

# Liquid Chromatography – Tandem Mass Spectrometry for Simultaneous Determination of Ticarcillin and Vancomycin in Presence of Degradation Products. Application to the Chemical Stability Monitoring of Ticarcillin-Vancomycin Solutions

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## Abstract

Acute bacterial conjunctivitis and their complications are commonly treated by 6 mg/mL ticarcillin and 50 mg/mL vancomycin eyes drops, formulated separately in hospitals. A rapid, selective and specific LC-tandem MS method has been developed and validated for simultaneous quantification of ticarcillin and vancomycin in solution and in presence of degradation products. Atlantis<sup>®</sup> C18 Column T3 (250×4.6 mm I.D., 5 μm) and gradient mobile phase composed of 44 mM trifluoroacetic acid/methanol allowed for good separation. Degradation products were separated on LC and detected with mass spectrometry in full scan mode. The method was suitable for the stability study of ticarcillin-vancomycin pH 5.2 solutions over an 8-day period storage at 5 ± 3°C and at room temperature (25 ± 2°C). The solutions remained stable up to 5 days at 5 ± 3°C. At room temperature, degradation of ticarcillin was accelerated in presence of vancomycin, while vancomycin stability was not further affected by ticarcillin. High-resolution mass spectrometry was used for the characterization of the degradation products.

**Keywords:** LC-MS/MS; Ticarcillin; Vancomycin; Stability; Degradation products

## Introduction

Acute bacterial conjunctivitis is one of the most common eye diseases. It is often caused by *staphylococcus aureus*, *staphylococcus epidermitis*, *streptococcus pneumonia*, *streptococcus viridans*, *haemophilus influenza*, *pseudomonas aeruginosa* and gram-negative intestinal bacteria [1-4]. It often evolves spontaneously to remission but could deteriorate into ocular keratitis, corneal abscess or endophthalmitis. In such cases, topical or systemic antibiotic treatment is required, reducing contagiousness and the emergence of bacterial resistance [5]. One of these treatments involves association of a β-lactamase ticarcillin and a glycopeptide vancomycin [3,6-8]. Because of their well-known instability in aqueous solutions, these antibiotics are only available as powder for injectable preparations and not as long-term stable eye-drops drug products. Locally eye drops are commonly prepared at hospital for standard clinical use [9]. So far, fortified antibiotic is individually formulated at high concentrations, required for cornea penetration [10]. Ticarcillin at 6 mg/mL and vancomycin at 50 mg/mL are commonly prepared [10-12].

In order to help formulation combining the two antibiotics, the stability of drugs mixtures stored at 5 ± 3°C and at room temperature (25 ± 2°C) was investigated. That's why, an LC-tandem MS (MRM) method for the simultaneous determination of the two antibiotics in presence of degradation products was developed and validated. High-resolution mass spectrometry (HR-MS) was used for the characterization of the degradation products formed.

The literature survey reveals a great number of HPLC methods for individual quantifications of ticarcillin and of vancomycin in body fluids [13,14] and in pharmaceutical formulations [15,16]. Ticarcillin as well as vancomycin have been successfully separated from their respective synthesis impurities [17,18]. LC-MS methods were also described for chirality study [19], but no one had dealt with the

simultaneous quantification of the two antibiotics in prepared mixtures and in presence of degradation products. Data on the individual drugs stability are available [20,21] but still no clue about their behaviour in mixtures.

## Experimental

### Instruments

The HPLC system consisted of an Ultimate 3000 HPLC from Dionex<sup>®</sup> (Sunnyvale, CA, USA), which is composed of a binary pump, a C18 Column Atlantis<sup>®</sup> T3 (250×4.6 mm I.D., 5 μm) from Waters<sup>®</sup> (Milford, MA, USA) and a refrigerated autosampler with a 100 μL syringe. Gradient mobile phase was made up with methanol (A) and 44 mM trifluoroacetic acid (TFA) (B). The injection volume was set at 50 μL, the flow rate at 0.8 mL/min and the column temperature at 20°C. The mobile phase gradient program was set as follows: 5 min: A:B (20:80 v/v); 25 min: A:B (90:10 v/v) and 30 min: A:B (20:80 v/v).

ABSciex<sup>®</sup> (Framingham, MA, USA) Mass Spectrometer 3200QTRAP<sup>®</sup> system was fitted with an electrospray ionization (ESI) interface operating in positive ion mode. MS data were treated using

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Received September 17, 2014; Accepted October 28, 2014; Published October 31, 2014

**Citation:** Belissa E, Nino C, Bernard M, Henriët T, Sadou-Yaye H, et al. (2014) Liquid Chromatography–Tandem Mass Spectrometry for Simultaneous Determination of Ticarcillin and Vancomycin in Presence of Degradation Products. Application to the Chemical Stability Monitoring of Ticarcillin-Vancomycin Solutions. J Chromatogr Sep Tech 5: 243. doi:10.4172/2157-7064.1000243

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Analyst Software® from ABSciex® (Framingham, MA, USA). Direct infusion of each antibiotic was realised to achieve common optimal MS and collision-induced dissociation (CID) parameters: collision energy=20 eV, capillary temperature=700°C, nitrogen as curtain gas=50 arbitrary units (a.u), air as sheath gas=50 a.u and as auxiliary gas=70 a.u. The degradation products were detected in full-scan mode within a mass/charge range of 50–800 *uma*.

OrbitrapVelos Pro LTQ Tune Plus 2.7.0.1103 SP1 (Thermo Fisher Scientific, CA, USA) was used in positive ion mode for accurate mass measurement as follows: the source voltage was set at 3.4 kV and the temperatures were fixed at 53°C (source) and 298°C (capillary). Data were treated with Xcalibur® software (version 2.2 SP 1.48).

## Materials and reagents

**Chemicals:** Ticarcillin disodium salt from Sigma Aldrich® (Saint-Louis, MO, USA) and Vancomycin hydrochloride from Xellia® (Oslo, Norway) were used. A Milli-Q water purification system from Millipore (Bedford, MA, USA) was used to generate ultrapure water. Sodium hydroxide 1.0 M and sodium hydroxide 0.1 M were prepared from sodium hydroxide 5.0 M Combi-Titrisol® purchased from Merck laboratory® (Darmstadt, Germany). Sodium acetate buffer (pH 5.2; 0.305 M) was made from anhydrous acetic acid purchased from Merck® (Billerica, MA, USA) where pH was adjusted to 5.2 with sodium hydroxide 1.0 M. Methanol HPLC grade was obtained from Sigma Aldrich® (Saint-Louis, MO, USA) and TFA analysis grade from VWR international® (Leuven, Belgium).

**Samples preparation:** Ticarcillin, vancomycin and ticarcillin-vancomycin working solutions were prepared from the same stock solutions obtained by dissolution of appropriate amounts of ticarcillin disodium salt and of vancomycin hydrochloride in ultrapure water. Stock solutions of ticarcillin were diluted to 2.3 mg mL<sup>-1</sup> of ticarcillin base into pH 5.2 acetate buffer. Solutions of vancomycin were set at a concentration of 16.7 mg mL<sup>-1</sup> vancomycin base in the same solvent. Ticarcillin-vancomycin mixture solutions were prepared in pH 5.2 acetate buffer with the same concentrations in antibiotics as for the individual solutions. Each solution, prepared in triplicate, was allocated into sealed glass vials to be stored for 8 days at 5 ± 3°C or at 25 ± 2°C. Stability was monitored at days 0, 3, 5 and 8. In order to have a standard degraded solution, an aliquot of ticarcillin-vancomycin solution was kept until 2 months at 5 ± 3°C. Working solutions were systematically diluted at 1/250 in acetate buffer/ultrapure water (75:25 (v/v)) prior to analysis.

## Validation of the LC-MS/MS method

**Linearity, accuracy and limits of detection and quantification:** Linearity over concentration ranges 2.3–9.2 µg mL<sup>-1</sup> for ticarcillin base and 16.7–66.8 µg mL<sup>-1</sup> for vancomycin base was established by plotting the peak areas versus the concentration of each analyte. Accuracy was also determined over these concentration ranges. LOQ was determined at signal to noise (S/N)10, by injecting a series of dilute solutions with known concentration.

**Precision:** The precision of the method was established by analysing the standard solutions at low (0.58 mg mL<sup>-1</sup> ticarcillin and 4.2 mg mL<sup>-1</sup> vancomycin) and high (2.3 mg mL<sup>-1</sup> ticarcillin and 16.7 mg mL<sup>-1</sup> vancomycin) concentration levels for each analyte. As mentioned above, solutions were diluted at 1/250 prior to analysis. To determine the intra-day precision of each standard, the same standard solutions were examined six times within one day. The inter-day precision was established by analysing each standard solution on three consecutive

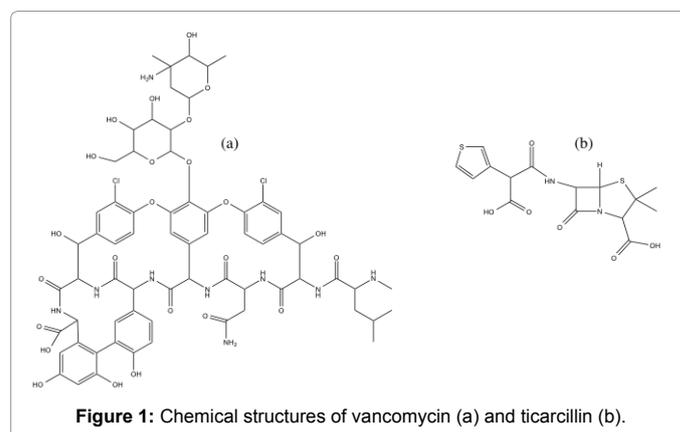
days. The precision of the assay was expressed by the RSD (%) of the replicate measurements.

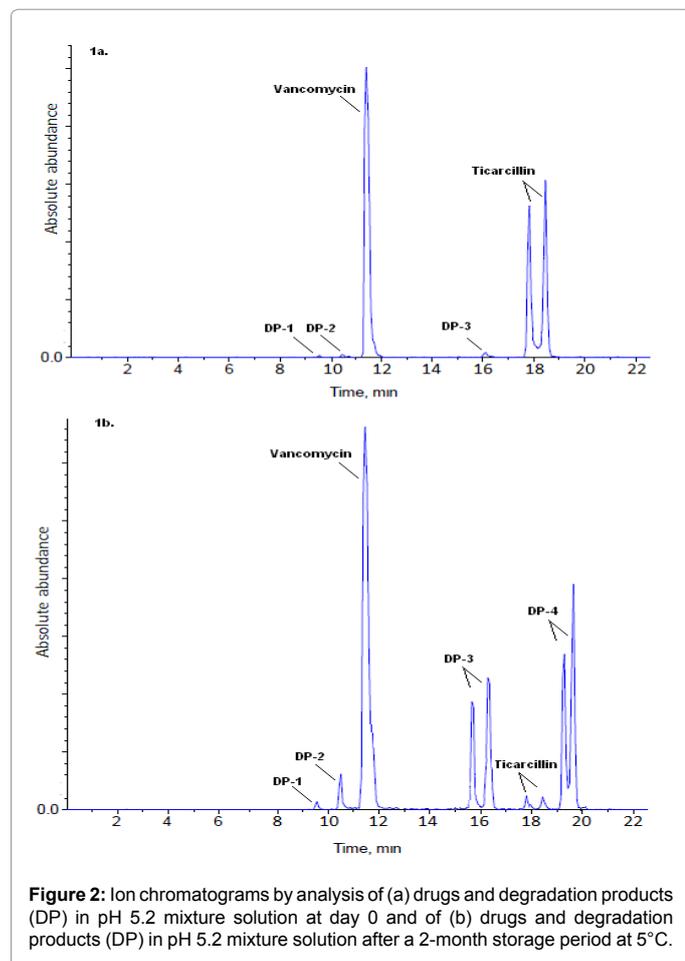
## Results and Discussion

### Chromatographic performance and MS<sup>2</sup> studies

HPLC-UV-MS<sup>2</sup> was used to specifically quantify the antibiotics and also to characterize the degradation products detected. HPLC allowed separating the active substances and their degradation products in a single run. Owing to their respective apparent pK<sub>a</sub>s, the use of TFA led to the formation of ion pairs with vancomycin, whereas ticarcillin would be chromatographed upon its molecular form. Chemical structures of ticarcillin and vancomycin were presented in figure 1. To improve the resolution between related substances generated during stability studies, mobile phase was tuned in gradient mode. Vancomycin was satisfactorily separated from ticarcillin epimers [22] as is shown in Figure 3a. “Ticarcillin active pharmaceutical ingredient (API) is basically composed of 2 epimers [18]. The two peaks, which result from analysis of ticarcillin reagent, present identical mass spectra so that confirms that the product is composed of epimers and shows the capacity of the method to also resolve them from each other. Besides, the more the elution is delayed, the better are the drugs separated from the degradation products generated in the 2-month storage solutions used for the LC development (Figure 3b, Table 1). The full-scan mass spectrum measured for the peak of each drug is comparable to that of the reference, suggesting lack of co-elution.

Parallel to LC development, 0.1 mg/mL vancomycin and ticarcillin solutions were individually infused into ESI+ mass spectrometer in order to select the most relevant transitions for specific quantification of the antibiotics in MRM mode. The full MS<sup>2</sup> spectrum of vancomycin showed an abundant precursor ion at *m/z*=725 corresponding to ion [M+2H]<sup>2+</sup> (Figure 3a). Among the major fragmentation mechanisms detected, the loss of vancosamine molecule (transition *m/z* 725 (307) was considered specific of vancomycin. Indeed, the degradation products formed by change upon the vancosamine part could hardly produce such an MS<sup>2</sup> transition. Besides, the rupture-rearrangement process resulting in the separation of the two parts of the glycoside group yielded the *m/z* 144 ion, which accounts for the base-peak. Therefore, *m/z* 307 ion and *m/z* 144 ion were set as the confirmation ion and the quantitative ion for vancomycin determination, respectively. As a result, quantitative determinations were performed in multiple reactions monitoring (MRM) using the following transitions: (i) 725 (*z*=2) 307 (*z*=1) for confirmation and 725 (*z*=2) 144 (*z*=1) for quantitation (vancomycin) and (ii) 385 198 for confirmation and 385 315 for quantitation (ticarcillin).





**Figure 2:** Ion chromatograms by analysis of (a) drugs and degradation products (DP) in pH 5.2 mixture solution at day 0 and of (b) drugs and degradation products (DP) in pH 5.2 mixture solution after a 2-month storage period at 5°C.

The full MS<sup>2</sup> spectrum of ticarcillin includes the protonated ion as well as [M+Na]<sup>+</sup> ion commonly observed for β-lactam antibiotics [21]. Similarly to the other penicillins, [M+H-26]<sup>+</sup> ion ( $m/z=359$ ) was formed by β-lactam ring opening due to hydration and by loss of CO<sub>2</sub> (Figure 3b). Another loss of CO<sub>2</sub> yielded  $m/z$  315 ion, accounting for the base-peak. Instead of CO<sub>2</sub> departure, loss of a 161 Da moiety from  $m/z$  359 ion (affording  $m/z$  198 ion) could be considered as quite specific to ticarcillin. As a result,  $m/z$  315 ion and  $m/z$  198 ion were set as the confirmation ion and the quantitative ion for ticarcillin determination, respectively.

### Method validation

The responses of vancomycin and of ticarcillin were linear with respect to the concentration range 2.0-9.2 μg mL<sup>-1</sup> for ticarcillin base and 13.2-66.8 μg mL<sup>-1</sup> for vancomycin base, yielding a correlation coefficient R of 0.9923 and of 0.9984, respectively. Basically, as ticarcillin is composed of 2 epimers eluted at t<sub>R</sub>17.8 and t<sub>R</sub>18.4 min, the sum of the two areas accounted for its signal response.

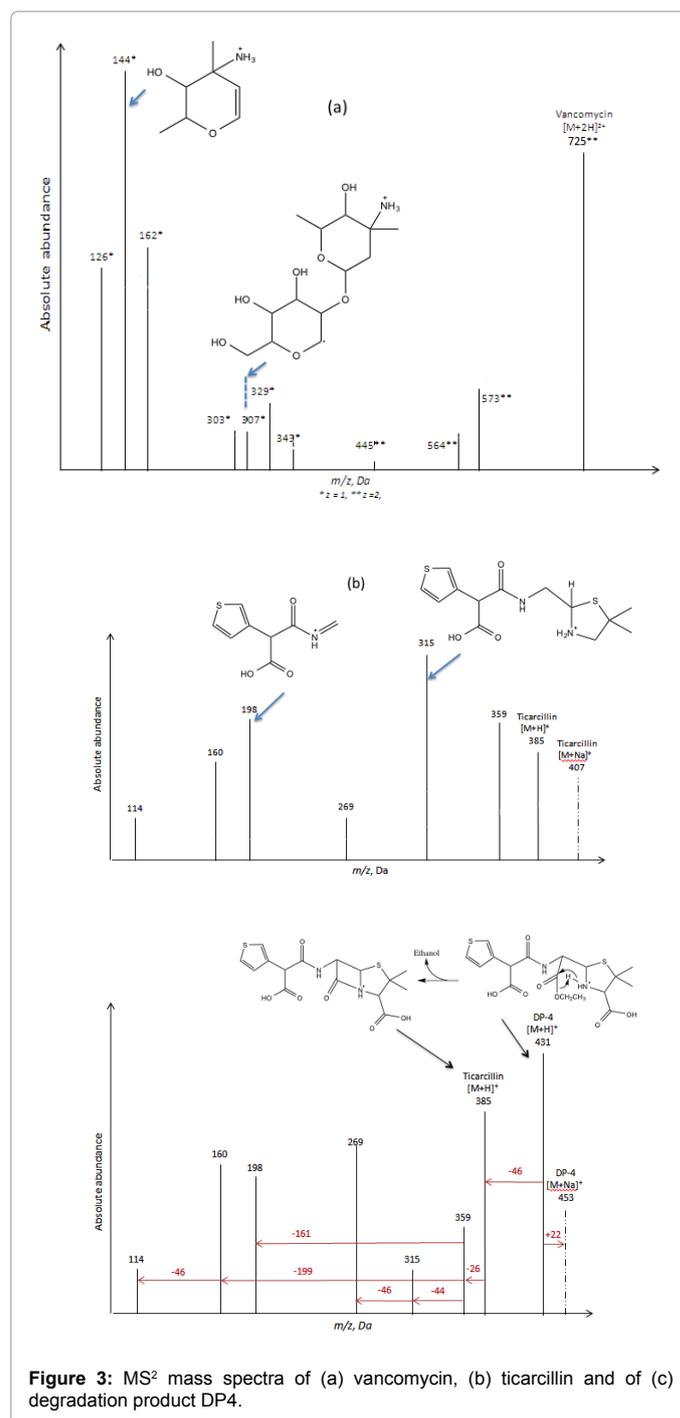
LOD and LOQ, based on ratios S/N 3 and S/N 10 measurement, were found to be 0.6 and 1.7 μg mL<sup>-1</sup>, respectively for ticarcillin base and 2.7 and 8.2 μg mL<sup>-1</sup>, respectively for vancomycin base.

The method was found to be precise with % RSD intermediate precision <2.86 at the calibration low level and <1.67 at the calibration high level for ticarcillin. % RSD intermediate precision was <1.19 at the calibration low level and <1.34 at the calibration high level for vancomycin.

The method was also shown accurate with excellent recoveries and low relative errors over the calibration range tested (Figure 4).

### Stability of individual and of mixture solutions fixed at pH 5.2

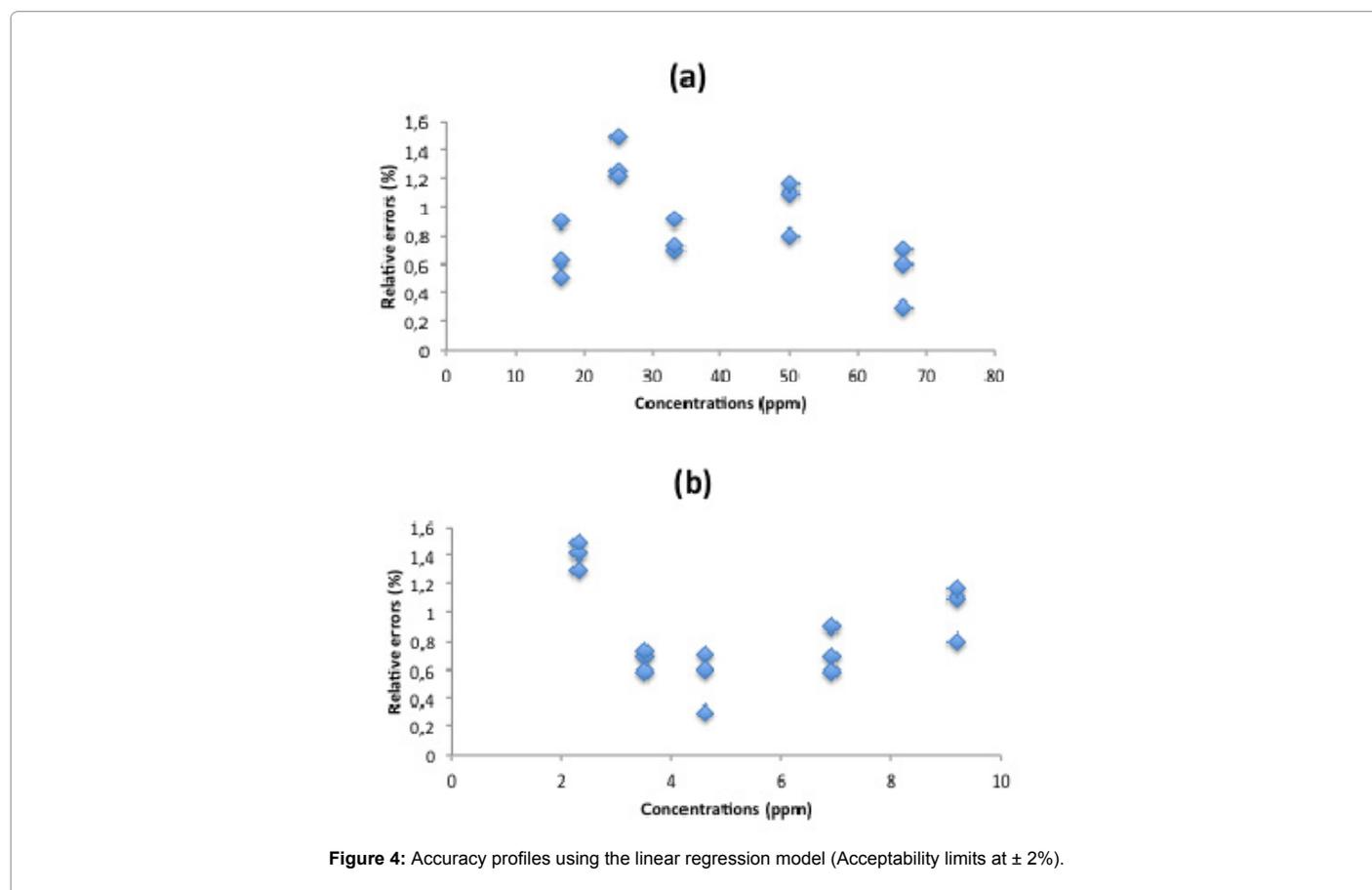
**Degradation products:** DP1 and DP2 are related to vancomycin as absent from the ticarcillin individual solutions (Table 1). DP3s and DP4s pertain to ticarcillin as not detected in the vancomycin individual solutions. The MS spectra of DP1 and of DP2 both exhibited a molecular mass with 1 Da greater than vancomycin's doubly protonated ion (Table 1). Accurate masses of DP1 and of DP2 are then consistent



**Figure 3:** MS<sup>2</sup> mass spectra of (a) vancomycin, (b) ticarcillin and of (c) degradation product DP4.

	DP1	DP2	Vancomycin	DP3/epimer	Ticarcillin/epimer	DP4/epimer
<b>RT (min)</b>	9.6	10.4	11.6	15.8/16.3	17.8/18.4	19.2/19.7
<b>Resolution factors</b>	2.5	1.67	4.65	1.81	1.53	
<b>(M+nH)<sup>+</sup> m/z</b>	725.3 (z=2)	725.3 (z=2)	724.7 (z=2)	403.0/403.0	385.0/385.0	431.0/431.0
<b>Accurate masses (relative errors ppm)</b>	725.2190 (-2.04)	725.2190 (-2.04)	724.7208 (-2.17)	403.0620 (-2.03)	385.0516 (-1.69)	431.0569 (-1.92)
<b>Elemental composition</b>	C <sub>66</sub> H <sub>76</sub> Cl <sub>2</sub> N <sub>8</sub> O <sub>25</sub> <sup>2+</sup>	C <sub>66</sub> H <sub>76</sub> Cl <sub>2</sub> N <sub>9</sub> O <sub>25</sub> <sup>2+</sup>	C <sub>66</sub> H <sub>77</sub> Cl <sub>2</sub> N <sub>9</sub> O <sub>24</sub> <sup>2+</sup>	C <sub>15</sub> H <sub>19</sub> N <sub>2</sub> O <sub>7</sub> S <sub>2</sub> <sup>+</sup>	C <sub>15</sub> H <sub>17</sub> N <sub>2</sub> O <sub>6</sub> S <sub>2</sub> <sup>+</sup>	C <sub>16</sub> H <sub>19</sub> N <sub>2</sub> O <sub>8</sub> S <sub>2</sub> <sup>+</sup>

**Table 1:** Retention times (RT), resolution factors (Rs) and MS data from ion chromatogram of drugs pH 5.2 antibiotics mixture solution after a 2-month storage period at 5°C. Accurate masses were measured by flow injection analysis and best possible elemental formula are proposed.



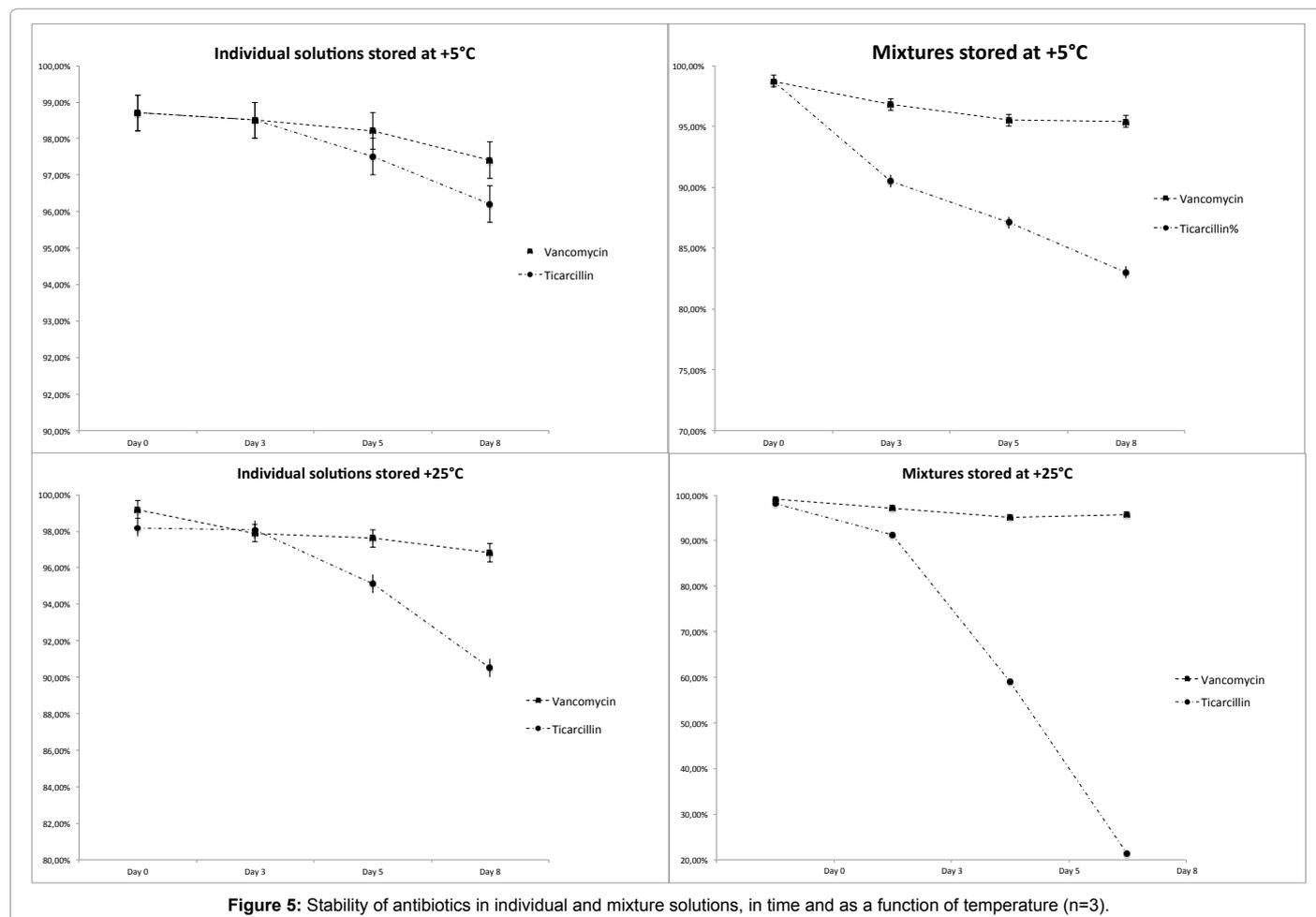
**Figure 4:** Accuracy profiles using the linear regression model (Acceptability limits at  $\pm 2\%$ ).

with the elemental formula C<sub>66</sub>H<sub>76</sub>Cl<sub>2</sub>N<sub>8</sub>O<sub>25</sub><sup>2+</sup>. The stability data have shown that DP1 was more likely a synthesis impurity than a degradant as it was already detected at T0 and at a variable concentration rate  $\leq 0.3\%$ . A derivative in which the asparagine residue is replaced by an aspartic acid residue has already been described as a synthesis by-product of vancomycin [23,24]. DP2 ion was assumed to be a crystalline degradation product (CPD1), a well-known degradation product of vancomycin [25-27]. Chemically, a vancomycin in pH 5.2 individual or mixture solution was quite stable over a 5-day storage period at 5°C as well as at room temperature (Figure 5). However, beyond a certain threshold, DP2 was shown to crystallize notably at day 5 at ambient temperature, based on HR-MS analysis of the particles isolated.

DP3s and DP4s are two groups of epimers formed from ticarcillin degradation. The epimers produced comparable mass spectra (Table 1). With a mass shift of 18 Da (Table 1), DP3s likely accounted for the two-penicilloic acid derivative epimers, which is consistent with the

literature data and the elemental formula deduced from the observed accurate mass (Table 1) [17,28-30]. DP3s increased in time parallel to a drop in ticarcillin concentration and even went through the roof with temperature or in presence of vancomycin. Unlike DP3s, DP4s were only detected in the 2-month storage solutions. Thereof yielded a protonated ion at  $m/z$  431.0569, which might correspond to C<sub>17</sub>H<sub>23</sub>N<sub>2</sub>O<sub>7</sub>S<sub>2</sub><sup>+</sup> elemental formula and be consistent with penicilloic ethanolate ester. Its CID mass spectrum has confirmed the structure (Figure 3c). An internal rearrangement mechanism leading to ethanol loss gave rise to the formation of protonated ticarcillin, explaining the great similarity with the MS/MS spectrum of ticarcillin (Figure 3b and 3c).

**Stability of the mixture:** Basically, at the concentrations used, the mixtures containing ticarcillin and vancomycin precipitated as soon as the two antibiotics were mixed in solution at the aforementioned concentrations, likely by formation of poorly soluble ticarcillin-



**Figure 5:** Stability of antibiotics in individual and mixture solutions, in time and as a function of temperature (n=3).

vancomycin ion-pairs. The precipitate was partly solubilised in 0.01 M sodium hydroxide ethanol and analysed by LC-MS. The sample was shown to exclusively contain ticarcillin and vancomycin. Based on this outcome, some solubilisation experiments were undertaken and the use of pH 5.2 acetate buffers had made co-solubilisation possible.

Unlike vancomycin, stability of ticarcillin in pH 5.2 individual solutions differed from that of ticarcillin in pH 5.2 mixture solutions (Figure 5). At day 8 and at 5°C, ticarcillin concentration dropped by 10% in presence of vancomycin, whereas its individual solutions still contained at least 96% of the drug. The phenomenon was much more significant at room temperature with sharp increase of DP3s. It seems that nucleophilic functions of vancomycin could catalyse ticarcillin hydrolysis [29-32].

At day 5 and similarly to what was previously described for the pH 5.2 individual vancomycin solutions, DP2 crystals were formed in the mixture solutions and thereof could initiate vancomycin-ticarcillin precipitation, actually progressively formed and visually detected from day 5-6 in the solutions stored at 5°C and at room temperature.

## Conclusion

A method for the simultaneous determination of ticarcillin and vancomycin in presence of degradation products has been developed and validated. It is based on the gradient LC separation performance and *MRMMS* detection. It has allowed the stability monitoring of the

pH 5.2 antibiotics individual and mixture solutions. It was shown that ticarcillin mixed with vancomycin was much less stable than ticarcillin alone in solution. Unlike ticarcillin, vancomycin stability was not affected by the presence of ticarcillin at the studied concentration levels. Vancomycin degradation could make the solutions physically unstable.

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**Citation:** Belissa E, Nino C, Bernard M, Henriët T, Sadou-Yaye H, et al. (2014) Liquid Chromatography–Tandem Mass Spectrometry for Simultaneous Determination of Ticarcillin and Vancomycin in Presence of Degradation Products. Application to the Chemical Stability Monitoring of Ticarcillin-Vancomycin Solutions. *J Chromatogr Sep Tech* 5: 243. doi:[10.4172/2157-7064.1000243](https://doi.org/10.4172/2157-7064.1000243)

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