Programa de Pós-Graduação em Ciências Farmacêuticas[1], Faculdade de Farmácia[2], Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre-RS; Programa de Pós-Graduação em Ciências Farmacêuticas[3], Universidade Federal do Pampa (UNIPAMPA), Uruguaiana-RS, Brazil

Quantitative determination of the β-methyl carbapenem doripenem in powder for injection by a stability-indicating capillary zone electrophoresis method

P. K. Paliosa[1,2], C. V. Garcia[1,2], E. E. S. Schapoval[1,2], A. S. L. Mendez[2,3], M. Steppe[1,2]

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Andreas S. L. Mendez, Faculdade de Farmácia, Universidade Federal do Rio Grenade do Sul (UFRGS), Av. Ipiranga 2752, Porto Alegre-RS, Brazil
andreas.mendez@ufrgs.br

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A capillary zone electrophoresis method for quantitative determination of doripenem in synthetic matrix was developed. The stability-indicating capability was performed applying stress testing protocols. The selected analytical conditions include 100 mM sodium borate buffer (pH 8.0) as run electrolyte, voltage of + 15 kV, hydrodynamic injection of 5 s (50 mBar), detection at 298 nm and temperature of analysis of 25 °C. The electrophoretic separation was carried out in a fused silica capillary (effective length 40 cm, 50 μm i.d.), using procainamide hydrochloride as internal standard. The proposed method showed quickness and reproducibility, with an analytical run in a total time of 5 min. The percentage of drug amount estimated was 101.33% (RSD=0.80), with satisfactory intra-day and inter-day precision. In the recovery test, the method was found to be reliable and accurate in the drug quantitation (mean recovery = 101.86%). The robustness was performed applying the Plackett–Burman experimental design which confirmed the assay reliability. Based on results from forced degradation study, the stability-indicating capability was established, being observed a major degradation in alkaline, photolytic and thermal conditions. In comparison to HPLC method previously developed, the proposed capillary electrophoresis assay is statistically equivalent.

1. Introduction

Doripenem (Fig. 1), a β-methylcarbapenem antibiotic, is routinely used for the treatment of serious infections, i.e. intra-abdominal and urinary tract infections (Lucasti et al. 2008; Fujimura et al. 2009). It is active against a broad range of gram-positive and gram-negative bacteria, as well as for anaerobic organisms (Jones et al. 2004; Livermore 2009; Matthews and Lancaster 2009). It is well-tolerated and clinically effective which led to an increased clinical use (Castanheira et al. 2009; Pankuch et al. 2010; Clock et al. 2013). The class is well studied with focus on drug analysis and stability, considering the known instability of carbapenems when obtained as reconstituted solution and exposed to inappropriate external conditions as heat and oxidation (Sajonz et al. 2001; Mendez et al. 2008; Cielecka-Piontek et al. 2011; Cielecka-Piontek et al. 2012). Monitoring of drug concentrations in biological matrices needs to consides low drug levels and the presence of other substances (Sutherland and Nicolau 2007; Ikeda et al. 2008; Dailly et al. 2011).

Several methods have been proposed for routine analysis of doripenem, each one studying the drug analysis through experimental protocols well established for development and analytical validation. For quantitative determination, instrumental analysis by HPLC, UV spectrophotometry and capillary electrophoresis have been proposed (Cielecka-Piontek and Jelinska 2010; Mendez et al. 2011; Michalska et al. 2011; Mantovani et al. 2012; Kathirvel and Devalarao 2013; Kurien et al. 2014), all investigating the drug profile in terms of response to variations into stability-indicating capability. By HPLC, reversed-phase and isocratic systems are easily applied to routine analysis, using as methanol and acetonitrile during elution. An UV spectrophotometric assay is also described by derivative function, intending to eliminate the interferences from degraded sample during quantitative analysis, even with limited method selectivity (Cielecka-Piontek and Jelinska 2010). Recently, Michalska et al. (2011) presented a CE method for determination of doripenem and other carbapenems. The experimental protocol was optimized for analysis, with the proposal to determine the antibiotic in extensively degraded samples. Alternatively, a quantitative microbiological agar diffusion assay is reported, applying the analytical protocol for drug estimation in degraded matrix through inhibition zone measurements (Fuhr et al. 2013). Concerning the stability, doripenem have been

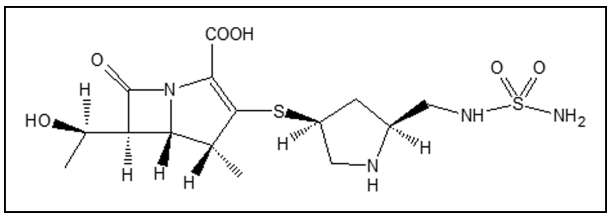

Fig. 1: Chemical structure of doripenem.

Table 1: System suitability parameters obtained for CE method applied to doripenem analysis

Parameter	Recommended*	CE Results
Resolution (R)	R > 1.5	22
Area repeatability	RSD ≤ 2.00%	0.80%
Tailing	T < 2	0.8
Theoretical plates (N)	N > 2,000	158,000

*Recommended parameters for HPLC [21].

investigated in views of accelerated decomposition, kinetics reaction and degradation products (Cielecka-Piontek and Jelinska 2011; Führ et al. 2013; Reddy et al. 2014).

In the present work, a rapid CE method is proposed as an alternative, with rigorous validation protocol, focusing on good sensitivity of the method, rapid analysis and reliable performance. In addition, robustness was tested by Plackett-Burman design and the method was statistically compared to a previously reported HPLC method.

2. Investigations, results and discussion

2.1. Method development

Initially, the proposed CE method was conducted under different critical conditions that may interfere on analytical performance. System suitability parameters were continuously verified, focusing on the stability-indicating profile desired. Several buffers were tested as run electrolytes: potassium phosphate, sodium phosphate, acetate, citrate, tris and borate in presence or absence of sodium dodecyl sulfate (SDS). Alternatively, methanol 5 and 10% were also tested. The electrolyte was modified in terms of concentration (10-100 mM) and pH (3.0-9.3). Different voltages were also applied: 10, 15, 20 and 25 kV. As internal standard, several drugs, such as sodium diclofenac, nimesulide, ranitidine, glibenclamide, duloxetine, doxycycline, trimethoprim, procainamide, atenolol, chloroquine, tetracycline and cefadroxil were evaluated.

After these experiments, the best conditions for doripenem analysis were established as follows: 100 mM borate buffer at pH 8.0 as electrolyte, applied voltage of 15 kV, hydrodynamic injection at 50 mbar for 5 s, UV detection at 298 nm and procainamide hydrochloride as internal standard. The capillary was thermostated at 25 °C and daily conditioned with 0.1 M sodium hydroxide, water and electrolyte for 10, 5 and 5 min, respectively. Under these conditions, fast and adequate migration times were obtained for the internal standard and doripenem: 3.1 and 4.2 min, respectively. System suitability parameters were satisfactory, as can be seen in Table 1.

From the recent study published by Michalska et al. (2011) about a CE method for the determination of doripenem, it can be seen that the analytical run occurs in a total time of 20 min, with a prolonged migration time for the drug (about 13 min). However, the absence of an internal standard could represent a disadvantage, since hydrodynamic injection can generate very variable results. Accuracy was established by comparing the quantitative results obtained with those from a HPLC method described in the study. Robustness evaluation was not performed, which impedes a critical evaluation of assay variability. Considering CE methods, the robustness is critical, since the analysis presents intrinsic variations that can interfere during routine determinations (Heyden et al. 2001), mainly in the cited study, where the authors describe the simultaneous determination of doripenem and related substances and poor signal resolution was achieved.

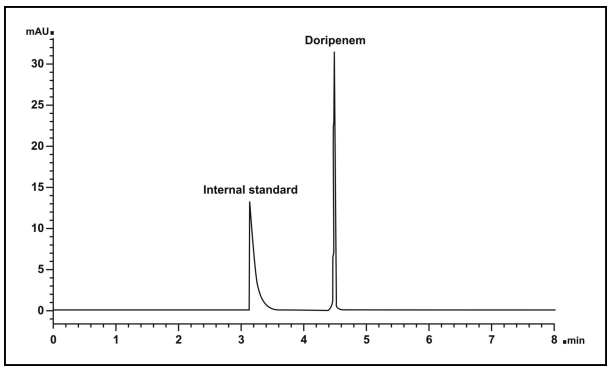

Fig. 2: Electrophoretic analysis of doripenem reference standard at 100.0 µg/mL in aqueous solution. Internal standard: procainamide at 200.0 µg/mL. Detection at 298 nm.

2.2. Method validation

2.2.1. Specificity and forced degradation studies

Figure 2 shows the illustrative electrophoretic run for the analysis of doripenem and the internal standard. The use of this reference becomes the drug quantitation less susceptible to variations. In the present work, we propose a rapid analysis method, allowing drug quantitation in a total time of 5 min. In order to evaluate the stability-indicating profile, doripenem was submitted to extensive decomposition. Figure 3 shows the electropherograms of acid, alkaline and photolitic (UVA) degradations, where no degradation product signal could be detected, although drug decomposition could be verified through area reduction. Under alkaline conditions, 60 % degradation was observed, while for acid and UVA light exposition, 22 % and 20 % were found, respectively. Despite a reduction of drug content the monitoring by UV ranging did not demonstrate signals along the electrophoretic run including an extended time, even considering the opened β-lactam ring product, very common to carbapenems (Takeuchi et al. 1995; Mendez et al. 2008). Probably, the exhaustive decomposition formed minority compounds, structurally fragmented. Also, the absence of electrophoretic mobility of the minority compounds can be considered.

Carbapenem antibiotics are known for their instability under thermal and alkaline conditions (Mendez et al. 2008; Berthoin et al. 2010; Cielecka-Piontek 2011; Keel and Nicolau 2011). Doripenem is extensive decomposed in reconstituted solution after storage at 45 °C during different times (Fuhr et al. 2013). Oxidation is also mentioned as a critical factor for drug degradation. A recent report demonstrated the formation of two more polar degradation products after oxidative treatment with hydrogen peroxide 10% (Mantovani et al. 2012). Another study described the influence of buffer solutions on catalytic reactions when the drug is reconstituted as aqueous solution (Cielecka-Piontek and Jelinska 2011). Studies exploring the chemical structures of degradation products from doripenem are limited, although Reddy et al. (2014) have reported a UPLC method for analysis of two impurities. The CE method proposed by Michalska et al. (2011) is presented as stability-indicating, and illustrates the analysis of the drug under different thermal storage conditions. Doripenem related substances are mentioned although their chemical structures or probable sources are not reported. The electropherograms presented contain many minoritary signals as degradation products, as a sign of extensive degradation. Probably, more controlled decomposition conditions could make the identification of the degradation products easier.

In the present study, doripenem was also submitted to oxidative decomposition using 3% hydrogen peroxide. A 30 % reduction in the doripenem peak area was observed (Fig. 4). Evaluating

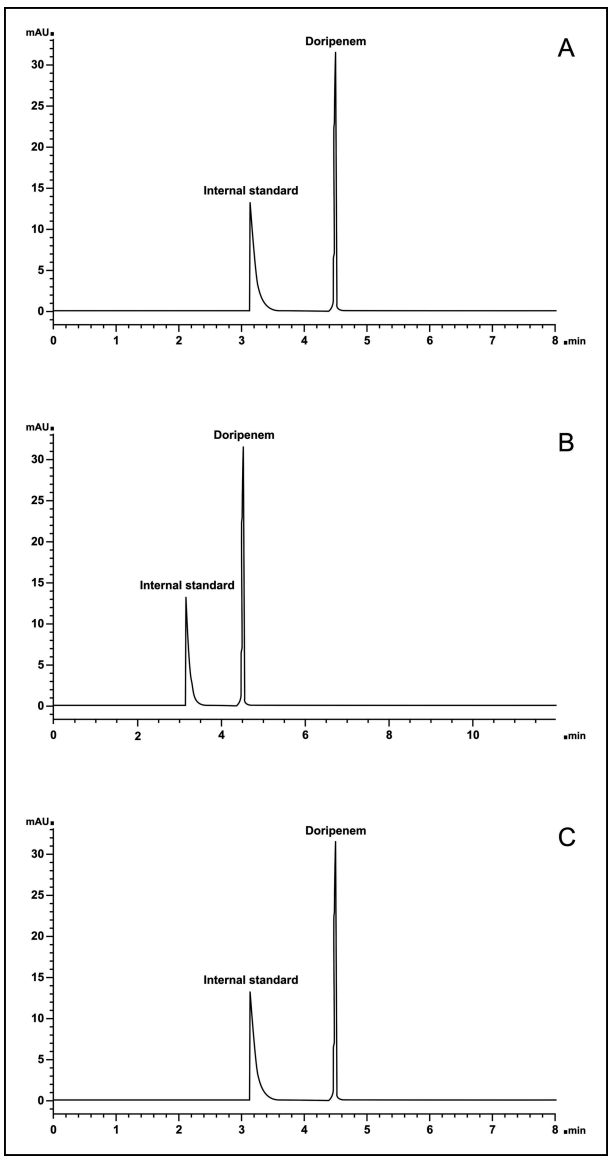

Fig. 3: CE electropherograms of doripenem degraded samples. Detection at 298 nm. (A) doripenem sample solution after alkaline degradation (NaOH 0.01 N, 5 min); (B) doripenem sample solution after acid degradation (HCl 0.01 N, 5 min); (C) doripenem sample solution after exposition to UVA light (254 nm, 24 h).

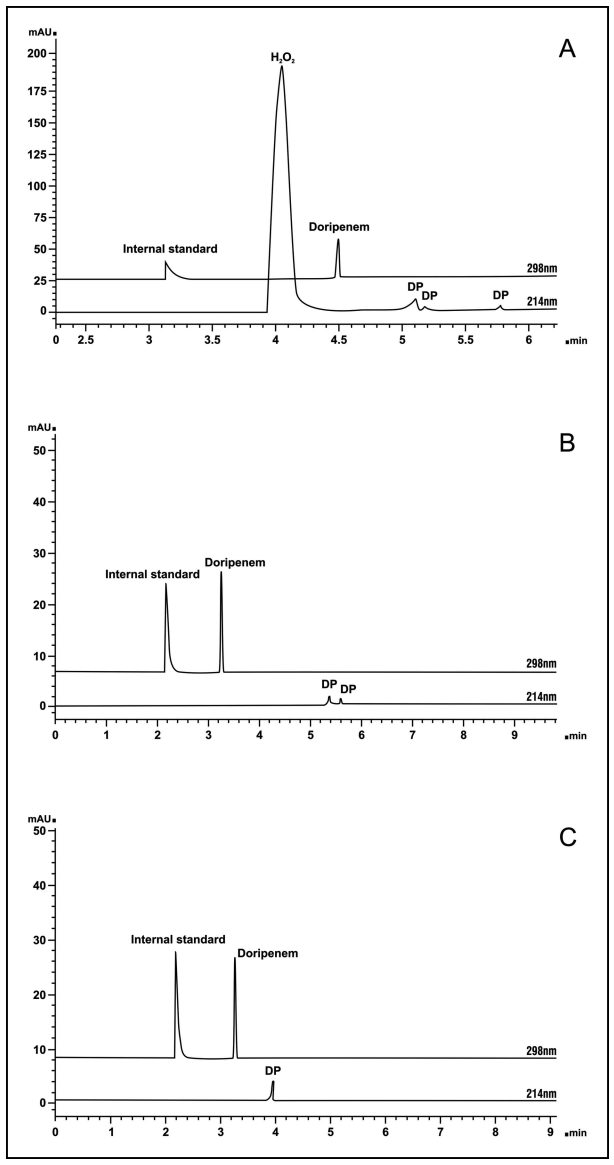

Fig. 4: CE electropherograms of doripenem degraded sample after stress testing. Detection at 298 nm and 214 nm. The drug was submitted to oxidation (A), UVC light (B) and heat (C). DP: degradation product.

the electrophoretic run in PDA detection system, three peaks were visualized at 214 nm, at migration times of approximately 5.1, 5.2 and 5.8 min (Fig. 4A). Some degradation products were also observed when the drug was decomposed under photolytic (UVC light) and thermal conditions (Figs. 4B and 4C), where the drug content was reduced to 50% and 30%, respectively. Although not described yet, some decomposition reactions could be expected for doripenem based on carbapenemic drugs stability studies. Dimerizations and β-lactam ring cleavages are very common and could be easily determined by LC-MS and NMR analyses (Cai and Hu 2005; Zajac et al. 2007; Mendez et al. 2008). The stability-indicating profile for the proposed CE method demonstrated the absence of interferences with the drug peak. The peak purity tool indicated total purity under these conditions.

2.2.2. Linearity, LOD and LOQ

Linearity was evaluated through the construction of three standard curves at three different days. For the concentration range of 25.0-250.0 μg/mL, the regression equation was $y = 0.003x + 0.005$ and the correlation coefficient was $r = 0.9995$. The ANOVA demonstrated significance in regression ($F_{calc} = 10895.34 > F_{tab} = 2.97$; $p = 0.05$) and absence of linearity deviation ($F_{calc} = 0.41 < F_{tab} = 2.15$; $p = 0.05$). The calculated LOD and LOQ values were 2.58 and 7.89 μg/mL, respectively, which proves the sensitivity of the proposed analytical method. In the work of Michalska et al. (2011), the linearity range of CE method was 30-4500 μg/mL, and LOD and LOQ values were 3.0 and 10.33 μg/mL, respectively. The low values for detection and quantitation limits were very similar to our work.

2.2.3. Precision and accuracy

Results obtained during intra-day and inter-day analyses are shown in Table 2. Small values for RSD Could be observed, which indicates a satisfactory precision of the CE method. In respect to accuracy, the percentages of recovery of added standard for the three levels analyzed were: 102.71%, 101.78% and 101.11%, respectively. The mean recovery was 101.86% (RSD = 0.79), indicating a good performance of the method for this parameter. In comparison to published works, our results demonstrated good reproducibility results. Mantovani et al.

(2012) conducted a precision assay at a minor concentration (30 μg/mL) and also observed low variation in the concentration range of 99.48-100.45% (RSD = 1.37%). Cielecka-Piontek and Jelinska (2010) established an accurate UV spectrophotometric assay, with results in recovery testing ranging from 99.91 to 101.08%.
Many advantages are known for CE methods, although the data reproducibility can be critical since it is influenced by intrinsic experimental variations dependent of the electric field applied. Thus, is an exhaustive repetition of the analytical assay is very important and of reliable conditions are to be established by a validation procedure.

2.2.4. *Robustness*

In CE, separation is governed by two factors: electric field or electrophoretic velocity and flow of electrolyte or electroosmotic flow. All these factors may depend on from applied voltage, electrolyte, pH, temperature and capillary (Suntornsuk 2010). For this reason, the robustness of the developed method was evaluated through small modifications of these factors following the Plackett-Burman factorial design. This tool allows the observation of a relatively large number of factors with a relatively small number of experiments. According to the obtained results, expressed by Pareto's graphic (Fig. 5), electrolyte concentration is the most important factor that could interfere with quantification followed by pH of the electrolyte, temperature and applied voltage. Since the effect of all these parameters did not overlap the significant value, the method can be considered robust.

2.3. *Method comparison*

In order to establish a comparative evaluation between CE and HPLC methods (Mantovani et al. 2012), a statistical analysis by t-student test was performed. The results show that there was no statistically significant difference between CE (mean content = 500.5 mg) and HPLC (mean content = 506.1 mg) to quantify doripenem at a 5% significance level (Table 3). Thus, the methods are interchangeable, being both adequate to quantify doripenem with reliability.

3. Experimental

3.1. *Chemicals*

Doripenem reference standard (99.40 %) was purchased from AK Scientific, Inc. (Mountain View, USA). Samples of Doribax® powder for injection (570 mg of doripenem monohydrate containing 500 mg of doripenem as anhydrous basis) were acquired in the market. Procainamide hydrochloride was obtained from Sigma-Aldrich (St. Louis, MO, USA). Sodium borate buffer, sodium hydroxide, ortophosphoric acid and monobasic sodium phosphate were obtained from Synth® (São Paulo, Brazil). Acetonitrile was purchased from Tedia (Fairfield, OH, USA). Purified water was prepared using Milli-Q Plus® (Millipore, Bedford, USA). All chemicals used were analytical or HPLC grade.

3.2. *Capillary electrophoresis*

3.2.1. *Apparatus and electrophoretic conditions*

Capillary electrophoresis (CE) was carried out on an Agilent ^{3D}CE system equipped with a G1311A pump, G1329A autosampler, G1330B thermostat, G1322A deaerator, G1315A diode array detector and ChemStation software (Agilent Technologies Inc., Palo Alto, CA, USA).
The experimental conditions were: 40 cm fused silica capillary (effective length) with 50 μm of internal diameter, 100 mM sodium borate buffer (pH 8.0) as run electrolyte, applied voltage of 15 kV, hydrodynamic injection using 50 mBar for 5 s, detection at 298 nm, temperature of 25 ± 1 °C. To observe potential degradation products peaks, the wavelength of 214 nm was also used. Daily, the capillary was first conditioned with 0.1 M sodium hydroxide, water and electrolyte for 10, 5 and 5 min, respectively, and between each analysis, for 2, 1 and 2 min, with the same solutions. All of them were filtered through a 0.45 μm membrane (Millipore®) before use.

3.2.2. *Standard and sample preparation*

Doripenem reference standard was accurately weighed and diluted with water until a 100.0 μg/mL concentration. For internal standard, procainamide hydrochloride was prepared in water at the concentration of 200.0 μg/mL. For samples, a solution of doripenem powder for injection was obtained at 100.0 μg/mL using water. All solutions were filtered through a 0.45 μm membrane (Millipore®) before injection.

3.3. *Validation procedure*

The electrophoretic method was validated according to international guidelines, evaluating the parameters specificity, linearity, limits of detection, limits of quantitation, precision, accuracy and robustness (ICH 2005; USP 2012). In order to evaluate the variability and the performance, the system suitability parameters resolution, repeatability of injection, tailing factor and theoretical plates (N) were monitored.

3.3.1. *Specificity*

The specificity was evaluated through forced degradation studies. Doripenem reference standard and commercial sample were assayed. For all electropherograms obtained, the peak purity tool was used to check possible interference in the peaks. The stress conditions applied were:
A) Alkaline hydrolysis: Doripenem solutions 1.0 mg/mL were prepared in NaOH 0.01 M. After 5 min, they were neutralized with HCl 0.01 M and diluted to 100.0 μg/mL for analysis;
B) Acid hydrolysis: Doripenem solutions 1.0 mg/mL were prepared in HCl 0.01 M. After 2 h, they were neutralized with NaOH 0.01 M and diluted to 100.0 μg/mL for analysis;
C) Thermal degradation: Doripenem solutions 1.0 mg/mL were stored in oven at 45 °C for 48 h. Before the analysis, they were diluted to 100.0 μg/mL;
D) Photolysis: Doripenem solutions 1.0 mg/mL were transferred to quartz cells and stored at different mirror chambers containing UVC (352 nm) and UVA (254 nm) lamps for 24 h. After the period, the solutions were diluted to 100.0 μg/mL and analyzed;
E) Oxidation: Doripenem solutions 1.0 mg/mL were prepared in 3% hydrogen peroxide solution. After 15 minutes, they were diluted to 100.0 μg/mL and analyzed.

3.3.2. *Linearity*

The linearity of the proposed method was evaluated at three different days through the construction of standard curves with seven drug concentrations (25.0, 50.0, 75.0, 100.0, 150.0, 200.0 and 250.0 μg/mL). All solutions were daily prepared in water and analyzed in triplicate. The analysis of variance (ANOVA) was conducted to validate the linearity range.

3.3.3. *Limits of detection (LOD) and limits of quantitation (LOQ)*

The parameters LOD and LOQ were calculated from the residual standard deviation (δ) and slope (S) of the regression line of three calibration curves obtained during linearity assay, following the equations: LOD = 3.3 (δ/S) and LOQ = 10 (δ/S) (USP 2012).

3.3.4. *Precision*

Six different doripenem sample solutions at 100.0 μg/mL, in water, were daily prepared and analyzed during three days. The relative standard deviation (RSD) obtained for the amounts found in each day and between days were used to evaluate the repeatability and the intermediate precision. The electrophoretic parameters were also determined, being compared for reproducibility.

3.3.5. *Accuracy*

The accuracy of the assay was evaluated by the recovering test, following reported protocols. Known aliquots of doripenem reference substance were added to volumetric flasks containing doripenem sample solutions at 100.0 μg/mL, obtaining final concentrations of 125.0, 150.0 and 175.0 μg/mL. The solutions were prepared in triplicate, and the % of recovery and the RSD values were calculated.

3.3.6. *Robustness*

The robustness was evaluated using an experimental procedure where four factors were modified in the electrophoretic conditions in two levels: high (+) and low (-). The parameters evaluated were: concentration of the electrolyte,

pH of the electrolyte, applied voltage and temperature of analysis (Table 4). These variations were defined considering the effective influence on routine analysis and the reported performances for CE methods applied to drugs determination in synthetic and biological matrix (Garcia et al. 2005; Wang et al. 2009; Mikuš et al. 2009).
The experiments were performed according to Plackett-Burman combinations of the parameters suggested by the statistical program Minitab 15® (Minitab Inc., State College, PA, USA) (Table 5). Results were expressed by Pareto graphics.

3.4. Method comparison

The proposed CE method by was compared to a previously published HPLC method for the determination of doripenem content in commercial samples (Mantovani et al. 2012). Analytical data were statistically evaluated by t-student test.

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