How to Cite:
Raffat, S. M., & Rashid, Q. N. (2022). Determination of cefdinir in pharmaceutical preparations by oxidative conjugation method. *International Journal of Health Sciences*, *6*(S4), 4734–4747. https://doi.org/10.53730/ijhs.v6nS4.8896

Determination of cefdinir in pharmaceutical preparations by oxidative conjugation method

Sawsan Madhat Raffat
Chemistry Department - College of Education for Pure Sciences - Tikrit University. Salah Al-Din – Iraq

Qabas Naji Rashid
Chemistry Department - College of Education for Pure Sciences - Tikrit University. Salah Al-Din – Iraq

***Abstract*---**In order to detect of Cefidinir (CEF) in its pure form and in its pharmaceuticals have been devised the proposed methods were: (I) oxidative conjugation in an alkaline medium between (CEF) and regent "p-Aminobanzoicacid" to produce an intense yellow colored product, (II) oxidative conjugation between (CEF) and 2,4-Dipyridin in an alkaline medium to generate a bright golden yellow colored product. Absorption of the reagent p-Aminobanzoicacid is 0.589 in 467nm, and highest absorption of the reagent 2,4-Dipyridin is 0.851 in724 nm, with molar absorptivity of 4.99×10^4 Lmol.cm, and 9.25×10^4 Lmol.cm. The limits of detection (LOD) for p-Aminobanzoicacid" and 2,4-Dipyridin were found to be 0.033 g/ml, and 0.007 respectively. In both its pure form and pharmaceutical forms, the proposed approach was successful in estimating "This drug.**".**

***Keywords*---**cefdinir, spectrophotometry, p-Aminobanzoicacid, 2,4-Dipyridin, N-Bromo Succinimid.

Introduction

Cefdinir (Figure 1), is an antibacterial agent that can be taken orally (1), It belongs to BCS Class IV, a semisynthetic broad-spectrum third-generation cephalosporin with low solubility and permeability (2) , for him a consistent white to yellow brown color (3), It is water insoluble and pH affects its solubility (4) , When it enters the body, some enzymes transform it into an active chemical that is poisonous to microscopic and parasitic organisms, preventing them from reproducing by interfering with their DNA (5), is processed insignificantly and eliminated in the urine (6) , Allergic responses to cefdanir have been observed, including rash, itching, fever, and arthralgia (7), headache(8) , cholestatic jaundice(9), It's also used to treat infections of the urinary tract. (10). The

research amis at finding a"simple fast economical spectral methods for determination of Cefidinir by using reagent p-Aminobanzoicacid in alkaline medium and reagent 2,4-Dipyridin in alkaline medium, as well as the success of the proposed methods for determination of (Cef) in its pharmaceutical preparations" (as tablets).

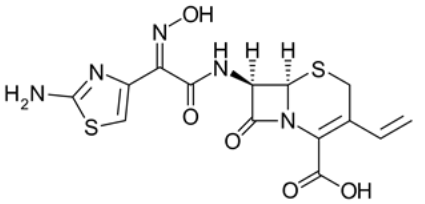


Fig. (1): Chemical structure of Cefidinir

Experimental

Apparatus: UV- VIS Spectrophotometer, 2-T92+ UV Spectrophotometer ''PG INSTRUMMENTS with1cm PLastic cells''. UV-VIS Spectrophotometer ''Single beam from Genesis UV10. UV-VIS Spectrophotometer ''double beam from Shimadzu (model UV-1800 2- Balance Kern 770GS/GJ from Sartorius BL210S. Semi-Micro Analytical Balances. Oven from Memmert, Schutzart DIN 40050-IP20. Hot Plate. Materials: Cefidinir 99% from (SDI Samarra. Iraq). P-aminobenzoicacid 99% from (Fluka), 2,4 Dipyridin 99% from (BDH), N-Bromo Succinimid 99% from (Fluka), Sodium hydroxid 99% from (GCC), DMSO 99% from GCC

Solutions

- Cefidinir stock solution (1000 µg\ml): an exactly (0.1000 gm) of (Cef) "standard" were dissolved in (100 ml) DMSO.
- P-aminobenzoicacid (1×10^{-2}M): was prepared by dissolving (0.137 gm) of it in ethanol and volume is completed (100 ml) distilled water.
- 2,4-Dipyridin (1×10^{-2}M): was prepared by dissolving (0.156gm) of it in (100) ethanol.
- N-Bromo Succinimid (1×10^{-3}M): was prepared by dissolving (0.0088 gm) of it in 3ml aceton and volume is completed with distilled water.
- A Sodium hydroxide solution: was prepared by dissolving (4g) of it in (100 ml) distilled water.

Procedures

Determination of (Cef) by P-aminobenzoicacid: The optimum conditions were reached after conducting an initial test, as 1ml of the oxidizing agent with a concentration of 0.001M was added to 5ml of cefdinir at a concentration of 250 mg/ml in a 10ml capacity, then 1ml of the reagent at a concentration of 0.01M was added, then followed add 0.5 ml of sodium hydroxide at a concentration of 1M, then supplement the volume with distilled water to the mark and the maximum absorption of the product is 0.589 at laboratory temperature at 467 nm versus its photo solution, while the photo solution did not give any absorption in this region [12-15], as in figure (2):

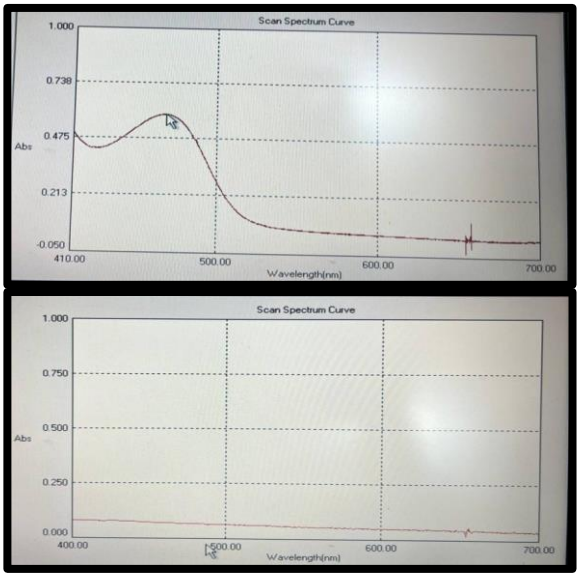


Fig. (2): Absorption spectrum of (Cef) product against blank and blank against distilled water

Application of proposed methods: The proposed approach was utilized to calculate Cef in a pharmaceutical tablet formulation. Ten tablets weighed 6.2030 g and were finely pulverized till they were turned into a fine powder. To assess Cef in a pharmaceutical preparation in the form of tablets, a weight of 0.1032 g of the preparation was collected and dissolved in 100 ml of dimethyl sulfoxide, then the solution was filtered and three concentrations were extracted from the filter. It was successful suggested methods of estimating (Cef) in various commercial tablets [16-20].

Results and Discussion

Optimal Conditions

Effect of reagent concentration: To observe how increasing amounts of reagent para-aminobenzoic acid at a concentration of 0.01 M, influenced uptake, the largest supplied volume of the reagent was 1 ml, as shown in figure (3):

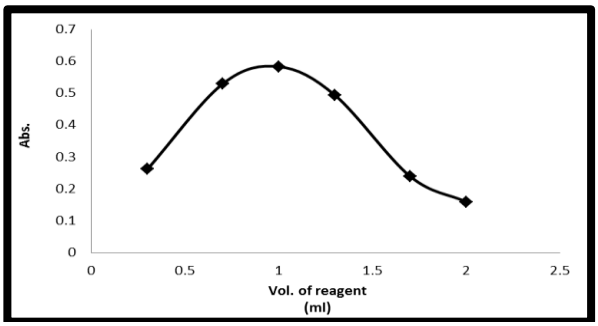


Fig. (3): Effect Vol.(ml) of P-aminobenzoicacid on (Cef) product

Effect of the use the bases different: Determine which base has the best absorption while forming the product, the bases (NaOH, NH4OH, and KOH) were employed with a concentration of 1.0M for each, as well as the same volume of 0.5ml, (table 1) reveals that the best base to produce the product is sodium hydroxide [21,22].

Table (1): Effect of different types of abse on absorption values of product

Bases	Abs.
NH_4OH	0.052
NaOH	0.589
KOH	0.506

Effect of base volume: The volume that delivers the maximum absorption was determined by adding increasing volumes of NaOH at a concentration of 1.0 molar, with the optimal volume added from the base being 0.5 m [23-26], is shown in (Fig. 4).

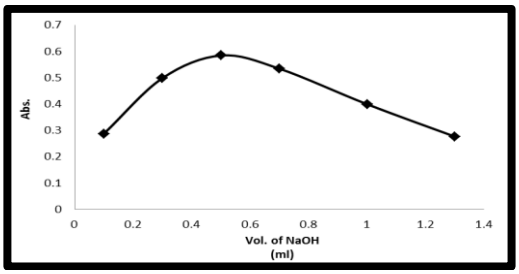


Fig. (4): Effect of Vol. (ml) of NaOH on the absorption values of the product

Effect of Time: The effect of product stability was investigated for its significance in determining the period of time during which it remains constant, as well as the interaction that time was followed using optimum conditions every ten minutes for 30 minutes,t he stability of the absorption values at max is shown in (Table 2).

Table (2): Effect of Time of the product

Abs.	Tim(min)
0.582	5
0.585	10
0.589	15
0.587	20
0.585	25
0.584	30
0.581	35
0.578	40
0.572	45

Effect of the type of oxidizing agent: Several oxidizing agents were used, including potassium iodate KIO3, sodium iodate NaIO3, and N-bromosuccinamide at a concentration of 0.001 molar for each of them, and the absorption value was for

the product formed only using NBS reagent, while in the rest of the oxidizing agents the sample and the mock solution were the same color (that is, there is no absorption).

Effect of oxidizing agent volume: Increasing volume of the oxidizing agent was used with a concentration of 0.001 molar to find out the volume that gives the highest absorption, and the results are shown in Figure (5), as it was found that the best volume of acid added is (1ml)

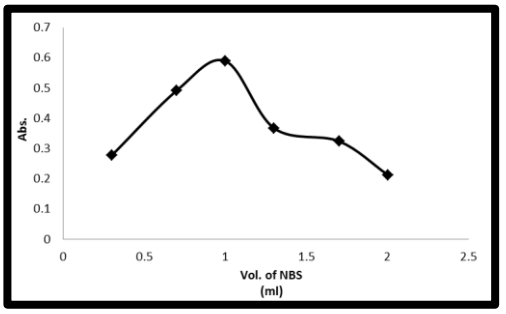


Figure (5): Effect of oxidizing agent volume

Effect of oxidation time: The time at which the drug is oxidized using the oxidizing agent NBS was studied, and before completing the rest of the additions and completing the volume in the volumetric vial, and the results are shown in Table (3) by adopting the same optimal conditions, where the time 10 minutes was sufficient to complete the oxidation process.

Table (3): Effect of oxidation time

Abs.	Tim
0.581	0.00
0.586	5
0.588	10
0.588	15
0.587	20
0.588	25
0.586	30

Effect of Additives: The influence of additives on the product's composition was investigated, but no effect was found, as indicated in the graph, as in table (4).

Table (4): Effect of Additives

RE%	Added con. µg/ml	RE%	Added con. µg/ml	Interference
3.77	400	2.04	300	Lactose monohydrate
2.46	400	-1.85	300	Magnesium stearate
-2.72	400	1.66	300	Sodium lauryl sulfate

4.33	400	3.19	300	Cellulose

Calibration curve: The calibration curve for (Cef) with P-aminobenzoicacid showed the linearity at concentrations rang of (5-75) µg/ml, as show in figure (6).

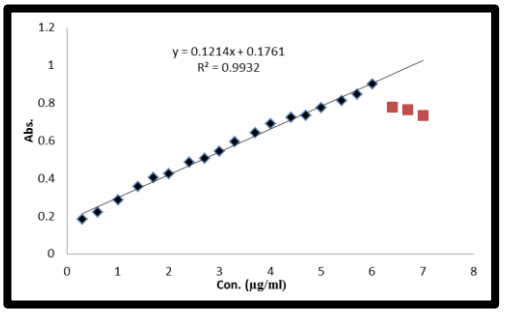


Fig. (6): Calibration curve of (Cef- P-aminobenzoicacid) product

The stoichiometry of the product: The "equivalence of the product" was studied for the interaction of Cefdinir with the reagent under optimal conditions by the molar ratio method, as the initial concentration used was 1×10^{-2}, as well as by the continuous change method at an initial concentration of 8×10^{-2}, where the ratio of equivalence between the drug and the reagent was (1:1) [27,28], (Figures.7)

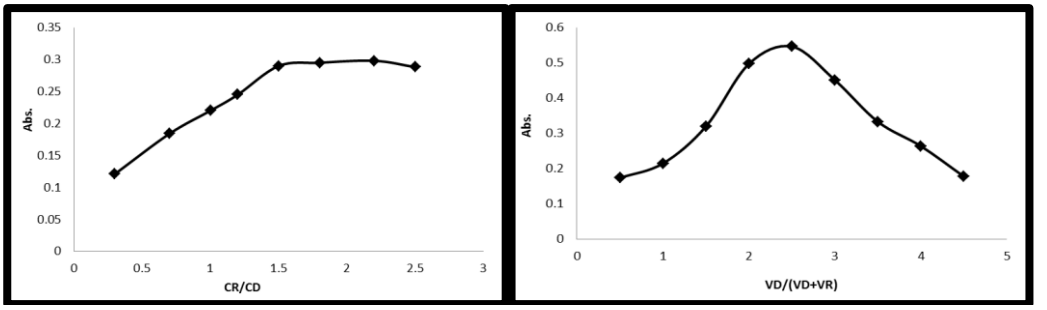
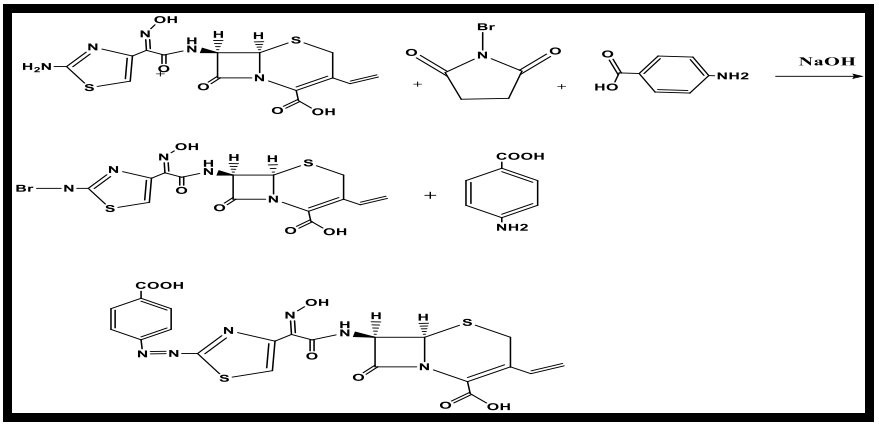


Fig. (7): Mole-ratio method of Cef and Continuous variation method of Cef

Suggested interaction: The proposed reaction can be based on a condensation reaction between Cefdinir and p-Aminobanzoicacid in a base medium to produce a dense, yellow colored product [29]



Application of the proposed methods: In table 5, the result of determination of (Cef) in the pharmaceutical preparations (as tablet)

Table (5): Determination of Cef(as tablet)

Pharmaceutical preparations	Content (µg/ml) declared	Found (µg/ml) by proposed method	%Recovery
Ceftinex	15	14.46	96.40
	30	30.52	101.73
	45	44.07	97.93

Determination of (Cef) by 2,4 Dipyridin: After conducting a preliminary test, the best conditions were determined by adding 0.5 ml of the oxidizing agent at a concentration of 0.001 M to 4 ml of cefdinir at a concentration of 250 mcg / ml in a 10ml capacity, followed by 0.5 ml of the reagent at a concentration of 0.01 M. Add 0.5 ml sodium hydroxide at a concentration of 1 mo, then top up with distilled water to achieve a maximum absorption limit of 0.851 at 472 nm in the laboratory vs the dummy solution, which did not show any absorption in this area**.**

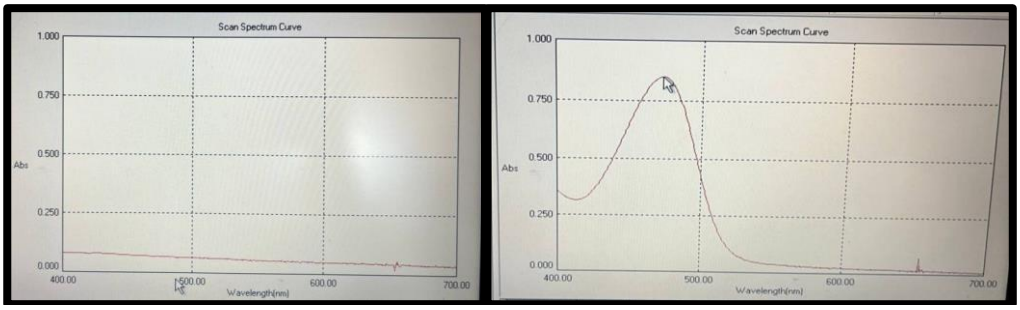


Fig. (8): Absorption spectrum of (Cef) product against blank and (Cef) product against

Study the optimal conditions for the formation of the product

Effect of the volumes of the oxidizing agent: Increased volumes of the oxidizing agent with a concentration of 0.001 molar were used to find out the volume that gives the highest absorption,as it was found that the best added volume of acid is 0.5 ml.

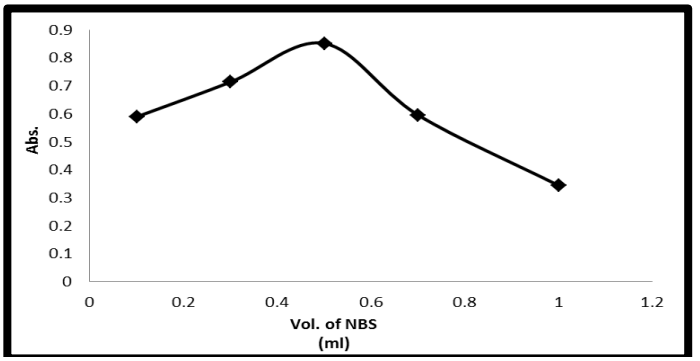


Fig. (9): Effect of Vol. (ml) of oxidizing agent on the absorption values of the product

Effect of the type of oxidizing agent: Several oxidizing agents were used, including potassium iodate KIO3, sodium iodate NaIO3, and N-bromosuccinamide, all at a concentration of 0.001 molar, and the absorption value was for the product formed only with NBS reagent, while the sample and mock solution were the same color in the other oxidizing agents (that is, there is no absorption).

Effect of base volume: The volume that delivers the maximum absorption was determined by adding increasing volumes of NaOH at a concentration of 1.0 molar, with the optimal volume added from the base being 0.5 m.

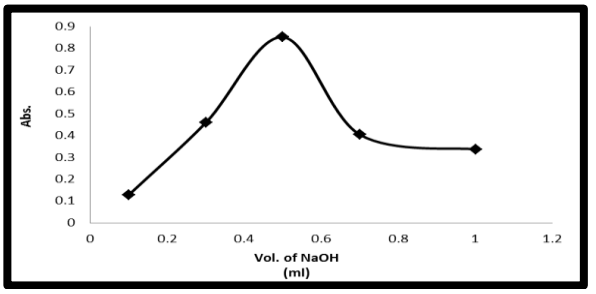


Fig. (10): Effect of vol. (ml) of NaOH on the absorption values

Effect of the used different bases: The bases of NH4OH, KOH, NaOH with a concentration of 1.0M each of them, as well as the same added volume of 0.5 ml, were used to find out which base gives the best absorption when forming a total, as it was found that the best M base is NaOH, and it is shown in Table (6)

Table (6): Effect of the used different bases

Bases	Abs.
NH_4OH	0.032

NaOH	0.853
KOH	0.802

Effect of reagent volume: Increasing volumes of 2,4dipyridine were added at a concentration of 0.01 molar, to know the extent of its effect on the absorption of the product,as it is noted that the best added volume of the reagent is 0.5 ml

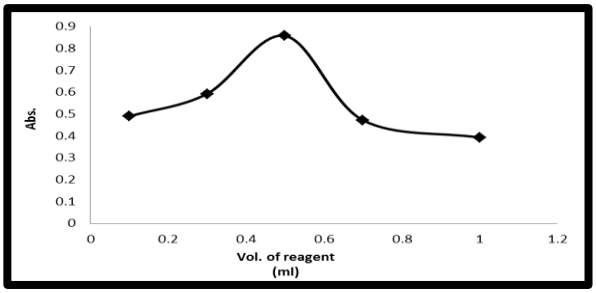


Fig. (11): Effect of reagent volumes

Effect of Time: The effect of product stability was investigated for its significance in determining the period of time during which it remains constant, as well as the interaction that time was followed using optimum conditions every ten minutes for 30 minutes.

Table (7): Effect of time on stability of product

Abs.	Tim (min)
0.849	5
0.850	10
0.850	15
0.851	20
0.851	25
0.850	30
0.842	35
0.839	40
0.836	45

Effect of oxidation time: The time at which the drug is oxidized using the oxidizing agent NBS was studied, and before completing the rest of the additions and completing the volume in the volumetric vial, and the results are shown in Table (8), depending on the same optimal conditions, where the time 10 minutes was sufficient to complete the oxidation process.

Table (8): Effect of oxidation time

Abs.	Tim (min)
0.848	0.00
0.850	5
0.851	10
0.852	15

0.851	20
0.850	25
0.851	30

Effect of Additives: The effect of additives on the composition of the product between (Cef) with reagent was studied, and not observed any effect, shown in the table (9).

Table (9): Effect of Additives

RE%	Added con. µg/ml	RE%	Added con. µg/ml	Interference
-0.59	160	-0.12	80	Lactose monohydrate
3.53	160	3.94	80	Magnesium stearate
-3.82	160	-2.29	80	Sodium lauryl sulfate
-3.63	160	-3.64	80	Cellulose

Calibration curve: The calibration curve for (Cef) pure form with 2,4 Dipyridin showed the linearity at concentration rang of (2-60) µg/ml, as shown in figure (12).

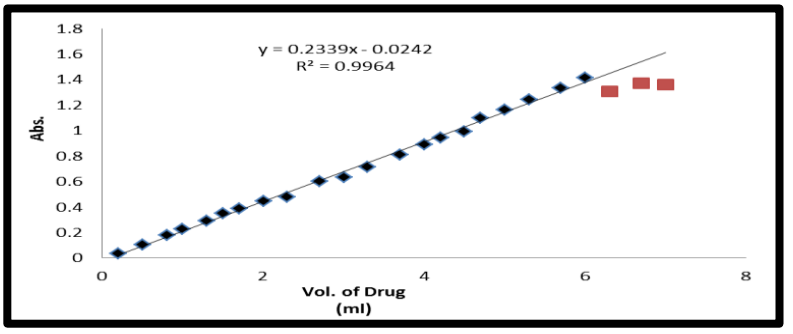


Fig. (12): Calibration curve of (Cef-2,4 Dipyridin) product

Application of the proposed method: In table (10), the result of determination of (Cef) in the pharmaceutical preparations (as tablets).

Table (10): Determination of Cef(as tablet)

Pharmaceutical preparations	Content (µg/ml) declared	Found (µg/ml) by proposed method	Rec.%
Ceftinex	20	20.55	102.75
	42.5	42.06	98.96
	75	74.98	99.97

Equivalence of the generated product: Under the optimum conditions, "the stoichiometry" of the reactions between (Cef), with reagent were studied by mole–ratio (upon initial concentration 1×10^{-2}M), and continuous variation (upon initial

concentration 8×10^{-2}M) methods. The equivalence between reagent and this drug was1:1, (Figures. 16, 17).

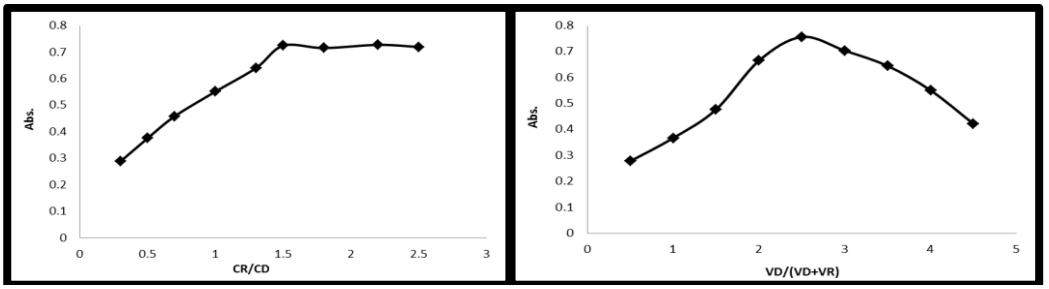
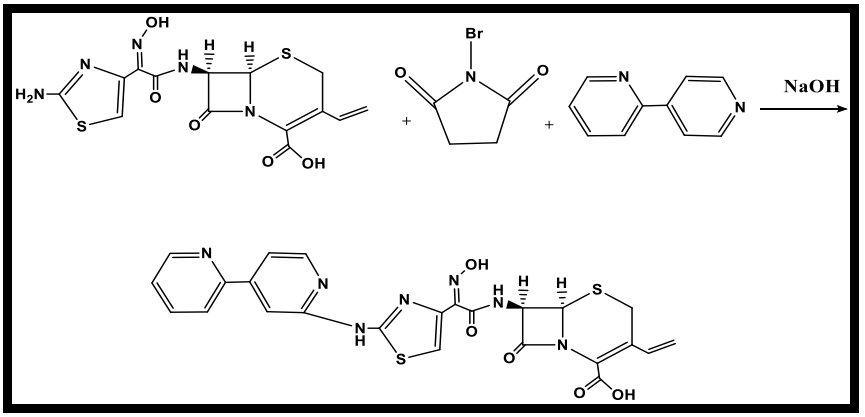


Fig. (13): Mole-ratio method of Cef and Continuous variation method of Cef

Suggested interaction: The proposed reaction can be based on a condensation reaction between Cefdinir and 2,4-Dipyridin in an alkaline medium to generate a bright golden yellow colored product [30].



Conclusion

These methods described here are simple, rapid, convent and do not require special working conditions unlike many other reported methods. The procedures showed shorter reaction time, stable colored species with inexpensive reagents. The determination can be performed at room temperature and do not require heating step. The proposed methods can be applied to determination of Cef in pharmaceutical preparation.

References

1. BALI, Dina E., et al. Nanographene oxide for enhanced dissolution rate and antibacterial activity of cefdinir. Journal of Drug Delivery Science and Technology, 2021, 62: 102411.
2. Salih, B. D., Dalaf, A. H., Alheety, M. A., Rashed, W. M., & Abdullah, I. Q. (2021). Biological activity and laser efficacy of new Co (II), Ni (II), Cu (II), Mn (II) and Zn (II) complexes with phthalic anhydride. *Materials Today: Proceedings*, 43, 869-874.

3. Patil, Omkar A., et al. "Formulation optimization and evaluation of Cefdinir nanosuspension using 23 Factorial design." Marmara Pharm J 22.4 (2018): 587-98.
4. Aftan, M. M., Talloh, A. A., Dalaf, A. H., & Salih, H. K. (2021). Impact para position on rho value and rate constant and study of liquid crystalline behavior of azo compounds. *Materials Today: Proceedings*.
5. Hassouna, Mohamed EM, and Mahmoud A. Mohamed. "Application of Lean Six Sigma Methodologies and In-Vitro Dissolution Studies for Simultaneous Determination of Cefdinir and Sodium Benzoate by RP-HPLC and UPLC Methods in their Dosage Forms." Biomed J Sci & Tech Res 16 (2019): 1-13.
6. Dalaf, A. H., Jumaa, F. H., Aftana, M. M., Salih, H. K., & Abd, I. Q. (2022). Synthesis, Characterization, Biological Evaluation, and Assessment Laser Efficacy for New Derivatives of Tetrazole. In *Key Engineering Materials* (Vol. 911, pp. 33-39). Trans Tech Publications Ltd.
7. Morina, Deniz, et al. "Oral tablet formulations containing cyclodextrin complexes of poorly water soluble cefdinir to enhance its bioavailability." Journal of Drug Delivery Science and Technology 57 (2020): 101742.
8. Salwa, A. J., Ali, L. H., Adil, H. D., Hossam, S. A. (2020). Synthesis and Characterization of Azetidine and Oxazepine Compounds Using Ethyl-4-((4-Bromo Benzylidene) Amino) Benzoate as Precursor and Evalution of Their Biological Activity. *Journal of Education and Scientific Studies*, ISSN: 24134732. 16(5): 39-52.
9. Bryant, Maria C., L. Terry Spencer, and Ali Yalcindag. "A case of ANCA-associated vasculitis in a 16-year-old female following SARS-COV-2 infection and a systematic review of the literature." (2022).
10. Yass, I. A., Aftan, M. M., Dalaf, A. H., & Jumaa, F. H. (Nov. 2020). Synthesis and Identification of New Derivatives of Bis-1,3-Oxazepene and 1,3-Diazepine and Assess the Biological and Laser Efficacy for Them. *The Second International & The Fourth Scientific Conference of College of Science – Tikrit University*. (P4): 77-87.
11. Bryant, Maria C., L. Terry Spencer, and Ali Yalcindag. "A case of ANCA-associated vasculitis in a 16-year-old female following SARS-COV-2 infection and a systematic review of the literature." (2022).
12. Dalaf, A. H., Jumaa, F. H., & Salih, H. K. (2021). Preparation, Characterization, Biological Evaluation and Assess Laser Efficacy for New Derivatives of Imidazolidin-4-one. *International Research Journal of Multidisciplinary Technovation*, 3(4), 41-51.
13. S.C. Sweetman, Martindale: The complete drug reference, 36th ed., Vol. A. The Pharmaceutical Press, 2009: 223-224.
14. Dalaf, A. H., Jumaa, F. H., & Salih, H. K. (2021). *MULTIDISCIPLINARY TECHNOVATION*. *Red*, *15*(A2), C44H36N10O8.
15. Makii, Jason M., Jessica Traeger, and Justin Delic. "Antimicrobial prophylaxis." Essentials of Evidence-Based Practice of Neuroanesthesia and Neurocritical Care. Academic Press, 2022. 77-88.
16. Saleh, R. H., Rashid, W. M., Dalaf, A. H., Al-Badrany, K. A., & Mohammed, O. A. (2020). Synthesis of Some New Thiazolidinone Compounds Derived from Schiff Bases Compounds and Evaluation of Their Laser and Biological Efficacy. *Ann Trop & Public Health*, 23(7): 1012-1031.

17. Al Haboob, Ali Abdu N. "Cefixime-induced hepatotoxicity and acute renal failure: A case report." European Journal of Medical Case Reports 2.2 (2018): 55-58.
18. Aftan, M. M., Jabbar, M. Q., Dalaf, A. H., & Salih, H. K. (2021). Application of biological activity of oxazepine and 2-azetidinone compounds and study of their liquid crystalline behavior. *Materials Today: Proceedings*, 43, 2040-2050.
19. Vilvanathan, Saranya. "Penicillins, Cephalosporins, and Other b-Lactam Antibiotics." Abialbon Paul Nishanthi Anandabaskar Jayanthi Mathaiyan (2021): 821.
20. Dalaf, A. H., & Jumaa, F. H. (2020). Synthesis, Identification and Assess the Biological and Laser Efficacy of New Compounds of Azetidine Derived from Benzidine. *Muthanna Journal of Pure Science (MJPS)*, 7(2):12-25.
21. L.K. Abdulrahman, A.M. AI-Abachi, M.H. AI-Qassy ((spectrophotometric micro determination of promethazine Hydrochloride in pharmaceutical dosage froms via oxidative coupling reaction with p-Aminobanzoicacid and N-Bromo Succinimid)) ,Um Salama science Journal , 2005 , 2(3): 471-476.
22. Khalaf, S. D., Ahmed, N. A. A. S., & Dalaf, A. H. (2021). Synthesis, characterization and biological evaluation (antifungal and antibacterial) of new derivatives of indole, benzotriazole and thioacetyl chloride. *Materials Today: Proceedings*. 47(17), 6201-6210.
23. T.Madrakian , A. Afkhami , L. Khalafi and M. Mohammad nejad ((spectrophotometric determination of catecholamines base on theier oxidation reaction followed by coupling with 4-Aminobanzoicacid)) , J.Braz.chem.soc. 2006, 17 (7): 1259-1265.
24. Dalaf, A. H. (2018). Synthesis and Characterization of Some Quartet and Quinary Hetero cyclic Rings Compounds by Traditional Method and Microwave Routes Method and Evaluation of Their Biological Activity. *M.Sc. Thesis, Tikrit University*, Tikrit, Iraq: 1-94 pp.
25. K.N.Prashant, K. Basavaiah and M.S. Raghu, ((Utilization of N-BromoSuccinimid as a brominating agent for the determination of sumdtriptan succinate in bulk drug and tablets)),International Journal of Analytical chemistry,2013, 2013(2): 1-11.
26. Dalaf, A. H., & Jumaa, F. H. (2018). Synthesis, Characterization of some 1,3-Oxazepane -4,7-Dione by Traditional and Microwave routes method and evaluation of their biological activity. *Al-utroha for Pure Science*. (8): 93-108.
27. Jabar, S. A., Hussein, A. L., Dalaf, A. H., & Aboud, H. S. (2020). Synthesis and Characterization of Azetidine and Oxazepine Compounds Using Ethyl-4-((4-Bromo Benzylidene) Amino) Benzoate as Precursor and Evalution of Their Biological Activity. Journal of Education and Scientific Studies, 5(16).
28. I.S. Mohammed, K. A. Nasser, A.H. Mhemeed , ((spectrophotometric determination of Bisacodyl in pure and pharmaceutical preparation via oxidative coupling organic reaction,, , Baghdad science Journal, 2017,14(1): 181-188.
29. Aftan, M. M., Toma, M. A., Dalaf, A. H., Abdullah, E. Q., & Salih, H. K. (2021). Synthesis and Characterization of New Azo Dyes Based on Thiazole and Assess the Biological and Laser Efficacy for Them and Study their Dyeing Application. *Egyptian Journal of Chemistry*, 64(6), 2903-2911.

30. Dalaf, A. H., Jumaa, F. H., & Jabbar, S. A. S. (2018). Synthesis and Characterization of some 2, 3-dihydroquinozoline and evaluation of their biological activity. *Tikrit Journal of Pure Science*, 23(8): 66-67.
31. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). Get vaccinated when it is your turn and follow the local guidelines. *International Journal of Health Sciences*, *5*(3), x-xv. https://doi.org/10.53730/ijhs.v5n3.2938
32. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). Health and treatment of diabetes mellitus. *International Journal of Health Sciences*, *5*(1), i-v. https://doi.org/10.53730/ijhs.v5n1.2864
33. Widyaningrum , I. ., Wibisono, N. ., & Kusumawati, A. H. . (2020). Effect of extraction method on antimicrobial activity against staphylococcus aureus of tapak liman (elephantopus scaber l.) leaves. *International Journal of Health & Medical Sciences*, *3*(1), 105-110. https://doi.org/10.31295/ijhms.v3n1.181