International Research Journal of Pure and Applied Chemistry

Volume 25, Issue 6, Page 134-144, 2024; Article no.IRJPAC.128259
ISSN: 2231-3443, NLM ID: 101647669

Ultra Sensitive Visible Spectroscopic Methods for Cefpodoxime Proxetil Using NQS and PDAC Reagents

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/irjpac/2024/v25i6891

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/128259

Original Research Article

Received: 14/10/2024
Accepted: 16/12/2024
Published: 26/12/2024

ABSTRACT

Very sensitive and accurate visible spectrophotometric methods were developed and validated to quantify Cefpodoxime Proxetil in API and marketed formulation. Method A is based on the measurement of absorbance of a reddish-orange coloured chromogen at 454.9 nm, formed by the condensation reaction of the primary amino group of Cefpodoxime Proxetil with NQS reagent.

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Cite as: *Mathew, Ceema, Shashikala Metri, C. Raja Vardhan, B. Lakshmi Prasanna, Shakapuram Neha, and Nekkanti Subash. 2024. "Ultra Sensitive Visible Spectroscopic Methods for Cefpodoxime Proxetil Using NQS and PDAC Reagents". International Research Journal of Pure and Applied Chemistry 25 (6):134-44. https://doi.org/10.9734/irjpac/2024/v25i6891.*

Method B is based on the measurement of absorbance of a light yellowish green coloured chromogen at 401.3 nm, due to the Schiff's base formed between Cefpodoxime Proxetil and PDAC reagent in acidic medium. Beer-lambert's law is obeyed in the concentration range of 0.1-1µg/mL for method A, and for method B, it was 1-10 µg/mL. The values of LOD and LOQ were found to be 0.009 µg/mL and 0.027 µg/mL, respectively, for the condensation reaction with NQS reagent. For Schiff's base reaction, LOD and LOQ values were 0.154 µg/mL and 0.467 µg/mL respectively. The results of method validation done in accordance with ICH guidelines were satisfactory. The developed method can be successfully employed in routine analysis of Cefpodoxime Proxetil in pharmaceutical dosage forms.

Keywords: Cefpodoxime proxetil; 1 2-napthoquinone 4-sulphonate (NQS); P-dimethylamino cinnamaldehyde (PDAC).

1. INTRODUCTION

Cefpodoxime Proxetil (CFP) is chemically 1-(Isopropoxy carbonyloxy) ethyl (6R,7R)- 7-[2-(2-amino-4-thiazolyl) - (z)-2-(methoxyimino) acetamido]-3-methoxymethyl-3-cephem-4-carboxylate (O'Neill,2006) a semi-synthetic third-generation cephalosporin antibiotic with a chemical structure given in Fig. 1. CFP is a prodrug de-esterified in vivo to its active metabolite, cefpodoxime, to exhibit antibiotic activity (Borin, 1991). It is active against most Gram-positive and Gram-negative organisms. It is commonly used in the treatment of a variety of infections of the skin, respiratory tract, urinary tract, and systemic infections and to treat acute otitis media, pharyngitis, and sinusitis (Bergogne-Berezin, 1991, Geddes, 1991, Kakumanu, 2006). The drug is absorbed readily from the gut. It reaches adequate levels exceeding most body fluids' minimum inhibitory concentration (MIC). It is excreted by kidneys, unchanged. Also, the dose needs adjustment in compromised renal function. It is a bactericidal agent like the rest of the cephalosporins. After de-esterification by the intestinal esterases, the drug inhibits bacterial cell wall synthesis. The molecular weight of the active molecule is 557.6, which allows its free passage through the pores in the bacterial cell wall. Then, it crosses the periplasmic space and binds with the penicillin-binding proteins (PBP-1 and PBP-3) in the cell membrane. This binding then affects the cell membrane's peptidoglycan synthesis, ultimately damaging the cell (Kakumanu et al.,2006, Chocas et al., 1993).

1, 2-Naphthoquinone-4-Sulfonate (Sodium-3, 4 dioxo -3, 4 dihydro naphthalene-1-sulphonate) is used as functional group reagent for amines. The analytical methods available in public domain includes Spectrophotometric method (Asnani et al., 2012, Naresh et al., 2011, Abirami et al., 2012), colorimetric methods (Kamalesh et al., 2014, Subbayamma and Ram, 2008) spectrofluorimetric methods **(**Mohamed et al., 2011, Mostafa et al., 2015). TLC **(**Singh and Maheshwari,2010) HPLC methods **(**Camus etb al., 1994, Kakumanuet al, 2006, Lovdahl et al., 1994). Hyphenated techniques and stability indicating methods **(**Patel and Rajput**,** 2011). A thorough literature survey revealed the presence of less visible spectroscopic methods for CFP; the authors developed ultrasensitive methods using **1**, 2-Napthoquinone 4-Sulphonate (NQS), P-Dimethylamino Cinnamaldehyde (PDAC) reagents (Krishna, 2014, Ainwale and Chipade, 2015, Patel et al., 2012, Dahiya et al.,2022, Sunkara and Vijayalakshmi, 2018). Both methods depends on the chemical reaction of aromatic amino group with the reagents yielding coloured moieties (Acharya and Patel, 2013).

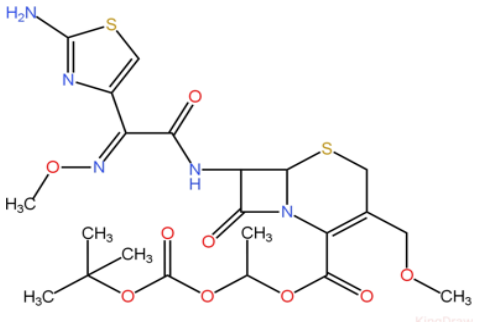

Fig. 1. Structure of CFP

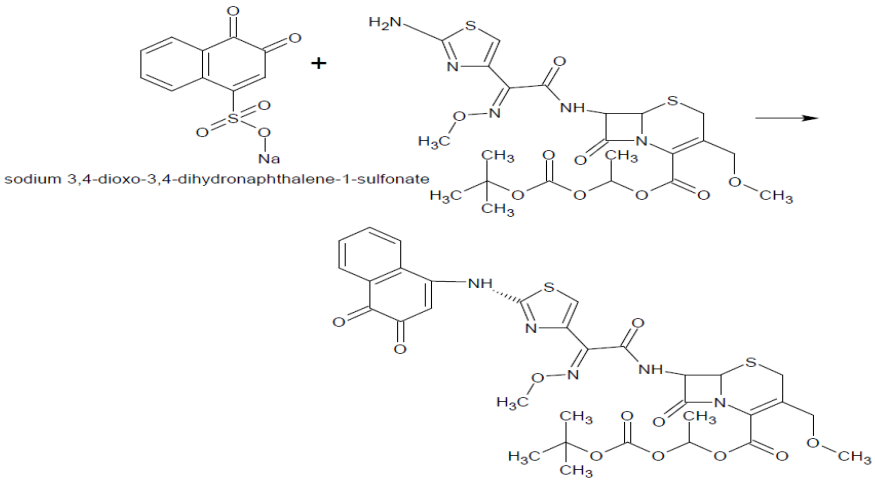

Fig. 2. Chromogenic reaction of CFP with NQS Reagent

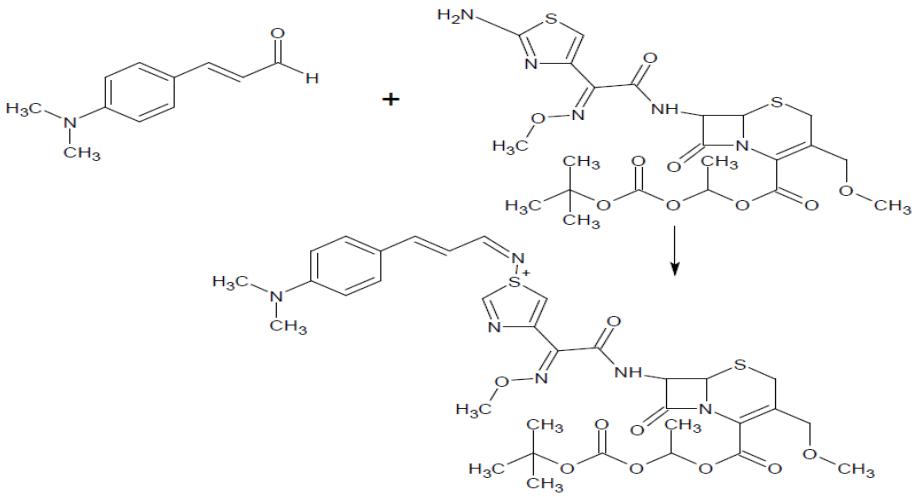

Fig. 3. Chromogenic reaction of CFP with PDAC Reagent

PDAC (4- (Dimethylamino) Cinnamaldehyde) is used as a functional group reagent for amines. The principle of aldehydes, which condenses the aromatic amines, involves the release of oxygen molecules. Then it combines with the amine group to form the yellow Schiff's base in the presence of acidic medium such as HCl or H_2SO_4. The chromogenic reactions with NQS and PDAC are given in Figs. 2 and 3 respectively (Malathi et al., 2009, Molina et al., 1991).

2. EXPERIMENTAL PROCEDURE

2.1 Materials

A Gratis sample of CFP obtained from SEE GEE Pharmaceutical Ltd was used. Methanol was obtained from (Qualigens); NQS, sodium hydroxide, PDAC, and Hydrochloride acid were procured from Sd fine-Chem Ltd.

2.2 Instruments

UV-Visible Spectrophotometer Shimadzu UV-1800, analytical balance.

2.3 Experimental Methods

Optimization of Methods: The main factors that affect any chemical reaction are concentration, time and temperature and are optimised by one factor at a time approach (OFAT).

Method A: A set of 10 mL volumetric flasks held the standard stock solution of CFP; NaOH (0.1 - 1.0%) 0.5%) and NQS reagent (0.1 - 1.0%) in varying concentrations were added to each flask and stirred. They were then set aside for the colour to develop for 10 to 15 minutes. Each solution was then diluted with distilled water to a

volume of 10 mL. Next, using the reagent as a blank, the absorbances of the resultant solutions were measured between 350 and 700 nm. Considering the maximum absorbance as the criterion for the same concentration of CFP,1 mL of 0.1% NQS reagent and 2 mL of 0.5% NaOH were optimised for the reaction.

Method B: A set of 10 mL volumetric flasks held the standard stock solution of CFP. The PDAC reagent (0.1 – 0.5%) and HCl (Conc. HCl 3 drops, 0.1 N, 1 N) were added in varying concentrations to each flask and stirred. Each solution was then diluted to 10 mL with distilled water after being left aside for 10 to 15 minutes to allow the colour to develop. Compared to the reagent blank, the absorbances of the resultant solutions were measured between 350 and 700 nm. Considering the maximum absorbance as the criterion for the same concentration of CFP, mL of PDAC (0.2%) reagent and three drops of conc. HCl were optimised for the reaction.

Preparation of 0.1% NQS reagent solution: 10 mg of NQS reagent was accurately weighed and dissolved in sufficient distilled water to produce 10 mL.

Preparation of 0.5% of NaOH solution: Accurately weighed 0.5 gm of NaOH and dissolved in sufficient distilled water to produce 100 mL.

Preparation of stock solution and standard solution (10 µg/mL and 100 µg/mL): The standard stock solution (1000 µg/mL) of CFP was prepared by dissolving 10 mg of CFP in 10 mL of methanol. From this, 0.1 mL was diluted to 10 mL with methanol to obtain the standard solution of CFP having a final concentration of 10 µg/mL (for method A). In a similar fashion, 1 mL solution was diluted to 10 mL with methanol to obtain a standard solution of CFP having a final concentration of 100 µg/mL (for method B).

Preparation of 0.2% PDAC reagent solution: Accurately weighed 200 mg of PDAC Reagent and dissolved in sufficient distilled methanol to produce 100 mL.

2.4 Validation

The method was validated for accuracy, precision, linearity, LOD, and LOQ as per ICH guidelines, and the detailed procedure is given below (ICH, 1996).

2.4.1 Linearity

Method A: 10 mL volumetric flasks were filled with aliquots of CFP standard drug solution (10 µg/mL), with concentrations ranging from 0.1 to 1 mL (0.1, 0.2, 0.4, 0.6, 0.8, and 1 µg/mL). Each flask was filled with 1 mL of the 0.1% NQS reagent and 2 mL of the 0.5% NaOH, then thoroughly shaken. After allowing the colour to develop for ten to fifteen minutes, each solution was diluted with 10 mL of distilled water. After scanning the coloured solutions, a calibration graph was created by plotting absorbance Vs concentration.

Method B: A different set of 10 mL volumetric flasks were filled with aliquots of the standard drug solution of CFP (100 µg/mL), which ranged from 0.1-1 mL (1, 2, 4, 6, 8, 10 µg/mL). Each flask was filled with 1 mL of PDAC reagent and 3 drops of conc. HCl, and thoroughly shaken. After allowing the color to develop for 10 to 15 minutes, each solution was diluted with 10 mL of distilled water. After scanning the coloured solutions, a calibration graph was plotted with absorbance versus concentration.

Accuracy: The method's accuracy was determined by calculating CFP recoveries by the standard addition method. A known amount of standard solutions of CFP were added at 80%, 100%, and 120% levels to pre-quantified sample solutions of CFP using NQS (0.4 µg/mL) and PDAC (4 µg/mL). The amount of CFP was estimated by substituting the measured absorbance at 454.9 nm using NQS and 401.3 by PDAC reagent into the regression equation obtained in the linearity studies.

Precision: The intra-day precision of the proposed colourimetric method was determined by estimating the corresponding response three times on the same day for three different concentrations of CFP with NQS (0.2, 0.6, 1.0 µg/mL) and PDAC (2, 6, 10 µg/mL). The results were reported in terms of %RSD.

The inter-day precision of the proposed colourimetric method was determined by estimating the corresponding response three times on three different days for the similar concentrations used for intra-day precision. The results were reported in terms of %RSD.

Limit of Detection (LOD) and Limit of Quantification (LOQ): The limit of detection (LOD) and quantification (LOQ) of the CFP were

derived by calculating the signal-to-noise ratio using the following equations per ICH guidelines.

LOD = 3.3 * S.D/Slope

LOQ = 10 * S.D/Slope

Where, S.D = Standard Deviation of the response

S = Slope of the Calibration Curve of the analyte.

3. RESULTS AND DISCUSSION

Optimization results: The optimization results for the effect of concentration of NaOH, NQS, PDAC were plotted in Figs. 4,5 and 6.

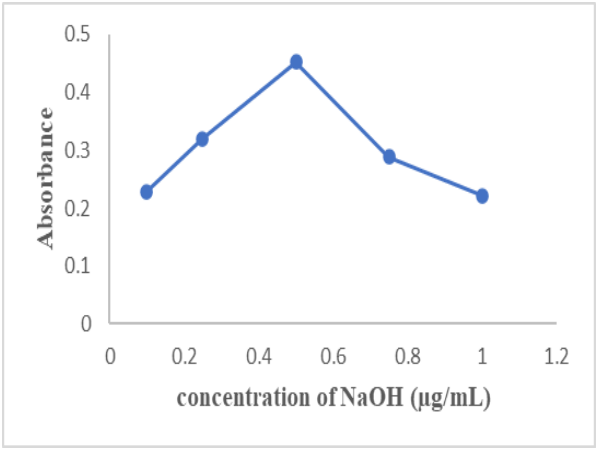

Fig. 4. Effect of concentration of NaOH

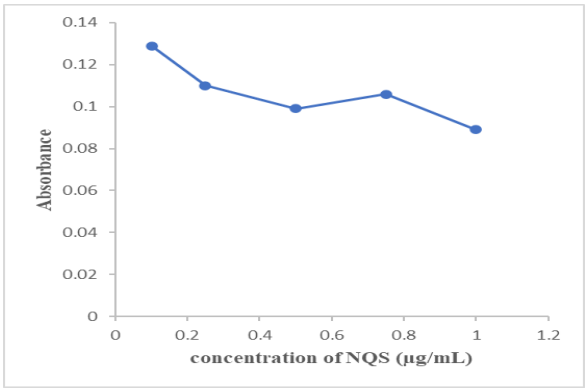

Fig. 5. Effect of concentration of NQS

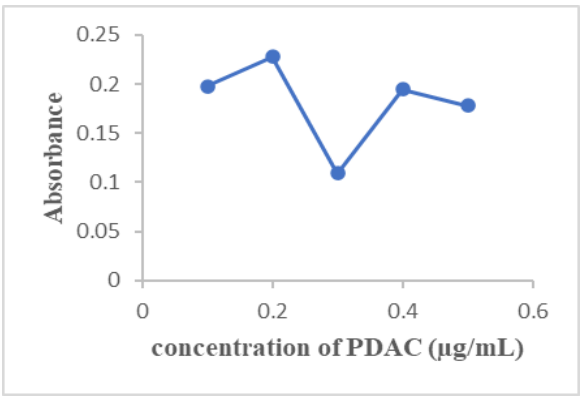

Fig. 6. Effect of concentration of PDAC

3.1 UV Spectrophotometric Methods

Determination of λ $_{max:}$ The visible spectra obtained for the coloured solution of CFP obtained after derivatization with NQS and with PDAC are shown in Fig. 7 and Fig. 8, and it depicts a λmax value of 454.9 nm for method A and 401.3 nm for method B.

3.2 Analytical Methods Validation

Calibration Plot for CFP using NQS Reagent and PDAC Reagent: Figs. 9A and 10A show the overlay spectra of CFP following chemical derivatization with NQS reagent and PDAC reagent, respectively. Tables 1 and 2 provide the related linearity data for methods A and B, respectively. It was found that the absorbance response at 454.9 nm using NQS and 401.3 nm using PDAC reagent increased with the rise in CFP concentration. The respective linearity graphs are given in Figs. 9B and 10B. For CFP, the linearity of the calibration curve (absorbance Vs concentration) was examined throughout a concentration range of roughly 0.1-1 µg/mL with NQS and 1-10 µg/mL with PDAC reagent. The linearity of the procedure was demonstrated by the correlation coefficient value (R^2) for CFP utilizing NQS, which was 0.999, and for PDAC, which was 0.9991, according to the linear regression analysis.

Table 1. Linearity Data of CFP using NQS reagent

Conc. (µg/mL)	Absorbance AM ± S.D (n=3)
0.1	0.129 ± 0.003
0.2	0.245 ± 0.004
0.4	0.452 ± 0.006
0.6	0.657 ± 0.006
0.8	0.880 ± 0.005
1	1.1 ± 0.09

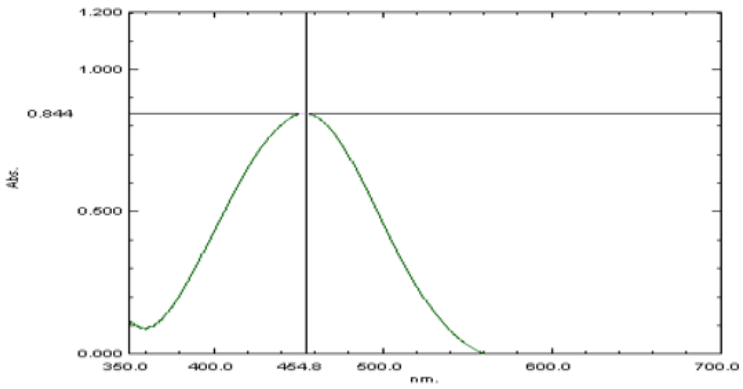

Fig. 7. Visible Spectrum of CFP using NQS

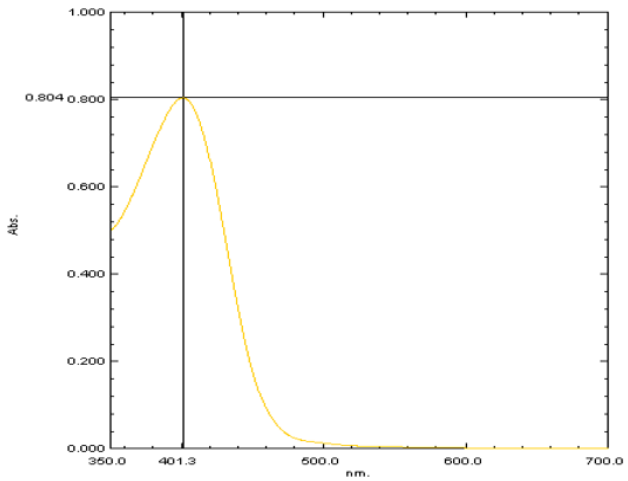

Fig. 8. Visible Spectrum of CFP (8 µg/mL) using PDAC

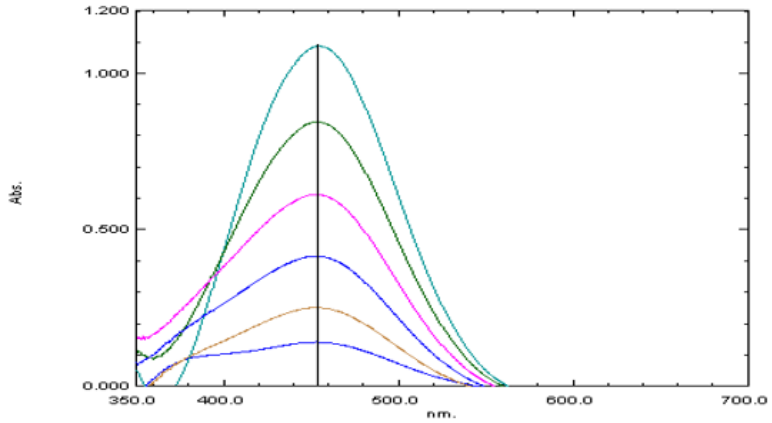

Fig. 9A. Overlay Spectra of CFP using NQS (0.1-1.0 µg/mL)

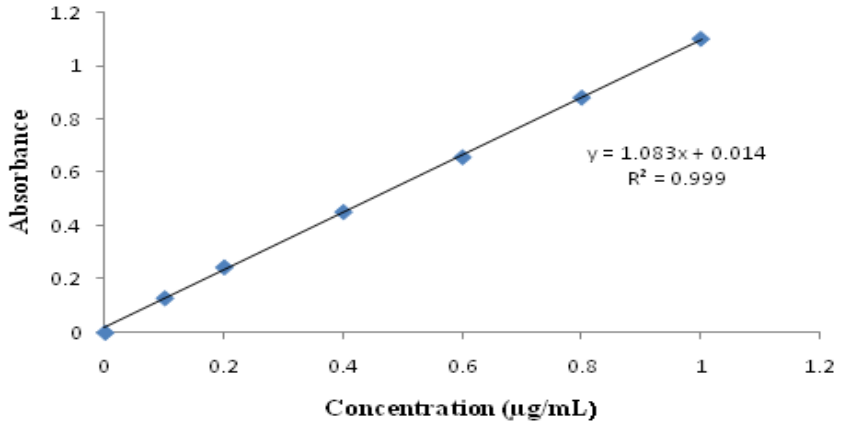

Fig. 9B. Linearity graph of CFP using NQS reagent

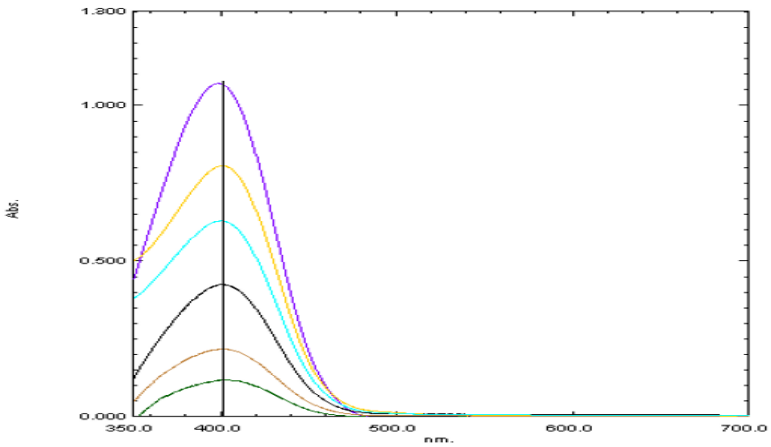

Fig. 10A. Overlay spectra of CFP using PDAC reagent (1-10 µg/mL)

Precision: The repeatability (intra-day precision) of the method was determined by intra-day (n=3) analysis of three standard solutions of CFP of the concentration of 0.2, 0.6, 1.0 µg/mL for NQS and 2, 6, 10 µg/mL for PDAC reagent. Intermediate precision was determined by the inter-day (n=3) analysis of three standard solutions of CFP at the above-mentioned concentrations. The data

obtained from precision studies are given in Tables 3 and 4. The % RSD values for intra-day and inter-day precision studies were less than 2.0, confirming that the method was precise.

Accuracy (Recovery Studies): The accuracy was determined by the standard addition method. Three different levels (80%, 100% and 120%) of standards were spiked to commercial powder in triplicate. The mean of percentage recoveries and % RSD values were calculated and reported in Table 5. The %recovery of CFP was found to be in the range of 100.5-101.4% for NQS and 98.9-101.6% for PDAC reagents, which are satisfactory.

Table 2. Linearity data of CFP using PDAC reagent

Conc. (µg/mL)	Absorbance AM ± S.D (n=3)
1	0.123 ± 0.005
2	0.228 ± 0.007
4	0.438 ± 0.005
6	0.628 ± 0.007
8	0.856 ± 0.006
10	1.09 ± 0.07

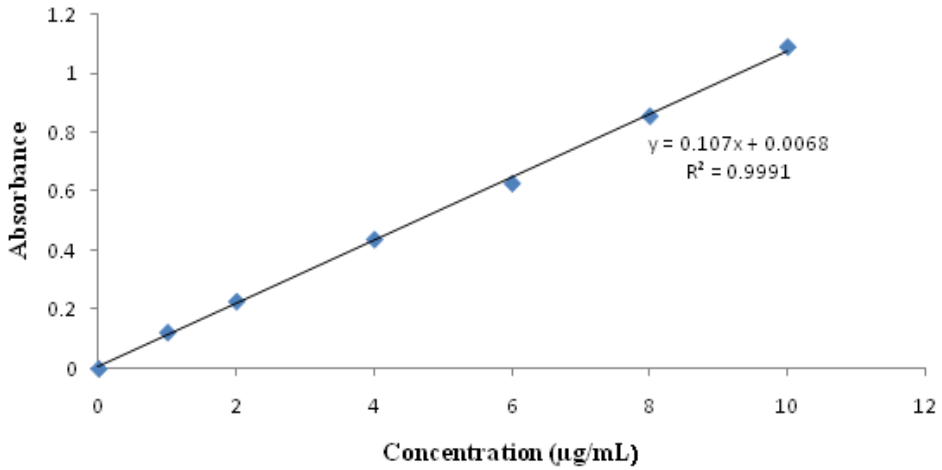

Fig. 10B. Linearity graph of CFP using PDAC reagent

Table 3. Precision Data for CFP using NQS reagent

Theoritical Amount (µg/mL)	Intra-day		Inter-day	
	Amt found (µg/mL) AM ± S.D (n=3)	%RSD	Amt found (µg/mL) AM ± S.D (n=3)	%RSD
0.2	0.218 ± 0.004	1.79	0.210 ± 0.002	0.95
0.6	0.608 ± 0.007	1.06	0.58 ± 0.005	0.85
1.0	1.086 ± 0.007	0.58	1.09 ± 0.008	0.66

Acceptance Criteria: % RSD should not be more than 2

Table 4. Precision Data for CFP using PDAC reagent

Theoritical Amount (µg/mL)	Intra-day		Inter-day	
	Amt found (µg/mL) AM ± S.D (n=3)	% RSD	Amt found (µg/mL) AM ± S.D (n=3)	% RSD
2	2.2 ± 0.002	0.82	1.9 ± 0.0036	1.6
6	6.2 ± 0.007	1.03	5.8 ± 0.01	1.5
10	9.4 ± 0.015	1.4	9.65 ± 0.015	1.44

Acceptance Criteria: % RSD should not be more than 2

Table 5. Accuracy data for CFP using PDAC and NQS reagent

Spiking Level	Theoretical Content (µg/mL)		Amt found (µg/mL) AM ± S.D (n=3)		%Recovery		%RSD	
Method	PDAC	NQS	PDAC	NQS	PDAC	NQS	PDAC	NQS
80%	7.2	0.72	7.31 ± 0.01	0.720 ± 0.002	101.6	100.6	1.4	0.27
100%	8	0.8	7.9 ± 0.006	0.811 ± 0.001	98.9	101.4	0.76	0.123
120%	8.8	0.88	8.86 ± 0.007	0.885 ± 0.007	100.7	100.5	0.79	0.8

Acceptance Criteria: % RSD should not be more than 2

Table 6. Analysis of Commercial tablets using NQS and PDAC reagent (assay)

Formulation with label Claim	Reagents	Amt found (mg)AM ± S.D (n=3)	% Assay	%RSD
CEPODEM® 100mg	NQS	102.1 ± 0.0049	102.1 %	0.722
	PDAC	100.32 ± 0.004	100.32 %	0.613

Limit of Detection (LOD) and Limit of Quantification (LOQ): LOD was found to be 0.009 µg/mL for NQS and 0.154 µg/mL for PDAC reagent; LOQ was found to be 0.027 µg/mL using NQS and 0.467 µg/mL using PDAC reagent for CFP.

Analysis of Marketed Formulations (Assay): The assay of commercially available tablets (Cepodem® 100) containing 100 mg of CFP was used to assess the accuracy of the suggested approach. Table 6 presents the comparison between the CFP results and the corresponding indicated quantities. The assay value was determined to be 100.32% using PDAC reagent and 102.1 mg using NQS and 100.32 mg using NQS; the amount of CFP was found to be 102.1 mg using NQS and 100.32 mg using PDAC reagent. These sums fell inside the permitted range. The assay result's % RSD was determined to be less than 2, indicating the suggested method's correctness.

4. CONCLUSION

Due to its ease of use, sensitivity, and selectivity, visible spectrophotometry has maintained its competitiveness in the field of pharmaceutical analysis. Using NQS and PDAC Reagents, two straightforward, accurate, and exact visible spectrophotometric techniques were created to measure CFP. The absorbance maxima (λmax) in the linearity range of 0.1-1 (µg/mL) with NQS and 1-10 (µg/mL) with PDAC reagent were found to be at 454.9 nm using NQS and 401.3 nm using PDAC reagent. The methods were optimized and subsequently validated on par with ICH guidelines for accuracy, precision, etc, to ensure its utility and rightness. The research findings demonstrated that the colourimetry method that was created is straightforward, linear, accurate, exact, selective, and above all, sensitive, as indicated by the lesser linearity range and the lesser LOD and LOQ values. In order to ensure CFP quality control in API and pharmaceutical dosage forms, the established colourimetric approach can be utilized.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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