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Simultaneous quantification of daptomycin and rifampicin in plasma by ultra performance liquid chromatography: Application to a pharmacokinetic study

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ABSTRACT

A rapid and simple method based on ultra performance liquid chromatography (UPLC) with ultra violet detection has been developed for the determination of daptomycin (DPT) and rifampicin (RFM) in rabbit plasma using 4-nitrophenol as internal standard (IS). Sample preparation involved protein precipitation with an acetonitrile:methanol mixture and centrifugation. Chromatographic separation was achieved on an Acquity BEH C18 column (100 mm × 2.1 mm, 1.7 μm) using gradient elution with methanol and 0.1% aqueous TFA. The total analysis time was 4.5 min with DPT and RFM eluting at 1.9 and 2.1 min, respectively. The method was fully validated with a lower limit of quantitation (LLOQ) of 2 μg mL^{-1} for both DPT and RFM. The intra- and inter-day precision, measured as % relative standard deviation, were less than 12.1 for DPT and 10.7 for RFM, respectively. This validated method was successfully applied to a pharmacokinetic study involving intravenous administration of 14 mg kg^{-1} DPT and 30 mg kg^{-1} RFM to rabbits.

1. Introduction

The medical treatment of enterococcal endocarditis in the era of antibiotic resistance is a real challenge for the clinicians. Resistance to β-lactams, glycopeptides and aminoglycosides is a common feature especially for *Enterococcus faecium* hospital isolates [1]. Daptomycin (DPT), a rapidly bactericidal *in vitro* lipopeptide agent [2] (Fig. 1A) could be a suitable alternative. Although the drug exhibits excellent bactericidal effects *in vitro*, *in vivo* (human and animal data) treatment failures are not uncommon [3]. More effective treatment could be achieved either by higher dosing regimens [4] or by adding a second antimicrobial agent to achieve a synergistic effect [5]. In methicillin-resistant *Staphylococcus aureus* (MRSA) prosthetic staphylococcal endocarditis, rifampicin (RFM) (Fig. 1B), is part of the three drug regimen in case the strain is sensitive. Up to date, only scarce data exist for enterococcal endocarditis and the adjunct of RFM [6]. Synergy was observed *in vitro* between DPT and RFM against strains of high-level vancomycin resistant enterococci [7]. Thus, the DPT efficacy was tested in an experimental endocarditis model due to *E. faecium* in co-administration with RFM (mimicking human doses of 6 and 12 mg kg^{-1} o.d. of DPT and RFM, respectively).

Because DPT is co-administered with RFM in this protocol, the development of a new analytical method for the simultaneous quantification of the above-mentioned drugs would be an invaluable tool. At the moment, a number of methods have been published for the quantification of RFM [8–11] in plasma using high-performance liquid chromatography (HPLC). Limited published data are available for the analysis [12,13] of DPT in plasma and application to DPT pharmacokinetics studies thereof [14]. To our knowledge, there is no validated analytical methodology describing quantitative analysis of DPT simultaneously with RFM. The goal of the present study is to develop a novel, simple and rapid assay based on ultra performance liquid chromatography (UPLC) capable of monitoring plasma concentrations of both DPT and RFM after administration of an intravenous dose to rabbits.

2. Experimental

2.1. Reagents and chemicals

DPT was generously donated by Novartis Hellas, while RFM (Vetranal® grade) was obtained by Riedel de Haën (Seelze, Germany). 4-Nitrophenol (Pestanal® grade, internal standard—IS-) was

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purchased from Sigma (Buchs, Switzerland). Trifluoroacetic acid (TFA) was obtained from Acros (NJ, USA). Acetonitrile and methanol (gradient HPLC grade) were purchased from Merck (Darmstad, Germany). Ultra pure water was produced in the laboratory by a Direct-Q system (Millipore, France) and was used throughout the study. All substances and solvents have been used without any further purification.

2.2. Preparation of standard solutions and quality control samples

Stock standard solutions of the analytes (DPT and RFM) and the IS were prepared in methanol at a concentration of 1 mg mL^{-1} and stored at −35 °C. Working standard solutions of the analytes and the IS at a concentration of 100 μg mL^{-1}, were prepared by dilution of the aforementioned stock solutions in water:methanol 50:50 (v/v) and were kept refrigerated at −35 °C in dark. The solutions of the analytes and the IS were stable for at least one month, under the described conditions.

The plasma calibration standards were prepared at concentrations of 2, 4, 10, 20, 50, 100, 148, 200, 300, 400 and 500 μg mL^{-1} for DPT and RFM and 10 μg mL^{-1} for IS by spiking appropriate aliquots of working solutions to 25 μL of blank rabbit plasma. Low, medium and high concentration quality control (QC) samples at concentrations of 6, 120 and 440 ng mL^{-1} for DPT and RFM together with 10 μg mL^{-1} for IS were prepared by spiking blank plasma samples. The spiked samples were then treated as described in the plasma sample preparation section.

2.3. Plasma sample preparation

Plasma samples collected from rabbits were stored at −35 °C until analysis. Frozen plasma samples were thawed at room temperature and subjected to protein precipitation as follows. Plasma aliquot of 25 μL (or a calibration standard or a QC sample) and 10 μL of IS working solution (100 μg mL^{-1}) were added to a 1.5 mL Eppendorf tube and the mixture was vortexed for 60 s. Then, 600 μL of a methanol:acetonitrile 1:2 (v/v) mixture were added and the mixture was vortexed for 1 min followed by centrifugation at 10,000 rpm for 2.45 min at 15 °C. The supernatant was transferred into a clean Eppendorf tube and evaporated to dryness under a gentle nitrogen stream. The residue was reconstituted in 50 μL of mobile phase, vortexed for 30 s, centrifuged again under the same conditions for 3 min, transferred into a plastic autosampler vial

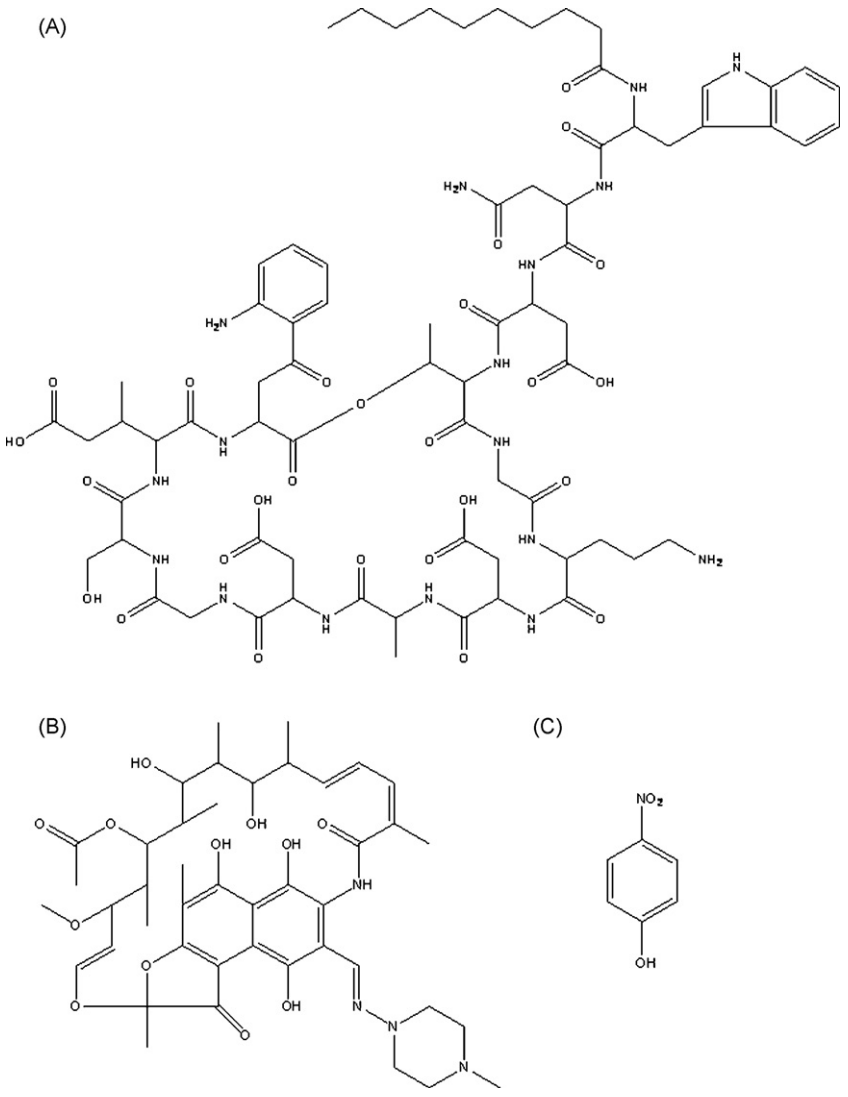

Fig. 1. Chemical structures of (A) daptomycin, (B) rifampicin and (C) IS (4-nitrophenol).

with pre-slit septum (Waters, USA), and 10 μL were injected into the UPLC–UV system.

2.4. Instrumentation

All analyses were performed on an Acquity UPLC™ system (Waters Corp., Milford, MA, USA) comprised of a Binary Solvent Manager, a Tunable UV Detector and an autosampler (Sample Manager) capable of maintaining the sample temperature from −5 to 40 °C. Chromatographic separation was achieved on a C18 BEH column (Waters Acquity, 100 mm × 2.1 mm, 1.7 μm), preceded by a precolumn (Waters VanGuard) of the same packing material. Mobile phases consisting of 0.5% formic acid or 0.1% aqueous TFA and either methanol or acetonitrile were evaluated, with 0.1% aqueous TFA (solvent A)–methanol (solvent B) being selected as this solvent mixture provided best peak shape and separation. The total analysis time was 4.5 min per injection and the flow rate was 0.5 mL min^{-1}. The gradient elution program used was as follows: from 5% B to 80% in 1.5 min; from 80% to 100% B in 0.1 min; 0.9 min at 100% B isocratic; from 100% to 5% B in 0.3 min. The column temperature was maintained at 40 °C throughout all experiments, whereas the sample temperature was maintained at 10 °C avoiding light exposure in order to prevent any possible degradation. Samples were injected in a 10 μL loop using the partial loop with sample overfill mode. The detection wavelength was set at 220 nm for the detection of DPT and at 342 nm for the detection of RFM and the IS. The Empower v2 software has been used for acquiring and processing the data.

2.5. Assay validation

The assay validation was performed to meet the acceptance criteria according to the FDA guidelines for bioanalytical methods validation [15]. The quantification of the analytes was performed by UPLC–UV using 4-nitrophenol as IS (Fig. 1C). The choice of the IS has been made based on the following: 4-nitrophenol is not an endogenously occurring substance, it exhibits high absorbance at the same λ_{max} as the analyte, it is stable under the conditions described, it can be easily separated from DPT and RFM with the column and mobile phase employed and it is inexpensive. The analytes under study were quantified by assessing the peak area ratios of each analyte vs. that of the IS.

2.5.1. Selectivity

The selectivity was assessed by analyzing six different blank plasma samples obtained by six different subjects, after sample processing according to the procedure described in Section 2.3. The corresponding chromatograms were tested for possible interferences at the retention times (t_R) of the analytes under study and the IS.

2.5.2. Calibration and LLOQ

The calibration curves of the analytes under study ($n = 6$) were constructed using blank rabbit plasma samples spiked with appropriate volumes of the analyte working standards and the IS. Each calibration curve consist of 11 points derived from spiked blank rabbit plasma samples with standard solutions of the analytes and the IS (plasma calibration samples, Section 2.2), which were analyzed by the developed methodology.

The model describing DPT and RFM concentrations in rabbit plasma has been assessed using non-linear regression analysis employing a quadratic model with 1/y weighting. The 0,0 value was neither included as a point nor the calibration curve was forced to pass through it. The lower limit of quantification (LLOQ) was defined as the lowest concentration of the analyte that can be determined with an inter-day precision below 20%, whereas the response of the blank was at least five times lower compared to that of a spiked sample, at the t_R of both the analytes and the IS.

2.5.3. Precision and accuracy

The intra-day precision expressed as relative standard deviation (%) (RSD%), and the accuracy expressed as relative error (%) (RE%), were evaluated by analyzing six different rabbit QC samples ($n = 6$) at each of the low, medium and high concentrations of the analytes. The inter-day precision was assessed by analyzing six batches of all QC samples on three different days.

2.5.4. Recovery

The recovery of the analytes under study from rabbit plasma was assessed by comparing six replicates of plasma samples at each of the three QC concentration levels (low, medium, high) with those of post-extraction spiked blank plasma samples.

2.5.5. Stability

The stability of DPT and RFM in plasma was studied by subjecting QC samples (at low, medium and high concentrations) to a variety of storage and handling conditions. Short-term stability was assessed at room temperature for 6 h, whereas long-term stability was assessed at −35 °C for 20 days. Stability during three successive freeze–thaw cycles from −35 to 25 °C was evaluated, as well as autosampler (in process sample) stability, by analyzing extracted QC samples stored in the autosampler at 10 °C for 16 h. The stability of the stock solutions in methanol was also evaluated at −35 °C for one month.

2.6. Bioavailability study

The developed analytical method was applied to study the plasma concentration–time profile after intravenous administration of 14 mg kg^{-1} DPT and 30 mg kg^{-1} RFM to four rabbits. All animal studies were approved by the Veterinary Department of the Prefecture of Athens (Athens 25/6/2008, K4180), according to Greek and European legislation. Experiments were performed in the Center of Experimental Surgery of Biomedical Research Foundation of the Academy of Athens. Blood samples (about 1 mL at each point) were withdrawn from the marginal ear vein prior to dosing at 0, 0.05, 0.5, 1.0, 2.0, 4.3, 9.0, 12.2 h after dosing and were collected in tubes with EDTA as anticoagulant. Plasma was separated by centrifugation at 3000 × *g* for 10 min and the removed plasma was kept frozen at −35 °C in Eppendorf tubes until analysis. Plasma concentration vs. time profiles were analyzed by non-compartmental analysis.

3. Results and discussion

3.1. Method development

The plasma sample preparation procedure, which consisted only of protein precipitation and subsequent centrifugation, was simple and provided almost quantitative recovery for both DPT and RFM and the IS. Other protein precipitation procedures, such as methanol 100% or acetonitrile 100%, were studied with no better results. More specifically, in the case of methanol, interferences from plasma matrix have been detected, whereas in the case of acetonitrile lower recovery was observed. The proposed method is also easy, time-saving and inexpensive.

The standards and the rabbit plasma samples were analyzed by the developed UPLC–UV methodology. The chromatograms of a blank rabbit plasma sample analyzed by the described UPLC–UV method is shown in Fig. 2 A (at 220 nm (i) and 342 nm (ii)), where none of the matrix components interferes with the analytes under

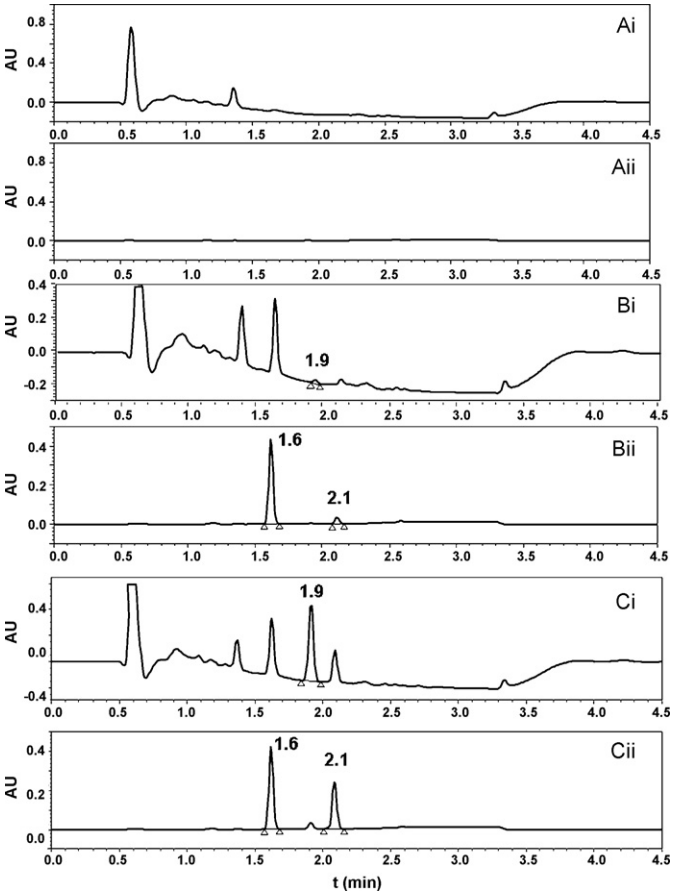

Fig. 2. Representative chromatograms of (A) blank plasma sample; (B) LLOQ rabbit plasma sample spiked with DPT and RFM (2 μg mL^{-1}) and IS (10 μg mL^{-1}), and (C) rabbit plasma sample collected 0.85 h after intravenous administration of DPT (14 mg kg^{-1}) and RFM (30 mg kg^{-1}) to a rabbit, at (i) 220 and (ii) 342 nm. The t_R for DPT, RFM and IS are 1.9, 2.1 and 1.6 min, respectively.

study or the IS at their corresponding retention times. Representative chromatograms of rabbit plasma samples spiked with DPT and RFM at the LLOQ are shown in Fig. 2B. DPT and RFM eluted at 1.9 and 2.1 min, respectively and the IS at 1.6 min, whereas the chromatograms of a study sample taken 0.85 h after intravenous administration of the antibiotics (14 mg kg^{-1} of DPT and 30 mg kg^{-1} of RFM) are shown in Fig. 2C.

3.2. Method validation

The assay was validated in terms of specificity, calibration, precision and accuracy, lower limit of quantitation (LLOQ), recovery of spiked rabbit plasma samples, and stability (short- and long-term, autosampler and freeze–thaw).

3.2.1. Selectivity

The assay was found to be selective since there were no interference peaks from endogenous plasma substances at the t_R of the analytes or the IS.

3.2.2. Calibration and LLOQ

The statistical analysis of the calibration curve samples shows that the response can be best described as a quadratic function of DPT and RFM concentration with 1/y weighting. The peak area ratios of the analytes to IS in rabbit plasma varied over the concentration range 2–500 μg mL^{-1}. The correlation coefficients (r) of the calibration curves were 0.998 and 0.9990 for DPT and RFM, respectively, indicating good correlation, whereas the equations of the fitted model are shown in Table 1. The back calculated values obtained are within the proposed 15% margin of the nominal values [15] indicating the adequacy of the proposed non-linear model.

The LLOQ was 2 μg mL^{-1} for DPT and RFM (Table 1) with signal to noise ratio > 5 (n = 6).

It should be noted that the calibration curves for DPT and RFM have been constructed using the aforementioned quadratic model employing *only* the peak areas of the analytes. Nevertheless, these results were inferior compared to the ones using the analyte/IS peak area ratios for the same concentration range, i.e., exhibited lower correlation coefficients (r).

3.2.3. Precision and accuracy

The intra- and inter-day precision and accuracy for DPT and RFM were evaluated by assaying QC samples (Table 2). The intra-day precision (RSD%) was less than 12.1% for all the analytes assayed. The accuracy (RE%) was better than 10.7% for both analytes (Table 2). These values were within the acceptable range, demonstrating that the method is reproducible, accurate and suitable for the quantitative determination of the analytes in rabbit plasma samples.

Similarly, the precision and accuracy results for DPT and RFM were also calculated without the use of the IS. In that case, the respective results were much inferior compared to the ones employing the IS.

3.2.4. Recovery

The recovery (R%, ±RSD%) of the analytes under study at three different levels (low, medium and high) is shown in Table 3, as well as the recovery of the IS at the level of 10 μg mL^{-1} (n = 6). The results show that the recovery is almost quantitative for DPT, RFM and IS.

3.2.5. Stability

The stability tests were performed for the low, medium and high QC samples as described in Section 2.5.5 and the results are shown

Table 1
Calibration data resulting from regression analysis for the determination of DPT and RFM in rabbit plasma by the developed UPLC–UV methodology.

	DPT[a]	RFM[a]
Calibration equation	$y = -0.13 \times 10^{-5}x^2 + 0.017x - 0.029$	$y = -2.93 \times 10^{-6}x^2 + 0.013x - 0.0058$
Slope X^2 (±SD[b])	$-0.13 \times 10^{-5} \pm 1.71 \times 10^{-6}$	$-2.93 \times 10^{-6} \pm 1.25 \times 10^{-6}$
Slope X (±SD[b])	$0.017 \pm 0.68 \times 10^{-3}$	0.013 ± 0.00047
Intercept (±SD[b])	-0.029 ± 0.011	-0.0058 ± 0.0077
SE[c]	0.078	0.064
Correlation coefficient (r)	0.998	0.9990
Range (μg mL^{-1} of plasma)	2–500	2–500
LLOQ (μg mL^{-1} of plasma)	2	2

[a] The quantification of the compounds and the construction of the calibration curves were performed as an area ratio vs. IS.
[b] SD, standard deviation.
[c] SE, standard error of the estimate.

Table 2
Precision (intra-day and inter-day) and accuracy data for the determination of DPT and RFM in rabbit plasma.

Level	Spiked conc ($\mu g\,mL^{-1}$)	DPT					
		Intra-day ($n=6$)			Inter-day ($n=18$)		
		Mean conc. found ($\mu g\,mL^{-1}$)	RE (%)	RSD (%)	Mean Conc. Found ($\mu g\,mL^{-1}$)	RE (%)	RSD (%)
LLOQ	2	2.19	9.5	12.1	2.22	4.2	9.5
LQC	6	5.92	−1.3	6.4	5.95	−0.9	11.7
MQC	120	115.3	−4.0	4.1	116.7	−6.3	4.3
HQC	440	443.4	0.8	10.7	438.8	−0.3	2.1
ULOQ	500	509.4	1.9	8.7	483.1	−3.4	1.3
Level	Spiked Conc ($\mu g\,mL^{-1}$)	RFM					
		Intra-day ($n=6$)			Inter-day ($n=18$)		
		Mean conc. found ($\mu g\,mL^{-1}$)	RE (%)	RSD (%)	Mean conc. found ($\mu g\,mL^{-1}$)	RE (%)	RSD (%)
LLOQ	2	2.21	10.5	9.2	2.18	9.4	3.3
LQC	6	5.42	10.7	10.2	5.98	−0.28	8.1
MQC	120	117.3	2.3	3.5	116.9	−2.6	4.0
HQC	440	445.0	−1.1	1.4	432.2	−1.8	3.4
ULOQ	500	450.6	−1.9	7.4	488.4	−2.3	1.4

RE%, % relative error and RSD%, % relative standard deviation.

Table 3
Recovery of DPT, RFM and IS in rabbit plasma ($n=6$).

Statistical variable	Nominal DPT concentration ($\mu g\,mL^{-1}$)			Nominal RFM concentration ($\mu g\,mL^{-1}$)			Nominal IS concentration ($\mu g\,mL^{-1}$)
	6	120	440	6	120	440	10
Extraction recovery							
Mean R (%)	102.5	100.6	96.5	99.7	102.	97.3	104.1
RSD (%)	4.3	5.1	3.6	4.6	6.1	3.5	4.4

Table 4
Stability results of DPT and RFM under various conditions.

Storage conditions	Nominal concentration ($\mu g\,mL^{-1}$)	DPT		RFM	
		RE (%)	RSD (%)	RE (%)	RSD (%)
Freeze–thaw (from −35 to 25 °C, $n=3$)	6	−0.6	6.7	−2.2	4.2
	120	4.5	6.2	2.9	10.6
	440	3.1	8.7	−0.4	11.0
Short-term (5 h, 25 °C, $n=3$)	6	7.2	5.0	−13.3	7.5
	120	3.3	11.2	−6.3	13.2
	440	2.6	7.8	5.8	12.9
Autosampler (16 h, 10 °C, $n=3$)	6	−4.5	1.4	−6.5	9.1
	120	−10.8	8.0	−8.7	6.7
	440	2.2	11.9	−5.5	12.6
Long-term (20 days, −35 °C, $n=3$)	6	6.6	4.9	9.6	7.1
	120	−1.2	4.2	−0.5	13.3
	440	−4.8	5.3	−6.6	14.1

in Table 4. The *short- and long-term stability* samples were determined in triplicate and the concentrations obtained were compared with the actual values of QC samples. The RSD% of short-term stability was found to be less than 13.2%, whereas for long-term stability the RSD% was less than 14.1% for all the analytes studied. The *autosampler stability* RSD% values obtained were found to be less than 12.6% for all the analytes under study. QC samples undergone *freeze–thaw stability* and the deviation found to be less than 11.0% of the nominal values for all the analytes under study.

3.3. Bioavailability study

After intravenous administration of 14 mg kg^{-1} DPT and 30 mg kg^{-1} RFM to four rabbits, plasma concentrations of DPT and RFM were determined by the described UPLC–UV method. The mean plasma concentration–time curves of DPT and RFM after intravenous administration of the antibiotics are shown in Fig. 3. The corresponding pharmacokinetic parameters are presented in Table 5. More than 200 rabbit plasma samples have been analyzed with the developed methodology with no degradation of performance. The results confirm that the assay is suitable for pharmacokinetic studies of DPT and RFM given at therapeutic doses for the treatment of enterococcal endocarditis.

Table 5
Pharmacokinetic parameters of DPT and RFM after intravenous administration to rabbits ($n=4$, mean ± SD).

Parameter	DPT	RFM
T_{max} (h)	0.06 ± 0.02	0.06 ± 0.02
C_{max} ($\mu g\,L^{-1}$)	133.77 ± 12.01	149.40 ± 38.19
$AUC_{(0-12\,h)}$ (h $\mu g\,mL^{-1}$)	619.66 ± 133.67	261.00 ± 37.90
$AUC_{(0-\infty)}$ (h $\mu g\,mL^{-1}$)	936.83 ± 298.75	283.31 ± 38.03
$T_{1/2}$ (h)	10.93 ± 4.81	4.33 ± 0.79
Kel (h^{-1})	0.076 ± 0.039	0.164 ± 0.021

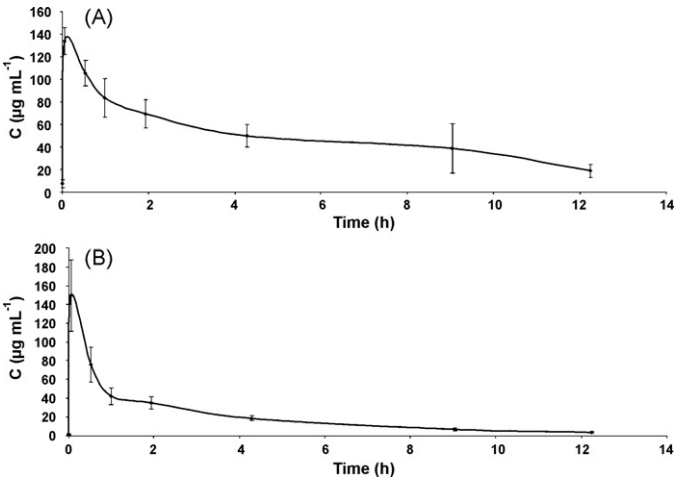

Fig. 3. Mean plasma concentration–time profile of (A) DPT and (B) RFM after intravenous administration of 14 mg kg^{-1} DPT and 30 mg kg^{-1} RFM to rabbits (mean ± SD).

4. Conclusions

A rapid UPLC–UV method for the quantification of DPT and RFM in rabbit plasma samples has been developed and validated. The method demonstrates good calibration fit, precision, accuracy and recovery. The selectivity of the developed methodology enables the accurate monitoring of the pharmacokinetics and bioavailability of the antibiotics under study. The small total analysis time of the method along with the simple sample pretreatment involved, allows the efficient analysis of the large number of samples involved in clinical studies.

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