

Development and validation of spectrophotometric methods for determination of ceftazidime in pharmaceutical dosage forms

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Two spectrophotometric methods for the determination of ceftazidime (CFZM) in either pure form or in its pharmaceutical formulations are described. The first method is based on the reaction of 3-methylbenzothiazolin-2-one hydrazone (MBTH) with ceftazidime in the presence of ferric chloride in acidic medium. The resulting blue complex absorbs at λ_{\max} 628 nm. The second method describes the reaction between the diazotized drug and *N*-(1-naphthyl)ethylenediamine dihydrochloride (NEDA) to yield a purple colored product with λ_{\max} at 567 nm. The reaction conditions were optimized to obtain maximum color intensity. The absorbance was found to increase linearly with increasing the concentration of CFZM; the systems obeyed the Beer's law in the range 2–10 and 10–50 $\mu\text{g mL}^{-1}$ for MBTH and NEDA methods, resp. *LOD*, *LOQ* and correlation coefficient values were 0.15, 0.79 and 0.50, 2.61. No interference was observed from common excipients present in pharmaceutical formulations. The proposed methods are simple, sensitive, accurate and suitable for quality control applications.

Keywords: ceftazidime, diazotization, spectrophotometry, pharmaceutical formulation

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Ceftazidime is (Z)-(7R)-7-[2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methoxyimino)acetamido]-3-(1-pyridinylmethyl)-3-cephem-4-carboxylate pentahydrate (CFZM) (1, 2). It is a third generation cephalosporin antibiotic characterized by a broad antibacterial spectrum and resistant to beta-lactamase producing organisms in addition to its antimicrobial activity against *Streptococci*, *Staphylococci*, *Pneumococci*, etc. Several analytical procedures are available in the literature for the analysis of ceftazidime, *via* high performance liquid chromatography (4–7), charge transfer complexation (8), and spectrophotometric methods (9–14). Most of the spectrophotometric methods reported earlier suffer from disadvantages like a narrow linearity range, requiring heating or extraction, long time for the reaction to complete, use of non-aqueous systems, low stability of the colored prod-

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uct formed. In continuation of our research on spectrophotometric determination of organic compounds of pharmaceutical importance (15, 16), the present communication reports two spectrophotometric methods for the determination of ceftazidime in either pure form or in pharmaceutical preparations. Both reagents are used for the first time in ceftazidime analysis.

EXPERIMENTAL

Apparatus

An ELICO Model SL-164 double beam, UV-VIS spectrophotometer (Elico India Ltd., India) with 1.0 cm matched quartz cells was used for absorbance measurements.

Reagents and materials

Ceftazidime (gift sample from Alkem Laboratories Ltd., India), 3-methylbenzothiazolin-2-one hydrazone (MBTH) (Himedia Laboratories Pvt. Ltd., India, certified to be 99.0%) and *N*-(1-naphthyl)ethylenediamine dihydrochloride (NEDA) (S. d. Fine Chem., India, certified to be 98.5%) were used. All other chemicals and solvents used were of analytical reagent grade.

The following dosage forms containing ceftazidime were purchased from local commercial sources: 1 – Tazid injections equivalent to 250 mg ceftazidime (Alkem Laboratories Ltd., India), 2 – Tizime injections equivalent to 500 mg (Lupin Laboratories Ltd.) and 3 – Cefazid injections equivalent to 1000 mg (Biochem Pharmaceutical Inds., India).

Standard solutions

A stock solution of ceftazidime (1 mg mL⁻¹) in water was kept in dark to avoid drug degradation. The working standard solution of ceftazidime containing 100 µg mL⁻¹ was prepared by dilution.

Aqueous solutions (0.2%) of MBTH (8.6 × 10⁻³ mol L⁻¹) and NEDA (8 × 10⁻³ mol L⁻¹) were freshly prepared.

Analytical procedures

Method I (MBTH method). – Aliquots of the working standard solution of the drug (0.2–1.0 mL) (100 µg mL⁻¹) were transferred into 10-mL calibrated flasks. To each aqueous solution of FeCl₃ (1.5 mL, 3 × 10⁻² mol L⁻¹), an aqueous solution of MBTH (1.0 mL, 8.6 × 10⁻³ mol L⁻¹) was added. The solutions were swirled and allowed to stand for 5 min. Then hydrochloric acid (1.0 mL, 1 × 10⁻² mol L⁻¹) was added and made up to the mark with water. The absorbance was measured at 628 nm against the corresponding reagent blank and calibration graph was constructed.

Method II (NEDA method). – Aliquots of the working standard solution of the drug (1.0–5.0 mL) (100 µg mL⁻¹) were transferred into 10-mL calibrated flasks. Hydrochloric acid (0.2 mL, 11.3 mol L⁻¹) was added, cooled in an ice bath and aqueous solution of

NaNO_2 (1.0 mL, 0.145 mol L^{-1}) was added. The solutions were cooled to 0°C and an aqueous solution of ammonium sulfamate (0.5 mL , $8.8 \times 10^{-2} \text{ mol L}^{-1}$) was added and stirred for 5 min. Then the aqueous solution of NEDA (1.0 mL , $8 \times 10^{-3} \text{ mol L}^{-1}$) was added and made up to the mark with water. The solutions were mixed thoroughly and the absorbance was measured at 567 nm against reagent blank and a calibration graph was constructed.

Validation

The linearity, slope and the intercepts were calculated using the regression equation. Precision and accuracy of the proposed methods were tested by carrying out the determination of eight replicates of pure and commercial samples of the drug, whose concentration was within Beer's law range. Values of the standard deviation (SD), relative standard deviation (RSD) and range of error at 95% confidence level were calculated (17). The two methods have been applied to various pharmaceutical formulations and recovery studies have been made by the standard-addition method.

Intra-day precision and intra-day error of the methods were assessed from the results of eight replicate analyses on the pure drug solution. The mean values and relative standard deviation values for replicate analysis at three different concentration levels were calculated.

Accuracy of the methods was determined by recovery studies *via* the standard-addition method.

The limit of detection (LOD) and limit of quantification (LOQ) were calculated according to the current ICH guidelines (18) as the ratio of 3.3 and 10 standard deviation of the blank ($n = 7$), respectively, and the slope of the calibration line.

Selectivity studies. – To check the interference $10 \mu\text{g mL}^{-1}$ CFZM was selected for the MBTH method; for the NEDA method, $20 \mu\text{g mL}^{-1}$ CFZM was used. Before adding the reagents, a known amount of the interfering substance was added and the reaction was carried out for both methods. The extent of interference by various excipients that often accompany pharmaceutical formulations are tabulated in Table I.

Assay of the drug in injection dosage forms

The content of ten to twenty vials (depending on the content per vial) were mixed thoroughly. An amount of the powder equivalent to 100 mg of active component was weighed into a 100-mL volumetric flask, about 60 mL of water was added and shaken thoroughly for about 20 min. The volume was made up to the mark with water, shaken and filtered using filter paper. The filtrate was diluted sequentially to get $100 \mu\text{g mL}^{-1}$ of the drug.

RESULTS AND DISCUSSION

The methods are based on (i) the oxidative coupling reaction of the drug with 3-methylbenzothiazolin-2-one hydrazone (MBTH) in the presence of ferric chloride in acidic

Table I. Determination of ceftazidime in the presence of excipients and other substances

Substance ^a	Recovery (%) ^b	
	MBTH ^c	NEDA ^d
Magnesium stearate	99.8 ± 0.4	99.4 ± 0.2
Lactose	99.5 ± 0.2	99.8 ± 0.7
Dextrose	99.9 ± 0.5	99.7 ± 0.1
Starch	99.9 ± 0.5	99.5 ± 0.3
Gum acacia	99.8 ± 0.3	100.0 ± 0.1
Talc	99.6 ± 0.4	99.8 ± 0.3
Carboxy methyl cellulose	99.6 ± 0.4	99.7 ± 0.1
Sodium alginate	99.7 ± 0.3	99.9 ± 0.3

^a Amount: 40 mg.

^b Mean ± SD, *n* = 5.

^c Concentration ratio drug to excipient 1:400.

^d Concentration ratio drug to excipient 1:200.

medium, and (ii) the coupling reaction between the diazotized drug and *N*-(1-naphthyl)ethylenediamine dihydrochloride (NEDA) in aqueous medium.

Reaction products

The absorbance spectra of the bluish colored product (CFZM-MBTH) with λ_{\max} of 628 nm and that of the purple colored product (CFZM-NEDA) with λ_{\max} 567 nm are shown in Fig. 1. The above mentioned blanks have practically negligible absorption in both systems.

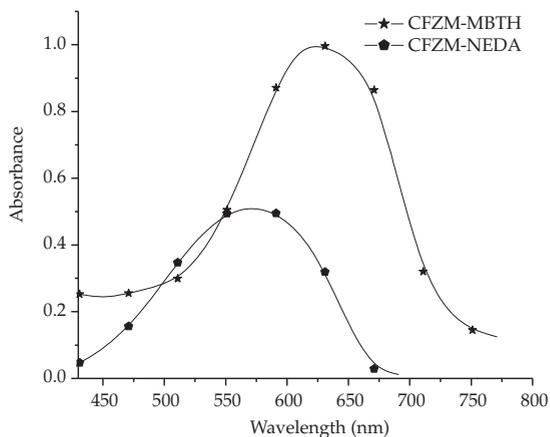
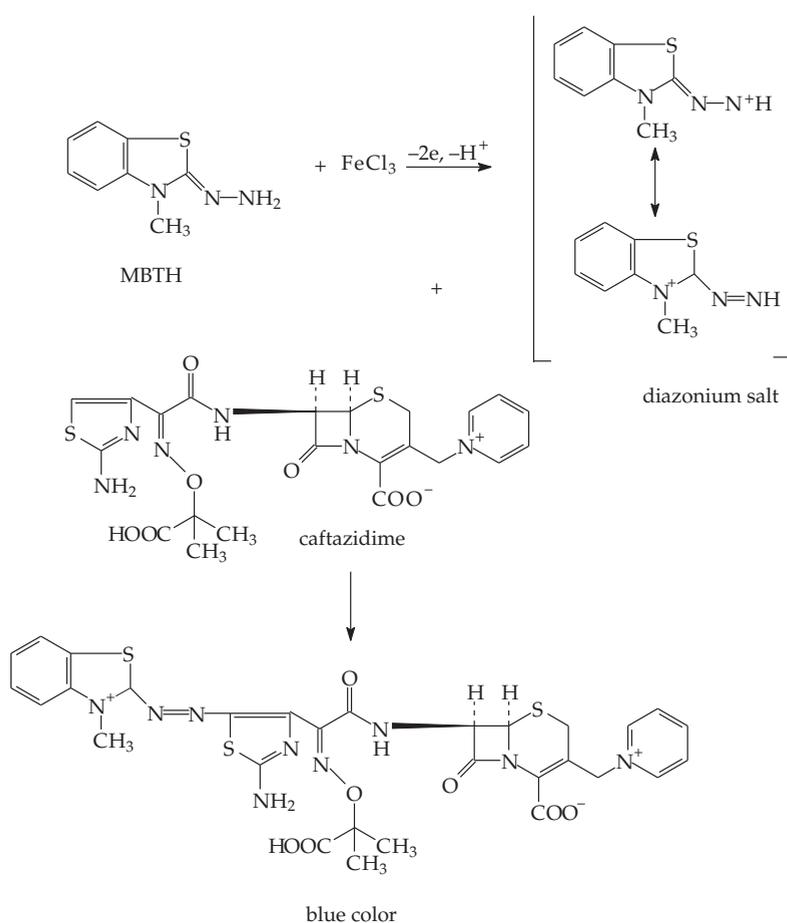


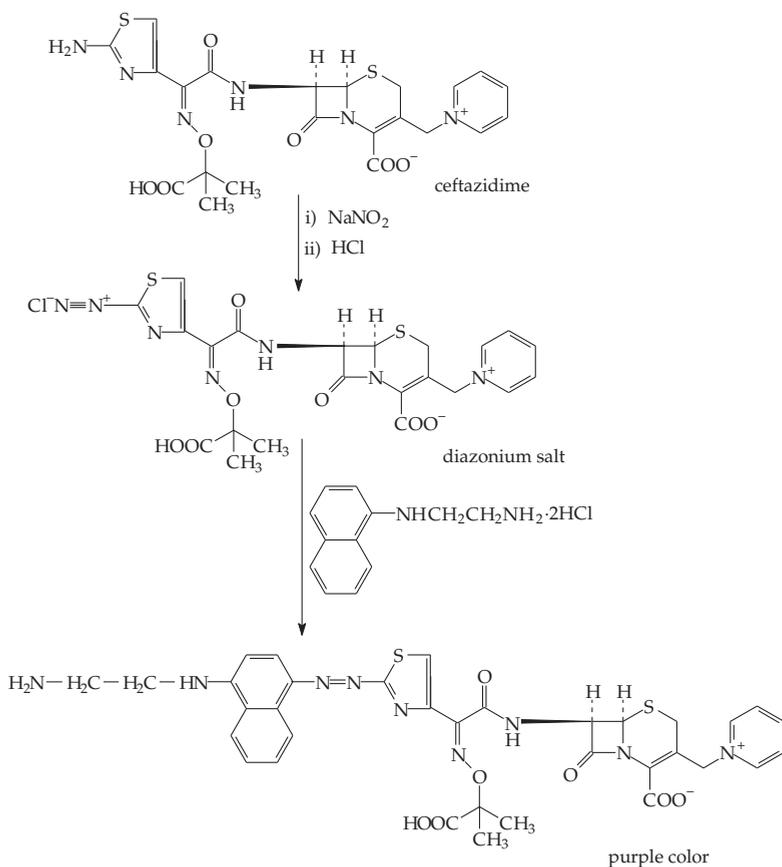
Fig. 1. Absorbance spectra of (CFZM-MBTH) and (CFZM-NEDA) reaction products (initial concentration of CFZM was 10 and 20 $\mu\text{g mL}^{-1}$, respectively).

In the MBTH method, the drug reacts with MBTH in the presence of FeCl_3 in acidic medium to give a blue colored product. Actually, this is an iron catalyzed oxidative coupling reaction of MBTH with the drug. Under the reaction conditions, on oxidation, MBTH loses two electrons and one proton forming an electrophilic intermediate, which is the active coupling species. This intermediate undergoes electrophilic substitution with the drug to form the colored product. The NEDA method includes diazotization of the drug to form diazonium salt, which on coupling with NEDA yields a purple azo dye. The reaction mechanisms (CFZM-MBTH) and (CFZM-NEDA) for both methods are shown in Schemes 1 and 2, respectively.

The colored products were found to be stable for 18 and 6 hours, respectively, at room temperature. Reproducible results were obtained in the temperature range of 20–40 °C. An increase in temperature above 40 °C decreased the absorbance readings in the NEDA method, indicating decomposition of the product.



Scheme 1



Scheme 2

Optimization of reaction conditions

For the MBTH method, to achieve maximum color intensity 8.6×10^{-4} mol L⁻¹ MBTH, 4.5×10^{-3} mol L⁻¹ ferric chloride and 1×10^{-3} mol L⁻¹ hydrochloric acid were necessary.

For NEDA method, for the development of maximum color intensity 0.226 mol L⁻¹ hydrochloric acid, 1.45×10^{-2} mol L⁻¹ sodium nitrite, (4.4×10^{-3} mol L⁻¹) ammonium sulfamate and 8×10^{-4} mol L⁻¹ NEDA were necessary. The excess of nitrite could be removed by the addition of (4.4×10^{-3} mol L⁻¹) ammonium sulfamate solution. An excess of ammonium sulfamate has no effect on the color intensity of the product formed. In the case of NEDA as a coupling agent, dilution of the colored solution with different solvents like water, methanol, ethanol, acetic acid and acetonitrile was tested. However, dilution with water gave maximum intensity and stability of the color. Temperature of 30 °C is recommended for the absorbance measurements of colored products.

Figures of merit

Linear correlations were found between absorbance at λ_{\max} and CFZM concentration and are described by the regression equations:

$$A = 0.078 + 0.138 \gamma; R = 0.9999, n = 8 \text{ (MBTH method)}$$

$$A = 0.0199 + 0.00534 \gamma, R = 0.9989, n = 8 \text{ (NEDA method)}$$

where A is the absorbance and γ is the concentration in $\mu\text{g mL}^{-1}$, R is the correlation coefficient and n is the number of measurement levels. Beer's law is obeyed for 2–10 and 10–50 $\mu\text{g mL}^{-1}$ for the MBTH and NEDA methods, respectively. Calculated apparent molar absorptivity values were found to be 6.0×10^4 and $1.3 \times 10^4 \text{ L mol}^{-1} \text{ cm}^{-1}$ for the MBTH method and NEDA methods, respectively.

The LOD values were found to be 0.15 and 0.79 $\mu\text{g mL}^{-1}$ for CFZM with MBTH and with NEDA, respectively. The LOQ values were 0.50 and 2.61 $\mu\text{g mL}^{-1}$ for CFZM with MBTH and with NEDA, respectively. These values indicate that the MBTH method is more sensitive than the NEDA method.

Table II summarizes the intra-day precision and intra-day error data for the assay of CFZM in pure drug solution by the proposed methods. The intra-day RSD values ranged from 0.1–0.4%, reflecting the usefulness of the method in routine use, and e_r data was $\leq 2.0\%$.

The results of the selectivity study as shown in Table I confirm that the proposed methods are accurate and precise even in the presence of various excipients. Amines such as aniline, piperidine, morpholine, interfere in the NEDA method, because of the diazotization reaction. It was found that in both methods, excipients like magnesium stearate, lactose, dextrose, starch, gum acacia, talc, carboxymethyl cellulose and sodium alginate in the concentration excess (1:400 and 1:200) over the drug do not interfere in MBTH and NEDA methods, respectively. Recoveries of CFZM in selectivity testing were found to be

Table II. Intra-day precision and intra-day error of the methods

Method	CFZM ($\mu\text{g mL}^{-1}$) taken	CFZM ($\mu\text{g mL}^{-1}$) found	e_r (%)	RSD (%)	CL ($\mu\text{g mL}^{-1}$)
MBTH	0.5	0.49	0.8	0.4	$0.49 \pm 0.00_2$
	1.50	1.49	0.13	0.2	$1.49 \pm 0.00_2$
	2.50	2.49	0.1	0.2	$2.49 \pm 0.00_4$
	3.0	2.99	0.15	0.1	$2.99 \pm 0.00_1$
NEDA	3.50	3.49	0.11	0.10	$3.49 \pm 0.00_3$
	4.00	3.99	0.25	0.1	$3.99 \pm 0.00_2$

e_r – relative error.

CL – confidence limits at 95% confidence level for seven degrees of freedom.

99.7 ± 0.4 and 99.7 ± 0.3% for MBTH and NEDA methods, respectively, indicating selectivity of both methods. Even precisionwise, the proposed methods are satisfactorily, with low RSD values ranging from 0.1 to 0.7%.

Application to dosage forms

The proposed methods were applied to the analysis of CFZM in vials and the results were statistically compared with those obtained by the official HPLC method (7) by calculating the Student's *t*- and *F*-values. The evaluated *t*- and *F*-values were less than the tabulated values at the 95% confidence level for seven degrees of freedom (18), as revealed by the results compiled in Table III. This actually suggests that the proposed methods are accurate and precise as the official method (7).

In order to further ascertain the accuracy and reliability of the methods, recovery experiments were performed by the standard-addition method. Pre-analyzed formulation was spiked with pure CFZM at three different levels and the total was found by the proposed methods. The percent recovery of pure drug added was in the range of 99.3–102.3% for MBTH and from 97.6–101.5% for NEDA. RSD ranged from 0.3 to 0.9%. The results of this study summarized in Table IV indicate that neither the accuracy nor the precision of the methods is affected by the coformulated substances.

The proposed methods are simple, rapid and reliable. In contrast to the charge transfer complex method (6) reported earlier, the proposed methods are more sensitive, with a range of 2–10 µg mL⁻¹ (7.85×10^{-7} – 1.57×10^{-6} mol L⁻¹), and can be applied to a single vial so that vial to vial variation, if desirable, can be followed. Performance characteristics of the existing spectrophotometric methods (15, 16) and the present methods are compared in Table V, from which it is obviously clear that the proposed methods are free from drastic experimental conditions such as heating or extraction unlike many reported procedures. Both methods are highly sensitive compared to all the existing spectrophotometric methods, as shown by the molar absorptivity values and, in fact, the method using MBTH is the most sensitive method ever reported for CFZM. The proposed methods use eco-friendly and inexpensive chemicals and seldom employ organic solvents.

Table III. Assay of drug in pharmaceutical formulations (injections)

Preparation	Label claim (mg per vial)	Percent found ^a			Student <i>t</i> -value ^b		<i>F</i> -value ^c	
		MBTH	NEDA	Reference method (7)	MBTH	NEDA	MBTH	NEDA
1	250	99.8 ± 0.5	99.9 ± 0.4	99.9 ± 0.6	0.03	0.15	1.87	2.74
2	500	99.7 ± 0.3	99.9 ± 0.3	100.0 ± 0.4	1.70	0.24	1.41	1.98
3	1000	99.8 ± 0.4	99.9 ± 0.3	99.8 ± 0.6	0.44	0.21	2.03	3.17

^a Mean ± SD, *n* = 8.

^b Tabulated value at 95% confidence level is 2.365.

^c Tabulated value at 95% confidence level is 3.79.

Table IV. Recovery by the standard-addition method

Formulation	MBTH			NEDA		
	Amount of drug in formulation (mg)	Amount of drug added (mg)	Recovery (%) ^a	Amount of drug in formulation (mg)	Amount of drug added (mg)	Recovery (%) ^a
1	3.96	6.0	102.3 ± 0.3	2.96	5.0	99.6 ± 0.4
	3.96	9.0	100.0 ± 0.4	2.96	10.0	100.3 ± 0.6
	3.96	12.0	101.0 ± 0.4	2.96	15.0	101.1 ± 0.3
2	3.88	6.0	102.0 ± 0.8	3.07	5.0	99.4 ± 0.4
	3.88	9.0	100.3 ± 0.6	3.07	10.0	100.5 ± 0.3
	3.88	12.0	99.3 ± 0.7	3.07	15.0	101.5 ± 0.6
3	3.90	6.0	100.3 ± 0.4	2.96	5.0	97.6 ± 0.9
	3.90	9.0	99.6 ± 0.8	2.96	10.0	99.7 ± 0.3
	3.90	12.0	100.2 ± 0.3	2.96	15.0	100.8 ± 0.7

^a Mean ± SD, n = 3.

Table V. Comparison of spectrophotometric methods for ceftazidime assay

Reagent(s) used	λ_{\max} (nm)	Beer's law limits	Molar absorptivity (L mol ⁻¹ cm ⁻¹)	Reference
Pd(II)/SLS	330	3.0-60 mg mL ⁻¹	-	9
KMnO ₄	430.5	0.0-30 mg mL ⁻¹	-	10
NBD-Cl	414	63.66-254.66 mg mL ⁻¹	-	12
Ammonium molybdate	716	2-70 mg mL ⁻¹	2.70 × 10 ³	14
MBTH	628	2-10 µg mL ⁻¹	6.02 × 10 ⁴	This paper
NEDA	567	10-50 µg mL ⁻¹	1.29 × 10 ⁴	This paper

SLS - sodium lauryl sulfate

NBD-Cl - 4-chloro-7-nitrobenzofurazan

MBTH - 3-methylbenzothiazolin-2-one hydrazone

NEDA - N-(1-naphthyl)ethylenediamine dihydrochloride

CONCLUSIONS

Ceftazidime has been assayed in dosage forms using visible spectrophotometry. Two methods can be used to monitor the content uniformity of injections and purity of ceftazidime raw material. The methods could be considered for the determination of CFZM in quality control laboratories.

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S A Ž E T A K

Razvoj i validacija spektrofotometrijskih metoda za određivanje ceftazidima u farmaceutskim doziranim pripravcima

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Razvijene su dvije spektrofotometrijske metode za određivanje ceftazidima (CFZM), čistog ili u farmaceutskim pripravcima. Prva metoda se temelji na reakciji 3-metilbenzotiazolin-2-on hidrazona (MBTH) sa ceftazidimom u prisutnosti željezovog(III) klorida u kiselom mediju. Nastaje plavi kompleks s maksimumom apsorpcije pri λ_{\max} 628 nm. Druga metoda se temelji na reakciji između diazotiranog lijeka i *N*-(1-naftil)etilendiamin dihidroklorida (NEDA), pri čemu nastaje ljubičasti produkt s λ_{\max} pri 567 nm. Reakcijski uvjeti su optimirani da se dobije maksimalni intenzitet boje. Apsorbancija raste linearno s porašću koncentracije CFZM; sustavi slijede Beerov zakon u koncentracijskom području 2-10 za MBTH metodu i 1050 $\mu\text{g mL}^{-1}$ za NEDA metodu. LOD i LOQ te vrijednosti korelacijskog koeficijenta su 0,15, 0,79 i 0,50, 2,61. Uobičajene pomoćne tvari ne smetaju određivanju ceftazidima. Predložene metode su jednostavne, osjetljive, točne i pogodne za primjenu u kontroli kvalitete.

Ključne riječi: ceftazidim, diazotacija, spektrofotometrija, farmaceutski pripravak

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