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Accurate Quantification of Amoxicillin in Different Drug Formulations using Advanced Chemometric Methods

Yahya S. Al-Degs*, Amjad H. El-Sheikh, Duaa M. Harb

Chemistry Department, The Hashemite University, Zarqa ,Jordan

ABSTRACT

Amoxicillin is an excellent antibiotic that used on daily basis. Moreover this compound is often used in combination with clavulanic acid. Therefore, there is an urgent need to develop sensitive and fast analytical method to detect amoxicillin over many commercial formulations. In this work, a simple and fast analytical method based on partial least squares PLS calibration was proposed to quantify amoxicillin in different pharmaceutical formulations including tablet and suspension forms. Due to the intense matrix effect, simple univariate calibration (at 228 nm) was found impractical in formulations containing clavulanic acid which negatively interfere with spectral analysis beside other excipients. Multivariate calibration by PLS was applicable for amoxicillin quantification in all formulations with high accuracy (98-103%) and precision (<8%). The proposed analytical method was able to quantify amoxicillin even in the presence of clavulanic acid and other excipients. Before running PLS, the optimum pH for analysis was7.0 and at pH>7.0 hydrolysis of amoxicillin was initiated. The proposed PLS method would be a good substitute for HPLC due to saving of time, energy and organic solvents.

Keywords: Drugs quantification; Amoxicillin; PLS calibration; Matrix effect.

INTRODUCTION

Antibiotics are drugs used to kill organisms such as bacteria, viruses, funguses and protozoa.[1]Since their discovery in the 1930s, antibiotics have made it possible to treat diseases caused by bacteria such as pneumonia, tuberculosis and meningitis. Antibiotics save the lives of millions of people around the world. Some antibiotics are produced from living organisms such as bacteria and funguses. Other antibiotics are totally or partially produced synthetically.[1] Amoxicillin (7-[2-amino-2-(4-hydroxyphenyl)-acetyl] amino-3,3-dimethyl-6-oxo-2-thia-5-azabicyclo[3.2.0] heptane -4-carboxylic acid)is very popular antibiotic and is often used to treat a wide variety of bacterial infections such as; tonsillitis, bronchitis, pneumonia, gonorrhea, and infections of the ear, nose, throat, skin, or urinary tract.[2] This drug is also acts against bacterial activity by inhibiting the synthesis of bacterial cell walls by stopping the cross-linkage between the linear peptidogly can polymer chains that make up a major component of the bacterial cell wall.[3] Clavunilic acid is an irreversible inhibitor of many bacterial β-lactamases by blocking the active sites of these enzymes.[4] Therefore, clavulanic acid is added to amoxicillin formulations for enhancing its effectiveness against amoxicillin-resistant bacteria. So that pharmaceutical industry combined both drugs in the same formulation for better functionality.[5]

Several methods have been reported for the analyses of amoxicillin and clavulanic acid, such as microbiological assay, enzymatic assay, ultraviolet spectrometry, polarography and liquid chromatography.[6,7] In fact chromatographic-based methods were highly used but requires highly qualified analysts and continuous maintenance of the instrument. In addition chromatographic methods also required expensive columns

* yahya@hu.edu.jo.

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and solvents. Hence, developing new analytical methods is often needed for the quantitative estimation of amoxicillin in pharmaceutical formulations. Recently, multivariate calibration methods have been tested for analyzing drug formulations. For example, amoxicillin has been quantified in drug formulations using multivariate calibration with high accuracy and without implementing laborious chromatographic or electrochemical procedures.[6,7] Compared to liquid chromatography, assaying drugs formulations by multivariate calibration requires less solvent consumption and avoids using tedious chromatographic instruments. In a recent study, Müller co-workers have been reported a simple and fast method based on PLS-calibration for accurate quantification of amoxicillin in pharmaceutical formulations.[8] The proposed method was validated against liquid chromatography.[8] In another study, Muller and co-workers have reported a method for quantification of amoxicillin in the presence of clavulanic acid and in commercial tablets using multivariate calibration with excellent accuracy and precision.[9]

Generally, the reported multivariate calibration methods on amoxicillin quantification in commercial formulations are rather limited. Moreover, local research on drugs quantification is mainly concentrated on chromatographic-based methods and very rare research on multivariate calibration was reported. In this work, the possible application of PLS as efficient multivariate calibration method for quick quantification of amoxicillin in marketed formulations will be investigated. Although previous studies reported analysis of amoxicillin by MVC, however the novelty of the present work arises on application of PLS which not reported for amoxicillin quantification (in the presence clavulanic acid) in commercial formulations.

2. Partial least squares calibration: Theoretical background

In multivariate calibration the analysts often deal with large data sets. Vectors and matrices are a reasonable way to handle with large data sets. In multivariate calibration, a mathematical relationship between large data matrix contains absorbance values **A** and a vector containing concentration values of solute/drug **c**:[10,11]

$$\mathbf{A}_{m\times n}=\mathbf{c}_{m\times 1}\mathbf{b}_{1\times n} \quad (1)$$

Where *m* and *n* are number calibration samples and *n* number wavelengths used in the analysis. Number of calibrated solutes is one (i.e., amoxicillin). Using PLS algorithm, **b** (calibration vector of amoxicillin) is the estimated as:[10-13]

$$\mathbf{b}=\mathbf{W}^t(\mathbf{P}\mathbf{W}^t)^{-1}\mathbf{q} \quad (2)$$

Where **W**, **P** and **q** represented the PLS-weight matrix for **A**, PLS-loading matrix for **A**, and PLS-loading vector for **c**, respectively. The optimum number of PLS variables needed for estimation of **b** were estimated using cross-validation technique.[10] Once **b** was estimated by Eq2, prediction of calibrated drug from the unknown spectrum **a** was carried out as:[10,11]

$$c_{un} = \mathbf{ab} \quad (3)$$

PLS calibration has the ability to find amoxicillin level in new samples even in the presence of un-calibrated solutes like clavulanic acid or other excipients.[13] All calculations were carried out using MVC1 program which is available on internet.[14]

3. Experimental Procedures

3.1. Materials and Instruments

Amoxicillin was kindly donated from Dar Al-Dwaa pharmaceutical company (Amman, Jordan). The medicine was provided in high purity (>99.9%). Stock solutions of amoxicillin and drug extracts were analyzed directly after preparation to minimize amoxicillin degradation or hydrolysis. The chemical structure of amoxicillin is provided in Figure 1.

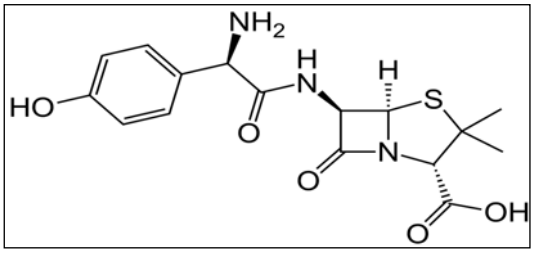

Figure 1: Chemical structure of amoxicillin (*pKa* values 2.67, 7.11 and 9.55)[15]

Hydrochloric acid and sodium hydroxide were purchased from BDH (UK) and double distilled water used for preparation of solutions. UV spectra were recorded using double beam Spectrophotometer (Thermo evolution 100 electro corporation, USA). pH was measured using digital pH meter (WT, Germany). All solutions were filtered using 0.45 mm cellulose membrane filter.

3.2. Spectral measurements of amoxicillin

Due to the acid-base equilibria of amoxicillin, the spectral behavior of amoxicillin was investigated at different pH values. Three solutions of amoxicillin (5.0 mg/L) were prepared at 3.0, 7.0 and 10.0 (pH was adjusted using diluted NaOH or HCl solutions) and scanned over the range 200-300 nm with 1.0 step to give 101 spectral point per spectrum.

3.3. Preparation of standard solutions: Calibration and validation sets

A 100.0 mg/L standard solution of amoxicillin was prepared by dissolving 100 mg (±0.0001 g) in distilled water in a 1.0 liter volumetric flask. The calibration solutions (1.0, 2.0, 4.0, 6.0, 8.0, 10.0, and 12.0 mg/L) and validation solutions (3.0, 5.0, 7.0, 9.0, and 11.0 mg/L) were directly prepared from the stock solution with appropriate dilution using distilled water. Calibration set was used to build PLS model while validation set was used for external validation of the model. The size of matrix **A** is 7×101 and vector **c** is 7×1. After building both univariate and PLS models, the level of amoxicillin was estimated in the extracts of the drugs using the created models.

3.4. Commercial formulations of amoxicillin

The models were assessed by quantification of amoxicillin in many commercial formulations. Six formulations were collected from different local pharmacies within Amman area. Half of the formulations were containing amoxicillin and clavulanic acid with different ratios while the rest of formulations were containing amoxicillin (250-1000 mg per tablet). Both tablet and suspension forms were tested. In most formulations, the added excipients were sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, hydroxypropyl methyl cellulose, titanium dioxide, propylene glycol, and ethyl cellulose. For table form, amoxicillin was assayed by weighing the content of five tablets and grounding to a fine powder. An amount exactly corresponding to the average tablet weight was suspended in 50 mL distilled water. The final suspension was sonicated for 10 min and then diluted to 1.0 liter and the final pH was adjusted to 7.0. For suspensions, 10 mL aliquot was diluted to 1.0 L and the pH was adjusted to 7.0 and stored in a cold place before analysis. The extracts were further diluted, filtered through 0.45 µm-membrane and scanned over the range 200-300 nm with 1.0 nm step.

3.5. UV scanning and PLS calibration

The absorbance measurements were obtained using a quartz cuvette of 1.0 cm optical path. The spectra were recorded over the wavelength range of 200–300 nm and the digitalized absorbance values (1.0 nm step, 101 points/spectrum) were exported to matlab® (MATLAB® (version 7.0) for PLS calibration. Both PLS and cross-validation techniques were carried out using MVC1 program as outlined in section 2.

4. Results and discussion

4.1. Spectral behavior of amoxicillin at different pH

To find the appropriate pH for scanning, the spectrum of amoxicillin (5.0 mg/L) was measured at different pH values and the results are provided in Figure 2.

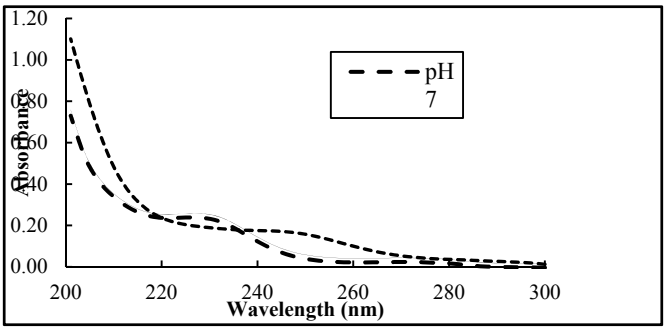

Fig 2: Effect of pH on spectral shape of amoxicillin (5.0 mg/L)

It is important to mention that amoxicillin is a weak acid with *pKa* values of 2.67, 7.11 and 9.55 [51]. Accordingly, it is possible that spectral behavior of amoxicillin will be sensitive to solution pH. At pH 3.0 and 7.0, identical spectral shape was observed as the intensity and peak position were not changed. However at pH 10.0 the spectral shape of amoxicillin was significantly changed where the intensity at 228 nm was decreased. The spectrum recorded at pH 10.0 was attributed to the basic form of amoxicillin (*pKa* of amoxicillin is 9.55). In fact, amoxicillin has a better UV signal at pH 3 or 7.0 due to the intense peak at 228 nm, hence, PLS calibration was carried out at pH 7.0 for better detection of the solute.

4.2. Application of univariate calibration for amoxicillin quantification: Direct and indirect matrix effect

Formulations containing amoxicillin only: In fact, matrix has a negative influence on spectroscopic analysis. There are two types of matrix effect, direct and indirect interference. In pharmaceutical analysis, direct interference is attributed to the co-existed drugs while excipients represented indirect interferences. Both interferences would affect the final accuracy of the proposed method. Compared to univariate calibration, multivariate calibration can handle both direct and indirect interferences if they included in the calibration stage. To apply univariate calibration, a linear calibration graph was initially created. Fig 3 shows amoxicillin spectra measured at different concentrations (1.0-12.0 mg/l0). Calibration equation was created by plotting $A_{228\ nm}$ (λ_{max} of amoxicillin) against concentration. The following equation was obtained by linear regression: $A_{228\ nm} = 0.023\ C_{amoxicillin} - 0.001$, $r^2 = 0.9997$

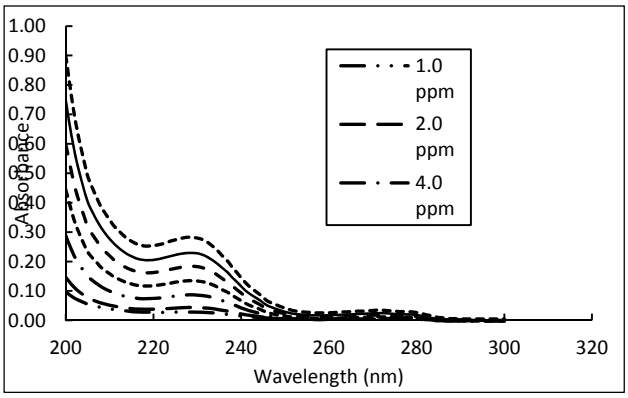

Fig 3: UV spectra of amoxicillin at pH 7.0 and at different concentrations

As indicated in Fig 3, UV spectrum of amoxicillin (at 12.0 mg/L for example) indicated that it has one distinct absorption wavelength at 228.0 which was attributed to $\pi \rightarrow \pi^*$ electronic transition. As shown in Fig 3, absorption at 228 nm was increased by increasing concentration. The estimated figures of merit were: molar absorptivity (8504 mol L^{-1} cm^{-1}), detection limit (0.15 mg/L), limit of quantification (0.52mg/L), and dynamic range (0.52-12.0 mg/L). The final results of amoxicillin quantification in all formulations are summarized in Table 1.

Table 1. Application of univariate calibration for amoxicillin quantification in marketed formulations[a]

Formulation	Amoxicillin content mg/tablet	DF[b]	$A_{228\ nm}$	C (mg/L)[c]	Predicted dosage mg/tablet	Rec%[d]
A	250	30	0.158	6.9	207.4	86.0
B	500	40	0.349	15.2	608.7	121.7
C	1000	40	0.684	29.8	1191.3	119.1
D	500 mg125 mg[e]	40	0.417	18.2	727.0	145.4
E	875 mg125 mg[e]	50	0.585	25.5	1273.9	151.6
F	125 mg/5 ml31.25 mg/5ml[e]	4000	0.246	10.7	214[f]	171.3

a. $n = 3$, RSD < 10%
b. Dilution factor before measurements
c. Estimated from calibration quation: $A_{228\ nm} = 0.023\ C_{amoxicillin} - 0.001$
d. Recovery% estimated from the claimed level of amoxicillin that indicated on the label
e. clavulanic acid content
f. per 5 ml suspension

In general, determination of amoxicillin in A-C formulations (containing only amoxicillin) was better when compared to those containing clavulanic acid beside amoxicillin (D-F formulations). In fact, the performance of univariate calibration was not acceptable for amoxicillin prediction. High recoveries were obtained (145-171%) which is not acceptable for pharmaceutical analysis. As shown in Table 1, the predicted level of amoxicillin is always higher than claimed value indicating the presence of systematic error in the analysis. Indeed, the presence of clavulanic acid (formulations D-F) was attributed to the positive error in the analysis. Another interested point in Table 1was the intense dilution (30-4000) of the extracts before UV scanning. The high dilution was necessary due to the high level of amoxicillin in the sample. The extreme case was observed for F formulation with final recovery of 171.3% and this would be attributed to the high content of clavulanic acid. The precision of analysis was estimated by repeating the test three to four times for each formulation. The final RSD was less than 10% indicating the acceptable precision of the applied method. Beside clavulanic acid, the added excipients including sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, hydroxypropyl methyl cellulose, titanium dioxide, propylene glycol, and ethyl cellulose should have a negative influence on drug quantification. The spectral overlapping between amoxicillin and other excipients is possible and this may retard chemical analysis by univariate calibration even in the formulations that contain amoxicillin only. However, the high dilution (40-4000) should reduce the negative influence of excipients on amoxicillin. Fig 4 shows the spectra of commercial formulations (A-C) and after intensive dilution.

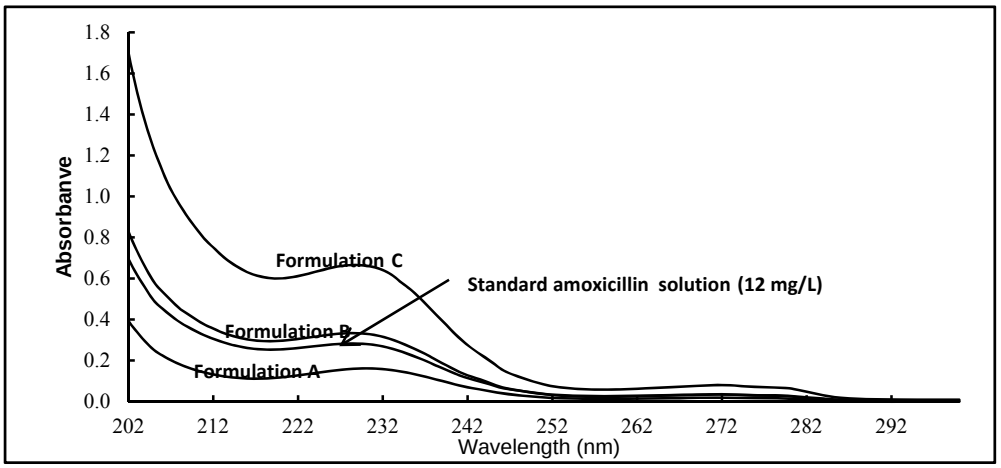

Fig 4: UV spectra of commercial formulations along with a standard solution of amoxicillin (pH 7.0).

As indicated in Fig 4, all formulations have similar spectral shape which is also comparable with standard solution. The main conclusion is that excipients have no serious overlapping with UV signal of amoxicillin and this is essential for application of univariate calibration. Application of univariate calibration for determination of amoxicillin in commercial formulations (containing only amoxicillin) are reported in the literature.[16,17] Prakash and co-workers have reported simple, sensitive, precise and economical univariate calibration at 230 nm for quantification of amoxicillin in commercial formulations and at pH 7.2. The dynamic range of the method was 2.5-50 mg/L and high absorptivity of amoxicillin was reported 1.0×10^4 L mol^{-1} cm^{-1}.[16] The main conclusion from the

earlier studies was the applicability of univariate calibration for amoxicillin quantification in formulations containing amoxicillin.

4.3. PLS calibration and handling matrix effect

Obviously, the next step is the application of PLS calibration which supposed to handle both direct and indirect matrix effect and predicts amoxicillin with high accuracy. PLS is suitable for modeling different sizes of **A** matrices which containing the spectral data. As outlined earlier, PLS decomposes **A** while using concentration information (vector **c)** into smaller matrices to estimate calibration vector **b** that will be used for drug prediction in real samples. Simply, PLS is an efficient numerical tool that generate a quantitative relationship between matrix **A** (containing spectral measurements) and a property of interest **c** (amoxicillin content). An important parameter in PLS calibration is the number of latent variables needed for good prediction. This number is highly dependent on the number of un-calibrated interferences in the matrix.[18-20] PLS calibration was carried out using the entire spectral data (200-300 nm, 101 points/sample) while changing number of latent number variables for amoxicillin prediction in different matrices and the results are provided in Table 2.

Table 2. PLS variables for optimum amoxicillin in different formulations

PLS prediction (mg/tablet) at different variables (*h*)					
Formulation	1 PLS	2 PLS	3PLS	4 PLS	5 PLS
B (amoxicillin only 500 mg)	477	492	532	536	552
D (amoxicillin 500 mg with clavulanic acid 125 mg)	408	422	475	508	544

As indicated in Table 2, number of PLS latent variables needed for optimum prediction was dependent on the presence of clavulanic acid in the matrix. The performance of PLS is getting better by adding more variables and a stable performance was observed at 2 variables for formulation containing amoxicillin only. For D, higher number of PLS variables (4) were needed to account for the negative influence of clavulanic acid in the matrix. In fact, number of PLS variables may have some physical meaning for the analytical system.[11,12] The higher number of variables are needed to account for new compounds (or excipients) that present in the extract.[12] For both formulations, it was necessary to mention that using higher number of PLS variables resulted in over prediction of the drug. For example, the predicted values of amoxicillin in B and D (using five variables) were 552 and 532 mg, respectively, and this obviously higher than the claimed value (500 mg). It is important to mention that number of variables needed for optimum prediction is highly dependent on the matrix of the formulation. Prediction of amoxicillin in all formulations is provided in Table 3.

Table 3. PLS calibration for amoxicillin quantification in commercial formulations [a]

Formulation	**Amoxicillin content mg/tablet**	**DF[b]**	**C (mg/L)[c]**	**Predicted dosage mg/tablet**	**Rec%[d]**
A	250	30	8.1 (3)	243	97.2
B	500	40	12.3 (3)	492	98.4
C	1000	40	24.6 (3)	984	98.4
D	500 mg 125 mg[e]	40	12.0 (5)	508	96.0
E	875 mg 125 mg[e]	50	16.9 (5)	845	96.6
F	125 mg/5 ml 31.25 mg/5ml[e]	4000	6.4 (5)	128[d]	102.4

a. $n = 3$, RSD < 10%

b. Dilution factor before measurements

c. PLS was applied over the range: 200-300 nm. Number of PLS variables were selected to get the best prediction of amoxicillin in the formulation (PLS variables are between brackets)

d. Recovery% estimated from the claimed level of amoxicillin that indicated on the label

e. clavulanic acid content

f. per 5 ml suspension

As shown in Table 3, PLS calibration showed an excellent performance for amoxicillin detection in all formulations with high recoveries 96-102%. In fact, 3-PLS factors were needed to predict amoxicillin in formulations A-C. The need for three factors was to remove the effect of excipients and accurately predict amoxicillin content. The results indicated that PLS calibration was more effective than univariate calibration for predicting amoxicillin in formulations containing only this drug. It was important to mention that the extracts of drugs were extensively diluted with water and this would reduce the negative influence of excipients on the analytical signal. As already know, multivariate calibration has been successfully used for quantification of many active ingredients in commercial formulations.[21] In fact, few studies has been reported for quantification of amoxicillin in drug formulations.[18-20] Furthermore, application of PLS for amoxicillin prediction in local formulations is not reported. As indicated in Table 3, amoxicillin was quantified in clavulanic acid-containing-formulations (D-F) with convincing recoveries. The overall precision was also within the acceptable limits (<10% in all cases). Compared with univariate analysis, the performance of PLS was excellent with final recoveries 96-102.4%. The proposed analytical procedure is very practical where amoxicillin was quantified without running HPLC.

CONCLUSION

Univariate calibration (i.e., Beer`s law) would be applicable for amoxicillin quantification but in formulation that do not contain clavulanic acid as it interfere with analysis. PLS was workable with good recoveries for amoxicillin quantification in all formulation. PLS can accurately predict amoxicillin even in the presence of clavulanic acid. The proposed analytical method is simple were no special cleaning procedures are needed like liquid-liquid or solid-liquid extractions. MVC1 program is very simply to apply and no previous knowledge in complex multivariate calibration mathematics is needed.

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القياس الصحيح لمركب الأموكسيسيللين في عدد من العقاقير باستخدام طرق الكيمومتركس المتطورة

يحيى سالم الدقس*، امجد حسين الشيخ*، دعاء حرب*

* قسم الكيمياء، الجامعة الهاشمية، الزرقاء

ملخص

الأموكسيسيللين هو مضاد حيوي ذو فعالية عالية يستخدم بشكل يومي. وعلاوة على ذلك يستخدم هذا المركب في كثير من الأحيان مع حمض كلافولانيك. لذلك، هناك حاجة لتطوير طريقة تحليلية حساسة وسريعة للكشف عن الأموكسيسيللين في العديد من التركيبات التجارية. في هذا العمل، تم اقتراح طريقة تحليل بسيطة وسريعة تقوم على استخدام PLS لتحديد الأموكسيسيللين في التركيبات الصيدلانية المختلفة بما في ذلك العقار الحبيبي والسائل المعلق. بسبب تأثير المواد المضافة على الدواء، فإن المعايرة أحادية المتغير البسيطة للدواء (عند 228 نانومتر) غير دقيقة خصوصا في العقاقير التي يتواجد بها حمض كلافولانيك الذي يتداخل سلبا مع التحليل الطيفي بجانب الإضافات الأخرى في الدواء. كانت الطريقة المعتمدة التي تعتمد على المتغيرات المتعدده جيدة جدا في تحديد الأموكسيسيللين في جميع التركيبات بدقة عالية (98–103٪). إن الطريقة المقترحة كانت قادرة على قياس الأموكسيسيللين حتى في وجود حمض كلافولانيك. تم تطبيق الطريقة عند درجة حموضة 7.0. إن الطريقة المطبقة ستكون بديلا جيدا عن الكروماتوغرافيا السائلة المطبقة حاليا بسبب توفير الوقت وتوفير طاقة التشغيل وكذلك الاستغناء عن المذيبات العضوية المستخدمة بكثره في الكروماتوغرافيا السائلة.

الكلمات الدالة: الأموكسيسيللين، القياس الصحيح للمركب، طرق الكيمومتركس.

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