New monolithic chiral stationary phases for the enantioselective nano-liquid chromatographic separation of racemic pharmaceuticals

by

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Abstract

Pharmaceutical enantiomers have distinctive stereoselective binding interactions with the biological receptors and consequently enantiomers of a single drug may be considerably different in their pharmacokinetic and pharmacodynamic properties. As chiral drugs constitute approximately one-third of all drug sales worldwide, regulatory authorities such as the US Food and Drug Administration (FDA) have strict requirements to approve new chiral entities. Commercialization of enantiomerically pure drugs was previously considered a desirable challenge with many practical limitations. Nowadays, the technical advances of chiral separation and asymmetric synthesis allowed the availability of many single enantiomers on a commercial scale. Compared to the various available techniques to access enantiomerically pure drugs, separation of racemic mixtures has been demonstrated to be economically more feasible than diastereomeric crystallization or asymmetric synthesis to produce single enantiomers on a commercial scale.

Different separation techniques are available for the separation of racemic mixtures, such as Gas Chromatography (GC), High Performance Liquid Chromatography (HPLC), Supercritical Fluid Chromatography (SFC), Capillary Electrophoresis (CE) and Capillary Electrochromatography (CEC). Among them, HPLC is the workhorse of chiral separations for industrial applications. Miniaturization of conventional HPLC to nano-HPLC enables high throughput, reduced sample size and small consumption of hazardous solvents and consequently the chiral separation can be achieved under environmentally friendly conditions.

Monolithic stationary phases have been known for the past three decades. They are composed of a single piece of porous material through which the mobile phase percolates leading to the
chromatographic separation. Monoliths enable high mobile phase flow rate and hence faster separation compared to the particle-packed columns.

This thesis is concerned with the development of new monolithic chiral stationary phases in hair-thin columns called capillary columns for the chiral separation of thirteen classes of racemic pharmaceuticals using nano-HPLC. In this research, three chiral selectors namely lipase, β-cyclodextrin and single-walled carbon nanotubes were used for the preparation of polymer- or silica-based monolithic chiral stationary phases in capillary format. Different approaches were adopted for the preparation of the capillary columns; columns’ reproducibility was also investigated to ensure their efficiency for industrial applications.
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<th>Full Form</th>
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<td>ADMPC</td>
<td>Amylose tris(3,5-dimethylphenylcarbamate)</td>
</tr>
<tr>
<td>AGP</td>
<td>α1-acid glycoprotein</td>
</tr>
<tr>
<td>AIBN</td>
<td>Azobisisobutyronitrile</td>
</tr>
<tr>
<td>B0</td>
<td>Column permeability</td>
</tr>
<tr>
<td>BSA</td>
<td>Bovine serum albumin</td>
</tr>
<tr>
<td>BuMA</td>
<td>Butyl methacrylate</td>
</tr>
<tr>
<td>CAGR</td>
<td>Compound annual growth rate</td>
</tr>
<tr>
<td>CCC</td>
<td>Countercurrent Chromatography</td>
</tr>
<tr>
<td>CDMPC</td>
<td>Cellulose tris(3,5-dimethylphenyl-carbamate)</td>
</tr>
<tr>
<td>CDs</td>
<td>Cyclodextrins</td>
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<td>CE</td>
<td>Capillary electrophoresis</td>
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<tr>
<td>CEC</td>
<td>Capillary electrochromatography</td>
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<tr>
<td>CLC</td>
<td>Capillary liquid chromatography</td>
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<tr>
<td>CMPA</td>
<td>Chiral mobile phase additive</td>
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<tr>
<td>CS</td>
<td>Chiral selector</td>
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<tr>
<td>CSP</td>
<td>Chiral stationary phase</td>
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<td>Dimethylformamide</td>
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<td>2,2-Dimethoxy-2-phenyl-acetophenone</td>
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<td>Dimethylsulfoxide</td>
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<td>EDMA</td>
<td>Ethyleneglycol dimethacrylate</td>
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<td>EEO</td>
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<td>HSA</td>
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<td>HOMs</td>
<td>Highly ordered mesoporous silica monoliths</td>
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<td>HPLC</td>
<td>High performance liquid chromatography</td>
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<td>ID</td>
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<td>-----------------------------------------</td>
</tr>
<tr>
<td>IOC</td>
<td>International Olympic committee</td>
</tr>
<tr>
<td>IPA</td>
<td>Isopropyl alcohol (2-propanol)</td>
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<td>k</td>
<td>The retention factor</td>
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<tr>
<td>KIT</td>
<td>Kyoto Institute of Technology</td>
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<tr>
<td>LC</td>
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<td>OD</td>
<td>Outer diameter</td>
</tr>
<tr>
<td>OVM</td>
<td>Ovomucoid</td>
</tr>
<tr>
<td>PEEK</td>
<td>Poly(ether-ether-ketone)</td>
</tr>
<tr>
<td>PO</td>
<td>Polar organic</td>
</tr>
<tr>
<td>POSC</td>
<td>Polar organic solvent chromatography</td>
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<tr>
<td>RP</td>
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</tr>
<tr>
<td>SCX</td>
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<tr>
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<td>SPMA</td>
<td>3-Sulfopropyl methacrylate</td>
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<tr>
<td>SWCNTs</td>
<td>Single-walled carbon nanotubes (SWCNTs)</td>
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<td>TEOS</td>
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<tr>
<td>γ-MAPS</td>
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