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Comparative study of the micellar enhanced spectrophotometric determination of β-lactamic antibiotics by batch and flow injection analysis using a multisimplex design

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Abstract

A study has been made on the spectrophotometric determination of the β-lactamic antibiotics, amoxicillin and ampicillin, in micellar media using Cu ions as catalyst. Batch and flow injection approaches were compared. Multisimplex design was used to determine the optimal values of the flow injection analysis (FIA) system. Chemical (buffer, pH and Cu(II) concentrations) and physical (flow rate, temperature and reaction coil length) variables were considered. The analytical performance characteristics were as follows: the detection limits for batch and flow-through systems were 2.5×10^{-7} and 2×10^{-6} M, respectively, and a relative standard deviation less than 1% was found for both methods. The proposed FIA methodology was satisfactorily applied to the determination of the antibiotics in pharmaceutical formulations.

Keywords: Amoxicillin; Ampicillin; Cu–antibiotic-complex micellar media; FIA; Multisimplex

1. Introduction

Amoxicillin and ampicillin are semi-synthetic, broad-spectrum, acid stable, orally absorbed β-lactamic antibiotics that inhibit bacterial cell synthesis and are normally used for the treatment of commonly bacterial infections both in humans and animals. The presence of these compounds in food chains can result in the development of new strains of bacteria resistant to these antibiotics and in allergic reactions. Development of simple, rugged, and reliable techniques for the detection of trace level of these antibiotics in different matrices is becoming increasingly important.

Many analytical procedures have been adopted for the determination of these compounds in pharmaceutical preparations or biological matrices, mainly carried on by high-performance liquid chromatography with fluorescence detection

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[1–3] UV detection [4–6], UV and mass spectrometry determination [7], on-line post-column derivatisation [8], integrated pulsed amperometric detection [9], or even micellar electrokinetic capillary chromatography [10] are described. The usefulness of non-chromatographic techniques in antibiotic analysis has been shown in many papers as, for example, optical and electrochemical sensing of ampicillin and amoxicillin [11–13] kinetic determination of amoxicillin and clavulanic acid by stopped-flow mixing technique [14] or luminescent and spectrophotometric methods for the determination of clavulanic acid, sulbactam, α-cephalosporines, 6-aminopenicillanic acid, ampicillin, amoxicillin, cloxacillin, dicloxacillin and flucloxacillin [15–19]. Some of these reported methods use toxic chemicals [11], have high detection limits [4,10,12,13] and/or are time-consuming and laborious.

It has been reported that surfactants can enhance the absorbance of many metal–ligand systems [20]. Cationic surfactants, such as cetyltrimethylammonium bromide (CTAB), have been shown to be the most effective surfactant type in enhancing the analytical performance characteristics of metal–ligand complexes, probably due to a strong ion-pairing effect likely to occur between the positive quaternary ammonium group of CTAB and those negatively charged groups of the ligand [20,21].

In this paper, we report on the use of CTAB micelles to greatly improve the sensitivity of a spectrophotometric method for the determination ampicillin and amoxicillin. The approach is based on the catalytic effect of Cu(II) ions on the hydrolysis of ampicillin and amoxicillin which results in the formation of a coloured product whose enhanced absorbance in micellar medium is measured at 338 nm.

Since its introduction as tool for serial assays [22], flow injection analysis (FIA) has become a widely accepted analytical technique. In this context, FIA is an important approach in the development of kinetic- and catalytic-based methods because control of the reagents addition and the reaction time are easy [23]. So, catalytic methods offer better reproducibility and sampling frequency.

In the present work, endeavour was directed to use the flow-injection mode to the Cu(II)-catalysed spectrophotometric determination of ampicillin and amoxicillin. Simplex optimisation was used as a method of maximising the response, instead of the classical one-factor-at-a-time-approach. Simplex optimisation is a highly efficient, multifactor, empirical feedback, procedure that 'homes in' on the optimum response region by driving experiments in the direction of steepest ascent response surface [24,25].

The micellar enhanced spectrophotometric FIA system developed makes full use of the analytical potential of micellar media and that of flow systems that simplify and speed-up the batch procedure. The development and validation of the proposed method and its application to amoxicillin and ampicillin determination in pharmaceutical formulations are described in this paper.

2. Experimental

2.1. Chemicals

Amoxicillin trihydrate (D[−]-α-amino-4-hydroxybenzylpenicillin) and ampicillin (D[−]-α-aminobenzylpenicillin sodium salt) were purchased from Fluka and Sigma-Aldrich, respectively. Copper sulfate was obtained from Merck and CTAB, sodium dodecyl sulfate (SDS) and polyethylene glycol *tert*-octylphenyl ether (Triton® X-100) were from Fluka. For validation method mercuric nitrate and acetic anhydride were from Merck and potassium thiocyanate volumetric standard, 0.0981 N solution in water from Aldrich. All other chemicals were of analytical-reagent grade and were used without further purification unless stated otherwise. The standard antibiotic solutions were prepared in distilled water every 3 weeks and were kept under 4 °C, to avoid degradation. The pH of the solutions was adjusted using an acetic/acetate buffer.

2.2. Instrumentation and flow set-up

A Mettler DL25 Titrator was used for the potentiometric titrations, which was coupled to an

Epson LX800 Junior chart recorder. A platinum wire electrode, as the working electrode, and a double liquid junction Ag/AgCl electrode with a 1 M potassium nitrate solution in the salt bridge as reference electrode were used.

Absorption measurements were made with an UV–Vis Ati-Unicam 5625 spectrometer, connected to a personal computer. Instrument path band was set at 2 nm throughout this study.

Fig. 1 illustrates the FIA manifold employed. A conventional Hellma absorptiometric quartz flow cell (model 942316814351) 1 cm pathway (80 μl) was used. A four channel Gilson Miniplus-3 peristaltic pump was employed to generate the flowing streams. An Onmifit 5020 rotatory valve was used for sample introduction. PTFE tubing (0.8 mm i.d.) and fittings were used for reaction coil and for connecting the flow-through cell, the rotatory valve and the carrier solution reservoirs. The coil was introduced in a heating bath (Tectron 3473100) during the measurements. pH measurements were made with an Orion-pHmeter 720A.

2.3. Construction of calibration graphs

In the bulk solutions: Prepare stock solutions of ampicillin and amoxicillin (0.37 and 0.36 mg ml^{-1}, respectively) in distilled water. Adequate aliquots containing antibiotic stock solution were transferred into 10 ml volumetric flasks. Then, 1.0 ml acetate buffer 1.0 M of pH 5.4, 0.5 ml copper solution 2.0×10^{-2} M and 1.0 ml CTAB 0.05 M were added. Finally, the solutions were diluted to volume with distilled water. After 30 min at 45 ± 1 °C in a water bath for full colour development, the absorbance intensity was measured at 338 nm.

Flow-through system: In the flow-injection manifold used in this study, the peristaltic pumps propel CTAB 0.02 M, copper(II) 0.0045 M and buffer (acetate/acetic acid 0.1 M at pH 4.2) solutions along the channels A, B and C, respectively. Serial dilutions of the stock solution of each compound within the concentration range stated in Table 3 using distilled water were prepared. The calibration graph was obtained by injecting the standards (350 μl) into the buffer solution (channel C) through the sampling valve. This stream is merged with the copper(II) sulphate stream and then with the CTAB solution that provides the micellar medium. This final solution is driven into a reaction coil, which is immersed in a temperature controlled water bath (85 °C). The absorbance of the reaction products was measured at 338 nm and the transient signal was recorded.

2.4. Procedure for pharmaceuticals

2.4.1. Ampiplus and Britapen capsules

The Ampiplus and Britapen capsules contain ampicillin as the active compound and include talc, magnesium stearate, colloidal silica, TiO_2,

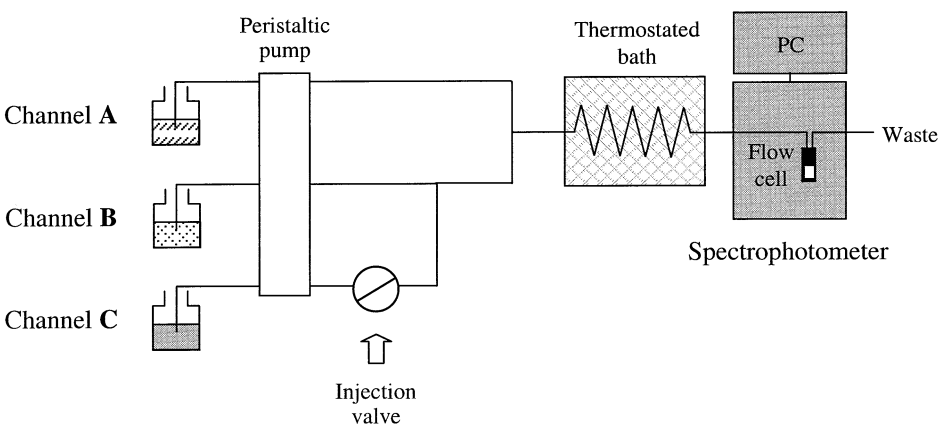

Fig. 1. FIA manifold. (A) CTAB 0.02 M; (B) copper(II) sulphate 0.0045 M; and (C) acetic acid/sodium acetate 0.115 M pH 4.2.

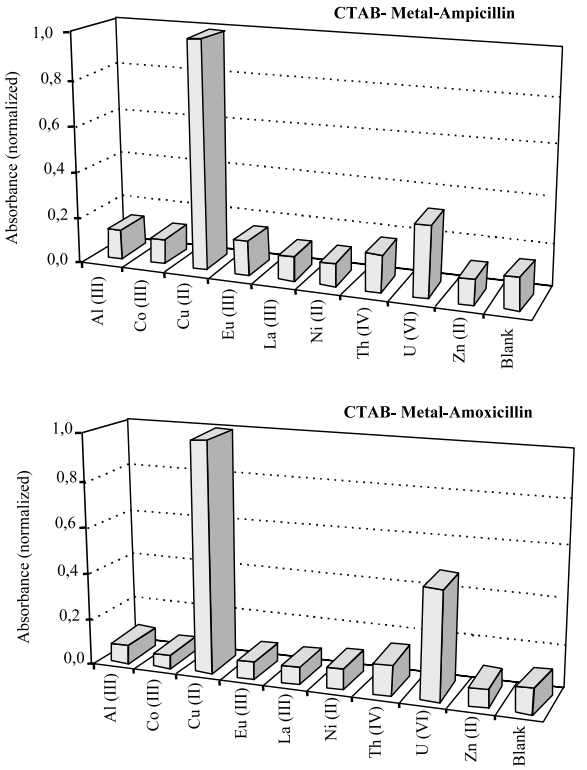

Fig. 2. Catalytic effect of different metal ions on the ampicillin and amoxicillin hydrolysis.

gelatinised starch and iron oxide (Ampiplus) or only magnesium stearate (Britapen) as excipients and, finally a coating. The nominal content of the active compound in the products is 500 mg/capsule.

Different amounts of the core capsule content of each formulation (Table 5) were dissolved in 70 ml of the water and stirred magnetically for 15 min and then diluted to 100 ml with distilled water. The resulting solutions were filtered through an Albert® 140 filter paper and these filtrates were injected into the flow line. Ampicillin concentration was calculated using the calibration graph or regression equation.

2.4.2. Clamoxyl tablets, Augmentine capsules and Augmentine syrup

A tablet (750 mg amoxicillin/tablet) was weighed and the whole amount was then used to prepare 100 ml of aqueous solution. Augmentine capsules (500 mg amoxicillin/capsule plus 125 mg clavulanic acid) were prepared under similar conditions to those used for Ampiplus and Britapen capsules. Augmentine syrups (250 mg amoxicillin plus 125 mg clavulanic acid/5 ml) were prepared by appropriate dilution in 1000 ml of distilled water.

Excipients in tablets (magnesium stearate, polyplasdone stearate, TiO_2, colloidal silica, microcrystalline cellulose, diethyl-phthalate, dimethicone, hydroxypropylmethylcellulose, starch) and syrup (sucrose, colloidal silica, flavours) resulted to be poorly soluble. For this reason solutions were filtered through Albert® 140 filter paper prior to injection into the flow system. Amoxicillin concentration was calculated using either the calibration graph or regression equation.

3. Results and discussion

3.1. Chemical requirements and experimental conditions for the batch system

3.1.1. Preliminary studies

It is known that some metal ions such as Cu^{2+}, Cd^{2+}, Zn^{2+} or Co^{2+} are complexed by ampicillin and that those complexes decompose to give metal ion complexes with ligands derived from the antibiotics [26]. In our preliminary studies, the decomposition of ampicillin and amoxicillin in aqueous solution catalysed by different metal ions (Cu^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Fe^{2+}, Fe^{3+}, Al^{3+}, La^{3+}, Eu^{3+}, Th^{4+} and UO_2^{2+}) was carried out at pH 5.4. Allowing the reaction to proceed for 120 min, the Vis–UV spectra of the resulting solutions were recorded. Results demonstrated that only in presence of Cu^{2+} ions, an intense absorption band centered at 324 nm appeared due to the complex formed between Cu^{2+} and the degradation products of the antibiotics. Such band was not observed on carrying out the reaction with the other metal ions (Fig. 2). Fig. 3 shows the spectra of a buffered solution of amoxicillin in presence and absence of Cu^{2+} ions. Similar results were obtained for the Cu–ampicillin complex. These

results suggested that Cu^{2+} could be used as a spectroscopic probe for the antibiotics determination.

The copper complex stoichiometry was obtained for amoxicillin and ampicillin using the continuous variation method [27], in which concentration of both copper and antibiotic was varied, while the sum of the concentrations of the two reactants was kept constant (2.8×10^{-3} M). Job plots show an intersection point corresponding to a 1:1 copper–antibiotic molar ratio. The complex formation constant determined from quantitative analysis of spectrophotometric data of the Job's ampicillin and amoxicillin plots were found to be 2.5×10^5 and 2.2×10^5 M^{-1}, respectively.

3.2. pH and ionic strength influence

The influence of the pH on the Cu-catalysed hydrolysis of ampicillin and amoxicillin was assayed by changing the buffer solution (acetate/acetic acid 0.1 M) varying the pH values between 3.5 and 6.0. The absorbance versus pH graph showed a plateau from 5.0 to 6.0. For further studies a pH 5.4 was used throughout as a compromise between sensitivity and preventing copper hydroxide precipitation.

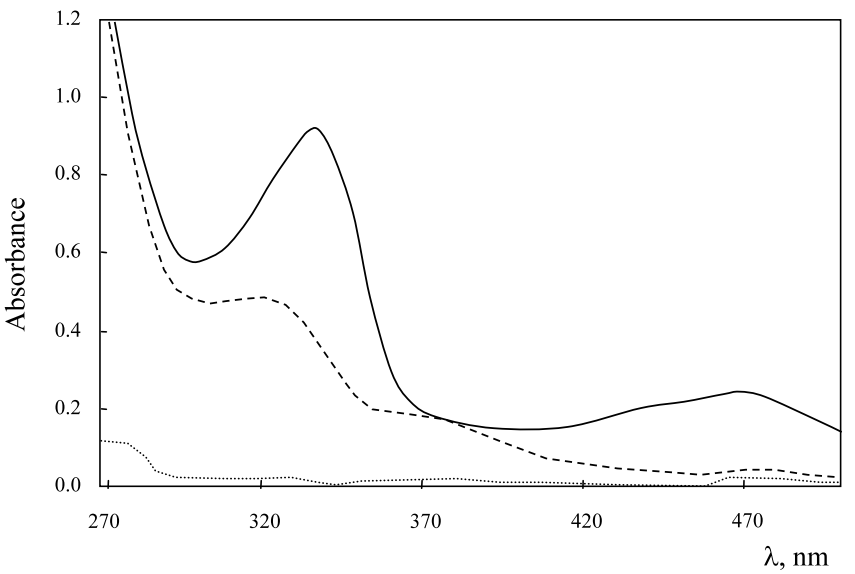

Fig. 3. Absorption spectra (···) amoxicillin, (-----) Cu(II)–amoxicillin complex and (—) Cu(II)–amoxicillin complex in CTAB media. Metal ion 10^{-3} M, antibiotic 6.8×10^{-5} M, CTAB 5×10^{-3} M, and acetic acid/sodium acetate buffer 0.1 M pH 5.4.

Table 1
Spectral characteristics in micellar media

Surfactant	Critical micellar concentration (cmc)[a]	Sensitization effect, absorbance change (%)	Wavelength shift, $\Delta\lambda$ (nm)
Sodium dodecylsulphate	8.1×10^{-3} M	−25	16 (red-shift)
Cetyl trimethyl ammonium bromide	9.2×10^{-4} M	+106	14 (red-shift)
Triton X-100	2×10^{-4} M	+20	0
Zwittergent	Unknown	+96	16 (red-shift)

[a] Refs. [20,21].

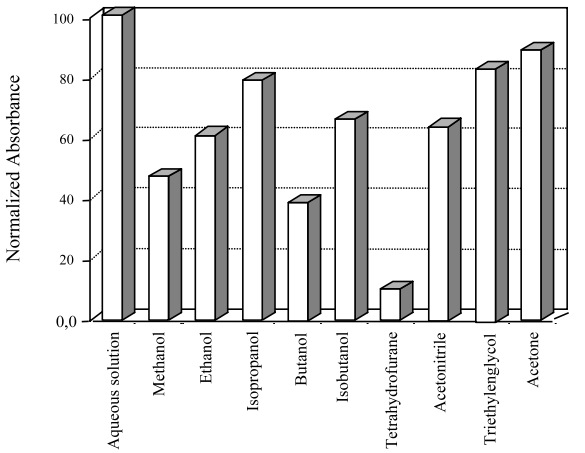

Fig. 4. Effect of solvent polarity on absorbance intensity of Cu–ampicillin-complex.

In order to determine whether the ionic strength of the medium affected the sensitisation process, the absorbance of the Cu–antibiotic–CTAB system was monitored at 338 nm in the presence of increasing concentrations of NaCl. There was only a slight decrease in absorbance (less than 20%) levelling out near 0.15 M NaCl for both complexes.

3.3. Enhancement of signal by surfactants

It is well known that in aqueous solution surfactants give rise to micelles when their concentration is higher than a critical value, the critical micellar concentration (cmc) [20]. We have investigated the influence of different surfactant micellar media (cationic, anionic, non-ionic and zwitterionic) on the spectral characteristics of the Cu–ampicillin and –amoxicillin complexes.

The spectroscopic characteristics of the Cu–ampicillin complex in presence of surfactants is summarised in Table 1. Interaction of the Cu–ampicillin complex with cationic (see Fig. 3) or zwitterionic micelles resulted in significant increase of the absorbance while only a modest increase was observed for non-ionic micellar system. Comparison of the absorbance maximum of the complex in micellar solution with that in aqueous medium indicated a red-shift ranging from 14 to 16 nm in presence of ionic micelles. No such shift was observed for the non-ionic surfactant. A similar spectroscopic behaviour was obtained for the Cu–amoxicillin complex.

The observed effects are consistent with the results reported for other systems in which metal complexes are involved [21]. The magnitude and direction of the spectral changes seem to be related to the charge of the micelle and that of the metal complex. In our work a cationic micellar medium of CTAB was selected for further studies.

Isotherms for the interaction of the Cu antibiotic complex (1.4×10^{-4} M ampicillin or amoxicillin) with CTAB by absorbance titration of a fixed amount of Cu–antibiotic with varying CTAB concentrations were obtained. Examination of the results revealed that the hyperchromic effect and the red-shift (14 nm) took place when the surfactant concentration reached the cmc re-

Table 2
Optimal operation conditions

Variable	Symplex method			Batch optimum values
	Lower limit	Upper limit	FIA optimum values	
pH	3.7	5.7	4.2	5.4
Buffer concentration (M)	0.080	0.220	0.115	0.01 0
Cu(II) concentration ($M \times 10^{-3}$)	1.50	5.50	4.50	1.05
Temperature (°C)	20	90	85	No heating
Flow rate (ml min^{-1})	0.5	2.5	2.6	–
Reaction coil length (cm)	25	275	234	–
Response variable ($A/(\Delta t)^{1/2}$) (s^{-1})	0	100	–	–
Time for reaction (min)	–	–	–	120

Table 3
Determination of pure samples ampicillin and amoxicillin by the micellar–FIA spectrophotometric system

Compound	μg Taken	μg Found	% Found	Official method [31] (% found)
Ampicillin	5.6	5.6	99.5	
	11.3	11.2	99.3	
	17.0	16.8	99.1	
	22.6	22.5	99.5	
	28.3	28.5	100.7	99.2 ± 2
Mean ± SD			99.7 ± 0.6	
Amoxicillin	5.0	4.8	95.3	
	10.0	9.7	97.6	
	15.0	14.7	98.4	
	19.9	19.7	99.0	
	24.9	24.9	100.0	98 ± 2
Mean ± SD			98 ± 2	

Table 4
Analytical figures of merit

Analytical figure	Batch method		FIA system	
	Amoxicillin	Ampicillin	Amoxicillin	Ampicillin
ε (l mol^{-1} cm^{-1}) $\times 10^{-3}$ (SD)	9.87 (0.04)	9.21 (0.07)	1.69 (0.01)	1.70 (0.02)
Linear range (M)	D.L.—3.00×10^{-4}	D.L.—2.0×10^{-4}	D.L.—3.00×10^{-4}	D.L.—2.00×10^{-4}
Intercept (SD)	0.001 (0.002)	0.003 (0.003)	−0.0001 (0.002)	−0.0001 (0.003)
Correlation coefficient (r)	0.9999	0.9999	0.9999	0.9999
Detection limit (D.L.) (M[a] $\times 10^6$)	0.27	0.26	1.6	2.1
Repeatability (CV)[b]	0.9%	0.6%	0.4%	0.8%
Reproducibility (CV)[b]	–	–	4.5%	4.7%

[a] DL was defined as the concentration corresponding to a signal that is the signal of three times the standard deviation of the blank signal.
[b] CV means coefficient of variation.

gion (9.2×10^{-4} M). These results clearly indicated that micelles were necessary for sensitisation by CTAB in both cases.

The absorbance increased with copper concentration up to 7.2×10^{-5} M, above which a steady state was reached. A copper concentration 15-folder excess over the antibiotic concentration was thus chosen to obtain high sensitivity.

3.4. Study of organic solvent modifiers

The influence of organic solvents on the spectrophotometic characteristics of the system was studied. We could observe that changes in the spectral characteristics of the Cu–ampicillin–CTAB or Cu–amoxicillin–CTAB micellar system accompanied the addition of organic solvents. The absorbance at 338 nm decreased substantially and the general trend observed followed the relative polarity of the solvent [28,29] (Fig. 4). A closer look to this figure revealed that not only the polarity but also the nature of the solvent (e.g. hydrophobic–hydrophilic balance, proton donor/acceptor properties, etc.) seemed to have an important influence. Also, significant changes in size, aggregation number, solubilization properties and micellar integrity may occur upon addition of organic solvents, even at very low concentrations

[30]. This fact could explain the hypochromic effects observed with either the solvent was added.

3.5. Temperature influence

The effect of temperature on the absorbance of the Cu–antibiotic-complex was studied between 20 and 60 °C.After heating for 30 min, the solutions were cooled at room temperature (20 °C) and the absorbance measured. In the range 20–30 °C, the absorbance shows a positive temperature coefficient about 0.06 absorbance units per 1 °C and over 35 °C no further absorbance increase was observed for ampicillin and a low positive temperature coefficient (about 0.03 absorbance units per 1 °C) for amoxicillin. This sensitisation by temperature could be adscribed to an enhancement of the Cu^{2+} catalysed decomposition of the antibiotics, which resulted in an increased concentration of the decomposition products, available to react with copper. Similar behaviour can be observed in presence of CTAB surfactant with an enhancement in absorbance of about 72% in the range 20–30 °C.

3.6. Order and timing of reagents addition

The batch procedure typically involved the addition of three of the required reagent combinations (e.g. buffer–copper–antibiotic–surfactant, buffer–surfactant–copper–antibiotic, copper–antibiotic–surfactant–buffer), into volumetric flasks and waiting for a specified reaction time before measurement. It was found that the order in which the reagents were added had an appreciable effect on the signal. The optimum absorbance and the shorter reaction time were consistently achieved in all those cases in which the metal and the antibiotic were mixed in the presence of the buffer solution, suggesting that the aqueous pH is the factor affecting the initial degradation. On the other hand, it was found that there was not significant difference in the quantitative results as a function of waiting time (incubation period for the copper–antibiotic reaction) before adding the surfactant solution as long as the reaction time was equal or higher than 10 min. Absorbance of the amoxicillin and ampicillin coloured products remained stable at least for 24 h.

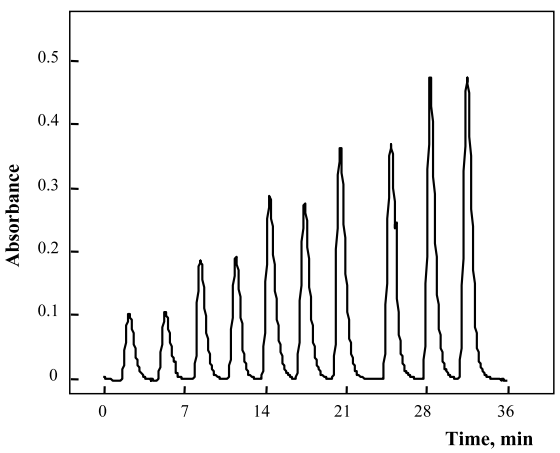

Fig. 5. Response profile for amoxicillin in FIA system.

3.7. Development of the FIA system

The physical and chemical variables affecting the flow-injection system were optimised using a multisymplex method. Among the physical parameters temperature, reaction coil, length and solution flow rates were optimised. pH, buffer and copper concentration were the chemical variables optimised.

In all symplex experiments, flow was measured after the three solutions were mixed. In order to avoid sample dilution, pH buffer solution flow is twice that of copper or CTAB. The surfactant concentration was kept constant at 0.02 M, above its cmc, in all symplex experiments. After all FIA channels are mixed, CTAB concentration became 5×10^{-3} M, which is also over its cmc. As no-significative difference between the absorptive molar coefficients (see Table 2) and batch characteristics for both Cu–ampicillin and –amoxicillin complexes were found, ampicillin at 2.5×10^{-4} M, was chosen as model analyte for this study.

After carrying out all symplex experiments, FIA system optimum conditions were found at pH 4.2, temperature 85 °C, reaction coil length 234 cm, copper(II) concentration 0.0045 M, pH buffer concentration 0.115 M and total flow 2.6 ml min^{-1}.

Table 5
Determination of ampicillin and amoxicillin in dosage forms

Compound	μg Taken	μg Found	% Found	Official Method [31] (% found)
Ampiplus capsules (500 mg ampicillin/capsule)	14.0	17.2	123.2	
	21.0	25.4	121.8	
	28.0	34.3	122.6	
	35.0	42.6	121.9	121.6 ± 0.2
Mean ± SD			122 ± 1	
Britapen capsules (500 mg ampicillin/capsule)	14.0	13.6	97.3	
	21.0	21.2	101.0	
	28.0	28.4	1016	
	35.0	35.2	100.4	100.4 ± 0.3
Mean ± SD			100 ± 2	
Augmentine capsules (500 mg amoxicillin/capsule)	14.0	13.7	97.8	
	21.0	20.4	97.1	
	28.0	28.2	100.7	
	35.0	33.9	96.9	97.3 ± 1.0
Mean ± SD			98 ± 2	
Augmentine syrup (250 mg amoxicillin 5 ml^{-1})	14.0	13.8	98.3	
	21.0	20.9	99.7	
	28.0	28.8	102.9	
	35.0	35.9	102.6	100.9 ± 0.2
Mean ± SD			101 ± 2	
Clamoxyl tablets (750 mg amoxicillin/capsule)	14.0	13.9	92.9	
	21.0	21.0	96.2	
	28.0	27.8	100.0	
	35.0	34.9	99.3	96.0 ± 0.5
Mean ± SD			97 ± 3	

The response factor in the optimisation studies was selected to be absorbance/(peak width)$^{1/2}$ as a compromise between sensitivity and time analysis. In Table 2, we have summarised the range in which the variables were studied and the results of this study.

3.7.1. Analytical features

Under the optimum experimental conditions described above, Beer's law was obeyed throughout the concentration range studied, as shown in Table 3. Both, batch and FIA approaches, showed a good linearity ($r = 0.9999$). Calibration graphs were obtained as the results of triplicate response of each standard solution. The relative standard deviation was calculated measuring standard of the same concentration of ampicillin and amoxicillin five times each, at two different concentration levels, 4.1×10^{-5} and 1.5×10^{-4} M, for the batch and the FIA approach, respectively. Results were obtained for measurements under the same (repeatability) and different (reproducibility) operation conditions such as analyst, day analysis, temperature and stock solutions. Data, expressed as percentage (coefficient of variation), are tabulated in Table 4. The detection limit, calculated as the concentration corresponding to a signal that was three times the standard deviation of the blank signal, was ca. 2.7×10^{-7} M in the batch method and ca. 2.1×10^{-6} M using the FIA system.

Within the experimental conditions, small variations of heating temperature (± 1 °C), copper (between 4 and 12×10^{-3} M), surfactant (over the cmc value) and buffer (over 0.08 M) concentrations affected the analytical results in less than $\pm 2.5\%$ for each factor. This fact provides an indication of the ruggedness/robustness of the proposed analytical systems.

Typical signal profile for the amoxicillin FIA system under optimum analytical conditions at different concentrations is shown in Fig. 5. The sampling frequency was about 70 h^{-1} for both antibiotics.

3.7.2. Applications

To assess the validation of the proposed flow injection system it was applied to the determination of amoxicillin and ampicillin in five different pharmaceutical products (Table 5). The proposed FIA method was also compared with the official method of the Spanish Pharmacopoeia [31].

4. Conclusions

The cationic micellar medium provided by CTAB has demonstrated to be an excellent way for the enhancement of the Vis–UV spectrophotometric method for ampicillin and amoxicillin determination based on the catalytic effect of Cu(II) ions on the antibiotics hydrolisis. This capability allowed us to develop sensitive and selective spectrophotometric batch and FIA systems for the antibiotics.

The proposed micellar enhanced spectrophotometric FIA method agrees well with the potentiometric official method for ampicillin and amoxicillin determination, whilst being significantly faster (60 s per analysis versus ca. 30 min) and using much less sample (0.350 versus 35 ml). Also, among its advantages should be emphasised that it is unnecessary to quantify the degradation products nor using toxic chemicals as in the reference method. Most common excipients present in pharmaceuticals do not interfere amoxillin or ampicillin determination, which renders the method suitable for routine control.

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