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Development and Validation of Highly Sensitive Spectrophotometric Methods for Cefpirome Determination in Pharmaceutical Dosage Forms

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Quantitative spectrophotometric determination of cefpirome in pure and pharmaceutical dosage has been developed. Method I produces a pink-coloured chromogen peak at λ_{max} 510 nm by reacting diazotized cefpirome drugs with diphenylamine (DPA) in a neutral medium. Method II obtained of a coloured Schiff bases when cefpirome reacts with alcoholic *p*-dimethylaminobenzaldehyde (PDAB) to produce a yellow-coloured chromogen with a maximum absorption wavelength of 415 nm. In both methods I and II, Beer's law is followed in the concentration ranges of 0.3-3.0 and 0.5-5.0 µg/mL, respectively, with molar absorptivity of 5.13×10^4 and 2.54×10^4 for each form. At three separate concentrations, intra-day and inter-day (RSD) and relative error (RE) are measured. The current methods are simple, reliable, inexpensive, speedy and highly reproducible and have been tested in broad range of pharmaceutical formulations with statistical comparisons to reference methods.

Keywords: Cefpirome, Diphenylamine, Diazotization, Schiff's bases, Chromogen.

INTRODUCTION

Cephalosporin is a group of broad-spectrum derived from species of fungi of the genus Cephalosporium and related to the penicillins in both structure and mode of action but relatively penicillinase-resistant antibiotics. These antibiotics have low toxicity for the host, considering their broad antibacterial spectrum. They have the active nucleus of β-lactum ring which result in a variety of antibacterial and pharmacological characteristics when modified mainly by substitution at 3- and 7 - positions. Their antibacterial activities result from the inhibition of mucopeptide synthesis in the cell wall. Traditionally, the cephalosporins are divided into first-, second-, third-, fourth- and fifith-generation agents [1-3].

Cefpirome, [6*R*-[6α,7β(Z)]]-1-[[(2-amino-4-thiazolyl)-(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0.]oct-2-em-3-yl]methyl]-6,7-dihydro-5*H*-cyclopenta[*b*]pyridinium inner salt [4], is an injectable broad spectrum aminothiazolyl cephalosporin and manufactured as sulfate salt. It is considered to be highly active against both Gram-negative organisms including *Pseudomonas aeruginosa* and Gram-positive organisms including *Staphylococci*. It is stable to both plasmid and chromosomal β-lactamases and has been shown to induce less class I β-lactamase resistance than cephalosporins [2,5-7]. The increased spectrum of activity, together with high stability against β-lactamase and rapid transmembrane transport, distinguishes cefpirome as an example of a fourth-generation cephalosporin and its principal use is in treatment for patient's septic shock or several sepsis [8].

The reported analytical procedures are available in the literature for the analysis of cefpirome *via* HPLC [9-11], RP-HPLC [12-14], UPLC [15] and UV-visible spectrophotometric method [16-19]. However, these methods present adequate linearity, precision and recovery, they exhibits a series of disadvantages including lack of sensitivity, which results in the lower LOQ and long reaction time. Although, these methods are relatively imprecise, laborious, heating of reaction product at high temperature for long time and wide linear range (Table-1).

The aim of the work was to develop and validate an assay for determination of cefpirome in pure and pharmaceutical dosage forms to make it extremely sensitive, simple, rugged, robust and rapid, less expansive, accurate and highly precise. The proposed methods were validated according to International Conference on Harmonization (ICH) guidelines [20].

TABLE-1
COMPARISON OF THE PROPOSED SPECTROPHOTOMETRIC METHODS WITH THE EXISTING METHODS

Method	Experimental details	Detection	Linear range	LOQ (μg/mL)	Remarks	Ref.
HPLC	Acetonitrile-0.02 M potassium dihydrogen phosphate buffer (6:94, v/v, pH 2.0) was the mobile phase (1 mL mn^{-1})	UV at 263 nm	0.5-200 μg/mL	NA	Less accurate and precise % relative error -0.70 – 15.0, intra-day and inter-day Coefficient of variance 1.67 % and 6.27 % respectively.	[9]
Visible spectrophotometry	Folin-Ciocalteau reagent	700 nm	5-20 μg/mL ($\varepsilon = 1.852 \times 10^3$ L/mol/cm)	NA	High basic condition required	[16]
RP-HPLC	Mediterranea C18 Column; Methanol and water (30:70 v/v) was the mobile phase (1 mL min^{-1})	UV at 265 nm	0.5-50 μg/mL	0.021	Less accurate and precise % relative error –0.42 – 3.84, intra-day and inter-day Coefficient of variance 0.01 % and 2.36 % respectively.	[13]
i) UV spectrophotometery ii) HPLC	i) 0.01M HCl solution ii) Techsphere ODS Column; Methanol and water (30:70 v/v) was the mobile phase (0.8 mL min^{-1})	UV at 271 nm UV at 265 nm	6-22 mg/mL 2-20 mg/mL	NA	Less sensitive; narrow linear dynamic range; less precise (RSD > 0.8%)	[17]
Visible spectrophotometry	1,10-Phenanthroline reagent	515 nm	0.2-6 μg/mL	0.614	Involves heating at > 60 °C for 15 min. during the reaction	[18]
HPLC	μ-Bondapak C_{18} Column, Acetonitrile – acetate buffer (13:87 v/v, pH = 5) was the mobile phase (1.0 mL min^{-1})	258 nm	0.5-64.0 μg/mL	0.5	Less accurate and precise, recoveries < 88.80 % with RSD of 5%	[12]
RP-HPLC	B144A, OD-5-100, C_{18} Column, Methanol-Water (15:85 v/v) was the mobile phase (1.0 mL min^{-1})	UV at 265 nm	10 ng	20 ng	Drug metal ion interaction occurs only at 37 °C, scrupulous control of experimental variables and special equipment for kinetic measurement required	[14]
UPLC	Phenomnex C_{18} column, 0.01M phosphate buffer and acetonitrile (50:50 v/v) was the mobile phase (0.3 mL min^{-1})	PDA at 265 nm	7.5-75 μg/mL	1.08	Less sensitive; narrow linear dynamic range; less precise RSD > 0.81%.	[15]
Visible spectrophotometery	i) α-Naphthylamine ii) N-(1-naphthyl)-ethylenediamine iii) 1,10-phenanthroline	512 nm 565 nm 510 nm	5.0-40 μg/mL 2.5-20 μg/mL 2.5-40 μg/mL	NA	Colour stable for upto 30 min; involves heating at > 60 °C for 15 min. during the reaction	[19]
Visible spectrophotometery	i) Diphenylamine (DPA) ii) *p*-Dimethylamino-benzaldehyde (PDAB)	510 nm 415 nm	0.3-3.0 μg/mL 0.5-5.0 μg/mL	0.90 0.96	Simple, highly sensitive, accurate and precise, (intra-day and inter-day RSD < 0.87%) and accurate (% RE < 0.6), colour stability 6 h and 7 h respectively.	Present methods

EXPERIMENTAL

The chemicals used in the current methods were grade of analytical reagent (AR) and running solutions were made in deionized water. The diphenylamine 0.2% solution (S d Fine-Chem., India) was prepared by dissolving a accurate weighed quantity in alcohol and diluted up to 100 mL in a calibrated flask. An aqueous solution of 0.1% ammonium sulfamate (S d Fine-Chem., India) was prepared by dissolving precise weighed quantity in deionized water and diluted to get 0.1% solution. The measured sum of alcoholic *p*-dimethylaminobenzaldehyde (PDAB) (0.2% v/v) was made by dissolving in alcohol to make a 0.2% solution. Alkem Laboratories, India provided pure cefpirome as a gift sample. Pharmaceutical formulations got from market such as Forgen 250 mg, P Rom 500 mg and Refzil 1 g vials of injections.

A standard stock solution (100 mg/mL) was made by adding a accurately measured quantity in 100 mL deionized-water in a standard flask and the running solution of cefpirome (10 μg/mL) was obtained by diluting the standard stock solution. An ELICO Model SL-164 double beam UV-Visible spectrophotometer and 1.0 cm matched quartz-cells were used for all absorbance measurements.

General procedures

Method I: Fresh aliquots of the running standard solution (0.3-3.0 mL) of cefpirome (1.0 mL = 10 μg/mL) were added to a series of 10 mL standard calibrated flasks, followed by 1.0 mL of 0.1 M HCl and 0.5 mL of 0.1 % $NaNO_2$ solutions. Each flask was then filled with an aqueous solution of 0.5 mL 0.1% ammonium sulfamate followed by an alcoholic solution of 1.0 mL 0.2% DPA. Final volume was made upto the mark

with deionized water and the absorbance of each solution is measured at 510 nm against the reagent blank and the amount of CFP is determined by using the calibration graph.

Method II: A series of 10 mL calibrated flasks was filled with varying aliquots of normal working solution (0.5-5.0 mL) of cefpirome (1.0 mL = 10 µg/mL). 1.0 mL of 0.1 M HCl and 1.0 mL of alcoholic 0.2% PDAB solution were applied to each flask and warmed at 40 ºC. After a minute, the volume was made up to the mark using alcohol and at λ_{max} 415 nm, an absorbance was measured against reagent blank and the amount of cefpirome was determined from its calibration graph.

Procedure for vial of injection: The cefpirome containing pharmaceutical dosage was purchased from local medicinal shop . Five vials were weighed and thoroughly mixed and an amount of the drug liquid substance equivalent to 100 mg of the drug weighed and transmitted into a 100 mL volumetric flask, depending on the material per vial. Around 60 mL deionized water was poured and thoroughly mixed for almost 10 min, with the final amount being made up with deionized water. The solution was thoroughly mixed and 10 µg/mL drug solution. A suitable portion was used for analysis.

RESULTS AND DISCUSSION

The existence of an amines group present in cefpirome facilitates the diazotization of cefpirome drug with nitrous acid and coupling reaction of the resulting diazotized salt with diphenylamine (DPA) to produce a pink-coloured chromogen in a method I at 510 nm (**Scheme-I**). For the spectrophotometric determination of cefpirome in its pure and pharmaceutical dosage, the drug was allowed the use of its condensation reaction with PDAB to obtain a yellow-coloured chromogen at 410 nm (**Scheme-II**). These two observations were used as the sources for the spectrophotometric determination of cefpirome in pure and pharmaceutical formulations.

Method development

Method-I: Cefpirome was diazotized with HCl and $NaNO_2$ solution and then coupled with DPA to produce a pink-coloured chromogen with absorption peaks at λ_{max} 510 nm, where the reagent blank shows insignificant absorbance (Fig. 1). The univariate approach was used to examine the reaction in conditions of acid concentration, reaction time and DPA concentration (changing one parameter at a time). The absorbance was found to be same within the limit (Fig. 2), when the concentration of 0.1 M HCl acid varied from 0.2 to 5.0 mL in a total volume of 10 mL. At higher concentration of HCl, there was an undesirable constant absorbance after 5 min of constant time, however, it achieved the optimum absorbance at 1.0 mL and 0.1% $NaNO_2$ in the wide range of 0.5-2.5 mL. The reaction time between cefpirome and diphenylamine was optimized to 5 min and the colour remains constant for 6 h (Fig. 3). The concentration of 0.2% diphenylamine was optimized by varying the volume from 0.2 to 5.0 mL and the highest absorbance was found at 1.0 mL and further increasing the volume, no significant difference in the absorbance (Fig. 4) was found; hence, 0.2% diphenylamine solution (1.0 mL) was used in the experiment.

Method II: Cefpirome reacted with *p*-dimethylaminobenzaldehyde (PDAB) in the presence of acid to form a yellow-

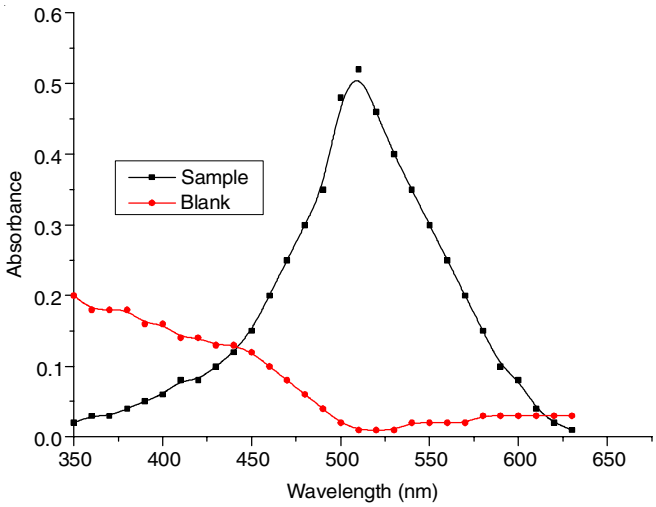
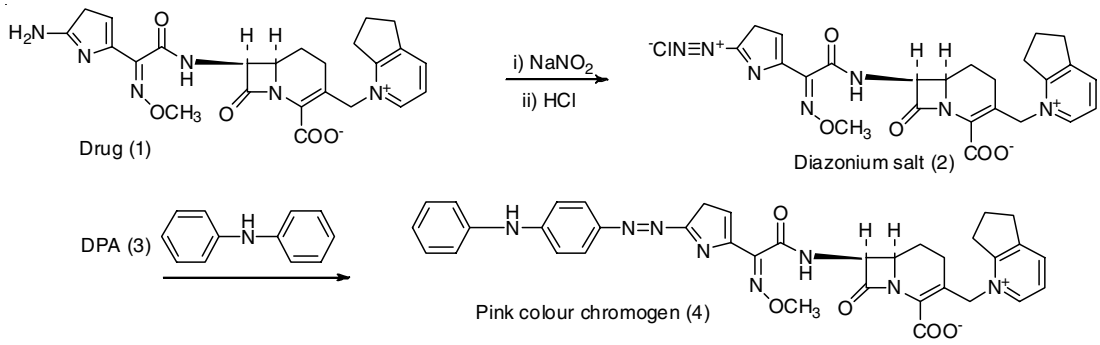
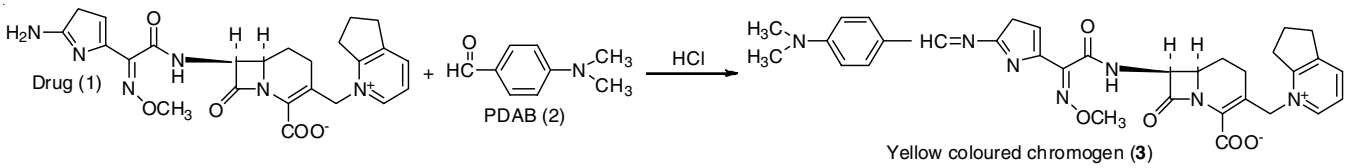


Fig. 1. Absorption spectra of cefpirome (method I)



Scheme-I



Scheme-II

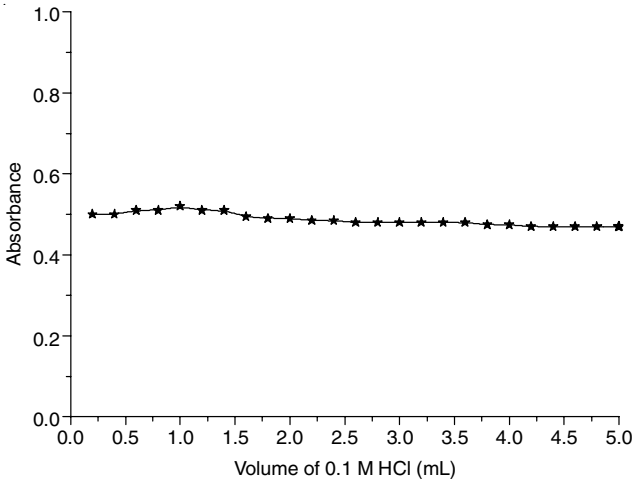


Fig. 2. Effect of 0.1 M HCl volume (cefpirome 3.0 µg/mL for method I)

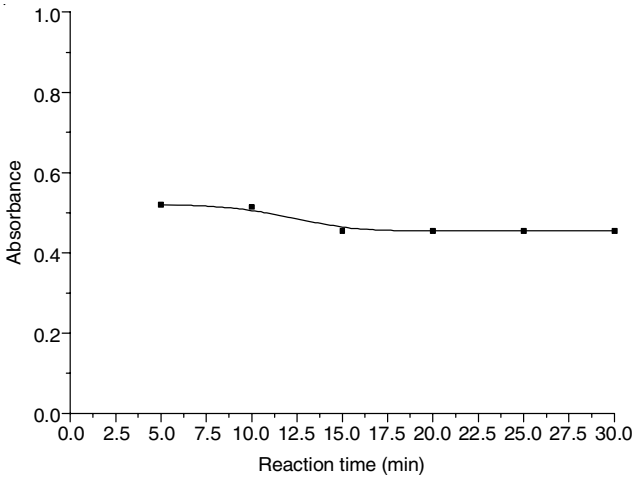


Fig. 3. Effect of reaction time (cefpirome 3.0 µg/mL for method I)

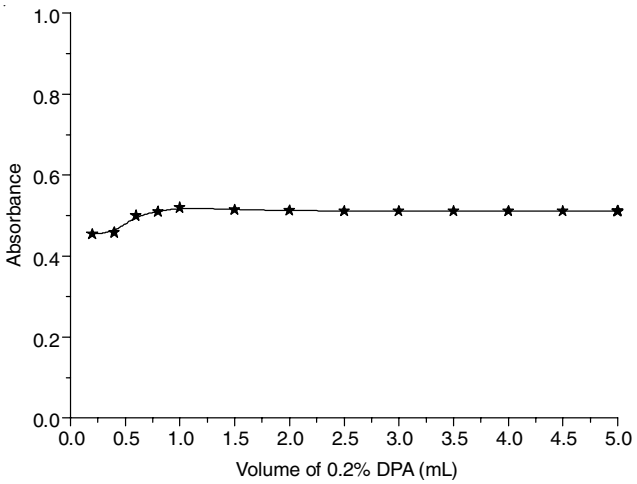


Fig. 4. Effect of 0.2 % DPA volume (cefpirome 3.0 µg/mL for method I)

coloured chromogen which λ_{max} absorbance of 410 nm in comparison to a reagent blank. For the assay of cefpirome, the experimental conditions were same as that of method I, using 1.0 mL of 0.1 M HCl in a range of (0.2-5.0 mL), the effect of reaction rate and its sensitivity were investigated. The amount of 0.1 M HCl volume was increased from 1.0 mL to 5.0 mL while kept the sensitivity of the reaction after 1.0 mL unchanged. Hence, 1.0 mL was kept constant throughout the experiment. Optimization of 0.2% alcoholic PDAB was conducted in a range of 0.2-1.0 mL and the maximum absorbance was obtained by varying the volume. The 1.0 mL of 0.2% alcoholic PDAB confirmed the maximum absorbance in the overall experiment (Fig. 5). To calculate the contribution of the other reactants to the method's absorbance, a second blank was prepared except for diphenylamine and cefpirome, which provided an insignificant absorbance *versus* water used as a blank in the current method.

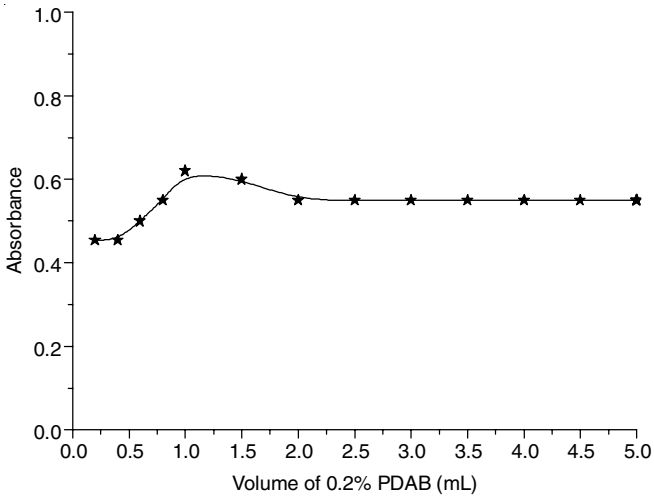


Fig. 5. Effect of 0.2 % PDAB volume (cefpirome 5.0 µg/mL for method II)

Validation of method

Analytical data: Under the optimized conditions, the plots of absorbance *versus* concentration within the range studied (Table-2), current methods revealed a linear relationship. The intercept (b), slope (a), correlation coefficient (r), confidence limit of intercept ($\pm$ t S_b) and slope ($\pm$ t S_a) at 95% confidence level and the square standard deviation variance (S_D^2) is calculated by least squares. The linearity of the calibration graph was verified with the correlation coefficients value of regression equations and intercepts value for **method-I**, which was close to zero. Because of the reverse association between absorbance and concentration in **method II**, the intercept was equal to the absorbance of the reagent blank. The elevated sensitivity of both methods were due to Sandell's sensitivity and maximum of detection (LOD). Variance in the small values indicates the lack of scattering of experimental values from the line of best fit for these two methods.

Precision and accuracy: Three different doses of cefpirome in seven replicates on the same day, intermediary precision (intra-day/inter-day) were used to test the precision of both methods (intra-day precision). For methods I and II, the percentage of RSD values was less than 0.87% and 0.38%, respectively. The number of RSD values in inter-day ranged from 0.51 to 0.61%.

The proportionality concerning the reference values and the produced values reveal the analytical methods' accuracy. The accuracy of the current methods was assessed using the percent relative error (RE %) between the measured mean

TABLE-2
SENSITIVITY AND REGRESSION PARAMETER

Parameter	Method I	Method II
Colour	Pink	Yellow
λ_{max} (nm)	510	415
Stability (h)	6	7
Beer's law limits (µg/mL)	0.3-3.0	0.5-5.0
Molar absorptivity (L/mol/cm)	5.13×10^4	2.54×10^4
Limit of detection (µg/mL)	0.2758	0.2917
Limit of quantification (µg/mL)	0.9103	0.9625
Sandell's sensitivity (µg/cm^2)	0.01195	0.02415
Regression equation (Y)[a]		
Slope (a)	0.02175	0.02057
Intercept (b)	0.08000	0.04005
Correlation coefficient (r)	0.9999	0.9999
S_a	0.01146	0.01209
S_a^2	0.00014	0.00015
Confidence limit, slope	0.02175 ± 0.00950	0.02057 ± 0.01010
S_b	0.01246	0.01488
S_b^2	0.00016	0.00015
Confidence limit, intercept	0.08000 ± 0.01042	0.04000 ± 0.01244

[a]Y = ax + b, where x is the concentration in µg/mL; [b]Eight replicates. S_a = Standard deviation of slope; S_b = Standard deviation of intercept.

concentration and the taken concentrations. The accuracy of the current methods can be considered acceptable (Table-3), where the results were obtained by three concentrations (within Beer's law range) with (RE %) in the ranged of 0.67-0.78.

Selectivity: To assess the selectivity of the current method, the analyte's difference in the absorbance with respect to the reagent blank sources was verified. After preparing the solution using the technique mentioned for vials, the current methods were used to prepare and analyze the interference of common excipients present in the vials.

The percentage recoveries of cefpirome were 99.58 ± 0.32 (n = 7) and 99.37 ± 0.28 (n = 7), respectively, for methods I and II, under the defined optimum conditions and suggested no interference by excipients in the assay of cefpirome. There was no noticeable difference between the slopes, which signifies that excipients do not interfere during the determination of the drug's active constituent.

Robustness and ruggedness: Robustness of an analytical technique as per the ICH guidelines [20] refers to its ability to remain unchanged by small and deliberate changes in process parameters. To test the robustness of the current method, two significant parameters such as reagent intensity and reaction time were intentionally modified and the values are represented in Table-4. The current methods were found to be unaffected by a small value of % RSD (intermediate precision).

The obtained intermediate precision gives the ruggedness. Four independent analysts were studied at the three different concentrations of cefpirome and three different instruments controlled by a single analyst were used to validate these results. Table-4 specified that the analytical method had reasonable accuracy as indicated by the lower % RSD values.

Analysis of vials: The current methods were used to test the cefpirome in the commercial vials and compared to those obtained by using reference methods. The findings were compared statistically using the Student's t-test and the variance F-test and the results are suitably illustrated in Table-5. There is no statistical difference between the proposed methods and the reference methods. Hence, no significant difference in the accuracy and precision of the Student t-test and variance F-test found.

Recovery study: The accuracy and reliability of the current methods are well demonstrated through standard addition procedure recovery experiments. The total was determined using the current method at three different levels and the esti-

TABLE-3
EVALUATED INTRA-DAY AND INTER-DAY PRECISION AND ACCURACY of CEFPIROME (CFP)

Method	Nominal concentration taken (µg/mL)	Intra-day accuracy and precision (n = 7)			Inter-day accuracy and precision (n = 7)		
		CFP found (µg/mL)	RE (%)	RSD (%)	CFP found (µg/mL)	RE (%)	RSD (%)
I	1.5	1.49	0.667	0.120	1.49	0.352	0.166
	3.0	2.99	0.271	0.872	2.98	0.667	0.513
	4.5	4.49	0.267	0.126	4.49	0.222	0.222
II	3.0	2.980	0.670	0.387	2.980	0.667	0.384
	6.0	5.970	0.500	0.270	5.980	0.330	0.613
	9.0	8.980	0.222	0.144	8.930	0.778	0.552

TABLE-4
ROBUSTNESS AND RUGGEDNESS EXPRESSED AS INTERMEDIATE PRECISION (%RSD)

Method	CFP taken (µg/mL)	Parameter altered			
		Method robustness		Method ruggedness	
		Acid concentration*	Reaction time**	Inter-analyst RSD%, (n = 4)	Inter-instruments, RSD%, (n = 3)
I	1.5	0.62	0.76	0.88	0.57
	3.0	0.57	0.67	0.57	0.24
	4.5	0.67	0.91	0.64	0.94
II	5.0	0.92	0.63	0.36	0.43
	10.0	0.81	0.57	0.25	0.71
	15.0	0.49	0.37	0.41	0.34

*In method I and II, HCl concentration used 0.05, 0.1 and 0.15 M; **Reaction times were 5, 10 and 15 min. for method I and II.

TABLE-5
ASSAY RESULTS IN INJECTION AND STATISTICAL COMPOSITION WITH THE REFERENCE METHOD

Injection brand name*	Nominal amount	Percent of label claim ± SD		
		Reference method	Method I	Method II
Forgen[a]	100 mg	99.86 ± 0.10	99.72 ± 0.19; t = 1.90; F = 0.28	99.83 ± 0.17; t = 0.48; F = 0.35
P Rom[b]	500 mg	99.96 ± 0.99	99.79 ± 0.13; t = 0.48; F = 1.42	99.66 ± 0.16; t = 0.86; F = 1.70
Refzil[c]	1000 mg	99.56 ± 0.57	99.20 ± 0.65; t = 1.12; F = 0.77	99.20 ± 0.64; t = 1.20; F = 0.79

*Marketed by: a. Alkem Laboratories Ltd., India; b. Global Mediscience Ltd., India; c. Sun Pharmaceutical Industries Ltd., India. Tabulated t-value at the 95% confidence level is 2.365. Tabulated F-value at the 95% confidence level is 3.79.

TABLE-6
RESULTS OF RECOVERY STUDY *via* STANDARD ADDITION METHOD

Vial of injection studied	Method I				Method II			
	CFP in injection (µg/mL)	Pure CFP added (µg/mL)	Total found (µg/mL)	Pure CFP recovered% ± SD*	CFP in injection (µg/mL)	Pure CFP added (µg/mL)	Total found (µg/mL)	Pure CFP recovered% ± SD*
Forgen 100 mg	1.5	1.0	2.49	99.00 ± 0.92	3.5	2.5	5.98	99.20 ± 0.75
	1.5	2.0	3.47	98.50 ± 0.56	3.5	5.0	8.42	98.40 ± 1.06
	1.5	3.0	4.48	99.33 ± 1.08	3.5	7.5	10.93	99.06 ± 0.63
P Rom 500 mg	3.0	2.0	4.97	98.50 ± 1.22	4.0	1.5	5.47	98.25 ± 1.26
	3.0	4.0	6.96	99.00 ± 0.89	4.0	3.0	6.95	98.30 + 0.83
	3.0	6.0	8.92	98.67 ± 1.04	4.0	4.5	8.46	99.11 ± 1.07
Refzil 1000 mg	2.5	1.5	3.98	98.66 ± 0.76	5.0	3.0	7.95	98.33 ± 1.25
	2.5	3.0	5.48	99.34 ± 1.41	5.0	6.0	10.97	99.52 ± 0.57
	2.5	4.5	6.98	99.56 ± 1.36	5.0	9.0	13.92	99.11 ± 0.98

*Mean value of three determinations.

mation was repeated three times; the results were tabulated in Table-6 and the low SD values indicate the reproducibility of the current methods and also indicates that there is no evidence of contamination for the recovery of cefpirome in the presence of excipients.

Conclusion

The spectrophotometric assays of cefpirome in pure and pharmaceutical dosage were performed by using two extremely sensitive proposed methods using diphenylamine (DPA) and *p*-dimethylaminobenzaldehyde (PDAB) as reagents and shows wavelength of maxima at 510 and 415 nm for method I and II, respectively. The LOD values for method I and II were 0.27 and 0.29 µg/mL. The methods can be successfully applied to determine cefpirome levels in vial of injections. The proposed methods have large linear dynamic linear ranges and high sensitivity that are unmatched by even some of the reported HPLC methods. Both methods are selective, precise, stable and rugged and can be used for regular analysis with ease.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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