Journal of Chromatography A, 1217 (2010) 941–952

Contents lists available at ScienceDirect

Journal of Chromatography A

journal homepage: www.elsevier.com/locate/chroma

Review

Chiral silica-based monoliths in chromatography and capillary electrochromatography

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ARTICLE INFO

Article history:
Available online 2 December 2009

Keywords:
Monolith
CEC
Chromatography
Enantiomeric separation
Enantioselectivity
Chiral

ABSTRACT

Chiral-modified silica-based monoliths have become well-established stationary phases for both high performance liquid chromatography (HPLC) and capillary electrochromatography (CEC). The silica-based monoliths were fabricated either *in situ* in the capillaries for nano-HPLC and CEC or in a mould for "conventional" HPLC. The present review summarizes the chiral modification of silica monoliths and the recent development in the field of enantioselective separations by nano-HPLC and CEC.

Contents

1. Introduction

Columns with particulate silica beds are well known and are extensively used for separation in HPLC and CEC. For increasing the performance of traditional HPLC columns, sorbents of progressively more narrow grain size composition and finer particles were used. The result was a significant increase in the pressure that should be necessary to ensure the optimal flow of the mobile phase. A novel concept in column technology has received considerable attention in recent years. Monoliths consisting of one single piece of a porous solid were employed as highly efficient stationary phase in chromatography and electro-driven methods [1–3]. Monolithic columns represent a good alternative to particle-packed columns for both HPLC and CEC separations because of their enhanced mass transfer and lower pressure drop. Little is known about the use of monolithic columns in GC [4]. Despite the fact that the monolith is characterized by high porosity, it significantly resists the carrier gas flow. The permeability was about three times lower than that of open tubular capillary. As expected a higher loadability but lower HETP values could be found.

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doi:10.1016/j.chroma.2009.11.079

Table 1
Chiral silica-based monolithic columns for "conventional" HPLC.

Silica backbone	Chiral selector	Analyte	Mobile phase	Reference
Chromolith Si	β-CD	Chromakalim, prominal, norgestrel, methadone, MTH-phe, PTH-phe, metoprolol, oxazepam	Hydro-organic, polar organic	[8]
Chromolith, RP-18e	Cellulose tris(3,5-dimethylphenyl carbamate)	2,2,2-trifluoro-1-(9-anthryl)ethanol, piprozolin, 2,2′-dihydroxy-6,6′-dimethylbiphenyl	Apolar organic	[9]
Chromolith Si	Cellulose tris(3,5-dimethylphenylcarbamate)	2,2,2-trifluoro-1-(9-anthryl)ethanol, benzoin, 2,2′-dihydroxy-6,6′-dimethylbiphenyl, flavanone 2-phenylcyclohexanone, 1,2,2,2-tetraphenyl-ethanol, Tröger's base, Co(III) acac	Apolar organic	[10]
Chromolith-NH_2	Penicillin G acylase	2-Aryloxyalkanoic acids	Hydro-organic	[11]
Chromolith Si	2,3-Methylated 3-mono-acylated 6-*O*-*tert*-butyldimethylsilylated β-CD 2,3-methyl 6-O-tert butyldimethyl-silylated β-CD	14 and 7 compounds, respectively	Hydro-organic	[12]
Chromolith Si	*tert*-Butylcarbamoylquinine	*N*-derivatized amino acids, suprofen	Hydro-organic	[13]
Onyx monolith	Proline-derived chiral selector	*N*-(3,5-dinitrobenzoyl)amino acids	Apolar organic	[14]
Chromolith Si	α_1-acid glycoprotein	Warfarin, propranolol	Hydro-organic	[15]
Chromolith Si	HSA	trp, warfarin, ibuprofen	Aqueous, hydro-organic	[16]

The monolithic stationary phases can be classified into two types: (i) silica-based monoliths prepared by sol–gel technology, by entrapping particles in inorganic gels or sintering silica beds and (ii) rigid organic polymer-based monoliths prepared by polymerization of suitable organic monomers in the presence of a porogen. In the present review only silica-based monolithic columns were considered. Silica monoliths were prepared by sol–gel technology either in a mould to produce a rod column (e.g., 4–7 mm I.D.) or *in situ* in a fused silica capillary (e.g., 50–530 μm I.D.) [1]. Once formed, the silica monoliths could be modified by covalently attaching chiral selectors to the silanol groups of the silica surface. To the author's best knowledge no enantiomeric separation with monolithic stationary phases in GC was described before.

2. Chiral-modified silica monolithic columns in "conventional" HPLC (see Table 1)

Chiral monoliths can be used in both in "conventional" HPLC (columns with internal diameters in a range of 2–4.8 mm) and nano-HPLC (capillaries with internal diameters up to 500 μm) systems. Nakanishi and Soga [5] developed a new sol–gel process which allows the preparation of monolithic materials with a bimodal pore structure (throughpores and mesopores) suitable for chromatography. The production is based on acid-catalyzed hydrolysis and polycondensation of alkoxysilanes. Tanaka and coworkers [6], and Lubda et al. [7] used this method for preparing monolithic silica columns of conventional format with high efficiencies and low backpressures for HPLC. The first commercially available monolithic silica column (Chromolith) was introduced by MerckKGaA in 2000. Classical HPLC columns with monolithic separation beds of this size are prepared in a column mould in which the monolith can later be replaced. In a further step the monolithic silica has to be coated or clad with a suitable material such as PEEK (poly(ether ether ketone) to which the column end fittings can be attached for use in HPLC-Systems [1]. *In situ* polymerization, the usually used method for preparing monolithic silica capillaries, is not applicable for conventional HPLC columns due to shrinkage. However, conventional HPLC apparatus which are available in nearly every lab, can be equipped with a classical monolithic column.

In the year 2003, the first enantiomeric separations with chiral-modified silica monoliths were described by Lubda et al. [8] and by Chankvetadze et al. [9]. As silica backbones both groups used commercially available monoliths (Chromolith) and modified the silica surface with chiral selectors. Lubda et al. [8] compared the chromatographic behaviour of a β-cyclodextrin modified silica monolith with a commercially available β-cyclodextrin bonded particulate material (ChiraDex). While the enantioselectivities of both columns were comparable, the retention factors and thus the analysis time were in most cases lower on the silica monolith than on the packed column. Even if the amount of β-cyclodextrin bound to the silica monolith was only half of the amount of β-cyclodextrin bound to particles (ChiraDex) good separation factors were achieved for several chiral drugs such as chromakalin, prominal, oxazepam and methadone (see Fig. 1). Due to the flat van Deemter curve, fast enantiomeric separation could be observed. To modify the plain silica monolith two different synthesis routes were described: (i) batch modification of the unclad silica monolith and (ii) *in situ* modification of silica monolith in the clad column in the flow-through mode. Unsatisfactory heterogeneity of the surface modification were found for the batch modification, thus in situ modification (ii) was preferred. Chankvetadze et al. [9] described the enantiomeric separation of 2,2,2-trifluoro-1-(9-anthryl)ethanol, 2,2′-dihydroxy-6,6′-dimethylbiphenyl and piprozolin on a silica monolith with octadecyl-functionalities coated with cellulose tris(3,5-dimethylphenylcarbamate). The baseline separation of the enantiomers of 2,2,2-trifluoro-1-(9-anthryl)ethanol was accomplished in less than 30 s (see Fig. 2). A disadvantage of the coated-type polysaccharide monoliths is the solubility or swelling of the material. To overcome this, cellulose tris(3,5-dimethylphenylcarbamate) was covalently attached *in situ* onto native silica monoliths clad in a 50 mm × 4.6 mm PEEK HPLC column [10]. The chiral modification of the silica monolith occurs in three steps: (i) reaction with γ-glycidoxypropyltrimethoxysilane, (ii) modification with the polysaccharide derivative and (iii) treatment with 3,5-dimethylphenylisocyanate in order to convert the hydroxyl groups of cellulose into carbamate moieties. However no significant improvement of enantiomer resolving ability was observed for the covalently modified monolith. Massolini et al. [11] immobilized