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Original Article

# Development and Validation of Highly Precise Methods for the Spectrophotometric Determination of Cefpirome in Pharmaceutical Dosage Forms

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## ABSTRACT

**Aim:** Cefpirome (CFP) in pure and pharmaceutical dosage forms determination by spectrophotometer; two very sensitive techniques have been developed. **Materials and Methods:** By mixing alkaline β-Naphthol (2-NPL) with diazotized cefpirome drug, we get the pink colour at $\lambda_{max}$ 544 nm in procedure I. Drug undergoes oxidation by ferric ion followed by complex formation with 2,2'bipyridine (2,2'BPD) to obtain a blood red colour at $\lambda_{max}$ 520 nm in procedure II. Under ideal conditions, the goal is to maximize the efficiency of procedure I and II. **Results:** Concentrations of 0.3-3.0 and 0.5-5.0 µg/ml are used in procedures I and II, respectively, where Beer's rule of molar absorptivity of $1.837 \times 10^5$ and $1.470 \times 10^5$ is followed. It is possible to calculate three different concentrations of RSD as well as RE (relative error). **Conclusion:** It was found that the novel procedures may be used to a wide variety of pharmaceutical formulations, and they are simple, consistent, economical, fast and highly reproducible.

**Keywords:** Accuracy, Cefpirome, Chromogen, Diazotization, Formulation, Oxidation.

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## INTRODUCTION

However, unlike other broad-spectrum fungi, penicillinase-resistant cephalosporins are physically and functionally identical to penicillin. These antibiotics are deemed safe for human ingestion because of their wide range of antibacterial action. The beta-lactam ring's active nucleus can be given antibacterial and medicinal properties by swapping out nuclei at positions 3 and 7. Antibacterial properties are attributed to the cell wall's inhibition of mucopeptide production. Traditionally, the cephalosporins are divided into first, second, third, fourth and fifth-generation agents.[1-3]

Cefpirome (CFP),[6R-[6α,7β(Z)]]-1-[[(2-Amino-4-thiazolyl) (methoxyimino)acetyl]ami-no]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0.]oct-2-em-3-yl]methyl]-6,7-dihydro-5H-cyclope-nta[b]pyridinium inner salt,[4] is an injectable broad-spectrum aminothiazolyl cephalosporin, produced as sulphate salt. With this antibiotic, Pseudomonas is one of several Gram-positive and Gram-negative bacteria that it is effective against. Class I–lactamase resistance is less likely to develop against this antibiotic than cephalosporins.[5-7] The fourth- generation cephalosporin (CFP) can be used to treat patients with septic shock or multiple sepsis because of its broad range of activity and ability to withstand lactamase degradation.[8]

It is possible to measure the concentration of CFP using variety of techniques, including HPLC,[9-11] RP-HPLC,[12-14] UPLC[15] and UV-visible spectrophotometric method.[16-18] Even though these systems have the required linearity, precision, and recovery, they have a lower limit of detection (LOD) and longer reaction time due to their intrinsic lack of sensitivity. In addition to being time consuming and inaccurate, long heating durations and a large linear temperature range are demerits of these approaches. Comparing the suggested methods outcome to those of the reported methods has shown in Table 1.

A simple, robust, quick and inexpensive assay for the detection of CFP in pure and pharmaceutical dosage forms was developed in this work. The ICH criteria were followed and these methods was proven to be successful.[19]

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**Table 1: Comparison of the proposed spectrophotometric methods with the existing methods.**

| Sl. No. | Method | Experimental details | Detection | Linear range | LOQ in µg/ml | Remarks | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | HPLC | Acetonitrile (0.02M)-Potassium dihydrogen phosphate buffer (6:94, v/v, pH 2.0) was the mobile phase (1 ml/min) | UV at 263 nm | 0.5-200 µg/ml | NA | Less accurate and precise % RE: 0.70-15.0, intra-day and inter-day coefficient of variance 1.67% and 6.27% respectively. | 9 |
| 2 | Visible Spectrophotometry | Folin-Ciocalteau reagent | 700 nm | 5-20 µg/ml ($\epsilon = 1.852 \times 10^3$ L/mol/cm) | NA | High basic condition required | 16 |
| 3 | RP-HPLC | Mediterranea $C_{18}$ Column; Methanol and water (30:70 v/v) was the mobile phase (1 ml/min) | UV at 265 nm | 0.5-50 µg/ml | 0.021 | Less accurate and precise % RE: 0.42-3.84, intra-day and inter-day coefficient of variance 0.01% and 2.36% respectively. | 13 |
| 4 | i) UV Spectrophotometry<br>ii) HPLC | i) 0.01M HCl solution<br>ii) Techsphere ODS Column; Methanol and water (30:70 v/v) was the mobile phase (0.8 ml/min) | UV at 271 nm<br>UV at 265 nm | 6- 22 mg/ml<br>2-20 mg/ml | NA | Less sensitive; narrow linear dynamic range; less precise (RSD > 0.8%) | 8 |
| 5 | 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 |
| 6 | HPLC | µ-Bondapak $C_{18}$ Column, Acetonitrile: acetate buffer (13:87 v/v, pH = 5) was the mobile phase (1.0 ml/min) | UV at 258 nm | 0.5-64.0 µg/ml | 0.5 | Less accurate and precise, recoveries < 88.80% with RSD of 5% | 12 |
| 7 | RP-HPLC | B144A, OD-5-100, $C_{18}$ Column, Methanol-Water (15:85 v/v) was the mobile phase (1.0 ml/min) | 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 |
| 8 | UPLC | Phenomnex $C_{18}$ column, 0.01M phosphate buffer and acetonitrile (50:50 v/v) was the mobile phase (0.3 ml/min) | PDA at 265 nm | 7.5-75 µg/ml | 1.08 | Less sensitive; narrow linear dynamic range; less precise RSD > 0.81%. | 15 |
| 9 | Visible Spectrophotometry | i) α-naphthylamine<br>ii) N-(1-naphthyl)ethylenediamine<br>iii) 1,10-phenonthraline | 512 nm<br>565 nm<br>510 nm | 5.0-40 µg/ml<br>2.5-20 µg/ml<br>2.5-40 µg/ml | NA | Colour stable for up to 30 min; involves heating at > 60°C for 15 min. during the reaction | 19 |
| 10 | Visible Spectrophotometry | i) 2NPL<br>ii) 2,2' BPD | 544 nm<br>520 nm | 0.3-3.0 µg/ml<br>0.5-5.0 µg/ml | 0.27<br>0.20 | Simple, highly sensitive, accurate and precise, (intra-day and inter-day RSD < 0.87%) and accurate (% RE < 0.6), colour stability 6 hr and 7 hr respectively. | Present method |

## MATERIALS AND METHODS

### Instrumentation

ELICO Model SL-164 quartz cells were used for all absorbance measurements, which were carried out using double-beam UV-visible spectrophotometer.

### Reagents and Standards

An analytical reagent (AR) grade from SD Fine Chem., Mumbai and deionised water were utilized for the running solutions in the current study. Correctly weighed quantity of 2-naphthol is dissolved in alkaline medium to produce 0.2% solution. Conc. HCl is diluted with deionized water to produce 0.1% HCl. Ammonium sulfamate carefully weighed and dissolved in deionized water to get a 0.2%. Dissolving the accurately weighed quantity of 2,2'-bipyridine in alcohol to obtain a solution of 0.2% of 2,2'-bipyridine. 0.03 M solution of $FeCl_3$ is prepared by dissolving an accurate amount of $FeCl_3$ in deionised water. An Indian company, Alkem Laboratories Inc., graciously donated pure cefpirome (CFP) to the cause. Forgen 250 mg, P Rom 500 mg, and Refzil 1 gm injections are all readily accessible for purchase on the open market today.

Cefpirome (CFP) accurately weighed quantity dissolved in deionized water to generate a stock solution (100 mg/ml). Further dilution of stock solution in deionized water to produce a solution of concentration (10 µg/ml).

### General procedures

*Procedure I*

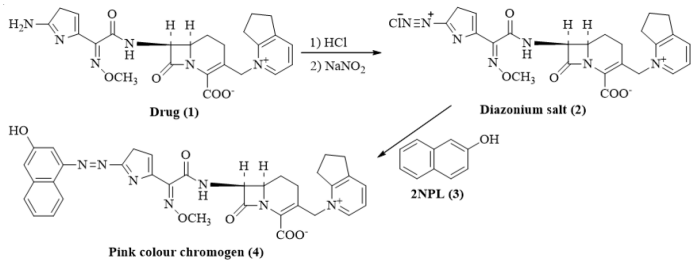
CFP (1.0 ml = 10 µg/ml) running standard solution (0.3-3.0 ml) poured into 10 ml calibrated flasks. To each flask 1.0 ml of 0.1 M HCl and 0.5 ml of 0.1% $NaNO_2$ solutions were added. Ammonium sulfamate 0.5 ml of 0.2% and an alkaline 2NPL 1.0 ml of 0.2% were added to every flask. The final amount was diluted with deionized water in order to meet the requirement. CFP concentration was estimated by measuring the absorbance at 544 nm of each solution and comparing it to the calibration curve. The colour doesn't change throughout the course of 6 hr.

*Procedure II*

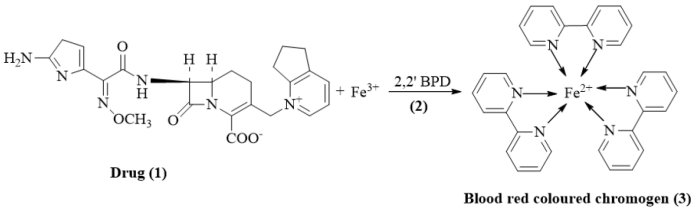
CFP (1 ml =10 µg/ml) was diluted to various quantities in volumetric flasks (ranging from 0.5 -5.0 ml). A 0.2 ml of 0.03 M aqueous solution of $FeCl_3$ and 0.5 ml of 0.2% alcoholic solution of 2,2' BPD were added to each flask. The final volume was made to 10ml with deionized water. Blood red coloured species were compared to a reagent blank for absorbance at 520 nm. Colour retention lasts for almost 8 hr. Calibration curve was used to determine the exact quantity of CFP.

### Procedure for Pharmaceutical Dosage

Pharmaceutical dosage containing CFP was obtained from local market sources. A volumetric flask with a capacity 100 ml was used to transfer 100 mg of drug's constituents from five well-mixed vials. Firstly 60 ml deionized water was poured into the flsak and final volume made to 100 ml with deionized water. Working solution of 10 µg/ml was obtained by further dilution and the desired volume was used for the CFP determination.




**Scheme 1**




**Scheme 2**

## RESULTS

CFP was diazotized with nitrous acid followed by coupling with 2NPL to obtain a pink coloured species due to the presence of an amine group in CFP, shows $\lambda_{max}$ at 544 nm (Scheme 1) for procedure I. In procedure II CFP drug reduces the $Fe^{3+}$ to $Fe^{2+}$ ion which on reaction with 2, 2' BPD to obtain a blood red coloured species which shows $\lambda_{max}$ at 520 nm (Scheme 2). These experimental procedures have been used for quantitative determination of CFP in pure and pharmaceutical dosage forms.

## DISCUSSION

### Method development

*Procedure I*

A pink coloured species with maximum absorbance at $\lambda_{max}$ 544 nm obtained by the diazotization of CFP with HCl and $NaNO_2$ followed by coupling with 2NPL.The blank, on the other hand, appears to have almost little absorption at this wavelength in contrast (Figure 1). At 544 nm, all absorbance measurement was made due to the declining trend in blank absorbance. Concentration and volume of the acid and alkaline 2NPL solution along with reaction time were evaluated (changing one parameter at a time). As shown in Figure 2, there is no significant difference in absorbance when 0.1% HCl acid used in volume of between 0.2 to 5.0 ml. From this it was observed that 1.0 ml of 0.1% HCl shows maximum absorbance. 0.5 to 2.5 ml of 0.1% $NaNO_2$ solution was used to reach the maximum absorbance. As shown in the Figure 3 reaction time between CFP and 2NPL

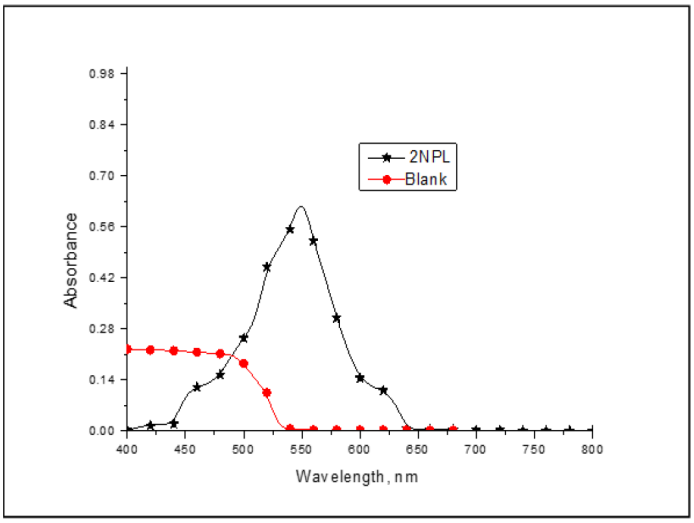



**Figure 1:** Absorption spectra of Method I.

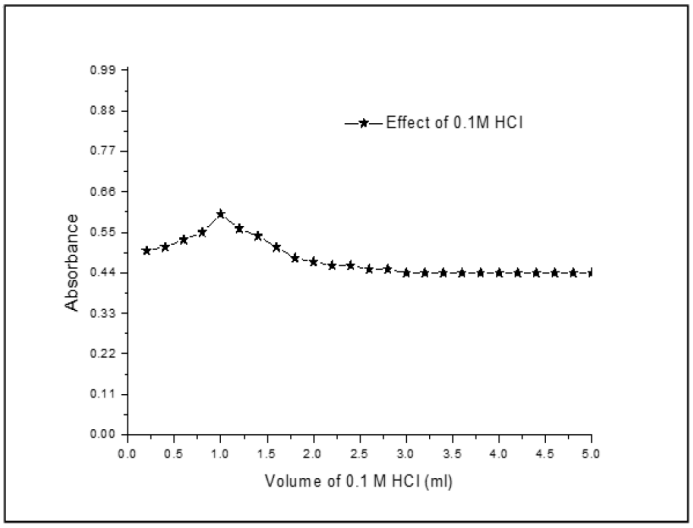



**Figure 2:** Effect of 0.1M HCl (CFP 3.0 µg/ml for Method I).

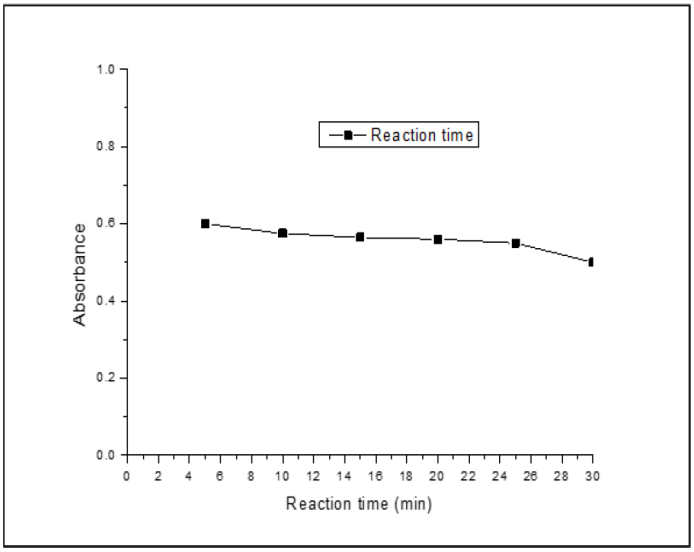



**Figure 3:** Effect of reaction time (CFP 3.0 µg/ml for Method I).

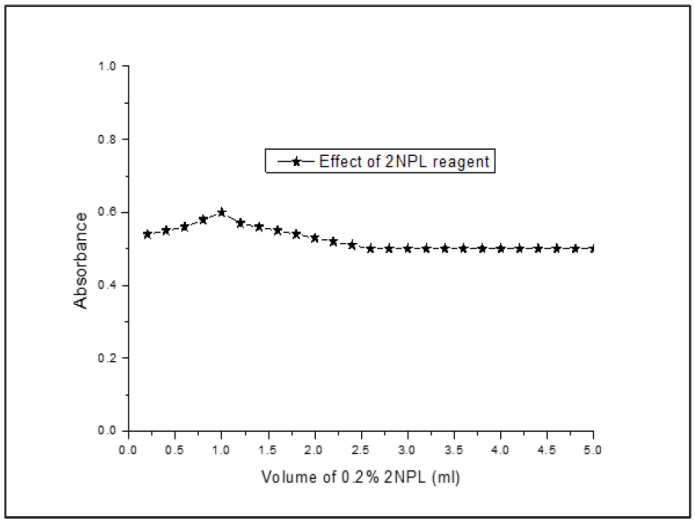



**Figure 4:** Effect of 0.2% 2NPL (CFP 3.0 µg/ml for Method I).

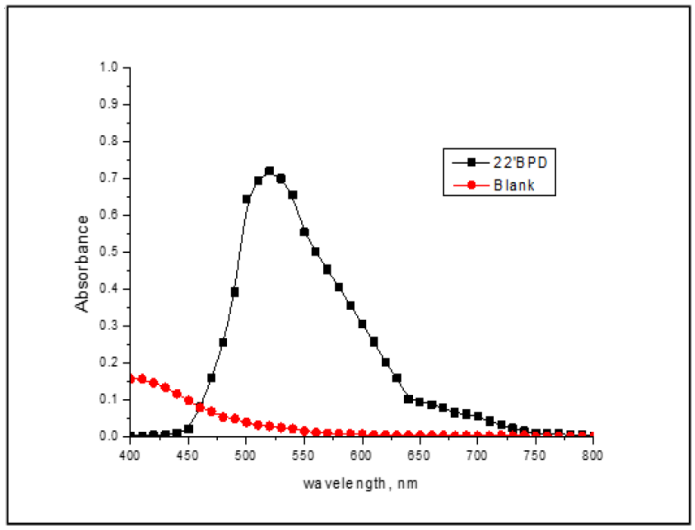



**Figure 5:** Absorption spectra of Method II.

was optimized to 5 min and colour remains unaltered about 6 hr. 0.2% 2NPL solution volume was varied in the range of 0.2 to 5.0 ml and maximum absorbance is shown at the volume of 1.0 ml, there is no significant change in the absorbance for increasing the volume Figure 4. Therefore, 1.0 ml of 0.2% 2NPL solution was used in the procedure.

### *Procedure II*

When cefpirome (CFP) react with 2,2'BPD in the presence of $FeCl_3$, a blood red colored species was obtained and shows maximum absorbance at $\lambda_{max}$ 520 nm with respect to blank Figure 5. Optimization procedure for the assay of CFP most similar as that of procedure I, 0.03 M $FeCl_3$ solution was used in the range of 1.0 to 5.0 ml and maximum absorbance occur at the volume of 1.0 ml, at higher concentration there is no changes in the absorbance and sensitivity. Therefore, the volume of 1.0 ml of 0.03 M $FeCl_3$ solution was used throughout the experiment. As

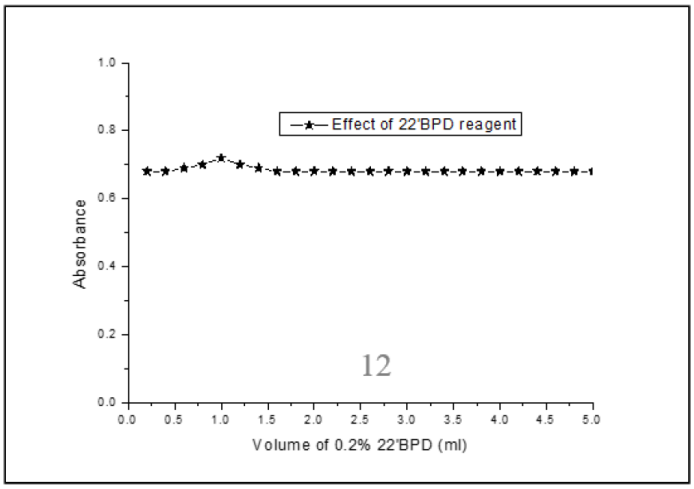



**Figure 6:** Effect of 0.2% 2,2'BPD (CFP 5.0 µg/ml for Method II).

**Table 2: Sensitivity and regression parameter.**

| Parameter | Method I | Method II |
|---|---|---|
| Colour | Pink | Blood- red |
| $\lambda_{max}$ (nm) | 544 | 520 |
| Stability (h) | 6 | 8 |
| Beer's law limits, (µg/ml) (C) | 0.3-3.0 | 0.5-5.0 |
| Molar absorptivity L/mol/cm | $1.837 \times 10^5$ | $1.470 \times 10^5$ |
| Limit of detection (LOD) (µg/ml) | 0.0812 | 0.0589 |
| Limit of quantification (LOQ) (µg/ml) | 0.2679 | 0.1945 |
| Sandell's sensitivity (µg/cm$^2$) | 0.0033 | 0.00463 |
| Regression equation (Y)[a] | | |
| Slope (a) | 0.0738 | 0.1017 |
| Intercept (b) | 0.2499 | 0.1757 |
| Correlation coefficient (r) | 0.9995 | 0.9993 |
| $S_a$ | 0.0113 | 0.01543 |
| $S_a^2$ | 0.000128 | 0.000238 |
| Confidence limit, slope | 0.0738± 0.0095 | 0.1017± 0.0129 |
| $S_b$ | 0.0480 | 0.01103 |
| $S_b^2$ | 0.0023 | 0.000121 |
| Confidence limit, intercept | 0.2499, ± 0.0401 | 0.1757 ± 0.0092 |

[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.

shown in the Figure 6, alcoholic of 0.2% 2,2'BPD solution volume was varied from 0.2 to 1.0 ml, the maximum absorbance was found at 1.0 ml, this volume was fixed in the procedure and the colour remained stable for upto 8 hr.

## Validation of the method

### *Analytical data*

Plots of absorbance vs concentration in the examined range indicate the experiment conditions. Table 2 shows a linear relationship between sensitivity and regression parameters. At 95% confidence level intercept (b), slope (a), correlation coefficient (r), confidence limit of intercept (± t $S_b$) and slope (± t $S_a$) were calculated. Least square is used for the calculation of square standard deviation variance ($S_D^2$). For Procedure I, the correlation coefficient and intercept were both close to zero, in Procedure II since absorbance is inversely proportional to concentration.

## Precision and accuracy

Precision of the current procedures (intra-day/inter-day) were tested by the use of three different pharmaceutical dosage of CFP in seven replicates. Both procedure I and II have a relative standard deviation (RSD) of less than 0.4% and 0.5%. RSD readings ranged from 0.53 to 0.45% throughout the period.

When the ratio between the reference values and the obtained findings is high enough, analytical procedures are accurate. The percentage relative error (RE %) between the measured mean concentration and the concentration collected was used to evaluate the accuracy of the result. Table 3 results shows the acceptable accuracy of the current procedures within the Beer's law limit of three concentration having percentage of relative error (% RE) is 0.76 -0.95.

## Selectivity

Analytical test material was used to assess the selectivity of the procedure. We have confirmed the analytes difference in absorbance for the blank sample. The excipients in the vials were tested using the current procedure after the vail solution was prepared utilizing the aforementioned method.

It appears form the 99.58±0.32 (*n*=7) and 99.37±0.28 (*n*=7) CFP recoveries made under optimal circumstances that excipients were not a factor in the CFP tset. Slope variation indicates that excipients are not affecting the active ingredient.

## Robustness and ruggedness

As per the ICH guidelines[19] what matters most is how effectively the procedures can deal with small and purposeful changes in the way it process data. The methods sturdiness was tested by varying the reagent intensity and reaction time, two critical criteria. The existing procedure is unaffected by even the small change in RSD

**Table 3: Evaluation intra-days and inter-day precision and accuracy.**

| 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 | 2.0 | 1.986 | 0.714 | 0.396 | 1.984 | 0.800 | 0.529 |
| | 4.0 | 3.983 | 0.428 | 0.189 | 3.970 | 0.750 | 0.361 |
| | 6.0 | 5.979 | 0.357 | 0.150 | 5.958 | 0.700 | 0.423 |
| II | 3.0 | 2.977 | 0.762 | 0.373 | 2.971 | 0.952 | 0.359 |
| | 6.0 | 5.980 | 0.333 | 0.193 | 5.966 | 0.571 | 0.452 |
| | 9.0 | 8.974 | 0.285 | 0.108 | 8.959 | 0.460 | 0.236 |

% (intermediate precision). In order to conduct a drug test, a lot of tools and analyzers must be gathered in a single laboratory (ICH guidelines 2005). Ruggedness is a result of achieving intermediate precision. Analyses of CFP in pharmaceutical dosage form were conducted by four separate analyst using three different concentration and three different tools are used by one analyst, and results were compared. Table 4 shows that when the RSD % values are low, the procedures being employed are accurate.

## Application to the analysis of vials

Cefpirome (CFP) results are compared to those from other procedures utilizing commercial vials of injections. Student's t-test and variance F-test were used to analyze the data in Table 5. Proposed and reference procedures are statistically indistinguishable. As a result, the Student's *t*-test and variance *F*-test have the same level of precision and accuracy.

## Recovery study

A recovery using the standard addition method shows that the current procedures are accurate and reliable. Each of the three levels of estimate was performed three times. It is clear form Table 6 that present procedures are repeatable and that CFP recovery from excipients is not compromised by the low standard deviation.

# CONCLUSION

For procedure I and II, the maximum wavelength of the cefpirome (CFP) spectrophotometric assays using 2 NPL and 2,2'BPD reagents was 544 nm and 520 nm. Procedure I and II have LOD values of 0.081 and 0.159, respectively. Injectible vials of CFP may be tested for accuracy using these procedures. Due to the high cost of HPLC equipment and reagents, many researchers are unable to use the already published methods due to their limited linear dynamic ranges and sensitivity (Table 1). The present procedures are the most sensitive spectrophotometric procedures for CFP ever described in terms of linear range and sensitivity.

**Table 4: Robustness and ruggedness expressed as intermediate precision (%RSD).**

| Method | CFP taken, µg/ml | Method robustness | | Method ruggedness | |
|---|---|---|---|---|---|
| | | Parameter altered | | | |
| | | Acid Concentration* | Reaction Time** | Inter-analyst RSD%, ($n$ = 4) | Inter-instruments, RSD%, ($n$ = 3) |
| I | 2.0 | 0.49 | 0.74 | 0.78 | 0.42 |
| | 4.0 | 0.73 | 0.53 | 0.42 | 0.76 |
| | 6.0 | 0.51 | 0.81 | 0.61 | 0.31 |
| II | 3.0 | 0.39 | 0.49 | 0.49 | 0.59 |
| | 6.0 | 0.86 | 0.56 | 0.65 | 0.41 |
| | 9.0 | 0.46 | 0.83 | 0.81 | 0.56 |

*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 | 99.77 ± 0.11<br>t = 1.78<br>F = 1.21 | 99.81 ± 0.13<br>t = 0.94<br>F = 1.69 |
| P Rom[b] | 500 mg | 99.96 ± 0.99 | 99.87 ± 0.82<br>t = 1.68<br>F = 1.45 | 99.89 ± 0.94<br>t = 1.31<br>F = 0.90 |
| Refzil[c] | 1000 mg | 99.56 ± 0.57 | 99.48 ± 0.41<br>t = 1.50<br>F = 1.93 | 99.52 ± 0.39<br>t = 0.75<br>F = 2.13 |

*Marketed by: a. Alkem Laboratories Ltd., India; b. Global Mediscience Ltd., India; c. Sun Pharmaceutical Industries Ltd., India.

Tabulated *t*-value and *F*-value at the 95% confidence level is 2.365 and 3.79 respectively.

**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 percent ± SD* | CFP in injection µg/ml | Pure CFP added µg/ml | Total found µg/ml | Pure CFP recovered percent ± SD* |
| Forgen 100 mg | 2.0 | 1.0 | 2.99 | 99.00±0.46 | 2.5 | 1.5 | 3.98 | 98.66±0.56 |
| | 2.0 | 2.0 | 3.97 | 98.50±0.71 | 2.5 | 2.5 | 4.99 | 99.60±0.31 |
| | 2.0 | 3.0 | 4.96 | 99.66±0.34 | 2.5 | 3.5 | 5.97 | 99.14±0.74 |
| P Rom 500 mg | 3.0 | 2.0 | 4.97 | 98.40±0.61 | 3.5 | 2.0 | 5.48 | 99.00±0.41 |
| | 3.0 | 3.0 | 5.95 | 99.33±0.84 | 3.5 | 3.0 | 6.45 | 98.33+0.24 |
| | 3.0 | 4.0 | 6.97 | 99.25±0.73 | 3.5 | 4.0 | 7.47 | 99.25±0.19 |
| Refzil 1000 mg | 4.0 | 5.0 | 8.97 | 99.40±0.31 | 4.5 | 2.5 | 6.95 | 98.00±0.29 |
| | 4.0 | 6.0 | 9.95 | 99.16±0.59 | 4.5 | 3.5 | 7.96 | 98.85±0.66 |
| | 4.0 | 7.0 | 10.97 | 99.57±0.77 | 4.5 | 4.5 | 8.97 | 99.33± 0.85 |

Because they are simple to execute, accurate, stable, and durable, these procedures are well-suited for routine analysis.

## ACKNOWLEDGEMENT

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

**CFP:** Cefpirome (CFP); **2NPL:** 2-naphthol; **2,2' BPD:** 2,2'bipyridine; **RSD:** Relative Standard Deviation; **SD:** Standard Deviation; **RE:** Relative error; **LOQ:** Limit of quantitation; **ICH:** Conference on Harmonization; **AR:** Analytical Reagent.

## SUMMARY

The spectrophotometric assays of cefpirome (CFP) in pure and pharmaceutical dosage are performed by using two highly sensitive proposed methods by 2NPL and 2,2'BPD are the reagent and shows the wavelength of maxima at 544 and 520 nm for the method I and II respectively. The method I produces a pink-colored chromogen peaking at $\lambda_{max}$ 544 nm by reacting diazotized cefpirome drugs with 2-naphthol (2NPL) in an alkaline medium. Method II is based on the oxidation of the drug with ferric ion followed by complex formation with 2,2'bipyridine (2,2'BPD) to form a blood red colored chromogen exhibiting $\lambda_{max}$ at 520 nm. At best possible conditions, methods I and II are optimized. For 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 1.837 X $10^5$ and 1.470 X $10^5$ for each form. At three separate concentrations, intra-day and inter-day (RSD) and relative error (RE) are measured. The methods are selective, precise, stable, and rugged, and can be used for regular analysis with ease.

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