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Light-assisted preparation of cyclodextrin-based chiral stationary phase and its separation performance in liquid chromatography

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Cyclodextrin-based chiral stationary phase (CD-CSP) is one of the most widely applied CSPs due to its powerful enantioseparation ability. In this study, a facile method was developed to prepare CD-CSP via carboxyl methyl β-cyclodextrin (CD-COOH) and diazo-resin (DR). Monodisperse silica particles were synthesized by a modified Stöber method. Then DR and CD-COOH was coated on the silica particles via ionic bonding successively and UV light was finally used to couple silica, DR and CD-COOH and the ionic bonds turned into covalent bonds. The resultant CD-DR silica particles were characterized by Fourier transform infrared spectroscopy (FT-IR), thermo-gravimetric analysis (TGA) and scanning electron microscopy (SEM). The enantioselectivity of the CD@SiO_2 particles was explored in reversed phase high-performance liquid chromatography (RP-HPLC). Baseline separation of chiral drugs was achieved and the effects of separation parameters (elution mode, buffer and analyte mass) were investigated in details. By using water soluble non-toxic DR to replace highly toxic and moisture sensitive silane agent to modify silica microspheres, this light-assisted stategy can provide a green and effective technique to manufacture packing materials for enantioseparation applications.

Introduction

With an increasing demand for the exploration of different properties like toxicities and metabolic pathways of enantiomers, many efforts have been made on the analysis and purification of chiral drugs, and it has become a prerequisite process prior to the clinical use of drugs.[1] Enantioseparation of chiral compounds has been attracting great interests due to that enantiomers of racemic drugs tend to show markedly different pharmacological activities.[1-5] Enantioseparation of chiral compounds will continue to be a key research area in pharmaceutical industry,[6] food additives and life science.[7-9]

Most commercial available synthetic chiral drugs are obtained as a mixture of two enantiomers through synthesis methods.[10] It is well established that direct enantioseparation by high performance liquid chromatography (HPLC) with CSP can serve as a robust technique for separation at both analytical and preparative scale, which feature high efficiency, quick analysis and precise resolutions.[11-13]

Chiral selectors bonded or coated on silica particles are considered state of art materials for separating enantiomers in HPLC. After a few decades' development, the enantiomeric separation has become an essential, mature technique in pharmaceutical, bioanalytical, and synthetic organic laboratories.[14-17] However, there are no CSP that can separate all classes of chiral molecules up to now. Thus, many researchers who are engaged in stationary phase development have extensively focussed on synthesizing chiral selectors, which have high selectivity for various classes of enantiomers.[14, 18-20]

A lot of chiral stationary phases (CSPs), which are based on ligand-exchange, protein, glycoprotein, cyclodextrin, polysaccharide, macrocyclic glycopeptide and crown ether, are available for separations of enantiomers in HPLC.[21, 22] Cyclodextrins (CDs) are one of the most commonly used chiral selectors for enantioseparation due to their ability to form host-guest inclusion with a large variety of chiral compounds, which are naturally-occurring cyclic oligosaccharides which consisting of several (6, 7, 8) glucose units.[22-24] Due to consisting small number of glucose units, α-CD contained a small cavity that can only package part of small molecules, which limited its application. For γ-CD, the cavity is the biggest, but the high manufacturing cost restricts its application. By contrast, the cavity size of β-CD is appropriate, and the inclusion can be many kinds of chiral molecules. β-CD has been widely used for its low cost and industrialized production but the poor water solubility of β-CD limited the application to some extent. Chemical modification can improve the water solubility of β-CD and broaden its application scope and then achieve better separation effect. The enantioseparation

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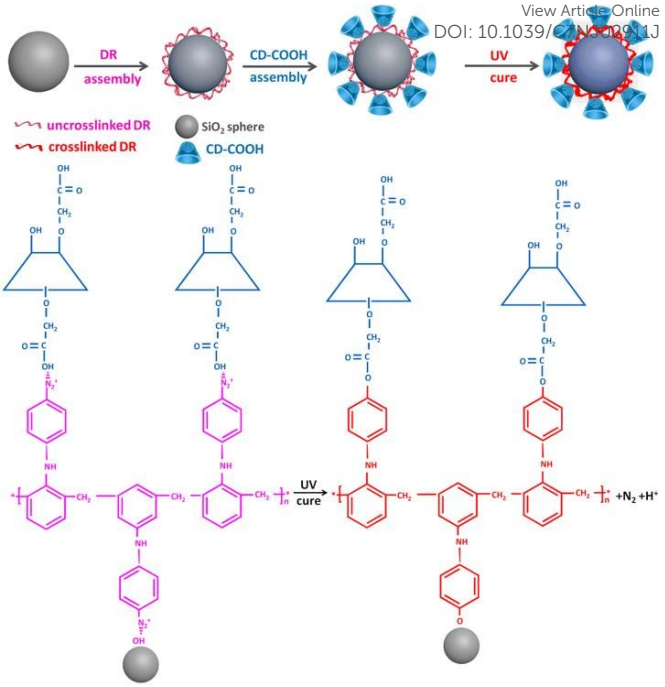
abilities of CDs could be enhanced by derivatizing its hydroxyl groups.[25]

As we all know, the most commonly used columns for chromatographic separation are packed with particle-based stationary phase[26]. The modified silica particles have almost been the most widely used stationary phase for chromatographic separation among various types of particles used for packings duo to some advantageous characteristics such as a relatively high specific surface area, narrow particle size distribution, and good mechanical stability.[27] However, the modification process of silica particles is usually complicated which contains multiple time-consuming steps. Moreover, the highly toxic and moisture sensitive silane coupling agents are traditionally used in the modification process, which often cause environmental and quality problems during the manufacture and application. Thus, a much easier and greener way for modifying silica particles is essential.

According to the previously proposed preparation mechanism using the layer-by-layer self-assembly technique combined with photochemistry reactions,[13, 28] the modification of silica particles using photosensitive diazoresin is expected to be superior to traditional modified methods using moisture sensitive silane coupling agents. DR is a non-toxic photoactive component which often used in cell culture supports.[29] The unique photo-crosslinking reaction of DR is expected to apply for instead of silane coupling agents. Ionic bonding between DR, silica and CD-COOH can be converted into covalent bonding after treatment with UV light through a unique photochemistry reaction of DR.

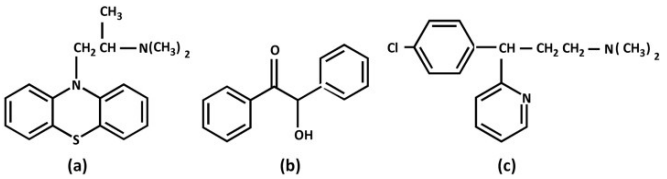
To improve the efficiency of the preparation procedure, we develop a CSP bonded to silica particles with DR instead of silicon alkylation reagents.[30, 31] In this paper, we synthesized water soluble carboxyl methyl β-CD (CD-COOH) and monodisperse silica particles by a modified Stöber method. A light-assisted modification method of silica particles is developed by ionic bonding between positive charged photosensitive DR with hydroxyl groups of silica particles and carboxyl group of CD-COOH. With the treatment of UV light, the ionic bonding between DR and silica particles, DR and CD-COOH were turned into covalent bonding through a unique photochemistry reaction of DR (Scheme 1). Thus, CD could be attached on the surface of silica particles steadily and novel CSP was obtained. The separation properties of the resultant CSP of three chiral drugs (chlortrimeton, promethazine and benzoin, Scheme 2) were investigated in details.



Scheme 1 Light-assisted preparation of cyclodextrin-based CSP.

Experimental

Chemicals and apparatuses



Scheme 2 Chemical structures of the chiral compounds used in this study. (a) promethazine, (b) benzoin, (c) chlortrimeton.

The structures of the chiral compounds are shown in Scheme 1. DR was synthesized by polycondensation of 5 diphenylamine-4-diazonium salt and paraformaldehyde in concentrated H_2SO_4 according to a method described in our previous report.[32-35] Ammonia (28%) was purchased from Sanhe Chemical Reagent Company (Yantai, China). KCl (99.5%), NaOH (98%), $AgNO_3$, sodium chloroacetate (98%) ethanol (99.5%), hydrochloric acid, acetic acid, triethylamine and isopropanol (99.7%) were obtained from Hengxing Chemical Reagent Company (Tianjin, China). Tetraethyl orthosilicate (TEOS, 98%), β-cyclodextrin, chlortrimeton, promethazine and benzoin (99%) were obtained from Aladdin Reagent Company (Shanghai, China). Methanol (MeOH, 99.9%) and acetonitrile (ACN, 99.9%) were obtained from Tianjin Kemiou Chemical Reagent Co. All chemicals were used as received without further purification. Water was distilled before use.

Instrumentation

The morphology and structure of the silica particles was investigated by scanning electron microscopy (SEM, JEOL JSM-6309LV). The photo-crosslinking of the CD-COOH and SiO_2 by DR was carried out using a 365 nm UV curing system (EXFO Omnicure S1000) with a lamp power of 100 W. Thermogravimetric analysis (TGA) data were recorded using a Mettler Toledo TGA/DSC1/1600LF simultaneous thermal analyzer at a heating rate of 10 °C/min. Fourier transform infrared spectroscopy (FT-IR) was obtained using Nicolet 6700 produced by Thermo Fisher Scientific. Chromatographic study was carried out using a SEV P500 HPLC equipped with a UV detector.

Preparation of CD-COOH

CD-COOH was synthesized according to the reported method.[36] In brief, a certain amount of NaOH and β-CD was added into 20 mL of water under stirring at 0 °C. After the substances were dissolved, the mixture solution was stirred 1 h at 90 °C and a certain amount of sodium chloroacetate was added in it and stirred for 3 h. Next, the reaction solution was cooled to room temperature and its pH value 4-6 was adjusted by HCl. Superfluous organic solvent (methanol and ethanol, v:v=1:3) was added into the obtained solution to get white precipitates of carboxyl methyl-β-cyclodextrin (CD-COOH). The supernatant was removed and the precipitates were redissolved in water. The purification process was repeated again until there were no precipitates produced. The supernatant was treated with $AgNO_3$ to test whether surplus chloride ions remains or not. Finally, CD-COOH was dried at RT in vacuum drying oven before use.

Preparation of the silica particles

The synthesis of silica particles was conducted by a modified Stöber method.[37] In a 250 mL semibatch chemical reactor where an ethanolic solution of TEOS (solution I) was continuously supplied with a syringe pump to the reaction mixture (solution II) of water, KCl electrolyte, ethanol, TEOS and ammonia. The amounts of ethanol and TEOS in solution I were 26.12 g and 4.12 g. The amounts of water, KCl, ethanol, TEOS and ammonia in solution II were 9.45 g, 0.0238 g, 75.39 g, 1.648 g and 4.039 mL, respectively. The supply rate of solution I was 0.1 mL/min and the stirring speed was 260 rpm. After further reaction for another 1 h, the obtained particles were purified by centrifugation and washed with ethanol for no less than three times. Finally, the SiO_2 particles were dried under vacuum at ambient temperature.

Light-assisted preparation of the CD-CSP

The preparation of CD-COOH CSP was shown in Scheme 1. The DR coated silica particles were carried out as follows: the SiO_2 particles were firstly treated in 0.1 M HCl for 30 min and washed to neutral with water. These particles were added into the aqueous solution of DR (10mg/mL) with magnetic stirring for 30 min, and washed with deionized water. These particles were added into the aqueous solution of CD-COOH (10 mg/mL) with magnetic stirring for 30 min, and washed with deionized water. The process was conducted in the dark condition and low temperature. The obtained coated silica particles were dried under vacuum at room temperature for 12 h. The coated silica particles were then exposed to 365 nm UV light with an intensity of 350 mW/cm^2 for 15 min in order to form the covalently linked CD coatings.

Chromatographic conditions

The CSP were packed into stainless columns (15 × 4.6 mm, I.D.) using a typical slurry-packing technique with isopropyl alcohol as the solvent by the chromatographic column packing machine (GLK 2000, GALAK). The packing pressure was maintained for at least 30 min. The column was connected to the HPLC system with methanol passing through at a flow rate of 0.1 mL/min for about 3 h to equilibrate the column until a constant UV baseline was obtained. Samples for chromatography were dissolved in MeOH or ACN at a concentration of 10 mg/mL if not mentioned. The injection volume was 1 μL if not mentioned. Each solution was injected in triplicate and the average values are reported. Triethylammonium acetate buffer (TEAA) was prepared by dissolving 0.3% (v/v) triethylamin in ultrapure water and adjusting to the pH 4.0 with acetate acid. All the buffers and samples were filtered through 0.22 μm membranes before use and detection was performed at 250 nm.

Results and discussion

Light-assisted preparation of CD-CSP

In this work, monodisperse silica particles were synthesized by a modified Stöber method, in which TEOS was continuously added into the reaction mixture containing KCl electrolyte, water, ethanol and ammonia at room temperature. CD-COOH was ironically bonded on the surface by the charged photosensitive DR. SEM images of bare SiO_2 and CD@SiO_2 are shown in Fig. 1. The surface of bare silica is smooth as shown in Fig. 1(a). After CD was bonded on the SiO_2 surface by DR, the surface becomes less smooth and a clear coating can be observed (Fig. 1(b)).

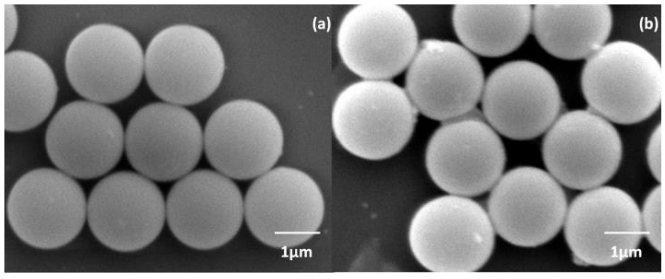


Fig. 1 SEM images of (a) bare SiO_2 and (b) CD @SiO_2.

As shown in Fig. 2, the successful conjugation of CD onto the surface of silica particles was confirmed by FT-IR spectra. The spectrum of CD modified silica particles by DR was shown in Fig. 2. Compared with the FT-IR spectrum of bare silica

particles, the peaks at 2926, 1607 and 1037 cm^{-1} were ascribed the characteristic peaks of CD-COOH. The results indicate that the CD-COOH modification was successfully carried out on the surface of SiO_2.

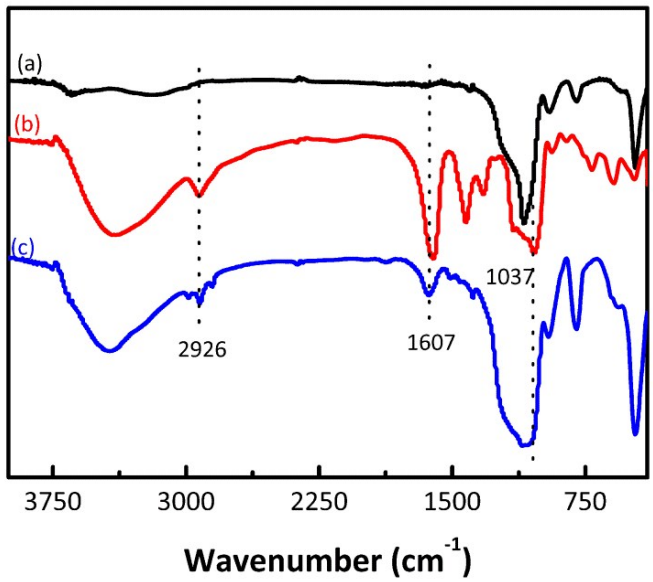


Fig. 2 The FTIR spectra of (a) bare SiO_2, (b) CD-COOH and (c) CD@SiO_2.

As shown in Fig. 3, TGA tests are performed on the bare and CD-COOH modified SiO_2 particles. The samples lost weight with the increase of the temperature due to the removal of physically adsorbed water and degradation of TEOS residuals in the samples. However, the CD-COOH modified SiO_2 particles have more weight loss than the bare particles from 100 to 600 °C, which induced by the decomposition of CD and DR on the surface of silica particles. According to the difference in weight loss of the bare and modified SiO_2 particles, the CD content of modified SiO_2 particles is calculated to be 10.6 wt%.

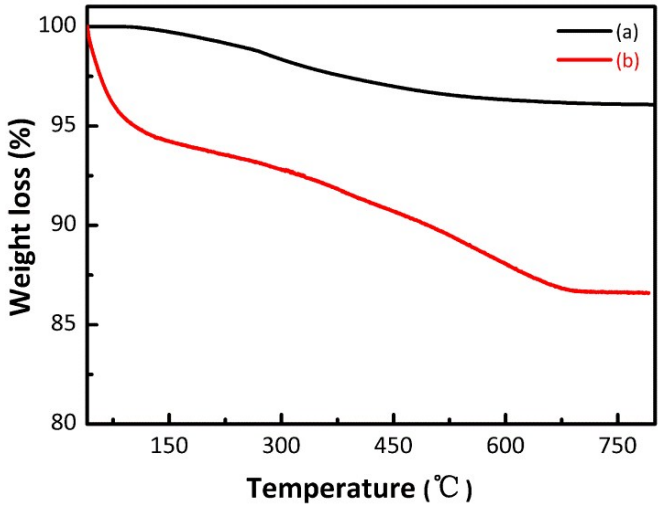


Fig. 3 TGA curves of (a) bare SiO_2 and (b) CD@SiO_2.

Enantioseparation Performance of CD-CSP in PO and RP mode

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Nature of CSPs[38-41] and separation conditions[39-43] have significant effect on elution of enantiomers. β-CD is widely used for seperation of enantiomers for its chiral molecular recognition. In the ring paste molecules, the sugar unit is used as a chair configuration, and the shape of a hollow cone structure, water solubility and non-water-soluble compounds can be entered into the cavity to form a clathrate.Object molecules can paste essence in whole or in part in ring cavity, mainly through the object and chiral cavity horse matchs with in chiral recognition and separation, and benzene ring compounds can and cyclodextrin cavity to carry on the good horse matchs, so cyclodextrin more types of chiral stationary phase for separation of chiral compounds with benzene ring. Herein, PO (polar organic) and RP (reverse phase) elution modes of enantiomers were investigated on the as-prepared CD-CSP.In RP-HPLC, the organic solvent can greatly influence the enantioseparation. In this study, MeOH and ACN were used as the mobile phase for enantioseparations of the above mentioned chiral compounds on the as-prepared CSP.

In PO elution mode, the enantioseparations of promethazine and benzoins were evaluated using MeOH as mobile phase. As shown in Fig. 4, promethazine (Rs=2.675) and benzoin (Rs=1.131) enantiomers were separated with MeOH as the eluting phase. The results suggest that the prepared CD-CSP has a resolving ability under PO elution mode. Furthermore, the separation of some other racemates (ESI,† Fig. S1) were reported in the supplementary materials.

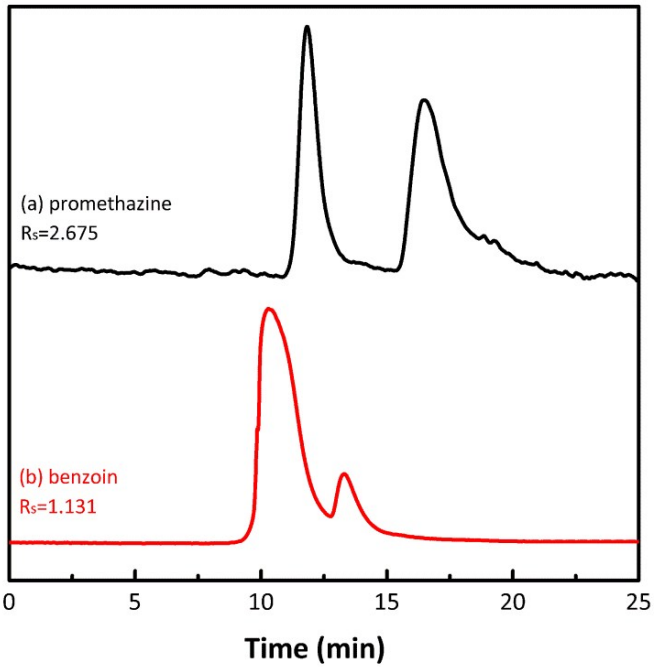

Fig. 4 Enantiomeric separation of (a) promethazine and (b) benzoin on CD@SiO_2 column (15 cm × 4.6 mm i.d.); mobile phase, MeOH; flow rate, 0.2 mL/min; UV detector, 250 nm; temperature, 25 °C.

In RP elution mode, the inclusion complexation between CD and the analytes is considered as the main driving force for

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enantioseparations.[44] Evaluation of chiral recognition ability of CSP in RP-elution mode was shown in Fig. 5. Promethazine (Rs=2.498) and benzoin (Rs=1.59) enantiomers were separated with V_{ACN}:V_{H_2O}=7:3 as the eluting phase as shown in Fig. 5. The results suggest that the prepared CSP has a resolving ability under RP elution mode.

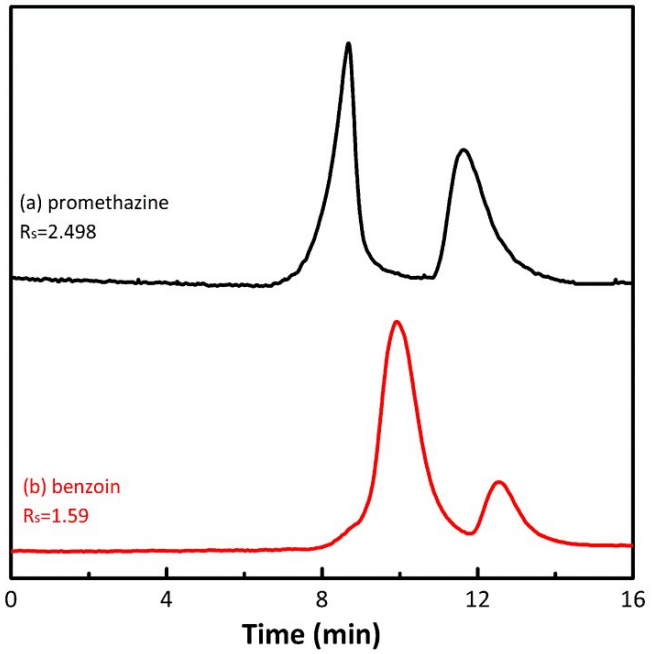

Fig. 5 Enantiomeric separation of (a) promethazine and (b) benzoin on CD@SiO_2 column (15 cm × 4.6 mm i.d.); mobile phase, ACN-H_2O 7:3 (v/v); flow rate, 0.2 mL/min; UV detector, 250 nm; temperature, 25 °C.

Effect of buffer

Very often, buffers are recommended to be added into mobile phases to enable the separation of basic drugs or to improve the chiral resolutions of some drugs.[45] In this study, chlortrimeton, which could not be resolved in PO mode, were successfully separated with the addition of TEAA buffer (0.3%, pH 4.0) to ACN. The UV spectra of chlotrimeton isomers (ESI,† Fig. S2) were reported in the supplementary materials. As shown in Fig. 6 (a), when there is no TEAA buffer was added into the mobile phase, only one peak of chlortrimeton could be observed. When 10% TEAA buffer (0.3%, pH 4.0) were added into ACN (Fig. 6 (b)), there are two peaks can be observed, which indicated that the chlortrimeton enantiomers were separated by the addition of TEAA. Further increasing of the ratio of TEAA buffer could give rise to the increase of Rs (Fig. 6 (c) and (d)). Both two entatiomers of chlortrimeton can generate hydrogen bonding easily, and the two entatiomers can form π-π conjugate bond. Thus, entatiomers and stationary phase is easy to form molecular inter-atomic forces (such as hydrogen bonds or static electricity, etc.). In the acidic condition, the interaction between the two and the ring paste is strengthened and obtained a good separation. The adhesion strength of the two enantiomers differences because of the difference of the force strength with stationary phase.

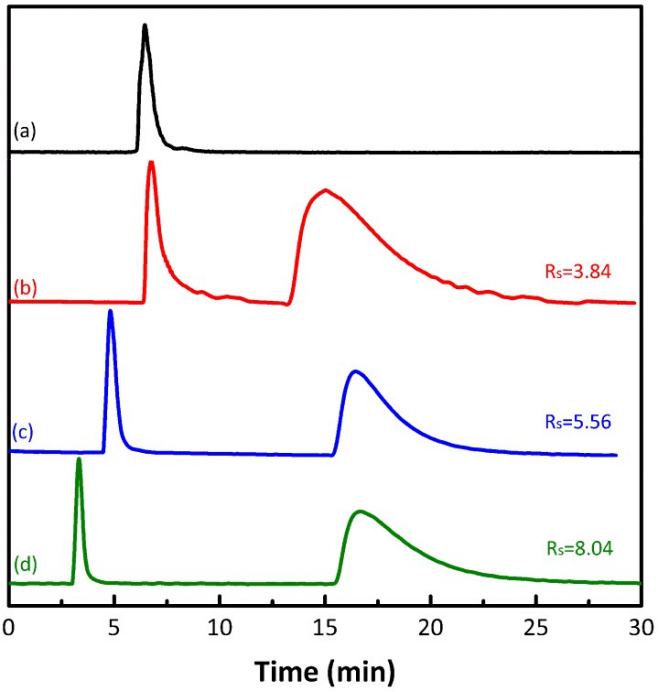

Fig. 6 Enantiomeric separation of chlortrimeton on CD@SiO_2 column (15 cm × 4.6 mm i.d.); flow rate, 0.2 mL/min; UV detector, 250 nm; temperature, 25 °C; mobile phase conditions: (a) ACN 100%, (b) TEAA-ACN 1:9 (v/v), (c) TEAA-ACN 2:8 (v/v), (d) TEAA-ACN 3:7 (v/v).

Effect of the Analyte Mass

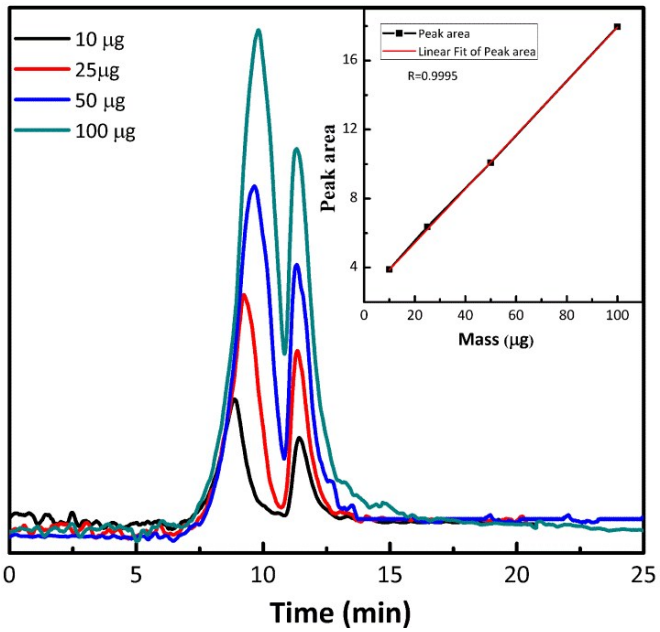

Fig. 7 Enantiomeric separation of promethazine on CD@SiO_2 column (15 cm × 4.6 mm i.d.); mobile phase, MeOH; flow rate, 0.2 mL/min; UV detector, 250 nm; temperature, 25 °C; injected mass: 10 μg (1 μL, 10 mg/mL), 25 μg (2.5 μL, 10 mg/mL), 50 μg (5 μL, 10

mg/mL), 100 μg (10 μL, 10 mg/mL). Inset: relationship between injiected mass and peak area of promethazine.

To examine the loading capacity of the CSP without compromising resolution, a loading test was carried out using different injection masses. It was evident that the retention time of the enantiomer for promethazine became closer with increasing injection mass from 10 to 100 μg with flow rate of 0.2 mL/min at 25°C (Fig. 7). When the promethazine loading was increased from 10 to 100 μg of each racemate, the chromatographic peak area of each single antipode rises linearly (as shown in the inset of Fig. 7). The result may be due to stronger hydrogen bonding between carboxyl groups of CD-COOH and amino groups of promethazine. In addition, the reproducibicity of the CSPs and the effect of flow rate were also been investigated (ESI,† Fig. S3 and Fig. S4).

Conclusions

In summary, we developed a green and effective light-assisted strategy to prepare CD-CSP for enantioseparation of racemic drugs. This material's morphology and chemical composition were characterized using FTIR, TGA and SEM. The enantioseparation performance of as-prepared CD-CSP was evaluated with racemates in mixed modes HPLC. The effect of separation parameters including different mobile phase, buffer and analyte mass on the enantioselectivity of the as-prepared CSP were investigated in details. Meanwhile, the possibility of successful separation for this CSP might be dependent on the hydrogen bonding and dipole-dipole interaction between analytes and the CSP.

Conflict of interest

The authors confirm that this article content has no conflict of interest.

Acknowledgements

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Graphic abstract

Light-assisted preparation of cyclodextrin-based chiral stationary phase and its separation performance in liquid chromatography

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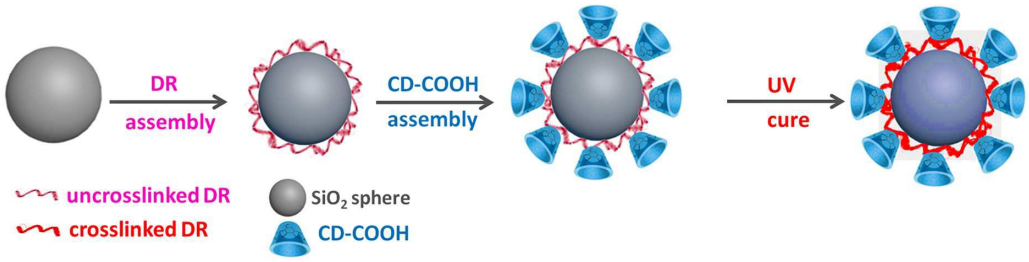

A facile light-assisted preparation of cyclodextrin-based chiral stationary phase was developed for enantioseparations in HPLC.