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Original Article

DEVELOPMENT AND VALIDATION OF SPECTROPHOTOMETRIC DETERMINATION OF CEFPODOXIME PROXETIL IN PURE AND TABLET DOSAGE FORMS THROUGH ION-PAIR COMPLEX FORMATION USING BROMOTHYMOL BLUE

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ABSTRACT

Objective: A simple, direct and accurate spectrophotometric method has been developed for the determination of cefpodoxime proxetil (CEFP) in pure and pharmaceutical formulations by complex formation with bromothymol blue (BTB).

Methods: The method involves the formation of yellow ion-pair complexes between BTB reagent and CEFP in chloroform. The two formed complexes ([CEFP]: [BTB] and [CEFP]: $[BTB]_2$) have maximum absorption at λ_{max} 422 nm. The proposed method was validated for specificity, linearity, precision and accuracy, repeatability, sensitivity (LOD and LOQ) and robustness with an average recovery of 99.0-101.4%.

Results: The formed complex ([CEFP]: $[BTB]_2$) was measured against the reagent blank prepared in the same manner. Variables were studied in order to optimize the reaction conditions. Molar absorptivity (ε) for two complexes were 8100 and 12600 L. mol^{-1}. cm^{-1}, respectively. Beer's law was obeyed in the concentration range of 0.5576-55.760 µg/ml in the present of $1x10^{-3}$ mol/l of BTB with good correlation coefficient (R^2= 0.9995). The relative standard deviation did not exceed 4.7%. The limit of detection (LOD) and the limit of quantification (LOQ) were 0.088 and 0.27 µg/ml, respectively.

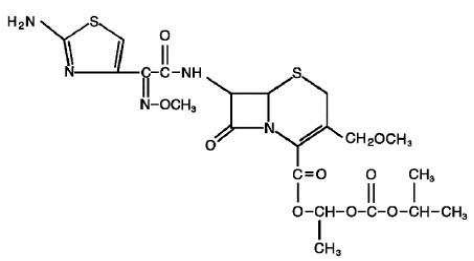
Conclusion: The developed method is applicable for the determination of CEFP in pure and different dosage forms with the average assay of marketed formulations 99.5 to 103.2%, and the results are in good agreement with those obtained by the RP-HPLC reference method.

Keywords: Direct spectrophotometric method; Cefpodoxime proxetil; Bromothymol blue; Ion-pair complex.

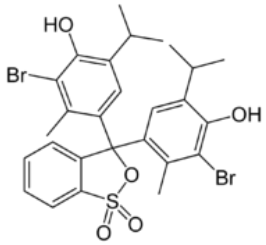
INTRODUCTION

Cefpodoxime Proxetil (CEFP) is a third generation cephalosporin antibiotic indicated for the treatment of patients infected with susceptible strains of microorganisms which include a wide range of gram-positive and gram-negative bacteria. It is commonly used to treat acute otitis media, pharyngitis, and sinusitis. It is chemically described as (RS)-1(isopropoxycarbonyloxy) ethyl (+)-(6R, 7R)-7-[2-(2-amino-4-thiazolyl)-2-[(Z) methoxyimino] acetamido]-3-methoxy methyl- 8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylate. The molecular formula of cefpodoxime proxetil is $C_{21}H_{27}N_5O_9S_2$ and the molecular weight is 557.6 g/mol. It is freely soluble in dehydrated alcohol, acetonitrile, methanol and very slightly soluble in water [1-3], see Scheme 1.

Bromothymol blue $C_{27}H_{28}Br_2O_5S$ (BTB), acts as a weak acid in solution. It can thus be in protonated or deprotonated form, appearing yellow or blue, respectively. It is bluish green in neutral solution. The deprotonating of the neutral form results in a highly conjugated structure, accounting for the difference in color. An intermediate of the deprotonating mechanism is responsible for the greenish color in neutral solution, mol. mass 624.38 g [4], see scheme 2. Bromothymol blue has been used as a reagent to form ion pair complexes with drugs as diltiazem HCl [5].



Scheme 1: Chemical structure of cefpodoxime proxetil (CEFP)



Scheme 2: Chemical structure of bromothymol blue ($C_{27}H_{28}Br_2O_5S$)

A simple, sensitive, accurate and rapid UV-Vis spectrophotometric methods have been developed for the estimation of cefpodoxime proxetil in bulk drug and in pharmaceutical dosage form, which shows maximum absorbance at 415 and 425 nm for ion-pair complexes between cefpodoxime proxetil with bromocresol purple and bromocresol green, receptively, in acidic medium and the subsequent extraction of the ion-pair in chloroform [6].

Various spectrophotometric methods [6-24] have been reported for the determination of cefpodoxime proxetil in pure as well as in dosage forms. Most spectrophotometric methods employ extraction procedures. In this case, the extracted complexes were into an organic solvent, which is immiscible with water, and the concentration of the resulting complex in the organic phase is determined spectrophotometrically. The complex extraction technique has some difficulties and inaccuracies due to incomplete extraction or the formation of emulsions between the hydrocarbon solvent and the basic compound-containing solution. In response to the problems resulting from the extraction of the complex, it is better to determine formed complex without extraction [25]. Also, none of the methods reported in the literature is based on the formation of a complex between BTB and CEFP.

In this study, a extraction-free spectrophotometric method for determination of CEFP through ion-pair complex formation with BTB was developed.

MATERIALS AND METHODS

Instruments and apparatus

Spectrophotometric measurements were made in Spectro scan 80 DV UV-VIS spectrophotometry with 1 cm quartz cells. An ultrasonic processor model Powersonic 405 was used to sonicate the sample solutions. The diluter pipette model DIP-1 (Shimadzu), having 100 µl sample syringe and five continuously adjustable pipettes covering a volume range from 20 to 5000 µl (model Piptman P, GILSON). Centrifuge (Centurion Scientific Ltd., Model: K2080-Manufactured in the United Kingdom) was used for the preparation of the experimental solutions. SARTORIUS TE64 electronic balance was used for weighing the samples.

Reagents

Cefpodoxime proxetil (96.138%) was supplied by Virchow group company (INDIA), its purity as cefpodoxime was (73.7%), (Mfg. 07/2015, Exp. 07/2018). Bromothymol blue (97%) of analytical grade and chloroform of extra pure were from MERCK. All solvents and reagents were analytical grade chemicals.

Stock standard solution of bromothymol blue (BTB) $1x10^{-2}$ mol/l

Accurately weighed 160.92 mg of BTB was dissolved in chloroform into a volumetric flask (25 ml) and diluted up to mark with chloroform.

Stock standard solution of CEFP $1x10^{-3}$ mol/l

This solution was prepared by dissolving 14.50 mg of CEFP in chloroform into a volumetric flask (25 ml) and diluted up to mark with chloroform.

Working standard solutions of CEFP

The stock solution was further diluted daily just before the use to obtain working solutions of CEFP in the concentrations: 1.0, 2.0, 5.0, 7.5, 10, 15, 20, 40, 60, 80 and 100 µM (0.5576, 1.1152, 2.788, 4.182, 5.576, 8.364, 11.152, 22.304, 33.456, 44.608 and 55.760 µg/ml) by transferring different aliquots from stock standard solution: 10, 20, 50, 75, 100, 150, 200, 400, 600, 800 and 1000 µl into 10 ml volumetric flasks, then 1 ml from stock standard solution of BTB was added, diluted to 10 ml with chloroform.

Sample preparation

Commercial formulations (as a tablet) were used for the analysis of CEFP. The pharmaceutical formulations subjected to the analytical procedure were:

(1) *Oracef* tablets, ELSaad pharma, Aleppo–SYRIA, (Mfg. 09/2014, Exp. 09/2018), each tablet contains 100 and 200 mg of cefpodoxime (CEF).

(2) *Oraxime* tablets, Asia pharmaceutical industries, Aleppo–SYRIA, (Mfg. 11/2014, Exp. 11/2017), each tablet contains 100 and 200 mg of CEF.

(3) *Oraluxe* tablets, ALPHA. Aleppo pharmaceutical industries, Aleppo-SYRIA, (Mfg. 01/2015, Exp. 01/2018), each tablet contains 100 and 200 mg of CEF.

Stock solutions of pharmaceutical formulations

20 tablets of each studied pharmaceutical formulation were weighed accurately, crushed to a fine powder and mixed well. An amount of the powder equivalent to the weight of one tablet was solved in chloroform using ultrasonic for 10 min, 20 ml of chloroform was added, filtered over a 25 ml flask and washed by the same solvent, then diluted to 25 ml with chloroform. This solution contains the follows: 4 and 8 mg/ml of CEF for all studied pharmaceutical formulations contain 100 and 200 mg/tab, respectively.

Working solutions of pharmaceuticals

Five solutions were prepared daily by diluting 100 and 50 µl from a stock solution of pharmaceutical formulations for contents: 100 and 200 mg/tab, respectively. Then adding 1 ml from a stock standard solution of BTB and adjusting the volume up to 10 ml with chloroform (these solutions contain 40 µg/ml of CEF; test solutions).

Procedure

A solution (10 ml) containing an appropriate concentration of CEFP (or working solutions of pharmaceuticals) with appropriate amount of BTB in chloroform was ready for spectrophotometric measurement at λ_{max} 422 nm.

RESULTS AND DISCUSSION

The different experimental parameters affecting the spectrophotometric determination of CEFP through ion-pair complex ([CEFP]:$[BTB]_2$) formation with BTB in chloroform were studied in order to determine the optimal conditions for the determination of CEFP.

Spectrophotometric results

UV-Vis spectra of CEFP, BTB and the formed complexes CEFP: BTB solutions (using chloroform or $1x10^{-3}$M of BTB in chloroform as blank) were obtained. CEFP solutions do not absorb in the range 360-600 nm. BTB solutions have small absorption at λ_{max} 410 nm ($\varepsilon \approx 120$ L. mol^{-1}. cm^{-1}). [CEFP]: [BTB] and [CEFP]:$[BTB]_2$ complexes solutions have maximum absorption at λ_{max} 422 nm, (ε for two complexes were 8100 and 12600 L. mol^{-1}. cm^{-1}, respectively), see fig. 1.

The effect of time and temperature

The effect of time and temperature on the complex ([CEFP]:$[BTB]_2$) formation was studied within the ranges 5-120 min and 15-30°C. It was found that the formed complex wasn't affected by time or temperature at those ranges.

The effect of BTB concentration

The effect of BTB concentration on complex ([CEFP]:$[BTB]_2$) formation was investigated. It was observed that the absorbance of the formed complex increased coinciding with increasing the ratio of C_{BTB}: C_{CEFP} until the ratio (2:1), then slowly increased until the absorbance became a quasi-static at ratio more than 10.

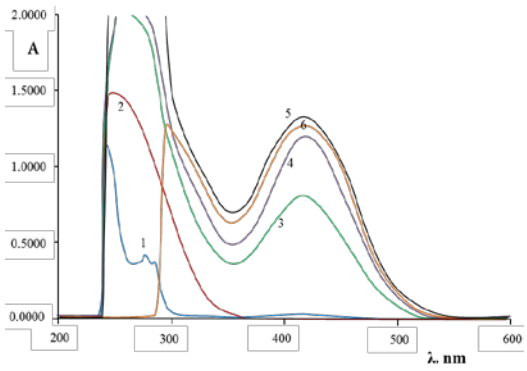


Fig. 1: UV-Vis spectra in chloroform of: 1-$1.0x10^{-4}$ mol/l of BTB; 2-$1.0x10^{-4}$ mol/lof CEFP; 3-$1.0x10^{-4}$ mol/l ion-pair complex [CEFP]:[BTB]($1.0x10^{-4}$ mol/l of CEFP with $1.0x10^{-4}$ mol/l of BTB); 4-$1.0x10^{-4}$ mol/l ion-pair complex [CEFP]:$[BTB]_2$ ($1.0x10^{-4}$ mol/l of CEFP with $2.0x10^{-4}$ mol/l of BTB); 5, 6-$1.0x10^{-4}$ mol/l ion-pair complex [CEFP]:$[BTB]_2$ ($1.0x10^{-4}$ mol/l of CEFP with $1.0x10^{-3}$ mol/l of BTB); 1-5: Blank is chloroform; 6-Blank is $1.0x10^{-3}$ mol/l of BTB, ℓ =1 cm

Composition of CEFP: BTB complexes

The composition of CEFP: BTB complexes were determined by the molar ratio method and Job's method of continuous variation.

Molar ratio method

The stoichiometry of CEFP: BTB complexes were studied by molar ratio method according to following equation: A_{max}= f([BTB]/[CEFP])

at λ_{max} 422 nm. It confirmed that the binding ratio of CEFP: BTB complexes are equal to (1:1 and 1:2); where the concentration of CEFP was constant (100 µM) and the concentrations of BTB changed from 0 to 400 µM (fig. 2). The formation constant of the ion pair complexes [CEFP]:[BTB] and [CEFP]:$[BTB]_2$ are $1.6x10^5$ and $9.1x10^5$, respectively.

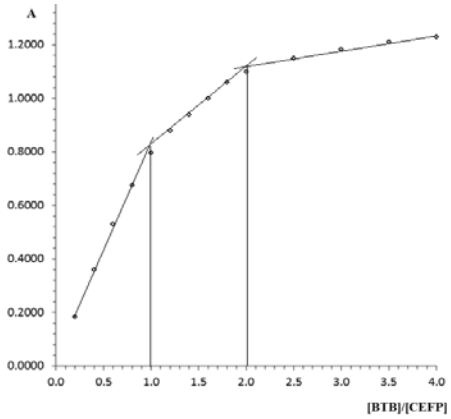


Fig. 2: Molar ratio method to calculate binding ratio of CEFP: BTB complexes at λ=422 nm ([CEFP]= 100 µM, blank is chloroform, ℓ =1 cm)

Job's method of continuous variation

Continuous variation was utilized to check the composition of CEFP: BTB complexes at λ_{max} 422 nm. The absorbance of the complexes were plotted against the mole fraction [BTB]/([CEFP]+[BTB]), where [CEFP]+[BTB]=200 µM. The plot reached maximum values at a mole fraction of 0.5 and 0.67, see fig. 3. This indicated complexes formation (CEFP: BTB) in the ratio of 1:1 and 1:2. The formation constant of the ion-pair complexes [CEFP]:[BTB] and [CEFP]:$[BTB]_2$ are $1.7x10^5$ and $9.2x10^5$, respectively.

The optimum conditions for spectrophotometric determination of CEFP through ion-pair complex formation using BTB in chloroform are shown in table 1.

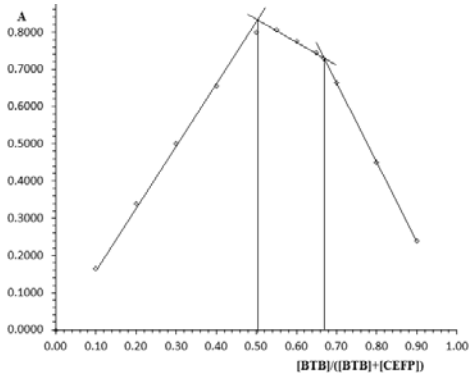


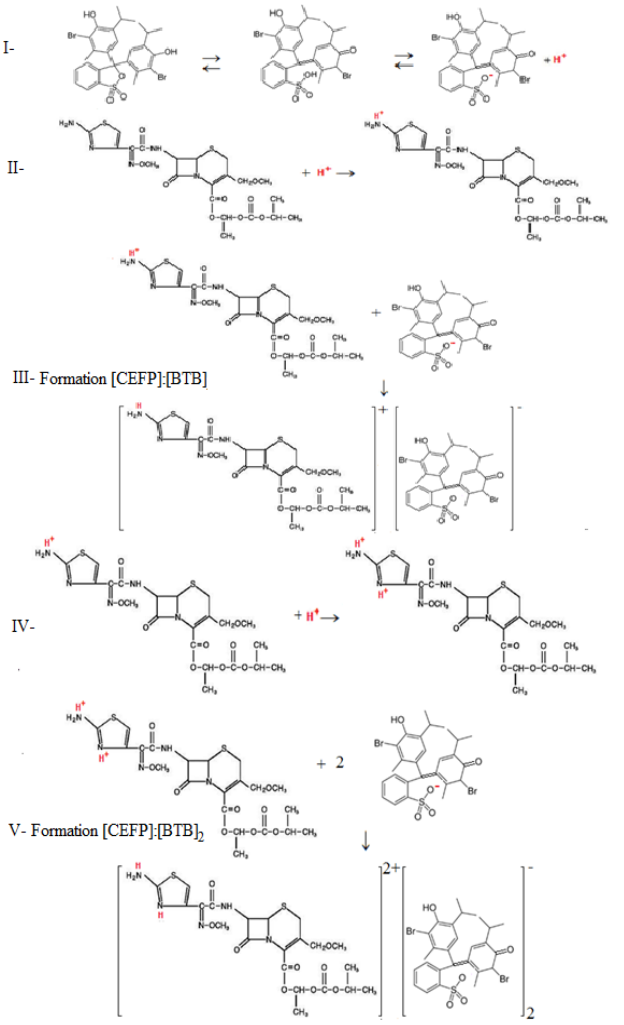
Fig. 3: Job's method of continuous variation to calculate binding ratio of CEFP: BTB complexes at λ 422 nm ([CEFP]+[BTB]=200 µM, blank is chloroform, ℓ =1 cm)

Table 1: The optimum conditions for spectrophotometric, determination of CEFP by complexes formation with BTB in chloroform

Parameters	Operating modes
Temperature of solution	20±5 °C
C_{BTB}: C_{CEFP}, M	≥10
Solvent	chloroform
Stability	12 h
λ_{max} of CEFP: BTB complexes	422 nm
Light path (ℓ)	1.0 cm
Spectra range	300–600 nm

Mechanism of reaction

Anionic dyes such as BTB form ion-pair complexes with the positively charged nitrogen-containing molecule. The colour of such dyes is due to the opening of lactoid ring and subsequent formation of the quinoid group (deprotonated). CEFP is protonated and forms yellow ion-pair complexes [CEFP]:[BTB] and [CEFP]:$[BTB]_2$ with the dye. Each drug-dye complex with two oppositely charged ions (positive on the drug and negative on the dye) behaves as a single unit held together by an electrostatic binding. The suggested mechanism of CEFP: BTB ion-pair complexes formation are shown in Scheme 3.



Scheme 3: Mechanism of [CEFP]: [BTB] and [CEFP]:$[BTB]_2$ complex formation

Calibration curve

The calibration curve of CEFP in pure form through complexation with BTB showed excellent linearity over the concentration range of 1.0-100.0 µM (0.5576–55.760 µg/ml). Regression equations at λ_{max} 422 nm were as the follows:

$$y=0.023x+0.0004 \text{ ..... (I)}$$

$$y=0.0227x+0.0035 \text{ ..... (II)}$$

For concentrations of CEFP 0.5576-11.152 µg/ml and 0.5576-55.760 µg/ml, respectively, (fig. 4and5). The spectra characteristics of the method such as the molar absorptivity (ε), Beer's law, regression equation at λ_{max} 422 nm (y=a. x+b); where y=absorbance, a=slope, x=concentration of CEFP in µM or µg/ml,b=intercept,the correlation coefficient, limit of detection (LOD) and limit of quantification (LOQ) are summarized in table 2.

Analytical results

Spectrophotometric determination of CEFP through complexation with BTB in chloroform within optimal conditions using calibration curve was applied. The results, summarized in table 3, showed that the determined concentration of CEFP was rectilinear over the range of 1.0 to 100.0 µM or 0.5576 to 55.760 µg/ml with relative standard deviation (RSD) not more than 4.7%. The results obtained from the developed method have been compared with the official RP-HPLC method [26] and good agreement was observed between them (table 3).

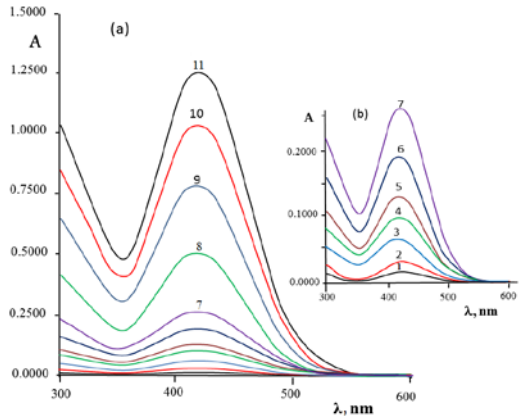


Fig. 4: Spectra of [CEFP]:[BTB]$_2$ complex in present 1.0×10^{-3} M of BTB; where C_{CEFP} as the follows: 0.5576, 1.1152, 2.788, 4.182, 5.576, 8.364, 11.152, 22.304, 33.456, 44.608 and 55.760 µg/ml for curves (1-11) {Blank is BTB solution in chloroform 1x10^{-3}M; ℓ = 1 cm}

Method validation

The developed method for estimation of CEFP has been validated in accordance with the International Conference on Harmonization guidelines (ICH) [27].

Specificity

Specificity test determines the effect of excipients on the assay result. To determine the specificity of the method, standard solution of CEFP, commercial product solution and blank solutions were analyzed. The results of the tests proved that the components other than the drug did not produce any interfere.

Linearity

Several aliquots of a standard stock solution of CEFP were taken in different 10 ml volumetric flask and diluted up to the mark with chloroform such that their final concentrations were 0.5576-55.760 µg/ml for CEFP. Absorbance was plotted against the corresponding concentrations to obtain the calibration graph, see fig. 5. Linearity equations obtained were y = 0.023x+0.0004 for the range 0.5576-11.152 µg/ml (R^2=0.9993) and y=0.0227x+0.0035 for the range 0.5576-55.760 µg/ml (R^2=0.9995).

Precision and accuracy

The precision and accuracy of proposed method were checked by recovery study by addition of standard drug solution to pre-analyzed sample solution at three different concentration levels (80%, 100% and 120%) within the range of linearity for CEFP. The basic concentration level of sample solution selected for spiking of the CEFP standard solution was 11.152 µg/ml. The proposed method was validated statistically and through recovery studies and was successfully applied for the determination of CEFP in pure and dosage forms with average percent recoveries ranged from 99.0% to 101.4%, see table 4.

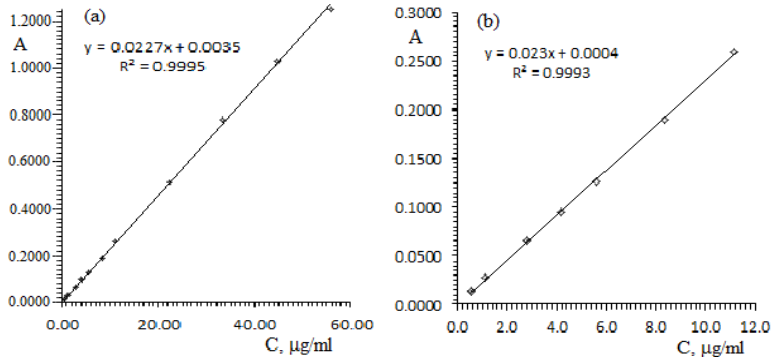


Fig. 5: Calibration curve for determination of CEFP according to optimal conditions (at λ_{max} 422 nm in present of 1×10^{-3} M of BTB) where C_{CEFP}: 0.5576, 1.1152, 2.788, 4.182, 5.576, 8.364, 11.152, 22.304, 33.456, 44.608 and 55.760 µg/ml {Blank is BTB solution in chloroform 1x10^{-3}M; ℓ = 1 cm}

Table 2: The parameters established for spectrophotometric determination of CEFP by complex formation with BTB in chloroform

Parameters	Operating values
Molar absorptivity of [CEFP]:[BTB] complex (ε_1), L. mol^{-1}. cm^{-1}	8.1x10^3
Molar absorptivity of [CEFP]:[BTB]$_2$ complex (ε_2), L. mol^{-1}. cm^{-1}	1.26x10^4
Regression equation for [CEFP]:[BTB]$_2$ at λ_{max}=422 nm (C_{CEFP}= 0.5576-11.152 µg/ml):	
Slope	0.023
Intercept	0.0004
Correlation coefficient (R^2)	0.9993
Regression equation for [CEFP]:[BTB]$_2$ at λ_{max}=422 nm (C_{CEFP}= 0.5576-55.760 µg/ml):	
Slope	0.0227
Intercept	0.0035
Correlation coefficient (R^2)	0.9995
Beer's Law Limit, for C_{CEFP} by µM	1-100
Beer's Law Limit, for C_{CEFP} by µg/ml	0.5576-55.760
RSD%	4.7
LOD(3.3SD), for C_{CEFP} by µg/ml	0.088
LOQ (10SD), for C_{CEFP} by µg/ml	0.27

n=5, t=2.776.

Table 3: Spectrophotometric determination of CEFP through complex formation with BTB within optimal conditions using calibration curve in chloroform

X_i, µg/ml (Taken)	* $\overline{X}$ ±SD, µg/ml (mean±SD)	$\frac{SD}{\sqrt{n}}$, µg/ml	$\bar{x} \pm \frac{t.SD}{\sqrt{n}}$ µg/ml	RSD %	* $\overline{X}$, µg/ml RP-HPLC [26]
0.5576	0.57±0.027	0.012	0.57±0.034	4.7	0.559
1.1152	1.16±0.049	0.022	1.16±0.061	4.2	1.120
2.788	2.90±0.11	0.049	2.90±0.136	3.8	2.84
4.182	4.11±0.15	0.066	4.11±0.183	3.6	4.16
5.576	5.46±0.18	0.078	5.46±0.217	3.2	5.53
8.364	8.24±0.26	0.114	8.24±0.316	3.1	8.31
11.152	11.29±0.34	0.152	11.29±0.422	3.0	11.19
22.304	22.31±0.65	0.289	22.31±0.802	2.9	22.31
33.456	34.21±0.96	0.428	34.21±1.188	2.8	33.84
44.608	45.31±1.22	0.547	45.31±1.518	2.7	44.92
55.760	54.91±1.43	0.639	54.91±1.774	2.6	55.21

* n=5, t= 2.776

Table 4: Results of recovery studies

Level	% Recovery
80% (n=5)	99.0
100% (n=5)	101.2
120% (n=5)	101.4

Repeatability

The repeatability was evaluated by performing 10 repeat measurements for 11.152 µg/ml of CEFP using the studied spectrophotometric method under the optimum conditions. The found amount of CEFP ($\bar{x}$±SD) was 11.29±0.30 µg/ml and the percentage recovery was found to be 101.2±2.5 with RSD of 0.027. These values indicate that the proposed method has high repeatability for CEFP analysis.

Sensitivity (limit of detection [LOD] and limit of quantitation [LOQ])

The sensitivity of the method was evaluated by determining the LOD and LOQ. The values of LOD and LOQ for CEFP are 0.088 and 0.27 µg/ml, respectively.

Robustness

The robustness of the method adopted is demonstrated by the constancy of the absorbance with the deliberated minor change in the experimental parameters such as the change in the concentration of excipients, BTB (±5%), temperature (±5°C) and reaction time (30 min).

Applications

The developed spectrophotometric method was applied to determine CEFP in some pharmaceutical preparations through complex formation by BTB in chloroform according to the optimal conditions. The amount (m) of CEFP in one tablet was calculated from the following relationship: m = h. m', where: m' is the amount of CEFP in tablet calculated according to the regression equation (II), h conversion factor is equal to 2.5 and 5.0 for pharmaceutical formulations contain 100 and 200 mg/tab, respectively. The results of quantitative analysis for CEFP in pharmaceutical preparations were summarized in Tables 5. The proposed method was simple, direct, specific and successfully applied to the determination of CEFP in pharmaceuticals without any interference from excipients. Average assay of marketed formulations ranged between 99.5 to 103.2%. The results obtained by this method agree well with the contents stated on the labels and were validated by RP-HPLC method [26].

Table 5: Determination of CEFP, as cefpodoxime (CEF), in some Syrian pharmaceutical preparations using spectrophotometric method through complex formation with BTB in chloroform, λ_{max} 422 nm

Tablet dosage form	Label claim of CEFP as CEF, mg/tab.	*mean±SD (as CEF), mg/tab.	RSD%	Assay%	* (Assay%), by RP-HPLC [26]
Oracef	100	99.8±2.79	2.8	99.8	100.1
	200	202.0±5.46	2.7	101.0	101.2
Oraxime	100	101.4±2.84	2.8	101.4	101.1
	200	203.0±5.48	2.7	101.5	101.7
Oraluxe	100	103.2±2.86	2.8	103.2	103.5
	200	199.0±5.37	2.7	99.5	99.4

* n=5, Assay=(found mean/label claim)x100.

CONCLUSION

The developed spectrophotometric method is simple, direct (extraction-free) and cost-effective for the determination of CEFP in pure and tablet dosage forms. This method is based on formation of two ion-pair complexes between CEFP and BTB in chloroform ([CEFP]:[BTB] and [CEFP]: $[BTB]_2$). Beer's law in the optimum experimental conditions using [CEFP]: $[BTB]_2$ complexes is valid within a concentration range of 0.5576-55.760 µg/ml. The developed method is applied for the determination of CEFP in pure and its commercial tablets without any interference from excipients with the average assay of marketed formulations between 99.5 to 103.2%.

This method was validated for specificity, linearity, precision and accuracy, repeatability, sensitivity (LOD and LOQ) and robustness with an average recovery of 99.0-101.4%.

CONFLICT OF INTERESTS

The authors have declared that no conflict of interests exists.

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