduces to Fe (II), followed by complexation with either 1,10-phenanthroline [Phen] or 2,2′-bipyridyl [Bip] with an absorbance at 510 or 520 nm, respectively. The present study was dedicated to investigate the application of these reagents in a new spectrophotometric determination of three carbapenem derivatives (imipenem, meropenem and ertapenem) in their pharmaceutical dosage forms. The proposed methods can be used for quality control analysis, where modern and expensive apparatuses, such as GLC, HPLC and HPTLC, are not available.

2. Experimental

2.1. Materials and reagents

All chemicals were of analytical reagent grade, and double-distilled water was used throughout the experiments. The carbapenem pharmaceutical preparation vials were purchased from the Kingdom Saudi Arabia local drug stores. The pharmaceutical preparations were as follows: Tienam (Tienam*-500 imipenem/cilastain sodium, Merck Sharp & Dohme B.V. Harlem, Netherlands), Meronem (Meronem™, meropenem trihydrte 500 mg, Astra Zeneca UK limited, Macclesfield, Cheshire, Sk 10 2NA, United Kingdom) and Ertapenem (Invanz®, 1-g vials, BN: NE20790, labelled to contain 1 g of ertapenem (equivalent to 1.046 g of ertapenem sodium, 175 mg of sodium bicarbonate). The concentrations of the corresponding active ingredients were estimated according to the official methods [22,24]. Drug stock solutions (100 $\mu g\,m\,L^{-1}$) were always freshly prepared on the day of analysis and stored in a refrigerator to be used within 24 h.

Fe (III)-o-phenanthroline [Phen] reagent [25] was prepared by mixing 0.198 g of 1,10-phenanthroline monohydrate (Fluka, Swiss) with 2.0 mL of 1.0 M HCl and 0.16 g of ferric ammonium sulphate dodecahydrate