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SPECTROPHOTOMETRIC DETERMINATION OF CEFDINIR AS A CFD–1H2NA AZO DYE USING CENTRAL COMPOSITE DESIGN

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ABSTRACT:
This study established a spectrophotometric method for the determination of cefdinir (CFD) as a CFD–1H2NA azo dye, utilizing Central Composite Design (CCD) for optimization. The effects of four factors – the volume of (1:1) HCl, the volume of (1%) $NaNO_2$, the volume of (25%) NaOH, and reaction time – were optimized using CCD with three levels for each factor, a two-level factorial, full quadratic, and face-centered design. The initial procedure involves converting CFD to its diazonium salt, which is subsequently reacted with the 1-hydroxy-2-naphthalic acid reagent in an alkaline medium. The resulting purple azo dye exhibits λ_{max} at 570 nm, a correlation coefficient (R^2) of 0.997, a molar absorptivity (ε) of 0.92 x 10^4 $L/mol.cm$ and a detection limit of 0.47 $\mu g/mL$. Beer's law was obeyed within the concentration range of 1-50 $\mu g/mL$. The development of the recommended technique and the evaluation of the stability of the purple-colored product were conducted by assessing its chemical and physical properties. The proposed method was successfully applied to quantify CFD in pharmaceutical formulations, yielding satisfactory results.

keywords: Cefdinir, Central Composite Design, 1-hydroxy-2-naphthalic acid reagent, purple azo, spectrophotometric, face-centered design.

INTRODUCTION:

Cefdinir (CFD), ($C_{14}H_{13}N_5O_4S_2$, its Mwt is 395.416 g/moL), is one of the semi-synthetic antibiotics. It belongs to the Cephalosporin family (third-generation broad spectrum), which is a member of the beta-lactam class. Its scientific IUPAC name is (6R,7R)-7-{[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-(hydroxyimino)acetyl]amino}-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (Figure 1) (Abood et al.,2019 ; Hassan et al.,2019). Several papers have been published on the determination of cefdinir (CFD). These methods were identified using bibliometric analysis (Figure 2), such as CTAB-induced fluorescence sensing (Abdel-Hakim et al.,2024), spectrofluorimetric via degradation products of CFD (Boltia et al.,2021). spectrofluorimetric and spectrophotometric determination of CFD in mixture (Ibrahim et al.,2018). HPLC coupled with tandem mass spectroscopy (Tutunji et al.,2015). HPLC determination of CFD in mixture (Reçber et al.,2021), RP-HPLC/UV detection (Khan et al.,2011 ; Shahed et al.,2011) cloud point extraction coupled with spectrophotometric (Hassan et al.,2018). solid-phase extraction coupled with HPLC-DAD (Mahmoud et al.,2024). on-line solid-phase extraction coupled with HPLC (Li et al.,2018), magnetic

solid phase extraction (MSPE)-CQDs coupled with HPLC (Nakhostin Mortazaviet al.,2024). solid-phase extraction coupled with LC–MS (Ana et al.,2021). electrochemical assay with MWCNT/chitosan NCs/Fe_2O_3 as a Nano sensor (Aydogdu et al.,2022). electrochemical combined with molecularly imprinted polymer-based sensor (Alahmad et al.,2023), derivative spectrophotometry (Ba et al.,2013). Spectrophotometric via derivatization with 1,2-naphthoquinone-4-sulfonate and 4-chloro-7-nitrobenzo-2-oxa-1,3-diazole (Gouda et al.,2012). and spectrophotometric using silver nanoparticles (Ag NPs) (El-Alfy et al.,2019) In this study, a Central Composite Design (CCD) was used to optimize the effects of the volume of (1:1) HCl, volume of (1%) $NaNO_2$, volume of (25%) NaOH, and Time to develop a spectrophotometric method via diazotization of cefdinir (CFD), which was then coupled with 1-hydroxy-2-naphthalic acid in an alkaline medium to give a purple azo color of CFD–1H2NA dye at λ_{max} 570 nm.

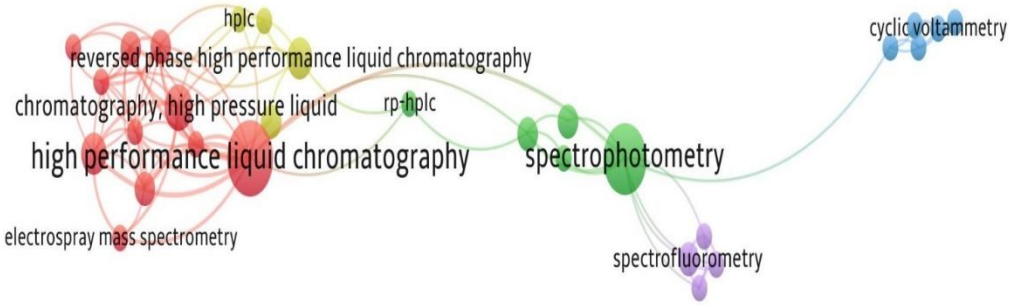


Figure 1: 2D and 3D Structural formulas for Cefdinir drug (MolView).

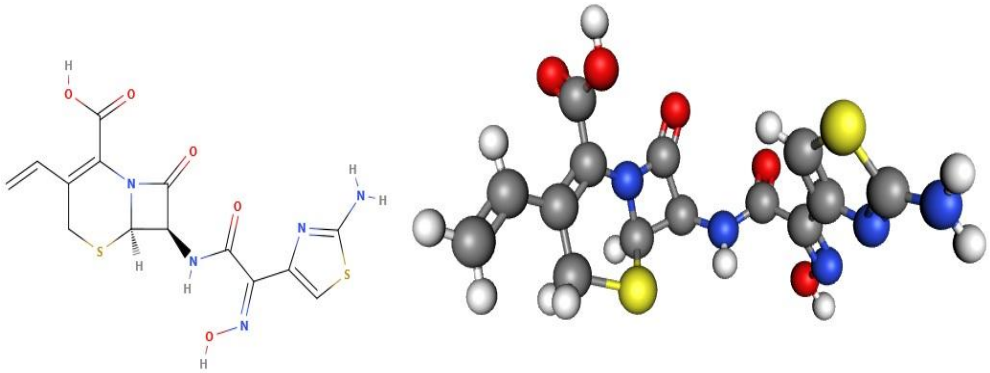


Figure 2: Bubble map of co-authorship by the analytical chemistry techniques for determination of cefdinir (CFD) from 2010-2025 (El-Alfy et al.,2019)

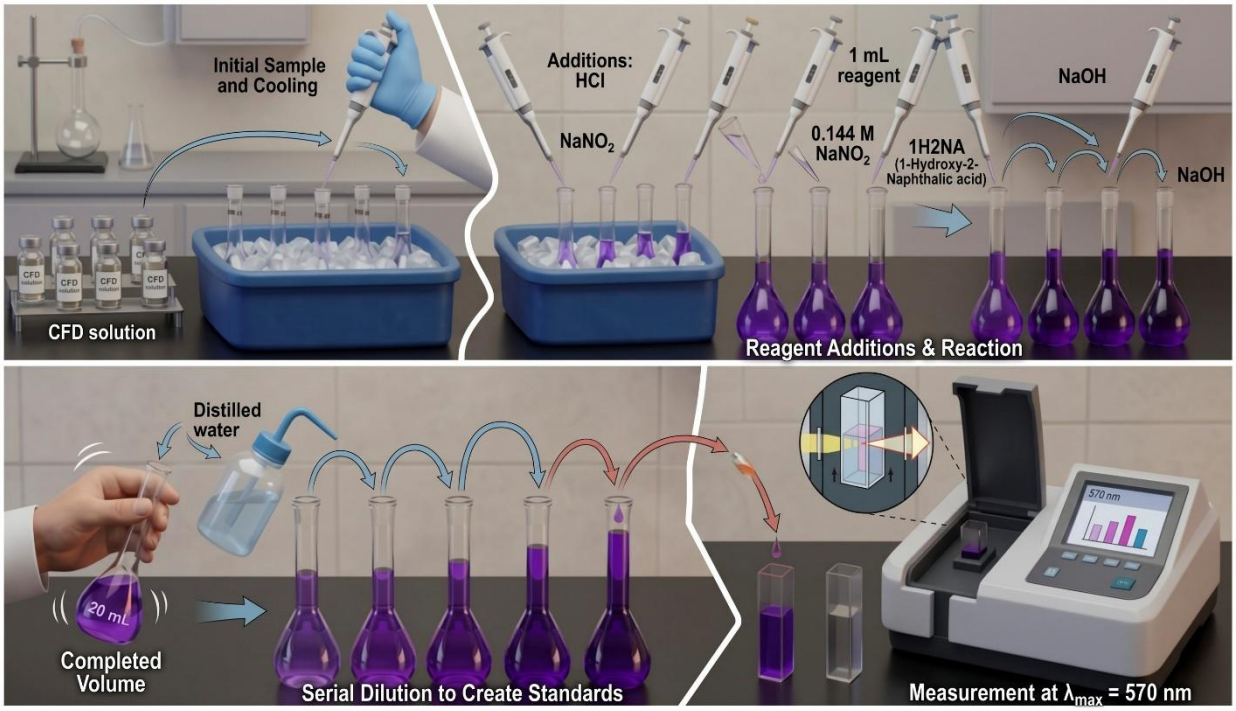
Experimental

General Procedure of the Diazotization Coupling

A several volumes from the standard solution (1000 µg/mL) of Cefdinir (CFD) (SDI, Samarra, Iraq) were transferred to a series of 20 mL volumetric flasks, which were placed in an ice bath for 2 min. Then 0.25 mL of (1:1)

HCl and 0.5 mL of (0.144 M) $NaNO_2$ were added, followed by 1 mL of the reagent 1-hydroxy-2-Naphthalic acid (1H2NA) ($C_{11}H_8O_3$, M.wt=188.18 g/mol). A 2 mL of 25% (w/v %) NaOH was added, and the volume was completed to 20 mL with distilled water and shacked carefully. Finally, the azo dye formed (CFD-1-Hydroxy-2-Naphthallic acid, CFD–1H2NA) was measured at λ_{max} .

570 nm against the reagent blank **(Scheme 1).** For commercial products analysis, capsules samples solutions were prepared (Sefarin and Azord). Ten cefdinir-containing capsules were carefully weighed. Each capsule was individually weighed, and the average weight of Sefarin and Azordin each capsule was 0.355 g and 0.367 g respectively



Scheme 1: General procedure of CFD–1H2NA Azo Dye

Central composite design

Four factors (Vol. of (1:1) HCl, Vol. of (1%) $NaNO_2$, Vol. of (25%) NaOH, and Time) were employed for the determination of cefdinir (CFD) after conversion to diazonium salt. Each factor was divided into three levels (–1, 0, and +1) as shown in Table 1. Table 2 shows 31 experiments (N = 31), which were achieved by using a CCD design in Minitab 18 with a two-level factorial, full quadratic, face-centered design.

Table 1: The variables used for central composite design (CCD)

Coded factor levels			
Factor	-1	0	+1
Vol. of (1:1) HCl	0.5	1.5	2.5
Vol. of (1%) $NaNO_2$	0.25	0.75	1.25

Vol. of (25%) NaOH	1	2	3
Time (min)	5	15	25

Results and discussion

Model development and factors effect on CFD–1H2NA azo dye

Table 2 shows the design matrix containing the factors that affected the determination of cefdinir (CFD) after conversion to diazonium salt. Figure 3 shows the spectrum of a 50 µg/mL solution of CFD–1H2NA against its blank solution, recorded under optimum conditions determined by CCD-RSM. The cefdinir maximum wavelength was 570 nm for CFD–1H2NA dye according to the spectra. The diazotization-coupling method is expressed by the following regression equation in uncoded units, obtained using Minitab software: Absorbance = -0.472 + 0.248 HCl + 1.125 $NaNO_2$ + 0.418 NaOH + 0.0281 Time - 0.0758 $(HCl)^2$ - 0.803 $(NaNO_2)^2$ - 0.1073 $(NaOH)^2$ - 0.001028 $(Time)^2$ + 0.0316 HCl* $NaNO_2$ - 0.0271 HCl*NaOH + 0.00206 HCl*Time + 0.0614 $NaNO^2$ ∗NaOH - 0.00239 $NaNO_2$*Time + 0.00469 NaOH*Time

The positive coefficient values of HCl, $NaNO_2$, NaOH, and Time suggest that as these factors increase, the absorbance tends to increase. The large positive coefficient of $NaNO_2$ (1.125) indicates a strong and significant positive effect of $NaNO_2$ concentration on absorbance. Moreover, negative coefficients for the quadratic terms (HCl^2, $NaNO_2^2$, $NaOH^2$, and $Time^2$) will reduce the predicted absorbance. For antagonistic interaction terms (such as HCl*NaOH), an increase in one factor when the other interacting factor is at a higher level will decrease the predicted absorbance (or vice versa).

Interaction Terms (X_1*X_2) refer to the effect of one factor on the response (absorbance) that changes depending on the level of another factor. They indicate that the factors do not act independently (work together).

The positive coefficient values indicate a synergistic or enhancing interaction between the concentrations of both HCl and $NaNO_2$. The same applies to HCl*Time, $NaNO_2$*NaOH, and NaOH*Time.

The negative coefficient values indicate an antagonistic or counteracting interaction between the concentrations of both HCl and NaOH, and between $NaNO_2$ and Time.

ANOVA is a statistical technique used to assess the significance of the factors (HCl, $NaNO_2$, NaOH, and Time) and their interactions in explaining the variation in absorbance. The ANOVA table for the determination of CFD–1H2NA azo dye is listed in Table 5. A p-value less than 0.05 indicates that the CCD model is significant.

The p-values of the Model and Linear sources, being 0.000, indicate that the fitted regression CCD-RSM model is highly significant. The factors (HCl, $NaNO_2$, NaOH, and Time) and their interactions included in the CCD model collectively have a real effect on the determination of CFD–1H2NA azo dye and show a good and significant linear relationship with the absorbance.

Moreover, the linear terms of $NaNO_2$, Time, HCl, and NaOH have very significant linear effects (p-value less than 0.05).

The square terms of HCl^2, $NaNO_2^2$, $NaOH^2$, and $Time^2$ have highly significant effects (p = 0.000). Finally, the interaction terms also

show significance (such as HCl* $NaNO_2$, $NaNO_2$*NaOH, and $NaNO_2$*Time).

The p-value of "lack of fit" is 0.012 indicates that the exceptionally low pure error variance among precise replicates, rather than model inadequacy. Thus, the model provides a good predictive ability (Table 3).

The high values of R^2 (96.57%) and R^2-adj (93.56%) suggest that the quadratic CCD model provides a good fit to the experimental data and has good predictive ability.

A reasonable R^2-pred value (a value greater than 0.5 is considered acceptable) indicates that CCD model has good predictive ability. In this study, the value of 76.46% suggests that the CCD model will perform reasonably well in predicting absorbance for new experimental conditions within the studied factors (Table 4).

The close clustering of the points between predicated absorbance and experimental absorbance around the regression line and the high R^2value (0.955) indicate a reliable and accurate the CCD model (Figure 4).

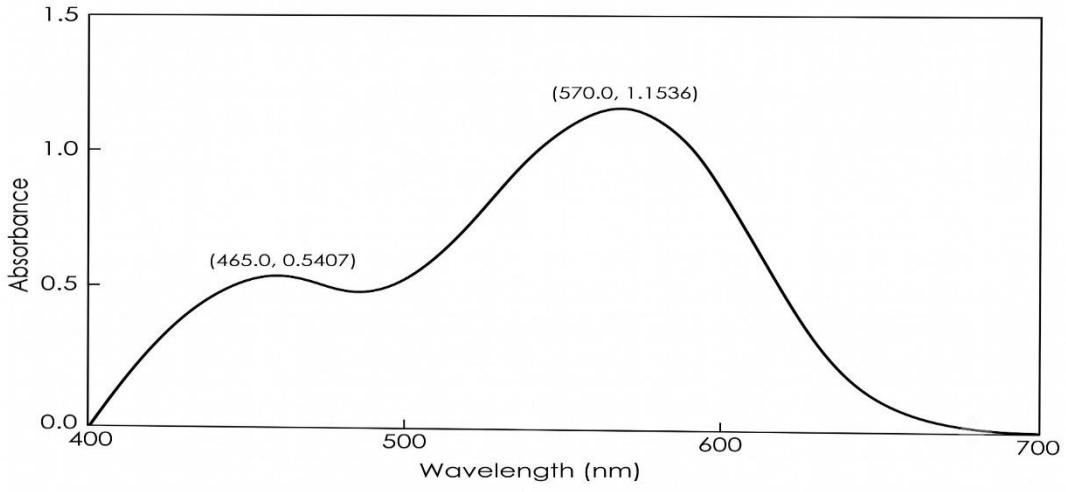


Figure 3: Absorption spectrum for 50 μg/mL of CFD–1H2NA against the reagent blank

Table 2: CCD Matrix

Run	Coded factor				Actual factor				Experimental Absorbance	predicate Absorbance
	Vol. of (1:1) HCl	Vol. of (1%) $NaNO_2$	Vol. of (25%) NaOH	Time (min)	Vol. of (1:1) HCl	Vol. of (1%) $NaNO_2$	Vol. of (25%) NaOH	Time (min)		
	x_1	x_2	x_3	x_4	x_1	x_2	x_3	x_4		
1	-1	-1	-1	-1	0.5	0.25	1	5	0.243	0.321
2	1	-1	-1	-1	2.5	0.25	1	5	0.313	0.345
3	-1	1	-1	-1	0.5	1.25	1	5	0.353	0.307
4	1	1	-1	-1	2.5	1.25	1	5	0.412	0.394
5	-1	-1	1	-1	0.5	0.25	3	5	0.367	0.350
6	1	-1	1	-1	2.5	0.25	3	5	0.335	0.265
7	-1	1	1	-1	0.5	1.25	3	5	0.442	0.458
8	1	1	1	-1	2.5	1.25	3	5	0.388	0.437
9	-1	-1	-1	1	0.5	0.25	1	25	0.447	0.370
10	1	-1	-1	1	2.5	0.25	1	25	0.462	0.475
11	-1	1	-1	1	0.5	1.25	1	25	0.208	0.307
12	1	1	-1	1	2.5	1.25	1	25	0.488	0.476
13	-1	-1	1	1	0.5	0.25	3	25	0.538	0.585
14	1	-1	1	1	2.5	0.25	3	25	0.566	0.583
15	-1	1	1	1	0.5	1.25	3	25	0.707	0.646
16	1	1	1	1	2.5	1.25	3	25	0.756	0.707
17	-1	0	0	0	0.5	0.75	2	15	0.866	0.829
18	1	0	0	0	2.5	0.75	2	15	0.832	0.871
19	0	-1	0	0	1.5	0.25	2	15	0.719	0.697
20	0	1	0	0	1.5	1.25	2	15	0.729	0.752
21	0	0	-1	0	1.5	0.75	1	15	0.822	0.754
22	0	0	1	0	1.5	0.75	3	15	0.813	0.883
23	0	0	0	-1	1.5	0.75	2	5	0.767	0.743
24	0	0	0	1	1.5	0.75	2	25	0.877	0.902
25	0	0	0	0	1.5	0.75	2	15	0.908	0.926
26	0	0	0	0	1.5	0.75	2	15	0.915	0.925
27	0	0	0	0	1.5	0.75	2	15	0.928	0.925
28	0	0	0	0	1.5	0.75	2	15	0.900	0.925
29	0	0	0	0	1.5	0.75	2	15	0.912	0.925
30	0	0	0	0	1.5	0.75	2	15	0.938	0.925
31	0	0	0	0	1.5	0.75	2	15	0.983	0.925

Table 3: ANOVA for the determination of CFD–1H2NA by CCD model

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	14	1.73554	0.123967	32.15	0.000
Linear	4	0.21029	0.052571	13.63	0.000
HCl(x_1)	1	0.00806	0.008064	2.09	0.167
$NaNO_2$ (x_2)	1	0.01350	0.013503	3.50	0.080
NaOH(x_3)	1	0.07527	0.075272	19.52	0.000
Time(x_4)	1	0.11345	0.113447	29.42	0.000
Square	4	1.45017	0.362543	94.02	0.000
HCl*HCl(x_1 x_1)	1	0.01490	0.014904	3.87	0.067
$NaNO_2$* $NaNO_2$ (x_2 x_2)	1	0.10462	0.104620	27.13	0.000
NaOH*NaOH(x_3 x_3)	1	0.02987	0.029869	7.75	0.013
Time*Time(x_4 x_4)	1	0.02742	0.027416	7.11	0.017
2-Way Interaction	6	0.07508	0.012514	3.25	0.028
HCl* $NaNO_2$ (x_1 x_2)	1	0.00400	0.004001	1.04	0.324
HCl*NaOH(x_1 x_3)	1	0.01172	0.011718	3.04	0.100
HCl*Time(x_1 x_4)	1	0.00677	0.006765	1.75	0.204
$NaNO_2$*NaOH(x_2 x_3)	1	0.01507	0.015068	3.91	0.066
$NaNO_2$*Time(x_2 x_4)	1	0.00228	0.002280	0.59	0.453
NaOH*Time(x_3 x_4)	1	0.03525	0.035250	9.14	0.008
Error	16	0.06170	0.003856		
Lack-of-Fit	10	0.05698	0.005698	7.25	0.012
Pure Error	6	0.00471	0.000786		
Total	30				

Table 4: Model Summary

R^2	R^2-adj.	R^2-pred.
96.57%	93.56%	76.46%

R^2: coefficient of determined, R^2-adj.: adjusted coefficient of determined and R^2-pred.: predicated coefficient of determined

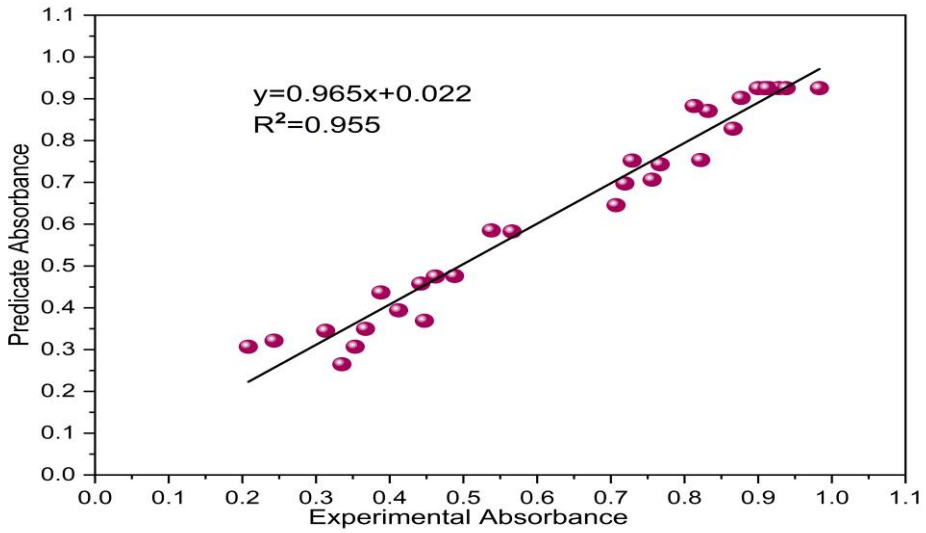


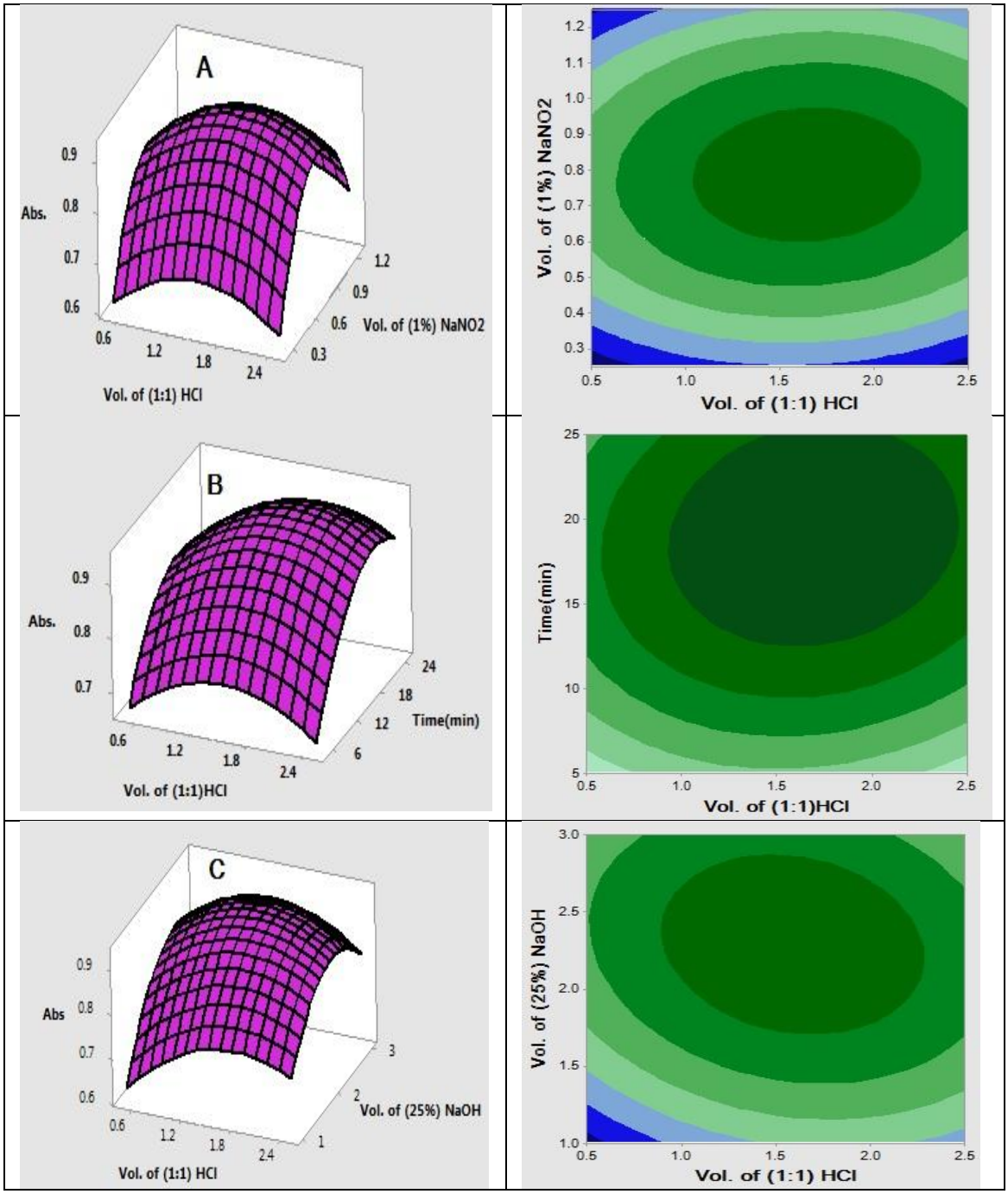
Figure 4: Correlation between experimental and predicted absorbance for CFD–1H2NA azo dye

The (1:1) HCl provides the necessary acidic conditions for the diazotization of the cefdinir drug and completes the reaction between the primary aromatic amine (1H2NA) and (1%) $NaNO_2$ to form the diazonium salt. The surface and contour plots (A) likely exhibit a peak, indicating an optimal combination of (1:1) HCl and (1%) $NaNO_2$volumes that maximizes the absorbance. The center of the concentric contours plot likely points to the optimal volumes for maximizing the (1:1) HCl and (1%) $NaNO_2$ related to the CFD–1H2NA azo dye.

The surface and contour plots (B) show the combinations of (1:1) HCl volume and reaction time where the absorbance increases with time up to a certain point and then plateaus.

The volume of (25%) NaOH plays an important role because (25%) NaOH affects the coupling and formation of the CFD–1H2NA azo dye to achieve the highest signal. The high peak absorbance in the surface and contour plots (C, D, and E) reflects the optimal combination of (25%) NaOH volumes with volumes of (1:1) HCl, Time, and volumes of (1%) $NaNO_2$.

The (1%) $NaNO_2$ provides the nitrite ions (NO_2^-) that are essential for the diazotization reaction. In acidic conditions, NO_2^- reacts with a primary aromatic amine (1H2NA) to form a diazonium salt. The surface and contour plots (F) show that the peak of the surface suggests an optimal interplay between the (1%) $NaNO_2$ and the time allowed for the azo dye formation and purple color development (Figure 5).


A
Abs.
0.9
0.8
0.7
0.6
0.6
1.2
1.8
2.4
Vol. of (1:1) HCl
1.2
0.9
0.6
0.3
Vol. of (1%) NaNO2
Vol. of (1%) NaNO2
Vol. of (1:1) HCl
B
Abs.
Vol. of (1:1)HCl
Time(min)
Time(min)
Vol. of (1:1)HCl
C
Abs
Vol. of (1:1) HCl
Vol. of (25%) NaOH
Vol. of (25%) NaOH
Vol. of (1:1) HCl

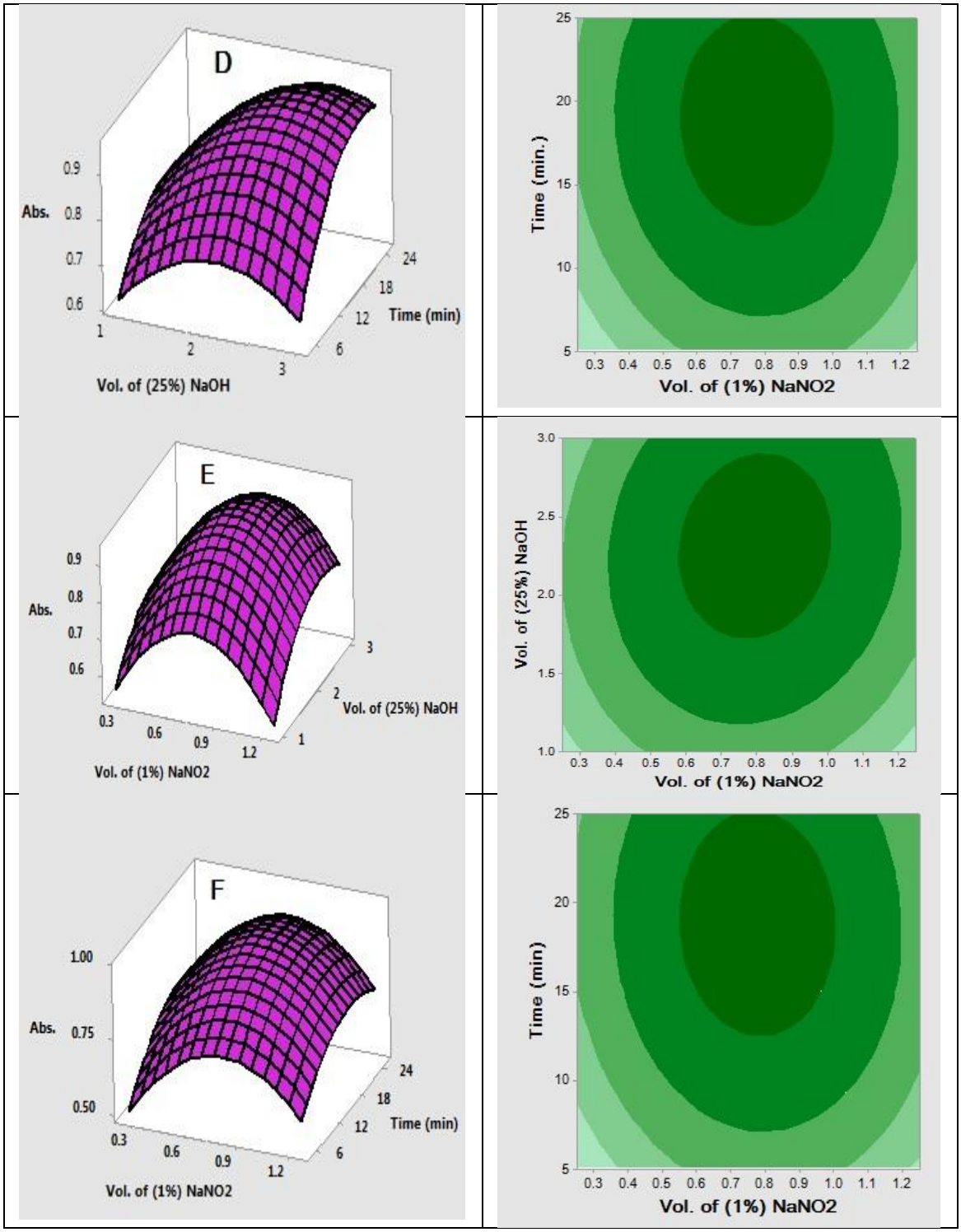


Figure 5 : 3D surface plots of determination CFD–1H2NA azo dye : (A) effect volume of (1:1) HCl/ volume of (1%) $NaNO_2$, (B) effect volume of (1:1) HCl/Time (min), (C) effect volume of (1:1) HCl/ volume of (25%) NaOH, (D) volume of (25%) NaOH/time (min), (E) effect volume of (1%) $NaNO_2$/volume of (25%) NaOH, and (F) volume of (25%) NaOH/ Time(min).

Analytical data and calibration curve

A calibration curve was created after determining the best experimental conditions, as illustrated in Figure 6.

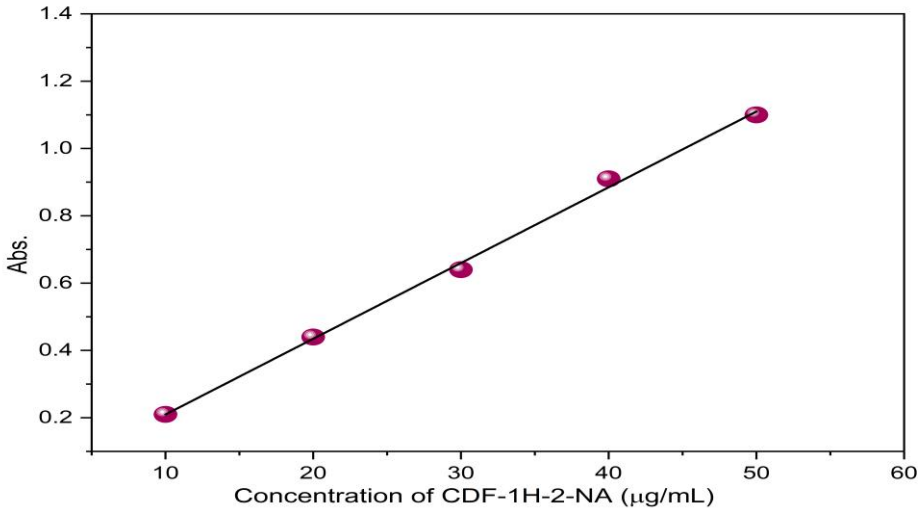


Figure 6: Calibration curve of CFD–1H2NA azo dye

The influence of the reagent volume was estimated at a concentration equivalent to the CFD concentration. The purpose of this step was to study the effect of the reagent volume on the intensity of the colored pigment. This study employs the same mole-ratio approach, various quantities (0.25-3.0 mL) of the 1H2NA reagent with 1 mL of CFD solution. At 1 mL of reagent, the best absorbance was achieved. The absorption was then nearly stable and the final-colored dye has a (1:1) ratio (Figure 7, Table 5).

Table 5: Data for regression equation

Parameter	CFD–1H2NA
Color of product	Violet
λ_{max} (nm)	570
Linearity range (µg/mL)	1-50
Molar absorptivity (ε) (L/mol. cm)	0.92×10^4
Regression equation	y=0.0218x+0.0055
Coefficient of determination R^2	0.997
Detection Limit (µg/mL)	0.47
Quantification Limit (µg/mL)	1.41

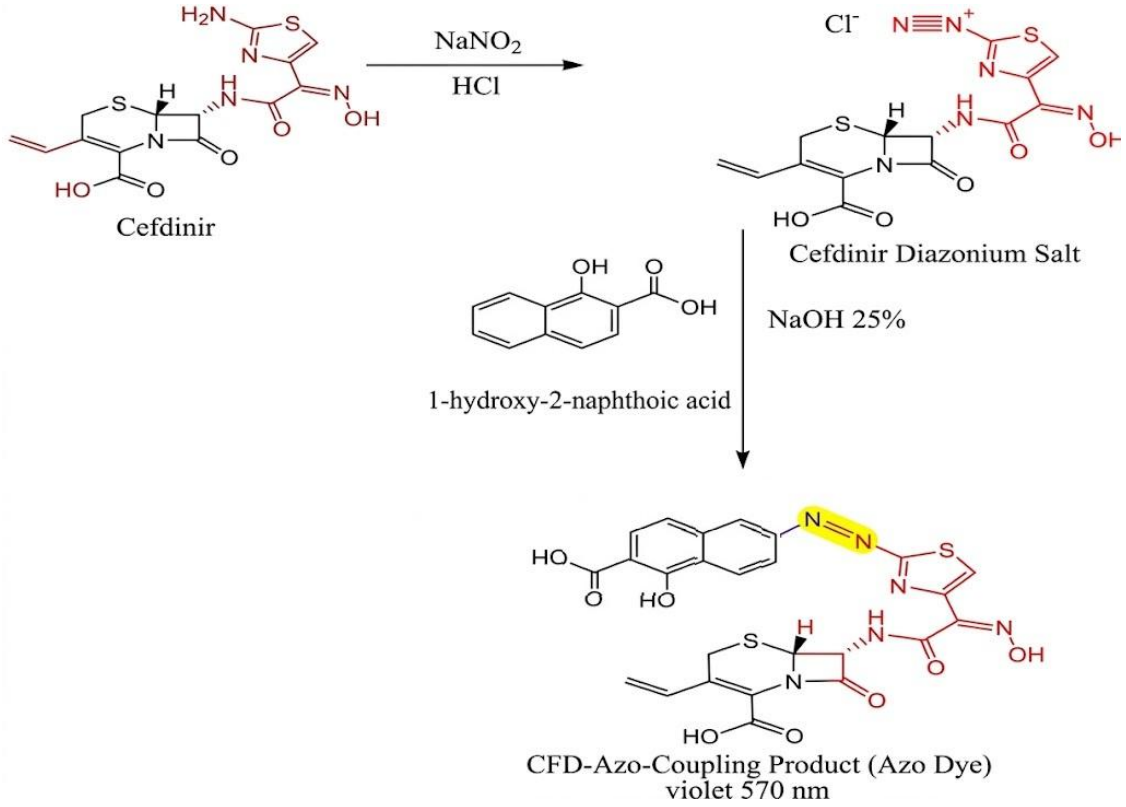


Figure 7: The suggested mechanism for the diazotization-coupling reaction

Precision, accuracy, and application

To check the precision and accuracy of the method, three concentrations (10, 30, and 50 /mL, n=5) of pure CFD were prepared. The results of t-test and F-test show that the proposed method is accurate and can be used for the determination of CFD in pharmaceutical preparations (Tables 6 and 7).

Table 6: Precision and accuracy

CFD concentration (µg/mL)		E%	t-value	F-value	RSD% (n=5)
Theoretically Used	Experimentally Calculated				
10	10.29	2.9	0.0168	1.009	4.87
30	30.39	1.3			0.272
50	50.16	0.32			0.166

Table7: Application in pharmaceutical formulation

Pharmaceutical	CFD concentration (µg/mL)		Recovery%	Average % Recovery	RSD% (n=5)
	Theoretically Used	Experimentally Calculated			
Sefarin Capsules 300 mg Product by	10	10.09	100.97	101.04	0.503
	30	29.84	99.47		0.231
	50	50.11	100.23		1.512

pharmaintessutional Co. Amman Jordan					
Azordin Capsules 300 mg Product by DAR ALDAWA	10	10.16	101.16	101.13	0.748
	30	29.93	99.77		0.198
	50	50.07	100.14		0.104

Conclusion

A new spectrophotometric method for the determination of CFD was developed, demonstrating simplicity, sensitivity, and affordability. The method involved the diazotization of the CFD followed by coupling with 1-hydroxy-2-naphthalic acid in an alkaline medium, resulting in a stable purple CFD–1H2NA azo dye at λ_{max} 570 nm. This batch spectrophotometric method, optimized using Central Composite Design, was effectively employed for the quantification of pure CFD and in pharmaceutical formulations, yielding results comparable to a standard method and exhibiting good precision (RSD% 0.104% to 1.512%) and accuracy (Recovery% 99.47% to 101.16% for pharmaceutical products). The proposed method offers a reliable and cost-effective alternative for the routine analysis of CFD in quality control laboratories.

Data Availability

All data generated or analysed during this study are included in this published article.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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