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

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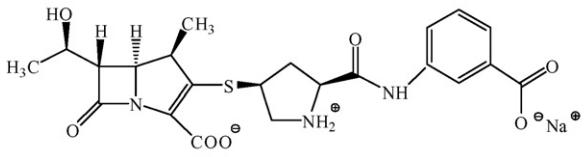
Abstract

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

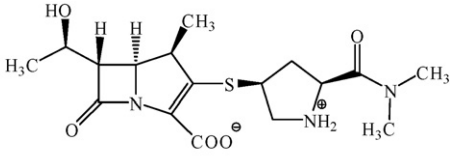
1. Introduction

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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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].

Table 1
The time periods during which the samples were studied and the intervals at which they were collected

Ertapenem			Meropenem		
Temperature (K)	Period	Frequency	Temperature (K)	Period	Frequency
76.4% RH					
343	0–120 min	10 min	343	0–160 min	15 min
333	0–210 min	15 min	333	0–135 min	15 min
323	0–8 h	1.0 h	323	0–7 h	0.5 h
313	0–18 h	1.0 h	313	0–10 h	1.0 h
0% RH					
393	0–408 h	24 h	393	0–6 h	0.5 h
388	0–869 h	48 h	388	0–18 h	0.5 h
383	0–869 h	48 h	383	0–14 h	1.0 h
378	0–839 h	48 h	378	0–20 h	1.0 h
373	0–839 h	30 h	373	0–48 h	3.0 h
			363	0–48 h	3.0 h
RH (%)	Period	Frequency	RH (%)	Period	Frequency
$T = 333$ K					
50.9	0–1440 min	90 min	50.9	0–9 h	60 min
60.5	0–600 min	30 min	66.5	0–14 h	30 min
66.5	0–420 min	30 min	76.4	0–135 min	15 min
76.4	0–210 min	15 min	90.0	0–180 min	10 min

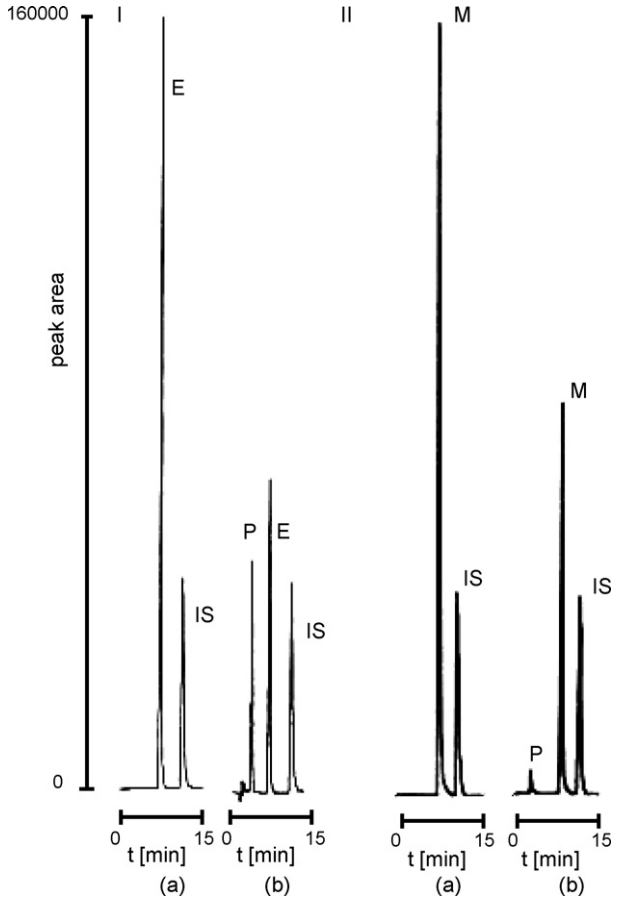

Fig. 1. HPLC chromatograms of ertapenem (E), meropenem (M), their degradation products (P) and internal standard (IS): Ia and IIa at $t = 0$ min; Ib after 20 h at 388 K, 0% RH; IIb after 4 h at 323 K, 76.4% RH.

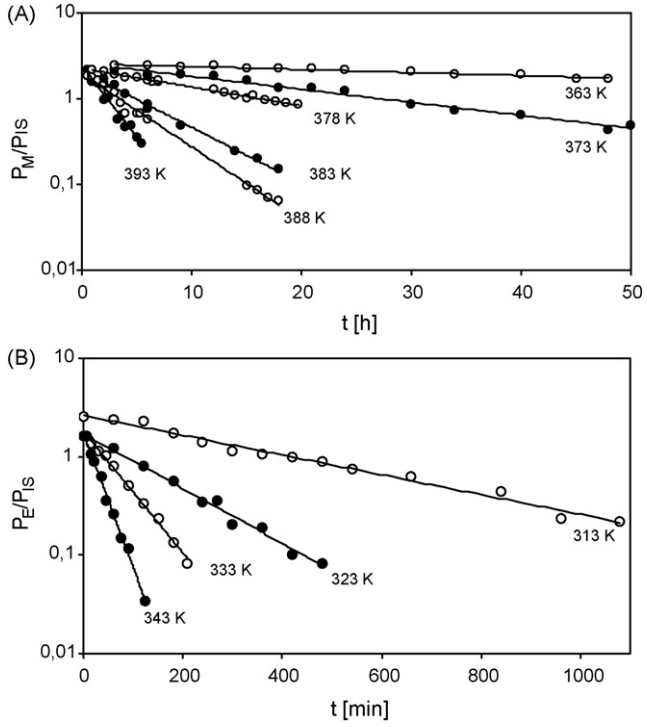

Fig. 2. Semilogarithmic plots $P_M/P_{IS} = f(t)$ for the degradation of meropenem in dry air (A) and $P_E/P_{IS} = f(t)$ for the degradation of ertapenem (B) at 76.4% RH, in solid state at various temperatures.

Table 2
Kinetic and thermodynamic parameters of the degradation of ertapenem and meropenem in solid state at 76.4% RH and at 0% RH

Temperature (K)	10^4 $(k \pm \Delta k)$ (s^{-1})	Statistical evaluation $\ln k_i = f(1/T)$	Thermodynamic parameters
76.4% RH			
Ertapenem			
313	0.39 ± 0.17	$a = -9230 \pm 800$, $S_a = 266$, $b = 19.4 \pm 2.6$, $S_b = 0.81$, $r = 0.9992$, $S_y = 0.06$	$E_a = 76.9 \pm 6.6$ (kJ mol^{-1}), $\Delta H^{\neq a} = 74.3 \pm 9.1$ (kJ mol^{-1}), $\Delta S^{\neq a} = 84.8 \pm 223$ (kJ mol^{-1})
323	1.07 ± 0.35		
333	2.35 ± 0.01		
343	5.23 ± 0.02		
Meropenem			
313	0.43 ± 0.29	$a = -7785 \pm 3905$, $S_a = 907$, $b = 14.8 \pm 11.9$, $S_b = 2.77$, $r = 0.9867$, $S_y = 0.1890$	$E_a = 64.7 \pm 32.5$ (kJ mol^{-1}), $\Delta H^{\neq a} = 62.2 \pm 34.9$ (kJ mol^{-1}), $\Delta S^{\neq a} = -122 \pm 146$ (J K^{-1} mol^{-1})
323	0.94 ± 0.80		
333	1.44 ± 0.18		
343	4.19 ± 0.31		
Temperature (K)	10^7 $(k \pm \Delta k)$ (s^{-1})	Statistical evaluation $\ln k_i = f(1/T)$	Thermodynamic parameters
0% RH			
Ertapenem			
373	3.08 ± 2.38	$a = -9880 \pm 1800$, $S_a = 5990$, $b = 11.50 \pm 4.9$, $S_b = 1.53$, $r = 0.9945$, $S_y = 0.06$	$E_a = 82.1 \pm 14.9$ (kJ mol^{-1}), $\Delta H^{\neq a} = 79.67 \pm 17.4$ (kJ mol^{-1}), $\Delta S^{\neq a} = -149 \pm 203$ (J K^{-1} mol^{-1})
378	4.68 ± 3.17		
383	5.90 ± 2.62		
388	8.06 ± 3.47		
393	12.7 ± 0.51		
Temperature (K)	10^5 $(k \pm \Delta k)$ (s^{-1})	Statistical evaluation $\ln k_i = f(1/T)$	Thermodynamic parameters
0% RH			
Meropenem			
363	0.22 ± 0.04	$a = -18385 \pm 2930$, $S_a = 1055$, $b = 37.6 \pm 7.73$, $S_b = 2.79$, $r = 0.9935$, $S_y = 0.18$	$E_a = 158 \pm 24$ (kJ mol^{-1}), $\Delta H^{\neq a} = 150 \pm 27$ (kJ mol^{-1}), $\Delta S^{\neq a} = -68 \pm 181$ (J K^{-1} mol^{-1})
373	0.97 ± 0.09		
378	1.38 ± 0.07		
383	4.17 ± 0.34		
388	5.46 ± 0.27		
393	10.70 ± 1.30		

$\Delta k = S_a t_{\alpha f}$; E_a, activation energy; $\Delta H^{\neq}$, enthalpy; $\Delta S^{\neq}$, entropy; $E_a = -aR$; $\Delta H^{\neq} = E_a - RT$; $\Delta S^{\neq} = R(\ln A - \ln(k_B T)/h$, where k_B, Boltzmann constant (1.3807×10^{-23} J K^{-1}); h, Planck's constant (6.626×10^{-34} J s); R, universal gas constant (8.314 J K^{-1} mol^{-1}); T, temperature in K ($t + 273$ K); a, vectorial coefficient of the Arrhenius relationship; A, frequency coefficient.
[a] Calculated for 298 K.

At specified time intervals (Table 1), determined by the rate of degradation the vials were removed, cooled to room temperature and their contents were dissolved in distilled water. The so obtained solutions were quantitatively transferred into measuring flasks and diluted with water to 25.0 ml. To 1.0 ml of each of these solutions 2.0 ml of the internal standard (diprophylline 0.8 mg ml^{-1}) was added.

3. Results and discussion

3.1. The validation of the HPLC methods

The HPLC methods were found selective for the determination of ertapenem (E) and meropenem (M) in the presence of their degradation products (P) and diprophylline (internal standard), as shown in Fig. 1. The calibration plots were linear in the following concentration ranges: $(1.07–6.41) \times 10^{-2}$ mg ml^{-1} ($n = 11$, $r = 0.9988$) for ertapenem and $(0.49–9.95) \times 10^{-2}$ mg ml^{-1} ($n = 11$, $r = 0.9996$) for meropenem. The parameters of regression were calculated for $f = n - 2$ degrees of freedom and $\alpha = 0.05$. The calibration curves were described by the equation $y = ac$; $y = (46.44 \pm 1.70) \times c$ for ertapenem ($b = 0.0486$) and $y = (64.59 \pm 6.17) \times c$ for meropenem ($b = 0.0218$). The values b, calculated from equation $y = ac + b$, were not significant. The methods had good inter-day repeatability (R.S.D. = 1.25% for ertapenem and R.S.D. = 1.34% for meropenem). Under the applied chromatographic conditions, the LOD of ertapenem was 2.80×10^{-3} mg ml^{-1} and

Table 3
The effect of relative air humidity on the stability of ertapenem and meropenem at 333 K

Relative humidity (%)	10^4 ($k \pm \Delta k$) (s^{-1})	Statistical evaluation $\ln k_i = f(\mathrm{RH}\%)$
Ertapenem		
50.9	0.42 ± 0.21	$a = (6.63 \pm 1.22) \times 10^{-2}$, $S_a = 6.08 \times 10^{-3}$,
60.5	0.98 ± 0.45	$b = -13.36 \pm 1.68$, $S_b = 0.39$,
66.5	1.34 ± 0.45	$r = 0.9917$, $S_y = 0.11$
76.4	2.35 ± 0.01	
Meropenem		
50.9	0.39 ± 0.04	$a = (4.22 \pm 2.98) \times 10^{-2}$, $S_a = 6.93 \times 10^{-3}$,
66.5	1.07 ± 0.06	$b = -12.14 \pm 2.16$, $S_b = 0.50$,
76.4	1.44 ± 0.18	$r = 0.9741$, $S_y = 0.19$
90.0	2.10 ± 0.15	

of meropenem 1.89×10^{-3} mg ml^{-1} (0.14 μg of ertapenem and 0.094 μg of meropenem injected onto the column) and the LOQ of ertapenem was 8.44×10^{-3} mg ml^{-1} and of meropenem 5.64×10^{-3} mg ml^{-1} (equivalent to 0.42 μg of ertapenem and 0.28 μg of meropenem injected onto the column).

3.2. The kinetic parameters of the degradation of ertapenem and meropenem

The degradation of ertapenem and meropenem after incubation at increased relative air humidity (50.9–90.0% RH) and in dry air was a first-order reaction described by the following equation:

$$\ln\left(\frac{P}{P_{IS}}\right) = \ln\left(\frac{P}{P_{IS}}\right)_0 - k_{obs} \times t$$

During the degradation of ertapenem and meropenem the ratio P/P_{IS} decreased in the time interval $t_0 \rightarrow t_\infty$ from $(P/P_{IS})_{max}$ to $(P/P_{IS}) = 0$ (Fig. 2). The observed rate constants are equal to the slopes of the plots $\ln(P/P_{IS}) = f(t)$ with the negative sign ($-k_{obs}$) and are presented in Tables 2 and 3. The following statistical parameters of the equation were calculated by using the least squares method—$y = ax + b$: $a \pm \Delta a$, $b \pm \Delta b$, standard deviations S_a, S_b, S_y, and the coefficient of linear correlation r. The values Δa and Δb were calculated for $f = n - 2$ degrees of freedom and $\alpha = 0.05$.

3.3. The thermodynamic parameters of the degradation of ertapenem and meropenem

The relationship between the reaction rate constants and temperature is described by the Arrhenius equation: $\ln k_i = \ln A - E_a/RT$, where k_i: the reaction rates constants of ertapenem and meropenem (s^{-1}), A: frequency coefficient, E_a: activation energy [J mol^{-1}], R: the universal gas constant (8.3144 J K^{-1} mol^{-1}), and T: temperature (K).

The straight-line relationship $\ln k_i = f(1/T)$ was obtained for ertapenem and meropenem in the temperature range 313–343 K, at increased relative air humidity (76.4%), and in dry air in the temperature range 373–393 K (ertapenem) or 363–393 K (meropenem) (Fig. 3). The least squares method was used to calculate the slopes (a) and frequency coefficient (ln A), which allowed calculation of activation energy ($E_a = -a \times R$), enthalpy ($\Delta H^{\neq}$) and entropy ($\Delta S^{\neq}$) at 298 K (Table 2).

Although samples of ertapenem and meropenem which were subjected to the impact of humidity (76.4% RH) were decomposed at a higher rate, humidity did not influence the kinetic mechanism of ertapenem and meropenem degradation. A comparison of the thermodynamic parameters of degradation at 76.4% RH and 0% RH (the lower value of E_a for degradation at 76.4% RH) confirm a significant influence of humidity on the stability of ertapenem and meropenem in the solid state (Table 2).

The slopes of plots $\ln k_i = f(1/T)$ obtained at 76.4% RH and 0% RH were compared by using the parallelism test for the evaluation of the influence of temperature on ertapenem and meropenem stability in the solid state. At increased relative humidity the difference between the influence of temperature on the stability of ertapenem and of meropenem was not significant.

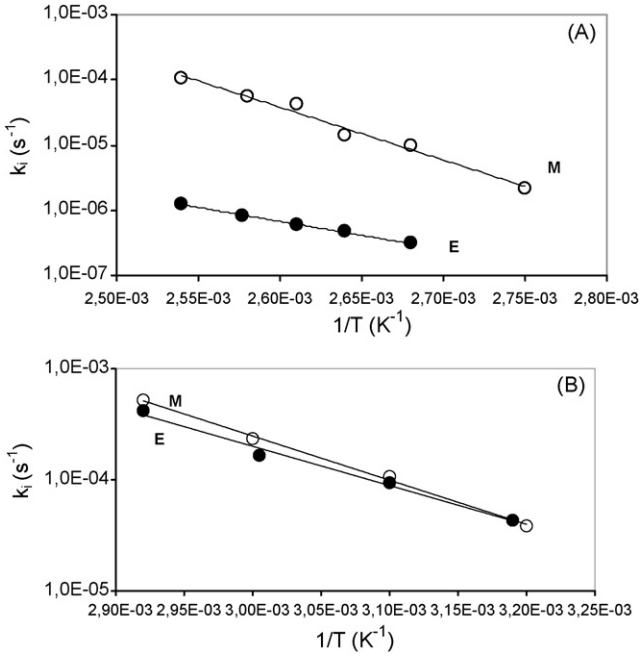

Fig. 3. The semilogarithmic relationship $k_i = f(1/T)$ for the degradation of ertapenem (E) and meropenem (M) in dry air (A) and at 76.4% RH (B).

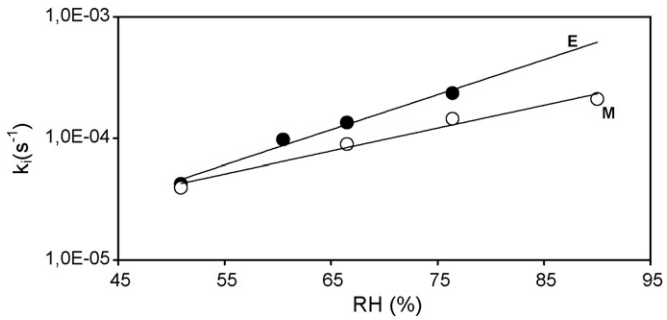

Fig. 4. The relationship $\ln k_i = f(\mathrm{RH}\%)$ for the degradation of meropenem and ertapenem in solid state, at 333 K.

In dry air this influence was statistically significant ($t_0 = 3.819$ obtained from the parallelism test was found to be higher than the critical $t_{crit} = 2.365$, 5% significant level). Although, in the case of meropenem the influence of temperature on its degradation rate constant was greater at 373–393 K, the degradation of ertapenem was slower in this range temperature. It was calculated that both antibiotics decomposed with the same rate constant at 324 K.

Humidity is a significant factor affecting the degradation of ertapenem and meropenem. Therefore, containers protecting drugs from moisture ensure their better stability. It appears possible to simulate the process of degradation inside an airtight container by studying drug stability at 0% RH. The evaluation of stability at 0% RH after extrapolating degradation rate constants to room temperature shows that ertapenem and meropenem are stable throughout their shelf life declared by producer. It was calculated that during a 2-year period (the shelf life of INVANZ) only 2.45% of the initial concentration of ertapenem will be decomposed ($t_{10\%}$ is 8.4 years at room temperature, 0% RH). During a 4-year period (the shelf life of MERONEM) only 0.43% of the initial concentration of meropenem will be decomposed.

3.4. The influence of relative air humidity on the stability of ertapenem and meropenem

The influence of air humidity on the stability of ertapenem and meropenem was described by the following equation:

$$\ln k_i = a(\mathrm{RH}\%) + b$$

The slope a expresses the effect of air humidity on the stability of ertapenem and meropenem in solid state and the value $10^b = k_0$ denotes their stability at 0% RH (Table 3, Fig. 4). Although the plots $\ln k_i = f(\mathrm{RH}\%)$ of ertapenem and meropenem at 333 K intersected at 50.67 RH, the parallelism test proved that the influence of relative air humidity on the stability of these compounds was similar. The differences between the observed rate constants of ertapenem and meropenem obtained at increased air humidity (50.9–90.0%) not statistically significant.

4. Conclusions

The study demonstrated that influence of humidity on the ertapenem and meropenem degradation are significant however similar. If INVANZ and MERONEM are stored in a package protecting from moisture at room temperature, they are stable throughout their shelf life declared by producer.

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