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Open tubular capillary columns with basic templates made by the generalized preparation protocol in capillary electrochromatography chiral separation and template structural effects on chiral separation capability

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ABSTRACT

Some open tubular (OT) molecule imprinted polymer (MIP) silica capillary columns have been prepared using atenolol, sulpiride, methyl benzylamine (MBA) and (1-naphthyl)-ethylamine (NEA) as templates by the pre-established generalized preparation protocol. The four MIP thin layers of different templates showed quite different morphologies. The racemic selectivity of each MIP column for the template enantiomers was optimized by changing eluent composition and pH. The template structural effects on chiral separation performance have been examined. This work verifies the versatility of the generalized preparation protocol for OT-MIP silica capillary columns by extending its boundary toward templates with basic functional group moieties. This study is the very first report to demonstrate a generalized MIP preparation protocol that is valid for both acidic and basic templates. The chiral separation performances of atenolol and sulpiride by the MIPs of this study were found better than or comparable to those of atenolol and sulpiride obtained by non-MIP separation techniques and those of some basic template enantiomers obtained by MIP based techniques.

1. Introduction

Pharmaceuticals often exhibit chiral structures and are most widely used as racemic mixtures. The pharmacological activity of these drugs, however, resides predominantly in the S-enantiomer and there are some side effects related to the R-enantiomer [1]. Such difference in pharmacological and pharmacokinetic effects between the two enantiomers has driven a strong demand for effective methods of enantioselective separation.

Molecular imprinting technology provides a way to synthesize the polymer with cavities of a template and the polymer is subsequently capable of selectively rebinding the template [2–4]. Molecular imprinted polymers (MIPs) have attracted significant interest in separation science because of their unique pre-determinative selectivities and practical abilities for template recognition. In the last two decades, this technique has been employed in variety of applications such as pharmaceutical study, environmental chemistry and chromatographic separation as well as isolation of drugs, toxins, pesticides and food components [5–7]. Although MIPs have shown a great potential in HPLC based analyses, the use of MIP coupled with CEC is still trying to make its niche in analytical science [8–10]. MIP–CEC studies have been well introduced in a review article [11]. Monodispersed spherical MIP particles as chromatographic media [12] and MIPs as media for sample preparation [13] have also been extensively reviewed in the recent literature.

Owing to the versatility and the potential that can be achieved, the future of this technique is promising. The basic concepts of MIP preparation are rather simple and easy. However, to obtain a highly efficient MIP requires tedious optimization in the formulation of polymerization mixture and reaction conditions via synthesis and evaluation of various polymers in extensive experiments. Furthermore, a very different MIP preparation protocol is generally required to resolve a new pair of enantiomers. The entire procedure is time consuming and needs to be generalized. In a particular study, a computational method (MIP dialing) using combinatorial screening and molecular modeling was proposed as a general procedure for fast preparation of a specific MIP [14]. In another report, the cross selectivity MIP synthesized using only one imprint showed chiral separation for several pairs of β-blockers [15].

Recently, we demonstrated a generalized preparation protocol for several pairs of non-steroidal anti inflammatory drugs (NSAIDs) by fabricating short OT-MIP CEC columns [16]. In one of our earlier reports, similar MIP preparation protocol was employed to acquire long open tubular molecularly imprinted columns (OT-MIP) in capillary, which offered exceptionally high chiral separation efficiencies for ketoprofen enantiomers [17]. We have

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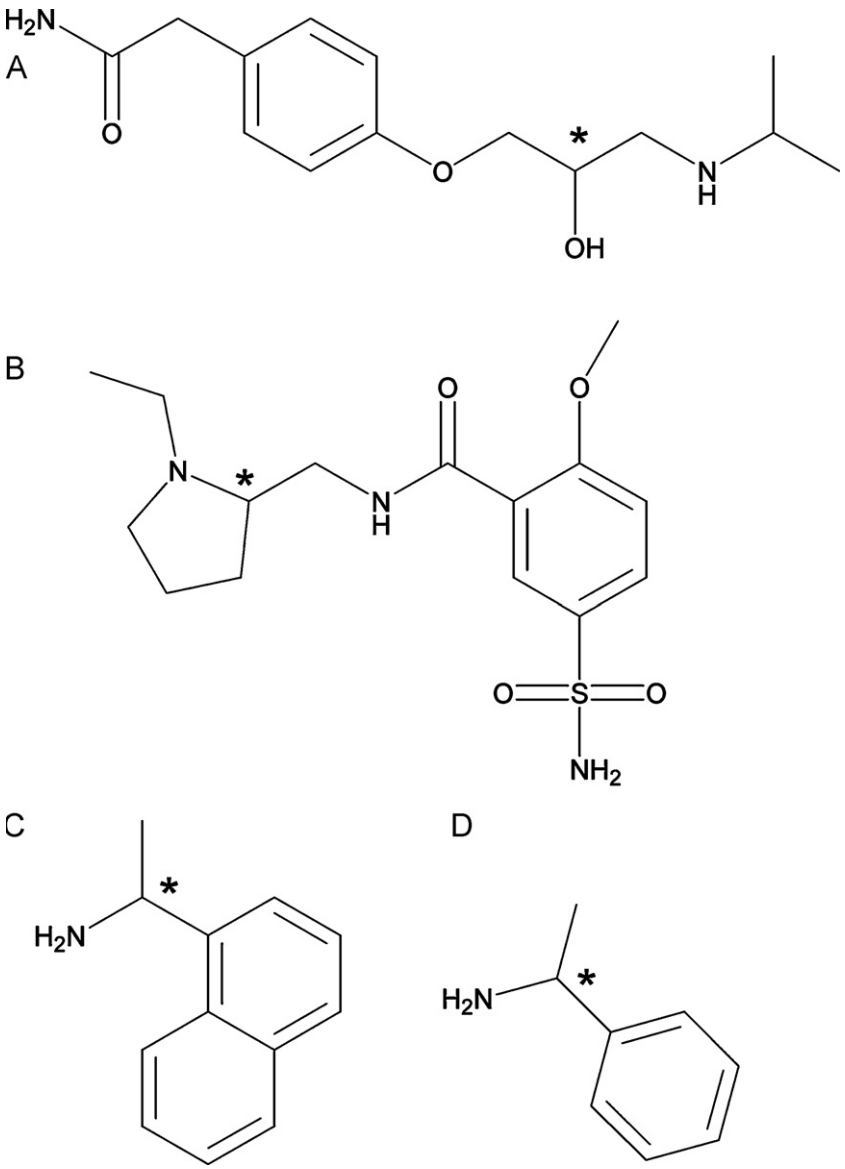

Fig. 1. Molecular structures of the templates employed in this study. (A) Atenolol, (B) sulpiride, (C) (1-naphthyl)-ethylamine, and (D) methyl benzylamine.

further extended the generalized protocol to some additional acidic templates and camphor derivatives [18,19]. However, the real generalized MIP preparation protocol should be valid for a variety of templates of a wide range of different chemical properties including typically opposing subgroups such as acidic vs. basic templates.

Thus, synthesis of MIPs with basic templates and their application in chiral separation have been explored in this work. The basic templates used in this study are atenolol, sulpiride, methyl benzylamine (MBA) and (1-naphthyl)-ethylamine (NEA). Atenolol is a β-blocker agent being used in the treatment of angina pectoris, hypertension, arrhythmias and in several cardiovascular disorders while sulpiride is a selective dopamine D_2 antagonist with antipsychotic and antidepressant activity. Several chromatographic separation procedures were employed for chiral separation of racemic atenolol, including HPLC separation on a Chiralcel OD column in normal phase mode [20], CE separation with dual cylodextrin additives composed of β-cyclodextrin and β-cyclodextrin–glucose [21], derivatization with a fluorogenic reagent followed by separation on a Chrialcel OJ-R column in reversed phase mode [22] to show excellent detection sensitivity, and HPLC separation on a Chiralpak AD-H column in normal phase mode with a small amount of ethanesulfonic acid incorporated in the eluent bringing up dramatically improved chromatographic resolution [23].

Chiral separation of sulpiride has been carried out by various chromatographic techniques such as CE with 2% sulfated β-cyclodextrin added to the mobile phase as a chiral selector [24], HPLC with a chiral cellobiohydrolase (CBH) column [25], and CE based on partial filling technique [26].

In addition to the above well known basic drugs, two other structurally different basic templates, methyl benzylamine (MBA) and (1-naphthyl)-ethylamine (NEA), were included in the group of basic templates to investigate the effects of template structure on the chiral recognition capability of the resultant MIPs.

This work handles the significant task of fabricating and evaluating OT-MIP capillary columns with basic templates using the generalized preparation protocol previously developed for acidic templates. The molecular structures of the basic templates employed in this study are given in Fig. 1.