RESEARCH ARTICLE

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Development and Validation of Dual Wavelength UV Spectrophotometric Method for Simultaneous Estimation of Cefixime and Dicloxacillin Sodium in Pharmaceutical Dosage Form

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Abstract:

The present manuscript describes simple, sensitive, rapid, accurate, precise and economical dual wavelength method for the simultaneous determination of Cefixime and Dicloxacillin sodium in tablet dosage form. The principle for dual wavelength method is "the absorbance difference between two points on the mixture spectra is directly proportional to the concentration of the component of interest". Cefixime was determined directly at 271.8 nm in methanol. The wavelengths selected for determination of dicloxacillin sodium were 271.8 nm and 218.4 nm in methanol. Regression analysis of Beer's plots showed good correlation in concentration range of 3-16 µg/ml for both the drugs. The method was successfully applied for the determination of these two drugs in tablet dosage form. No interference was observed from excipients present in the tablet. The suitability of this method for the quantitative determination of Cefixime and Dicloxacillin sodium was proved by validation. The proposed method was found to be simple and sensitive for the routine analysis of these two drugs in tablet dosage form. The results of analysis have been validated statistically and by recovery studies.

Keywords: Cefixime, Dicloxacillin sodium, Dual wavelength method, UV spectrophotometric method, Validation.

Introduction

Cefixime (CEF) is chemically (6R,7R)-7-[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2 [(carboxymethoxy) imino] acetamido]-3-ethenyl-8-oxo-5-thia-1-azabicyclo-oct-2-ene-2 carboxylic acid [1] (Figure-1). Cefixime (CEF), an antibiotic, is a third generation cephalosporin. The antibacterial effect of cefixime results from inhibition of mucopeptide synthesis in the bacterial cell wall [2]. Cefixime (CEF) is official in Indian Pharmacopeia (IP) [3], British Pharmacopeia (BP) [4], and United States Pharmacopeia (USP) [5]. These three pharmacopeias describe liquid chromatography method for its estimation. Literature survey reveals UV spectrophotometry [6-9], HPLC [10-13] methods for determination of CEF alone. Literature survey also reveals UV [14-25], HPLC [26-40] methods for the determination of CEF with other drugs combination. Dicloxacillin sodium (DIC) is chemically (2S,5R,6R)-6-[3-(2,6-dichlorophenyl)-5-methyl-1,2-oxazole-4-amido]-3,3-dimethyl-7-oxo-4-thia-1- azabi cyclo heptane-2-carboxylic acid [41] (Figure 2). Dicloxacillin sodium (DIC) is an anti-bacterial agent. It is official in Indian Pharmacopoeia (IP) [42], British Pharmacopoeia (BP) [43], and United States Pharmacopeia (USP) [44]. IP, BP, USP describe HPLC method for its estimation. Literature survey reveals HPLC [45-46] methods for estimation of DIC alone. Literature survey also reveals UV [47-49], HPLC [50-56] methods for determination of DIC with other drugs in combination. The combination of these two drugs is not official in any pharmacopoeia; hence no official method is available for the simultaneous estimation of CEF and DIC in their combined synthetic mixture or dosage forms. Literature survey reveals only HPLC [57-60] and HPTLC [61] methods for CEF and DIC in combined dosage forms. The present manuscript describes simple, sensitive, rapid, accurate, precise and cost effective spectrophotometric method based on dual wavelength method for simultaneous estimation of

both drugs in pharmaceutical dosage form.

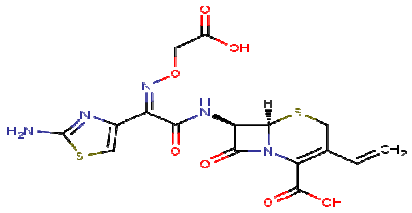

Figure 1- Chemical structure of Cefixime

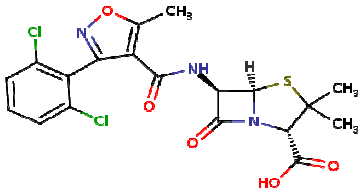

Figure 2- Chemical structure of Dicloxacillin

MATERIALS AND METHODS

APPARATUS

A shimadzu model 1700 (Japan) double beam UV/Visible spectrophotometer with spectral width of 2 nm, wavelength accuracy of 0.5 nm and a pair of 10 mm matched quartz cell was used to measure absorbance of all the solutions. Spectra were automatically obtained by UV-Probe 2.1 system software. A Sartorius CP224S analytical balance (Gottingen, Germany), an ultrasonic bath (Frontline FS 4, Mumbai, India) was used in the study.

REAGENTS AND MATERIALS

Cefixime (CEF) and Dicloxacillin sodium (DIC) were kindly supplied as a gift samples from Brussels Laboratories Pvt. Ltd, Changodar, Ahmedabad, Gujarat, AR grade Methanol (S.D. Fine Chemical Ltd., Mumbai, India.) as a solvent and Whatman filter paper no. 41 (Millipore, USA) were used in the study.

PREPARATION OF STANDARD STOCK SOLUTION

An accurately weighed CEF and DIC powder (10 mg) were transferred to 100 ml separate volumetric flasks and dissolved in methanol. The flasks were shaken and volumes were made up to mark with methanol to give a solution having concentration 100 µg/ml for both of drugs.

METHODOLOGY

The utility of dual wavelength data processing program is to calculate the unknown concentration of a component of interest present in a mixture containing both the components of interest and an unwanted interfering component by the mechanism of the absorbance difference between two points on the mixture spectra. This is directly proportional to the concentration of the component of interest, independent of the interfering components. From the overlay spectra of two drugs in figure-3, it is evident that direct determination of CEF at 271.8 nm (no absorbance of DIC at 271.8 nm). For estimation of DIC, two wavelengths selected (271.8 nm and 218.4 nm) where the CEF shows same absorbance whereas DIC shows significant difference in absorbance with concentration (figure-4). Eight working standard solutions having concentration 3, 4, 6, 8, 10, 12, 14, 16 µg/ml for both the drugs were prepared separately in methanol and the absorbance at 218.4 nm and 271.8 nm were measured and absorptive coefficients were calculated using calibration curve.

The concentration of two drugs in the mixture can be calculated using regression equation.

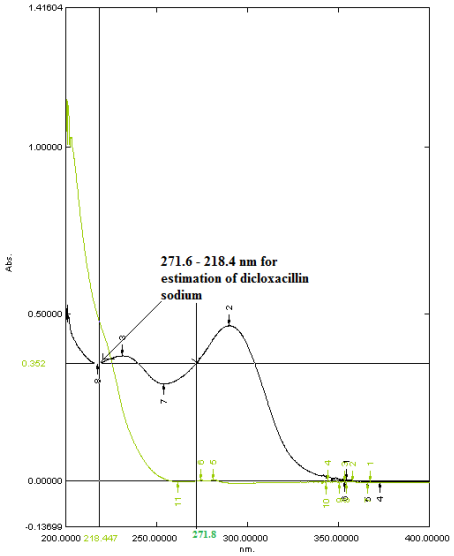

Figure 4: Overlain zero order absorption spectra of CEF and DIC in m

VALIDATION OF THE PROPOSED METHOD

The proposed method was validated according to the International Conference on Harmonization (ICH) guidelines.

LINEARITY (CALIBRATION CURVE)

The calibration curves were plotted over a concentration range of 3 to 16 µg/ml for both CEF and DIC. Accurately measured standard solutions of CEF (0.3,

0.4,0.6, 0.8, 1.0, 1.2, 1.4, 1.6 ml) and DIC (0.3, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6 ml) were transferred to a series of 10 ml of volumetric flasks and diluted to the mark with methanol. The absorbances of the standard solutions were measured at 218.4 nm and 271.8 nm against methanol as blank. The calibration curves were constructed by plotting absorbance versus concentrations and the regression equations were calculated.

METHOD PRECISION (REPEATABILITY)

The precision of the instrument was checked by repeated scanning and measuring the absorbance of solutions (n = 6) of CEF and DIC (10 µg/ml for both drugs) without changing the parameters of the proposed Method. The results are reported in terms of relative standard deviation (% RSD).

INTERMEDIATEPRECISION (REPRODUCIBILITY)

The intra-day and inter-day precision of the proposed method was evaluated by analyzing the corresponding responses 3 times on the same day and on 3 different days over a period of 1 week for 3 different concentrations of sample solutions of CEF and DIC (8, 10, and 12µg /ml). The results are reported in terms of relative standard deviation (% RSD).

LIMIT OF DETECTION (LOD) & LIMIT OF QUANTIFICATION (LOQ)

The limit of detection (LOD) and limit of quantification (LOQ) of the method were calculated by using the following equations.

$$LOD = 3.3 \times \sigma/S$$
$$LOQ = 10 \times \sigma/S$$

Where, σ = the standard deviation of the response
S = slope of the calibration curve

ACCURACY (% RECOVERY STUDY)

he accuracy of the method was determined by calculating recoveries of CEF and DIC by the standard addition method. Known amounts of standard solution of CEF and DIC were added at three levels (50 %, 75 % and 100 %) to pre-quantified sample solutions of CEF and DIC.

ANALYSIS OF TABLET SAMPLE

Twenty tablets were weighed individually and powdered. Labelled claim: 200 mg CEF and 500 mg DIC. Quantity of the powder equivalent to 10 mg CEF was transferred to 100 ml volumetric flask containing 50 ml methanol, cork it and sonicated for 20 min. The solution was filtered through Whatman filter paper No. 41 and the volume was adjusted up to the mark with distilled water. From this solution, 0.6 ml was taken in to a 10 ml volumetric flask and the volume was adjusted up to mark with methanol to get a concentration of CEF (6.0 µg/ml) and DIC (15.0 µg/ml). The absorbance of sample solution was measured against methanol as blank at 218.4 nm and 271.8 nm for quantification of CEF and DIC. The amount of CEF and DIC present in the sample solutions were determined by regression equation.

RESULTS AND DISCUSSION

The utility of dual wavelength method is to calculate the unknown concentration of a component of interest present in a mixture containing both the components of interest and an unwanted interfering component by the mechanism of the absorbance difference between two points on the mixture spectra. The calibration curves were prepared at 271.8 nm (only for CEF) and at absorbance difference of two wavelengths (271.8 nm – 218.4 nm) for the DIC. The response for the CEF (at 271.8 nm) was found to be linear in the concentration range 3 to 16 µg/ml and at absorbance difference of two wavelengths (271.8 nm – 218.4 nm), the response was found to be linear in the concentration range 3 to 16 µg/ml. The linearity of the calibration curve was validated by the high values of correlation coefficient.

The % RSD of repeatability for CEF at 271.8 nm was 0.49 % and at absorbance difference of two wavelengths for DIC was found to be 0.82 %. Low RSD value means the repeatability of the proposed method is good. The low % RSD of intraday and interday indicate that the proposed method is precise. LOD and LOQ values at 271.8 nm were found to be 0.24 and 0.71 respectively and at at absorbance difference of two wavelengths (271.8 nm – 218.4 nm) were found to be 0.21 and 0.64 respectively. These values indicate that the method is sensitive for the detection of CEF and DIC. The regression analysis data and summary of validation parameters for the proposed method is summarized in Table-1. The recovery experiment was performed by the standard addition method. The results (Table-2) obtained (n=3 for each level 50%, 75%, 100% level) indicated the mean recovery 100.99 ± 0.61 and 100.59 ± 0.43 for CEF and DIC, respectively. These values of recovery experiment reveal that the proposed method is highly accurate.

The proposed validated method was successfully applied for determination of CEF and DIC in their tablet dosage form of three different companies. The % assay of CEF and DIC in tablet samples was calculated compared with label claim and recorded in Table-3. No interference of the excipients with the absorbance of analytes of interest observed; hence the proposed method is applicable for the routine simultaneous analysis of CEF and DIC in tablet dosage form.

TABLE 1: REGRESSION ANALYSIS DATA AND SUMMARY OF VALIDATION PARAMETERS FOR CEF AND DIC

Parameters	CEF	Wavelengths for determination of DIC
Wavelength (nm)	271.8	218.4 and 271.8
Beer's law limit (µg /ml)	3-16	3-16
Regression equation (y = a + bc) Slope (b) Intercept (a)	y = 0.034x + 0.0156 0.034 0.0156	y = 0.0468x - 0.0038 0.0468 0.0038
Correlation coefficient (r^2)	0.9988	0.9989
Repeatability (% RSD[a], n= 6)	0.49	0.82
LOD (µg/ml)	0. 24	0.21
LOQ (µg /ml)	0. 71	0.64
Precision (% RSD, n =3) Inter-day Intra-day	 0. 43 – 1.1 0. 19 – 0.53	 0. 34 – 1.2 0.25 – 0. 54
Accuracy ± S.D. (n =6)	100.99 ± 0. 61	100.59 ± 0. 43

TABLE 2: RECOVERY DATA OF CEF AND DIC

Drug	Level	Amount taken (µg/ml)	Amount added (%)	% Mean recovery ± S.D. (n = 3)
CEF	I	6	50	100.73 ± 0.65
	II	6	75	101.55 ± 0.71
	III	6	100	100.68 ± 0.48
DIC	I	8	50	99.96 ± 0.58
	II	8	75	101.32 ± 0.39
	III	8	100	100.49 ± 0.32

S. D. is Standard deviation and n is number of replicate

TABLE 3: ANALYSIS OF CEF AND DIC IN TABLET DOSAGE FORM

Tablet	Label claim (mg)		% Label claim ± S. D. (n = 6)	
	CEF	DIC	CEF	DIC
I	200	500	98.97 ± 0.42	100.80 ± 0.28
II	200	500	99.57 ± 0.61	100.90 ± 0.52
III	200	500	99.36 ± 0.39	101.03 ± 0.45

S. D. is standard deviation and n is number of replicate

CONCLUSION

Based on the results which have been obtained from the analysis using proposed method, it can be concluded that the method has linear response in the range 3 to 16 µg /ml for both the drugs, CEF and DIC. The result of the analysis of three different marketed tablet dosage forms by the proposed method is highly reproducible, reliable, as well as in agreement with label claim of the drugs. The additive present in the synthetic mixture did not interfere in the analysis. So that, the method can be used for the routine analysis of drugs in combination.

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