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An application of high performance liquid chromatographic assay for the kinetic analysis of degradation of faropenem

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An isocratic RP-HPLC-DAD procedure was developed and validated for kinetic analysis of degradation of faropenem in bulk drug substance and in tablets. It involved the use of a C-18 analytical column (5 μm particle size, 250 mm × 4.6 mm), flow rate 1.3 ml/min and 50 μl injection volume. The mobile phase consisted of acetate buffer (pH 3.5) – acetonitrile (70:30 v/v). The determination was carried out at the wavelength of 323 nm. Kinetic studies of faropenem degradation in aqueous solutions included hydrolysis, oxidation, photolysis and thermal degradation. A derivative spectrophotometry was used as an alternative method to compare the observed rate constants.

1. Introduction

Derivatives of penem are a rapidly developing group of β-lactam antibiotics (Dalhoff et al. 2003). Beta-lactam analog derivatives – carbapenems and thiopenems – have a broad spectrum of antibacterial activity (including action against *Pseudomonas aeruginosa* and Enterobactericae), desired pharmacokinetic parameters and produce low side effects (Walsh et al. 2007; Zhanel et al. 2007). The greatest limitation of a therapy using penems is their significant enzymatic and chemical instability (Cielecka-Piontek et al. 2011).

Regarding carbapenems, the problem of enzymatic instability was solved by the introduction of a methyl group at C3 into the azabicyclo[3.2.0]heptan-7-ones structure. Unfortunately, the chemical instability of carbapenems continues to limit their application to parenteral administration. Therefore, the stability of carbapenems is being widely studied, including their metabolism in the human body (Kipper et al. 2009; Sutherland et al. 2007; Kameda et al. 2010), the influence of storage (Mendez et al. 2006, 2008; Zając et al. 2007; Cielecka-Piontek et al. 2008; Zając et al. 2006) and preparation of intravenous solutions (Grant et al. 2000; Patel et al. 1997; Keel et al. 1997; Psathas et al. 2008).

The chemical instability of thiopenems was improved by the introduction of a sulphur atom at C4 into the thiazolidine moiety of the bi-cyclic 4:5 fused ring, in contrast to carbapenems where suphur atom was substituted with a carbon atom. The sulphur atom affects the entire structure shape and by changing the C-S-C band angle resulting in reduced intra-ring stress, thus decreasing susceptibility to degradation under affecting factors both in solid and aqueous media (Schurek et al. 2007). Furthermore, in the chemical structure of faropenem, the chiral tetrahydrofuran substituent at position C2 is responsible for its improved chemical stability and reduced neurotoxicity (Dalhoff et al. 2003, 2006)

At present, faropenem (Fig. 1) is the only derivative of thiopenems approved for therapeutic use (Hamilton-Miller et al. 2003). In Japan, faropenem is currently available as orally administered sodium salt (FAROM®), while its ester prodrug (faropenem daloxate) is in Phase III of clinical trials in the USA (Dalhoff et al. 2003). Some chromatographic methods have been reported for quantification of faropenem, mainly in biological matrices (Nirogi et al. 2005; Gao et al. 2008; Wen et al. 2006; Hu et al. 2006). To the best of our knowledge, only one scientific publication describes an analytical method for the determination of faropenem in pharmaceutical matrix, but it does not report a method which is suitable for kinetic analysis of faropenem degradation (Menon et al. 2009).

During the development of analytical procedures for determination of penems, ensuring suitable selectivity is vital for calculating reliable rates of degradation. The influence of different factors (e.g., methanolytic degradation) on the rate of degradation of a penem derivative (Vailaya et al. 2005) and on the formation of carbapenem degradation products (Sajonz et al. 2005; Elragehy et al. 2008; Xia et al. 2009) has been proved.

Therefore, the aim of this study was to develop an LC method for calculating the kinetic parameters of faropenem degradation in bulk drug substance and in pharmaceutical preparations during accelerated stability studies.

2. Investigations, results and discussion

A method for the determination of the faropenem in pure substance and in pharmaceutical preparations in the presence of degradation products formed under various stress conditions was developed. An analysis of stressed samples was performed with an HPLC system using a C-18 column and the mobile phase composed of 30 volumes of acetonitrile and 70 volumes of acetate buffer (pH 3.5). Detection was carried out at 323 nm. The mobile phase flow rate was 1.3 ml/min. The HPLC-DAD method was developed and validated with regard to selectivity, linearity, accuracy, precision, limit of detection and limit of quantitation. Under the proposed chromatographic conditions,

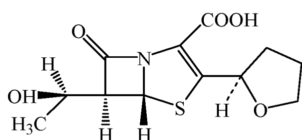

Fig. 1: Chemical structure of faropenem

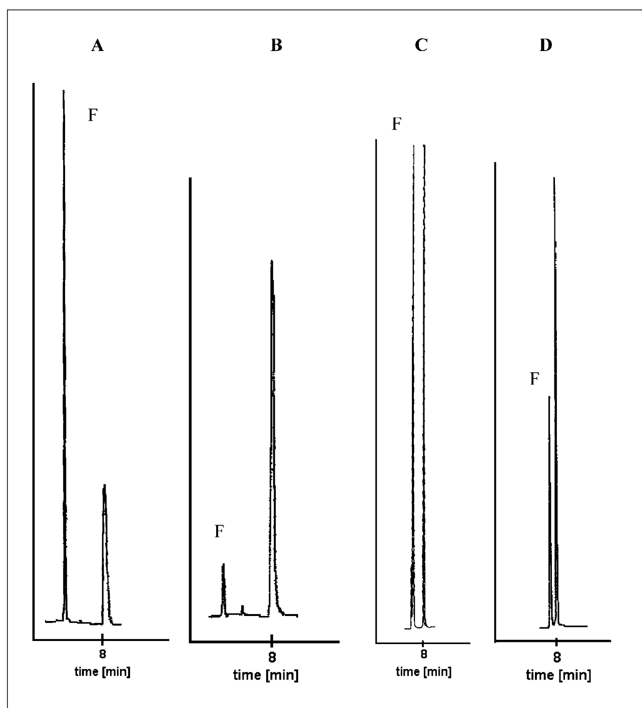

Fig. 2: The HPLC chromatograms of faropenem: A - substance in bulk, after degradation in NaOH (0.05 M), 343 K (180 min), B - substance in bulk after degradation in H_2O_2 (30%), 313 K (6 min), C - pharmaceutical dosage form after degradation in H_2O_2 (30%), 303 K (13 min), D – pharmaceutical dosage form after degradation in NaOH (0.05 M), 313 K (0.5 min) (F – faropenem)

the selectivity of the method was confirmed by examining the spectrophotometric purity of faropenem peaks (> 98.5%). Products formed during acidic and alkaline degradation, oxidation and photolysis as well as tablet excipients did not interfere at any level of determination. The run time of the analysis was 8.5 min. Typical retention times of faropenem were about 6.5 min, while the peaks originating from degradation products and excipients eluted after the faropenem peak (~ 8.0 min) (Fig. 2).

The calibration curve was described by the Eq. $y = ac$; $y = (46310 \pm 1500)\ c\ (b = 98.50)$. The b values, calculated from the Eq. $y = ac + b$, were not significant. The calibration plots were linear in the following concentration range 5.0–400.0 μg/ml ($n = 10$, $r = 0.9993$).

Recovery was performed at three levels: 80, 100 and 120% of the label claim of the substance. Good recoveries were obtained for each concentration, confirming that the method was accurate. The mean recovery from pure substance was 99.94% and from pharmaceutical preparation 101.18 % ($n = 3$). The intra-day and inter-day precision values of faropenem concentrations measured at 80, 100 and 120% of the label claim, demonstrated that the RSD values (Table 1) for the determination of faropenem in pure substance and in pharmaceutical preparation were in the range 1.31–2.97 %, indicating that the method was precise.

Under the applied chromatographic conditions, the LOD and LOQ of faropenem were 0.84 μg/ml and 2.58 μg/ml, respectively. The robustness of the procedure was evaluated by changing the following parameters: the composition and pH of the mobile phase, the mobile phase flow rate in the range of 1.0–1.5 ml/min, and the temperature in the range 23–27 °C (± 1 °C). With a change of each parameter, its effect on retention time, peak resolution, peak shape and peak area (height and width) was evaluated. No significant changes in the separation, shapes of areas and retention time of the peaks were observed when the temperature and flow rate were modified. The changes in pH and the type of the organic fraction in mobile phase influenced significantly the retention time and shape of the peaks. The atypical effects of tailing and symmetrical lack of peak were observed for the mobile phase when at its pH above 3.7. The introduction of acetonitrile resulted in a shorter time of analysis, symmetrical, non-tailing peaks and gave results of degradation analysis comparable with these determined with the alternative method.

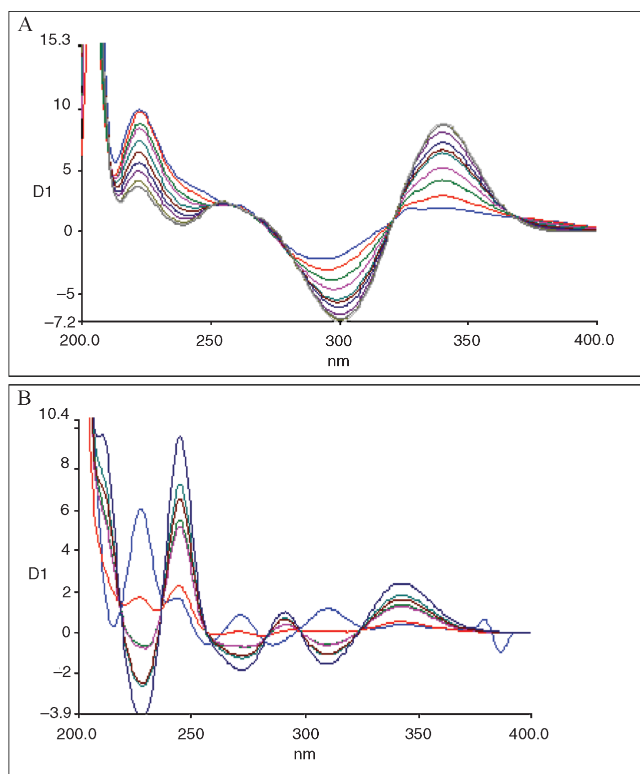

Fig. 3: First-derivative spectra of faropenem after heating of FAROM® preparation to 343 K during the degradation in HCl (0.4 M) from 0 to 45 min (A) and during the degradation of faropenem in bulk substance in NaOH (0.2 M from 0 to 264 h (B)

Kinetic studies of degradation of faropenem in hydrochloric acid (0.4 M, 343 K) in sodium hydroxide solution (0.2 M, 343 K), after oxidation (30% H_2O_2, 313 K) and after photolysis were conducted by using two chromatographic techniques – our current method and a reported one (Menon et al. 2009) and derivative spectrophotometry. Derivative spectrophotometry is widely used as stability-indicating analytical method for the determination of penem analogs (Elragehy et al. 2008; Cielecka-Piontek et al. 2011, 2010; Hassan et al. 2009).

Linear, selective changes of amplitude values of the first-derivative of the indirect spectra of faropenem in the presence of its degradation products were registered (after the crossing point, $\lambda = 323$ nm) using a peak-to-zero technique (Fig. 3) (Cielecka-Piontek et al. 2012).

The kinetic mechanism of faropenem degradation in aqueous solutions was described by a pseudo-first-order reaction and was expressed as follows:

$$\ln P_F = \ln P_F - k_{obs} t$$

$$\ln D_F = \ln D_F - k_{obs} t$$

Table 1: Validation parameters of faropenem

	Intra-day and inter-day precision (n = 6) studies	
	Pure substance	Pharmaceutical formulation
Intra-day precision	RDS	% RDS5
50.0 (μg/ml)	2.52	2.56
100.0 (μg/ml)	1.31	2.05
200.0 (μg/ml)	2.95	2.97
Inter-day precision		
100.0(μg/ml)	2.75	2.91
	Recovery studies (n = 3)	
Spiked concentration (μg/ml)	Measured concentration ± S.D (μg/ml), RSD (%)	
	Pure substance	Pharmaceutical preparation
50 (∼ 80%)	49.78 ± 0.04, 99.56	50,98 ± 0.02, 101,96
100 (∼ 100%)	101.32 ± 0.82, 100.32	101.23 ± 0.03, 101.23
200 (∼ 120%)	199.89 ± 0.03, 99.94	200.67 ± 0.04, 100.35

The observed rate constants were equal to the slopes of the plots $\ln P_F = f(t)$ and $\ln D_F = f(t)$ with the negative sign ($-k_{os}$); where P_F is the area of the faropenem peak and D_F – the value of the first derivative at 323 nm. The values of the observed rate constants determined with each method are shown in Table 2.

The differences in the values of the observed rate constants determined by using first-derivative spectrophotometry and the presented chromatographic procedure were not statistically significant. The differences in the kinetic parameters of faropenem degradation were observed only when comparing the results obtained by using the chromatographic techniques. That may be explained by the fact that the presence of methanol increases the rate of faropenem degradation and/or influences the formation of methanolysis products. A similar methanolytic effect was also present in an analysis of other analogs of a penem derivative (Vailaya et al. 2005). The influence of catalytic effects of degradation products, (3-vinyl-4-thia-1-azabicyclo[3.2.0]hept-2-en-7-one and 3-(tetrahydrofuran-2-yl)-4-thia-1-azabicyclo[3.2.0]hept-2-en-7-one), forming during hydrolysis, oxidation, photolysis and thermolysis on the rate of degradation of faropenem was excluded. However, a similar effect was observed during the degradation of penem derivatives. It was confirmed that the catalytic effect of degradation products and the amount of the undissociated form of the carboxylic group in a molecule increased the rate of degradation (Ito et al. 2005).

The introduction of a sulfur atom at position C4 into the thiazolidine moiety of bi-cyclic 4:5 fused ring in thiopenem analog did not change the kinetic mechanism of degradation, compared to that of carbapenem analogs. Changes of chemical structure, significantly influence the stability of thiopenem analogs, which was proved when the methanolytic effect was excluded. Our stability studies demonstrated that the influence of affecting factors on the degradation of the faropenem in pure substance (a) and in pharmaceutical preparation (b), may be presented as follows:

$$\text{oxidative factor} > \text{alkali factor} > \text{light factor} >> \text{acidic factor} \quad \text{(a)}$$

$$\text{alkali factor} > \text{oxidative factor} \sim \text{acidic factor} >> \text{light factor} \quad \text{(b)}$$

The current HPLC procedure not only allows determination of faropenem in the presence of its degradation products but also in pharmaceutical preparation with excipients. It was shown that by applying this procedure it is possible to obtain a more reliable chromatographic response, higher spectrophotometric peak purity and to analyse the kinetics of faropenem degradation in pure substance and in pharmaceutical preparation.

3. Experimental

3.1. Chemicals and reagents

Faropenem reference standard (purity > 98%) was supplied by Pharmachem International Co., (China). Commercially available 200 mg tablets (FAROM®) manufactured by Daichi Asubio Pharma (Japan), were purchased and used within shelf-life time declared by the producer. All other chemicals and solvents were obtained from Merck KGaA (Germany) and were of analytical grade. High quality pure water was prepared using a Millipore purification system (Millipore, Molsheim, France, model Exil SA 67120).

Table 2: Observed rate constants of degradation of faropenem in pure substance and in pharmaceutical preparation

Analytical methods	HCl (0.4 M, 343 K)	NaOH (0.2 M, 343 K)	H_2O_2, 30%, 313 K	Photodegradation
		pure substance, k_{obs} [s^{-1}]		
HPLC*	$(9.78 \pm 0.66) \times 10^{-8}$	$(1.03 \pm 0.11) \times 10^{-5}$	$(1.33 \pm 0.18) \times 10^{-4}$	$(6.17 \pm 0.42) \times 10^{-6}$
HPLC*	$(7.24 \pm 0.26) \times 10^{-7}$	$(5.98 \pm 0.43) \times 10^{-4}$	$(1.08 \pm 0.43) \times 10^{-4}$	$(6.65 \pm 0.98) \times 10^{-5}$
UV*	$(9.57 \pm 1.57) \times 10^{-8}$	$(1.55 \pm 0.32) \times 10^{-5}$	$(1.10 \pm 0.12) \times 10^{-4}$	$(6.11 \pm 0.30) \times 10^{-6}$
		pharmaceutical preparation, k_{obs} [s^{-1}]		
HPLC*	$(6.05 \pm 0.58) \times 10^{-4}$	$(3.52 \pm 0.38) \times 10^{-3}$	$(4.54 \pm 0.31) \times 10^{-4}$	$(1.18 \pm 3.11) \times 10^{-5}$
HPLC*	$(2.78 \pm 0.06) \times 10^{-3}$	$(7.18 \pm 0.11) \times 10^{-3}$	$(6.98 \pm 0.23) \times 10^{-4}$	$(2.78 \pm 0.23) \times 10^{-4}$
UV*	$(5.81 \pm 0.40) \times 10^{-4}$	$(3.44 \pm 0.32) \times 10^{-3}$	$(4.50 \pm 0.63) \times 10^{-4}$	$(1.19 \pm 2.95) \times 10^{-5}$

HPLC* observed rate constants of degradation of faropenem determined by using chromatographic procedure presented in the paper
HPLC* observed rate constants of degradation of faropenem determined by using chromatographic procedure (Menon et al.2009)
UV* observed rate constants of degradation of faropenem determined by using derivative spectrophotometry

3.2. Apparatus and study conditions

The chromatographic separation and quantitative determination were performed using a high performance liquid chromatography system containing a Shimadzu pump, model LC-6A, aUV-VIS detector (SPD-6AV, Shimadzu), a Rheodyne 7120 with a 50 μL loop. It involved the use of a C-18 analytical column (5 μm particle size, 250 mm × 4.6 mm); flow rate: 1.3 ml/min and 50 μl injection volume. The mobile phase consisted of acetate buffer (pH 3.5) – acetonitrile (70:30 v/v). The determination was carried out at the wavelength of 323 nm. For analysis of homogeneity of peaks of forced-degraded samples, a photodiode array detector (Merck, L-7455) was used in scan mode with a 200–600 nm scan range.
A UV-VIS Lambda 20 (Perkin Elmed) spectrophotometer equipped with 1.0 cm-in-width quartz cells and controlled via UV WinLab software was utilized. The first derivative of the ratio-indirect spectra (D^1 – the peak amplitude of the first-derivative curve $\Delta A/\Delta\lambda$ at the corresponding wavelength) with $\Delta\lambda = 4$ nm and a scaling factor of 10 was obtained. The amplitudes of the first derivative peaks of faropenem were measured at 323 nm.
Photodegradation stability studies of faropenem were performed using a Suntest CPS+ apparatus (Atlas®) with a Solar ID65 filter, where cells were exposed to light (300–400 nm).

3.3. Preparation of stock standard solutions

Standard stock solutions of faropenem were prepared in water by dissolving accurate amounts of working standards to obtain 100 μg/ml of sodium salt of faropenem. Stock standard solutions were stored in darkness at 4 °C and remained stable during the time of the study.

3.4. Preparation of tablets for assay

Twenty tablets (FAROM®) were accurately weighed and finely powdered. An aliquot of powder equivalent to the content of 5 mg of faropenem was accurately weighed, next it was transferred to a 50 ml volumetric flask with the addition of about 25 ml of water. For the stability studies, the obtained mixture was shaken with a solution of an affecting factor. Finally, the mixture was filtered through 0.45 micron nylon filter paper.

3.5. Validation of the method

The proposed HPLC method was validated according to the International Conference on Harmonization Guidelines (ICH 2003, 2005)
Selectivity was examined for non-degraded and degraded samples of faropenem in pure substance and in pharmaceutical preparation. Solutions of faropenem were exposed to the stress conditions of hydrolysis (acid, base) at 343K, photolysis (sunlight) and oxidation (H_2O_2) at 313 K.
The calibration plots P = f(c) were obtained in the 5.0–400.0 μg/ml concentration range, where P is the peak area of faropenem. Solutions used to check linearity were injected in triplicate.
The accuracy of the method was determined by recovering faropenem from the placebo. The recovery test was performed at three levels 80%, 100% and 120% of the nominal concentration of faropenem (50, 100 and 200 μg/ml) during degradation studies. Three samples were prepared for each recovery level. The solutions were analyzed and the percentage of recoveries were calculated from the calibration curves.
The precision of the assay was determined in relation to repeatability (intra-day) and intermediate precision (inter-day). In order to evaluate the repeatability of the method five samples were determined during the same day for three concentrations of faropenem. Intermediate precision was studied comparing the assays performed on two different days.
LOD and LOQ parameters were calculated from the regression equation for faropenem: $LOD = 3.3\, S_y/a$, $LOQ = 10\, S_y/a$; where S_y is a standard error and a is the slope of the corresponding calibration curve.
The robustness of the procedure was evaluated after changing the following parameters: the composition and the mobile phase (content of acetonitrile in the range 25–35%), the mobile phase flow rate (in the range 1.0–1.5 ml min^{-1}) and absorption wavelength (in the range 290–350 nm) and the temperature (25 ± 2 °C). For each parameter change its influence on retention time, resolution, area, shape (height and width) of peaks was evaluated.

3.6. Accelerated stability test conditions

In order to determine the kinetic parameters of degradation, tablets of faropenem and bulk substance were stressed under various conditions to conduct accelerated stability tests (ICH 2003). Degradation was initiated by dissolving an accurately weighed 5.0 mg of faropenem or powder containing 5.0 mg of faropenem in 25.0 ml of the solution equilibrated to a desired temperature in a stopped flask. At specified times, samples of the reaction solutions were taken and instantly cooled with a mixture of ice and water.
Solutions for oxidation studies were prepared in 30% H_2O_2 at 313 K.
Solutions for acidic degradation studies were prepared in water and hydrochloric acid (0.4 M) as well as in water and sodium hydroxide solution (0.2 M) at 343 K. The ionic strength of all solutions was adjusted to sodium chloride solution (4.0 M).
5.0 mg of faropenem or powder containing 5.0 mg of faropenem was prepared and exposed to light to determine the effect of light irradiation on the stability of faropenem in the solid state. All samples for photostability studies were placed in a light chamber and exposed to light at 300–400 nm for a specified time.

3.7. Derivative spectrophotometry

The observed rate constants of faropenem degradation were determined by using derivative spectrophotometry as an alternative method (Cielecka-Piontek et al. 2012). The accelerated stability tests were conducted under the same conditions as those used in chromatographic procedures for pure substance and in pharmaceutical preparation.

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