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Journal of Pharmaceutical and Biomedical Analysis 46 (2008) 52–57
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

A comparison of the stability of ertapenem and meropenem in pharmaceutical preparations in solid state

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Received 18 April 2007; received in revised form 19 July 2007; accepted 28 August 2007
Available online 1 September 2007

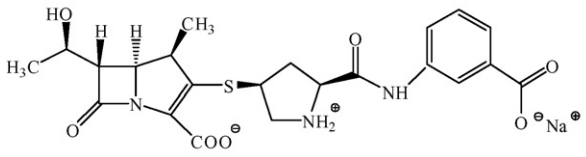
Abstract

The following first-order rate constants of the degradation of ertapenem in INVANZ and meropenem in MERONEM were determined: (a) in dry air at 363, 373, 378, 383, 388, 393 K; (b) at increased relative air humidity (76.4% RH) at 313, 323, 333 and 343 K; (c) at increased relative air humidity (50.9, 60.5, 66.5, 76.4% RH—ertapenem and 50.9, 66.5, 76.4 and 90.0% RH—meropenem) at 333 K. The dependence $\ln k_i = f(\mathrm{RH}\%)$ was described by the equations: $\ln k_i = (6.63 \pm 1.22) \times 10^{-2} \times (\mathrm{RH}\%) - 13.36 \pm 1.68$ (ertapenem) and $\ln k_i = (4.22 \pm 2.98) \times 10^{-2} \times (\mathrm{RH}\%) - 12.14 \pm 2.16$ (meropenem). The dependence $\ln k_i = f(1/T)$ was described by equations: $\ln k_i = 19.4 \pm 2.6 - (9230 \pm 800)(1/T)$ for ertapenem, at 76.4% RH; $\ln k_i = 11.5 \pm 4.9 - (9880 \pm 1800)(1/T)$ for ertapenem in dry air; $\ln k_i = 14.8 \pm 11.9 - (7785 \pm 3905)(1/T)$ for meropenem, at 76.4% RH; $\ln k_i = 37.6 \pm 7.73 - (18385 \pm 2930)(1/T)$ for meropenem in dry air. The thermodynamic parameters E_a, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ of the degradation of ertapenem and meropenem were calculated. The difference between the influence of temperature on the stability of ertapenem and meropenem was not significant at 76.4% RH. In dry air (363–393 K) this influence was greater in the case of meropenem. The degradation of ertapenem was slower in this temperature range. Humidity was a significant factor affecting the degradation of these antibiotics and it influenced their stability is similar ways.

Keywords: HPLC; Validation; Ertapenem; Meropenem; Stability in solid state; Kinetic and thermodynamic parameters

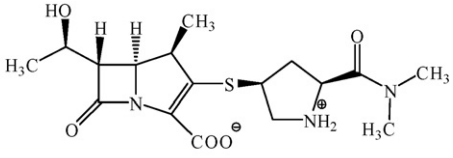
1. Introduction

Ertapenem and meropenem are parenteral carbapenems containing a 1-β-methyl group, which renders these antibiotics stable to renal dehydropeptidase (DHP-I) [1].



Ertapenem

Ertapenem and meropenem have a very broad spectrum of antibacterial activity against the majority of Gram-positive and Gram-negative bacteria [2]. Compared to ertapenem, meropenem is more active against *Enterobacteriaceae* and *Pseudomonas aeruginosa* [1]. The introduction of meta-substituted benzoic acid as a substituent into the structure of ertapenem increases the plasma half-life of ertapenem because of its greater affinity for plasma proteins [3].



Meropenem

Similarly to other β-lactam antibiotics, the carbapenems are easily degraded in aqueous solutions and in solid state. The hydrolysis of the β-lactam ring occurs in dilute aqueous solutions of ertapenem (<1 mg ml^{-1}) [4]. General and specific acid–base hydrolysis of ertapenem at pH 0.42–12.5, at 303, 313, 323 and 333 K was studied. Specific acid–base catalysis involves: (a) hydrolysis of ertapenem catalysed by

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doi:10.1016/j.jpba.2007.08.024

hydrogen ions; (b) hydrolysis of ertapenem dianions catalysed by hydroxide ions; (c) spontaneous hydrolysis of zwitter ions and dianions of ertapenem under the influence of water. The thermodynamic parameters of these reactions were calculated. It was observed that buffer catalysis occurred in acetate, phosphate and borate buffers [5]. The stability of ertapenem in solutions of sodium chloride, sodium lactate, sodium bicarbonate, mannitol, dextrose and Ringer's solution, at 25 and 4 °C [6], was also studied. When the concentration of ertapenem is high ($\geq$100 mg ml^{-1}) dimerization products are formed [4]. During the manufacture and purification of ertapenem, a methanolysis product, an oxazinone derivative and acetic acid adduct were also observed [7]. The gradient HPLC method was used to separate ertapenem and its degradation products [4,8].

The stability of meropenem at pH 4–8, at 298, 308 and 313 K was analysed. The relationship $k_{pH} = f(pH)$ involved the following reactions: hydrogen- and hydroxide-ion-catalysed reactions and spontaneous hydrolysis under the influence of water. The hydrolysis of meropenem was also catalysed by phosphate ions (HPO_4^{2-}). As degradation products, the β-lactam hydrolysed product and the dimer product resulting from intermolecular aminolysis of the β-lactam ring by the amine of the second molecule were described [9]. The stability of meropenem in various *i.v.* fluids stored in various containers for *i.v.* use was also studied [10].

The stability of meropenem (powder for injection) in solid state was investigated at 343, 353 and 363 K. First-order rate constants, $t_{1/2}$ and t_{90}, at each temperature were calculated [11].

The aim of this work was compare the stability of ertapenem and meropenem in pharmaceutical preparations in solid state in dry air and at increased relative air humidity at various temperature. An HPLC method described in our previous paper [12] was used to determine the stability of ertapenem in solid state. In order to investigate the stability of meropenem in solid state an modified method was developed [13].

2. Experimental

2.1. Chemicals and reagents

In the study pharmaceutical preparations of meropenem (MERONEM) and ertapenem (INVANZ) were used. They were sterile, white to off-white powders for injections. One vial of MERONEM (AstraZeneca, London, UK) contained 500 mg of meropenem (as anhydrous base) and 104 mg of anhydrous sodium carbonate as excipient. Each vial of INVANZ (Merck & Co. Inc. Whitehouse Station, NJ, USA) contained 1.046 g of ertapenem sodium (equivalent to 1 g of ertapenem) and inactive ingredients: 175 mg of sodium bicarbonate and sodium hydroxide to adjust pH to 7.5.

Diprophylline (conforming to FP VI) was used as an internal standard (IS) in both HPLC methods. All other chemicals and solvents were obtained from Merck KGaA (Germany) and were of analytical or high-performance liquid chromatographic grade.

2.2. Chromatographic conditions

Chromatographic separation and quantitative determination of both carbapenems were performed by using a high-performance liquid chromatograph equipped with an LC-6A pump (Shimadzu), a UV–vis (SPD-6AV) detector (Shimadzu), a Rheodyne 7120 with a 50 μl loop. As the stationary phase a LiChrospher RP-18, 5 μm particle size, 250 mm × 4 mm (Merck, Darmstadt, Germany) was used. The mobile phase consisted of 15 volumes of methanol and 85 volumes of phosphate buffer (pH 6.5), 25 mmol l^{-1} (ertapenem), 8 volumes of acetonitrile and 92 volumes of ammonium acetate, 12 mmol l^{-1} (meropenem). The flow rate of the mobile phase was 1.2 ml min^{-1} and the wavelength of the UV–vis detector was set at 298 nm.

2.3. Method validation

Both methods were validated according to the guidelines of the International Conference on Harmonisation [14].

2.3.1. Specificity

The specificity of the HPLC methods was evaluated for non-degraded and degraded samples of powder for injections (samples stored at 373 K in dry air and at 333 K, at 76.4% RH).

2.3.2. Linearity

The calibration curves $P/P_{IS} = f(c)$ were obtained in the concentration ranges (1.07–6.41) × 10^{-2} mg ml^{-1} (ertapenem) and (0.49–9.95) × 10^{-2} mg ml^{-1} (meropenem), where P/P_{IS} is the ratio of peak areas of ertapenem or meropenem to the peak area of diprophylline (internal standard).

2.3.3. Precision

To evaluate the repeatability (intra-day) eight samples were determined for concentration of ertapenem 4.27 × 10^{-2} mg ml^{-1} and for meropenem 9.95 × 10^{-3} mg ml^{-1}.

2.3.4. Detection and quantitation limits

The LOD and LOQ were calculated from the regression equation $P/P_{IS} = f(c)$; LOD = $3.3S_y/a$, LOQ = $10S_y/a$, where S_y is the standard deviation and a the slope of the corresponding calibration curve.

2.4. Kinetic studies

For the forced aging test 5 mg samples of INVANZ (equivalent to 3.025 mg of ertapenem sodium) and 10 mg samples of MERONEM (equivalent to 7.418 mg of meropenem) were weighed into 5 ml vials. To evaluate their stability in dry air, the vials were immersed in a sand bath placed in heat chambers at 363, 373, 378, 383, 388, 393 K. The samples to be examined at increased air humidity were placed in heat chambers at 313, 323, 333, 343 K, in desiccators containing saturated solutions of inorganic salts: sodium bromide (50.9% RH), potassium iodide (60.5% RH), sodium nitrate (66.5% RH), sodium chloride (76.4% RH) and zinc sulfate (90.0% RH) [15].