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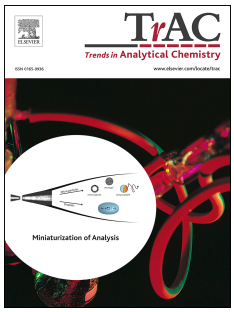

Recent advances in biological sample preparation methods coupled with chromatography, spectrometry and electrochemistry analysis techniques

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Recent advances in biological sample preparation methods coupled with chromatography, spectrometry and electrochemistry analysis techniques

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ABSTRACT

Biological samples are complex and often contain many proteins, lipids and other contaminants, which affect the separation and ionization properties of the analytes. Moreover, the concentration of the analytes is very low in comparison with that of the interfering substances. Therefore, the development of biological sample preparation methods has become more and more challenging. The objective of this review is to provide a broad overview of the main biological samples (urine, blood, plasma, serum, hair, human breast milk, saliva, sweat and skin surface lipids, fecal and tissue), recent advances and applications of various sample preparation methods prior to chromatography, spectrometry and electrochemistry analysis over the past five years. Novel and modern approaches in biological sample preparation are especially emphasized. Finally, challenges and future perspectives to improve development of sample preparation methods are described.

Keywords: Biological sample; Sample preparation; Chromatography; Spectrometry; Electrochemistry analysis

Abbreviations:

AAS: atomic absorption spectrometry; ASE: accelerated solvent extraction; BPA: bisphenol A; CPE: cloud point extraction; dCPE: dual-cloud point extraction; DBS: dried blood spot; DLLME: dispersive liquid-liquid microextraction; DLLME-SFO: DLLME with solidification of floating organic drop; DPX: disposable pipette tips extraction; EDTA: ethylenediaminetetraacetic acid; EIMS: electrospray ionization mass spectrometry; EME: electromembrance extraction; nano-ESI-MS/MS: nanoelectrospray ionization-mass spectrometry/mass spectrometry; FA: field amplication; FASI: field amplified sample injection; FSSLM: flat sheet supported liquid membrane; HF-LPME: hollow-fiber liquid phase microextraction; HFSLM: hollow fiber supported liquid membrane; HLB: hydrophilic–lipophilic balance; HLLE: homogeneous liquid-liquid extraction; ILs: ionic liquids; IS: internal standard; LLE: liquid liquid extraction; MAE: microwave-assisted extraction; MAX: mixed-mode/anion exchange; MCX: mixed mode/cationic-exchang; MEKC: sweeping micellar electrokinetic chromatography; MeOH: methanol; MEPS: microextraction by packed sorbent; MIPs: molecularly-imprinted polymers; MSPD: matrix solid phase dispersion; PDMS: polydimethylsiloxane; PLE: pressurized liquid extraction; PP: protein precipitation; QDs: quantum dots; SALLE: salting-out assisted liquid liquid extraction; SBSE: stir-bar sorptive extraction; SCS: Saliva Collection System; SDME: single drop microextraction; SDS: sodium dodecylsulfate; SFE: supercritical fluid extraction; SLE: supported liquid extraction; SLM: supported liquid membrane; SPE: solid phase extraction; dSPE: dispersion solid phase extraction; SPME: solid phase microextraction; UAE: ultrasonic assisted extraction; WAX: weak anion exchange; WCX: weak cation exchange.

Contents

1. Introduction

The development of biological sample analysis methods has become more and more challenging over the past years due to very demanding requirements in terms of method reliability, sensitivity, speed of analysis and sample throughput. The aim of quantitative analytical method is to provide accurate and reliable determination of the amount of a targeted or untargeted analyte, usually a drug, a metabolite or a biomarker, in complex biological samples. The biological samples usually encompass whole blood, serum, plasma, urine, saliva, breast milk, sweat, cerebrospinal fluid, gastric fluid, exhaled breath, and tissue samples (i.e., hair, nail, skin, bone, muscle) [1], cells, cell culture, culture media and so on. Types of biological samples used in CE-MS metabolomics studies were listed [2]. Except tissue and cell, urine and serum are the most often used samples. However, matrix effects, such as the presence of endogenous or exogenous macromolecules, small molecules and salts which interfere with analysis, low analyte concentration and biological matrix that are incompatible with instrument, all necessitate sample preparation before analysis [3]. Therefore, sample preparation starting from enhancement of selectivity and sensitivity of the analysis to improving analytical criteria and/or protecting the analytical instrument from possible damage might be employed. Sample preparation is of utmost importance for obtaining the analytes of interest in a suitable injection solution able to provide reliable and accurate results. It has substantial objectives before sample injection, including [4]:

1. reducing or eliminating matrix interferences or undesired endogenous compounds;
2. increasing selectivity for targeted analyte(s);
3. preconcentrating the sample to enhance sensitivity; and
4. stabilizing the sample by reconstituting it in an inert solvent.

A number of research efforts dealing with biological sample preparation methods have been

reported. There are also some valuable reviews about biological sample preparation.

Soltani *et al.* [3] and Namera [5] gave reviews focused on the achievements in the pretreatment of biological samples and investigated sample pretreatments in six categories (i.e., dilution, filtration/dialysis, precipitation, extraction (solid-phase extraction, liquid liquid extraction]), novel techniques (turbulent flow chromatography, immunoaffinity method, electromembrane extraction) and combined methods.

Nováková [6] reviewed some traditional biological sample preparation techniques, such as solid phase extraction (SPE), liquid liquid extraction (LLE), protein precipitation (PP), and modern biological sample preparation techniques such as solid phase microextraction (SPME), stir-bar sorptive extraction (SBSE), microextraction by packed sorbent (MEPS), disposable pipette tips extraction (DPX), single drop microextraction (SDME), hollow-fiber liquid phase microextraction (HF-LPME), dispersive liquid-liquid microextraction (DLLME) and dried blood spot (DBS) prior to liquid chromatography-mass spectrometry method (LC-MS).

Lum *et al.* [7] discussed four aspects of the recent development in metal preconcentration methods in clinical samples, namely the use of ionic liquids (ILs) in DLLME and SDME extraction, sorption by nanomaterials in SPE, preconcentration using surfactants in CPE and liquid phase extraction, and automation (on-line SPE and DLLME). Delafiori *et al.* [8] introduced some sample preparation methods of arsenic (As), selenium (Se) and mercury (Hg) elements in various clinical matrices.

Fernández-Peralbo and Luque de Castro [9] presented an overview of researches on preparation of urine samples prior to targeted or untargeted metabolomics mass-spectrometry analysis.

Oh and Lee [10] described sample preparation methods such as PP, LLE and SPE for liquid chromatographic analysis of phytochemicals in biological fluids.

An important bottleneck of biological sample preparation is the presence of matrix effects, which have recently received lots of attention. Biological matrices are complex and often contain proteins, lipids, drugs, salts, acids, bases and various other organic and inorganic compounds with similar properties to the analytes, which may interfere with the analytes measurement. Therefore, sample preparation is a very vital part prior to the instrument analysis. However, sample preparation step still remains the most time-consuming and labor-intensive step of biological analysis. An important trend shared by the fundamental researches on the above sample preparation techniques relates to the development of more accurate, precise, selective and robust preparation methods. It has become a hot issue to new sorbents, on/in-line sample preparation methods coupled with chromatography, spectrometry and electrochemistry analysis. In this review, we therefore summarized some biological samples such as urine, blood, plasma, serum, hair, human breast milk, saliva, sweat and skin surface lipids, fecal, some tissue samples and so on, highlighted sample preparation techniques of these samples. We provided an updated, essential summary of the most important sample preparation methods coupled with chromatography, spectrometry and electrochemistry analysis for biological samples. We also discussed the present limitations and expected future trends of biological sample preparation methods for better advancement. There is no restrict definition of sample pretreatment and preparation in the published researches. Some may consider both steps as a single step, they called them sample preparation. In this review, the former step, consisting of sampling time and collection, preservative addition, volume correction, pH adjustment, dilution, enzymatic hydrolysis and so on, is called sample pretreatment; the following step, consisting of PP, LLE, SPE, SPME, LPME and so on, is called sample preparation.

2. Biological samples and sample pretreatment

2.1 Urine

Urine is composed of over 95% water, plus sodium, ammonia, phosphate, sulfate, urea, creatinine, proteins and products processed by the kidney and liver, including drugs and metabolites [9]. Urine is slightly acid in the morning (pH = 6.5–7.0), generally becoming more alkaline (pH = 7.5–8.0) by evening in healthy people primarily because no food or beverages are consumed while sleeping. As a sample for analysis, it has its own advantages compared with serum:

(1) can be obtained in large volume by non-invasive sampling, and sampling repetition is not a problem; and,

(2) requires less complex sample preparation because it contains lower amounts of protein (60–80 g/L in serum, 0.5–1g/L in urine) [9], lipids and other high-molecular weight compounds because of the glomerular filtration.

Therefore, urine is a very good selection in biological samples researches. Fernández-Peralbo and his co-workers have already given a description of urine sample in detail [9]. Here, a short introduction about this sample is shown below.

2.1.1 Sampling time

Usually, urine samples are collected as random samples, timed samples or 24-h samples. Random sampling is performed at any time of day, while timed samples are needed to study time-related trends to catalogue metabolites with high diurnal variation in different species and to aid in the search for true biomarkers. However, 24-h sampling collection is preferred to eliminate large variability in metabolite profiles obtained in shorter collection periods [9]. In clinical practice, midstream portions or clean-catch urine of first morning urine samples

are the most commonly obtained specimens. In morphologic studies, using second morning urine specimens is sometimes recommended [11]. Midstream urine is likely to be the most appropriate sample because the presence of contaminating elements is minimized.

2.1.2 Sample collection

Bare polypropylene containers of the required volume suffice for urine which are not endowed with special characteristics or regents. However, urine for clinical practice is usually collected in a sterile container. For some special analytes, insulated ice packs are needed until the sample is arrived in the laboratory for proper storage.

Also, sometimes surfactants are added to the containers to increase the analytes' solubility and/or minimize interaction with container surfaces. However, an additional shortcoming of this is a side effect of surfactant addition can be ionization suppression in the subsequent mass spectrometry analysis, which should be minimized by using an isotopically-labeled internal standard (IS) [9].

2.1.3 Sample storage

Time between sampling and analysis procedure is critical for the reliability of urine results. Changes in concentration of analytes or formation of some endogenous urine reactants can appear [12], making the measured result useless. A standardized organization of storage time is needed as well as documentation of storage temperature [11]. In order to ensure the easiest and most effective preservation of analytes until the analysis, the refrigeration appears the best suitable storage solution. Also, the sample handling (e.g. freeze-thaw cycles) is another pivotal aspect, as it determines the exposition to degrading environmental conditions [12]. For example, on long-term stability of urine samples for untargeted analysis, it is recommended to avoid freeze-thaw cycles and rapidly freeze and

store pre-aliquoted samples at -80 °C to minimize potential degradation as much as possible[9]. In order to analysis some endogenous urine reactants which is so-called UA, it is recommended samples should be centrifuged after collection, temporarily stored at 4 °C and warmed before analysis to recover as much UA as possible. Long-term storage should be carried out at least at -20 °C, and frozen samples should be thawed by a hot bath [12].

In general, it can be said for analytes studies that [9]:

(1) storage of human urine for up to 6 months at -20 °C or below is suitable for metabolomic studies;

(2) the number of freeze–thaw cycles (up to 9) does not seem to affect sample integrity; and,

(3) short-term storage in a fridge (0 °C to 4 °C) or a cooled auto-sampler for up to 48 h still seems to provide useable samples that provide meaningful results.

However, there is not a given storage condition for all the components of the urine sample, so rigorous specific stability studies are essential for analytes analysis.

2.1.4 Preservative addition

The addition of preservatives has been used to prevent metabolic changes of urine analytes and bacterial contamination. However, preservatives may affect some chemical properties and alter the appearance of particles.

Boric acid is considered to be a good preservative which may inhibit growth of *Pseudomonas spp*. But there is a problem that the initial pH values of the urine sample are changed [11]. Moreover, boric-acid addition was avoided in the urine collected in the UK Biobank because of the potential formation of chemical complexes in the samples [9].

Sodium azide is recommended for preventing bacterial overgrowth. However, this preservative is toxic and may have potential impact on some unknown metabolites in urine

sample, so its use is also carefully considered.

The other common used preservatives such as formaldehyde, mercury salts, chloral hexidine and so on were summarized in Ref. [11].

2.1.5 Volume correction

Urine volume can vary widely based upon water consumption and other physiological factors. As a result, the concentration of targeted and untargeted analytes in urine vary widely. So, volume correction is necessary. Approaches based on urine volume, creatinine concentration, osmolality, and components that are common to all samples (total useful MS signal) are strategies successfully used [9]. There is no universally accepted procedure for correction of the urine volume, as each procedure has restrictions. Measurement of protein/creatinine ratio, osmolality and MS total useful signal is the most three frequent correction procedures [9]. In general, usually two of them are used in order to facilitate detection of statistically significant differences in the endogenous metabolite profile in urine samples.

2.2 Blood, plasma and serum

Blood, plasma and serum show the best correlation between pharmacologic effect and compound concentration and are preferentially selected for quantitative analyses. In vertebrates, blood is composed of blood cells suspended in blood plasma. Plasma, which constitutes 55% of blood fluid, is mostly water (92% by volume), and contains dissipated proteins, glucose, mineral ions, hormones, carbon dioxide (plasma being the main medium for excretory product transportation), and blood cells themselves. The blood cells are mainly red blood cells (also called RBCs or erythrocytes), white blood cells (also called WBCs or leukocytes) and platelets (also called thrombocytes). The initial pH of blood at

38 °C varies from 7.25 to 7.45 [13], so it has to make the appropriate corrections when measurement is taken at room temperature.

Dried blood spot (DBS) has recently gained a great attention in bioanalytical and clinical laboratories. DBS is obtained by depositing a blood sample onto a filter paper, followed by drying in air for several hours. Subsequently, a disk is punched out from the blood spot and this disk is extracted for the target analytes. Multiple advantages have been reported, including the ease of sampling (less invasive than conventional blood collection), the small sampling volume, the cost-effective long storage of filter papers at room temperature, the long-term analyte stability, and the low solvent volumes needed for the analytes extraction [14]. There are two kinds of DBS, one is venous DBS (V-DBS), the other is capillary DBS (C-DBS). The V-DBS can be generated from venous blood, while the C-DBS is typically generated by direct collection of blood drops appearing after a finger or heel prick [15]. It is obvious the latter offers the advantage of being less invasive and does not require a nurse or physician. The DBS sampling can be performed either in a volumetric (using a precision microcapillary) or a non-volumetric way (direct application from the finger/heel). DBS collected in a non-volumetric way are mostly processed by excision of fixed-size punches (typically 3–6 mm diameter) from the global spot [15].

In many clinical and biological studies, plasma or serum is used instead of whole blood, which can introduce certain complications in the interpretation of results. Both plasma and serum are derived from full blood that undergone different biochemical processes after blood collection. The separation of plasma or serum from blood is of outstanding importance since, in practice, it is required to carry out the analysis of dissolved blood components without disturbance. The normal and most conventional manner of separating plasma or serum from erythrocytes is refrigerated centrifuging. Serum is obtained from blood that has coagulated. Fibrin clots formed during coagulation, along with blood cells and related coagulation factors,

are separated from serum by centrifugation. During this process, platelets release proteins and metabolites into the serum [16]. To obtain plasma, an anticoagulant like ethylenediaminetetraacetic acid (EDTA), heparin, sodium fluoride, citric acid, citrate or serum [12, 17] is added before the removal of blood cells. Although blood plasma and serum are usually considered to have similar compositions and properties, many analytes, especially in metabonomic/metabolomic studies, show differences in plasma and serum [16, 18, 19]. These differences between them are of great interest.

The plasma and serum samples are usually collected as follows. A sample of venous blood is collected early in the morning after an overnight fast. The fresh blood is immediately divided into two parts: one is added to a blank tube and the other is added to a tube containing anticoagulant such as EDTA, citrate and so on. The blood serum and plasma were isolated by centrifugation and then stored at -80, -20, 0 or 4 °C [12, 17, 19] until analysis. For different analytes, the storage conditions may be different. For example, collection into EDTA or fluoride, and storage and transport at 0 – 4 °C is practicable for many hormones [17]. Cao et al. found samples stored at -80 °C undergo a steeper freezing and a slower thawing than at -20 °C, and this had been shown to cause a higher degree of protein degradation [20]. It is also recommended that plasma or serum samples should be preferably stored at -20 °C and thawed at least twice, possibly using a warm bath to prevent the protein unfolding [12].

2.3 Hair

Hair belongs to hard tissue [1]. As a biological sample, it is increasingly used in bioanalysis. Hair is a strong matrix, stable at room temperature, easily handled and transported, hardly tampered during the collection, noninvasively collected, and has a high resistance to decay in post-mortem cases [14]. Therefore, hair as an alternative matrix is

especially useful to provide long term information about consumption/ingestion of drugs, after their elimination from the body. Hair testing is also increasingly used in conjunction with urine samples and is able to confirm long-term exposure to xenobiotics over a period of several months [14]. Assuming hair grows approximately 1 cm per month, segmental analysis of hair strands allows the determination of the historic pattern of drug use [21].

In the case of abusers, most drugs are expected to be found in hair in the ng/mg range. However, there is a problem that drugs can be deposited on hair from the environment via smoke, pollution or physical contact, chemicals, *etc*. The Society of Hair Testing and Substance Abuse and Mental Health Services Administration produced a set of recommendations (wash-out analysis, metabolite identification, cut-off values) to be helpful for an appropriate interpretation of the results [21]. Therefore, the pretreatment and preparation of hair sample before the instrumental analysis is very important. Baciu *et al.* have summarized hair sample pretreatment, extraction and analytical methods in detail [21]. Typically, the hair sample pretreatment consists of the following steps: (1) sampling, (2) segmentation when a segmental analysis is carried out, (3) washing the hair to eliminate the external contamination, (4) pulverization in a ball-mill or cutting into small pieces.

2.3.1 Sample collection and storage

The best choice for hair collection is head hair, as body hair growth is more variable and slower than head hair, leading to difficulty in interpreting time of use for suspected users. It is usually stated that head hair grows at a rate of approximately 1 cm per month. It is recommended that hair collection be delayed until 8 weeks after suspected ingestion to ensure that the sample fully represents the exposure period [21]. Generally, the most recommended sampling site is the back of the head, where hair has less variability in growth and is less influenced by age and sex. There was a typical figure showed the procedure for hair sample

collection in Ref. [21].

After the sample collection, the hair should be stored in paper envelopes at room temperature in a dry, dark place. It is avoided that direct hair storage in plastic bags or plastic tubes owing to the risk of lipophilic extraction by plastic from the hair.

2.3.2 Sample washing

In order to avoid false-positive results, residues from hair such as sweat, sebum, some environmental contamination or even dust should be removed by washing before analysis. The usual washing solvents include organic solvents, aqueous buffers, water, soaps or a combination, e.g. Tween 80, sodium dodecylsulfate (SDS), n-hexane, methanol or water [21]. It is important to select the washing solvents which could clean up the external impurities but not extract the analytes from the hair. After being washed and dried, the samples should be pulverized in a ball-mill or cut into small pieces prior to the analytes extraction.

2.4 Human breast milk

Human breast milk is at the top of the food chain and one of the good markers for the determination of environmental pollution, drugs and some other analytes. Drug excretion in breast milk from plasma is a very important problem in maternal drug treatment. Most drugs taken by lactating mothers are transferred from the maternal circulation to her milk and to her baby. Some lipophilic compounds have the potency to partition into fat and breast milk. In particular, contamination of human breast milk with some environmental pollution and drugs is important, because breast milk is the first food for newborns. Since breast-feeding is the preferred nutrition, a good understanding of contamination in breast milk is essential.

The breast milk samples can be collected manually into breast pump with glass containers at the hospitals and transferred to polypropylene conical tubes that had been thoroughly

rinsed with methanol and acetone before use [22]. However, special attention should be paid for some analytes, for example bisphenol A (BPA) analysis, glass tubes were used throughout the sampling and storage to avoid contamination of BPA [23]. For drug analysis, samples were usually obtained in the morning i.e. 12–15 h after administration of drugs or 1.5–2.5 h after the drug ingestion [24, 25]. If needed, a second batch of samples is collected after 2 or 4 months [24]. As a variety of environmental and physiological factors (i.e. dietary intake, age, number of deliveries, purpose of breast feeding, health condition, area of residence) influence the accumulation of some analytes in breast milk, and breast milk is characterized by high protein, fat, and carbohydrate content [4, 26], which can affect the recovery and repeatability of the extraction procedure, a detailed questionnaire is prepared to obtain an informative record of donor [24]. After the collection, samples are kept frozen at -20 °C.

2.5 Saliva

Alongside with urine, saliva represents another biological matrix easily collectible through a non-invasive procedure compared with venous blood collection. Moreover, it does not pose major risks during collection, allowing a safer management.

Saliva is a very dilute fluid, composed of more than 99% water, which is a hypotonic fluid in relation to plasma, containing compounds produced in the salivary glands (immunoglobulin A [IgA] and α-amylase) as well as compounds diffused in the plasma (water, electrolytes, proteins, metabolites and hormones) [27]. The flow of plasma components into the saliva may involve several processes which is presented in Ref. [27]. The normal pH of saliva is 6 to 7. Saliva originates mainly from three salivary glands: 20% from parotid, 65% from submandibular and 7–8% from sublingual. And less than 10% from numerous minor glands. Each salivary gland secretes a characteristic type of saliva, with different ionic and protein concentrations. The average daily flow of whole saliva varies in

health between 1 and 1.5 L [28]. On average, unstimulated flow rate is 0.3 mL/min, with the average total for 16 hours of unstimulated flow (during waking hours) being 300 mL. During sleep, salivary flow is nearly zero. Stimulated saliva by gustatory stimulation, mastication or the use of citric acid is reported to contribute as much as 80–90% of the average daily salivary production. Stimulated flow rate is at a maximum value of 7 mL/min [28].

Neither teeth brushing nor food and liquid ingestion (except water) are recommended for at least 30 minutes prior to collection. There were three modes of saliva sampling, passive collection, stimulate collection and collection system called Saliva Collection System (SCS)® (Greiner Bio-One, GmgH, Kremsmuenster, Austria) [27]. The passive collection is the most recommended method, which collected through passive drool directly into plastic tubes. However, as mentioned above, the passive collection can't supply large volume of sample. The stimulate saliva can be collected through some commercial devices which contain a solid base, usually consisting of a small piece of cotton or polyester for saliva absorption and a conical tube for centrifugation and recovery of the collected liquid [27]. Currently the most commonly used systems are the Salivette® (Sarstedt), the Quantisal®, and the Intercept® (Orasure Technologies). It is not recommended to use the collection devices with cotton when the collection sample is used for the analysis of hormones because of the possibility of interference in the performance of immunoassays [29].The main disadvantage of the above two modes is indirect and inaccurate volume quantification. However, the SCS which uses a buffered base of citric acid is a system more elaborate. After applying a cleaning solution, the donors place the extracting solution in their mouth for 2 minutes and then spit out all the solution into a beaker. All the solution including the saliva and extraction solution is transferred to tubes which could be used to quantify the total volume of collection. Some of the saliva collection system were shown in Fig. 1 [29]. More information is presented in the two reviews [27, 28].

There is no agreement on storage temperature of saliva samples. It is recommended samples should be refrigerated (4 °C) if they are processed within 3 to 6 hours after collection. When the sample is stored for long periods, the temperature should be kept at -80°C to prevent bacterial growth [27].

2.6 Sweat and skin surface lipids

Sweat (perspiration) is approximately 99% water with the most concentrated solute being sodium chloride [30], secreted by the body through the skin to maintain a constant core body temperature. The rate of sweating, which is highly dependent upon environmental temperatures, is estimated between 300 and 700 mL per day and can be up to 2–4 L/h in the case of extensive exercise [15]. Approximately 50% of the total volume of sweat is produced by the trunk, 25% by the legs and 25% by the head and upper extremities [30]. The pH of the sweat ranges between 4 and 6.8 and increases with the flow rate, with the average sweat pH from resting individuals considered to be 5.8 [15, 29].

Skin surface lipids consist of a mixture of epidermal and sebaceous lipids. The percent of the two lipids depends on the body region. In regions with a high density of sebaceous glands (i.e. forehead, scalp, thorax and the upper part of the trunk), the skin surface lipids originate mainly (96–97%) from sebum which is composed of triglycerides (~41%), wax esters (~26%), squalene (~12%), and free fatty acids (~16%) [15].

Because some of the environmental contaminations or drugs are lipophilic, they are possible to excrete through passive diffusion from blood into sweat glands and via transdermal migration across the skin. Therefore, it is very important to pay attention to the sweat and skin surface lipids samples. The sampling of sweat and skin surface lipids was first collected using patches, worn for a variable period of time (from some hours up to some days), with the accumulation of analytes into these absorbent pads. Sebum has also been

collected by wiping a wetted cotton bud on the skin [15]. Early patch was made of absorbent cotton pads sandwiched between a waterproof, polyurethane, outer layer and a porous inner layer that was placed against the skin [30]. Giovanni *et al.* summarized some important characteristics about sample collection, such as the typology of collection device, application site of the patch on human body and time of wearing [30]. Like saliva, there is also a problem that the total volume of the sample is not known. In order to solve this problem, it can be performed by using pre-weighed patches/wipes or by measuring the sodium content in the sweat or the squalene (or total lipid) content in the sebum [15, 31]. After the sample collection, the sample or the patches are frozen stored at -5, -15 or -20°C until analysis [32-34].

2.7 Fecal

Some of the medicine or target analytes may be bio transformed by intestinal microbiota. The human intestinal microbiome can affect the metabolic function of some herbal medicines. Therefore, studies on the metabolism of medicines by human intestinal microflora are important. The fecal specimen is an excellent sample for this research. Usually, before sampling, the volunteer should be fasting. The fecal sample was collected in a plastic cup. Then the sample was suspended in cold physiological saline. The fecal suspension was centrifuged and the supernatant was filtered with gauze and then extracted by various sample preparation methods. If necessary, the resulting precipitates can be used as a metabolic intestinal microflora fraction [35].

2.8 Tissue

Analysis of compounds in tissue has become a more prevalent addition to biological sample analysis in recent times. As opposed to urine, plasma, blood and other liquid

biological samples, tissue samples are solid or semi-solid. Tissues sample can be divided into three categories: soft, tough and hard. Soft tissues including brain, lung, liver, spleen and kidney can be easily homogenized. Tough tissues such as heart, muscle, stomach, intestine, colon, placenta and artery are more fibrous and less liquid in content and need a suitable treatment process. Hard tissues, i.e. skeletal bone, cartilage, nail, skin and hair, are mostly non-vascularized tissues and need special treatment [1]. Therefore, tissue samples need appropriate preparation prior to instrumental analysis. There is a simplified workflow for tissue samples considered before the sample extraction. The first step of tissue sample pretreatment is precise and timely excision of the tissue or organ of interest. And then, the tissue is cleaned, weighed, homogenized and processed for analytes analysis. A recommended rinsing solvent is cold physiological saline (sterile 0.9% NaCl). The organ or tissue then blots dry with a lint-free tissue. Descriptions about the tissue sample preparation are made in detail in Ref. [1, 36].

Homogenization process is very important part in tissue pretreatment. In order to analyze the analytes interested, the tissue structure itself needs to be disrupted and homogenized. The most common used homogenization means are manual, physical or mechanical methods. Mechanical methods include grinding, shearing, cutting or chopping, bead-beating, blending and sonication. Soft tissues may be homogenized by sonication even simply vortexed. Tough tissues may benefit from snap freezing in liquid nitrogen, incubation in buffer at elevated temperature before continued processing, or enzymatic digestion [36]. It is generally good to ensure the tissue samples stay cool on ice or in liquid nitrogen during the mechanical homogenization because of the friction heat. Moreover, snap-frozen either in liquid nitrogen or on dry ice causes the tissue to become brittle, makes a fine powder. After pretreatment, the tissue samples are stored at -80°C or -20°C [1].

2.9 Some pretreatment procedures in common or special

2.9.1 Dilution

Dilution is considered as one of the necessary sample pretreatment methods prior to instrumental analysis. However, the contaminants and unwanted analytes cannot be removed. The productivity of dilution depends on the selected diluents and their fractions, i.e. mobile phase is selected as the diluent prior to chromatographic analysis. In addition, the productivity can be approved by using automatic techniques, such as microplates and auto-samplers [3].

2.9.2 Centrifugation and filtration

In order to clean up the biological samples, centrifugation and filtration are the two frequently applied methods. Deproteinization is an essential step for blood, serum, plasma and urine because of their high protein content. Centrifugation and filtration is also a usual step to remove materials such as calculi, cellular components or proteins in urine [9]. In some cases, vacuum devices are needed for accelerating the speed. According to the porous size of the utilized filters, ultra-, micro- and nano-filtration are used for clean-up of the samples. Conventional filtration is performed on a cellulose membrane (0.45 µm pore size), prior to a preservative addition. It was found that 0.22 µm filtration is superior to centrifugation or sodium- azide addition in preventing bacterial growth. It is recommended mild centrifugation (1000–3000 rcf for 5 min) immediately after blood collection to remove cellular components [9]. Some miniaturization and automation methods such as in syringe filters, 96-well plate filters and so on are used recently.

Ultrafiltration is a method which only allows molecular of certain molecular weight to pass through, and the filtration is achieved through application of pressure or through

centrifugation. Filters with molecular weight cut-offs of 3 kDa, 10 kDa and 30 kDa are commonly used [9]. Microdialysis sampling is a well-known method of direct sampling which has been applied in pharmacokinetic studies [3].

2.9.3 Internal standards

As a result of the challenging extraction of analytes from biological material, use of an internal standard (IS) is recommended for correction of the extraction procedure. Addition of an IS should eliminate variations in the injection volume and minimize the ion-suppression/enhancement effects (with MS analysis) caused by co-eluting compounds, i.e. a surfactant can result in ionization suppression. On the basis of current knowledge on biological applications, one should not use an IS that can be present in biological fluids. An IS which has a similar structure with analytes and is not present in biological matrices is good.

2.9.4 Saponification

For some lipophilic analytes in red blood cells and human breast milk, i.e. vitamins, saponification is widely used [37]. This method typically follows protein precipitation and is used to remove neutral lipids. Potassium hydroxide (2 or 10 mol/L) is almost exclusively used as the saponification solvent [37]. The whole process usually takes about 30 min in the temperature of 60–80 °C.

2.9.5 Cell lysis

The release of analytes from biological samples normally requires lysis of cells. Lysis is generally performed through the use of enzymes, detergents, heat or mechanical forces [38]. In addition, ultrasound sonication is also an ideal method for suspensions of cultured cells. It causes the cells to burst due to the cavitation effects in the water, which tear the cells apart

[38].

2.9.6 Enzymatic hydrolysis

Some analytes in biological samples are exclusively presented as conjugated compounds, i.e. female steroid hormones, as endogenous compounds, are presented in urine as glucuronides, sulfates, diglucuronides, disulfates and sulfoglucorodines compounds; another example is sunscreen agents, as exogenous compounds present in urine as glucuronide and sulfate derivatives [9]. Thereafter, in order to enhance the analytes' solubility, some biocatalysts such as β-glucuronidase and/or sulfatase are required to add for the enzymatic hydrolysis [9]. The process of enzymatic hydrolysis requires different times, from hours to overnight. An alternative to enhance enzymatic hydrolysis is assistance with ultrasonic energy which could promote the reaction rate between substrate and active sites of the enzyme [9]. Usually, an IS is required in this stage.

3. Sample preparation

Related description about liquid and solid phase extraction such as LLE, LPME (DLLME, SDME, HF-LPME and *etc.*), SPE, SPME, stir-bar sorptive extraction (SBSE), and matrix solid phase dispersion (MSPD) is presented in our previous review [39, 40]. Also, these methods used for biological samples are reviewed in detail by other research groups [3, 5-7, 9, 10, 41-44]. Sample preparation methods applied in bioanalytical sample and their important features including extraction time, solvent volume, repeatability, simplicity, cost and automation are summarized in Ref. [5]. Below, we provide a simple introduction of the preparation methods used in biological samples.

3.1 Liquid phase extraction

The classic liquid phase extraction method was LLE. It is still used very often in laboratory. However, it is time-consuming and tedious, and requires large amounts of potentially toxic organic solvents which is not very suitable for the environment-friendly need. Some liquid phase microextraction methods, such as salting-out assisted liquid liquid extraction (SALLE), HF-LPME, supported liquid extraction (SLE), electromembrance extraction (EME), cloud point extraction (CPE), DLLME, SDME and so on, become popular in recent years. As an important preparation method for most of the biological samples, PP is categorized as a LLE method in a few texts.

3.1.1 Protein precipitation

Although the selectivity and clean-up is considered to be very low, protein precipitation remains one of the leading and popular sample preparation method for analytes extraction due to its simplicity, speed, fast method optimization and no specific equipment requirement. Precipitability involved in PP is based on the differential solubility of endogenous proteins and the target compound. Moreover, some natural compounds containing phenolic groups such as flavonoids are known to be sensitive to light, heat and changes in pH. Protein precipitation, as a way of preventing degradation and oxidation method, is preferable for these analytes [10].

Adding a precipitation agent to biological samples causes protein denaturation so that analytes dissolve in the liquid phase and are separated from the protein pellet, whether they were previously bound to protein or not [10]. The precipitation agent could be organic solvents (acetonitrile, methanol, ethanol or acetone), acids (perchloric, trichloroacetic or phosphoric acid), concentrated salts or SDS [14, 37]. Commonly used volume ratios of sample to precipitation solvent are 1:1, 1:2, 1:4 and 1:5 [37]. The organic solvents can

remove ≥95% of plasmatic proteins; among them methanol is frequently used in protein precipitation because it is comparatively efficient; acetonitrile has shown a stronger precipitability than methanol and ethanol in some biological samples. The acids can be a very good precipitation agent. For example, in whole blood, water molecules surround plasma proteins. At a low pH values, positively charged amino acids become insoluble salts and these salts remove water from the protein surface, leading to their aggregation due to hydrophobic interactions between proteins [10]. In order to increase the productivity of PP, semi-automation and automation methods used 96-well plate are used [45-48].

However, recovery is different based on these precipitation agents. Organic solvents lead to the least trapped analytes in the protein aggregate, whereas salts or acids fail to dissolve an appropriate amount of the target analyte in the supernatant [3]. In order to overcome this problem, a combination of different solvents could be suggested. Among them, a combination of organic solvents and salts which called SALLE is very popular now.

3.1.2 SALLE

Salting-out liquid liquid extraction is a kind of homogeneous liquid-liquid extraction (HLLE). HLLE is a variation of solvent extraction that involves extraction with water-miscible organic solvents [49, 50]. It is based on the formation of a biphasic system of mutual miscibility of two liquids by addition of additives, i.e. salts and sucrose [51, 52]. One of the first demonstrations of this effect was demonstrated by Matkovich and Christian in 1973 for the separation of acetone from water [51]. Later, this technique became a popular extraction method, called SALLE. Two similar theories have been used to explain this salting-out assisted process. One applies only to the ionic compounds and states that the more polar of the two solvents (e.g. water) preferentially congregates around the salt because of the electrostatic forces. The other theory assumes that one of the solvents preferentially solvates

the electrolyte (ionic or not ionic) making it unavailable to dissolve the other solvent [51, 53].

Based on the salts addition, this method is especially suitable for high salinity samples, for example, sea water [50]. Considering the organic solvents as protein precipitation agents, SALLE is an excellent alternative used for biological sample. This method can couple sample clean-up (e.g. acetonitrile deproteinization) with enrichment (via salting-out extraction). The applications of SALLE will be discussed below.

3.1.3 CPE and dual-CPE

Cloud point extraction was introduced initially by Watanabe and co-workers in 1976 [5]. Similar to LLE, CPE is based primarily on the phase separation induced by temperature difference between neutral surfactants, including nonionic and zwitterionic surfactants. With the temperature above the cloud point and the concentration of surfactant close to the critical micellar concentration, a cloud solution is formed. After centrifugation, two distinct phases are formed. One is a surfactant-rich phase, the other is an aqueous phase. The hydrophobic species can be extracted into the surfactant-rich phase and thereafter interfere possibly with the analysis of the targeted analytes. Compared with LLE, SPE, SPME and some other extraction methods, CPE has its own advantages: no requirement of the organic solvents using, less toxic and cheaper surfactants, lower volume of sample necessary. What's more, the extraction and preconcentration can be achieved in only one step [5]. Many applications about CPE in element extraction from biological samples prior to spectrometry analysis are review in Ref. [54]. There were many applications about CPE combined with HPLC, but rare combined with GC. This is because the viscous nature of the surfactants which may block the capillary column of GC [5].

Based on CPE, dual-cloud point extraction (dCPE) is first reported by Yin [55]. The analytes were extracted from sample to surfactant-rich phase in the first CPE, then the

analytes were back-extracted from the surfactant-rich phase to some aqueous solution, e.g. alkaline solution in the second CPE [55, 56]. This method has already been used in element extraction in saliva and serum samples [57, 58]. Reports about some organic analytes are rare. In our previous work, sulfonamide antimicrobials were extracted by dCPE in urine sample [56].

3.1.4 DLLME

Dispersive liquid liquid microextraction was initially introduced as a new extraction method by Rezaee and co-workers in 2006 [59]. It is based on a ternary-component solvent system such as HLLE or CPE. In DLLME, an appropriate mixture of extraction and disperser solvents is rapidly injected into an aqueous sample by a syringe. The fine particle of extracting solvent that is dispersed into aqueous phase forms a cloudy solution and allows its interaction with the analytes. The analytes are extracted from the sample to the fine droplets of extraction solvents. After centrifugation, phase separation is achieved and the enriched analytes in the sediment phase is analyzed by some instrumental methods.

The extraction solvent of DLLME must be a high-density water immiscible solvent, such as chlorobenzene, carbon tetrachloride, tetrachloroethylene and ionic liquid, whereas the disperser solvent must be a water miscible, polar solvent, such as acetone, methanol, tetrahydrofuran, ethanol and ACN [40, 60]. El-Shahawi *et al.* had also reviewed DLLME application in trace-metal analysis of some biological samples such as serum and hair [61].

DLLME with solidification of floating organic drop (DLLME-SFO) is one of the most interesting sample preparation techniques developed in recent years. Instead of some high-density water immiscible solvent as extraction solvent, dodecanol and 2-dodecanol are used as extraction solvent in DLLME-SFO [62-65]. After centrifugation, the flotation of the organic phase at the top of the aqueous phase is later observed and solidified quickly by

cooling in an ice bath. Then the solidified extraction solvent is transferred and melted at room temperature for analysis.

3.1.5 SDME

Single drop microextraction was introduced by Liu and Dasgupta [66], and Jeannot and Cantwell in 1996 [67]. The simplest mode of LPME is the SDME, in which analytes are extracted from a stirred aqueous sample into a small drop of a water-immiscible organic solvent (approximately microliter) suspended from the needle of a microsyringe [40]. After the extraction, the drop is withdrawn into the syringe for analysis. Because of the high ratio of sample volume to organic phase volume, high enrichment factors are obtained. There are three different modes of SDME, named direct immersion SDME, headspace SDME and three-phase SDME, which are descripted in detail in Ref. [5] and Ref. [40]. However, SDME faces a major problem, that is the drop instability. An ionic liquid with higher viscosity than some organic solvents can improve the stability problem of the drop [68].

3.1.6 SLE, HF-LPME and EME

Supported liquid extraction is an extraction method used supported liquid membrane (SLM). In SLM, usually organic liquid is impregnated in small pores of a fiber (polymer support) and is kept there by capillary forces. Common configurations of SLM are flat sheet supported liquid membrane (FSSLM) and hollow fiber supported liquid membrane (HFSLM) [69].

The process of SLE is described as follows. Briefly, the lumen of a piece of fiber was filled with acceptor solution. Then the fiber was dipped into the membrane liquid for a few seconds to impregnate the pores of the fiber wall, thus forming the organic liquid membrane. The extraction device was obtained. For extraction, the finished extraction device was

immersed into the donor solution and shaken/stirred to perform the extraction and enrichment. The analyte was transferred from the sample to the acceptor solution through pores of the hollow fibers, depending on the analyte properties, such as the partition coefficient [5]. After extraction, the acceptor containing the extracted analytes was collected and analyzed [70]. Although hollow fiber modules are usually more expensive, they offer high surface area. Commercially available modules can be big enough and have up to 220 m^2 area [69].

Hollow fiber-liquid phase microextraction is firstly introduced by Pedersen-Bjergaard and his co-workers in 1999 [71]. There were two modes of LPME, called two-phase and three phases, see Fig. 2, A and B. In two-phase HF-LPME, the organic solution immobilized in the pores of the hollow fiber can be as same as the acceptor solution. The acceptor solution can be directly injected into chromatographic instruments. In three-phase HF-LPME, an aqueous solution can be used as the acceptor solution. The analytes are extracted from sample solution into the organic membrane and subsequently back-extracted from the organic membrane into the aqueous acceptor solution. Although this method is very popular now, there are some disadvantages. One problem is that adsorption of hydrophobic substances on the fiber surface may block the pores in real samples such as blood plasma and urine samples [5]. Therefore, PP is recommended before HF-LPME for these samples. Another disadvantage is the creation of air bubbles on the surface of the hollow fiber reduces the transport rate and decreases the reproducibility of the extraction. Also, a membrane barrier between sample and acceptor solvent reduces the extraction rate and increase the extraction time.

In order to decrease the extraction time of SLE, electromembrance extraction (EME) is first introduced by Pedersen-Bjergarrd and Rasmussen [72]. In this procedure, a potential difference was applied across the SLM that acts as the driving force. A platinum electrode was placed in the sample solution and the other platinum electrode was placed in the extractant. Charged analytes in the sample are migrated across the SLM toward the

oppositely charged electrode in the extractant [73], see Fig. 2C and D. For extraction of net positively charged analytes, the anode is located in the sample and the cathode is located in the acceptor solution. For extraction of net negatively charged analytes, the direction of the electrical field is reversed [74]. It was interesting to mention that the setup of Fig. 2D was a simultaneous extraction of acidic and basic analytes from wastewater in a single step [75]. The anode and cathode were placed into the acidic (pH 2) and basic (pH 12) buffer, respectively. Under the applied voltage, the basic drugs migrated toward the cathode and became deionized; negatively charged acidic drugs migrated toward the anode and became deionized. The two deionized drugs were finally transported to the organic acceptor solvent. This was the procedure for the simultaneous extraction of both acidic and basic drugs.

More information about the EME setup, general procedure and parameters affecting the extraction efficiency of EME is reviewed in other publications [73, 76]. And in Ref. [73] some innovations in EME, such as on-chip EME, low voltage EME, drop-to-drop EME, pulsed EME and EME followed by low-density solvent based ultrasound-assisted emulsification microextraction are also elaborated.

3.1.7 Ultrasonic assisted extraction (UAE), microwave-assisted extraction (MAE), pressurized liquid extraction (PLE) and supercritical fluid extraction (SFE)

Like the methods mentioned above, UAE, MAE, PLE and SFE are also extraction methods based on liquid phase extraction. These methods are usually used for solid or semi-solid samples and offer some benefits, such as a short extraction time, decreased solvent consumption, and decreased sample handling, which have replaced Soxhlet extraction most times. These methods are already reviewed in our previous review [40] and Ref. [44], herein, a simple description about these methods is presented.

Ultrasonic assisted extraction utilizes acoustic vibrations to cause cavitation in the liquid,

and cavitation enhances the removal of analytes from the matrix to the extraction solvent [40]. The typical extractants used in UAE are methanol, ethanol, acetonitrile and acetone, and the sonication time range from 2–120 min [44]. After the sonication, the analytes extracted are separated by filtration or centrifugation. In order to get a high extraction efficiency, the process can be operated for two or three times. Then the extractants are combined together, dried by nitrogen blowing and dissolved in a small volume solvent for analysis. The combined extractant can also be applied in a SPE clean-up procedure. However, the lack of uniformity in the distribution of ultrasound energy and low selectivity are the main disadvantages of UAE.

Microwave-assisted extraction is based on heating organic solvent or solvent mixtures by applying microwaves to the sample and extraction solvent and the partition of analytes from the sample matrix into the extractant. Microwave energy with a frequency from 300 to 3000,000 Hz causes molecular motion by ionic conduction and dipole rotation. Ionic conduction is the electrophoretic migration of ions in an applied electromagnetic field. The resistance of the solution to ions flow causes friction and thus heat the solution. Dipole rotation is the realignment of dipoles with the applied field which generates heating effect [77]. Therefore, only samples or solvents that contain dipolar materials or microwave absorbents are affected by microwaves in theory [44]. The solvents used in MAE are methanol, ethanol or water, binary or more solvents with high and low dielectric losses (e.g. hexane: acteone (1:1)). Hexane is not heated in a microwave. But heating will happen by a mixture with hexane and acetone. There are two modes of MAE: open or closed vessels. Open vessels are commonly used. In closed vessels, the solvent is heated above its boiling point at atmospheric pressure to enhance its extraction rate and efficiency. The main advantage of MAE is short extraction time (about 15–30 min) because the solvent is heated rapidly. Like UAE, the selectivity is the main disadvantage of MAE. There is a description of

MAE in detail in Ref. [77].

Pressurized liquid extraction, also known as accelerated solvent extraction (ASE), is an extraction method that keep the extractant in a liquid phase at the relatively high extraction temperatures (even up to 200 °C) by pressuring the sample cell. This make PLE reduce the extraction time and the solvent consumption. Commercial, automated systems are available and miniaturized versions of the PLE system have also been developed. Typically, some organic solvents, water and mixture of low- and high-polar solvents generally provide efficient extractions of analytes [40]. Recently, surfactant added in water is also used as the extraction solvent of PLE as pure water is too polarized to dissolve some bioactive compounds.

Supercritical fluid extraction relies on supercritical fluids for extraction in which a wide variety of compounds in complex matrices can be extracted. The properties of supercritical fluids are intermediate between those of gases and liquids and depend on the pressure, temperature, and composition of the fluids. The viscosity of supercritical fluids is lower than that of liquids, and the diffusion coefficients are higher, which leads to more efficient extractions [44]. Many solvents, such as CO_2, nitrous oxide, ethane, propane, n-pentane, ammonia, fluoroform, sulfur hexafluoride and water, can be used as supercritical fluids [40]. Among all these solvents mentioned above, pure CO_2 is the most popular because of its low critical properties, chemical inertness, low toxicity and cost, and its ability to dissolve a wide range of organic compounds. However, the use of CO_2 is restricted by its poor extraction recovery for highly polar analytes, which can, to some extent, be boosted by using an appropriate modifier, such as water or methanol [44].

3.2 Solid phase extraction

Solid phase extraction is a classic and very frequently used extraction method for

biological samples. It can be implemented in manual, semi-automatic or automatic ways. In the automatic case, on-line mode of SPE coupling with instrument (chromatography or capillary electrophoresis) can be implemented. Compared with LLE, the amount of organic solvent used in SPE is less and the emulsion formation during the extraction is disappeared. However, SPE involves laboratories and extensive preparatory procedures. Moreover, the elution solvent must be concentrated by evaporation, *e.g.* nitrogen blowing. To overcome these issues, new solid phase microextraction methods, such as SPME (including MEPS and DPX), SBSE, spin column extraction (SCE), MSPD have been developed and are very popular in recent years. Also, except for some classic solid sorbents such as C_{18}, C_8, hydrophilic–lipophilic balance (HLB), mixed mode/cationic-exchange (MCX), mixed-mode/anion exchange (MAX) weak cation exchange (WCX) and weak anion exchange (WAX), many kinds of solid sorbents for the above methods emerge very rapidly, such as nanomaterials (carbon nanotubes, nanocones, nanodisks and nanofibers, graphene and graphene oxide), molecularly-imprinted polymers (MIPs), metallic nanoparticles and metal-organic frameworks. These solid sorbents applied in SPE, SPME, MSPD and SBSE are described in our previous review [39]. As SPE is ubiquitous in environmental and bioanalytical labs, here no description about SPE is presented. A simple introduction about the solid phase microextraction is elaborated.

3.2.1 SPME

Solid phase microextraction was introduced as a solvent free sample preparation method by Pawliszyn and his co-workers [78]. Like SPE, the mechanism of SPME relies on the diffusion of the analytes from the sample matrix to the solid sorbents. Pawliszyn and his co-worker reviewed the concepts, techniques and devices associated with solid-phase microextraction [79]. The first commercial version of the laboratory SPME device was

introduced by Supelco in 1993 [79]. Nowadays, various implementations of SPME such as fiber SPME, in-tube SPME, *in vivo* SPME, in-tip fiber SPME, 96-well wire SPME and 96-blade SPME are developed, see Fig. 3 [5]. Some new SPME techniques, such as MEPS and DPX are very popular recently [5]. As a method combined sampling, isolation, and enrichment into one step, SPME is also used as an on/in-line sample preparation method coupled with GC or LC.

Liquid-like polymeric materials, e.g. polydimethylsiloxane (PDMS) or solid porous material, e.g. divinylbenzene/PDMS and carboxen/PDMS is the commonly used sorbents in SPME. However, because of the low distribution coefficient and the lack of selectivity of PDMS, some new nanomaterials or modified nanomaterials such as carbon nanotubes, graphene and graphene oxide, molecularly-imprinted polymers, metallic nanoparticles and *etc.* are now occupied the SPME market more and more.

3.2.2 SBSE

Stir bar sorptive extraction was developed by Sandra and co-workers in 1999 [80] and based on sorption extraction like SPME. In SBSE, the sorbent is coated on a magnetic stirring bar, and liquid samples are simply stirred with this bar. After extraction, the stir bar is removed and dried with a soft tissue. The analytes are desorbed through thermal desorption followed by GC analysis and liquid desorption followed by HPLC analysis. The most commonly used stir bar is PDMS stir bar and it is the commercially available. Due to the non-polar characteristic of PDMS, SBSE failed to the extract strongly polar and weakly polar compounds. To overcome this limitation, some other strategies are proposed: the use of dual-phase stir bar, higher polarity coating materials, MIPs and monolithic materials [5].

3.2.3 SCE

Spin column extraction was first introduced as a sample preparation method by Namera and his co-workers in 2008 [81, 82], see Fig. 4. In SCE, monolithic silica disk was packed into a spin column. All the procedures including sample loading, washing and analytes elution were only exhibited by a centrifugation of the column. This method owns a lot of advantages: simple operation procedure, low eluate volume requirement and no need of solvent evaporation. In addition, the biggest advantage of this method is many samples can be processed simultaneously which is very suitable for batches of biological samples.

3.2.4 MSPD

Matrix solid phase dispersion is a unique sample preparation method which can be directly applied for semi-solid and solid samples. As a process for the simultaneous sample disruption, sample cleanup and analytes extraction, MSPD involves mechanically blending a small amount of sample matrix with an appropriate sorbent followed by washing and elution of compounds with a small volume of solvent, see Fig. 5 [83]. Many solid sorbents such as C18, C8, silica gel, sand, graphitic fibers, Florisil, alumina, nanomaterials and so on can be used in MSPD [39, 40].

4 Applications

In order to obtain high sensitive results of analytes and protect the analytical instrument (including chromatography, spectrometry and electrochemical instrument), sample pretreatment/preparation must be an important part of the whole analysis. Below, we provide an elaborated update on the simple introduction of these sample preparation methods application.

4.1 Chromatography

4.1.1 LLE and SPE

As the traditional extraction methods, LLE and SPE are robust. On the one hand, LLE has many advantages, such as very fast sample treatment, easy and fast method optimization, minimum number of steps and no requirement for special equipment. However, the selectivity and clean-up of LLE is low. On the other hand, LLE is usually carried out with much organic solvent immiscible with water, such as hexane, diethyl ether, ethyl acetate and so on, which is not environment-friendly. Thanks to the various solid sorbents, the selectivity of SPE is further enhanced. By using different sorbents, the target analytes could be extracted and the matrix could be cleaned up efficiently, e.g. MIPs. But the problems are special equipment is needed and the batch-to-batch reproducibility of the SPE column cartridges must be concerned. Some applications are listed in Table 1 [84-125]. Here, some interesting works must be described.

An automatic LLE system was introduced by Purschke et al. [84]. Sample preparation was based on a MultiPurpose Sampler MPS (GERSTEL, Muelheim, Germany). The MPS was equipped with a centrifuge, a module for evaporation of solvents under controlled vacuum and temperature, a quick Mix for sample extraction, and a Solvent Filling Station for solvent supply. All sample preparation steps were performed in septum-sealed vials with magnetic screw caps enabling transport by the MPS. After the extraction, the samples could be injected directly into GC-MS.

Polyunsaturated fatty acids were extracted by SPE on 96-well plate Oasis^{TM} MAX. The wells were cleaned with methanol (MeOH) and conditioned with formic acid. After loading sample, the wells were washed with NH_4OH and MeOH/formic acid and hexane. The analytes were eluted with hexane/ethanol/acetic acid. After drying, the samples were

re-dissolved with MeOH and taken for HPLC-MS/MS analysis [85]. Oasis^{TM} MAX 96-well SPE plate was also applied for the extraction and enrichment of mono-clonal antibody surrogate peptide. Moreover, a post-pellet-digestion precipitation was processed to remove matrix-related clog-causing components prior to SPE, which efficiently improved the determination sensitivity [86]. Compared with the traditional SPE method, 96-well SPE plate belongs to a semi-automated or automated method. It is quick and robust due to 96 samples can be added at one time manually or automatically.

On-line SPE is more and more popular now because its simplicity and automatic operation [113-120]. For example, Mena-Bravo and his co-workers developed an automated on-line solid phase extraction coupled to two-dimensional liquid chromatography with tandem mass spectrometry detection method for vitamin D metabolite profiling in human serum. Two-dimensional LC was configured with two complementary analytical columns, pentafluorophenyl and C18 phases, for determination of 25-hydroxyvitamin D_3 epimers and the resting bioactive metabolites of vitamin D (D_3 and D_2)-25-hydroxyvitamin D_2, 1, 25-dihydroxyvitamin D_3, 1, 25-dihydroxyvitamin D_2 and 24, 25-dihydroxyvitamin D_3. Two-dimensional LC has shown to be the key to discriminate between 25-hydroxyvitamin D_3 epimers in a quantitative analysis also involving dihydroxyvitamin D metabolites [113].

Silica-coated iron oxide particles functionalized with C18 were successfully synthesized and used as a reverse-phase sorbent for in-line SPE-CE [112]. The magnetic C18 sorbents in Milli-Q water were bubbled by N_2 in order to obtain a suspension of the particles. Afterwards, the obtained suspension was injected at a pressure of 930 mbar for 3 min. In this step, the magnetic C18 particles are trapped by the magnetic field. Then the capillary was conditioned by MeOH and Milli-Q water. After injected, samples were cleaned up by buffer and eluted by MeOH with 2.0% of formic acid at 50 mbar for 20 s. The elution plug was then pushed with the buffer at 50 mbar for 4 min. Finally, a voltage of 15 kV was applied for the

electrophoretic separation of the analytes.

In recent years, Fe_3O_4 nanoparticles functionalized with various materials have also been used as adsorbents of dispersion SPE (dSPE) for selective enrichment and extraction many kinds of analytes because of their convenience, simplicity, reusable ability and specificity [121-123]. Moreover, magnetic MIPS are used more and more in order to enhance the selectivity. Tang *et al.* [122] synthesized Fe_3O_4 nanoparticles functionalized with ractopamine. The synthesized magnetic particles were successfully applied as sorbents of dSPE to extraction, followed by high performance liquid chromatography to determine ractopamine.

Not only magnetic materials but also other new nanomaterials are applied as the sorbents of dSPE. For example, a surface carbamazepine-imprinted polymer was grafted and synthesized on the SiO_2/graphene oxide surface. The surface molecularly imprinted polymer was utilized as an adsorbent of dSPE for separation and preconcentration of carbamazepine in human urine and plasma samples [126]. In our previous work, graphene oxide-based silica microspheres (SiO_2@GO) were synthesized and used as sorbents of dSPE to extract non-steroidal estrogens [127].

Another style of SPE called micro-SPE is similar to dSPE. The different between them is the sorbent was packed inside an envelope [124] or a device of cone [125] and heat sealed. After conditioned, the device was placed in sample solution for extraction.

Roughly speaking, MIPs, nanomaterials, magnetic materials and so on are the most popular sorbents for SPE. Gramine MIPs [128], Z-Sep [129] and Methyl-modified metal–organicframework-5/polyacrylonitrile composite nanofibers [130] showed excellent extraction efficiency for analytes in biological samples.

There is a special preparation method called QuEChERS (quick, easy, cheap, effective, rugged, and safe). Originally, QuEChERS extraction required two steps: (i) an

extraction-partitioning step where the matrix was mixed with ACN before adding anhydrous $MgSO_4$ and NaCl (in order to dry the organic phase and allowing the separation of the two phases) and (ii) a dSPE cleanup where the remaining impurities are removed by a sorbent such as primarysecondary amines [131]. Based on the theory above, we think it is an excellent sample preparation method based on LLE and SPE. Nowadays, QuEChERS are more and more used in biological samples [131-133].

4.1.2 Other microextraction and extraction methods

The first popular microextraction method applied to biological samples is DLLME. As a low-cost, easy-to-operate, reliable preconcentration technique, DLLME is an attractive sample-preparation technique offering high enrichment factors from low volumes of samples. It is applied to various biological samples [134-137], see Table 2. In the past several years, the number of papers devoted to the application of DLLME for trace analytes analysis has grown rapidly. Various styles of DLLME are developed, such as surfactant assisted DLLME [138], ultrasound-assisted DLLME [139, 140], magnetic stirring-assisted DLLME [141], DLLME used ionic liquid as extraction solvent or as dispersive solvent [142, 143] and solidification of floating organic droplet DLLME (some of them called ultrasound-assisted emulsification microextraction) [144, 145].

Some in-syringe DLLME methods are very popular now [146, 147]. For example, after a mixture of extraction solvent and dispersive solvent injected rapidly into the sample solution through the syringe, the emulsion formed, another part of dispersive solvent, serving as the de-emulsifier, was gently injected into the top surface of the aqueous bulk to breakdown the emulsion. Separation of the two phases was achieved and the extractant was floated on the surface of the solution. Then, the extractant containing the target analytes was easily collected and withdrawn by a microsyringe and injected into HPLC for analysis [146].

Another example is syringe to syringe DLLME. The authors designed a DLLME system by two syringes, see Fig. 6. First, the sample was drawn into syringe 1, and 1-dodecanol (extraction solvent) was added to it. Then, syringe 1 was connected to syringe 2, and the mixture in syringe 1 was rapidly injected into syringe 2 followed by back injection of the mixture in syringe 2 to syringe 1. This procedure was repeated four times until the emulsion formed. The emulsion mixture was transferred to a closed conical centrifuged tube and centrifuged. Finally, the sample tube was transferred into an ice bath where 1-dodecanol was solidified after several minutes, and the solidified organic drop was transferred. After the drop melted, it was injected to HPLC-UV instrument. This method applied successfully to determine albendazole and triclabendazole in several samples including human urine and cow milk samples [147]. The above in-syringe DLLME methods were proposed using the syringe as an alternative for the flask to carry out the extraction, dispersion and phase separation steps in syringe. The methods have the advantages of rapidity, simplicity, low cost and being environment-friendly. Similar to SPME, in-syringe DLLME methods also used syringe. However, the syringe is much cheaper than that used in SPME.

The second popular microextraction method applied to biological sample is membrane microextraction, including SLM, HF-LPME, EME and SPME [148-177] (Table 2). It seems like SLM can be easily applied in in-line mode coupled with CE [152, 153]. An interesting work was that a 96-well HF-LPME device was designed for steroids extraction in human urine, plasma and bovine milk. It also had 96 divided regions corresponding to the individual wells. Every region had its own hollow fiber membrane tube. Again, 96 samples can be added at one time manually or automatically which made this a fast and high-throughput sample preparation method [156]. Nowadays, nanomaterials such as MIPS, nanofiber, TiO_2 nanowire and MWCNTs are applied as efficient sorbents in SPME [168-172]. As two members of SPME, MEPS [173-176] and DPX [177] are more and more utilized for

biological samples. Compared with SPE, SPME is regarded as a solvent-free technique. This technique has many advantages such as reducing solvent consumption, reducing sorbent and other reagents consumption, reducing time of extraction and reducing sample amount and is easier to combined with GC. However, SPME fibers are frail, relatively expensive, and tend to degrade with repeated use. What's more, if special materials are used in SLM, HF-LPME, EME and SPME methods, the commercial materials are needed to buy or complicated synthesis processes are needed. Furthermore, special instruments are used in these methods. Therefore, these methods are more expensive and the membrane reproducibility is the important problem compared with some liquid microextraction methods such as DLLME, SALLE, CPE and so on.

The other sample preparation methods coupled with chromatography include CPE [56, 178-181], SALLE [53, 182-188], SDME [189, 190], SBSE [191, 192], SCE [193, 194], LLME [195-198], LLLME [199, 200], PLE [201-205], MAE and UAE [206-209]. These methods are all applied successfully to biological samples prior to chromatography. For example, bisoprolol in human plasma sample was extracted in human plasma by CPE using Triton X-114 as a surfactant. All analyses were performed using liquid chromatography–electrospray ionization-tandem mass spectrometry. The determination of bisoprolol concentration in human plasma in the range 1.0–70 ng/mL by the CPE method [180]. Another example is about the SDME method. A surfactant-assisted directly suspended droplet microextraction followed by GC–FID was applied for the determination of tramadol in human urine and plasma samples. This surfactant-assisted directly suspended droplet microextraction method used Triton X-110 to increase the extraction efficiency, and *n*-octanol as the extractant. Experimental design was used to optimize the extraction conditions. Under the best conditions, this extraction method coupled with GC showed high sensitivity and recovery [189].

4.2 Spectrometry

4.2.1 LLE and SPE

Although as traditional sample preparation methods, LLE and SPE are now using some popular extraction solvent or sorbents, such as ion-pairing agent bis-2-ethylhexylphosphate [210], aptamer [211], carbon nanotubes [212-214] for extraction of biogenic amines, tetracycline, cadmium, lead and amoxicillin in biological samples.

Recently, dSPE method is more and more utilized coupled with spectrometry analysis. And the important part of this method is the sorbents. For example, a novel functionalized absorbent was synthesized by attaching 4-mercaptophenylboronic acid to gold nanoparticles on modified attapulgite. The surface of the attapulgite was modified by poly (acryloyloxyethyltrimethyl ammonium chloride) by atom transfer radical polymerization, creating many polymer brushes on the surface. This sorbent exhibited excellent extraction efficiency for adenosine in human urine and plasma samples [215]. Another example is a dSPE procedure coupled with surfactant-enhanced spectrofluorimetric detection for the determination of ofloxacin and lomefloxacin from human plasma and urine samples. The sorbents were self-synthesized magnetic nanoparticle modified multi-walled carbon nanotubes [216]. Because of its simplicity of magnetic material, various kinds of magnetic sorbents such as Fe_3O_4@SiO_2 microspheres [217], sodium dodecyl sulfate (SDS)-coated nano-magnets Fe_3O_4 [218], polypyrrole-coated Fe_3O_4 magnetic nanocomposites [219], metal-organic framework magnetic graphene nanoporous composites [220] were used as sorbents of dSPE coupled with various spectrophotometric determination including surfactant-enhanced spectrofluorimetry, UV–visible spectrophotometry (UV-Vis), atomic absorption spectrometry (AAS), electrospray ionization mass spectrometry (EIMS), flame atomic absorption spectrometry and Raman spectrometry. Also, the combination of MIPs and

MWCNTs showed excellent selectivity and sensitivity [221].

4.2.2 other microextraction and extraction methods

Although the first article about DLLME in 2006 was devoted to the coupling of this technique with GC, the connection of DLLME with graphite furnace atomic absorption spectrometry appeared in 2007 [222]. Andruch et al. reviewed element determination by DLLME technique coupled with atomic spectroscopy [223]. Some applications of DLLME coupled with spectrometry technique are listed in Table 3 [224-231]. Arain and co-workers combined DLLME and CPE together to preconcentrate copper in human blood. Ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate ($[C_4mim][PF_6]$) and nonionic surfactant, TX-100 (as a stabilizer in aqueous media) were used to form the cloudy solution. Finally, the enhancement factor was 70. The DLLME-CPE-AAS method was successfully applied for the preconcentration and determination of trace levels of Cu in biological samples [230]. The other sample preparation methods such as CPE [232, 233], HF-LPME [234], LPME [235-237], SPME [238], SLM [239], MAE [240] and SFE [241] are also listed in Table 3. An interesting work is about SPME. Gómez-Ríos *et al.* presented the direct coupling of biocompatible SPME fibers to nanoelectrospray ionization-mass spectrometry/mass spectrometry (nano-ESI-MS/MS) as a powerful tool for fast quantitative analysis of cocaine, diazepam, salbutamol, and so on in human blood and urine, see Fig. 7 [238]. After the extraction and rinsing processes, the fiber was introduced into an emitter prefilled with desorption solution. Then after the analytes desorbed in the selected solvent, a high electrical field between the emitter and the mass spectrometer was applied, and analytes were ionized via electrospray mechanisms. Another interesting work is about cocaine MIP-Mn doped ZnS quantum dots (QDs). After SPE for avoiding matrix effect of human urine sample, the eluate (100 μL) was mixed with 1.5 mL of MIP-QDs solution and 0.4 mL of 0.1 M/0.1 M

KH_2PO_4−NaOH buffer, and fluorescence quenching was measured after 15 min. This material enhanced the selectivity of the method because of the MIP on the surface. Quenching of the fluorescence emitted by the MIP-QD nanoparticles provided a simple, fast and sensitive method to determine cocaine and metabolites in human urine samples [242]

4.3 Electrochemistry

Because of its special characteristic, the so-called sensor is very popular in electrochemical application. The electrode can be modified with different materials such as gold nanoparticle, MWCNTs, MIPs, graphene nanocomposite or the composition of these materials. Targeted analytes can be determined by cyclic voltammetry, potentiometry measurements, differential pulse stripping voltammetry and so on [243-255]. A big advantage of this is that the analytes can be extracted as meanwhile as determined. For example, a MIP-MWCNTs graphite electrode was used for detection of metoprolol in human serum sample. Under the selected optimal conditions, the MIP-MWCNTs sensor was showed a linear range from 0.06 to 490 mmol/L for metoprolol, a limit of detection of 2.88 nmol/L, a highly reproducible response (RSD 3.9%) and a good selectivity in the presence of structurally related molecules [249].

Except the sensors mentioned above, other sample preparation methods are also applied to extract different analytes in biological samples, including LLME [256], EME [257], dSPE [258], DLLME [259] and SDME [260]. These methods coupled with electrochemical methods were successfully applied to the determination of analytes in biological samples. For example, Timofeeva *et al.* developed SDME method for extracting of caffeine in saliva with subsequent solvent evaporation and dissolution of analyte in aqueous phase for potentiometric detection. What's important, stepwise injection analysis, called SWIA, was combined with SDME and solvent exchange procedure. The SWIA system included six-way

solenoid valve, syringe pump, mixing chamber, holding coil, flow-through potentiometric detector equipped with the saturated Ag/AgCl reference electrode, Hamiltons syringe and laboratory-made caffeine-sensitive electrode and communication tubes. The system was controlled automatically by the PC. The extraction and the determination procedure were integrated into this SWIA system. A linear range of 10^{-5}–10^{-2} M was established for caffeine with detection limit at 6×10^{-6} M. The results obtained by this novel flow method were in good agreement with reference HPLC method [260]. Another example was about DLLME method. A vortex-assisted ionic liquid DLLME method was used to extraction mercury in human urine samples. Mercury was extracted directly from human urine samples in a water-immiscible ionic liquid ([Hmim][NTf_2]), being back-extracted into 4 M HCl solution. Subsequently, it was determined using gold nanoparticle modified screen-printed electrodes by square-wave anodic stripping voltammetry.

4.4 CE on-line stacking

A number of strategies have been developed to improve the sensitivity in CE through the use of on-line enrichment techniques. The sample preparation methods mentioned above are off-line techniques, these strategies are on-line preconcentration techniques which could further improve the sensitivity coupled with the off-line techniques. CE on-line stacking includes four basic modes: field amplication (FA), sweeping, pH regulation, and isotachophoresis. The theory of the on-line stacking is described in detail in our previous review [40]. Herein, some applications of stacking are described [261-265]. Furmaniak *et al.* reported the determination of homocysteine thiolactone in urine sample by field amplified sample injection (FASI) and sweeping micellar electrokinetic chromatography (MEKC) method with UV detection. The lower limit of quantification was 0.09 nmol homocysteine thiolactone in 1 mL of urine [261]. A liquid–liquid extraction combined with FASI and

sweeping MEKC method for determination of β-blockers in human urine was described by Jouyban. The obtained results indicated that the FASI-sweeping-MEKC method enhanced analytes' peak heights by a factor of greater than 8000- and 14,000-fold, respectively [264]. A polarity switching electrophoretic stacking method has been developed for the sensitive determination of nitrates in cerebrospinal fluid. As with similar mobility values, chlorides were main matrix interference in nitrates electrophoresis analysis. This method provided an excellent technique. The sample was injected in a large volume into the short end of the separation capillary. Separation first occurred in the isotachophoretic mode, and was then completed by forcing the majority of the chlorides out of the capillary outlet. Then the polarity was switched and the separation occurred in the zone electrophoresis mode, in which the nitrates were separated from the zone of chlorides. The final results showed that the polarity switching technique was sufficiently sensitive for performance of routine analyses of cerebrospinal fluid for nitrates.

4.5 Microfluidics-based devices

The integration of miniaturized and automated extraction methods using microfluidics-based devices introduced chip-based extraction systems, which provide a convenient device for biological sample pretreatment. A microfluidic LLE system under stopped-flow manipulation mode with spectrometric detection was developed [266]. In this work, A Teflon AF liquid-core waveguide capillary was used to serve as both extraction channel for organic solvent flow and adsorption detection flow cell. The performance of the system was demonstrated in the determination of SDS extracted as an ion pair with methylene blue into chloroform. A linear response range of 1–10 mg/L SDS was obtained with 5 min extraction period. The LOD for SDS was 0.25 mg/L.

Lin’s group has published a series of work about microfluidics-based devices extraction

system [267-270]. They reviewed some chip-based SPE and LLE applications [267,268]. There were also some interesting works. For example, a chip-based continuously flowing system for online LLE was developed for the determination of fluorescein sodium [269]. Monodisperse droplets of extracting reagent were on-chip generated and dispersed in continuously flowing sample solution, and then LLE happened when organic droplets moved forward with sample solution flow. After extraction, the droplets were collected by guiding tracks and detected. Another interesting work is about chip based SPE with an online electrospray ionization quadrupole time-of-fight mass spectrometer. The microdevices were filled with unique polymeric SPE beads which were injected with a syringe at the flow rate of 5 μL/min and then conditioned, load, wash and elution. After that, the micro-SPE column was connected directly to an electrospray ionization ion source and analyzed on-line [270].

The microfluidics-based systems enable fast analysis without the need to store samples, thus eliminating the associated freeze-thaw problems, and allow the simultaneous analysis of multiple analytes. And it is robust for forensic application or metabolomic studies in which the sample amount is low [271]. However, the chip equipment is a little expensive and the operation is complicated.

5. Conclusions and perspectives

This review of sample preparation for biological samples coupled with chromatography, spectrometry and electrochemistry technique includes an enormous variety of methods (LLE, LPME, LLLME, DLLME, CPE, SPE, SPME, SBSE and so on). Undoubtedly, the sample preparation/pretreatment of biological samples is an important bottleneck of bioanalytical methods and has become a hot topic in analysis. Important features of some solid and liquid extraction methods, such as extraction time, solvent volume, simplicity, repeatability, cost per analysis, commercially available, cost of equipment and automation, were summarized by

Namera and his co-worker [5]. Sample preparation methods such as SPME, MEPS and DPX are easy to automate in combination with an auto-sampler or instrument, *e.g.* GC-MS. However, the need of additive equipment is expensive. Some liquid extraction methods such as LPME, DLLME and SDME are simple, fast and cost-effective, but they are difficult to automate and their selectivity are poor. Therefore, sample preparation/pretreatment is one of the most important processes in analysis, especially for biological samples. Four major issues associated with sample preparation and applications are yet to be resolved for continuous improvement of sample preparation, as follows.

First, the primary requirements of sample preparation methods are high selectivity and enrichment capability. Although some new agents (ILs, surfactants, gold nanoparticles and so on) and solid sorbents (nanomaterials, MIPs and so on) are increasing being utilized, new techniques of agents and sorbents synthesis are still needed to improve selectivity and adsorption ability. For example, MIPs is an alternative material for SPE, SPME, SBSE and so on due to their high selectivity. Chen *et al.* reviewed the recent advances in molecular imprinting including versatile perspectives and applications, concerning novel preparation technologies and strategies of molecular imprinting technology, and highlighted the applications of MIPs [272].

Second, the major trends in biological ample preparation methods will be towards more SALLE, SDME, DPX and SBSE applications. Because of the traditional usage of SPE, LLE, many research works have been reported on these two extraction techniques, including improving sorbents and related instruments, *e.g.* 96-well SPE and LLE. Recently, some microextraction methods such as DLLME and EME are more and more published. Although applications of SALLE, SDME, DPX and SBSE are still in their infancy, they have their own advantages and could become tools, routinely used in sample preparation in the near future. As these methods are simple, rapid and very suitable for micro-amount biological samples,

future research should be focus on these methods and on automatic and integrated devices research about these methods which could be robust in rapid determination and daily monitor.

Third, more biological samples should be selected in the future. Researches about biological samples have very intimate relationship with clinical work. Most of the applications mentioned in this review were focused on urine, blood, serum and plasma. Some not widely used samples such as hair, sweat, milk, fecal, tissue and so on also provided important information about some analytes. Therefore, these samples can be expected to be select in the future.

Fourth, the developments of microfluidics-based, on/in-line mode and automation, miniaturization of extraction methods systems will be very useful to biology and clinic development. Although expensive equipment and complicated operation are required in the fabrication of these systems which may limit their application in routine analysis, there are many advantages. For example, the advantages of chip-based solvent extraction systems are low consumption of sample and extractant and high extraction efficiency due to the microscale effect in micro-channels. The automation, integrated and microfluidics analysis system could speed the analysis process, eliminate the sample storage problems and detect unstable metabolites. Combined with the small sample amounts of biological samples, integration of several preparation steps into one, automation of preparation methods and on/in-line mode of extraction methods are in urgent need. What's more, automation of preparation methods will accelerate to facilitate preparing portable tools to measure target analytes and finally provide robust tools to beside monitor in clinic.

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Figure captions:

Fig. 1. Different commercial collection devices for saliva. (A) Three versions of the Salivette with inlays of polyester (1), polyethylene (2), or cotton (3) and the accompanying collection tubes. (B) The Quantisal® consists of a cellulose pad (4) on a plastic stem with a flag window (5), which signals adequate volume by a color shift. A sample container with preservative buffer (6) is part of the system. (C) The Intercept® also consists of a cellulose pad (7) on a plastic stem, with the sample being transported in a centrifuge container without preservatives (8). (D) The SCS® consists of a mouth-rinsing solution (9), yellow collection solution (10), a collection container for draining the saliva mix (11), and a storage unit coated with preservative powder (12). (Reprinted with permission from [29].)

Fig. 2. Hollow-fiber liquid-phase microextraction. (A) Two-phase mode; (B) three-phase mode; (C) electron-assisted mode; (D) electron-assisted mode for simultaneous extraction of basic and acidic analytes. (Reprinted with permission from [5].)

Fig. 3. Extraction device of several types of solid-phase microextraction segment. (A) Fiber SPME; (B) in-tube SPME; (C) *in vivo* SPME device; (D) in-tip fiber SPME; (E) 96-well wire SPME; and (F) 96-blade SPME system. SPME: Solid-phase microextraction. (Reprinted with permission from [5].)

Fig.4 Summary of the handling procedures for the extraction of amphetamines from urine. (Reprinted with permission from [80].)

Fig. 5. Schematic illustration of the MSPD procedure. (Reprinted with permission from [83].)

Fig. 6. Syringe to syringe dispersive liquid phase microextraction-solidified floating organic drop DLLME scheme. (Reprinted with permission from [147].)

Fig. 7. Experimental setup for Bio-SPME extraction from complex matrixes and desorption-ionization using nano-ESI-MS/MS. (Reprinted with permission from [238].)

Table 1 LLE and SPE methods coupled with chromatographic technique

Analytes	Sample	Sample preparation method	Analytical technique	LOD (ng/mL)	Ref.
Δ^9-tetrahydrocannabinol and its metabolites	Blood serum	LLE automatic	GC-MS	0.1–0.3	[84]
Indolederivative synthetic cannabinoids	Urine, blood and saliva	LLE	HPLC-MS/MS	0.1–0.5	[87]
Levornidazole and its metabolites	Human plasma and urine	LLE	UPLC-MS/MS	2.5–20	[88]
Bisphenol A diglycidyl ether and its hydrolyticmetabolites	Human plasma, serum or urine	LLE	HPLC-MS/MS	0.05–0.2	[89]
Paclitaxel	Rat plasma and brain tissue	LLE	HPLC-MS/MS	0.5	[90]
Epimedin C	Rat plasma	LLE	HPLC-MS/MS	2.5	[91]

Ofchloroquine, desethylchloroquine and primaquine	Human plasma	LLE	HPLC-DAD	0.89–21.4 nM	[92]
Hormone	Bovine serum	LLE	UPLC-MS/MS	0.0009–0.02	[93]
Naproxen	Human plasma	LLE	GC-MS	0.03	[94]
Lycorine Many tissues	Mice plasma and tissues	LLE	HPLC-MS	6.5–18.0 (LOQ)	[95]
Metoclopramide	Rabbit blood	LLE	HPLC-MS	0.42	[96]
Triptolide and its derivate	Dog blood	LLE	HPLC-MS/MS	0.25–1	[97]
Phillyrin and its metabolites	Rat bile, urine and feces	LLE	UPLC-MS	–	[98]
Retinoids	Animal raw milk	LLE	HPLC-MS/MS	6.4–130.0	[99]
Ketamine and metabolites	Dog blood	LLE	CE-DAD	10 (LOQ)	[100]
Cannabinoids and their metabolites	Human serum and urine	LLE	CE-MS	0.9–3.0	[101]

δ-viniferin	Rat plasma, urine and feces suspension	LLE	HPLC-MS/MS	1.42	[102]
Steroid Metabolome	Human breast tissues	LLE	UPLC-MS/MS	0.001−15.7 pmole	[103]
Kinase inhibitor and metabolite	Rat plasma and urine	LLE and SPE	HPLC-MS/MS	–	[104]
Persistent organic pollutants	Human blood	SPE	GC-MS	–	[105]
Beta-agonists	Porcine liver, muscle, and urine	SPE	HPLC-MS/MS	–	[106]
Polyunsaturated fatty acids	Human plasma, Mice brain and liver	96-well SPE	HPLC-MS/MS	0.49−15.63	[85]
Mono-clonal antibody surrogate peptide	Monkey and human serum	96-well SPE	UPLC-MS/MS	–	[86]

colistin methanesulphonate and colistin	Human plasma and urine	SPE	UPLC-MS/MS	13.0−25.1(LOQ)	[107]
Bromophenols	Human urine	SPE	GC-MS/MS	0.0018−0.0229	[108]
Catecholamines and metanephrines	Human urine	SPE	HPLC-MS/MS	3.5−7.4	[109]
Ketamine, norketamine and *etc.*	Human urine	SPE	HPLC-MS/MS	0.59−3440	[110]
Organophosphate flame retardants metabolites	Human urine	SPE	Ion-pair LC-MS/MS	0.02−0.19	[111]
Vitamin D metabolite	Human serum	On-line SPE	Two-dimensional HPLC-MS/MS	0.009−0.09	[113]
Prostaglandins	Rat and human hepatocytes, rat blood	On-line SPE	HPLC-MS/MS	−	[114]
Carcinogenic N-nitrosamines	Human urine	On-line SPE	HPLC-MS/MS	0.002−0.08 (LOQ)	[115]
Polyunsaturated fatty acids and eicosanoids	Human whole blood and plasma	On-line SPE	HPLC-MS/MS	−	[116]
Serum transthyretin	Human blood	On-line SPE	CE-MS	1000	[117]
Steroid hormones	Human urine	On-line SPE	HPLC-MS/MS	0.0033−0.076	[118]

Bisphenol A and its chlorinated derivatives	Human urine	On-line SPE	UPLC-MS/MS	0.025−0.25(LOQ)	[119]
Phthalate metabolites and bisphenol analogues	Human urine	On-line SPE	HPLC-MS/MS	0.01−0.5	[120]
Cocaine, codeine, methadone, andmorphine	Human urine	In-line SPE	CE-UV	0.5−20	[112]
Tricyclic antidepressant drugs	Urine and plasma	dSPE	HPLC-UV	0.51−1.4	[121]
Ractopamine	Pork extractant	dSPE	HPLC-UV	0.05	[122]
Monoamine neurotransmitters	Rabbit plasma	dSPE	HPLC-FD[a)]	0.16−0.43	[123]

[a)] HPLC-FD: high performance liquid chromatography-fluorescence detection

Table 2 Other extraction methods coupled with chromatographic technique

Analytes	Sample	Sample preparation method	Analytical technique	LOD (ng/mL)	Ref.
Fluoroquinolones	Chicken liver	DLLME	HPLC-DAD[a)]	5–19	[134]
Amantadine	Human plasma and urine	DLLME	GC-FID[b)]	2.7–4.2	[135]
Methadone	Human plasma, urine, saliva and sweat	DLLME	HPLC-UV	4.9–24.85	[136]
Neurotransmitters	Human urine	DLLME	Hydrophilic interaction chromatography	5–10	[137]
Zonisamide and carbamazepine	Human plasma and urine	DLLME	HPLC-UV	1.5–2.1	[138]
Benzodiazepines	Human plasma	DLLME	UPLC-PDA [c)]	1.7–5.3	[139]
Antidepressants	Human plasma	DLLME	UPLC-PDA [c)]	4–5	[140]
Serotonin reuptake inhibitors	Human plasma and urine	DLLME	HPLC-UV	0.30–4.43	[141]

Salmeterol	Dried blood spot	DLLME	HPLC-UV	0.30	[142]
Triclosan and methyltriclosan	Human urine and serum	DLLME	HPLC-UV	0.1184 – 0.1469	[143]
Haloperidol	Human plasma and urine	DLLME	HPLC-UV	1.5–3.0	[144]
Lovastatin and simvastatin	Rat urine	DLLME	HPLC-UV	20.00 – 20.08 (LOQ)	[145]
Doping agents	Human urine	SLM	SFC[d)]-MS/MS	–	[148]
Anabolic agents	Human urine	SLM	GC-MS/MS	0.1–5	[149]
Retinol and alpha-tocopherol	Human serum	SLM	HPLC-MS/MS	0.07 – 1.16 μmol/L (LOQ)	[150]
Cannabinoids	Human and rat plasma	SLM	HPLC-MS/MS	0.025–0.1	[151]
Nortriptyline, haloperidol, and *etc.*	Human urine and serum	SLM	CE-UV	12–100	[152]

Formate	Human serum albumin	SLM	CE-UV	30–35μmol/L	[153]
Androgens and progestogens	Human urine	HF-LPME	HPLC-MS	0.0017–0.264	[154]
Estrogens	Human urine	HF-LPME	HPLC-MS/MS	0.07–0.38	[155]
Steroids	Human plasma, urine, bovine milk	HF-LPME	HPLC-MS/MS	0.0022–0.3	[156]
Estrogens	Cow milk	HF-LPME	HPLC-DAD	0.28–107	[157]
Thyroid hormones	Human serum	HF-LPME	CE-UV	0.54–1.43	[158]
Benzodiazepines	Human serum	HF-LPME	HPLC-UV	10	[159]
Citalopram, loperamide, methadone, and sertraline	Dried blood spot	EME	HPLC-MS	0.4–5.3	[160]
Ketamine, naproxen and ibuprofen	Human urine	EME	HPLC-UV	6.7	[161]
Methamphetamine	Human urine and hair	EME	GC-FID	2.4	[162]
Sodium diclofenac and	Human urine	EME	HPLC-UV	0.1–0.7	[163]

naproxen					
Nortriptyline and amitriptyline	Human urine	EME	HPLC-UV	3.0–4.0	[164]
Mercury speciation	Animal liver and kidney	HS-SPME	GC-AFS [f)]	0.17–0.28	[165]
Carbonyl volatile compounds	Human urine	HS-SPME	GC-MS	0.009–0.942	[166]
8-hydroxy-2'-deoxyguanosine and creatinine	Human urine	On-line SPME	HPLC-MS/MS	0.0083 – 0.0168	[167]
Fluoroquinolone	Human plasma and serum	SPME	HPLC-UV	0.023–0.033	[168]
Amitriptyline and doxepin	Human blood and urine	SPME	GC-FID	0.05–0.3	[169]
Clotrimazole and tylosin	Bovine urine	SPME	HPLC-UV	0.67–0.91	[170]
Steroid sex hormones	Urine	SPME	HPLC-UV	0.027–0.12	[171]
Venlafaxine and *o*-desmethylvenlafaxine	Human urine	SPME	HPLC-UV	0.03–0.07	[172]
Biogenic amines and their	Human urine and plasma	MEPS	HPLC-MS	2.0–5.0	[173]

metabolites					
Polychlorinated biphenyls	Bovine serum	MEPS	GC-MS	0.06–0.53	[174]
Polyamines	Human urine	MEPS	GC-MS	0.18–2.70	[175]
Non steroidal anti-inflammatory drugs	Dialyzed samples	MEPS	UPLC-PDA	8–10	[176]
Indometacin and acemetacin	Human urine	DPX	HPLC-UV	0.026–0.027	[177]

[a] DAD: Diode array detection
[b] FID: flame ionization detection
[c] PDA: Photodiode Array Detector
[d] SFC: supercritical fluid chromatography
[e] C^4D: contactless conductivity detector
[f] Atomic fluorescence detector

Table 3 Other extraction methods coupled with spectrometry technique

Analyte	Sample	Sample preparation method	Analytical technique	LOD (ng/mL)	Ref
Ca	Human blood, serum and urine	DLLME	AAS	0.005	[224]
Pathogenic bacteria	Blood	DLLME	MALDI-MS[a)]	10^{-3}–10^{-4}cfu/mL	[225]
Bismuth	Human serum	DLLME	UV-Vis	1.6	[226]
Silver	Dogfish liver and muscle, bovine liver	DLLME	AAS	2	[227]
Ag, Cd, Cu, Pb	Dogfish liver, oyster tissue and bovine liver	DLLME	ICP-MS [b)]	1–90	[228]
Danazol	Mice serum	DLLME	UV	54–55	[229]
Cu	Human blood	DLLME+CPE	AAS	0.132	[230]
Cd	Human scalp hair	DLLME	AAS	0.05	[231]
Cd	Human blood and urine	CPE	AAS	0.04	[232]
Epinephrine	Human urine	CPE	Fluorescence	3×10^{-12} mol/L	[233]

			spectrum		
Co, Pd, Cd and Bi	Human urine	HF-LPME	ICP-OES	0.0037–0.0083	[234]
Cd	Human scalp hair and nail	LPME	AAS	0.4	[235]
Acylcarnitines	Human blood	LPME	ESI-MS[c)]	90–330(nM)	[236]
Amitriptyline, nortriptyline and pethidine	Human blood, saliva and urine	LPME	ESI-MS	17	[237]
Cocaine, diazepam, salbutamol, and *etc.*	Human blood and urine	SPME	ESI-MS/MS	0.1–2.3	[238]
Benzodiazepines	Urine	SLM	SERS[d)]	32–600	[239]
Cu, Fe, Ni and Zn	Fish muscle and liver	MAE	ICP-OES[e)]	80–560	[240]
Antimony	Human urine	SFE	AAS	3.75	[241]

[a)] MALDI-MS: matrix assisted laser desorption/ionization-mass spectrometry

[b)] ICP-MS: inductively coupled plasma-mass spectrometry

[c)]ESI-MS: electrospray ionization- mass spectrometry

[d)]SERS: surface enhanced Raman spectroscopy

[e)]ICP-OES: inductively coupled plasma-optical emission spectrometry

Fig. 1.

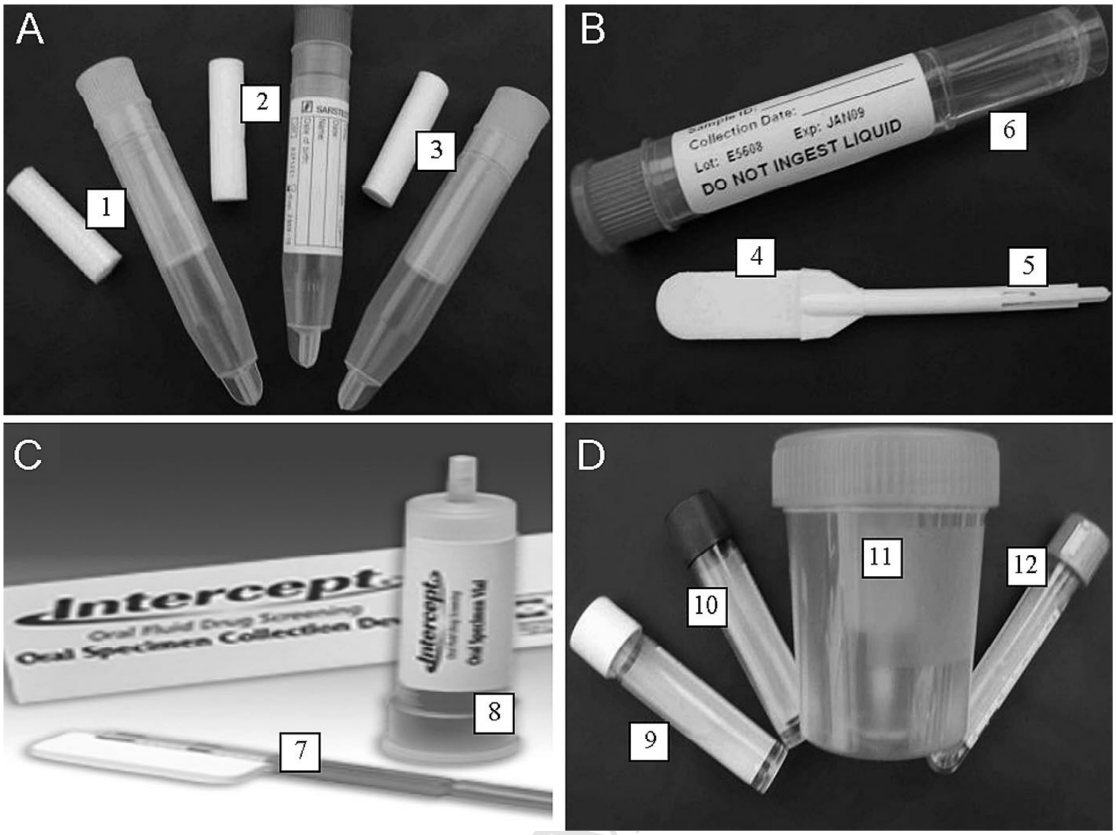


Fig. 2.

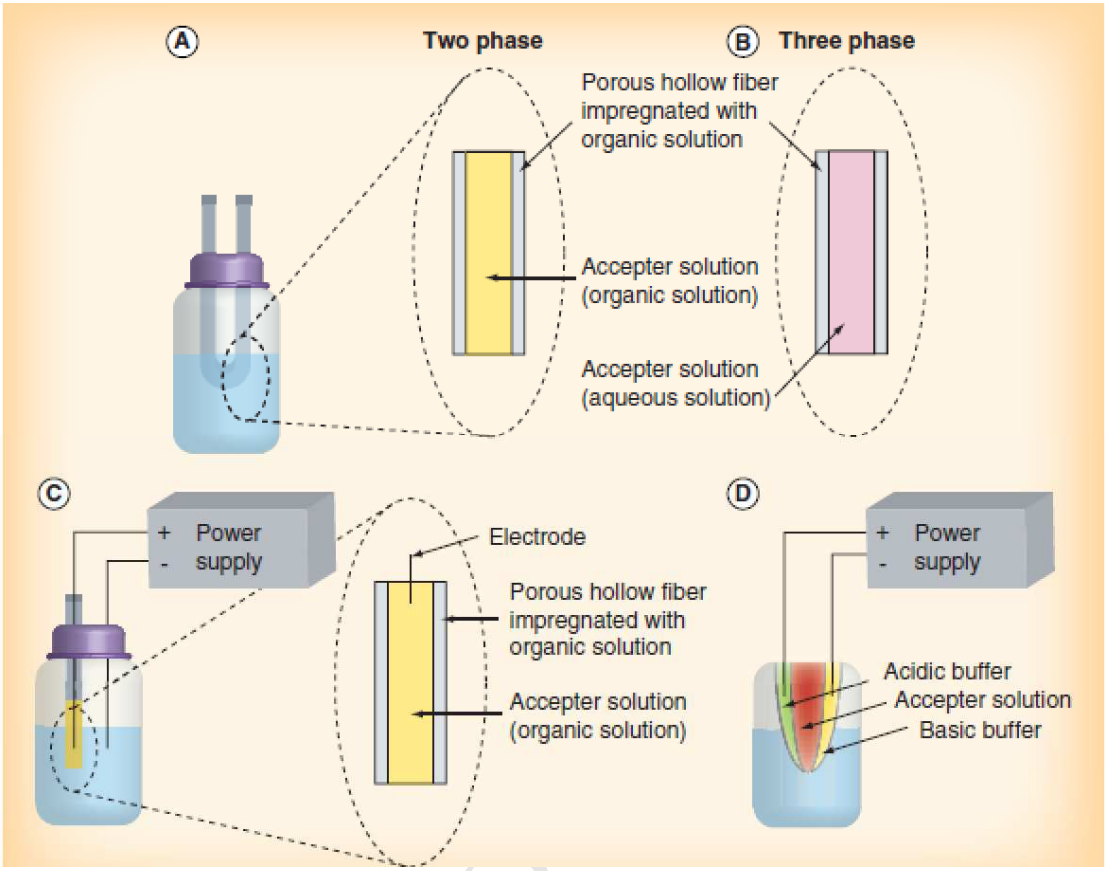


Fig. 3.

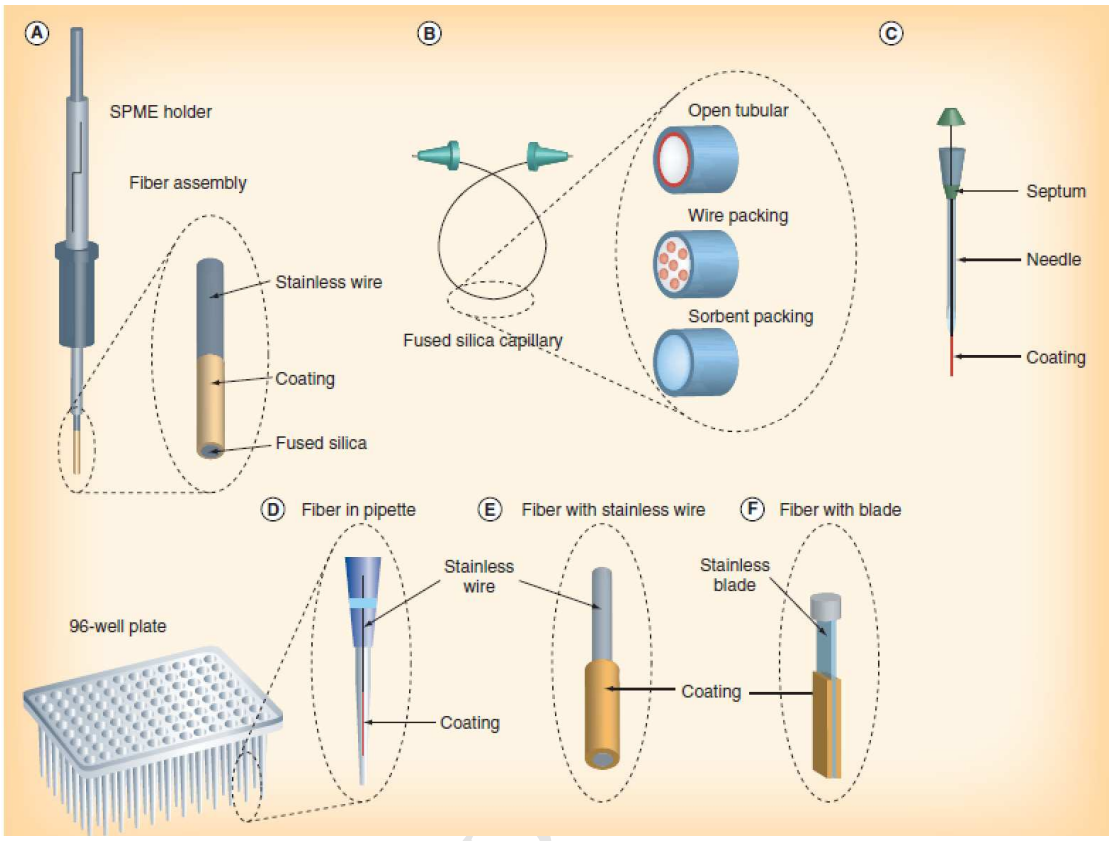


Fig. 4

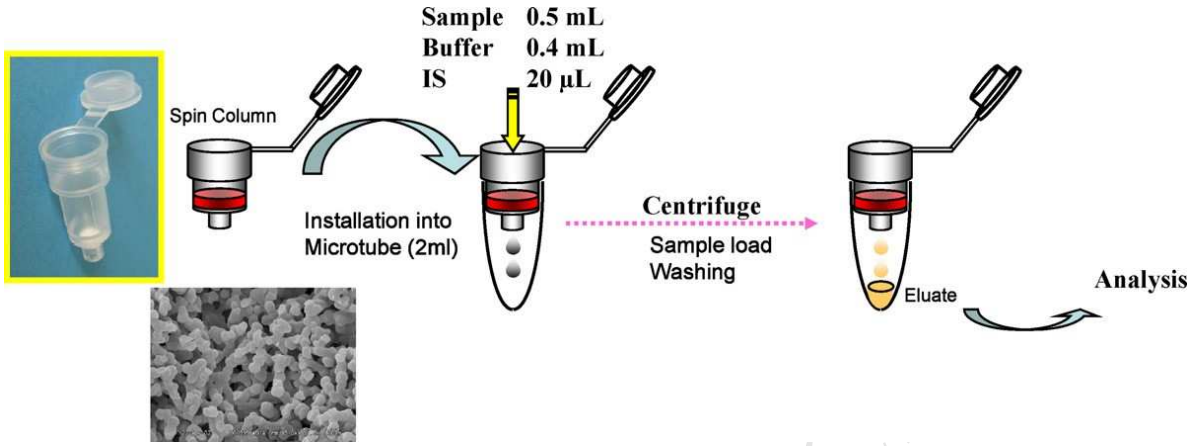


Fig. 5.

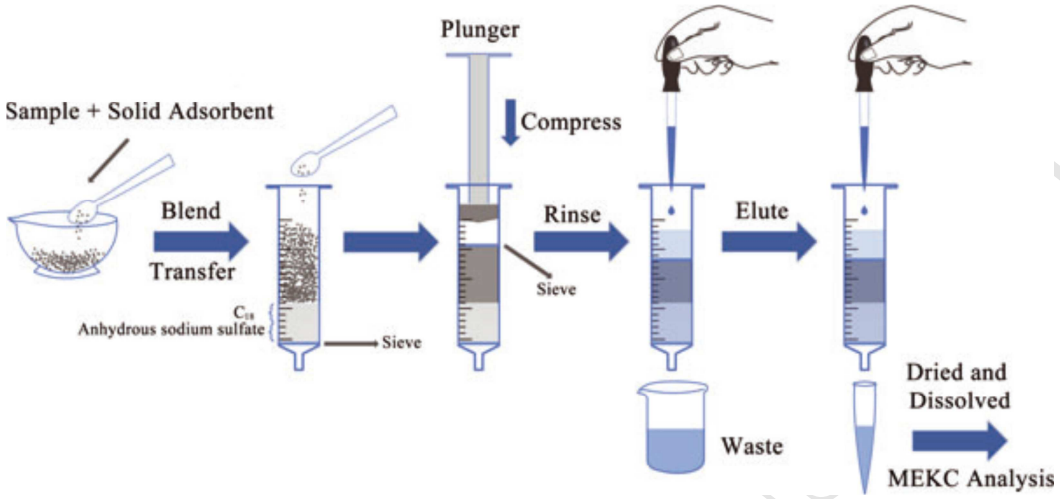


Fig. 6.

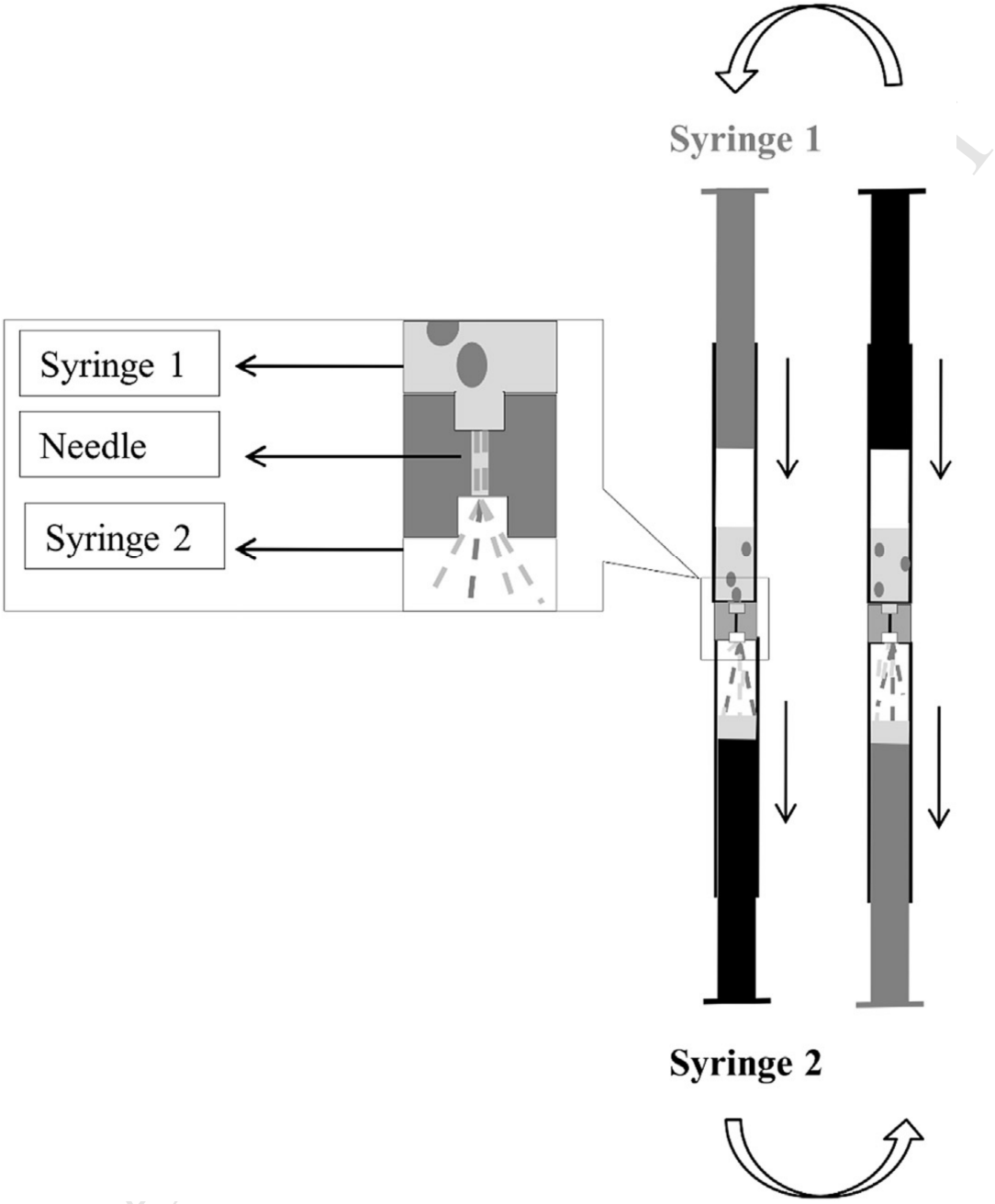
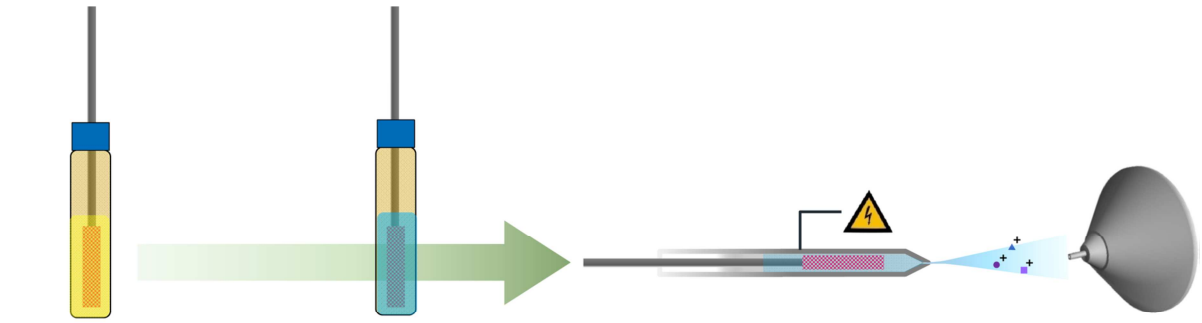


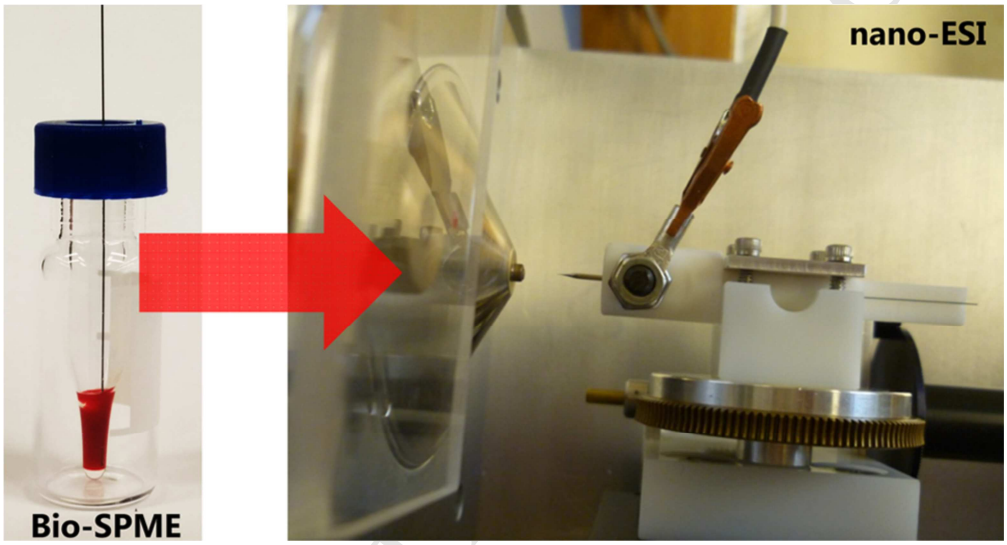
Fig. 7.



1. Extraction/sampling (≤ 2 min)
10µL-1.5 mL of sample
Vortex agitation

2. Quick Rinsing (5 s)
1.5 mL Water (LC/MS grade)
Vortex agitation

3. Solvent desorption (~120 s) / 4. Ionization (≥30 s)
1-4 µL MeOH (0.1% FA), 1.3 kV
Static desorption



Highlights

- A variety of biological samples were described.
- Recent advances of various biological sample preparation methods were listed.
- Applications prior to instrumental analysis were summarized.
- The trends and perspectives of sample preparation methods were proposed.