Focusing Review

Miniaturization for the Development of High Performance Separation Systems

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Abstract

Miniaturization is a key technological approach to realize high performance separation systems that have several important features required in modern analytical methods. A smaller scale of the stationary phase synthesis enables a systematic analysis of the retention behavior and also a more efficient development of novel stationary phases in liquid chromatography. Development of microscale sample preparation technique has been regarded as a valuable supporting approach to the development of microscale separation methods. Effective on-line coupling of the microscale sample preparation and separation allows an efficient and rapid analysis without a loss of sensitivity for most of the analytical separations. In this review, development of the miniaturized separation techniques and the applications have been described from the view point of the authors' research group, including the development of novel stationary phase, microscale sample preparation techniques for liquid and gas sample matrices.

Keywords: Miniaturization; Stationary phase; Retention behavior; Sample preparation; Fiber; Liquid chromatography; Gas chromatography

1. Introduction

Downsizing of analytical systems has been progressively more studied because of several advantageous features of the developed systems. In separation science, especially in liquid phase separations, the miniaturization of separation systems including the downsizing of the column, pump and detector is increasingly investigated to realize high performance separation systems [1-4]. Introduction of microcolumn separations in liquid chromatography (LC) has been regarded as one of the most effective solution to the recent requirements such as significantly high separation performance, short analysis time, high sensitivity with a reduced analysis cost and solvent consumption. Miniaturization of sample preparation techniques is studied for not only just a downsizing of sample preparation process but also an effective on-line coupling of the developed miniaturized sample preparation techniques to microcolumn separations. The resulting developed hyphenated system allows a comprehensive miniaturization

of the sample preparation and the chromatographic separation [1-3].

In this article, the miniaturization of the sample preparation and chromatographic separation techniques will be reviewed on the basis of the establishment by the authors' group in the past decades. Needle-type microscale sample preparation techniques are also described along with the development of fiber-packed capillaries for sample preparation and chromatographic separations.

2. Novel stationary design on the basis of systematic retention behavior analysis

Interpretation of the retention mechanism in LC has been widely carried out to understand the retention for developing a novel stationary phase that have a unique selectivity based on a specific interaction between the stationary phase ligand(s) and the target analyte [4-6]. A systematic analysis has been made for a set of retention data taken with a set of standard sample probes specially

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Fig. 1. Novel stationary phases synthesized by the molecular shape recognition concept. A) alkyl, alkyldiphenyl and triphenyl bonded phases; B) phenylpropyl and methoxylated phenylpropyl bonded phases; C) multi-legged phenyl bonded phases; D) liquid-crystal bonded phases and E) C₆₀ bonded phase. Reproduced from [3] with permission.

designed for the work. Numerous numbers of reports on the separation mechanism have been published on the basis of the retention analysis, however, there is still a long way to get the complete explanations of the whole separation mechanism. This is because many parameters are controlling the retention generated by a molecular recognition process in typical LC separations [5-8].

As the stationary phase in reversed-phase (RP) LC, octadecylsilica (ODS) stationary phases are most commonly employed due to a universal selectivity to wide range of target compounds and also the commercial availability [4]. Two types ODS phases, monomeric and polymeric, have been introduced to routine runs in separation laboratory, where the monomeric phase is

Fig. 2. Chemical structures of various PAHs. 1, naphthalene; 2, acenaphthene; 3, acenaphthylene; 4, diphenylmethane; 5, fluorene; 6, *cis*-stilbene; 7, *trans*-stilbene; 8, phenanthrene; 9, anthracene; 10, pyrene; 11, triphenylylene; 12, *o*-terphenyl; 13, *m*-terphenyl; 14, *p*-terphenyl; 15, naphthacene; 16, benzo[*c*]phenanthrene; 17, benzo[*ghi*]fluoranthene; 18, chrysene; 19, benz[*a*]anthracene; 20, benzo[*a*]pyrene; 21, perylene; 22, pentacene; 23, dibenzo[*c,g*]phenanthrene; 24, benzo[*ghi*]perylene; 25, phenanthro[3,4-*c*]phenanthrene; 26, coronene; 27, dibenzo[*g,p*]chrysene (tetrabenzonaphthalene); 28, dibenzo[*cd,lm*]perylene; 29, tribenzo[*a,cd,lm*]perylene; 30, tetrabenz[*a,cd,j,lm*]perylene; 31, pentabenz[*a,cd,f,j,lm*]perylene; 32, hexabenz[*a,cd,f,j,lm,o*]perylene; 33, C₆₀ and 34, C₇₀.

synthesized from mono-functional silanes in non-aqueous synthetic conditions, and the polymeric phase is typically synthesized from tri-functional silanes in aqueous conditions.

These phases offer different selectivities on the basis of the structure and the resulting ordering on the silica support surface, although these phases are both classified as ODS phases in terms of the bonded ligands onto the support. The correlation between the surface structure and the selectivities has been reported [9-13], however, the complete interpretation of the correlation is not established well mainly due to the difficulty in the surface characterization of these phases in real LC separation conditions.

In order to analyze the interaction mechanism in LC, a large number of bonded stationary phases have been experimentally synthesized, such as ODS phases of different surface coverage and carbon content, alkyl-bonded phases having different alkyl ligands and various aromatic bonded phases [10-35]. Miniaturization of the column can be regarded as one of the key technology to effectively develop novel stationary phases in LC [16-35], where microcolumns of 0.53 mm i.d. or 0.32 mm i.d. have been typically employed. Separations in a relatively small scale could offer several typical advantages such as, quick evaluation, an affordable synthetic cost, an easy introduction of expensive analytes and a limited cost for the waste disposal after the separations. Taking advantages of the down-sizing of LC separation, as shown in Fig. 1, many novel stationary phases have been developed, where a group of polycyclic aromatic hydrocarbons (PAHs) and fullerenes were employed as the solutes [3-6]. Introducing PAHs (Fig. 2) as the sample probes, a systematic analysis of the interaction between the bonded stationary phase ligand(s) and the analyte could be carried out, because of these relatively simple molecular structures than real analytes to be separated in actual LC applications [36-42].

3. Fibrous stationary phase in microscale separations

Fibrous materials (Fig. 3) were introduced as the stationary phase in microscale separations, where a bundle of fine fibrous materials was packed longitudinally into a capillary to prepare the column in microcolumn LC and capillary electrochromatography (CEC) [43-45]. As the fibrous materials, several synthetic polymers including poly(*p*-phenylene-2,6-bisoxazole) (Zylon, Toyobo, Ohtsu, Japan) and poly(*p*-phenylene terephthalamide) (Kevlar, Du Pont-Toray, Tokyo, Japan) were introduced, as listed Table 1, because of a certain resistance to typical organic solvents and also mechanical strength required for the packing process [46]. Upon successful introduction of fine fibrous materials to the stationary phase in LC and CEC, further

Fig. 3. Chemical structures of fibrous polymers. A) Zylon; B) Kevlar; C) Nomex and D) Technora.

applications of the fine fibrous stationary phases have been created in gas chromatography (GC), where a polymer-coating onto the surface of the fibrous materials was carried out, if necessary [47-49].

Coated with a polymeric material typically employed in the preparation of open-tubular GC capillary columns, the resulting selectivity could be interpreted by the selectivity of the coating used and the compatibility of the coating with the surface of the fibrous support material, suggesting a future possibility for the development of novel packed-capillary column. This is because a more suitable combination of the polymer-coating and the support material could be expected for synthetic polymeric filaments than conventional fused-silica capillaries widely used as the support. In order to further enhance the compatibility of the coating materials and the fiber surface, surface modification reactions of the filaments were studied. The preliminary experiments clearly demonstrated a successful surface modification of the filaments with several types of functional groups [50-52], although these reaction conditions should be further optimized to realize a novel stationary phase.

In general, synthetic fibrous materials having a high resistance to organic solvent also show a good stability in high temperature conditions. The heat resistance performance of Zylon and Kevlar is, in fact, quite satisfactory for the use in typical temperature-programmed

Table 1. Heat-resistant fibers used.

fiber	diameter (μm)	number of packed filaments ^a	weight-loss temperature ($^{\circ}\text{C}$)	
			5 %	10 %
Zylon	11.5	170	690	710
Kevlar	12.4	146	550	570
Nomex	17.5	73	430	450
Technora	12.5	144	480	490

^a For fused-silica capillary of 0.32 mm i.d.

Fig. 4. Separation of Polywax 655. Conditions: column, deactivated metal capillary (0.3 mm i.d., 1.0 m) packed with the HR-1 (3.0%) coated Zylon (166±2 filaments); temperature program, 130°C (1.0 min) to 450°C at 5°C/min; carrier gas and column inlet pressure, N₂ and 10 kPa; injector and detector temperature, 400 and 450°C, respectively; sample injection, 10 µL (splitless injection) of the 1.0% solution in 1,2,4-trichlorobenzene.

runs in GC [47,48] (Table 1). Miniaturization of the column diameter as a GC packed-capillary allows a faster temperature-programmed separation. Taking advantages of a large sample loading of the packed-capillary column and a faster temperature program, it has been created that efficient separations of complex sample mixtures consisted of a large number of components such as homologous sample mixtures [53,54]. As illustrated in Fig. 4, high temperature GC separations were demonstrated using a metal capillary instead of fused-silica capillary having a limited heat-resistance due to the polyimide-film outside the capillary [53-55]. Longitudinal miniaturization of a GC packed-capillary was also studied, as typically shown in Fig. 5 [55].

4. Microscale sample preparation on fiber-packed capillary

Down sizing of sample preparation techniques for liquid-phase separations has been studied along with the effective on-line coupling of the miniaturized sample preparation technique to LC separation methods [56-65]. As similar to the successful applications of particulate chemically-bonded stationary phases in LC to an extraction medium in solid-phase extraction, several types of fiber-packed capillaries were introduced as the extraction medium in microscale sample preparation techniques

Fig. 5. Chromatograms for the separation of dodecane, tetradecane and hexadecane on a short polymer-coated fiber-packed capillary column with the rapid temperature programming. Conditions: column, deactivated stainless steel capillary (0.3 mm i.d., 0.05 m) packed with polymer-coated (HR-1, 5%) Zylon filaments; number of packed-filaments, 450; temperature program, A) 50°C to 140°C at 45°C/min and B) 50°C to 140°C at 60°C/min; column head pressure, 50 kPa; sample injection volume, 1 µL (splitless injection) of 0.1% solution in dichloromethane.

[66-74]. The longitudinal parallel alignment of the fine filaments make it possible to create a set of many through-flow passes in the capillary, allowing a low pressure drop through the capillary. This is one of the

Fig. 6. Schematic diagram of a fiber-packed extraction capillary in an on-line coupled extraction/separation system. Simultaneous processing of the sample preparation and the separation is possible for consecutive runs.

advantages of the fiber-packed extraction capillary that enables a high flowrate pumping of the sample solution in the extraction process, and therefore, a larger volume ratio between the sample solution and the desorption solvent. In addition, even if insoluble particulate materials are existed in the sample solution to be analyzed, a relatively long life time of the extraction capillary is often possible.

As shown in Fig. 6, the extraction capillary is normally placed in between the injector and the switching valve in order to accomplish a simultaneous separation/extraction in the on-line coupled system [66-74]. Further miniaturization was studied as illustrated in Fig. 7, where, a very short extraction capillary was installed as an in-valve configuration in a commercially available micro-injector [71-74].

Fig. 7. In-valve installation of a miniaturized extraction capillary in a commercially available micro-injector.

5. Needle-type sample preparation device

Packed into a specially-designed needle, polymeric particles and filaments could be employed as the extraction medium [75-78]. In-needle derivatization methods were developed for several target analytes with a fiber-packed needle. Because of the inert surface of the fibers, the derivatization reaction in the needle was successfully processed, where the change of the chemical structure of the target analytes during the derivatization reaction make it possible for the derivatives to be extracted more effectively in the needle extraction device [79-82].

Needles packed with particulate materials have also been employed in a microscale extraction technique (Fig. 8). As well as the fiber-packed needle, the particle-packed needle device enables a simultaneous processing of the sampling and extraction in the needle. In addition, after the sampling,

the needle devices could be stored typically up to several days at room temperature with a set of the plug and cap specially designed for the needle, allowing 1) the effective on-site multipoint sampling, 2) an easy transportation of the sampled needle devices and 3) the precise analysis of the target compounds in an analytical laboratory located away from the sampling site.

As the sample matrix, a variety of environmental air samples were extracted with an advantageous feature of easy sampling without any electric pump [83-93]. Introducing a vacuum air sampling syringe, it takes about only 5 minutes to complete a typical air volume of 100 mL. Volatile organic compounds were also extracted from various aqueous matrices such as surface water and drinking water [94-100].

Fig. 8. Schematic illustration of needle-type sample preparation devices. A) Fiber-packed and B) particle-packed.

6. Future prospective

Miniaturized sample preparation with fiber-packed capillary and the effective coupling to microscale separation methods will suggest a future possibility to other related applications, such as an interface between two-dimensional chromatographic separations [101-105]. The applications of polymer-coated and surface-derivatized fibrous materials in miniaturized sample preparation process also demonstrate a possibility to the employment of similar fibrous separation media as the new format of the stationary phase materials in various chromatographic techniques.

Development of novel fibrous extraction/separation media having different chemical structures and then different functionalities on the surface could be realized in the near future based on the concept of molecular shape recognition [3-8] and the systematic retention mechanism analysis with a help of various modern computational data calculations in LC [106-118]. Miniaturization of packed columns in GC [119-123] is also possible for high speed analysis with a unique selectivity but without a loss of sample loading capacity.

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