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Validated spectrophotometric methods for determination of cefdinir in pure and dosage forms through charge transfer complexation using alizarin derivatives

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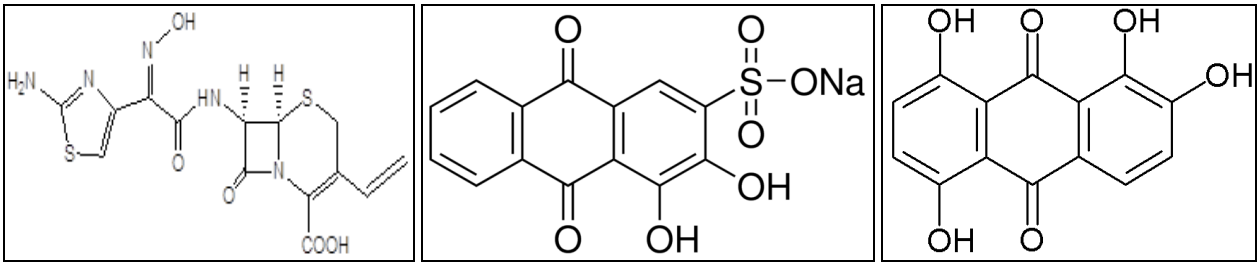
Abstract
Two new, rapid, accurate, and precise spectrophotometric methods have been developed and validated for the determination of cefdinir (CFD) in pure and dosage forms. The method is based on the formation of charge transfer complex between CFD and the chromogenic reagents alizarin red S (ARS) and quinalizarin (Quinz) in methanolic medium which showed an absorption maximum at 533 and 559 nm using ARS and Quinz, respectively. The optimization of the reaction conditions such as the type of solvent, reagent concentration and reaction time were investigated. Under the optimum conditions, beer's law is obeyed in the concentration ranges 0.5-8.0 and 1.0-10 μg mL^{-1} using ARS and Quinz, respectively with good correlation coefficient ($r^2 \geq 0.9996$) and with a relative standard deviation (RSD% ≤ 1.41). The molar absorptivity, Sandell sensitivity, detection and quantification limits are also calculated. The methods were successfully applied to the determination of CFD in its pharmaceutical formulations and the validity assesses by applying the standard addition technique.

Keywords: spectrophotometry, charge transfer reaction, cefdinir, alizarin red s, quinalizarin, dosage forms

Introduction
Cefdinir (CFD) Chemically, is [6R-[6α, 7β (Z)]]-7-[[(2-amino-4- thiazolyl) (hydroxyimino) acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (Figure 1). It is a semi-synthetic, broad-spectrum third-generation cephalosporin. It has broad spectrum of activity, excellent therapeutic action against susceptible Gram-positive and Gram-negative bacteria as having potent antimicrobial activity, excellent efficacy, convenient dosing and favorable tolerability compared with other antimicrobial agents [1, 2].



Cefdinir (CFD) Alizarin Red S (ARS) Quinalizarin (Quinz)

Fig 1: The chemical structures of CFD and reagents

Literature survey reveals that several methods for determination of CFD were developed using reversed phase-high performance liquid chromatography (RP-HPLC) [3, 8], electrochemical technique [9, 12] and spectrofluorimetry [13]. These methods require long and tedious pre-treatment of the samples and laborious clean up procedures prior to analysis.
A through literature search has revealed that only few spectrophotometric methods [14, 25] available for determination of CFD in bulk drug and pharmaceutical formulations. However, many of the above methods suffered from one or other disadvantage like poor sensitivity, require high cost solvents in addition to elaborate treatment, need tedious extraction procedures, measurements done at shorter wavelengths, heating or cooling step, use of expensive chemical and/or complicated experimental set-up as can be seen from Table 1.

Table 1: Comparison between the report spectrophotometric methods for determination of CFD.

	Method	λ_{max} (nm)	Beers law (µg mL^{-1})	LOD (µg mL^{-1})	Molar absorptivity (L $mol^{-1}cm^{-1}$) X 10^4	References
1.	Catechol / sodium meta periodate	460	50-250	-	0.45	[14]
2.	NBS / HCL / Rhodamine-B	557	1.2-8.4	1.18	3.33	[15]
3.	a. 1, 2- napthaquinone-4- sulfonic acid sodium (NQS) in an alkaline medium	490	10-80	1.097	0.363	[16]
	b. 4-chloro-7-nitrobenzo-2-oxa-1,3-diazole (NBD-Cl) /0.5 M NaOH	390	5.0-30	0.280	0.618	
4.	Ferrous ammonium sulfate	550	8.0-160	0.56	0.372	[17]
5.	a. 0.1N NaOH	242.4				[18]
	b. Folin-Ciocalteu reagent	612				
	c. MBTH / $FeCl_3$	625				
6.	a. Phosphate buffer (0.1 M)(pH 7.0)	287	3.0-17			[19]
	b. Folin-Ciocalteu reagent	720	4.0-20			
7.	a. Alkaline hydrolysis/ P-aminophenol	545	3.0-36	2.16	1.09	[20]
	b. Palladium (II) chloride (pH 3.5)	314	3.0-26	2.36	1.65	
	c. Ninhydrin/ bicarbonate	433	4.0-30	6.34	0.12	
8.	Excess of N-bromosuccinimide/a. celestine blue	540	1.-5.0		4.735	[21]
	b. *p*-N-Methylamino phenol sulfate–sulfanilamide	520	2.0-10		2.0	
9.	a. Fe(III) / 1, 10-phenanthroline	512	2.0-8.0		0.2991	[22]
	b. Fe(III) /2, 2'-bipyridyl	510	8.0-24		0.7176	
	c. Fe(III) /Potassium ferricyanide	700	4.0-12		1.423	
10.	a. Fe(III) / 1, 10-phenanthroline	520	0.3-2.4		13	[23]
	b. Folin-ciocaltu	710	1.5-7.5		3.3	
11.	NaOH + Iodate/ toluidine blue	630	0.6-6.3			[24]
12.	ARS	533	0.5-8.0	0.14	1.7778	Proposed work
	Quinz	559	1.0-10	0.28	1.8516	

Visible spectrophotometry, because of simplicity and cost effectiveness, sensitivity and selectivity, fair accuracy, precision and available in most quality control laboratories, has remained competitive in an area of chromatographic techniques for pharmaceutical analysis. Furthermore, they do not need costly instrumentation required for published HPLC methods. On the basis of the aforementioned reasons, it was decided to develop simple and quantitative analytical spectrophotometric methods for the determination of CFD in bulk and pharmaceutical formulations.

In the present work, we report a very simple, rapid, accurate, and sensitive visible spectrophotometric method to assay CFD in pure and dosage forms. The proposed methods involves the formation of charge transfer complex between CFD and alizarin derivatives; alizarin red S (ARS) and quinalizarin (Quinz) as chromogenic reagents.

Experimental

Apparatus

All the absorption spectral measurements were made using Varian double beam UV-VIS spectrophotometer (Tokyo, Japan) equipped with 10 mm matched quartz cells.

Materials and Reagents

All employed chemicals and solvents (methanol, dimethyl sulfoxide, ethanol, acetone and acetonitrile) were of analytical-reagent grade and high-purified water was used throughout the study.

Pure CFD drug and pharmaceutical formulations

- Pharmaceutical grade CFD was received from Adwia Pharmaceuticals Co., El-Oubor city, Egypt. The following commercial pharmaceutical formulations containing the studied drug were purchased from local market were subjected to the analytical procedure. Dinar tablets (Adwia Pharmaceuticals, El-Oubor city, Egypt), labeled to contain 300 mg cefdinir per tablet. Omnicef capsules (Hikma Pharmaceuticals), labeled to contain 300 mg cefdinir per capsule.

Stock standard Solutions

A standard stock solutions of CFD containing 100 µg mL^{-1} was prepared by dissolving 10 mg of pure drug in 20 mL methanol and was further diluted to 100 mL with the same solvent to obtain the working concentration. The standard solution was kept in the refrigerator and was found to be stable for at least one week if they had been stored in a cool (< 25 ºC) and dark place.

Reagents

Alizarin red S, 3,4-dihydroxy-9, 10-dioxo-2-anthracene sulfonic acid (ARS) and quinalizarin 1,2,5,8-tetrahydroxy-anthraquinone (Quinz) were Aldrich products and used without further purification. A stock solution 1.0 x 10^{-3} mol L^{-1} was prepared by dissolving the appropriate weight of the reagent in approximately 25 mL of methanol, then completed to the mark with methanol in 100 mL volumetric flask. This solution was stable for one week.

Construction of calibration curve

To a set of 10 mL volumetric flasks, appropriate aliquots of the standard CFD solution were transferred, in the

concentration ranges (0.5-8.0 µg mL^{-1}) and (1.0-10 µg mL^{-1}) using ARS and Quinz, respectively. To each flask 2.0 and 1.5 mL of (1.0 x 10^{-3} mol L^{-1}) ARS and Quinz solution, respectively were added. Afterwards, the obtained mixture was shaken in order to promote the reaction and the volume was completed to the mark with methanol. The absorbance of the resulting solutions were measured at 533 and 559 nm using ARS and Quinz, respectively against a reagent blanks prepared simultaneously. The calibration graph was constructed by plotting the absorbance *versus* the final concentration of CFD. The corresponding regression equations were derived.

Assay procedure for pharmaceutical dosage forms

The content of ten tablets or capsules each containing 300 mg CFD was finely powdered using an agate mortar and weighed accurately. An accurately weighed quantity of the powder equivalent to 100 mg CFD were transferred into 100 mL calibrated flask and dissolved in 25 mL methanol. The content of the flask was shaken and sonicated for about 10 min, mixed well and then filtered using What man No.42 filter paper. The first portion of the filtrate was rejected and the solution was then completed to volume with methanol to prepare a stock solution of 1000 µg mL^{-1}. This solution was further diluted with the same solvent as appropriate to obtain the working concentration ranges. Aliquots covering the working concentration ranges for each method were transferred into a series of 10 mL volumetric flasks and the proposed methods were applied. The nominal content of the tablets or capsules was determined using the corresponding regression equations or the calibration graphs.

Stoichiometric relationship

The stoichiometric ratios of the charge transfer complexes formed between the studied drugs and reagents were determined by applying the continuous variation method attributable to Job [26] and modified by Vosburgh and Coober [27] at the optimum wavelengths of maximum absorbance. Job's method of continuous variation was employed, a 1.0 × 10^{-3} mol L^{-1} standard solution of CFD and 1.0×10^{-3} mol L^{-1} solution of reagent were used. A series of solution were prepared in which the total volume of CFD and reagent was kept at 2.0 ml. The reagents were mixed in various proportions with CFD and diluted to volume in a 10 mL calibrated flask with methanol following the above mentioned procedures

Results and Discussion

Absorption spectra

Solutions of reagents in methanol exhibits an absorption bands with a well defined maximum at 421 and 491 nm for ARS and Quinz, respectively, while CFD solution in methanol showed no absorption in the 400-700 nm range. At optimum conditions, the addition of CFD to reagent solution in methanol caused an immediate change in the absorption spectrum with the appearance of a new characteristic band for the radical anion (absorbing species) with maximum absorption at 533 and 559 nm using ARS and Quinz, respectively (Figures 2, 3). The high difference between maximum wavelength of the reagent and the charge transfer product absorption bands ~ 112 and 68 nm using ARS and Quinz, respectively, allowed the measurement of the charge transfer products with only a small contribution of the reagents that was added in excess in the medium.

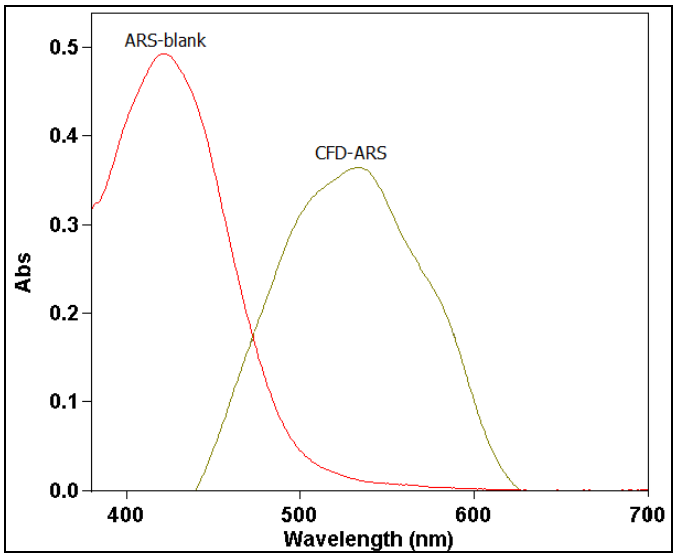


Fig 2: Absorption spectra of charge transfer complexes of 8.0 µg mL^{-1} CFD with (1.0 x 10^{-3} mol L^{-1}) ARS in methanol solvent obtained against ARS reagent blank solution prepared in the same solvent.

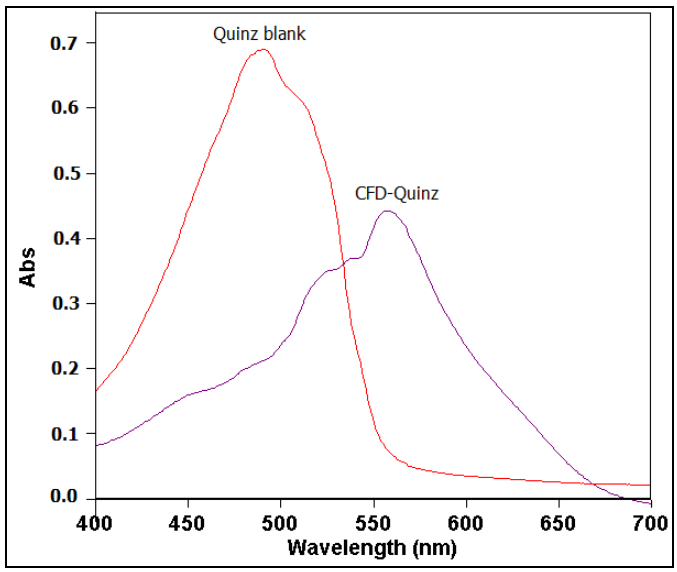


Fig 3: Absorption spectra of charge transfer complexes of 12 µg mL^{-1} CFD with (1.0 x 10^{-3} mol L^{-1}) Quinz in methanol solvent obtained against Quinz reagent blank solution prepared in the same solvent.

Optimization of the experimental conditions

The effect of the solvent

The solvent plays an important role in some charge transfer reactions, since it must be able to facilitate the total charge transfer and then allow the complex dissociation and stabilization of the radical anion formed, which is the absorbing species. According to the literature, solvents with high dielectric constant are more effective to execute this task [28, 29]. Taking this fact into account, water would be an excellent solvent for the procedure. However, the poor

solubility of the reagents in water did not allow its use in the present case. So, the reaction was tested in etha DMSO, methanol, acetonitrile, acetone and ethanol solvents. Although the highest dielectric constant of DMSO and acetonitrile, best sensitivity was achieved with methanol, probably because of the capacity of this solvent to form stable hydrogen bonds with the radical anion. Then, methanol was chosen for further experiments (Figure 4).

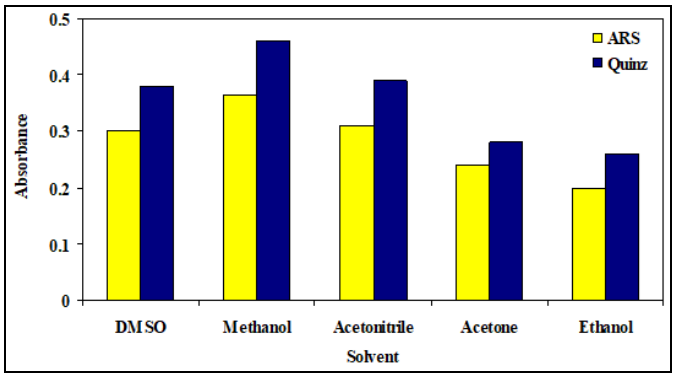


Fig 4: Effect of different solvents on the charge transfer complex of drug-reagent solution obtained against (1.0 x 10^{-3} mol L^{-1}) reagent solution prepared in each solvent. CFD concentration = 8.0 µg mL^{-1}.

Effect of the reagent concentration

In order to achieve this objective, an experiment was performed when various volumes of reagents solutions (1.0 x 10^{-3} mol L^{-1}) in the range of 0.2-3.0 mL were added to a fixed drug concentration (8.0 µg mL^{-1}) (Figure 5). The results are shown that 2.0 and 1.5 mL of (1.0 x 10^{-3} mol L^{-1}) ARS and Quinz reagents solution, respectively were enough to develop the color to its full intensity and gave the highest and constant absorbance values.

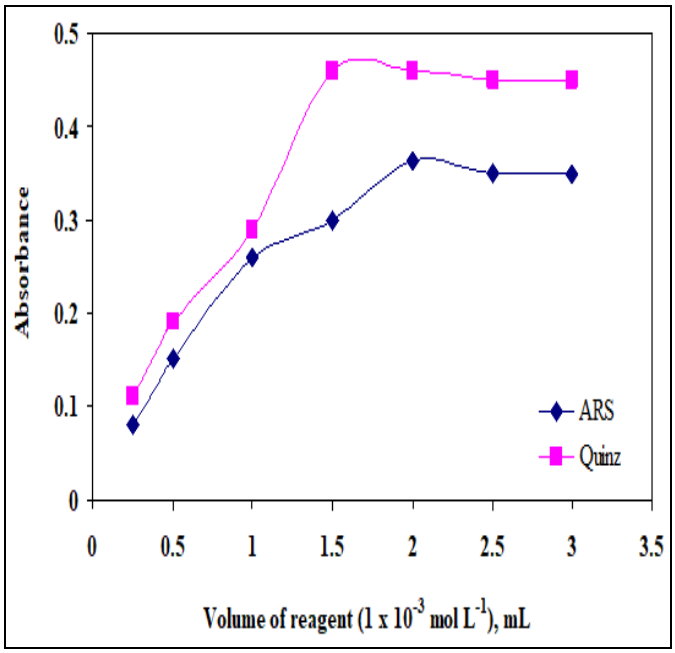


Fig 5: Effect of (1.0 x 10^{-3} mol L^{-1}) reagent concentration on the absorbance of charge transfer complex. CFD concentration = 8.0 µg mL^{-1}.

Effect of the reaction time and temperature

The optimum reaction time was determined by following the color development at laboratory ambient temperature (25±2°C). Complete color development was attained after 2.0 min for CFD with both reagents. On raising the temperature, the absorbance of the charge transfer complex was decrease with a hypochromic shift, until decayed at 50 °C.

Sequence of additions

The most favorable sequence of addition is "CFD-reagent-solvent" for complete colour development, highest absorbance and stability at the recommended wavelength. Other sequences needed longer time in addition to lower stability. The complexes with this sequence remain stable for at least 18 h.

Stoichiometric ratio

The molar ratio of CFD to reagent (ARS or Quinz) in the charge transfer complex was determined by Job's method [26] of continuous variations, keeping the sum of the molar concentrations of CFD and reagent fixed. As shown in Figure 6, the molar ratio which gave maximum absorbance was found to be (1:1) (CFD: reagent).

According to literature review in [29-32] molecular charge-transfer complexes are formed in non-polar solvents while radical anion species are predominant in polar solvents. Also, it is believed that the addition of basic compounds that contains a lone pair of electrons, such as CFD, results in the formation of charge-transfer complexes of n-π type. This kind of complexes can be considered an intermediate molecular-association compound that forms a corresponding radical anion in polar solvents. In this case, radical anions results from the total transfer of charge (Fig 6).

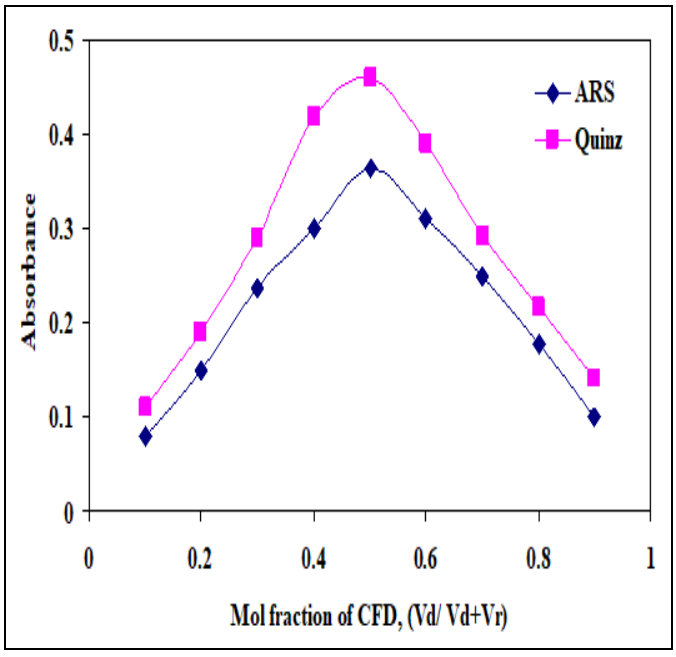


Fig 6: Application of Job's method to the reaction between reagents and CFD at optimum wavelength (nm).

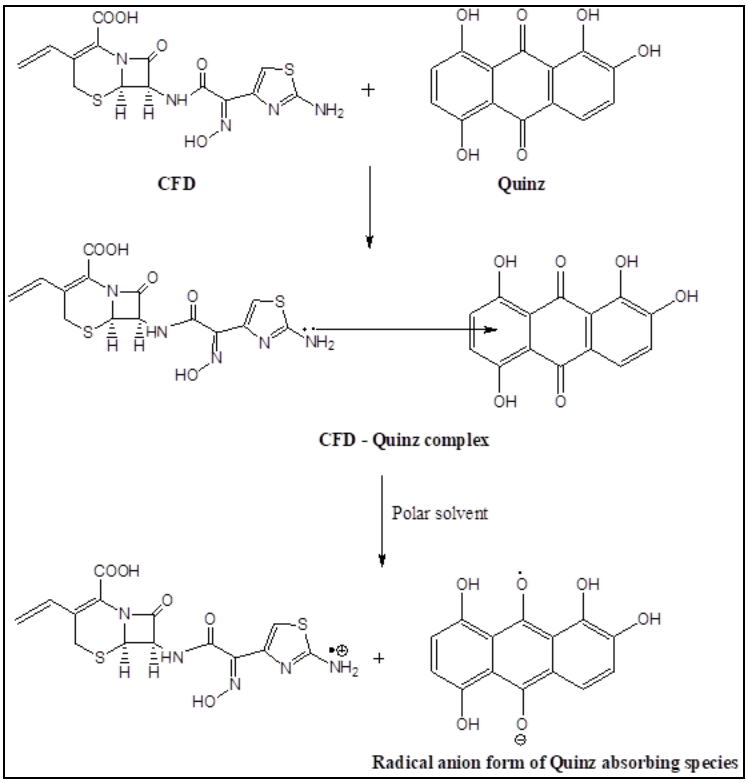


Fig 6: Possible mechanism of radical anion formation from Quinz and CFD reaction.

Validation of the proposed methods

The validity of the methods was tested regarding linearity, specificity, accuracy, repeatability and precision according to International Conference on Harmonization (ICH) [33] and United States Pharmacopeia [34] guidelines.

Linearity, detection, and quantification limits

Linear regression equations were obtained by using the above procedures. The regression plots showed that there was a linear dependence of the analytical response in the two methods to the concentration of CFD over the ranges cited in Table 2. Linear regression analysis of the data gave the following equations. For ARS, $A = 0.002 + 0.0427C$, $r^2 = 0.9998$ and $A = 0.0003 + 0.0467C$, $r^2 = 0.9996$ using Quinz, where A is the absorbance, C is the concentration of CFD (µg mL^{-1}), and r^2 is the correlation coefficient.

The limit of quantification (LOQ) was determined by establishing the lowest concentration that can be measured according to ICH [33]. The results are shown in Table 2. The limits of detection (LOD) were determined by establishing the minimum level at which the analyte can be reliably detected, and the results are also summarized in Table 2. LOQ and LOD were calculated according to the following equations:

$LOQ = 10s / b$

$LOD = 3.3s / b$

Where s is the standard deviation of replicate determination values under the same conditions as for the sample analysis in the absence of the analyte. b: is the slope of the calibration curve.

3.3.2. Accuracy and precision

In order to determine the accuracy and precision of the proposed methods, intraday and inter-day determination of CFD at three different concentrations for each method were prepared and analyzed. The intraday studies were performed in one day and inter-day studies in five days (for each level $n = 6$). The accuracy and precisions expressed as percent relative error (RE %) and relative standard deviation (RSD%) values, respectively and found to be within -0.90-0.60% and 0.50–1.70%, respectively for intraday analysis and within -1.50-0.80% and 0.65-2.10%, respectively for inter-day analysis (Table 3). The data proved good accuracy precision for the developed methods.

Table 2: Analytical parameters for the determination of the studied drugs by the proposed methods.

Parameters	ARS	Quinz
λ_{max}	533	559
Conc. Range(µg mL^{-1})	0.5-8.0	1.0-10
Molar absorpitivity ε, (L mol^{-1} cm^{-1}) x 10^4	1.7778	1.8516
Sandel sensitivity, (µg cm^{-2})	22.24	21.36
Regression equation [a]		
Intercept (a)	0.002	0.0003

Slope (b)	0.0427	0.0467
Correlation coefficient (*r*)	0.9998	0.9996
Mean ± SD [b]	99.30±1.40	99.60±1.20
Relative standard deviation; RSD%	1.41	1.20
Relative error, RE%	1.48	1.26
Variance	1.96	1.44
Detection limits, (LOD) (µg mL^{-1})	0.14	0.28
Quantification limits, (LOQ) (µg mL^{-1})	0.47	0.93
Calculated t-value (2.20) [c]	0.05	0.36
Calculated F-value(4.39) [c]	1.78	1.31

[a] $A=a + bC$, where C is the concentration in (µg mL^{-1}), A is the absorbance, a is the intercept and b is the slope.
[b] Mean of six determination
[c] Theoretical values of *t* and *F* for five degree of freedom and 95 % confidence level at p = 0.05.

Table 3: Evaluation of intra-day and inter-day precision and accuracy for CFD obtained by the proposed methods.

Method	Added (µg mL^{-1})	Recovery %	Precision RSD % [a]	Accuracy RE %	Confidence Limit [b]
		Intra-day			
ARS	2.0	99.10	0.50	-0.90	1.982 ± 0.01
	4.0	99.30	1.10	-0.70	3.972 ± 0.046
	6.0	99.60	1.50	-0.40	5.976 ± 0.094
Quinz	3.0	100.30	0.70	0.30	3.009 ± 0.022
	6.0	100.60	1.20	0.60	6.036 ± 0.076
	9.0	99.40	1.70	-0.60	8.946 ± 0.16
		Inter-day			
ARS	2.0	99.50	0.65	-0.50	1.99 ± 0.014
	4.0	99.00	0.90	-1.0	3.96 ± 0.037
	6.0	98.50	1.80	-1.50	5.91 ± 0.112
Quinz	3.0	99.10	0.80	-0.90	2.973 ± 0.025
	6.0	99.30	1.35	-0.70	5.958 ± 0.084
	9.0	100.80	2.10	0.80	9.072 ± 0.20

[a] Mean of six determination, RSD%, percentage relative standard deviation; R.E%, percentage relative error.
[b] Mean ± standard error.

Ruggedness and robustness

The ruggedness of the proposed method was assessed by applying the procedures using two different instruments in two different laboratories at different times and two different analysts. Results obtained from laboratory-to-laboratory and analyst-to- analyst variation were found to be reproducible because the RSD did not exceed 3.0%.

Robustness of the proposed method was assessed by evaluating the influence of small variation of experimental variables, i.e., concentrations of reagent and reaction time, on the analytical performance of the method. In these experiments, one experimental parameter was changed while the other parameters were kept unchanged, and the recovery percentage was calculated each time. The small variations in any of the variables did not significantly affect the results. The recovery values ± %RSD were 98.50 - 101.0 ± 0.50 - 1.60% for ARS and 99.00 - 100.80 ± 0.60 - 1.80% for Quinz. This indicated the reliability of the proposed method during its routine application for the analysis of CFD.

Specificity and effect of excipients

The specificity of the proposed method was investigated by observing any interference encountered from the common capsules excipients. The standard addition method was applied by adding known amounts of pure CFD to a previously analyzed tablet or capsule solution. The recovery of the added CFD was calculated by comparing the concentration of the spiked mixtures with that of the previously found value. As can be seen from Table 4, satisfactory results better than the reported spectrophotometric methods were obtained. The high recovery values of the proposed methods indicated that the excipients did not interfere with the proposed methods indicating the high selectivity of the proposed methods.

Table 4: Application of the standard addition technique for the determination of CFD in pharmaceutical preparations using the proposed methods.

Sample	Taken (µg mL^{-1})	ARS		Quinz	
		Added (µg mL^{-1})	Recovery [a] (%)	Added (µg mL^{-1})	Recovery [a] (%)
Dinar tablets (300 mg CFD /tab.)	1.0	-	99.00	-	100.30
		1.0	99.10	1.0	99.00
		2.0	100.60	2.0	98.50
		3.0	100.40	4.0	99.20
		5.0	99.20	6.0	100.10

		7.0	99.10	8.0	99.60
Mean ± SD			99.57 ± 0.73		99.45 ± 0.683
V [b]			0.531		0.467
RSD%			0.733		0.687
SE			0.297		0.279
Omnicef capsules (300 mg CFD /cap.)	1.0	-	99.30	-	99.10
		1.0	99.50	1.0	99.30
		2.0	98.60	2.0	100.20
		3.0	99.40	4.0	99.00
		5.0	100.10	6.0	99.50
		7.0	99.20	8.0	98.70
Mean ± SD			99.35 ± 0.485		99.30 ± 0.518
V			0.235		0.268
RSD%			0.488		0.522
SE			0.198		0.211

[a] The average of at least three determinations.
[b] V= variance; RSD%= percentage relative standard deviation; SE= standard error.

Analysis of the pharmaceutical preparation

The proposed method was applied to the determination of CFD in pharmaceutical formulations (Dinar tablets, 300 mg CFD per tablet) and (Omnicef capsules, 300 mg CFD per capsule). The method was tested for linearity, specificity, accuracy, repeatability, and precision according to ICH recommendations. The results of the proposed methods were statistically compared with those obtained using the reference methods [16]. Recovery ± SD values were obtained. Statistical analysis of the results, using Student's *t*-test and the variance ratio *F*-test at 95% confidence level revealed no significant difference between the performance of the proposed and reference methods regarding the accuracy and precision, respectively (Table 5) [35]. It is evident from these results that the proposed methods is applicable to the analysis of CFD in its dosage forms with comparable analytical performance.

Conclusion

The developed two methods are simple and rapid, sensitive, accurate, robust, and economic. It does not require extraction, heating, or pH adjustment. The chromophore formed is quite stable. These characteristics make the proposed methods very suitable for routine analysis of CFD in quality control laboratories.

Table 5: Application of the proposed method to the determination of CFD in dosage forms.

Samples	References method [16]	Proposed methods	
		ARS Quinz	
Dinar tablets (300 mg CFD /tab.)			
X ± SD [a]	99.65 ± 0.49	99.50 ± 0.52	99.80 ± 0.67
t-value (2.57) [b]		0.47	0.40
F-value (5.05) [b]		1.13	1.87
Omnicef capsules (300 mg CFD/cap.)			
X ± SD [a]	99.78 ± 0.31	99.60 ± 0.46	99.55 ± 0.25
t-value (2.57) [b]		0.736	1.29
F-value (5.05) [b]		2.20	1.54

[a] Average of six determinations.
[b] Theoretical values of t *and F* for five degree of freedom and 95 % confidence level at p = 0.05.

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