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# Online Automated Micro Sample Preparation for High-Performance Liquid Chromatography

*Hiroyuki Kataoka, Atsushi Ishizaki and Keita Saito*

## Abstract

Sample preparation is one of the most labor-intensive and time-consuming operations in sample analysis. Sample preparation strategies include the exhaustive or non-exhaustive extraction of analytes from matrices. Online coupling of sample preparation with the separation system is regarded as an important goal. In-tube solid-phase microextraction (SPME) is an effective sample preparation technique that uses an open tubular fused-silica capillary column as an extraction device. In-tube SPME is useful for trace enrichment, automated sample cleanup, and rapid online analysis. Moreover, this method can be used to determine the analytes in complex matrices by direct sample injection or merely by simple sample treatment such as filtration. In-tube SPME is frequently combined with high-performance liquid chromatography (HPLC) using online column-switching techniques. Various operating systems and new sorbent materials have been reported to improve extraction efficiency, such as sorption capacity and selectivity. This chapter discusses efficient micro sample preparation techniques for HPLC, especially online automated in-tube SPME.

**Keywords:** sample preparation, online automated analysis, column switching, in-tube solid-phase microextraction, high-performance liquid chromatography

## 1. Introduction

Sample analysis consists of various analytical steps, including sampling, sample preparation, separation, detection and data analysis. One of the most important steps is sample preparation, which involves the extraction, isolation and concentration of target analytes from complex matrices. Sample preparation [1–18] is the most labor-intensive and error-prone process in analytical methodology and markedly influences the reliability and accuracy of analyte determination. In addition, sample preparation requires large amounts of sample and organic solvents, and is therefore difficult to automate. An ideal sample preparation technique should be simple and fast; be specific for analytes through the efficient removal of coexisting components; provide high sample throughput; utilize fewer operation steps to minimize analyte losses; and be solvent-free, inexpensive, and compatible with chromatography systems. Online automated sample preparation [19–29], in which sample preparation is directly connected to chromatographic separation systems, eliminates further sample handling between the trace-enrichment and separation

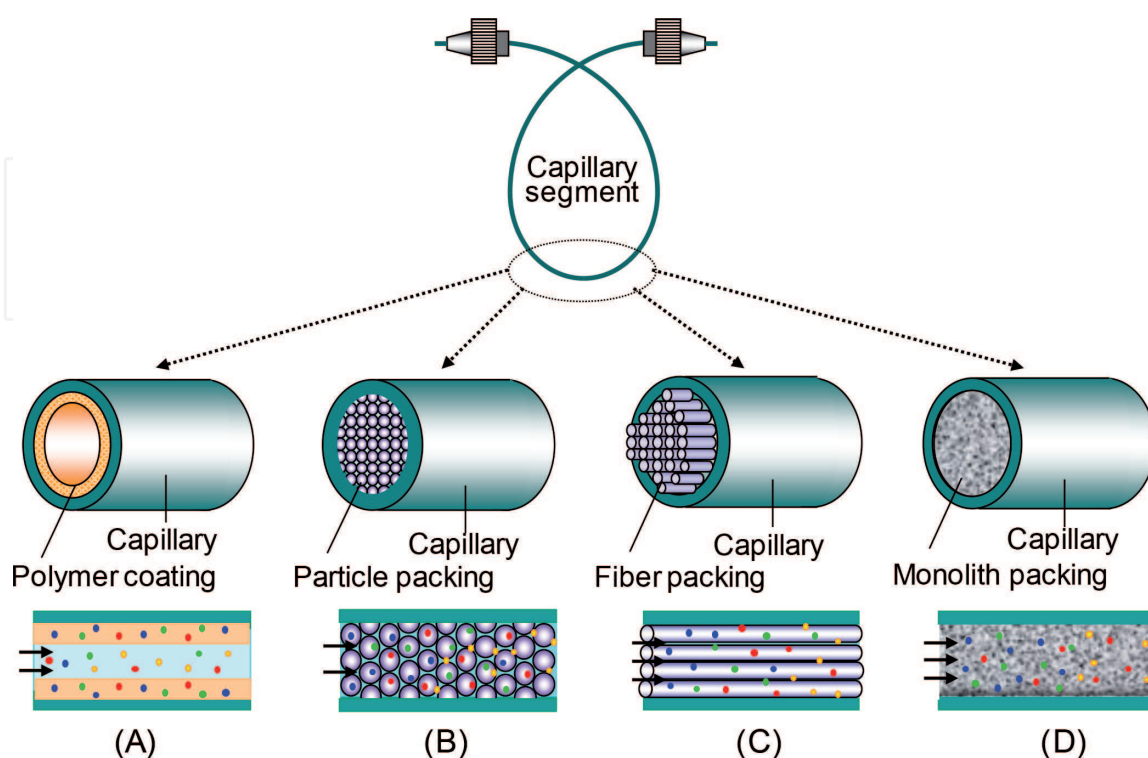
steps. Online automated sample preparation methods usually improve data quality, increase sample throughput, reduce costs, and improve the productivity of personnel and instruments.

In-tube solid-phase microextraction (SPME), using a capillary tube as an extraction device, was introduced by Eisert and Pawliszyn [30] to overcome the problems inherent to conventional fiber SPME. These drawbacks included fragility, low sorption capacity, bleeding from thick-film coatings on fibers, limited effectiveness for extraction of weakly volatile or thermally labile compounds not amenable to gas chromatography (GC) or GC-mass spectrometry (MS), and reduced stability in solvents used in high performance liquid chromatography (HPLC). In-tube SPME was also developed to completely automate the sample preparation process and to enable direct online coupling of in-tube SPME with HPLC using capillary column switching systems [31].

This chapter reviews the configurations and characteristics of in-tube SPME technology and discusses current and future directions, including the strategies involved in extraction efficiency and method development. The details of in-tube SPME have been described in well documented reviews [27, 32–50].

## 2. Configurations of in-tube SPME

In-tube SPME is an efficient sample preparation technique for extraction in capillary columns using stationary phases coated on the inner wall of the capillary or on the surface of the packing material (**Figure 1**). Various in-tube SPME capillary devices have been developed, such as inner wall-coated fused-silica open tubular (**Figure 1A**), fiber-packed (**Figure 1B**), sorbent-packed (**Figure 1C**), and rod-type porous monolith (**Figure 1D**) capillaries [16, 31]. The capillaries are easily fixed with the autosampler injection system, and are generally reusable without plugging or breaking the column and without exfoliation of coating materials.



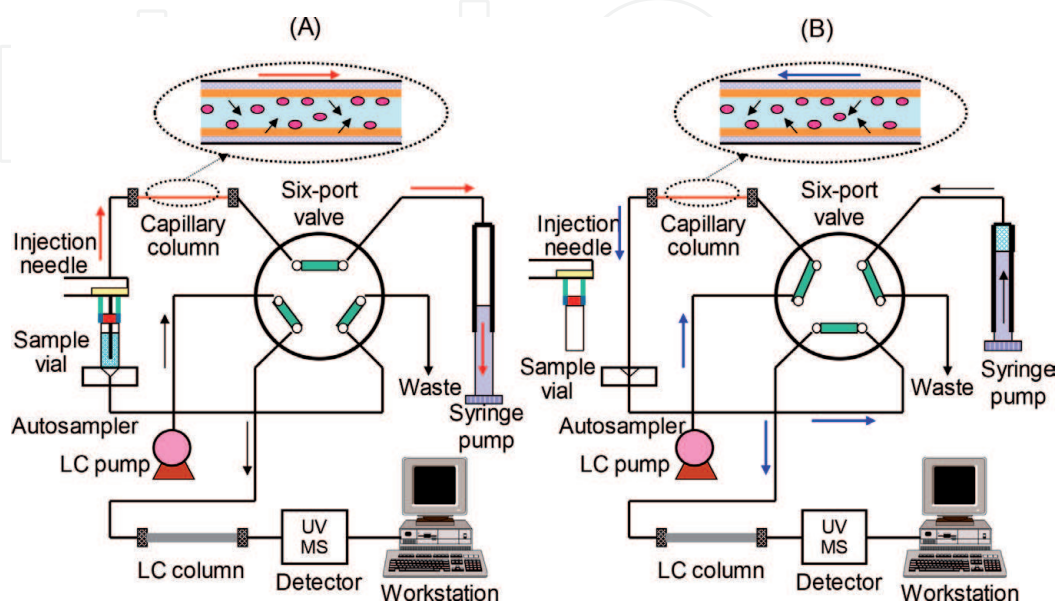
**Figure 1.** Capillary devices for in-tube SPME: (A) polymer coated, (B) sorbent-packed, (C) fiber-packed, and (D) monolith capillary tubes.

## 2.1 Operating systems of in-tube SPME

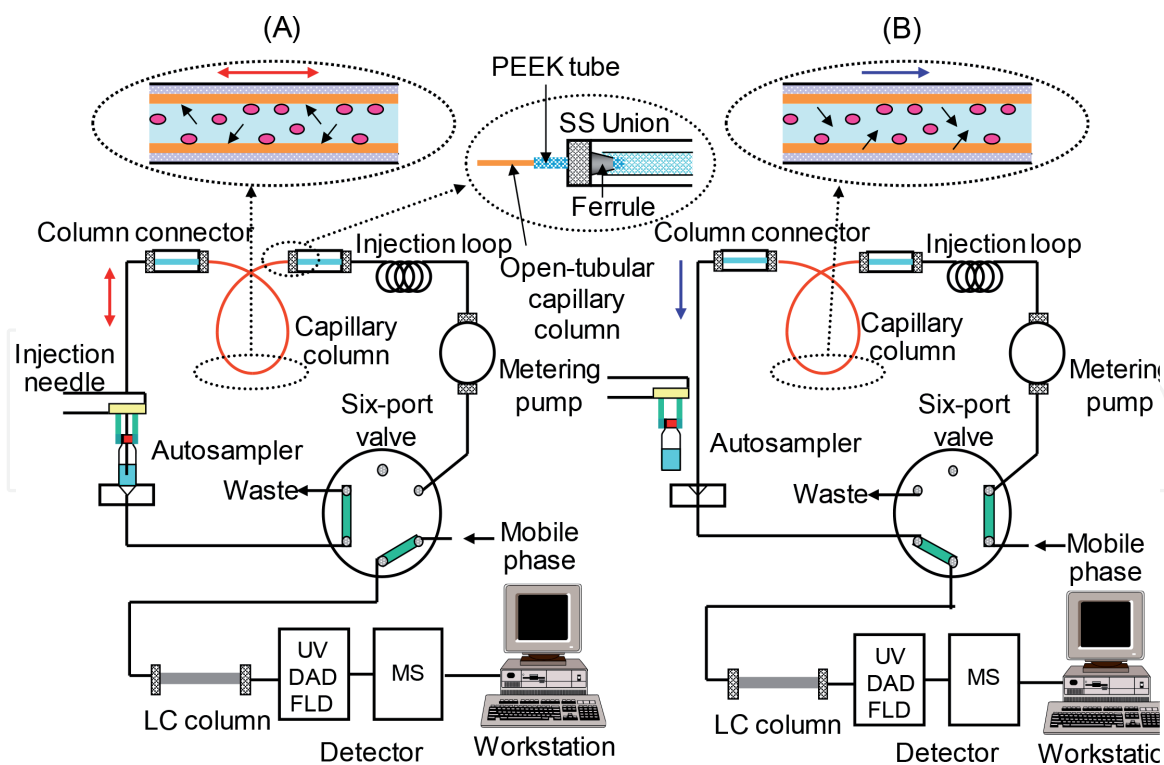
Flow-through systems (**Figure 2**), in which sample solutions are continuously passed in one direction through a capillary column; or as repeated draw/ejection systems (**Figure 3**), in which sample solutions are repeatedly aspirated and dispensed from a capillary column, are used as an operating system of in-tube SPME [18]. These systems are operated by column switching techniques under computer control.

In flow-through systems, the complete analytical system consists of an automatic six-port valve, two pumps (a sample pump and a wash pump) and a liquid chromatography (LC) system. A capillary column is installed in the six-port valve or sometimes placed in the loop. Although one or two six-port valves are available, one valve mode is used more frequently than others. The procedure consists of four steps, conditioning, extracting, washing and desorbing. After conditioning of capillary column with water, the aqueous sample is pumped through the column under the load position (**Figure 2A**). Remaining matrix and residues in capillary are removed by washing with water. After switching the six-port valve to the injection position, the LC mobile phase is passed through the column (dynamic desorption), with the flow-rate of the LC pump (**Figure 2B**). The desorbed analytes are subsequently transferred to the analytical column for separation and detection. The flow-through extraction system, however, may include systematic troubles, such as contamination of the switching valve by sample matrix [18, 31, 37, 41].

Repeated draw/ejection systems include the placement of a capillary column for extraction between the injection loop and the injection needle of the autosampler. Since the sample solution moves only in the capillary, the metering pump and switching valve are not contaminated by sample matrix [18, 31, 37, 41]. A built-in UV diode array detector (DAD) or fluorescence detector (FLD) between the HPLC and the MS can enhance the multidimensional and simultaneous multi-detections, improving analyte identification. During the extraction and concentration step (**Figure 3A**), the injection syringe is programmed to repeatedly draw and eject sample solution from the vial until the concentration of the analyte reaches distribution equilibrium between the sample solution and the stationary phase. After switching the six-port valve to the injection position, the extracted analytes can be directly desorbed from the capillary coating by LC mobile phase flow (dynamic



**Figure 2.** Schematic diagrams of a flow-through extraction system used for online in-tube SPME. (A) Load position (extraction), and (B) injection position (desorption).



**Figure 3.** Schematic diagrams of a draw/eject extraction system used for online in-tube SPME (reproduced from Ref. [37]). (A) Extraction and concentration step, and (B) desorption and injection step.

desorption) or by an aspirated desorption solvent (static desorption) (**Figure 3B**) [31]. The desorbed analytes are subsequently transferred to an LC column. The computer controls the drawing and ejection of sample solution; switching of the valves; control of peripheral equipment, such as the HPLC and MS; and analytical data processing, thus reducing labor and enhancing precision. In addition, the autosampler can automatically process a large number of samples without carry-over, because the injection needle and capillary column are washed in methanol and the mobile phase before the sample is extracted.

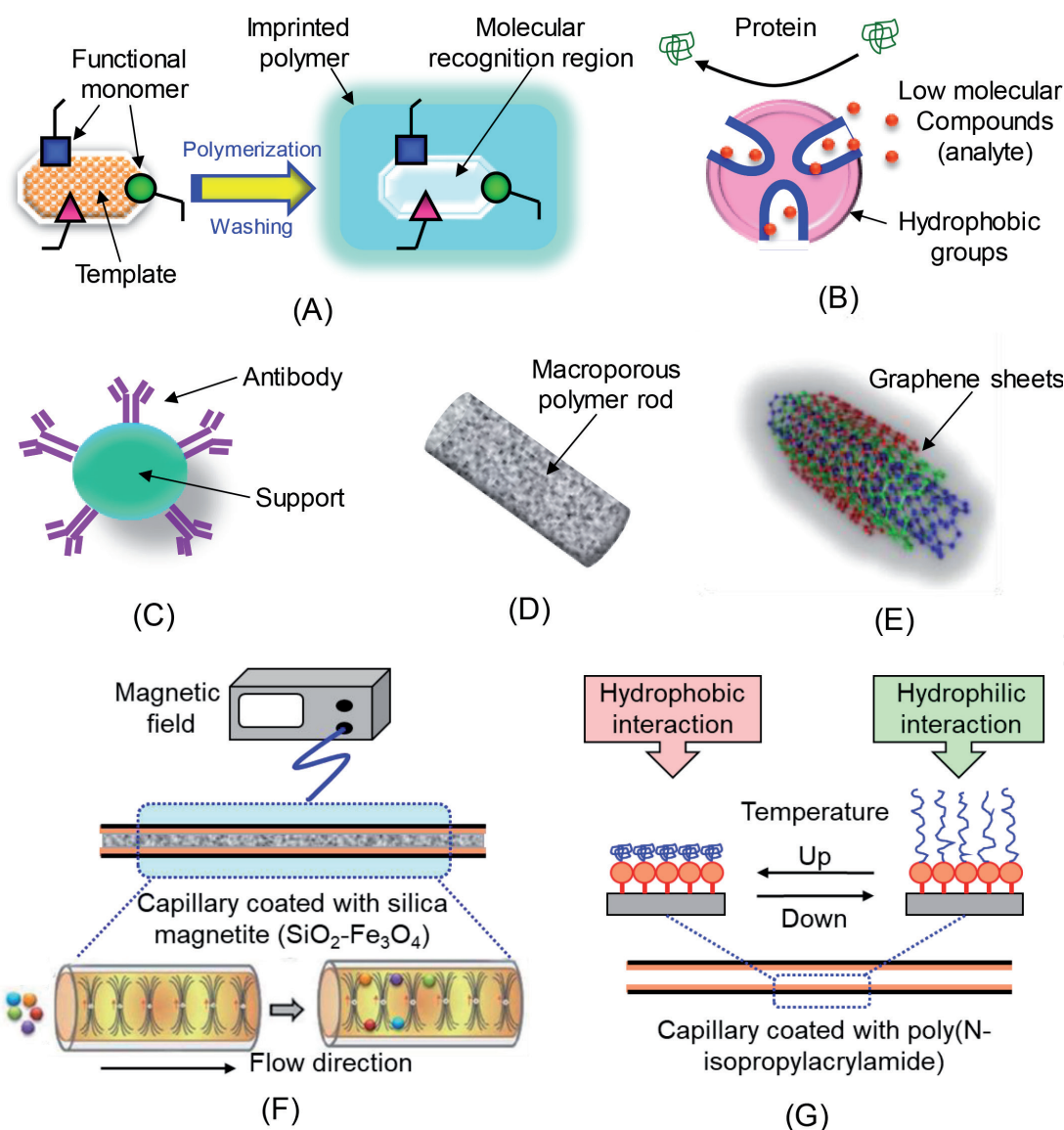
## 2.2 Extraction sorbent materials

The amount of analyte extracted into the stationary phase of the capillary during in-tube SPME is dependent on the characteristics of the capillary coating and the target analyte. Among the commercially available GC capillary columns, silica modified columns have been found more suitable for the analysis of nonpolar compounds. Porous polymer type capillary columns such as Supel-Q PLOT (divinylbenzene polymer, film thickness 17  $\mu\text{m}$ ) have shown better extraction efficiencies due to their large surface area for most organic compounds than other liquid-phase type capillary columns, such as CP-Sil 5CB (100% polydimethylsiloxane, film thickness 5  $\mu\text{m}$ ), Quadrex 007-5 (5% phenyl polydimethylsiloxane, film thickness 12  $\mu\text{m}$ ), CP-Sil 19CB (14% cyanopropyl phenyl methylsilicone, film thickness 1.0  $\mu\text{m}$ ), and CP-Wax 52CB (polyethylene glycol, film thickness 1.2  $\mu\text{m}$ ). CP-Sil 19CB was superior for extraction of polyaromatic hydrocarbons, although the film layer was thin. In contrast, some compounds were effectively extracted with other PLOT type coatings, including Carboxen-1006 PLOT (carboxen molecularsives, film thickness 17  $\mu\text{m}$ ) and CP-Pora PLOT amine (basic modified styrene divinylbenzene polymer, film thickness 10  $\mu\text{m}$ ).

Several unique phases and technical solutions have been developed to improve extraction efficiency and selectivity when extended to microscale applications

[44, 51–53]. These include polypyrrole (PPY) coated capillaries; PEEK tube capillaries packed with molecularly imprinted polymer (MIP) particles [54–61]; and highly biocompatible SPME capillaries packed with alkyl-diol-silica (ADS) particles as restricted access media (RAM) [62, 63], immunosorbents [64], ionic liquids [65–67], monolithic materials [68–73], carbon nanomaterials [74–82], silica-coated magnetite ( $\text{SiO}_2\text{-Fe}_3\text{O}_4$ ) [83–86], and temperature responsive polymers [87, 88]. Novel extraction sorbent materials for in-tube SPME are shown in **Figure 4**.

For example, chemically or electrochemically deposited PPY coatings have higher extraction efficiencies than commercial GC coatings due to the various types of interactions (e.g.,  $\pi\text{-}\pi$ , polar, hydrogen bonding, and ionic interactions) between these multifunctional PPY coatings and the analytes. Capillary tubes have been coated with MIP, consisting of cross-linked synthetic polymers produced by copolymerizing a monomer with a cross-linker in the presence of a template molecule (**Figure 4A**), and PEEK tubes have been packed with MIP particles. By removing the template after polymerization, it is possible to leave open sites of a specific size and shape suitable for binding the same or similar chemicals in a sample. MIPs



**Figure 4.** Novel extraction sorbent materials for in-tube SPME (reproduced from Ref. [37, 42, 84]). (A) Molecularly imprinted polymers, (B) restricted access media, (C) immunosorbents, (D) monolithic polymers, (E) carbon nanotubes, (F) silica-coated magnetite, and (G) temperature responsive polymers.

recognize chemicals through combination of shape, hydrogen bonding, and hydrophobic and electrostatic interactions [16, 18, 31]. RAM materials possess defined diffusion barriers with small sized pores and biocompatible outer particle surfaces (**Figure 4B**). The bifunctionality of ADS particles used as a RAM SPME device can prevent fouling of the capillary by protein adsorption while simultaneously trapping the analytes in the hydrophobic porous interior. Furthermore, a simple SPME device has been fabricated for use in online immunoaffinity capillaries packed with immunosorbent materials, consisting of covalently immobilized antibodies (**Figure 4C**).

An alternative approach consists of in-tube SPME using monolithic capillary columns comprised of one piece of organic polymer or silica rods with a unique flow-through double-pore structure (**Figure 4D**). Monoliths are also highly permeable to liquids and biological samples, enabling reduced solvent use, varied support formats, and/or automation. Monolithic capillaries are especially suitable for in-tube SPME media due to the low pressure drop, allowing a high flow-rate to achieve high throughput and a total porosity greater than that of particle-packed capillaries. Hydrophobic main chains and acidic pendant groups of poly (methacrylic acid-ethylene glycol dimethacrylate) enhance the ability to extract basic analytes from aqueous matrices. The physicochemical properties of graphene-based sorbents and carbon nanotubes (**Figure 4E**) enable their use in extraction, with these combinations showing excellent results when used for in-tube SPME. In addition, various cationic, anionic and zwitterionic liquid-mediated sol-gel coatings have been developed for effective in-tube SPME.

Other innovative extractive phases that enhance the affinity of the analytes include silica magnetite ( $\text{SiO}_2\text{-Fe}_3\text{O}_4$ ; **Figure 4F**) and poly (N-isopropylacrylamide; **Figure 4G**), which have been used in new microextraction processes involving magnetism and thermal energy, respectively. Magnetic and temperature controlled in-tube SPME are performed using flow-through systems, due to the need for additional equipment providing a magnetic or thermal field, which is easier to implement using flow-through devices. Other techniques include wire-in-tube SPME, using modified capillary columns with inserted stainless steel wires, and fiber-in-tube SPME, using PEEK tubes packed with fibrous rigid-rod heterocyclic polymers. These methods increase extraction efficiency by reducing capillary volume or increasing the extracting surface and have shown improved extraction efficiency when extended to microscale applications.

### 3. Method development and characteristics of in-tube SPME

#### 3.1 Optimization of in-tube SPME

In-tube SPME depends on the distribution coefficient of each analyte. Extraction conditions may be optimized by increasing the distribution factor in the stationary phase. The selectivity and efficiency of extraction depend on the type of stationary phase and on the internal diameter, length, and film thickness of the capillary column. Sorption equilibrium is attained by optimizing various extraction parameters for each type of analyte. These parameters include extraction rate, sample volume, sample pH, flow-rate, number of draw/eject cycles (only draw/eject system), and desorption conditions. As described in the preceding section, the choice of capillary coating is important for optimizing extraction selectivity and efficiency. Generally, low and high polarity columns selectively retain hydrophobic and hydrophilic compounds, respectively. Stationary phase consisting of a thicker film and longer column can extract larger amounts of compound, but quantitative desorption of compounds from capillary columns may be difficult. PLOT-type

columns have a larger adsorption surface area and thicker film layer than liquid-phase-type columns, enabling more analytes to be extracted [16, 18].

Generally, the optimal length and internal diameter of a capillary column used in combination with HPLC is 20–80 cm and 0.25 or 0.32 mm, respectively. Although thick-film capillaries often show higher sample capacity and extraction sensitivity, it is extremely difficult to reliably bind thicker chemical coatings to the inner surfaces of fused-silica capillary tubes using conventional approaches. In contrast, thin-film capillaries can minimize the time to reach extraction equilibrium due to their low sample capacity. Capillary columns with chemically bonded or cross-linked liquid phases are very stable in water and organic solvents and can prevent loss of phase by LC mobile phase [18].

The volume of sample passed through a capillary is usually 0.2–2 mL in flow-through extraction systems, and their optimum extraction flow rates are 0.25–4 mL/min depending on the volume of the column. Although increases in the number and volume of draw/eject cycles can enhance extraction efficiency in draw/ejection systems, peak broadening is often observed [16]. Optimal conditions for a capillary column of inner diameter 0.25 mm and length 60 cm include a draw/ejection volume of 30–40  $\mu$ L, a draw/ejection flow rate of 50–100  $\mu$ L/min and 10–15 draw/ejection cycles. Below this rate, extractions require an inconveniently long time, and above this rate, bubbles form on the inside of the capillary, reducing extraction efficiency. Furthermore, the extraction efficiency of the analyte to the stationary phase varies with the pH of the sample solution. The presence of hydrophilic solvents such as methanol in the sample reduces the extraction efficiency. The analyte extracted on capillary coatings can be easily desorbed statically or dynamically without carryover [18].

### 3.2 Characteristics of the in-tube SPME technique

**Table 1** summarizes the characteristics of in-tube SPME. The main advantage is that the series of processes can be automated, which enables continuous extraction,

Advantage	Disadvantage
<ul style="list-style-type: none"> <li>• Minimal sample adjustment</li> <li>• Large injection volume (flow-through system)</li> <li>• Applicable to polar and thermolabile liquid samples</li> <li>• Low solvent consumption</li> <li>• Decreased handling of biohazardous samples</li> <li>• Less sample loss due to online closed system</li> <li>• Lower likelihood of carryover</li> <li>• Higher mechanical stability of capillaries</li> <li>• Reusability of capillaries without plugging or breaking</li> <li>• Commercially available GC capillary columns</li> <li>• Applicability of various unique adsorbents to specific and efficient extraction</li> <li>• Easy on-line coupling with liquid chromatography</li> <li>• Enabling of full automation by column switching</li> <li>• Commercially available autosamplers</li> <li>• Improvements in selectivity and sensitivity</li> <li>• Better precision and accuracy</li> </ul>	<ul style="list-style-type: none"> <li>• Tendency of the capillary to clog</li> <li>• Limited to particulate-free samples</li> <li>• Stripping of non-bonding thick-film coatings</li> <li>• Possible peak broadening</li> <li>• Switching of valves, extraction columns, and pumps required</li> <li>• Complicated switching system</li> <li>• Relatively low enrichment factor</li> <li>• Relatively long extraction time</li> </ul>

**Table 1.**  
*Advantages and disadvantages of in-tube SPME.*



desorption and injection with column switching using a standard autosampler, and online coupling with the LC system [16, 18, 31]. In-tube SPME may be suitable for the determination of polar and thermolabile compounds. Compared with manual techniques, automated sample-handling procedures not only shorten the total analysis time but are more accurate and precise. Automated techniques are also suitable for miniaturization, high-throughput performance, and online coupling with analytical instruments, and reduce the consumption of solvent. Online procedures can limit contact with dirty and hazardous samples, reducing sample contamination and loss. Online column-switching systems are highly sensitive due to pre-concentration resulting from the injection of large sample volumes into the extraction support without loss of chromatographic performance. The main disadvantage is that the capillaries tend to clog, which may be avoided by removing interfering phases such as particles or macromolecules by filtration or centrifugation before extraction. Although the absolute recovery rate of the in-tube SPME method is generally low, it can be extracted and concentrated reproducibly using an autosampler, and all extracts can be introduced into the LC column [16, 18, 31].

The online in-tube SPME method can be applied to polar and nonpolar compounds in liquid samples, and can be coupled with various analytical methods, such as HPLC and LC-MS. Early applications of online in-tube SPME have involved draw/eject extraction systems and commercially available open-tubular GC capillaries such as Supel Q PLOT and Carboxen 1006 PLOT capillaries. The subsequent development of various operating systems and new sorbent materials improved extraction efficiency, such as sorption capacity and selectivity, and extended the range of applications. Last decade, numerous applications of online in-tube SPME methods have been reported to many types of pharmaceutical and biomedical [86, 89–124], food [125–137], and environmental [138–178] analyses.

#### **4. Conclusions and future directions**

The online in-tube SPME techniques described in this chapter have many desirable features for automated separation of analytes, using column-switching techniques. These methods are especially well suited to the analysis of samples requiring significant cleanup and concentration to improve their selectivity and sensitivity, as well as being useful for high-throughput sampling. Since the in-tube SPME method using capillaries as an extraction device is useful for online sample preparation to extract and concentrate polar and non-polar compounds from aqueous solution, it has become an effective technique for convenient analysis of a wide variety of compounds in complex matrices such as biological, pharmaceutical, food and environmental samples [31]. Furthermore, various operating systems and new sorbent materials have been developed to improve extraction efficiency and sorption capacity and selectivity, and to extend the range of applications. These include MIPs, RAM, immunosorbents, monolithic materials, carbon nanoparticles, ionic liquids, temperature responsive polymers and magnetic hybrid adsorbents.

The main future direction in sample preparation is the development of more sensitive and selective extraction sorbents [31]. Chiral active phases, ionic liquids, dendrimers, aptamer modified sorbents, magnetic materials, temperature responsive materials may be available as new polymer devices for effective sample preparation. Furthermore, biomimetic coating materials including ultrasound and light responsive polymers may be available as a selective extraction device in the future. These customized coating materials, differing in type, shape, and size, are expected to result in highly efficient extraction of various samples. Biocompatible RAM and monolithic sorbents are useful for direct analysis, without pre-treatment other than

dilution and centrifugation of biological samples. As another future direction, better integration of sampling/sample preparation and instrumental analysis will allow wider use of automated online analysis. Especially, the use of column-switching systems involving microextraction techniques and/or microdevices will offer convenient integration of sample preparation with various analytical instruments such as HPLC as well as other chromatographic systems, electrophoresis, direct MS, etc.

Finally, this chapter provides an overview of the configurations and characteristics of in-tube SPME technology for online automated micro sample preparation for HPLC. We hope that this chapter will serve as a guide to choosing the most effective sample preparation techniques for the analysis of various complex samples.

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## **Conflict of interest**

The authors declare no conflict of interest.

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