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Articles

Study on the Inclusion Behavior of Sulfobutylether-β-Cyclodextrin with Perphenazine by Flow Injection Chemiluminescence

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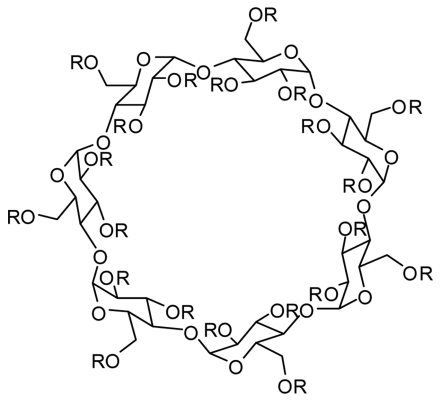
The inclusion behavior of sulfobutylether-β-cyclodextrin (SBE-β-CD) with perphenazine (PPH) was first studied by flow injection (FI)-chemiluminescence (CL) analysis with proposed $\lg[(I_0 - I_s)/I_s] = \lg K_{P\text{-}CD} + n\lg[C_{PPH}]$ model and molecular docking. Results showed that a 1:1 complex of SBE-β-CD/PPH could online form, with the formation constant $K_{P\text{-}CD}$ of 2.57×10^7 L mol^{-1} at 298 K. The thermodynamic parameters showed that the inclusion behavior of SBE-β-CD/PPH was a spontaneous process by hydrophobic interaction. The molecular docking results revealed PPH entered into the larger cavity of SBE-β-CD with two hydrogen bonds. Based on the linear relationship of the decrement of luminol/SBE-β-CD/PPH CL intensity against the logarithm of PPH concentration ranging from 0.03 to 30.0 ng mL^{-1}, the present FI-CL analysis using luminol/SBE-β-CD/PPH system was successfully applied to PPH determination in biological fluids and tablets with recoveries from 94.5 to 105.6% and RSDs less than 2.6% (n = 5).

Key Words : Inclusion behavior, Perphenazine, SBE-β-CD, Chemiluminescence, Flow injection

Introduction

Sulfobutylether-β-cyclodextrin (SBE-β-CD, Scheme 1), which possesses an extended hydrophobic cavity and an extremely hydrophilic exterior surface, is a negatively charged derivative of β-CD with the secondary hydroxyls substituted by SBE groups on the wide rim of β-CD.[1] SBE-β-CD, in terms of the advantages including higher aqueous solubility and less renal toxicity,[2,3] has been widely used as a pharmaceutical excipient for various poorly soluble drugs[4-6] to enhance their solubilities. The formation of inclusion complex between SBE-β-CD and small molecule drug is of great interest in different science fields. Due to relative non-polarity of the internal cavity, SBE-β-CD as a host can accommodate hydrophobic molecules of various sizes as guests, such as 2-(2-nitrovinyl) furan (G-0),[7] repaglinide,[8] α-lipoic acid,[9] voriconazole,[10] rutin,[11] chenodeoxycholate,[12] and flavonoids.[13] However, the inclusion behavior of SBE-β-CD with perphenazine (PPH) has not been described so far.



Scheme 1. The structure of SBE-β-CD sodium salt form (Captisol).

PPH, one of the piperazinyl phenothiazine derivatives, has been used in therapeutics as an antipsychotic agent to decrease restlessness, aggressiveness and impulsive behavior.[14,15] It has been reported that luminol can enter into the narrow neutral rim of SBE-β-CD and form a 1:1 complex online, which could accelerate the electrons transferring rate of excited 3-aminophthalate, leading to an augment of chemiluminescence (CL) intensity from luminol.[16] In this present work, based on the inhibitory effect of PPH on luminol/SBE-β-CD reaction, by the modified flow injection (FI)-CL model, $\lg[(I_0 - I_s)/I_s] = \lg K_{P\text{-}CD} + n\lg[C_{PPH}]$,[17] the formation constant $K_{P\text{-}CD}$ of SBE-β-CD with PPH (at 10^6-10^8 L mol^{-1} level) and the stoichiometric ratio (1:1) of SBE-β-CD/PPH were obtained. According to the thermodynamic parameters (ΔH, ΔS and ΔG) obtained, it was showed that the inclusion behavior of SBE-β-CD/PPH was a spontaneous process *via* hydrophobic force. The experimental results were confirmed by molecular docking, showing that PPH entered into the larger cavity of SBE-β-CD forming a 1:1 complex by hydrophobic force with two hydrogen bonds.

Table 1. Comparison of different methods for PPH determination

Methods	Linear ranges (ng mL^{-1})	LODs (ng mL^{-1})	Samples	Refs
UV-Vis	50-25000	49	Tablets, human serum	19
GC-MS	2-64	2	Rabbit plasma	20
EC	0.4-1212	0.13	Human urine	23
HPLC	2-500	4	Sheep plasma	27
CZE	40-40397	20	Human urine	28
FI-CL	3-2000	3	Pharmaceuticals, human serum	29
Proposed method	0.03-30	0.01	Tablets, human serum and urine	This work

At a flow rate of 2.0 mL min^{-1}, the whole analysis procedure including sampling and washing could be accomplished in 36 s. The proposed procedure was successfully applied to PPH determination in biological fluids and tablets with recoveries from 94.5 to 105.6% and RSDs less than 2.6% (n = 5). Many methods have been successfully applied to the determination of PPH in pharmaceuticals and biological fluids. A comparison of previously reported methods, including UV-Vis,[18,19] GC-MS,[20,21] titrimetry,[22] electrochemistry (EC),[23-25] HPLC,[26,27] capillary zone electrophoresis (CZE),[28] CL,[29,30] and the presented FI-CL for PPH determination was summarized in Table 1. As shown in Table 1, it can be seen that the limit of detection (LOD) of the reported methods and proposed FI-CL method was 49, 2, 0.13, 4, 20, 3 and 0.01 ng mL^{-1}, respectively, showing that the LOD of this proposed method was at least one magnitude lower than other methods.

Experimental

Reagents. All reagents used were of at least analytical reagent grade, and deionized water was passed through a Milli-Q system (Millipore, Bedford, MA, USA) before usage. Luminol (Fluka, Biochemika) was obtained from Xi'an Medicine Purchasing and Supply Station, China. SBE-β-CD (average total degree of substitution was seven, the SBE substituent groups mainly existed on the secondary rim on C2, C3 of the D-glucopyranose units) was purchased from Zibo Qianhui Fine Chemical Co., LTD, China. PPH was supplied by Material Evidence Identifying Center of Xi'an Public Security Bureau, China.

Luminol (2.5×10^{-2} mol L^{-1}) was prepared by dissolving 0.44 g luminol in 100 mL of 0.1 mol L^{-1} NaOH solution in a brown calibrated flask. The stock solution of SBE-β-CD (1 mmol L^{-1}) was prepared by dissolving 96.25 mg SBE-β-CD in 500 mL purified water. A stock solution of PPH (0.60 mg mL^{-1}) was prepared by dissolving PPH in ethanol-water solution (1:4, v/v) and stored at 4 °C. All working standard solutions of PPH were prepared daily from the above stock solution by appropriate dilution as required.

Apparatus. The FI-CL system used in this work was shown schematically in Figure 1. The flow system consisted four lines of luminol/NaOH, carrier (deionized water), SBE-β-CD and sample solution. A peristaltic pump of the IFFL-DD Luminescence Analyzer (Xi'an Remax Analysis Instrument Co. Ltd., Xi'an, China) was applied to deliver all streams. Poly Tetra Fluoro Ethylene (PTFE) tubing (1.0 mm i.d.) was used throughout the manifold for carrying the CL reagents. A six-way valve with a loop of 100.0 μL was used for quantitatively injecting luminol into carrier stream. The CL signal produced in flow cell was detected without wavelength discrimination, and the photomultiplier tube (PMT) output was recorded by PC with an IFFL-DD client system. A UV-2500 spectrophotometer (Shimazu, Japan) was employed for acquiring the absorption spectra.

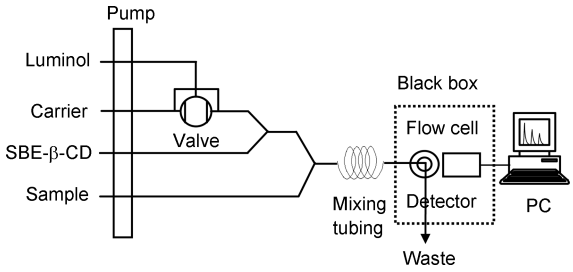


Figure 1. Schematic diagram of the present FI-CL. Luminol: 2.5×10^{-5} mol L^{-1}; NaOH 0.025 mol L^{-1}; SBE-β-CD: 1.0×10^{-4} mol L^{-1}. Flow rate: 2.0 mL min^{-1}; Mixing tube: 10.0 cm; High voltage: −750 V.

General Procedures. As shown in Figure 1, flow lines were inserted into luminol/NaOH, carrier (deionized water), SBE-β-CD and the drug solutions, respectively. The pump was started at a constant speed of 2.0 mL min^{-1}. The deionized water washed the whole system until a stable baseline was recorded. Then 100 μL luminol solution was injected into the carrier stream by injection valve and merged with SBE-β-CD, which was then mixed with PPH sample solution. The mixed solution was delivered into the CL cell, and the CL signal was detected by PMT without wavelength discrimination. The PMT negative voltage was set as 750 V. The concentration of PPH could be quantified on the basis of the decrement of CL intensity, $\Delta I = I_0 - I_s$, where I_s and I_0 were CL signals in the presence and in the absence of PPH, respectively.

Molecular Docking. The structure of SBE-β-CD was constructed by replacing seven hydroxyls in the extracted β-CD using sulfobutyls from crystal structure of 3M3R in the public resource of Protein Data Bank (PDB, www.rcsb.org/pdb/). The 3D conformer structure of PPH (CID: 4748) was retrieved from National Center for Biotechnology Information and converted to PDB format using OpenBabel 2.3.2. These

PDB structures of SBE-β-CD and PPH were used for docking by AutoDock 4.2 software (http://autodock.scripps.edu/). Docking simulation was performed using the Lamarckian Genetic Algorithm (LGA) to search for the optimum binding energy of SBE-β-CD with PPH. Docking parameters: Auto-Grid using a box 56 Å × 56 Å × 56 Å, thus SBE-β-CD could be completely contained in the box; AutoDock parameters used were population size: 150, and maximum number of energy evaluations: 250000.

Sample Pretreatment.

Preparation of Spiked Human Urine and Serum Samples: Human urine samples were collected from a health volunteer, serum samples were supplied by the Hospital of Northwest University. The spiked samples were prepared by adding known quantities of PPH into urine and serum samples. After homogenization, the spiked urine and serum samples with appropriate dilution were taken for PPH determination.

Preparation of Tablets Samples: Appropriate amount of tablets of PPH (Shanghai Zhaohui Pharmaceutical Co., Ltd.) were weighed and ground to fine powder using a pestle and mortar and then homogenized; a sample equivalent to approximately 4.00 mg of PPH was weighed accurately and dissolved in 2.0 mL ethanol solution and then diluted with deionized water in a 50 mL calibrated flask and ultrasound for 2 minutes. The solution was filtered by an ordinary filter paper, and suitable filtrate aliquots from this solution were diluted to a PPH concentration within the calibration range.

Results and Discussion

Relative CL Intensity-Time Profile. The relative CL intensity-time profile of luminol/SBE-β-CD system with PPH was studied using the static and flow procedure, with results presented in Figure 2. Figure 2(a) showed the CL kinetic curves using a static system, it was clear that the time T_{max} for the maximum CL intensity I_{max} of luminol-dissolved oxygen (curve 1) and the luminol/SBE-β-CD (curve 3) were 4.7 s and 4.4 s with I_{max} of 195 and 493, respectively; while in the presence of 0.05 ng mL^{-1} PPH, the I_{max} of luminol/SBE-β-CD decreases from 493 to 391 by 20.7% with the same T_{max} of 4.4 s. As shown in Figure 2(b) for the FI-CL system, it was observed that the T_{max} of luminol-dissolved oxygen (curve 1) and the luminol/SBE-β-CD (curve 3) were 8.4 s and 7.8 s with I_{max} of 195 and 554, respectively, indicating that SBE-β-CD could enhance the CL signal of luminol leading to CEC (complexation enhancement of CL); while in the presence of 0.1 ng mL^{-1} PPH, the I_{max} of luminol/SBE-β-CD decreases from 554 to 400 by 27.8% with the same T_{max} of 7.8 s, which may be caused by the interaction of SBE-β-CD and PPH.

Optimum Conditions for the Determination of PPH. The effect of luminol concentration on the CL intensity was investigated in the range of 5.0 × 10^{-7} to 5.0 × 10^{-4} mol L^{-1}. It was found that the CL intensity increased with increasing luminol concentration up to 2.5 × 10^{-5} mol L^{-1}, above which CL intensity decreased slightly. Thus, 2.5 × 10^{-5} mol L^{-1} was the optimum concentration of luminol. Similarly, the influence of SBE-β-CD concentration on the CL intensity was tested from 1.0 × 10^{-6} to 1.0 × 10^{-3} mol L^{-1}. The CL intensity increased rapidly with increasing SBE-β-CD concentration up to 1.0 × 10^{-4} mol L^{-1}, and then decreased slowly. Therefore, 1.0 × 10^{-4} mol L^{-1} was chosen as the optimum SBE-β-CD concentration for the following experiments.

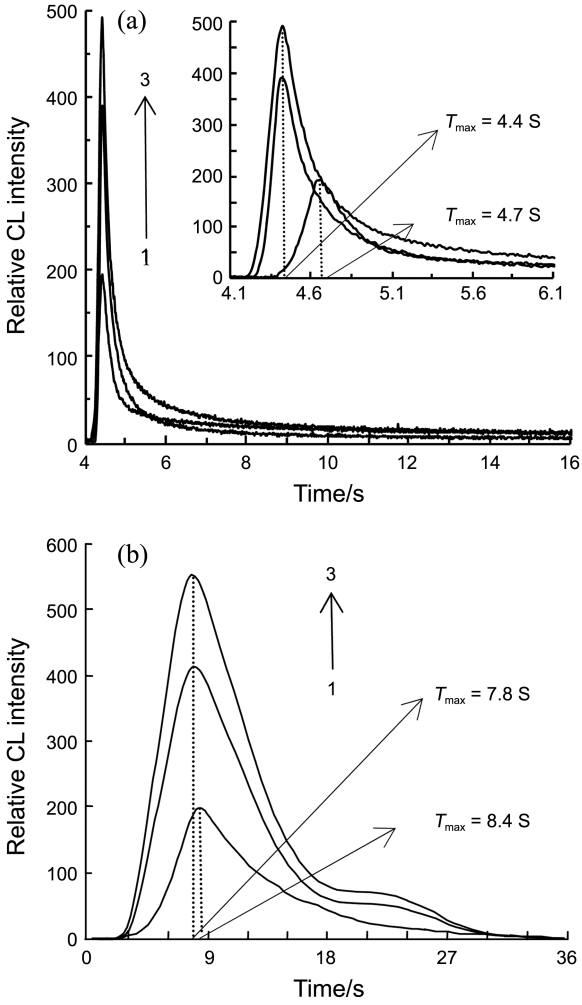


Figure 2. Relative CL intensity-time profile in the static system (A) and flow system (B). Curve 1: luminol/dissolved oxygen CL system; Curve 2: luminol/SBE-β-CD/PPH CL system; Curve 3: luminol/SBE-β-CD CL system. (A) Luminol 1.0 × 10^{-6} mol L^{-1}; SBE-β-CD 1.0 × 10^{-5} mol L^{-1}; PPH 0.05 ng mL^{-1}; (B) Luminol 2.5 × 10^{-5} mol L^{-1}; SBE-β-CD 1.0 × 10^{-4} mol L^{-1}; PPH 0.1 ng mL^{-1}.

Owing to the nature of the luminol CL reaction favoring under the alkaline condition, NaOH was introduced into luminol solution to improve the sensitivity of the system. A series of NaOH solutions ranging from 2.5 × 10^{-4} to 2.5 × 10^{-1} mol L^{-1} (pH: 10.4-13.4) was examined. The results were shown in Figure 3, indicating the CL intensity could reach a maximum value in the concentration of 2.5 × 10^{-2} mol L^{-1} and then decreased slowly. Hence, 2.5 × 10^{-2} mol L^{-1} NaOH was optimal in this work. The influence of PPH pH on CL was investigated ranging from 3.0 to 8.5, it was observed that a strong and stable CL intensity could be

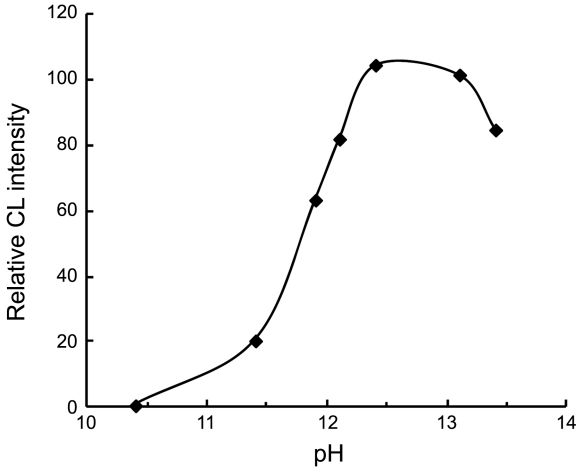


Figure 3. Effect of reaction system pH on relative CL intensity.

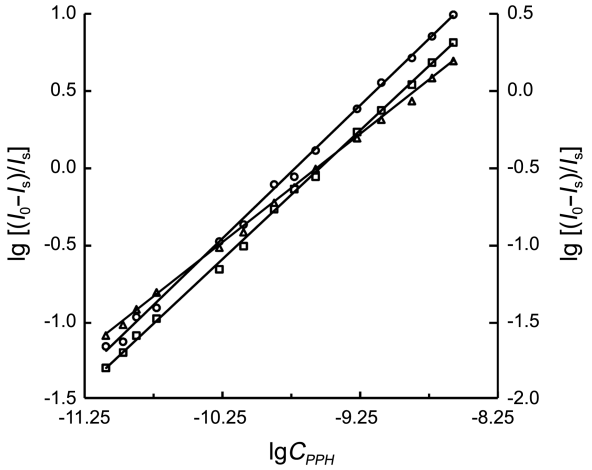


Figure 4. Double logarithmic plot for SBE-β-CD/PPH complex from the proposed CL model. PPH: 0.03-30.0 ng mL^{-1}; Luminol: 2.5×10^{-5} mol L^{-1}; SBE-β-CD: 1.0×10^{-4} mol L^{-1}. △: 288 K; □: 298 K; ○: 308 K.

Table 2. The stability test of luminol/SBE-β-CD/PPH FI-CL system[a]

Time day	I_{CL} blank	RSD %	I_{CL} 0.1 ng mL^{-1}	RSD %	I_{CL} 1.0 ng mL^{-1}	RSD %
1st	554	1.3	400	2.5	365	1.9
2nd	550	1.5	396	2.8	361	2.0
3rd	558	0.9	403	2.4	360	2.2

[a]Averaged from five determinations.

obtained at pH of 6.5-7.0.

The CL intensity was related to the flow rate and the mixing tube length. The effect of flow rate on CL intensity was examined in the range of 0.5 to 5.0 mL min^{-1}. It was found that the CL intensity increased with the augment of flow rate, however the CL intensity was unstable at a high flow rate. As a compromise between less reagents consumption and higher sensitivity, 2.0 mL min^{-1} of flow rate was recommended. The effect of mixing tubing on CL intensity was tested from 5.0 to 20.0 cm, and it was found that the CL intensity was strong and stable using 10.0 cm of mixing tubing. Accordingly, a 10.0 cm mixing tubing was selected as the optimum length.

The Stability of Luminol/SBE-β-CD/PPH FI-CL System. CL intensity was recorded to test the stability of the luminol/SBE-β-CD FI-CL system in the absence and presence of 0.1 and 1.0 ng mL^{-1} PPH. The experiment lasted for 3 days and the flow system was regularly used over 8 h per day, the results of these replicate experiments were listed in Table 2. The CL intensity was the average of every five separate determinations, and the RSDs were < 2.8%, suggesting the luminol/SBE-β-CD CL system exerted very good stability.

Analytical Performance for PPH Determination by Present FI-CL Analysis. Under the selected experimental conditions, the standard solutions of PPH were tested by FI-CL using luminol/SBE-β-CD system. It was found that the decrement of CL intensity was proportional to the logarithm of PPH concentration in the range of 0.03-30.0 ng mL^{-1}, giving a regression equation I_{CL} = 23.5LnC + 192.0 (R = 0.9907, n = 5) with the LOD of 0.01 ng mL^{-1} (3σ). At a flow rate of 2.0 mL min^{-1}, a complete analytical process including sampling and washing could be accomplished within 36 s, with the RSDs (n = 5) of 2.2, 1.6 and 1.0% for 0.3, 3.0 and 30 ng mL^{-1} PPH, respectively.

Interference Studies. The interference of potentially interfering species were tested by adding increasing amounts of interfering substance to the standard solution of PPH (1.0 ng mL^{-1}) and the error was controlled at 5% level. The tolerable ratios of interfering species were over 5.0×10^3 times for the excipients commonly existed in the pharmaceutical tablets, such as starch, agar, cellulose; 5.0×10^4 for Mg^{2+}, Ca^{2+}, Zn^{2+} and I^-; 2.4×10^3 for NO_3^-, SO_4^{2-}, PO_4^{3-}, CO_3^{2-} and Ac^-; 1.0×10^3 urea; 1.0×10^2 HCO_3^-. Compounds abundant in human serum such as salts, lipids and proteins had no obvious interference for the determination of PPH at picogram levels.

The Possible CL Mechanism of Luminol/SBE-β-CD/PPH. The possible mechanism of SBE-β-CD/PPH was studied by FI-CL, molecular docking and UV-Vis methods. Using the FI-CL model[17] by plotting lg[$(I_0 - I_s)/I_s$] versus lg[C_{PPH}] (Figure 4), the formation constant $K_{P\text{-}CD}$ and stoichiometric ratio n of SBE-β-CD with PPH at 288/298/308 K were given

Table 3. The formation constants and thermodynamic parameters of SBE-β-CD/PPH

T K	$K_{P\text{-}CD}$ L mol^{-1}	n	ΔH kJ mol^{-1}	ΔS J mol^{-1} K^{-1}	ΔG kJ mol^{-1}
288	$(4.39 \pm 0.02) \times 10^6$	0.70			−36.44 ± 0.02
298	$(2.57 \pm 0.01) \times 10^7$	0.83	142.78 ± 0.01	622.28 ± 0.01	−42.66 ± 0.01
308	$(2.12 \pm 0.01) \times 10^8$	0.86			−48.88 ± 0.01

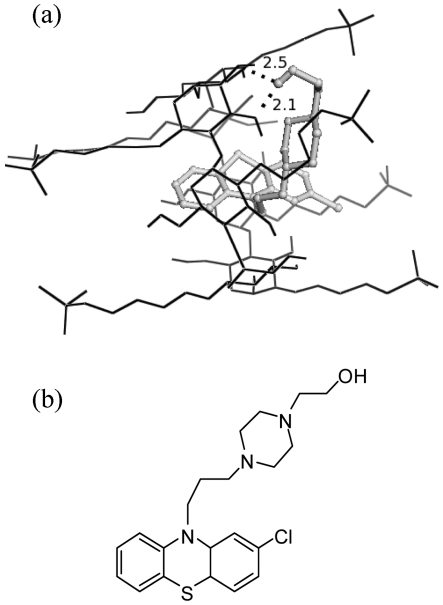


Figure 5. Docking result and chemical structure. (a) Docking result of SBE-β-CD/PPH; (b) Structure of PPH.

in Table 3. It was clear that the $K_{P\text{-}CD}$ was of 10^6-10^8 L mol^{-1} level, suggesting that there existed a strong inclusion interaction between SBE-β-CD and PPH, and the corresponding n was 0.79-0.86 (approximately 1.0), indicating that a 1:1 complex of SBE-β-CD and PPH formed online. The thermodynamic parameters of SBE-β-CD/PPH listed in Table 3 showed that the inclusion behavior of SBE-β-CD/PPH was a spontaneous process by hydrophobic interaction.

By molecular docking, it was found that PPH entered into the larger cavity of SBE-β-CD (Figure 5(a)), and two hydrogen bonds with distance of 2.5 Å and 2.1 Å were generated between H of PPH (Figure 5(b)) and O of SBE-β-CD; the free energy ΔG and the formation constant K at 298 K for binding of PPH inside the SBE-β-CD cavity were −40.96 kJ mol^{-1} and 1.53×10^7 L mol^{-1}, respectively, well agreeing with the experimental data by FI-CL model.

Figure 6 was the UV-Vis absorption spectra of different reaction systems. It can be seen that the spectra of luminol/PPH reaction nearly had no change (Figure 6(a)), suggesting there may not exist interaction between luminol and PPH. As shown in Figure 6(b), λ_{max} 255 nm of PPH (curve 1) shifted to 259 nm in the presence of SBE-β-CD (curve 2), while λ_{max} 255 nm of PPH shifted to 257nm in the presence of luminol/SBE-β-CD (curve 4), demonstrating that there may exist inclusion interaction of SBE-β-CD with PPH and luminol.

Thus, the schematic diagram of luminol/SBE-β-CD/PPH CL interaction process was described in Figure 7. Luminol entered into the narrow neutral rim of SBE-β-CD[31] with formation constant $K_{L\text{-}CD}$ (3.3×10^6 L mol^{-1}), giving the enhanced CL intensity of luminol and producing the effect of CEC[16]; hydrophobic PPH entered into the wide rim and formed a 1:1 complex (SBE-β-CD/PPH) with hydrophobic interaction, resulting in CL intensity of SBE-β-CD/luminol

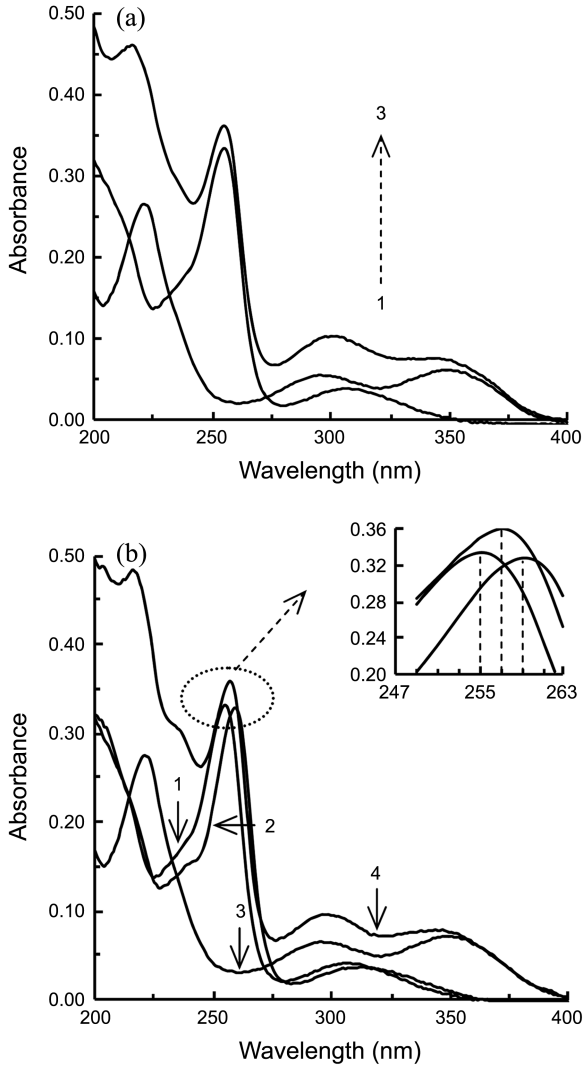


Figure 6. UV absorption spectra profile of different reaction system. Luminol: 1.0×10^{-6} mol L^{-1}; SBE-β-CD: 1.0×10^{-4} mol L^{-1}; PPH 1.0×10^{-6} mol L^{-1}. (A) Curve 1: luminol; Curve 2: PPH; Curve 3: luminol/PPH. (B) Curve 1: PPH; Curve 2: SBE-β-CD/PPH; Curve 3: luminol/SBE-β-CD; Curve 4: luminol/SBE-β-CD/PPH.

remarkably quenched and causing the effect of complexation enhancement of quenching (CEQ).

Applications

Determination of PPH in Spiked Human Urine and Serum Samples. The proposed CL method was applied to the determination of PPH in spiked human urine and serum. To prepare the spiked samples, known quantities of PPH were spiked into urine or serum, and were then diluted 1.0×10^5 folds, respectively. The influence of foreign species existing in serum and urine could be eliminated. The contents of PPH in the spiked samples were quantified applying the standard addition method and the obtained results are listed in Table 4. The recoveries were from 95.8% to 104.6% with RSDs < 2.6% (n = 5), confirming this method is reliable and sufficient for human urine and serum sample analysis.

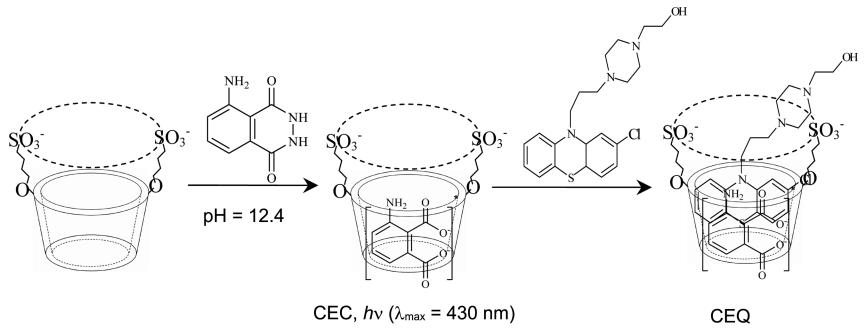


Figure 7. Schematic diagram of Luminol/SBE-β-CD/PPH interaction. CEC: Complexation enhancement of CL; CEQ: Complexation enhancement of quenching.

Table 4. Results of the determination of PPH in spiked urine and serum samples[a]

Sample No.[b]	Added/Found ng mL^{-1}	RSD %	Recovery %	Content/Spiked μg mL^{-1}
1-1	0/0.52 0.30/0.84	1.5 0.9	103.8	51.6/50.0
1-2	0/0.49 0.50/0.98	2.6 0.8	97.6	48.8/50.0
1-3	0/0.52 0.70/1.23	2.2 0.4	104.6	52.3/50.0
2-1	0/0.51 0.30/0.82	1.7 1.3	103.3	51.7/50.0
2-2	0/0.49 0.50/0.98	2.4 0.7	97.9	49.1/50.0
2-3	0/0.48 0.70/1.16	2.3 0.5	95.8	48.3/50.0

[a]Averaged from five determinations. [b]No. 1, urine samples; No. 2, serum samples.

Table 5. Results of the determination of PPH in tablets[a]

Sample No.	Added/Found ng mL^{-1}	RSD %	Recovery %	Content of perphenazine[b] mg per tablet
				Proposed method/UV
1	0/0.99 0.50/1.49	2.3 1.5	99.8	1.98±0.02/1.96±0.05
2	0/0.97 1.00/1.91	2.6 1.3	94.5	1.96±0.02/1.96±0.04
3	0/1.01 3.00/4.18	2.1 1.1	105.4	2.03±0.01/2.04±0.03
4	0/1.02 5.00/6.30	1.9 0.6	105.6	2.04±0.01/2.03±0.03

[a]Averaged from five determinations. [b]Declared content: 2.0 mg per tablet.

Determination of PPH in Tablets. The proposed method was applied to the determination of PPH in tablets. Appropriate amount of tablets were weighed and ground to fine powder. Then a sample equivalent to approximate two tablets were weighed accurately and dissolved in ethanol-water solution (1:24, v/v). The resulting solution was filtered through an ordinary filter paper and diluted to a 50 mL glass calibrated flask. Recovery studies were carried out using the samples spiked with the known amounts of PPH and the results are summarized in Table 5. It is shown that there were no significant differences between the results obtained by the proposed method (recoveries from 94.5 to 105.6%, RSDs < 2.6%) and those obtained by the Chinese Pharmacopoeia method.[32]

Conclusion

With high sensitivity, low LOD, wide linear range, small amount of chemical consumption, cost effectiveness, simple sample preparation and instrumentation, FI-CL method has been extensively used in a number of analytical applications.[33-35] A simple and sensitive FI-CL was first proposed for PPH determination in biological fluids and tablets and simultaneously investigating the inclusion behavior of SBE-β-CD and PPH based on the inhibition effect of PPH on luminol/SBE-β-CD system, with interaction parameters successfully obtained.

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