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Short communication

Selective spectrophotometric determination of phenolic β-lactam antibiotics

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Abstract

Two simple and selective spectrophotometric methods were developed for the quantitative determination of cefoperazone sodium, cefadroxil monohydrate, cefprozil anhydrous and amoxicillin trihydrate in pure forms as well as in their pharmaceutical formulations. The methods are based on the selective oxidation of these drugs with either Ce (IV) or Fe (III) in acid medium to give an intense yellow coloured product ($\lambda_{max} = 397$ nm). The reaction conditions were studied and optimized. Beer's plots were obeyed in a general concentration range of 5–30 μg ml^{-1} with correlation coefficients not less than 0.9979 for the four drugs with the two reagents. The methods are successfully applied to the analysis of pharmaceutical formulations containing amoxicillin, either alone or in combination with potassium clavulanate, flucloxacillin or dicloxacillin. They were also applied to the analysis of the other three studied drugs in vials, capsules, tablets and suspensions with good recovery; percent ranged from 99.7 (± 0.46) to 100.32 (± 1.05) in the Ce (IV) method and 99.6 (± 0.50) to 100.3 (± 1.32) in the Fe (III) method. Interferences from other antibiotics and additives products were investigated.

Keywords: Cefoperazone; Cefadroxil; Cefprozil; Amoxicillin; Ce (IV); Fe (III); Pharmaceutical analysis; Spectrophotomerty

1. Introduction

The phenolic β-lactam antibiotics, cefoperazone (**1**), cefadroxil (**2**), cefprozil (**3**) and amoxicillin (**4**) are penicillinase resistant with significant activity against both gram-positive and gram-negative bacteria [1].

Compounds **1**–**3** are dispensed singly while compound **4** is often dispensed with either potassium clavulanate β-lactamase inhibitor produced by fermentation of *Streptomyces clavuligerus*, flucloxacillin or dicloxacillin.

Many analytical procedures have been adopted for the determination of the investigated drugs. The British Pharmacopoeia 1998 specifies a liquid chromatographic method for the analysis of amoxicillin trihydrate and cefadroxil bulk drugs, amoxicillin trihydrate injection and oral suspension [2]. It gives an ultraviolet (UV) spectrophoto-

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metric method for amoxicillin trihydrate capsules [2]. Cefadroxil dosage forms as well as cefoperazone and cefprozil are not official.

The United States Pharmacopoeia (USP) 24 NF 19 describes an iodometric titration method for amoxicillin trihydrate oral suspension where it gives a high-performance liquid chromatography (HPLC) method for amoxicillin trihydrate bulk, capsules, tablets and in the presence of potassium clavulanate (in tablets and oral suspension), cefoperazone sodium bulk and injection, cefprozil bulk, tablets and oral suspension [3].

Adopting the BP 1998 or USP 24 NF 19 methods cannot achieve quantification of amoxicillin trihydrate combinations with either flucloxacillin or dicloxacillin. Other reported methods are based on spectrophotometry [4–15], fluorimetry [16–18], polarography [19,20] and chromatography [21–30]. Colourimetric procedures involving treatment with sodium cobaltinitrite [31], ninhydrine [32] or molybdophosphoric acid [17] have been reported. Few direct spectrophotometric methods have been reported for the determination of amoxicillin in the presence of potassium clavulanate [14,33] or dicloxacillin [21] or cefadroxil [16].

The USP chromatographic method for the determination of cefoperazone, cefadroxil and cefprozil requires an automated system, which is not available in many research laboratories. Therefore, it was considered worthwhile to develop rapid and selective procedures suitable for the routine quality control analysis of the investigated drugs.

Recently, we reported two selective spectrophotometric methods for the determination of amoxicillin trihydrate and cefadroxil monohydrate via their oxidation with either *N*-bromosuccinimide or *N*-chlorosuccinimide in alkaline medium [6]. Except this work, no data were available in the literature for the selective determination of the cited drugs.

In continuation, we wish here to develop simple and rapid selective spectrophotometric procedures for the determination of phenolic β-lactam antibiotics in the presence of structurally related penicillins. The structures of the studied drugs are given in Table 1.

2. Experimental

2.1. Apparatus

Spectronic Genesys 2PC, Ultraviolet-visible Spectrophotometer (Milton Roy Co., USA) with matched 1 cm quartz cuvettes was used.

2.2. Materials and reagents

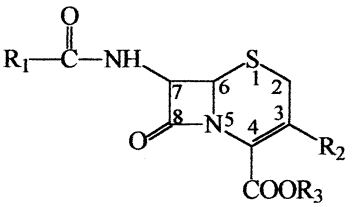
All solvents used were of analytical-reagent grade, and double distilled water was used throughout. Cefoperazone sodium (Pfizer Co., Egypt), cefadroxil monohydrate, anhydrous cefprozil (Bristol-Myers Squibb Co., Egypt), amoxicillin trihydrate, flucloxacillin sodium and dicloxacillin monohydrate (CID Co., Egypt), and potassium clavulanate (Beecham-Wulfing, Neuss, Germany) were used as working standards without further purification. Penicillic acid and 6-aminopenicillanic acid were obtained from Sigma (St. Louis, MO). Amoxipenicilloic and amoxipenicillenic acids were prepared by a standard method [34].

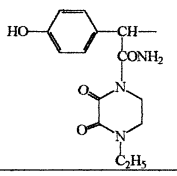
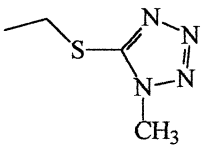
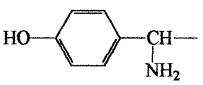
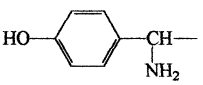
Cerium (IV) ammonium sulphate (Riedel De-Haen AG, Seelze-Hannover, Germany) 0.1% solution, was prepared in 4 M perchloric acid. Iron (III) ammonium sulphate (Riedel De-Haen AG), 0.5% solution was prepared in distilled water.

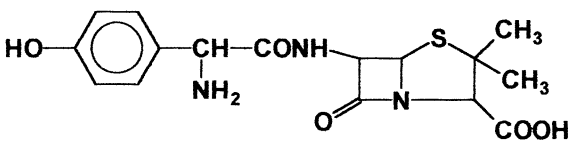
2.3. Pharmaceutical formulations

The following available commercial preparations were analyzed: Cefobid® vials (Pfizer Co.) labeled to contain 250 mg cefoperazone sodium; Duricef® capsules and powder for oral suspension (Squibb Co., Egypt) labeled to contain 250 mg of cefadroxil monohydrate per capsule or 5 ml of syrup; Cefzil® tablets and powder for oral suspension (Squibb Co.) labeled to contain 250 mg of anhydrous cefprozil per tablet or 5 ml of powder for oral suspension; Hiconcil® capsules and powder for oral suspension (Pharco Co., Egypt) labeled to contain 250 mg of amoxicillin trihydrate per capsule or 5 ml of syrup; Hibiotic® tablets and powder for oral suspension (Amoun Co., Egypt) labeled to contain 250 mg amoxicillin trihydrate and 125 mg potassium clavulanate per tablet and

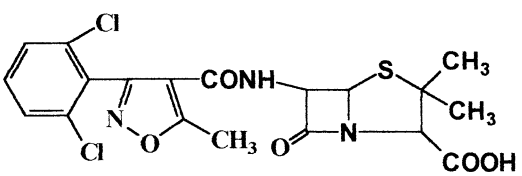
Table 1
The chemical structure of the investigated drugs



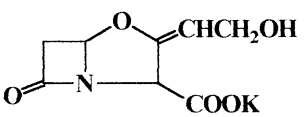
Drug	R_1	R_2	R_3
1-Cefoperazone sodium			Na
2-Cefadroxil monohydrate		—CH_3	H
3- Cefprozil anhydrous		—$CH_2CH_2CH_3$	H



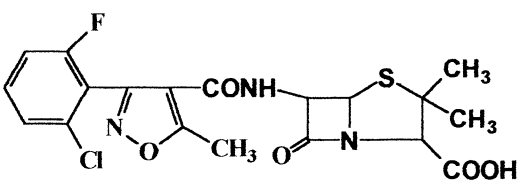
4- Amoxicillin



Dicloxacillin



potassium clavulanate



Flucloxacillin

250 mg amoxicillin trihydrate and 62.50 mg potassium clavulanate per 5 ml of the syrup; Flumox® capsules, vials and powder for oral sus- pension (Eipico Co., Egypt) labeled to contain 250 mg amoxicillin sodium and 250 mg flucloxacillin sodium per capsule, vial or 10 ml of syrup; Amoclox® capsules (Memphis Co., Egypt) labeled to contain 125 mg amoxicillin trihydrate and 125 mg dicloxacillin monohydrate per capsule.

2.4. Procedures

2.4.1. Preparation of standard stock solutions

Into a 100 ml calibrated flask, 100 mg drug was weighed accurately and dissolved in 2 ml methanol, completed to volume with distilled water and diluted quantitatively to obtain the suitable concentrations containing 50–300 μg ml^{-1} for each drug.

2.4.2. General analytical procedures

Aliquot volumes of standard stock solutions, containing 50–300 μg drug, were transferred to 10 ml calibrated flasks. One milliliter of 4 M perchloric acid was added followed by 2.0 ml of Ce (IV) or Fe (III) solutions, mixed well and completed to volume with distilled water. The absorbances of the resulting solutions were measured at 397 nm after 5 min at 25 ± 5 °C against reagent blanks treated similarly.

2.4.3. Stoichiometric study

Job's method of continuous variation [35] was employed. Master equi-molar solutions of each drug with either Ce (IV) or Fe (III) (1.0×10^{-3} mol l^{-1}) were prepared in 2.0 ml methanol and completed to volume with distilled water. A series of 10 ml portions of master solutions of each drug with the respective reagent was made, comprising different complementary proportions (0:10, 1:9,…, 9:1, 10:0) in 10 ml calibrated flasks. The absorbances of the resulting solutions were measured at 397 nm after 5 min at 25 ± 5 °C against reagent blanks treated similarly.

2.4.4. Analysis of tablets and capsules

The contents of 20 tablets or capsules of each drug were weighed and powdered or evacuated. A quantity of the powder equivalent to 100 mg was transferred into 50 ml calibrated flasks, dissolved in 2.0 ml methanol, swirled and sonicated for 2 min, completed to volume with distilled water, shaken well for 15 min and filtered, rejecting the first portion of the filtrate and then proceeding as in the general procedure.

2.4.5. Analysis of vials and powder for oral suspension

A quantity of the powder equivalent to 100 mg was transferred into a 50 ml calibrated flask, dissolved in 2.0 ml methanol, and then proceeding as in the analysis of tablets and capsules.

3. Results and discussion

3.1. Absorption spectra

Accurate UV absorption measurements of binary mixtures of amoxicillin with either potassium clavulanate, flucloxacillin sodium or dicloxacillin monohydrate are not possible because the absorption bands overlap. Moreover, the absorbances of excipients, flavour or co-formulated drugs in pharmaceutical preparations will give rise to additional problems for the analyst.

Cerium (IV) and iron (III) ammonium sulphates are strong oxidizing agents and are utilized extensively for the determination of organic compounds.

The four investigated drugs are the only phenolic compounds among the β-lactam antibiotics; they were found to behave differently from the penicillins and cephalosporins on oxidation with Ce (IV) or Fe (III) in acidic medium and gave an intense yellow colour with a maximum absorption at 397 nm with the two reagents (Fig. 1). Such colour was not observed on carrying out the same reaction with potassium clavulanate, flucloxacillin or dicloxacillin. The investigated drugs, Ce (IV) and Fe (III), have no absorption in this region.

3.2. Reagent's concentration

The results of reagent concentration variation indicated that 2 ml of either 0.1% Ce (IV) or 0.5% Fe (III) is suitable.

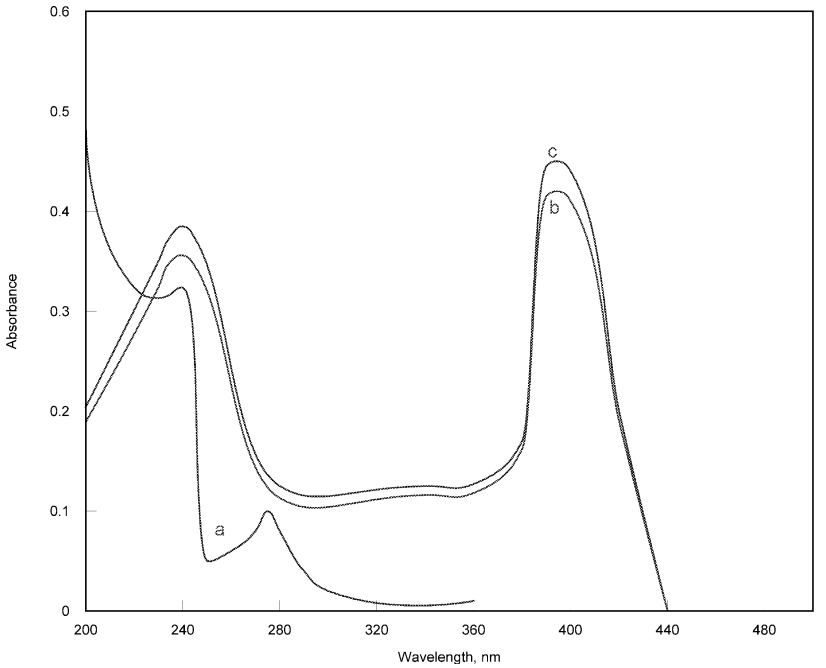


Fig. 1. Absorption spectra of amoxicillin trihydrate: (a) 30 ug ml $^{-1}$, its reaction products with Ce (IV) and Fe (III); (b and c, respectively).

3.3. Type and concentration of acid

In acidic medium, the yellow colour developed immediately. Neutral or alkaline medium is not suitable because hydrated cerric oxide and ferric hydroxide will precipitate. Different acids were tested and perchloric acid was found to be the most suitable (Table 2).

3.4. Effect of diluting solvents

Water, methanol, ethanol, propan-1-ol, propan-2-ol, acetone, dimethyl sulphoxide (DMSO), and *N*,*N*-dimethylformamide (DMF) were tested as diluting solvents (Table 3). The results obtained revealed that water and methanol were the best solvents. Other immiscible solvents such as halogenated solvents were not suitable as the coloured product formed could not be extracted into these solvents.

3.5. Reaction time

The colour developed immediately and remained stable for 1 h for the four drugs with the two reagents.

Table 2
Effect of different acids on the development of colour between amoxicillin and each of Ce (IV) or Fe (III)

Acid[a]	Absorbance at 397 nm[b]	
	Ce (IV)	Fe (III)
Acetic acid	0.114	0.125
Hydrochloric acid	0.264	0.277
Nitric acid	0.304	0.325
Sulphuric acid	0.414	0.430
Perchloric acid	0.450	0.475

[a] A 1.0 ml volume of 0.4 mol l^{-1} solution of each acid was used.

[b] Using 30 μg ml^{-1} amoxicillin trihydrate.

Table 3
Effect of different diluting solvents on the colour development

Solvent	λ_{max}/nm	Absorbance[a]	
		Ce (IV)	Fe (III)
Water	397	0.450	0.475
Methanol	395	0.444	0.469
Ethanol	400	0.420	0.449
Propan-1-ol	401	0.422	0.450
Propan-2-ol	390	0.427	0.460
Acetone	404	0.399	0.430
DMSO	410	0.370	0.402
DMF	410	0.381	0.414

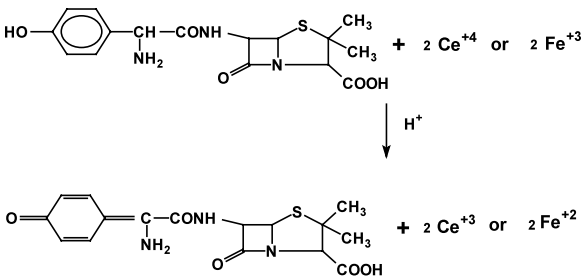
[a] Using 30 μg ml^{-1} amoxicillin trihydrate.

3.6. Concentration ranges and linearity

Under the specified reaction conditions, the absorbance at 397 nm was found to be proportional to the concentrations of the studied drugs over a final concentration range of 5–30 μg ml^{-1}. Beer's law plots ($n = 6$) were linear with very small intercepts (-0.004 to $+0.102$); slopes ranged from 0.013 to 0.032. The correlation coefficients ranged from 0.9979 to 0.9999. Table 4 shows the most important spectral characteristics and quantitative parameters of the reactions investigated.

3.7. Stoichiometry of the reaction

By the application of Job's method of continuous variation [35], the molar ratio of either Ce (IV) or Fe (III) to each of the tested drugs was 2:1.



Scheme 1.

3.8. Reaction mechanism

It is reported that phenols containing an –OH moiety in the *para* substituent can be oxidized by ferric chloride [36], alkaline potassium hexacyanoferrate (III) [36,37], lead dioxide, silver, silver oxide and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to the corresponding phenoxy radical, which is a transient species and undergoes spontaneous irreversible disproportionation to produce quinone [37]. In addition, amoxicillin is reported to be oxidized by 2-iodoxybenzoate [38], and also amoxicillin and cefadroxil are reported to be oxidized with *N*-bromosuccinimide or *N*-chlorosuccinimde to give the same product [6]. A possible reaction mechanism is illustrated in Scheme 1.

3.9. Precision

The mean of six replicate analyses of the drug solutions within the linear range gave coefficient of variations ranging from 0.98 to 1.25%. This level of precision is adequate for the quality control analysis of the dosage forms.

Table 4
Quantitative parameters and spectral characteristics of the coloured reaction products

Drug	Procedure	Linear range (μg ml^{-1})	€/10^4	*a*	*b*	*r*	LOD	LOQ
Cefoperazone sodium	Ce (IV)	5–30	0.86	−0.010	0.013	0.9998	0.023	0.077
	Fe (III)	5–30	1.45	0.023	0.021	0.9999	0.050	0.160
Cefadroxil monohydrate	Ce (IV)	5–30	0.82	0.004	0.021	0.9997	0.011	0.038
	Fe (III)	5–30	1.37	0.102	0.032	0.9979	0.096	0.320
Cefprozil anhydrous	Ce (IV)	5–30	1.19	0.011	0.030	0.9999	0.017	0.055
	Fe (III)	5–30	1.34	0.100	0.031	0.9999	0.097	0.323
Amoxicillin trihydrate	Ce (IV)	5–30	0.63	0.012	0.015	0.9999	0.038	0.128
	Fe (III)	5–30	0.58	−0.056	0.016	0.9999	0.189	0.630

a: intercept; *b*: slope; *r*: correlation coefficient; € in l mol^{-1} cm^{-1}.

3.10. Specificity

Owing to the phenolic character of the drugs investigated, the reaction was found to be specific for cefoperazone sodium, cefadroxil monohydrate, cefprozil anhydrous, also for amoxicillin trihydrate in the presence of potassium clavulanate, other related penicillins such as flucloxacillin sodium and dicloxacillin monohydrate and also other structurally related degradation products such as penicillinic acid, 6-aminopenicillinic acid and D-penicillamine. It was also shown that excipients and diluents such as starch and sugars, which are commonly formulated in dosage forms, do not interfere with the proposed procedures. Table 5 presents the results of the determination of amoxicillin trihydrate by the proposed procedures in the presence of some penicillin preparations and degradation products.

3.11. Interference studies

Interference studies were carried out in order to investigate the effect of some penicillin preparations, potassium clavulanate and degradation products that might be present in amoxicillin trihydrate dosage forms; no interference was observed from potassium clavulanate, flucloxacillin, dicloxacillin, penicillic acid, 6-aminopenicillic acid and penicillamine.

On the other hand, amoxipenicilloic acid and amoxipenicillenic acids affected the oxidation process to exactly the same extent as the intact amoxicillin trihydrate. Also, the same interference was observed when a standard solution of amoxicillin trihydrate was initially decomposed with 2 mol l^{-1} sodium hydroxide or 1 mol l^{-1} sulphuric acid for 15 min, and the reaction mixture was analyzed by the suggested procedures. The observed interference could be eliminated by adding 0.4 ml of 0.025 mg ml^{-1} methanolic iodine solution and allowing the mixture to stand for 5 min before carrying out the proposed procedures [6]. This modification depends on the fact that intact penicillins are reported not to react with iodine [29], whereas penicillin degradation products consume iodine by an exceedingly complex reaction mechanism [30].

3.12. Ruggedness of the method

The ruggedness of the methods was determined by measuring the reproduciblity througth analysis of aliquots from homogeneous lots in different laboratories by different analysts.

3.13. Analysis of pharmaceutical formulations

The proposed procedures were applied to the determination of amoxicillin, either alone or in combination with potassium clavulanate,

Table 5
Determination of amoxicillin trihydrate in the presence of some penicillin preparations and degradation products

Substance	Amount added[a]	Recovery ± S.D. (%)[b]	
		Ce (IV)	Fe (III)
Flucloxacillin sodium	50	99.11 ± 0.73	101.20 ± 0.95
Dicloxacillin monohydrate	50	100.89 ± 0.84	99.95 ± 1.00
Potassium clavulanate	50	101.49 ± 0.59	100.98 ± 1.03
Amoxipenicilloic acid[c]	10	97.24 ± 0.82	99.50 ± 0.52
Amoxipenicillenic acid[c]	10	98.21 ± 0.66	98.41 ± 0.66
Penicillic acid	10	100.30 ± 0.62	102.29 ± 0.75
6-Aminopenicillanic acid	10	102.20 ± 1.50	100.38 ± 0.66
D-Penicillamine	10	99.46 ± 0.73	101.49 ± 0.59

[a] Amount added per 50 mg of amoxicillin trihydrate.
[b] Mean of three determinations.
[c] Using 0.4 ml of 0.25 mg ml^{-1} methanolic iodine solution before adopting the procedure.

Table 6
Determination of the cited drugs in their pharmaceutical preparations by the proposed and reported methods

Preparation	Claimed (mg)	% Found, ± SD[a]		
		Ce (IV)	Fe (III)	Reported
Cefobid® vials	250	100.1 ± 0.52 $t = 1.94$ $F = 1.16$	99.9 ± 0.60 $t = 1.35$ $F = 1.15$	99.53 ± 0.56[b]
Duricef® capsules	250	99.3 ± 0.46 $t = 2.31$ $F = 2.94$	99.6 ± 0.50 $t = 2.0$ $F = 2.50$	98.16 ± 0.79[c]
Duricef® oral suspension	250	100.1 ± 1.20 $t = 1.28$ $F = 1.82$	100.0 ± 1.32 $t = 1.09$ $F = 2.20$	99.19 ± 0.89[c]
Cefzil® tablets	250	99.8 ± 0.55 $t = 1.17$ $F = 2.11$	99.9 ± 0.75 $t = 1.26$ $F = 1.14$	99.20 ± 0.80[b]
Cefzil® oral suspension	250	100.3 ± 1.09 $t = 0.82$ $F = 1.89$	100.2 ± 1.00 $t = 0.51$ $F = 2.25$	100.8 ± 1.50[b]
Hiconcil® capsules	250	99.9 ± 0.56 $t = 1.37$ $F = 4.59$	100.0 ± 0.57 $t = 1.59$ $F = 4.43$	98.90 ± 1.20[d]
Hiconcil® oral suspension	250	100.3 ± 1.55 $t = 1.08$ $F = 2.66$	100.2 ± 1.39 $t = 1.27$ $F = 2.14$	101.20 ± 0.95[b]
Hibiotic® tablets	250	99.7 ± 0.97 $t = 0.38$ $F = 1.53$	99.9 ± 0.100 $t = 0.62$ $F = 1.44$	99.40 ± 1.20[b]
Hibiotic® oral suspension	250	100.1 ± 1.22 $t = 0.40$ $F = 1.51$	100.3 ± 1.32 $t = 0.20$ $F = 1.29$	100.50 ± 1.50[b]
Flumox® capsules	250	99.8 ± 0.96	99.7 ± 1.00	–
Flumox® oral suspension	250	99.7 ± 0.23	99.6 ± 0.19	–
Flumox® vials	250	100.32 ± 1.05	100.25 ± 0.99	–
Amoclox® capsules	125	99.9 ± 0.56	99.9 ± 0.54	–

[a] Three and six determinations were used for the reported and the proposed methods, respectively. The tabulated values of t and F at 95% confidence limit are $t = 2.23$ and $F = 5.79$.
[b] Reference [3].
[c] Reference [15].
[d] Reference [2].

flucloxacillin sodium or dicloxacilin monohydrate, as well as cefoperazone sodium, anhydrous cefprozil and cefadroxil monohydrate dosage forms, with good recoveries (Table 6). The obtained mean values (± S.D.) of the labeled amounts ranged from 99.7 (± 0.46) to 100.32 (± 1.05) in the Ce (IV) method and 99.6 (± 0.50) to 100.3 (± 1.32) in the Fe (III) method. According to the t- and F-tests, there were no significant differences between the calculated and theoretical values at $p = 0.05$, demonstrating that the proposed methods are as accurate and precise as the reported methods.

4. Conclusion

The proposed methods are simpler, faster and more sensitive than the official titrimetric and chromatographic methods. In addition, they can

be applied to the quality control analysis of amoxicillin trihydrate, either alone or in combination with potassium clavulanate, flucloxacillin or dicloxacillin, as well as for cefoperazone sodium, cefprozil anhydrous and cefadroxil monohydrate dosage forms, without interference. Moreover, interference from degradation products bearing a phenolic functional group can be eliminated by adding a methanolic iodine solution before carrying out the proposed procedures.

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