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Research Article

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Construction of fluorescence system of felodipine–tetracyanovinyl–2,2′-bipyridine complex

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Abstract: Felodipine (FEL)–tetracyanoethylene (TCNE)–2,2′-bipyridine (Bpy) complex was prepared with FEL, TCNE–Bpy and characterized by fluorescence, ultraviolet, and infrared. By exploring the concentration and dosage of Bpy, it was found that 1 mL $2 \times 10^{-3}\,\text{mol·L}^{-1}$ of Bpy had the best effect. The sequence of reagent addition was determined to be followed by FEL, then by TCNE, and then followed by Bpy. The concentration of FEL was 2.5×10^{-4} to $9.0 \times 10^{-3}\,\text{mol·L}^{-1}$, which had a good linear relationship with fluorescence intensity. The compound had good accuracy, precision, and specificity, and could be used for the determination of phelodipine content in FEL sustained-release tablets.

Keywords: felodipine, felodipine complexes, fluorescence intensity

1 Introduction

Felodipine (FEL) is a novel calcium channel antagonist in the dihydropyridinium derivative family, which can selectively dilate peripheral blood vessels and thus reduce arterial pressure and is a commonly used drug in clinical treatment of hypertension [1,2]. It has no direct effect on myocardial contractility and cardiac conduction, so it will not cause postural hypotension [3]. It is suitable for the treatment of all types of hypertension, ischemic heart disease, and heart failure [4,5]. FEL can improve exercise tolerance and reduce angina pectoris attack. It is absorbed quickly through the gastrointestinal tract and is easily metabolized into inactive metabolites by the liver after oral administration, which reduces the bioavailability. It is clinically used in the treatment of mild to moderate essential hypertension, chronic stable angina pectoris, and Pratt's angina pectoris [6].

2,2′-Bipyridine (Bpy), $C_{10}H_8N_2$, in addition to its strong affinity for most transition metal ions, the extremely strong chelation due to the arrangement of two pyridine nitrogen atoms makes it a very useful ligand for research. It is widely used in the field of pharmaceutical and chemical engineering and is often used as synthetic intermediates of pesticides and medicines [7]. Due to the strong coordination between Bpy and many metal ions, it has attracted extensive attention of scientists in many fields, such as the synthesis of enemy grass fast [8–11],preparation of catalytic materials [12–15], electroless copper plating [16–19], and supercritical extraction [20–23].

Tetracyanoethylene (TCNE) is considered to be a strong acceptor and donor of π electron due to its large conjugated system and abundant π electron, which can form effective charge delocalization. These structural characteristics determine that the compounds formed by TCNE may have unusual electromagnetic properties [24–30]. There are four cyanide groups that can coordinate with metal ions in the molecular structure of TCNE, which can coordinate with metal ions through various coordination modes to form stable metal–organic complexes. The negative ions of the TCNE^- radical have a unit negative charge and can compensate for the positive charge of the metal cations and do not need to counterbalance ions to make the complex electrically neutral. In addition, intermolecular π–π packing further enhanced the

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structural stability of the complex. Based on the above characteristics, TCNE has been widely used in the synthesis of metal–organic complexes [31–33].

In this article, a ternary compound of FEL–TCNE–Bpy was successfully constructed, which can be used to detect the content of FEL. There was no significant difference between the test method and the labeled content of FEL sustained-release tablets. Therefore, the method can be used to determine the content of non-lodipine in drugs, providing an accurate and reliable method for the detection of FEL. The method has the characteristics of simple reaction conditions, easy control, simple operation, and high sensitivity.

2 Experiment

2.1 Preparation of FEL standard solution

Weigh 38.4 mg of FEL standard, add a small amount of anhydrous ethanol to dissolve it by sonication. Fix the volume with anhydrous ethanol in a 100 mL brown volumetric flask to obtain 1.0×10^{-3} mol·L^{-1} standard solution. Store it away from light and dilute it to the desired concentration when used.

2.2 Preparation of FEL sample solution

A box of FEL extended-release tablets (National Pharmaceutical Quantifier H20030414) manufactured by AstraZeneca Pharmaceutical Co., Ltd was purchased. Five tablets (500 mg) were crushed and powdered, evenly mixed, and accurately weighed 1/10. Dissolved in anhydrous ethanol and fixed in a 100 mL brown volumetric flask. The sample solution of FEL (10 mg·L^{-1}) was obtained by filtering through a 0.45 µm microporous membrane after diluting 100 times.

2.3 Preparation of TCNE standard solution

Weigh 64 mg of TCNE standard, add a small amount of acetone to dissolve it, fix the volume in a 50 mL volumetric flask. And configure it into a standard solution of 1×10^{-3} mol·L^{-1}. Store it in a cool and dry place away from light.

2.4 Preparation of Bpy standard solution

Weigh 7.81 mg of Bpy standard, add a small amount of anhydrous ethanol to dissolve it by ultrasonication, fix the volume in a 50 mL volumetric flask, and configure the solution to a concentration of 1×10^{-3} mol·L^{-1}. Store in a cool and dry place away from light.

2.5 Preparation of FEL–TCNE–Bpy complexes

About 5 mL of ethanol FEL standard solution, 0.5 mL of TCNE solution, and 1 mL of Bpy standard solution were accurately pipetted into a 10 mL stoppered colorimetric tube. Fixed with anhydrous ethanol and shaken to make it fully react. The shock makes it fully reactive. The colorimetric tube was heated in a constant temperature water bath at 40°C for 40 min and cooled to room temperature.

3 Results and discussion

3.1 Fluorescence spectra

The fluorescence spectra of the ternary complex system are shown in Figure 1. In Figure 1, there is a weak fluorescence peak at 443 nm when only FEL–TCNE is present. After the addition of Bpy, the fluorescence emission peak of the probe was blue-shifted from 443 to 440 nm. And the fluorescence peak intensity was enhanced. It can be inferred that the fluorescence system of the probe has been successfully constructed.

3.2 UV-visible spectroscopy

The UV-visible spectrum of the complex is shown in Figure 2. Bpy has characteristic absorption near 230 and 280 nm, which is attributed to the spinor-permitted (1π–π^*) transition in ligand. The weaker absorption bands in the range of 300–400 nm are attributed to a mixture of singlet and triplet metal–ligand charge transfers, ligand–ligand charge transfers, and ligand center charge transfers (3π–π^*). This is because the transition that was originally spin-barred becomes a spin-allowed transition under the spin–orbit coupling of nitrogen atoms, resulting in a weaker absorption peak in the spectrum. FEL–TCNE–Bpy

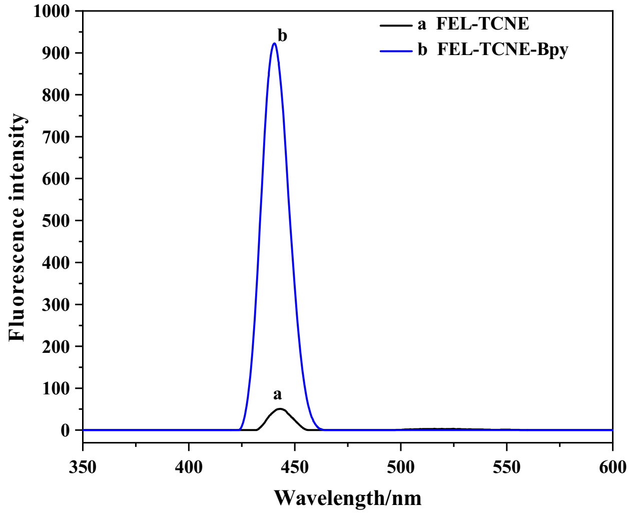

Figure 1: FEL–tetracyanovinyl fluorescence spectra of FEL–tetracyanovinyl–Bpy system UV spectrum.

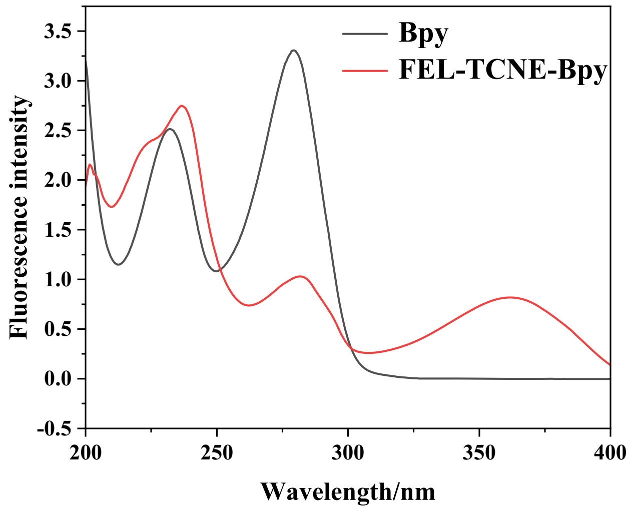

Figure 2: Ultraviolet absorption spectra of Bpy, FEL–tetracyanovinyl–Bpy.

has characteristic absorption at 235, 285, and 360 nm. Since the conjugated system increases after chelation coordination, n-electrons decrease, and π → π* transition mainly exists, resulting in redshift of the absorption peak. The 360 nm absorption peak is attributed to the charge transfer absorption between the metal and the ligand.

3.3 Infrared spectrum

The infrared spectra of the FEL–TCNE–Bpy ternary complexes are shown in Figure 3.

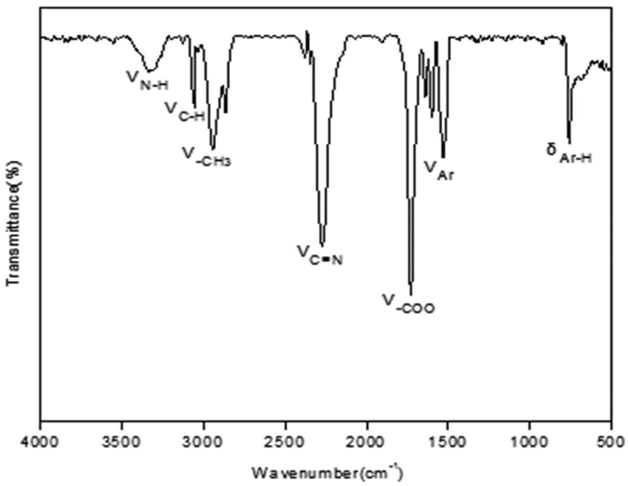

Figure 3: Infrared spectra of FEL–TCNE–Bpy ternary complex.

It can be seen from the figure that the absorption peak of the FEL–TCNE–Bpy ternary complex at 1,750 cm^{-1} is generated by ester group stretching vibration. At 2,218 cm^{-1} is the stretching vibration peak of cyanide group, 1,489 cm^{-1} is the stretching vibration peak of benzene ring. At 3,331 cm^{-1} is the stretching vibration peak of N–H bond, and at 3,050 cm^{-1} is the C–H stretching vibration. At 1,557 cm^{-1} is the stretching vibration peak of aromatic ring and 612 cm^{-1} is the out-of-plane bending vibration of aromatic hydrogen. The FEL–TCNE–Bpy ternary complex can be determined because of the characteristic peaks of each substance.

3.4 Selection of optimal experimental conditions for the system

3.4.1 Selection of Bpy concentration

Figure 4 shows the fluorescence spectrum of the FEL–TCNE reaction with different concentrations of Bpy. Bpy at concentrations of 0.5×10^{-3}, 1.0×10^{-3}, 2.0×10^{-3}, 3.0×10^{-3}, and 4.0×10^{-3} mol·L^{-1}. It can be seen from Figure 4 that the fluorescence intensity of the system gradually increases with the increase of Bpy concentration, and reached the maximum at the concentration of 2×10^{-3} mol·L^{-1}. After that, the fluorescence intensity of the system decreased with the increase in the concentration. With increasing concentration, the maximum fluorescence intensity is first shifted to red and then blue. Therefore, the optimal concentration of Bpy was determined to be 2×10^{-3} mol·L^{-1}.

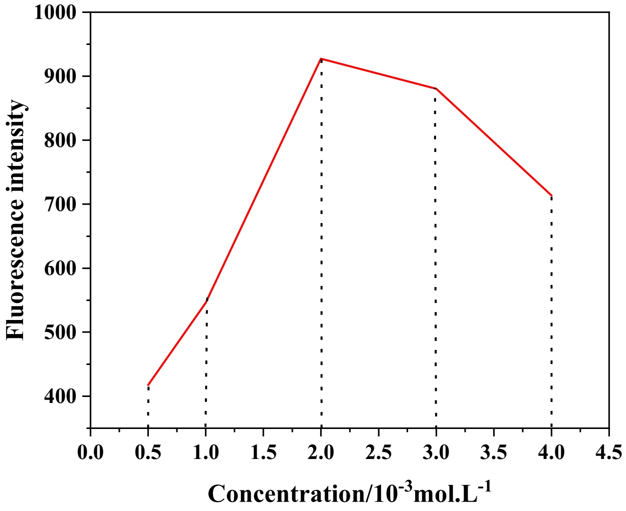

Figure 4: Effect of Bpy concentration on the maximum fluorescence intensity of the system.

3.4.2 Selection of Bpy dosage

Figure 5 shows the fluorescence spectrum of FEL–TCNE reaction with different amounts of Bpy. Configure 0.5, 1.0, 1.5, 2.0 mL of Bpy. The change in fluorescence intensity was measured by heating in a 40°C bath for 40 min. It can be seen from Figure 5 that the fluorescence intensity of the system is the strongest when the dosage of Bpy is 1 mL. Too much or too little will reduce the fluorescence intensity. So, this experiment chose the dosage of 1 mL of Bpy solution to continue the subsequent experimental research.

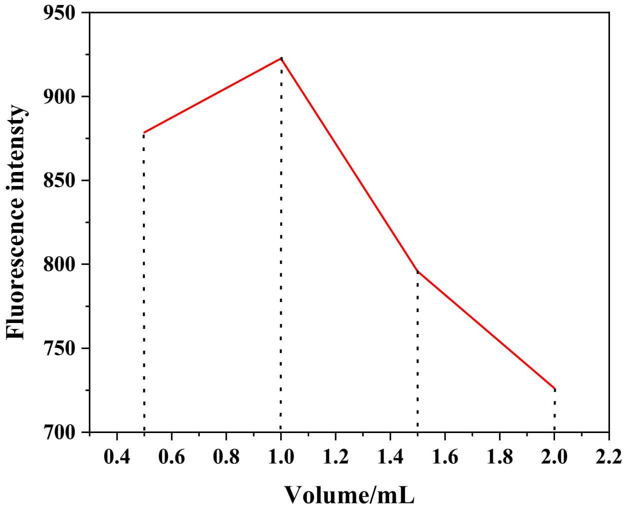

Figure 5: Effect of dosage of Bpy on maximum fluorescence intensity of system.

3.4.3 The order in which reagents are added

The effects of different reagent addition sequences on the fluorescence intensity of the system were also investigated. Using a single variable method, the FEL–TCNE–Bpy fluorescence system was separately measured with different addition orders, changes in light intensity, and the optimal order of addition of the screening reagents. The results are shown in Table 1.

As can be seen from Table 1, the fluorescence intensity of the system was maximum when the order of reagent addition was FEL–TCNE–Bpy. Therefore, in this experiment, FEL should be added first, then TCNE, and finally Bpy.

3.5 Methodological examination

3.5.1 Specificity inspection

To validate the specificity of the FEL–TCNE–Bpy probes, we performed the following study. The fluorescence profiles of the blank solvent, the fluorescence system containing the FEL standard solution, and the fluorescence system containing the same concentration of the FEL sample solution were detection separately.

According to Figure 6, it can be seen that blank solvent has no interference with the main peak of the system, and impurities do not interfere with the determination of FEL. It is proved that the complex has good specificity.

3.5.2 Linear relationship

The standard working curve of FEL was determined under other suitable conditions and constant experimental conditions. As can be seen from Figure 7, the fluorescence intensity of the system increased with the increase of

Table 1: Effect of adding different reagent sequence on fluorescence intensity of system

Number	First addition	Second addition	Third addition	Fluorescence intensity
1	TCNE	FEL	Bpy	941
2	TCNE	Bpy	FEL	940
3	FEL	Bpy	TCNE	945
4	FEL	TCNE	Bpy	952
5	Bpy	FEL	TCNE	930
6	Bpy	TCNE	FEL	924

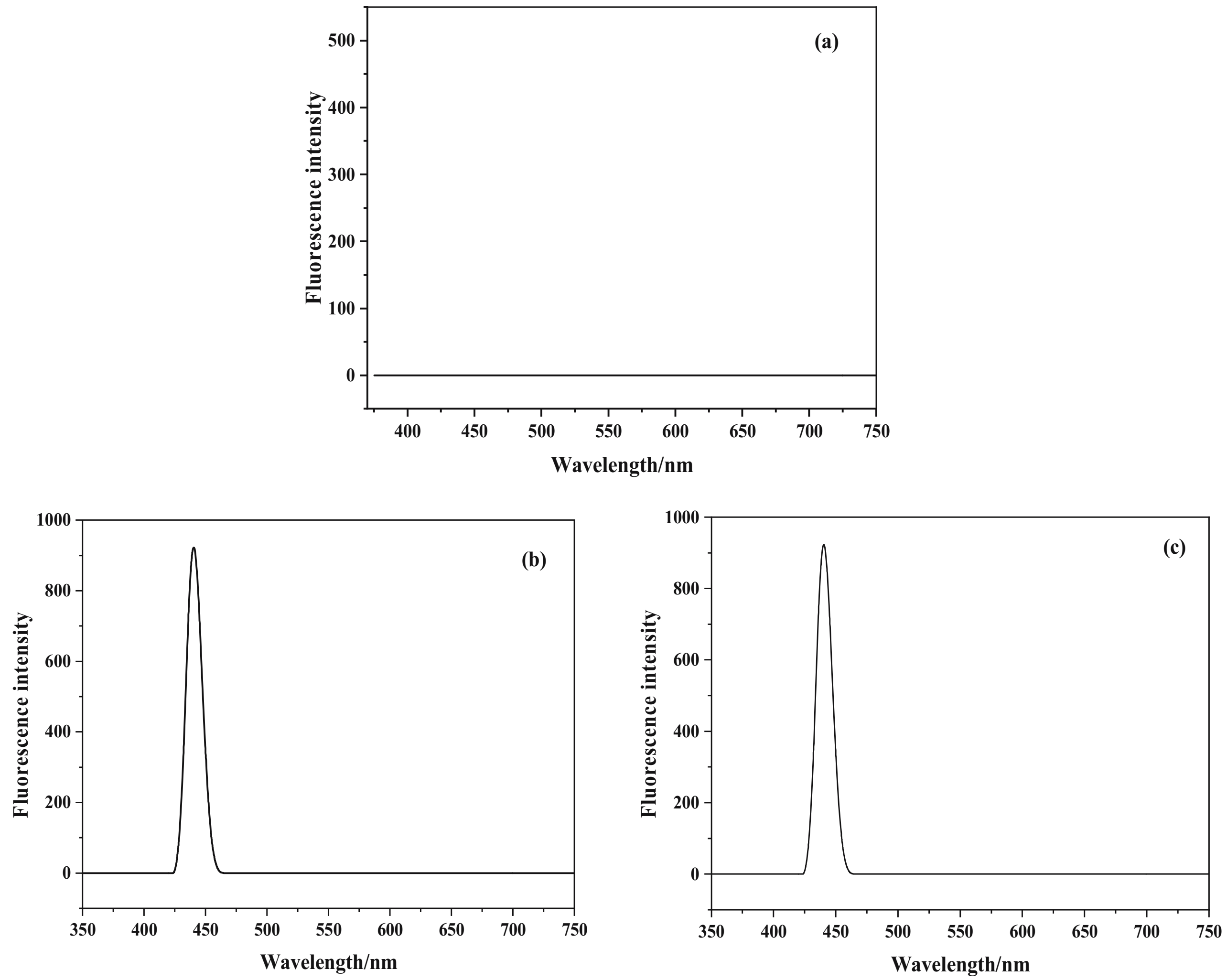

Figure 6: (a) Fluorescence map of blank solution, (b) fluorescence system containing standard FEL solution, and (c) fluorescence system containing sample FEL solution.

FEL concentration. The standard curve was drawn with fluorescence intensity as the ordinate and FEL concentration as the abscissa. In a certain range, the fluorescence intensity of the system has a good linear relationship with FEL concentration. The regression equation is

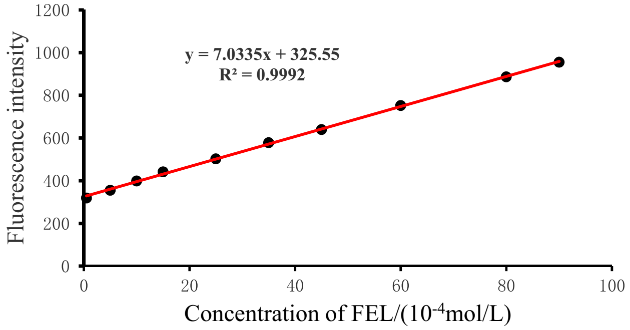

Figure 7: Standard curve of FEL concentration and fluorescence intensity.

Table 2: Precision test results of probe detection of FEL

Number of measurements	ΔF ($F - F_0$)	ΔF average value	RSD (%)
1	956.72		
2	947.61		
3	954.15	949.15	0.66
4	941.12		
5	946.14		

Table 3: Experimental results on the accuracy of probe detection of FEL

Concentration (10^{-3} mol·L^{-1})	Recovery mean ± SD (%)	RSD (%)
0.2	98.32 ± 1.76	1.79
1.0	101.19 ± 2.01	1.99
2.0	99.43 ± 1.32	1.33

Table 4: Determination of FEL sample and comparison with labeled quantity

Number	Sample measurement (mg·L^{-1})	Average measured value mean ± SD (mg·L^{-1})	Marking amount (mg·L^{-1})	RSD (%)
1	100.13, 98.81, 97.12, 96.79	98.21 ± 1.55	100	1.58
2	99.82, 97.88, 99.11, 100.43	99.31 ± 1.10	100	1.11

$$y = 9.8401x + 43.678, R^2 = 0.9976 \quad (1)$$

and the linear range is 2.5×10^{-4} to 9.0×10^{-3} mol·L^{-1}. It is proved that the ternary complex of FEL–tetracyanovinyl–Bpy can be used for the determination of FEL.

3.5.3 Degree of precision

Table 2 shows the precision experiment of the constructed FEL fluorescence system. Five groups of complexes of equal volume and concentration are configured. Add 1 mL of FEL solution with a concentration of 1×10^{-3} mol·L^{-1} to all of them, and measure 5 min later. In the table, F is the fluorescence value of the solution after the complex is fully combined with FEL, F_0 is the fluorescence value of the blank solution of the complex, and ΔF is the difference between F and F_0. Fluorescence intensity at 435 nm was recorded and the relative standard deviation RSD = 0.66% was calculated. Experimental data show that the complex measurement of FEL detection method error is small and can be used.

3.5.4 Accuracy

Table 3 shows the experimental results of the accuracy of this complex in measuring FEL. Three concentrations of 0.2×10^{-3}, 1×10^{-3}, and 2×10^{-3} mol·L^{-1} complexes of the same volume were selected, respectively, to determine the content of 1×10^{-3} mol·L^{-1} FEL. Fluorescence intensity at 435 nm was recorded and recovery rate and RSD were calculated to test the accuracy of FEL measurement. The recovery rate was 98.32 ± 1.76, 101.19 ± 2.01, 99.43 ± 1.32. RSDs were calculated to be 1.79%, 1.99%, and 1.33%, respectively, and RSDs were all less than 2%, indicating that the fluorescence detection accuracy of the constructed system was good.

3.6 Sample content determination

Table 4 shows the determination of phelodipine content in FEL sustained-release tablets. After fluorescence test and linear analysis, the content determination results were as follows: the detection amount of sample 1 was 100.13, 98.81, 97.12, 96.79 mg·L^{-1}, respectively, and the average detection amount was 98.21 mg·L^{-1}. The detection amount of sample 2 was 99.82, 97.88, 99.11, 100.43 mol·L^{-1}, respectively, and the average detection amount was 99.31 mg·L^{-1}. The RSD is less than 2%. The results indicated that the complex could be used for the determination of phelodipine in FEL sustained-release tablets.

4 Conclusion

In conclusion, this article successfully prepared the FEL–TCNE–Bpy ternary complex, which significantly enhanced the fluorescence intensity of the ternary complex. The concentration and dosage of Bpy, the order of adding reagents were investigated. The specificity, precision, and accuracy of the complex were also investigated. The detection of FEL has a good linear relationship at 2.5×10^{-4} to 9.0×10^{-3} mol·L^{-1}. It can be used for the determination of FEL. It provides an accurate and reliable method for the detection of FEL. The method has the characteristics of simple reaction condition, easy control, simple operation, and high sensitivity.

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Kuilin Lv: conceptualization, funding acquisition, writing – review and editing, supervision, project administration.

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References

[1] Yuqiu Z, Shengrong G. Development of felodipine sustained-release tablets and their in vitro release studies. J Pharm Pract. 2011;29(2):101–8.
[2] Na Z, Liju Y, Jie L. Felodipine and its tablet journal study. J Pharm. 2012;47(2):223–8.
[3] Xinqian C, Youyu J, Guang T. New pharmacology. 15th edn. Beijing: People's Health Press; 2003. p. 324–83.
[4] Chatki PK, Tabassum S. Analytical methods of dihydropyridines based calcium channel blockers – amlodipine, lacidipine, isradipine, nifedipine, felodipine, cilnidipine and its related formulations: a review. Asian J Res Chem. 2021;14(3):221–34.
[5] Zhang Y, Wu J, Liu F, Wang C, Cheng Y, Lv Y. Study on the determination of felodipine sample content by fluorescence method and its application. E3S Web of Conferences. Vol. 257. EDP Sciences; 2021. p. 02094.
[6] Yan L, Jin S, Zhonggui H. Dissolution of fibrodipine tablets in different media. Chin J Pharm. 2009;7(6):425–30.
[7] He WY, Fontmorin JM, Hapiot P, Soutrel I, Floner D, Fourcade F, et al. A new bipyridyl cobalt complex for reductive dechlorination of pesticides. Electrochim Acta. 2016;207:313–20.
[8] Dichiara AB, Harlander SF, Rogers RE. Fixed bed adsorption of diquat dibromide from aqueous solution using carbon nanotubes. RSC Adv. 2015;5(76):61508–12.
[9] Song GX, Tang Q, Huang Y, Wang R, Xi YY, Ni XL, et al. A host–guest complexation based fluorescent probe for the detection of paraquat and diquat herbicides in aqueous solutions. RSC Adv. 2015;5(121):100316–21.
[10] Tsao YC, Lai YC, Liu HC, Liu RH, Lin DL. Simultaneous determination and quantitation of paraquat, diquat, glufosinate and glyphosate in postmortem blood and urine by LC–MS–MS. J Anal Toxicol. 2016;40(6):427–36.
[11] Pizzutti IR, Vela GM, de Kok A, Scholten JM, Dias JV, Cardoso CD, et al. Determination of paraquat and diquat: LC–MS method optimization and validation. Food Chem. 2016;209:248–55.
[12] Bilyachenko AN, Khrustalev VN, Zubavichus YV, Shul'pina LS, Kulakova AN, Bantreil X, et al. Heptanuclear Fe_5Cu_2 phenylgermses-quioxane containing 2,2′-bipyridine: synthesis, structure, and catalytic activity in oxidation of C–H compounds. Inorg Chem. 2018;57(1):528–34.
[13] Fomenko I, Gushchin A, Abramov P, Sokolov M, Shul'pina L, Ikonnikov N, et al. New oxidovanadium (IV) complexes with 2,2′-bipyridine and 1,10-phenathroline ligands: synthesis, structure and high catalytic activity in oxidations of alkanes and alcohols with peroxides. Catalysts. 2019;9(3):217.
[14] Chen H, Kuranari S, Matsuoka M, Zhang J, Anpo M. Synthesis of the Ag^+–bipyridine complexes anchored within MCM-41 and their photocatalytic reactivity for N_2O reduction with CO. Catal Lett. 2008;126(3–4):218–23.
[15] Himeda Y. Highly efficient hydrogen evolution by decomposition of formic acid using an iridium catalyst with 4,4′-dihydroxy-2,2′-bipyridine. Green Chem. 2009;11(12):2018–22.
[16] Liu Q, Xu R, He S. Electrochemical properties of electroless copper plating solution. Chin J Process Eng. 2016;1:20–289.
[17] Chen W, Luo G, Li M, Shen Q, Wang C, Zhang L. Effect of 2,2′-dipyridyl on the plating rate, microstructure and performance of copper-coated tungsten composite powders prepared using electroless plating. Appl Surf Sci. 2014;301:85–90.
[18] Zhai L, Liu X, Li T, Feng Z, Fan Z. Vacuum and ultrasonic co-assisted electroless copper plating on carbon foams. Vacuum. 2015;114:21–5.
[19] Kondo K, Kojima K, Ishida N, Irie M. Effects of 2,2′-dipyridyl on electroless copper deposition in the presence of excess triethanolamine. J Electrochem Soc. 1993;140(6):1598–601.
[20] Onishi N, Iguchi M, Yang X, Kanega R, Kawanami H, Xu Q, et al. Development of effective catalysts for hydrogen storage technology using formic acid. Adv Energy Mater. 2019;9(23):1801275.
[21] Ghoreishi SM, Hedayati A, Ansari K. Experimental investigation and optimization of supercritical carbon dioxide extraction of toxic heavy metals from solid waste using different modifiers and chelating agents. J Supercrit Fluids. 2016;117:131–7.
[22] Bai Y, Yang HJ, Quan C, Guo CY. Solubilities of 2,2′-bipyridine and 4,4′-dimethyl-2,2′ bipyridine in supercritical carbon dioxide. J Chem Eng Data. 2007;52(5):2074–6.
[23] Bai Y, Yang HJ. Metal ion extraction using newly-synthesized bipyridine derivative as a chelating reagent in supercritical CO_2. Anal Sci. 2006;22(11):1469–71.
[24] Gisselbrecht JP, Moonen NNP, Boudon C, Nielsen MB, Diederich F, Gross M. Redox properties of linear and cyclic scaffolds based on di- and tetraethynylethene. Eur J Org Chem. 2004;2004:2959–72.
[25] Lü JM, Rosokha SV, Kochi JK. Stable (long-bonded) dimers via the quantitative self-association of different cationic, anionic, and uncharged π-radicals: structures, energetics, and optical transitions. J Am Chem Soc. 2003;125:12161–71.
[26] Oshima T, Kitamura H, Higashi T, Kokubo K, Seike N. Kinetic substituent and solvent effects in 1,3-dipolar cycloaddition of diphenyldiazomethanes with fullerenes C60 and C70: a comparison with the addition to TCNE, DDQ, and chloranil. J Org Chem. 2006;71:2995–3000.
[27] Urbaniak M, lwanek W. Complexation of crown and diamond conformers of octamethoxyr-esorc[4]arene with strong electron acceptors. Tetrahedron. 1999;55:14459–66.
[28] Miller JS, Novoa JJ. Four-center carbon–carbon bonding. Acc Chem Res. 2007;40:189–96.
[29] Sein LT, Jr, Wei Y, Jansen SA. Trimeric anilines as both donors and acceptors: an experimental and computational study. Synth Met. 2000;108:101–6.
[30] Liao MS, Lu Y, Parker VD, Scheiner S. DFT calculations and spectral measurements of charge-transfer complexes formed by aromatic amines and nitrogen heterocycles with tetracyano-ethylene and chloranil. J Phys Chem A. 2003;107:8939–48.

[31] Lin CN, Ren ST, Ye LP, Chen CH, Zhan SZ. Synthesis and electrocatalytic properties of a nickel (II) complex supported by bis (diphenylphosphino) methane. Inorg Chem Commun. 2016;69:24–7.

[32] Her JH, Stephens PW, Pokhodnya KI, Bonner M, Miller JS. Cross-linked layered structure of magnetically ordered [Fe $(TCNE)_2]_2CH_2Cl_2$ determined by Rietveld refinement of synchrotron powder diffraction data. Angew Chem. 2007;119(9):1543–6.

[33] Tang LZ, Lin CN, Zhan SZ, Xie XH. Synthesis and properties of an unexpected trinuclear copper (I)complex supported by diphenylphosphinomethane. Inorg Chem Commun. 2016;69:16–9.