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Short communication

Colourimetric and AAS determination of cephalosporins using Reineck's salt

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Abstract

Two simple, accurate, sensitive and selective procedures for the determination of eight cephalosporins are described. These procedures are based on the formation of ion-pair complexes between the drugs and ammonium reineckate, the formed precipitates are quantitatively determined either colourimetrically or by atomic absorption spectrometrically. The methods consist of reacting drugs with Reinecke's salt in an acidic medium at $25 \pm 2°$. The first colourimetric procedure (procedure I) is based on dissolving the formed precipitate with acetone, the volume was completed quantitatively and the absorbance of the solution was measured at 525 nm against pure solvent blank. Also, the formed precipitates on the atomic absorption spectrometric procedure (procedure II) are quantitatively determined directly or indirectly through the chromium precipitate formed or the residual unreacted chromium in the filtrate at 358.6 nm. The optimum conditions for precipitation have been carefully studied. Beer's law is obeyed for the studied drugs in the range 5–35 μg ml^{-1} with correlation coefficients $\not< 0.9989$. Both procedures I and II hold well accuracy and precision when applied to the analysis of the cited cephalosporins in different dosage forms with good recovery percent ranged from 98.7 ± 0.90 to 100.1 ± 0.74 without interference from additives.

Keywords: Cephapirin sodium; Cefuroxime sodium; Cefotaxime sodium; Cefoperazone sodium; Cefadroxil; Ceftazidime; Cefazolin sodium; Cefaclor; Reinecke's salt; Colourimetrically; Atomic absorption spectrometrically

1. Introduction

Cephalosporins are penicillinase-resistant antibiotics with significant activity against Gram positive and Gram negative bacteria [1]. Cephalosporins were determined by titrimetric [2–5], spectrophotometric [6–16], fluorimetric [17–20], chromatographic [21–25], potentiometric [26] and polarographic [27,28] methods.

Reineck's salt is ammonium tetrathiocyanotodiamminochromate (III) monohydrate in which it can be used for quantitative determination of many pharmaceutical compounds applying gravimetric [29], titrimetric [30] and spectrophotometric [31–35] procedures.

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The purpose of the present work is to describe the development of the two simple and accurate spectrophotometric procedures, as well as a selective and sensitive atomic absorption spectrometric procedure, for the analysis of the titled antibiotic in the pure form as well as in pharmaceutical preparations.

2. Experimental

2.1. Apparatus

- A Shimadzu UV1601, UV-visible spectrophotometer (Tokyo, Japan).
- A Shimadzu atomic absorption flame spectrophotometer model AA.640-13 with a chromium hollow cathode lamp under the following observation height above burner 1 cm; single slot type burner; air flow-rate 21.51/min; acetylene flow-rate 3.41/min operation conditions: lamp current 29 mA; slit width 0.7 nm; wavelength current 29 mA; slit width 0.7 nm; wavelength 358.6 nm.

2.2. Materials

All solvents and reagents were of analytical reagent grade. Pharmaceutically pure cefuroxime sodium and ceftazidime (Glaxo Co., Egypt); cephaprin sodium, cefazolin sodium and cefadroxil (Bristol-Myers Squibb Co., Egypt); cefotaxime sodium (Hoechst Co., Egypt); cefoperazone sodium (Pfizer Co., Egypt) and cefaclor (Kahira Co., Egypt) were used as working standards.

2.3. Pharmaceutical preparations

The commercial dosage forms subjected to analysis were Zinnat vials and tablets (labeled to contain 750 and 500 mg cefuroxime sodium, respectively), Glaxo-Wellcome; Cefatrexyl vials (labeled to contain 500 mg cephaprin sodium), Squibb Co.; Cefobid vials (labeled to contain 500 mg cefoperazone sodium), Pfizer Co.; Claforan vials (labeled to contain 500 mg cefotaxime sodium), Hoechst Co.; Duricef capsules (labeled to contain 500 mg cefadroxil monohydrate), Squibb Co.; Fortum vials (labeled to contain 500 mg ceftazidime pentahydrate), Glaxo-Wellcome; Totacef vials (labeled to contain 500 mg cefazolin sodium), Squibb Co. and Ceclor tablets (labeled to contain 500 mg cefaclor), Kahira Co.

2.4. Reagent

Ammonium reineckate (Prolabo, Paris, France) were of purity $\not< 99.9\%$. Some 3×10^{-3} M stock ammonium reineckate solutions were freshly prepared by dissolving in re-distilled de-ionized water.

2.5. General assay procedure

2.5.1. Procedure I

In a 10 ml volumetric flask, 2 ml volume of sample drug solution, 0.4 ml of hydrochloric acid was added, 2.5 ml of fresh saturated Reinecke's salt solution was added with agitation for 5 min and complete to the volume with re-distilled de-ionized water. The formed precipitate was filtered through a sintered glass funnel (G_4) after 1 h and washed three times with 5 ml ice water. Then, the precipitate was dried in a vacuum desiccator. The formed precipitate in the crucible was then dissolved with acetone into a 25 ml volumetric flask together with the successive washings of the funnel and filtration device. The volume was completed quantitatively with acetone to the appropriated volume and the absorbance of the solution was measured at 525 nm against pure solvent as a blank.

2.5.2. Procedure II

2.5.2.1. Direct procedure. The above (drug-reineckate) precipitates were collected on a G_4 sintered glass crucible and washed with five 2 ml portions of ice water. The drug-reineckate precipitates were dissolved in 25 ml acetone. The solution was nebulized in an air–acetylene flame of AAS measurement of chromium at 358.6 nm. The absorbance was compared with a calibration graph prepared from the pure drug-reineckate solid complex under identical conditions.

2.5.2.2. Indirect procedure. The filtrate and washings from the direct procedure were collected in 100 ml volumetric flask and completed to volume with acetone. The resulting solution (2 ml) was diluted to 25 ml with acetone. A blank (omitting addition of drugs) was prepared and absorbance was measured at the above flaming conditions. Chromium concentration was calculated from a calibration curve.

2.6. Preparation of samples

2.6.1. Tablets

The contents of 20 tablets of the drug were thoroughly ground. A quantity equivalent to 50 mg drug was accurately weighed into a 100 ml volumetric flask, completed to volume with re-distilled de-ionized water, filtered and the procedure was completed as under method I or II.

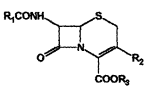
2.6.2. Capsules

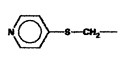
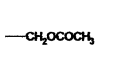
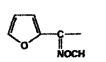
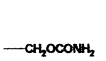
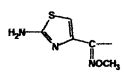
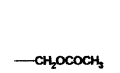
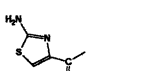
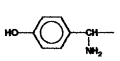
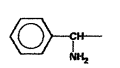
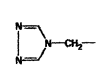
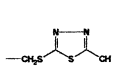
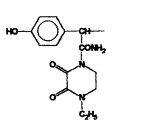
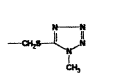
The contents of 20 capsules were weighed and finely powdered. A portion of the powder, equivalent to 50 mg of drug, was dissolved in re-distilled de-ionized water (by shaking for 5 min), filtered if necessary. The solution was completed to 100 ml with re-distilled de-ionized water and the procedure was completed as under method I or II.

2.6.3. Vials

An accurately measured weight of vials equivalent to 50 mg of drug was dissolved in re-distilled de-ionized water (by shaking for 5 min), filtered if necessary. The solution was completed to 100 ml with re-distilled de-ionized water and the procedure was completed as under procedure I or II.

Table 1
Structure of the studied cephalosporins



Name	R_1	R_2	R_3
Cephaprin sodium			Na
Cefuroxime sodium			Na
Cefotaxime sodium			Na
Ceftazidime			H
Cefadroxil			H
Cefaclor		Cl	H
Cefazolin sodium			Na
Cefoperazone sodium			Na

3. Results and discussion

Mixing each aqueous solution of cephaprin sodium, cefuroxime sodium, cefotaxime sodium, cefoperazone sodium, cefadroxil, ceftazidime, cefazolin sodium or cefaclor with ammonium reineckate in acidic medium at 25 ± 2 °C resulted in the formation of red precipitate. It is based on the formation of ion-pair complexes between the drugs and ammonium reineckate.

Formation of drug-reineckate ion-pair complexes allows indirect determination of these drug by atomic absorption spectrometric measurement of the chromium content of the reineckate counter anion.

On the colourimetric procedure (procedure I), the absorption spectrum of the reaction products was measured at 525 nm.

On the atomic absorption spectrometric procedure (procedure II), acidic solutions of the drugs gave purple coagulated precipitates with ammonium reineckate. These precipitates form the basis of the micro-quantitative determinations of the cited cephalosporins. The chromium ion content could be determined either directly in the precipi-

Table 2
Parameters for calibration curves construction

Drug	Procedure	Conc. range (μg/ml^{-1})	B	K	R	C.V. (%)
Cephaprin Na	Colourimetric		0.9801	2.1415	0.9999	0.45
	Direct AAS	10–35	0.0351	3.3215	0.9989	0.48
	Indirect AAS		−0.0584	1.9872	0.9997	0.40
Cefuroxime Na	Colourimetric		0.8751	3.6130	0.9996	0.23
	Direct AAS	5–30	0.0935	2.0654	0.9999	0.30
	Indirect AAS		0.1458	2.3218	0.9989	0.36
Cefotaxime Na	Colourimetric		1.003	4.1310	0.9999	0.75
	Direct AAS	5–30	0.0451	6.0011	0.9992	0.69
	Indirect AAS		−0.2643	3.3574	0.9999	0.66
Cefoperazone Na	Colourimetric		−0.0965	5.0511	0.9999	0.15
	Direct AAS	5–30	0.0679	1.0634	0.9999	0.20
	Indirect AAS		0.478	3.0321	0.9999	0.21
Cefadroxil	Colourimetric		0.9511	8.4165	0.9999	0.35
	Direct AAS	10–35	−0.3546	4.0985	0.9995	0.32
	Indirect AAS		0.0984	4.00985	0.9999	0.30
Ceftazidime	Colourimetric		0.1551	6.9610	0.9996	0.81
	Direct AAS	5–30	0.0984	2.0354	0.9999	0.76
	Indirect AAS		−0.0657	1.0036	0.9997	0.78
Cefazolin Na	Colourimetric		1.0060	7.0215	0.9999	0.47
	Direct AAS	5–30	0.6541	5.6515	0.9989	0.45
	Indirect AAS		0.7315	4.3847	0.9999	0.46
Cefaclor	Colourimetric		0.62870	2.6297	0.9999	0.90
	Direct AAS	10–35	0.9826	1.6874	0.9999	0.88
	Indirect AAS		0.9878	1.2685	0.9999	0.89

B, intercept; K, slope; R, correlation coefficient; C.V.%, coefficient of variance.

tate or indirectly in the filtrate by atomic absorption spectrometry.

The different variables that affects the colourimetric (procedure I) and atomic absorption spectrometric (procedure II) determinations of all studied cephalosporins with ammonium reineckate were studied and optimized.

3.1. Optimization of the reaction conditions

3.1.1. Type and concentration of the acid

The cited cephalosporins reineckate salts were prepared starting with the same concentration of the drug and the ammonium reineckate, while varying the type and amounts of the acid. The absorbances of the final salt solutions in the appropriate solvent were taken as a measure of better precipitation.

Some 0.4 ml hydrochloric acid per 10 ml of the final solution mixture was the most suitable amount for complete precipitation of the cited cephalosporins.

3.1.2. Ammonium reineckate concentration

The general procedure was applied using different concentrations of the reagent, while the cited cephalosporins and acid concentrations were constant. The absorbances of the final salt solutions in the appropriate solvent were taken as a measure of better precipitation

A total of 2.5 ml of 2% ammonium reineckate was sufficient for complete precipitation of cephalosporins-hydrochloric acid in the final solution.

3.1.3. Temperature

The effect of temperature on the formation of the coloured precipitate was investigated. The experiments were carried out at room temperature (25 ± 2 °C).

3.1.4. Reaction time

A series containing equal concentrations of the cephalosporin was analyzed using the corresponding standard procedure, but filtering the precipitate after various time intervals. The absorbance of the final cephalosporins-reineckate solution in the appropriate solvent was taken as a measure for the best precipitation time.

One hour was found to be sufficient for complete precipitation of cephalosporins-reineckate on standing at 25 °C.

Table 3
Statistical analysis of the results obtained using the proposed procedures and reference method for analysis of authentic samples

Drug		Color procedure	AAS procedure		Official method
			Direct	Indirect	
Cephaprin Na	$X^- \pm$ S.D.	100.1 ± 0.45	99.9 ± 0.48	99.7 ± 0.40	99.8 ± 0.54
	V	0.20	0.23	0.16	0.29
	t	1.06	0.34	0.37	
	F	1.45	1.26	1.80	
Cefuroxime Na	$X^- \pm$ S.D.	99.8 ± 0.23	99.6 ± 0.30	99.3 ± 0.36	99.5 ± 0.29
	V	0.05	0.09	0.13	0.08
	t	2.07	0.60	1.08	
	F	1.60	1.12	1.60	
Cefotaxime Na	$X^- \pm$ S.D.	100.0 ± 0.75	99.8 ± 0.69	99.5 ± 0.66	99.7 ± 0.71
	V	0.56	0.48	0.44	0.50
	t	0.72	0.25	0.50	
	F	1.12	1.04	1.14	
Cefoperazone Na	$X^- \pm$ S.D.	99.4 ± 0.15	99.3 ± 0.20	98.8 ± 0.21	99.1 ± 0.18
	V	0.12	0.14	0.14	0.13
	t	1.48	0.93	1.40	
	F	1.50	1.33	1.33	
Cefadroxil	$X^- \pm$ S.D.	100.2 ± 0.35	99.7 ± 0.32	99.7 ± 0.30	99.4 ± 0.34
	V	0.12	0.10	0.09	0.12
	t	2.97	1.57	1.62	
	F	1.00	1.20	1.33	
Ceftazidime	$X^- \pm$ S.D.	99.9 ± 0.81	99.8 ± 0.76	99.7 ± 0.78	99.6 ± 0.80
	V	0.65	0.58	0.61	0.64
	t	0.65	0.44	0.22	
	F	1.01	1.10	1.04	
Cefazolin Na	$X^- \pm$ S.D.	99.7 ± 0.47	99.3 ± 0.45	99.3 ± 0.46	99.4 ± 0.50
	V	0.22	0.20	0.21	0.25
	t	1.08	0.37	0.36	
	F	1.13	1.25	1.19	
Cefaclor	$X^- \pm$ S.D.	99.2 ± 0.89	99.0 ± 0.87	98.9 ± 0.88	99.1 ± 0.90
	V	0.79	0.78	0.77	0.81
	t	0.20	0.19	0.39	
	F	1.02	1.06	1.05	

Number of experiments (N) = 6. V, variance; tabulated (t) = 3.85; tabulated (F) = 4.28.

Table 4
Determination of cephalosporins in their pharmaceutical preparations by the proposed and official methods

Pharmaceutical preparations		Color procedure	AAS procedure		Official method
			Direct	Indirect	
Zinnat vials	$X^- \pm$ S.D.	99.3 ± 0.30	99.2 ± 0.32	99.1 ± 0.35	99.5 ± 0.29
	V	0.09	0.10	0.12	0.08
	t	1.19	1.73	2.16	
	F	1.13	1.25	1.50	
Zinnat tablets	$X^- \pm$ S.D.	99.6 ± 0.33	99.2 ± 0.36	99.2 ± 0.38	99.5 ± 0.29
	V	0.10	0.13	0.14	0.08
	t	0.58	1.62	1.57	
	F	1.25	1.63	1.75	
Cefatrexyl vials	$X^- \pm$ S.D.	100.1 ± 0.50	99.5 ± 0.56	99.5 ± .0.51	99.8 ± 0.54
	V	0.25	0.31	0.26	0.29
	t	1.00	0.94	1.00	
	F	1.16	1.07	1.11	
Cefobid vials	$X^- \pm$ S.D.	99.3 ± 0.20	99.2 ± 0.22	99.0 ± 0.25	99.1 ± 0.18
	V	0.14	0.15	0.16	0.13
	t	0.94	0.47	0.46	
	F	1.33	1.67	2.00	
Claforan vials	$X^- \pm$ S.D.	100.0 ± 0.74	99.5 ± 0.70	99.3 ± 0.75	99.7 ± 0.71
	V	0.55	0.49	0.56	0.50
	t	0.72	0.49	0.95	
	F	1.10	1.02	1.12	
Duricef capsules	$X^- \pm$ S.D.	99.5 ± 0.33	99.6 ± 0.37	99.2 ± 0.36	99.4 ± 0.34
	V	0.11	0.14	0.13	0.12
	t	0.51	0.96	0.99	
	F	1.10	1.17	1.08	
Fortum vials	$X^- \pm$ S.D.	99.3 ± 0.83	99.5 ± 0.78	99.2 ± 0.81	99.6 ± 0.80
	V	0.69	0.61	0.66	0.64
	t	0.63	0.22	0.85	
	F	1.08	1.05	1.03	
Totacef vials	$X^- \pm$ S.D.	99.6 ± 0.48	99.5 ± 0.49	99.3 ± 0.53	99.4 ± 0.50
	V	0.23	0.24	0.28	0.25
	t	0.71	0.35	0.34	
	F	1.09	1.04	1.12	
Ceclor tablets	$X^- \pm$ S.D.	99.0 ± 0.91	98.7 ± 0.90	99.0 ± 0.88	99.1 ± 0.90
	V	0.83	0.81	0.77	0.81
	t	0.19	0.77	0.19	
	F	1.02	1.00	1.05	

Number of experiments (N) = 6. V, variance; tabulated (t) = 3.85; tabulated (F) = 4.28.

3.1.5. Solubility and stability of the precipitated reineckates

Trials to find out the best solvent to dissolve cephalosporins-reineckate precipitate were performed using distilled water, acetone, dioxan, methanol and ethanol. Then the stability of the produced colour in each solvent was examined periodically at different time intervals over 24 h.

The colour of cephalosporins-reineckate acetone solution was stable for at least 24 h.

3.1.6. Washing liquid and solvent

The washing liquid of choice was ice water and acetone was the most suitable solvent.

3.2. Quantification

3.2.1. Beer's law

Standard curves were constructed by plotting the observed absorbances readings versus the concentrations of cephalosporins in μg ml^{-1} of the final solution of the experiments. Conformance to Beer's law was evident. Plots showed good linearity with high correlation coefficients (Tables 1 and 2).

Statistical analysis of the results obtained by the proposed procedures (I and II) compared with those of the official method [36] are given in Table 3 at 95% confidence level, the calculated t and F values do not exceed the tabulated ones, revealing equal precision and accuracy.

3.2.2. Stoichiometric relationships

For the atomic absorption spectrometric method, Job's method of continuous variation [37] indicated a molar ratio of 1:2 drug to reineckate.

3.2.3. Reaction mechanism

Cephalosporin hydrochloride + ammonium reineckate = ammonium chloride + cephalosporin reineckate

3.2.4. Application

The applicability of the methods to various dosage forms were checked by analyzing synthetic mixtures containing the cited cephalosporins in the presence of commonly encountered excipients. The results of the analysis of pharmaceutical preparations by the suggested procedures (I and II) are comparable to the official method and show good correlation and reveal good applicability without interference (Table 4).

In conclusion, the developed procedures are simple, sensitive and accurate. In addition, the atomic absorption spectrometric method is selective and suitable for routine quality control.

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