Turk J Pharm Sci 10(3), 321-328, 2013

Original article

FIRST DERIVATIVE SPECTROPHOTOMETRIC DETERMINATION OF CEFIXIME AND CEFDINIR IN PHARMACEUTICAL PREPARATIONS

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Abstract

In this study, a first derivative spectrophotometric method was developed for the determination of cefdinir and cefixime in pharmaceutical preparations. Cefdinir and cefixime were dissolved in 0.1 M Na_2HPO_4 (pH 8.0) and dA/dλ values were measured at 306.8 nm for cefdinir and 307.0 nm for cefixime in their first derivative spectra. Cefdinir and cefixime obey Beer's Law in the range of 2-30 µg/mL (r=0.9993) and 2.5-35 µg/mL (r=0.9997) respectively. LOD values were 0.28 µg/mL and 0.45 µg/mL and LOQ values were 0.98 µg/mL and 1.50 µg/mL for cefdinir and cefixime respectively. Method was validated and successfully applied to tablet formulations marketed in Turkey. The results were compared with an previously developed HPLC method.

Key words: *First derivative spectrophotometry, Cefixime, Cefdinir, Pharmaceutical preparations.*

Sefdinir ve Sefiksim'in Farmasötik Preparatlarda Birinci Türev Spektrofotometrik Tayini

Bu çalışmada sefdinir ve sefiksim'in farmasötik preparatlarda miktar tayini için birinci türev spektrofotometrik bir metot geliştirilmiştir. Sefdinir ve sefiksim 0.1 M Na_2HPO_4 (pH 8.0) içerisinde çözülmüş ve birinci türev spektrumlarında sefdinir için 306.8 nm'de, sefiksim için ise 307.0 nm'de dA/dλ değerleri ölçülmüştür. Sefdinir ve sefiksimin sırasıyla 2-30 µg/mL (r=0.9993) ve 2.5-35 µg/mL (r=0.9997) aralığında Beer kanununa uyduğu gözlenmiştir. LOD değerleri sefdinir ve sefiksim için sırasıyla 0.28 µg/mL ve 0.45 µg/mL ve LOQ değerleri ise 0.98 µg/mL ve 1.50 µg/mL olarak bulunmuştur. Metodun validasyonu yapılmış ve Türkiyede ticari olarak satılan tablet formülasyonlarına başarılı bir şekilde uygulanmıştır.Sonuçlar daha once geliştirilmiş bir YPSK yöntemiyle karşılaştırılmıştır.

Anahtar kelimeler: *Birinci türev spektrofotometri, Sefiksim, Sefdinir, Farmasötik preparatlar.*

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INTRODUCTION

Cefdinir, (CFD) ((-)-(6R,7R)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid) (Figure 1) and cefixime (CFX) ((6R, 7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-2-(carboxy-methoxyimino) acetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo-[4,2,0]-oct-2-ene-2-carboxylic acid) (Figure 2) are third-generation oral cephalosporin antibacterials.

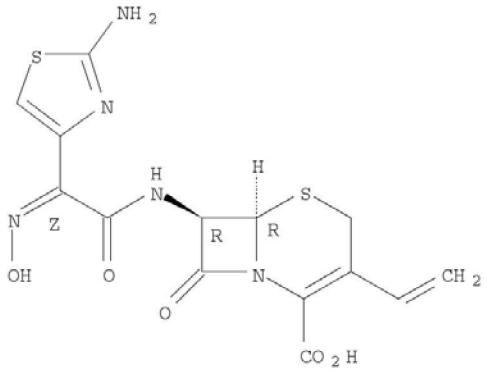

Figure 1. Cefdinir

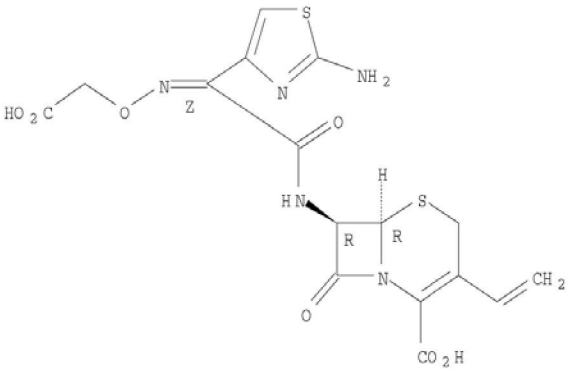

Figure 2. Cefixime

Cefdinir has been used for the treatment of community-acquired pneumonia, acute bacterial exacerbations of chronic bronchitis, acute maxillary sinusitis, pharyngitis/tonsillitis, acute bacterial otitis media, and uncomplicated skin and skin structure infections in adult and pediatric patients (1). Cefixime has been used mainly for the treatment of respiratory tract infections (RTIs), including pneumonia and acute exacerbations of chronic bronchitis; otitis media; sinusitis; urinary tract infections (UTIs); and gonorrhea (2).

Derivative spectrophotometry technique is useful in drug analysis, especially for resolving of overlapped spectra of mixtures. Any possible interference effect from the excipients in pharmaceutical preparation could be prevented by using this technique. Beside mixture analysis, taking derivative of a spectrum prevent unwanted effect (lamp or detector instabilities) arised from instrument or matrix effect arised from background matrix (3).

Several methods including liquid chromatography (4-15) and spectrophotometry (16-23) voltammetry (24-27) have been reported for determination of cefdinir and cefixime in pharmaceutical preparations.

Literature surveys show that most of developed spectrophotometric methods are based on complex formation reaction and requiring complex sample preparation steps. To our knowledge there is no report for first derivative spectrophotometric determination of CFD and CFX. The aim of this study is to develop simple, rapid, accurate, precise and inexpensive first derivative spectrophotometric method for the determination of cefdinir and cefixime in pharmaceutical formulations.

EXPERIMENTAL

Materials and reagents

CFD and CFX were obtained from Bilim Pharm. Ind. (İstanbul, Turkey). Disodiumhydrogen phosphate (Na_2HPO_4) and orto-phosphoric acid (H_3PO_4) (Sigma Aldrich) were of analytical grade. Zimax (400 mg cefixime/tablet) and Ceftimex (300 mg cefdinir/tablet) tablets were purchased from pharmacies in Turkey.

Apparatus

Shimadzu 1601 PC double beam spectrophotometer with a fixed slit width (2 nm) was used for measurements. For differentiation of spectrums, Shimadzu UVPC software was employed.

Agilent Technologies (Wilmington, DE) HP 1100 chromatographic system with an ACE C18 column (150 x 4.6 mm id, particle size 3 µm) was used for comparison test (4).

Method

In the selection of the media, we paid attention to get simple sample preaparation, freely solubility of substances, inexpensive method and not to use organic solvent. CFD and CFX are more soluble in basic and neutral media than in acidic media according to calculation done by Advanced Chemistry Development (ACD/Labs) Software V11.02 (28). pH of 0.1 M Na_2HPO_4 solution was adjusted to 8.0 by 0.1M H_3PO_4. As shown in the Figure 3 and 4, first derivative of CFD and CFX spectra have maximums and minimums above the UV cut-off value of buffer (210 nm). Mean recoveries and relative standart deviations were calculated in order to choose the best wavelength.

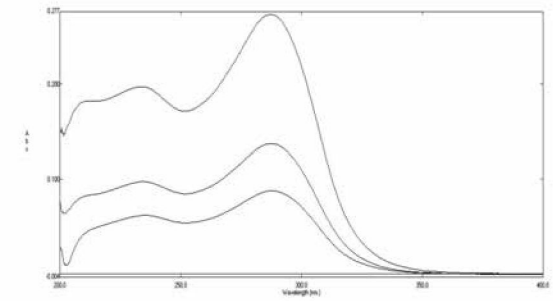

Figure 3a. Original spectrums of 2.5, 4.0 and 8.0 µg/mL CFX in 0.1M Na_2HPO_4 (pH=8)

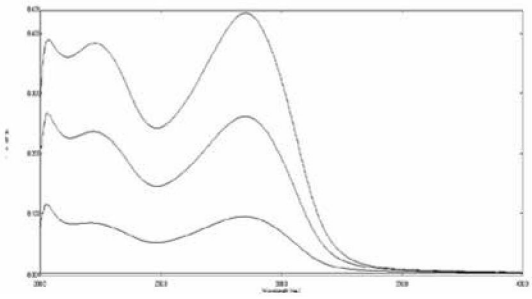

Figure 4a. Original spectrums of 2.0, 5.0 and 8.0 µg/mL CFD in 0.1M Na_2HPO_4 (pH=8)

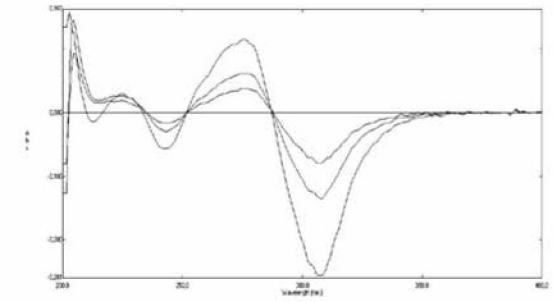

Figure 3b. First derivative spectrums of 2.5, 4.0 and 8.0 µg/mL CFX in 0.1M Na_2HPO_4 (pH=8)

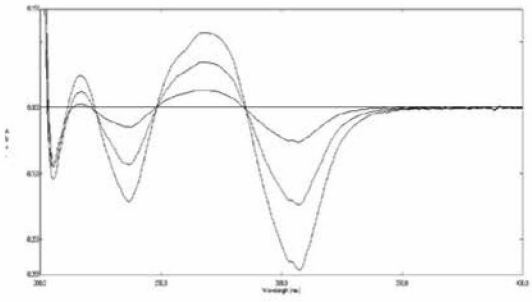

Figure 4b. First derivative spectrums of 2.0, 5.0 and 8.0 µg/mL CFD in 0.1M Na_2HPO_4 (pH=8)

Calibration curve

Stock solutions of 250 µg/mL CFD and CFX were prepared in 0.1 M Na_2HPO_4 (pH 8.0). Aliquots of stock solutions were taken into 25 mL volumetric flasks and diluted with the buffer to get 2.5 – 35 µg/mL for CFX and 2.0-30 µg/mL for CFD. Three replicate samples of eight different concentrations were prepared for both CFD and CFX. dA/dλ values were recorded at 306.8 nm for CFD and 307.0 nm for CFX.

LOD and LOQ

Limit of detection (LOD) and limit of quantitation (LOQ) values calculated according to ICH Guideline (29):

$$LOD = 3SD/m$$
$$LOQ = 10SD/m$$

where SD is the standart deviation of intercept and m is the slope of calibration curve.

Accuracy, precision and selectivity

Accuracy and precision of the method was tested by analyzing three sets of three concentrations (4, 16 and 28 µg/mL for CFD and 4, 14 and 20 µg/mL for CFX). These solutions were analyzed on the same day (intraday) and on 3 consecutive days (interday).

According to official guidelines, if all drug components are not available, it is acceptable to apply standart addition method. We applied standart addition method to test whether the exicipients in tablets interfere with the results of analysis. Known amounts (50%, 75% and 100%) of CFX and CFD were added to tablets and analyzed.

Sample preparation

We used pestle and mortar to grind the tablets to a fine powder. Amounts equivalent to one tablet were weighed and taken into 100 mL volumetric flasks. Samples were mixed by magnetic stirrers for 30 min. and filtered through 0.45 µm cellulose filter paper. Then aliquots of filtrates were diluted to get concentrations of 16 µg/mL for CFX and 12 µg/mL for CFD.

RESULTS AND DISCUSSION

Method Optimization

We observed experimentally that substances are freely soluble at pH 8.0 confirming the calculations of ACD/Labs Software V11.02. Then it was tested whether small variations in pH effect spectrum or not. No difference was observed when the pH was varied by ±0.1 unit.

According to recovery experiment results, 306.8 nm for CFD and 307 nm for CFX were more suitable in terms of accuracy and precision.

Linearity, LOD and LOQ

Regression equations were established by plotting dA/dλ values versus concentration. Linearities were within the ranges of 2.5-35 µg/mL for CFX and 2.0-30 µg/mL for CFD.

LOD values were found as 0.45 and 0.28 µg/mL and LOQ values were 0.93 and 1.50 µg/mL for CFD and CFX respectively (Table 1).

Table 1. Linearity parameters.

Parameters	CFD	CFX
Linearity range (µg/mL)	2.0 – 30	2.5 – 35
Slope	-0.03063	-0.03479
Standart error of slope	0.006255	0.004563
Intercept	0.001140	0.01376
Standart error of intercept	0.0003908	0.0002502
Regression coefficient	0.9993	0.9996
LOD (µg/mL)	0.28	0.45
LOQ (µg/mL)	0.93	1.50

Accuracy, precision and selectivity

Mean recovery and relative standart deviation values show accuracy and precision of the method (Table 2). Low RSD and high mean recovery values show good precision and good accuracy. Results of standart addition method indicate that the exicipients in tablets didn't interfere with the results of analysis in first derivative spectrums (Table 3).

Table 2. Accuracy and precision.

	Intra day				Inter day			
Standarts (µg/mL)	Mean ± SD (µg/mL)	RSD %	Mean recovery %	Bias %	Mean ±SD (µg/mL)	RSD %	Mean recovery %	Bias %
CFD								
4	4.03 ±0.02	0.47	100.78	0.78	4.03 ±0.03	0.84	100.91	0.91
16	15.77 ±0.14	0.90	98.58	-1.42	15.71 ±013	0.82	98.22	-1.78
28	28.28 ±0.14	0.50	100.99	0.99	28.44 ±0.28	0.99	101.55	1.55
CFX								
4	4.08 ±0.01	0.18	101.98	1.98	4.02 ±0.07	1.63	100.60	0.60
14	13.94 ±0.03	0.18	99.54	-0.46	14.28 ±0.27	1.88	102.02	2.02
20	20.16 ±0.09	0.45	100.82	0.82	20.03 ±0.17	0.83	100.14	0.14

Table 3. Results of standart addition method.

CFX			CFD		
Added (mg)	Found (mg)	% Recovery	Added (mg)	Found (mg)	% Recovery
150	147.76	98.51	200	202.62	101.31
225	229.38	101.95	300	305.24	101.75
300	300.03	100.01	400	412.56	101.66

Analysis of Pharmaceutical Preparations

Analyses of pharmaceutical preparations were carried out according to steps mentioned in *Sample Preparation* part. Results were fitting with the label claims for each of the substances. The results of the proposed method were compared with those of the published LC method (4). According to the Student's t-test and the Fisher F-test at P = 0.05 level there was no statistically significant difference in the commercial formulations (Table 4).

Table 4. Assay results (mg/tablet).

	CFD (300 mg/tablet)		**CFX (400 mg/tablet)**	
	^{1}D	LC [4]	^{1}D	LC [4]
Mean ±SE	303.86 ±1.86	303.68 ±1.92	399.66 ±1.36	399.23 ±1.14
RSD %	1.37	1.55	0.97	0.70
Bias %	1.29	1.23	-0,08	-0.19
	^{1}D – LC [4]			
t	0.23		0.07	
F	1.29		1.92	

SE: Standart error of mean, 1D: First derivative spectrophotometry,
LC:Liquid chromatography
Tabulated t value at p:0.05 = 2.18 F value at p:0.05 = 4.28

CONCLUSION

In this study, a spectrophotometric method for determination of CFX and CFD was developed. Method was validated in terms of accuracy, precision, selectivity, robustness, linearity, detection limits. Method was successfully applied to pharmaceutical preparations and compared with a HPLC method previously published. Therefore it can be used in routine analysis of CFD and CFX in pharmaceutical preparations and bulk forms.

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Received: 18.10.2011
Accepted: 17.01.2011