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Chemiluminescence determination of trimetazidine via inducing the aggregation of gold nanoparticles

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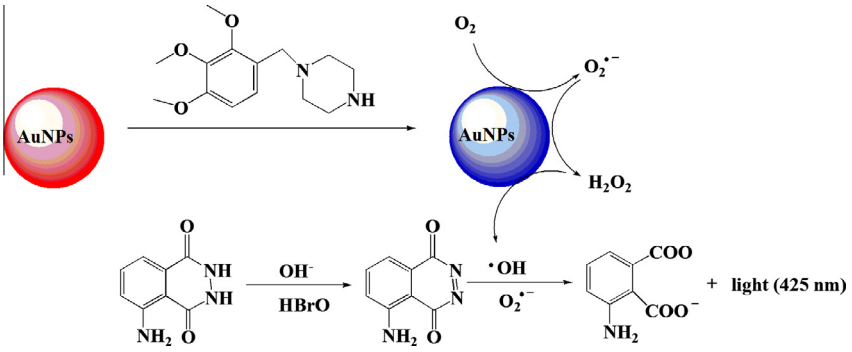
HIGHLIGHTS

- A simple and sensitive CL method was developed for the determination of trimetazidine.
- Trimetazidine enhanced the CL signal of N-bromosuccinimide-luminol reaction in the presence of gold nanoparticles.
- The method was successfully applied to the determination of trimetazidine in tablets and in spiked serum samples.
- A possible CL reaction mechanism was suggested.

GRAPHICAL ABSTRACT

Trimetazidine induced the aggregation of gold nanoparticles (AuNPs), resulting in signal amplification in luminol-N-bromosuccinimide-AuNPs chemiluminescence system, providing a simple and sensitive detection method for trimetazidine.



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ABSTRACT

A simple, rapid and sensitive chemiluminescence (CL) method combined with flow injection analysis was developed for the determination of trimetazidine. Trimetazidine was found to significantly increase the CL signal arising from N-bromosuccinimide-luminol reaction in the presence of gold nanoparticles. The enhanced CL intensity was proportional to trimetazidine concentration in the range of 0.01–5.0 μg/mL, with a limit of detection ($3s_b$) of 6.7 ng/mL. The relative standard deviation was 2.8% for 11 repetitive measurements of 0.1 μg/mL trimetazidine solution. The practicality of the method was evaluated by determining trimetazidine in pharmaceutical formulations and in spiked human serum samples. Moreover, the possible CL reaction mechanism was also discussed.

Introduction

Trimetazidine [1-(2,3,4-trimethoxybenzyl)-piperazine] is an effective and well-tolerated antianginal metabolic agent that improve myocardial glucose utilization through inhibition of fatty acid metabolism [1]. It is clinically prescribed as a long-time treatment of angina pectoris [2] and in some countries for tinnitus and dizziness. Growing interest in metabolic modulation in recent years urged the development of analytical methods for the detection of trimetazidine. Several analytical methods have been reported for the determination of trimetazidine in pharmaceutical formulations and in biological fluids, including spectrophotometry [3,4], fluorescence [5,6], chemiluminescence (CL) [7], voltammetry [8], HPLC [9,10], and LC–MS [11–13]. Among these techniques, the CL promises the advantages of inexpensive instrumentation, high

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sensitivity, and good reproducibility [14,15]. Only one batch CL method was available for the determination of trimetazidine, which was based upon its direct oxidation by acidic $KMnO_4$ [7].

The application of nanomaterials in CL analysis has becoming a growing area of interest in analytical chemistry. Nanomaterials amplify the CL signal and improve the sensitivity and the stability of the CL detection. Analytes of interest can enhance or inhibit the nanomaterial-amplified CL signal, thus providing the basis for expanding analytical application of CL detection [16].

Here we found that trimetazidine could induce the aggregation of AuNPs, which caused a significant enhancement on the CL signal of luminol-N-bromosuccinimide reaction. Based on these facts, a simple, rapid and sensitive flow injection CL method was developed for the determination of trimetazidine. The experimental conditions were carefully optimized and the CL reaction mechanism was discussed. The application of the method in tablets and in spiked human serum samples was evaluated.

Experimental

Apparatus

CL measurements were carried out on an IFFM-E CL analyzer (Xi'an Remex, China). CL spectra were obtained by means of an F-4600 fluorescence spectrophotometer (Hitachi, Japan) with turning off the excitation source. Absorption spectra were taken on a TU-1901 spectrophotometer (Purkinje General, China). TEM images of AuNPs without and with trimetazidine were measured on H-600 transmission electron microscope (Hitachi, Japan).

Reagents and solutions

All chemicals were of analytical grade except for luminol, which was synthesized by Shaanxi Normal University (purity > 95%). Deionized distilled water was obtained from a SZ-93 automatic deionized, distilled water system (Shanghai Yarong Biochemistry Instrument Factory). Stock solution of trimetazidine (500.0 μg/mL) was prepared by dissolving appropriate amount of trimetazidine hydrochloride standard (State Food and Drug Administration of China) in water, stored at 4 °C in a refrigerator and protected from the light. Trimetazidine working solutions were prepared by gradually diluting trimetazidine stock solution with water when used. Luminol solution (2.0 μmol/L) was prepared by diluting a 0.01 mol/L stock solution of luminol (prepared in 0.01 mol/L NaOH) with a desirable concentration of NaOH. N-bromosuccinimide solution (40.0 μmol/L) was freshly prepared by dissolving N-bromosuccinimide (Tianjin Fuchen Chemical Reagent Factory) in water. Chloroauric acid and sodium borohydride (Sinopharm Chemical Reagent Co. Ltd.) and sodium citrate (Xi'an Chemical Reagent Factory) were used to synthesis of AuNPs.

The 6 nm AuNPs was synthesized by sodium borohydride reduction method, and the 16 nm, 25 nm and 38 nm AuNPs were synthesized by sodium citrate reduction method, and the detailed procedures have been described elsewhere [17]. The concentration of AuNPs solution was calculated according to the amount of $HAuCl_4$ added initially. The as-prepared AuNPs solutions were stored in 4 °C refrigerator when not used.

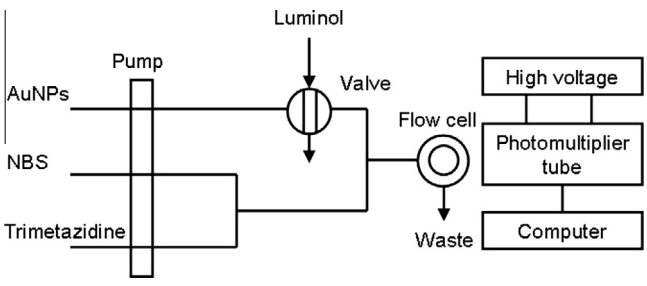

Fig. 1. Schematic diagram of CL flow system.

Procedure

As shown in Fig. 1, flow lines were connected with luminol solution, AuNPs solution, N-bromosuccinimide solution and trimetazidine solution, respectively. Peristaltic pumps were started to drive the solutions into the flow system. After a stable baseline was recorded, luminol solution (90 μL) was injected into AuNPs solution by an injection valve, which was then combined with the merged stream of trimetazidine solution and N-bromosuccinimide solution. The CL signal produced in the flow cell was detected with a CR105 photomultiplier tube (Hamamatsu Photonics (China) Co., Ltd.). The concentration of trimetazidine was quantified by the enhanced CL intensity ΔI ($\Delta I = I_s - I_b$), where I_s and I_b were the CL signals in the presence of trimetazidine and blank, respectively.

Results and discussion

CL behavior of trimetazidine in AuNPs-catalyzed luminol-N-bromosuccinimide system

The oxidation of luminol by N-bromosuccinimide accompanied by CL emission in alkaline condition (Fig. 2, curve a) [18]. This CL system could be catalyzed by AuNPs (Fig. 2, curve b). Replacing AuNPs solution with the supernatant of AuNPs solution only caused a very weak enhancement (Fig. 2, curve c). Thus, the catalytic role was originated from AuNPs rather than other substances. When trimetazidine was added into the luminol-N-bromosuccinimide-AuNPs system, the CL signal was further enhanced significantly (Fig. 2, curve d). However, trimetazidine alone slightly inhibited the CL signal of luminol-N-bromosuccinimide reaction in the absence of AuNPs (Fig. 2, curve e).

Discussion on the CL reaction mechanism

The CL spectra of the reactions were shown in Fig. 3. All of the reactions had the same spectral profiles and the same maximum emission wavelength at 425 nm, indicating that they shared the

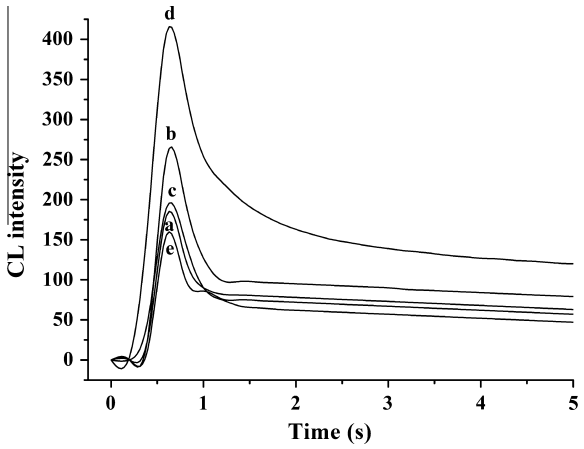

Fig. 2. Kinetics profiles of CL reactions by injecting 0.5 mL of 40.0 μmol/L N-bromosuccinimide into 1.50 mL of (a) 2.0 μmol/L luminol; (b) 2.0 μmol/L luminol-76.0 μmol/L AuNPs; (c) 2.0 μmol/L luminol-the supernatant of AuNPs; (d) 2.0 μmol/L luminol-76.0 μmol/L AuNPs-1.0 μg/mL trimetazidine; and (e) 2.0 μmol/L luminol-1.0 μg/mL trimetazidine.