Focussing Review

Recent Developments in Column Technology for Fritless Packed Capillary Electrochromatography

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Abstract

During the past several years a large variety of fritless packed columns have been developed for CEC separations. These can be categorized into two major types : *in-situ* polymerized columns and particle-immobilized columns ; organic polymer and silica-based columns are included in the former type. This review is concerned with the progress in fritless packed column preparation that has been made until April 2001. In addition to a short introduction and conclusion, this review contains four main sections : (i) synthetic polymer columns (SPCs) ; (ii) in-situ polymerized silica columns ; (iii) particle-immobilized silica columns ; and (iv) molecular imprinted SPCs. In each section, details of different approaches are summarized in tabular form.

Keywords: capillary electrochromatography, fritless columns, rod columns, continuous beds, capillary columns, packed columns

1. Introduction

With the goal of achieving a significant improvement in liquid chromatographic (LC) efficiency, electroosmotic flow (EOF) has been used to propel the mobile phase through silica-based particles packed in a capillary [1-6]. This method is called capillary electroosmotically-driven chromatography, electro-driven chromatography, or capillary electrochromatography (CEC). EOF can arise from the surface of LC packings and the inner wall of the capillary. When charged compounds are separated by CEC, both partitioning and electromigration contributes to the separation. Thus far a number of researchers have published their experimental works using packed capillaries. However, the method is not yet mature enough to be used as a routine, practical tool. The formation of bubbles within the packed section or the frits is the primary problem in using packed columns for CEC separations. The bubble formation was ascribed to the non-uniformity in EOF along the capillary [7-9], in addition to the self-heating effect. Pressurization of both ends of the capillary column is useful for preventing the bubble formation, but this requirement not only increases the overall complexity of the equipment but also makes the coupling of CEC and mass spectrometry very difficult. Moreover, efficient packing of silica particles into a small inside diameter (i.d.) fused silica capillary as well as fabrication of high permeable frits in a reproducible manner continues to be practical problems.

The above-mentioned problems can be solved by using a so-called fritless packed column. The formation of bubble would be minimized provided that a homogeneous stationary phase is prepared by polymerizing monomers in a capillary. Obviously, troublesome and less reproducible procedures such as frit-fabrication and particle-packing are eliminated. In our papers published in 1995 [10, 11], we used the term fritless packed column to refer to columns whose stationary phases are prepared within the confines of a fused silica capillary. In this approach, monomeric precursors are introduced into the capillary to be *in situ* polymerized, forming a continuous bed. The concept of an *in situ* formed column is not really new ; large i.d. columns consisting of a continuous bed were prepared by Hjertén et al. [12] in 1989, and by Svec et al. [13] in 1992 for the purpose of use in LC. (Note that this concept further dates from early studies on LC and gas chromatography columns in the early 1970's [14-17].) The principal difference in column preparation between LC and CEC is that in order for the resultant column to generate strong EOF, functional monomers must be contained in the polymerization solution. We first utilized 2-acrylamido-2-methylpropanesulfonic acid as the functional mono-

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mer to obtain enough EOF for CEC separation of neutral compounds.

In this review we focus on the preparation of *in situ* polymerized columns or fritless packed columns. This type of column is often called a monolithic column, a rod column, or a continuous bed column. There are a few cases in which the term a fritless packed column has different meanings : a column having fine tapered ends to hold the packing in a capillary [18, 19] ; a column packed with sol-gel bonded silica particles ; and a column packed with thermally bonded silica particles. The latter two types of columns come within the scope of this review, but we are not concerned here with the first category.

2. Synthetic polymer columns

Many groups have so far been involved in the preparation of organic polymer-based columns. The polymerization mixture typically includes a monovinyl monomer, a divinyl monomer (cross-linker), and an ionogeneric monomer (an EOF functional monomer). Porogenic solvents or polymeric surfactants have been used to form a porous structure. According to Luo and Andrade [20], sub-μm channels should be formed in the bed in order to reduce the tortuosity and attain enough EOF. The formed bed can be either soft or rigid. The surface chemistry of the columns can be modified to yield selected separation mechanisms either by copolymerization with specific monomers or by chemical modification after polymerization. Depending on the chemistry or composition used for polymerization, it is possible to control the EOF to be generated in the column. Also, polymer-based materials allow their use under extreme pH conditions. Using a fritless packed columns, proteins and peptides can be well separated at a low pH. From the standpoint of separation efficiency, this type of fritless packed columns possesses an advantage over particle-packed columns that the so-called “wall effects” common to slurry-packed columns are minimized. To make good use of their experience acquired in the studies of fritless packed columns for use in HPLC, Hjertén et al. and Fréchet et al. have reported various columns for CEC (see Table 1). Extensive reviews of different approaches for the preparation of synthetic organic polymers were recently published by Svec et al. [21, 22]. A list of synthetic polymer columns (SPCs) which have been developed for achiral CEC separation is given in Table 1.

Fritless column technology has been also used for enantiomeric separations. The derivatives of β-cyclodextrins, valine, chiral crown ether, and quinidine were incorporated into the stationary phase to be used as a chiral selector. In Table 2, a list of

Table 1. A summary of literature on SPCs for achiral separations.

Research Group	Ref	Monomers; Comments	Solutes	Maximum efficiencies (plates/m)
Fujimoto	10, 11	AAm, BIS, AMPS	Ketones	145 000
Fujimoto	23	IPAm, BIS, AMPS	Ketones PAHs, steroids	159 800
Hjertén	24	HEMA, MAm, VSA GMA, PDAm; Post-derivatized with C_{18}-groups	PAHs	Not available
Hjertén	25	HEMA, PDAm, AGE; Two-step polymerization and post-derivatization	PAHs	Not available
Hjertén	26	AAm, PDAm, VSA, C_4- or C_{18}-MA; Emulsified	PAHs	Not available
Hjertén	27	PDAm, MAm, C_{18}-MA, DMDA; Emulsified; Two-steps	PAHs	Not available
Hjertén	28	PDAm, MAm, IPAm, VSA	Antidepressant drugs	200 000
Novotny	29	AAm, BIS, AA, C_4-, C_6-, or C_{12}-A	Ketones, peptides, oligo-saccharides	398 000
Fréchet	30-32	EDMA, C_4-MA, AMPS	Aromatics, polystyrenes	120 000
Fréchet	33	*ibid.*	Aromarics, peptides	210 000 (for thiourea)
Horváth	34	ST or VBC, DVB; Quaternary ammonium functionalized	Peptides, proteins	Not available
Horváth	35	GMA, MMA, EGDM; Tertiary amino functionalized.	Peptides, proteins	Not available
Zhang	36	ST, DVB, MAA	Aromatics	140 000
Zou	37	C_4-MA, EDMA	Acids, bases	140 000
Shepodd	38	C_4-A, BDDA, AMPS or AOETM (quaternary ammonium)	PAHs	220 000

Table 2. A summary of literature on SPCs for chiral separations.

Research Group	Ref	Monomers; Comments	Solutes	Maximum efficiencies (plates/m)
Hjertén	39	AAm, BIS, AMPS or DMDA(quaternary ammonium), Ally-CD (selector)	Propranolol (cation), ibuprofen (anion), baritals (neutral), etc.	570 000
Hjertén	40	MAAm, PDA, VSA, *N*-(2-hydroxy-3-allyloxypropyl) L-4-hydroxyproline); Chiral ligand-exchange	Phenylalanine	Not available
Fréchet	41	HEMA, EDMA, AMPS, C_4-MA or GMA, 2-hydroxyethyl methacrylate (*N*-L-valine-3,5-dimethylanilide) carbamate (selector)	*N*-(3,5-Dinitrobenzoyl) leucine diallylamide	61 000
Fréchet	42	EDMA, GMA or HEMA, MCQ (selector)	Derivatized leucines	74 000
Fréchet	43,44	EDMA, HEMA, MCQ (selector)	Derivatized amino acids, etc.	250 000
Koide	45,46	AAm, BIS, AMPS or AAmET (quaternary ammonium), Neutral β-CD polymers incorporated	Anions, cations	240 000
Koide	47,48	AAm, BIS, AMPS or AAmET(quaternary ammonium) ally carbamoylated β-CD (selector)	Dansylated amino acids, terbutalin, benzoin, propranol	151 000
Koide	49	AAm, BIS, AMPS, ally carbamoylated β-CD (selector); achiral crown ether in the buffer	Primary amines, cations, neutral	151 000
Koide	50	AAm, BIS, AMPS, (+)-tetraally 18-crown-6 carboxylate or (+)-18crown-6 tetracarboxylic acid 2-allyl ester (selector)	Primary amines	135 000

chiral CEC separations carried out with synthetic polymer columns is given. For enantioselective separations by molecular imprinted polymers, see Section 5.

3. *In-situ* polymerized silica columns

Early studies on CEC have focused on the use of silica-based, reversed-phase packing materials. The primary advantage of using silica gels is that they have a long history in HPLC application. With such stationary phases, our knowledge on retention and selectivity adjustment can be transferred directly for neutral compounds. Moreover, silica particles can generate a reasonable EOF. In recent years, the production of porous silica by a sol-gel process has received tremendous attention in HPLC. In a series of publications [51-53], Ishizuka et al. described a sol-gel process which consisted of acid-catalyzed hydrolysis and polycondensation of tetraethoxysilane in the presence of poly (ethylene glycol). This technique has been modified for the fabrications of a silica-based column for use in CEC [54-58]. A novel sol-gel chemistry was used to prepare octadecylated silica columns in a single-step process [59]. Examples of the various *in-situ* prepared silica columns that have appeared in the literature are summarized in Table 3.

Table 3. A summary of literature on in-situ polymerized silica columns.

Research Group	Ref	Monomers; Comments	Solutes	Maximum efficiencies (plate height)
Wendelken	60	Potassium silicate; Post-octadecylation	Aromatics	10 μm
Tanaka	54,55	TMOS; Post-octadecylation	Alkylbenzenes, PAHs	7-8 μm
Fujimoto	56-58	*ibid.*	Ketones, parabens	9 μm
Malik	59	TMOS, C_{18}-TMS (Anodic EOF)	PAHs, ketones, aldehydes	5.7 μm

Table 4. A summary of literature on particle-immobilized silica columns.

Research Group	Ref	Immobilization solution or method	Immobilized particles	Maximum efficiencies (reduced plate height)
Horváth	61	Mild sintering or hydrothermal treatment; Resilanization	6 μm ODS	1.3
Unger	62,63	Mild sintering or hydrothermal treatment;	3 μm ODS	Not available
Honda	64	A croslinking silylating agent	3 μm bare silica	Not available
Zare	65	TEOS	5- or 3 μm ODS	4.1
Henry	66,67	*ibid.*	3 μm ODS	2.8
Zare	68	*ibid.*	5 μm silica with chiral selectors	2.8
Lee	69	TMOS, ethyltrimethoxysilane	5 μm ODS	1.56
Lee	70-72	*ibid.*	5 μm ODS; 80 Å.	1.9
			7 μm ODS; 1400 Å	0.65
Roed	73,74	*ibid.*	5- or 7 μm ODS; 4000 Å	1.9
Remcho	75	Potassium silicate	5 μm ODS	1.2-1.5
Remcho	76	TEOS, *tert*-butyl-triethoxysilane or *n*-octyltriethoxysilane	5 μm ODS	1.1-1.4
Remcho	77	C_1-or C_3-MA, EDMA	5 μm ODS	1.1-1.5

4. Particle-immobilized silica columns

Another alternative to prepare fritless packed columns is to immobilize HPLC packing particles inside the capillary column. The immobilization of the packing material has been accomplished by the use of an entrapping solution or sintering the particles by heat. In the former approach, a capillary may be filled with a suspension of packing particles in a sol-gel solution, or a sol-gel solution may be introduced into a column that has been packed with particles. Once the particles are fixed, the capillary no longer requires frits. Obviously, this renders a more stable packed bed without problems associated with the retaining frits. The immobilization methods that have been employed for the fabrication of fritless packed columns are listed in Table 4.

5. Molecular imprinted SPCs

Molecular imprinted SPCs would represent a complementary alternative to chiral-ligand bonded SPCs. It is believed that the application of molecular imprinting technology to CEC would greatly improve the performance of imprinted polymer-based separations in LC (see ref 78, for a review). For noncovalent imprinting, polymerization is performed in an environment as apolar as possible. In addition to the polymerization solvent, the choice of chiral functional and cross-linking monomers as well as the duration and temperature of the polymerization reaction are often important parameters for the polymerization system to form well-defined imprints. Molecular imprinting provide a predictable elution order, the imprinted enantiomer being the most strongly retained. Although molecularly imprinted columns are dominantly utilized for the separation of a racemic mixture of the imprinted molecule, they often show good chiral recognition ability for other structural analogues. Table 5 summarizes molecular imprinted columns that have developed for fritless packed CEC.

6. Conclusion

A numerous number of methods for the preparation of fritless packed columns have been appeared over the last few years. Due to the advantages described in this article, fritless packed columns will hold an important place in CEC in time, although some researchers believe that CEC will need more time to be used routinely and find its unique applications. It is certain that the increasing research activity in this area accelerates the development of CEC. This review only summarized fritless packed columns that

Table 5. A summary of literature on molecular imprinted synthetic polymer columns.

Research Group	Ref	Monomers	Imprinted species	Separated enantiomers
Hobo	79,80	MAA, EDMA	L-Phenylalanine anilide and analogues	L-Phenylalanine
Hobo	81	AAm, BIS	Imprinted polymer particles entrapped in gel	L-Phenylalanine and analogues
Nilsson	82-84	MAA,TRIM	(*R*)-Propranolol or (*S*)-Metoprolol	β-Blockers
Nilsson	85	MAA or 2Vpy, TRIM, PETRA, PETEA, or EDMA	(*S*)-Ropivacaine	Anesthetics

have been prepared on the capillary scale. There is tremendous interest today in performing chromatographic separation in a microchip format. The methods described in sections 2, 3, and 5 will be utilized to prepare separation media within narrow channels, because polymerization solutions can readily fill available spaces, irrespective of the size or shape of the channels. A few attempts in this direction [86, 87] were made more recently ; further developments in the area are awaited.

Glossary of abbreviations

A	acrylate
AA	acrylic acid
AAm	acrylamide
AAmET	*N*-(2-acrylamidoethyl) triethylammonium chloride
AGE	allyl glycidyl ether
AMPS	2-acrylamido-2-methyl-1-propanesulfonic acid
AOETM	[2-(acryloyloxy) ethyl] trimethylammonium methyl sulfate
BDDA	1, 3-butanediol diacrylate
BIS	*N*, *N'*-methylenebisacrylamide
C_{18}-TMS	*N*-octadecyldimethyl [3-(trimethoxysilyl) propyl] ammonium chloride
DVB	divnylbenzene
EDMA	ethylene dimethacrylate
GMA	glycidyl methacrylate
HEMA	2-hydroxyethyl methacrylate
IPAAm	*N*-isopropylacrylamide
MA	methacrylate
MAA	methacrylic acid
MAm	methacrylamide
MCQ	*O*-[2-(acryloylxy) ethylcarbamoyl]-10, 11-dihydroquinidine
MAA	methacrylic acid
MMA	methyl methacrylate
ODS	octadecylsilica
PDAm	piperazine diacrylamide
PEO	poly (ethylene oxide)
PETEA	pentaerythritol tetraacrylate
PETRA	pentaerythritol triacrylate
TEOS	tetraethoxysilane
TMOS	tetramethoxysilane
TRIM	trimethylolpropane trimethacrylate
VBC	vinylbenzene chloride
2 Vpy	2-vinyl pyridine

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