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

by

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List of publications

Papers in refereed journals and in preparation

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2. Cara E. Humphrey, **Marwa Ahmed**, Ashraf Ghanem and Nicolas J. Turner, "Applications of enzymes in kinetic resolutions, dynamic kinetic resolutions and deracemization reactions" Separation of Enantiomers: Synthetic Methods, First Edition. Edited by Matthew Todd, Wiley-VCH Verlag GmbH & Co, ISBN: 978-3-527-33045-4,123-160, 2014.

3. **Marwa Ahmed** and Ashraf Ghanem, "Enantioselective nano liquid chromatographic separation of racemic pharmaceuticals: a facile one-pot *in situ* preparation of lipase-based polymer monoliths in capillary format" Chirality, 26, 754-763, 2014.

4. **Marwa Ahmed** and Ashraf Ghanem, "Chiral β-cyclodextrin functionalized polymer monolith for the direct enantioselective reversed phase nano liquid chromatographic separation of racemic pharmaceuticals" Journal of Chromatography A, 1345, 115-127, 2014.

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1. **Marwa Ahmed** and Ashraf Ghanem, "New silica bonded chiral β-cyclodextrin based capillary column for enantioselective separation of different classes of pharmaceuticals", Chirality 2012, Fort Worth, Texas, USA.

2. **Marwa Ahmed** and Ashraf Ghanem, "Chiral and achiral polymer monolithic columns for separation of a mixture of different classes of pharmaceuticals using nano-HPLC", HPLC 2012, Anaheim, USA.

3. **Marwa Ahmed** and Ashraf Ghanem, "New silica bonded β-cyclodextrin-based capillary column for enantioselective nano liquid chromatographic separation of different classes of pharmaceuticals", HPLC 2013, Hobart, Australia.

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7. Ashraf Ghanem and **Marwa Ahmed**, "New Lipase-based polymer monoliths for the enantioselective nano-liquid chromatographic separation of racemic pharmaceuticals", Chirality 2014, Prague, Czech Rebublic.

8. Ashraf Ghanem and **Marwa Ahmed**, "Preparation of a novel β-cyclodextrin functionalized polymer monolith for the enantioselective nano-liquid chromatographic separation of racemic pharmaceuticals, Chirality 2014, Prague, Czech Republic.

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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Abbreviations

ADMPC	Amylose tris(3,5-dimethylphenylcarbamate)
AGP	α1-acid glycoprotein
AIBN	Azobisisobutyronitrile
B0	Column permeability
BSA	Bovine serum albumin
BuMA	Butyl methacrylate
CAGR	Compound annual growth rate
CCC	Countercurrent Chromatography
CDMPC	Cellulose tris(3,5-dimethylphenyl-carbamate)
CDs	Cyclodextrins
CE	Capillary electrophoresis
CEC	Capillary electrochromatography
CLC	Capillary liquid chromatography
CMPA	Chiral mobile phase additive
CS	Chiral selector
CSP	Chiral stationary phase
DCM	Dichloromethane
DMF	Dimethylformamide
DMPAP	2,2-Dimethoxy-2-phenyl-acetophenone
DMSO	Dimethylsulfoxide
EDMA	Ethyleneglycol dimethacrylate
EEO	Enantiomer elution order
ee_p	Enantiomeric excess of product
ee_s	Enantiomeric excess of starting material
EIA	Exercise-induced asthma
ER	Eudismic ratio
ε_T	Total porosity
EtAC	Ethylacetate
FDA	Food and drug administration
GC	Gas chromatography
GMA	Glycidyl methacrylate
h	hour
HSA	Human serum albumin
HOMs	Highly ordered mesoporous silica monoliths
HPLC	High performance liquid chromatography
ID	Inner diameter

IOC	International Olympic committee
IPA	Isopropyl alcohol (2-propanol)
k	The retention factor
KIT	Kyoto Institute of Technology
LC	Liquid chromatography
MIP	Molecularly imprinted polymer
MMA	Methyl methacrylate
MP	Mobile phase
MS	Mass spectroscopy
MtBE	Methyl *tert*-butyl ether
MTMS	Methyltrimethoxysilane
N	Theoretical plate number
Nano-LC	Nano-liquid chromatography
NP	Normal phase
OD	Outer diameter
OVM	Ovomucoid
PEEK	Poly(ether-ether-ketone)
PO	Polar organic
POSC	Polar organic solvent chromatography
RP	Reversed phase
SA	Selectand
SCX	Strong cation exchange
SEM	Scanning electron microscopy
SFC	Supercritical fluid chromatography
SPMA	3-Sulfopropyl methacrylate
SWCNTs	Single-walled carbon nanotubes (SWCNTs)
TEOS	Tetraethoxysilane
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMOS	Tetramethoxysilane
USD	US Dollars
VBTA	Vinylbenzyl trimethylammonium
w/w	weight/weight
γ-MAPS	3-(trimethoxysilyl)propyl methacrylate