Hybrid monolithic columns coated with cellulose tris(3,5-dimethylphenyl-carbamate) for enantioseparations in capillary electrophromatography and capillary liquid chromatography

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A hybrid monolithic capillary column synthesized with (3-chloropropyl)-trimethoxysilane (CPTMS) and tetramethoxysilane (TMOS) via sol–gel chemistry was in situ coated with cellulose tris(3,5-dimethylphenyl-carbamate) (CDMPC) for enantioseparations in capillary electrophotomography (CEC) and capillary liquid chromatography (CLC). Prior to coating, the prepared CP-silica hybrid monolith was straightforwardly modified with diethylamine (DETA) to introduce –NH2 functionalities via the nucleophilic substitution reaction, which generate the stronger EOF for CEC. The coating condition was optimized to obtain a stable and reproducible chiral stationary phase for enantioseparation. The results indicated that racemic benzoin was baseline separated on the resulting hybrid monolith coated with 30 mg/mL CDMPC in CEC, while several racemates were successfully enantioseparated on the resulting CP-silica hybrid monolithic column coated with 60 mg/mL CDMPC in CLC with RP and NP modes.

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1. Introduction

The development of enantioseparation methods has received great interest during the past several decades. Capillary-based microscale separation technique including capillary electrophotomography (CEC) and capillary liquid chromatography (CLC) is preferred in analytical scale of chiral separation due to low cost, speed, effectiveness and reproducibility [1–6]. The state-of-the-art in microseparation techniques has been reviewed, and it has been concluded that monolithic capillary columns are particularly suitable for both CEC and CLC because monolithic columns eliminate the need for frits retaining the stationary phase, and possess good permeability and good peak capacity [7–12]. To date, the monolithic enantiomer-selective stationary phases utilized in CEC or CLC can be classified into four categories: particle-fixed monoliths, silica-based monoliths, polymer-based monoliths and molecularly imprinted monoliths [13–20].

Polysaccharide derivatives have occupied a unique place among these chiral stationary phases (CSPs) and have been the most widely used chiral selector for enantioseparation of a broad range of chiral compounds [21–24]. Several kinds of polysaccharide derivatives such as cellulose tris(3,5-dimethylphenyl-carbamate) (CDMPC), cellulose tris(4-methylbenzoate), cellulose tris(3,5-dichlorophenyl carbamate) and amylose tris(3,5-dimethylphenylcarbamate) have been coated or immobilized onto the silica-based monoliths and successfully applied for enantioseparations in CLC or CEC [25,26,27,28,29]. However, the drawbacks of silica-based stationary phases are also well known, including a limited pH range of 2–8 in mobile phases due to unstable nature of Si–O–Si bond in acidic and basic solutions. Zou et al. [30] and Park et al. [31,32] coated CDMPC onto the hydrophilic poly(acrylamide-co-N,N′-methylene-bisacrylamide) monolith and porous zirconia monolith with confines of fused-silica capillaries for CEC enantioseparation, respectively.

The hybrid organic-silica monoliths are receiving more and more interests in analytical research field, which combine the advantages of organic polymer-based and pure silica-based monoliths, such as easy fabrication, wide pH range tolerance, good mechanical stability and high permeability [33]. Many hybrid monoliths have been used as stationary phases for CLC or CEC separation, as well as for sample pretreatment [34–36]. To the best of our knowledge, however, few hybrid monoliths were applied for preparation of CSPs. Chankvetadze et al. [26,37] first prepared the hybrid monolith from tetramethoxysilane (TMOS) and methyltrimethoxysilane (MTMS), and then modified

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by in situ coating with amyllose tris(3,5-dimethylphenylcarbamate) and CDMPC for CLC enantioseparations. In this work, CDMPC was coated onto a hybrid chloropropyl-functionalized silica (CP-silica) monolith, which was synthesized via the co-condensation of (3-chloropropyl)-trimethoxysilane (CPTMS) and TMOS. The monolithic CSP was evaluated for chiral separation in CEC and CLC.

2. Materials and methods

2.1. Chemicals and reagents

Microcrystalline cellulose was obtained from Merck (Darmstadt, Germany). 3,5-Dimethyiphenoxyisocyanate and racemic benzoin, indapamide, praziquantel, Tröger’s base, trans-stilbene oxide, alpenolol, pindolol, and propranolol were purchased from Sigma (St. Louis, MO, USA). Racemic flavanone was obtained from Acros (NJ, USA). Racemic tetrahdropalmatine (THP) was obtained from National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). All sample solutions had a concentration of about 1.0 mg/mL in either ethanol or isopropanol depending on the mobile phases. CDMPC was self-synthesized as described in the literature [38], and then dissolved in acetone with different concentration prior to coating. CPTMS (97%), poly(ethylene glycol) (PEG, Mn = 10,000), ethylene diamine and diethylenetriamine (DETA) were purchased from Aldrich (Milwaukee, WI). TMOS was obtained from Chemical Factory of Wuhan University (Wuhan, China). Fused-silica capillary with 75 μm I.D. and 375 μm O.D. was purchased from the Realfine Chromatography Ltd. (Hebei, China). Water used in all experiments was purified by a Milli-Q system (Millipore Inc., Milford, MA). HPLC-grade ACN, n-hexane and 2-propanol (IPA) from Merck (Darmstadt, Germany) were used for the preparation of mobile phases. Other chemical reagents were of analytical grade.

2.2. Preparation of the capillary hybrid monolithic CSP

The preparation of hybrid CP-silica monolith coating with CDMPC involved three steps, as illustrated in Fig. S1 of the Supplementary material.

2.2.1. Fabrication of hybrid monolith and modification

The hybrid CP-silica monolith was prepared in a 40-cm long capillary (75 μm I.D.) according to our previous report [39] with minor modification. First, a mixture of acetic acid (0.01 M, 5.0 mL), TMOS (1.8 mL) CPTMS (0.6 mL) PEG and urea was magnetically stirred at 0 °C for 4 h to form a homogeneous sol solution. Then, the sol solution was sonicated for 30 min at 0 °C, and manually injected into the pretreated capillary with an appropriate length by a syringe. After both ends of the capillary were sealed with rubbers, the condensation reaction was carried out at 60 °C for 12 h. The resulting CP-silica hybrid monolith was then flushed with water and methanol to remove the PEG, urea and other residuals. Prior to surface modification of hybrid monolith, the column was flushed with ethanol for 30 min. The solution of ethylene diamine or DETA in ethanol with different concentration was pumped through the CP-silica hybrid monolithic columns for 30 min using a manual syringe pump. Finally, the modification of the hybrid monolithic columns was carried out at 70 °C for 12 h in a water bath. The resulting hybrid monolith was completely flushed with ethanol to remove the residue.

2.2.2. In situ coating of hybrid monolith with CDMPC

The in situ coating of the hybrid monolithic capillary column was performed according to the approach presented by Chankvetadze et al. [37]. In brief, a 40-cm long hybrid monolithic capillary column was connected to a blank stainless-steel HPLC column (50 × 4 mm I.D.), which served as a reservoir. The opposite end of the stainless-steel column was connected to an HPLC pump (Shimadzu, Kyoto, Japan). The mobile phase was acetone. The hybrid capillary column was flushed with acetone for 1 h under a pressure of 6 MPa. Then, the acetone in stainless-steel column was replaced by the prepared CDMPC solution, and the pump was kept at a constant pressure of 10 MPa to drive the CDMPC solution through the capillary column for 1 h. After filled with CDMPC solution, the capillary column was disconnected from HPLC system and left to dry at ambient pressure and temperature. It would take more than 3 weeks to evaporate acetone in the capillary.

2.3. Capillary electrochromatography

Electrochromatographic experiments were carried out on an Agilent CE system (Hewlett-Packard, Waldbronn, Germany) equipped with a UV detector and a ChemStation software for data acquisition and processing. The mobile phases were composed of ACN with varying concentration of acetate buffer and filtered prior to use. The standard samples with a concentration of 1.0–10.0 mg/mL were prepared with ACN. For CEC evaluation, a 30-cm long hybrid monolith was formed in a 40-cm long capillary, while the other was blank. The detection window was created by removing outer coating of a 2- to 3-mm segment with a razor blade in the empty section of capillary, which was located as close to the monolith as possible. As a result, the effective length of monolithic column was 24 cm with a total length of 33 cm after cut. Prior to CEC, the column was placed in the CE cartridge and preconditioned with mobile phase for at least 30 min with an HPLC pump. Then, the cartridge was installed in the CE instrument, and the column was equilibrated by applying a voltage of 5 kV until stable current and baseline were observed. Both electrokinetic injection of sample and separation were performed at room temperature, and the detection was set at wavelength of 214 nm. Thiourea was selected as EOF marker. The CEC retention factor of the neutral analytes tested, k_{EC}, was calculated as: k_{EC} = (t - t_{0})/t_{0}, where t is the migration time of the analyte and t_{0} is the migration time of an unretrained EOF marker. The EOF velocity was calculated by the equation, \( \mu = 1 \times L / (V \times t_{0}) \), where \( \mu \) is the effective mobility, \( V \) is the applied voltage, \( t_{0} \) is the migration time of the EOF marker, and \( I \) and \( L \) are the effective and total length of the capillary, respectively. All data were obtained based on three runs.

2.4. Capillary liquid chromatography

The chromatographic experiments were carried out by using an LC system equipped with an Agilent 1100 LC micropump (Hewlett-Packard, Waldbronn, Germany) and a UV detector (K-2501, Knauer, Germany). Data was collected at 214 nm, and processed by a chromatography workstation (Beijing Caili Scientific Instrument Ltd., Beijing, China). A Rheodyne standard 7725i injector (Elite, Dalian, China) with a 20 μL sample loop was used. The flow rate of the pump was set at 50–200 μL/min. For obtaining a flow rate of nanoliters per minute, a T-union connector served as a splitter with one end connected to the capillary monolithic column and the other end to a blank capillary (95-cm long, 50 μm I.D.). The split ratio was controlled at about 1/400, and the actual flow rate in the monolithic column was 100–500 nl/min. The outlet of the hybrid monolithic column was connected with a Teflon tube to an empty fused-silica capillary (75 μm I.D.), where a detection window was made by removing a 2 mm length of the outer polyimide coating in a position 5.5 cm from the separation monolithic column outlet. Mobile phases for RP mode were prepared by mixing appropriate volumes of ACN and H₂O (or salt solutions) to reach desired organic levels (and salt concentrations), while the mobile phases for NP mode
were the mixtures of n-hexane and 2-propanol with various volume ratios.

2.5. Other instruments for characterization

Scanning electronic microscopic (SEM) images were acquired by using a Jeol JSM-840 scanning microscope (Tokyo, Japan). Monolithic bulk material was prepared in a stainless-steel HPLC column (15 cm × 4 mm I.D.) as the same conditions as in a capillary. Pore size distribution was measured on an Autopore IV 9500 (Micromeritics, Norcross, USA). The specific surface area was calculated from nitrogen adsorption/desorption measurements using a Quadrasorb SI surface area analyzer (Quantachrome, Boynton Beach, USA).

3. Results and discussion

3.1. Preparation and characterization of hybrid monolithic column coating with CDMPC

The hybrid CP-silica monolithic matrices were prepared by using CPTMS and TMOS via sol–gel chemistry according to our recently reported approach [39]. In this work, the influences of PEG and urea content as well as poly-condensation temperature on the column morphology were further carefully investigated by keeping volume ratio of TMOS/CPTMS at 3/1 as they played vitally important roles in the 3D-skeleton formation of CP-silica hybrid monolith. It was found that a transparent gel-like monolith was formed in a capillary when PEG was less than 300 mg in the mixture at any temperature (40, 50, 60 and 70 °C), while increasing PEG led to occur a phase separation, but the capillary was not filled with monolith matrices. However, this phenomenon was alleviated by adding urea. The influence of urea dosage in precondensation mixture on monolith formation and morphology was studied by keeping the PEG at 810 mg and the temperature at 60 °C. It was observed that the monolith gradually occupied the whole capillary as the amount of urea was increased to 800 mg, and no obvious difference was seen with an optical microscope when the urea amount was higher than 1000 mg. The hybrid monoliths prepared with different urea at 1100, 1200, 1300 mg and 1400 mg were characterized with SEM, and the results were shown in Fig. 1. The macropores with about 2 μm in diameter were observed (as in Fig. 1A), and their diameters were decreased with an increase of urea amount. That is, the addition of urea would affect the pore size distribution, which in turn affect the permeability. In addition, the condensation temperature also had an effect on the formation of the CP-silica hybrid monolith. A series of monoliths were fabricated at different condensation temperatures (40, 50, 60 and 70 °C) by using 810 mg PEG and 1200 mg urea in the mixture. The results indicated that the monolith was seriously detached from the inner wall of the capillary formed at lower condensation temperature (40 °C), while a little detachment from the inner wall was even observed when fabricated at 50 °C. At relatively high temperatures (60 and 70 °C), the monoliths could be fully filled in the capillary and homogenous matrices were obtained, however, the monolith fabricated at 70 °C exhibited higher backpressure during the permeability measurement.

As a result, the bulk CP-silica hybrid monolith was prepared by adding 810 mg PEG and 1200 mg urea and polycondensation at 60 °C for the following characterization. Pore size measurement indicated unimodal pore size distribution as shown in Fig. S2 of the Supplementary material, where mean pore size was calculated at ~1.0 μm in diameter. The specific surface area was calculated as 358.6 m²/g based on nitrogen adsorption/desorption isotherm. Furthermore, the mechanical stability of the hybrid monolithic column was examined. A straight-line plot (R² = 0.997) of back pressure as a function of flow rate ranged in 50–500 mL/min indicated that the hybrid monolith possesses good mechanical stability under pressure of 15 MPa. The permeability of the column was calculated based on the Darcy’s Law, \( B_0 = \frac{F q}{\eta \pi r^2 \Delta P} \), where \( F \) is the flow rate of the mobile phase, \( \eta \) is the viscosity of the mobile phase, \( L \) is the effective length of column, \( r \) is the inner radius of the column, and \( \Delta P \) is the pressure drop of the column [40]. The permeability of the resulting CP-silica hybrid monolithic column was calculated as 8.65 × 10⁻¹⁰ m², demonstrating the good permeability of the prepared hybrid column.

The CDMPC has been successfully coated on either native silica monolith [25] or hybrid monolith synthesized with MTMS/TMOS [37] for chiral separation. Herein, CP-silica monolith would be similarly coated with chiral selectors after straightforward modification with nucleophiles such as ethylene diamine or DETA to form —NH₂ functionalities via the nucleophilic substitution reaction, which generates the stronger EOF for CEC. Therefore, the effect of derivatization with ethylene diamine or DETA on the EOF was investigated, and the results were compared with that on native CP-silica monolith. The cathodic EOF was formed on the native CP-silica, and increased with an increase of pH in mobile phase ranging in 3.0–7.0, generating from the silanol groups in the surface of CP-silica hybrid. After modified with ethylene diamine or DETA, however, the direction of EOF on the hybrid monoliths was reversed, and anodic EOF was decreased with an increase of pH value of mobile phase ranging between 3.0 and 7.0, confirming the effective modification with ethylene diamine or DETA. This phenomenon could be also found in the CP-silica hybrid monolith modified with \( \text{N,N-dimethyl-N-dodecylamine} \) [39]. Due to the relatively high EOF generated by DETA-modified hybrid monolith, this column was adopted for the following CDMPC-coating experiments.

3.2. Effects of coating conditions on enantioseparation

As the coating conditions including coating time and concentration of CDMPC solution had influences on the enantioseparation and reproducibility of the resulting monolithic CSP, these factors were investigated and optimized. Due to the high viscosity of CDMPC solution, a longer time would be taken to homogeneously coat CDMPC onto the hybrid monolith at a certain pressure, which depended on the concentration of CDMPC in acetone. The 30 mg/mL CDMPC solution was first introduced to coat the DETA-modified hybrid monolith at a pressure of 10 MPa. A little dried and white solid appeared at the end of hybrid monolith after 1 h, which was assigned to CDMPC after acetone evaporating. This meant that the capillary column was filled with CDMPC solutions. After thorough evaporation of acetone for several weeks, the dried column was used for characterization. Fig. S3 of the Supplementary material presents the SEM images of a hybrid monolithic column coated with CDMPC. It was revealed that the morphology of hybrid monolith was not obviously changed, and the monolith was still connected to the inner wall of capillary. In addition, the permeability of the monolithic CSP was also measured, and no remarkable change was found.

After fabricated a detection window, which was located at the blank section of capillary, the resulting monolithic column was applied for enantioseparation in CEC and CLC. Fig. 2A indicates the electrochromatogram of benzoin enantioseparation on hybrid monolith coated with 30 mg/mL CDMPC by using the mobile phase of 35% acetonitrile/acetate buffer solution (5 mM, pH 3.50) with CEC. The result of baseline separation of benzoin demonstrated that the chiral selector of CDMPC was well coated onto the hybrid monolith matrices. Compared to the reported data on the CDMPC coated onto pure silica monolith [25] or organic monolith [30], the
resolution and efficiency on this hybrid monolith was remarkably lower. The same result was also observed for enantioseparation of benzoin with CLC, as shown in Fig. 2B. The poor efficiency in CEC may be due to the following reasons. In this case, a blank section of capillary with 8.5 cm long was required to fabricate a detection window for on-column CEC analysis and detection, which was different from the on-column detection mode in either pure silica monolith [25] or organic monoliths [30] coated with CDMPC. As a result, the CP-silica monolithic matrices at the interface were not homogeneous, perhaps resulting from the solvent evaporation in the sol–gel process. Additionally, the blank section of capillary would be filled with CDMPC solution for coating. A lot of CDMPC was deposited at the interface of monolithic matrices after evaporation of acetone when using the CDMPC solution of 30 mg/mL. In a word, the heterogeneous hybrid matrices and unsatisfied coating led to low efficiency in CEC mode.

A lot of racemates could not be well separated on this column in CEC and CLC. These proved that the amount of CDMPC coated onto the monolithic support may result in different chromatographic properties of the column, such as the retention, resolution, and efficiency. As a result, more CDMPC was tried to coat onto the hybrid monolith by using the CDMPC solution of 60 or 90 mg/mL. Unfortunately, this column was not permeable for CEC separation, as a lot of CDMPC was deposited at the interface of monolithic matrices and blocked hybrid column when using the CDMPC solution of 60 mg/mL, while it did not occur when using the CDMPC solution of 30 mg/mL. This could be evitable in the preparation of hybrid chiral monolithic column for CLC as the hybrid matrices were full of the capillary, and off-column detection mode was adopted in an Agilent 1100 LC system for CLC analysis. The resulting column coated CDMPC in solution with concentration of 60 mg/mL was thus measured with CLC in the following experiments.
3.3. *Enantioseparations in CLC*

Polysaccharide derivative CSPs have been widely used under the mobile phases of n-hexane/alcohol (NP mode), and in combination with aqueous-organic (RP mode) and pure organic (polar organic mode) mobile phases. Here the enantiomeric separation using the synthesized cellulose-based monolithic CSP was performed with NP CLC mode. In order to obtain a broad perspective on the performance of the monolithic CSP, a 30-cm long monolithic capillary column was examined in the chiral separation of different kinds of compounds (neutral, acidic and basic analytes) by using mobile phases of n-hexane/IPA at different ratios. Fig. 3 presents several typical chromatograms of *enantioseparations* on a CDMPC-coated hybrid monolithic capillary column by using mobile phase of n-hexane-IPA (90/10, v/v). It can be seen that racemic benzoin, trans-stilbene oxide and praziquantel could be baseline separated within 10 min, though other racemates were not well-separated. The obtained chromatographic data including retention time, resolution and plate number are listed in Table S1 of the Supplementary material. The plate numbers varied in the range 8020–37,000 m−1 for the first eluting peak and in the range 4610–26,000 m−1 for the second eluting peak. These results demonstrated that *in situ* coating of hybrid CP-silica monolith with polysaccharide derivatives represents a useful approach for preparation of monolithic capillary columns for *enantioseparations*.

To evaluate the separation ability of the prepared hybrid monolithic CSP, several acidic, basic, and neutral racemates were tested using aqueous mobile phases with different pH value. The results are also listed in Table S1 of the Supplementary material. Most of racemates were successfully resolved, and their resolution (Rs) varied from 0.49 to 3.48. Neutral benzoin and trans-stilbene oxide were successfully resolved using mobile phase of ACN/H₂O (40/60, v/v), while basic tetrahydroapalmitine and pindolol were completely resolved with a mobile phase of ACN/H₂O (containing 5 mM NaH₂Ac, pH 9.7) (30/70, v/v). Typical chromatograms are illustrated in Fig. 4. No remarkably peak tailing of the basic racemates was observed ascribing to the existence of the amino groups on the surface of the monolithic matrices.

As the organic solvents in mobile phases had effect on the enantioseparation, benzoin was selected as a testing analyte for investigating the influence of the ACN in mobile phase on retention factor, resolution and efficiency. The results are given in Table S1 of the Supplementary material. Both retention factor and efficiency decreased with the increase of ACN content in mobile phases from 30 to 50%. The results indicated the hydrophobic interaction between CDMPC and chiral analytes. As a result, the fairy good separations of other enantiomers were acquired after optimizing the composition of mobile phases as presented in Table S1 of the Supplementary material.

3.4. *Column-to-column reproducibility and stability*

The run-to-run repeatability of the monolithic CSP was evaluated through the relative standard deviation (RSD) for the retention of benzoin as the model analyte for CLC when the mobile phase was 30% ACN/H₂O. The column-to-column and batch-to-batch reproducibility was also investigated in terms of both Rs and the retention factor of benzene under the same CLC conditions. It was calculated that the repeatability of run-to-run injections was less than 3.8% (n = 3), indicating that the stability of hybrid monoliths was satisfactory and acceptable. To investigate the reproducibility of column preparation process, other two columns were prepared with the same process (60 mg/mL). The RSDs of retention time and resolution were less than 4.5% and 8.8% (n = 3), demonstrating satisfied reproducibility for column preparation of the CDMPC coated monolithic columns. In addition, the prepared monolithic CSP was used with highly acidic (pH 2.7) and basic (pH 9.7) mobile phases as well as with mobile phase of n-hexane-IPA for one week. No significant decrease of resolution factors, efficiencies and obviously column deterioration were observed after the columns were repeatedly
used for multiple injections. This indicated the good stability and pH resistance ability of CDMPC-coated hybrid monolithic column in CLC.

4. Conclusions

A novel enantioselective hybrid monolithic capillary column was successfully developed by in situ coating polysaccharide derivative, CDMPC, onto the hybrid CP-silica monolith, which was straightforwardly modified with DETA to form —NH$_2$ functionalities via nucleophilic substitution reaction prior to coating. The resulting monolithic capillary CSP was applied for enantioseparation in CEC and CLC. Only racemic benzoin was baseline separated on the obtained CSP coating with relative low concentration of CDMPC in CEC. More efforts should be made to improve the CEC separation ability of this hybrid monolithic CSP, and it indicates the possibility of in situ modification of monolithic hybrid columns with CDMPC and applicability of these columns for CEC enantioseparations. Fortunately, several chiral compounds were successfully enantioseparated on the CSP coating with relative high concentration of CDMPC in CLC with RP and NP modes. This CP-silica hybrid column can be applied for coating other cellulose/amyllose derivatervives, as well as for immobilizing other chiral selectors.

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**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jchroma.2012.09.022.

**References**