液相微萃取技术及其在生物样品预处理中的应用进展

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摘要: 液相微萃取是在液相萃取技术基础上发展起来的新型生物样品前处理技术, 具有简便、快速、经济、环保等特点, 已在血液、尿液、唾液等生物基质样品分析中广泛应用。本文通过查阅近5年文献, 对液相微萃取技术的主要模式, 即单液滴微萃取、分散液-液微萃取和中空纤维液相微萃取的基本原理, 以及其在生物样品预处理中的应用进展进行综述, 以期为体内药物分析、药代动力学研究以及新药研发等领域样品前处理提供技术支撑和参考。

关键词: 液相微萃取; 单液滴微萃取; 分散液-液微萃取; 中空纤维液相微萃取; 生物样品分析

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Advances in liquid-phase microextraction technology and its application in biological sample pretreatment

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Abstract: Liquid-phase microextraction is a novel pretreatment technique for biological samples developed on the basis of liquid-phase extraction technology, which is simple, rapid, economical, and environmentally friendly, and has been widely used in the analysis of biological matrix samples such as blood, urine, and saliva. In this paper, we review the basic principles of the main modes of liquid-phase microextraction techniques, i.e., single-drop microextraction, dispersive liquid-liquid microextraction, and hollow-fiber liquid-phase microextraction, and the progress of their applications in biological sample pretreatment by reviewing the literature in the past five years, with a view to providing technical support and reference for sample pretreatment in the fields of *in vivo* drug analysis, pharmacokinetic studies and new drug development.

Key words: liquid-phase microextraction; single-drop microextraction; dispersive liquid-liquid microextraction; hollow-fiber liquid-phase microextraction; biological sample analysis

近年来, 随着绿色化学新理念、新技术的发展, 微萃取技术优势凸显, 其倡导使用尽可能少的溶剂, 与传统的萃取方法相比成本效益更好并且更加绿色环保。其中, 液相微萃取 (liquid-phase microextraction, LPME) 是在液−液萃取基础上发展起来的微型化技术。虽然固相微萃取 (solid-phase microextraction, SPME) 是最早提出并应用的微萃取方法, 但是与SPME相比, LPME技术要求更低, 且操作简便、经济, 在环境分析、食品安全、法医学和药学等领域的生物样本分析中有着较为广泛的应用。

液相微萃取技术已经衍生出包括单液滴微萃取 (single-drop microextraction, SDME)、分散液−液微萃取 (dispersive liquid-liquid microextraction, DLLME) 和中空纤维液相微萃取 (hollow-fiber liquid-phase microextraction, HF-LPME) 三种主要模式在内的多种技术模式。本文拟对LPME三种主要模式及其在生物样品

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预处理中的应用进行综述。

1　单液滴微萃取技术及应用

1.1　基本原理与模式

SDME使用单独的溶剂液滴作为待分析物的萃取介质, 是液相微萃取中最早应用的一种模式, 由Liu和Dasgupta[1]于1996年提出。SDME最常用的两种模式是直接浸入单液滴微萃取 (direct immersion single-drop microextraction, DI-SDME) 和顶空单液滴微萃取 (headspace single-drop microextraction, HS-SDME)。如图1所示, DI-SDME通过将微液滴直接浸入水相基质中并保持静止来富集非极性/弱极性化合物, 萃取完成后液滴被撤回注射器; 而HS-SDME通过将微液滴暴露在待分析样品的顶空中提取极性/非极性的挥发性和半挥发性化合物[2-4]。

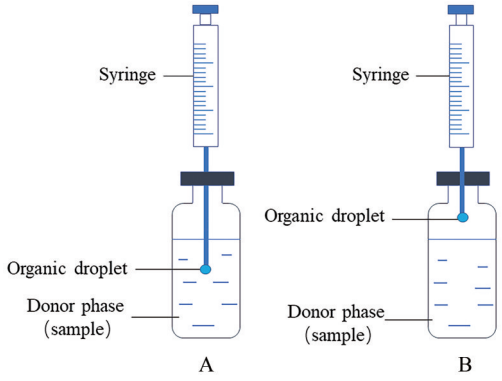

Figure 1　Two main modes of single-drop microextraction. A: Direct immersion single-drop microextraction (DI-SDME); B: Headspace single-drop microextraction (HS-SDME)

影响SDME萃取效率的主要因素包括: 受体相 (萃取溶剂) 的类型和体积、分析物性质、供体相 (样品) 的pH值和体积、萃取时间和温度、搅拌和离子强度等[5,6]。SDME中萃取溶剂一般应与水相互不溶解并能有效萃取待分析物, 还应具有热稳定性、低蒸气压、低挥发性和足够的黏度等以确保液滴稳定[7]。与DI-SDME相比, HS-SDME的萃取溶剂不需要与样品溶液接触, 选择上更加灵活, 同时可以避免复杂样品基质对于实验结果的干扰[8]。

SDME的主要优点是简单、萃取富集因子高、有机溶剂消耗少、成本低、可以与气相色谱 (GC)、高效液相色谱 (HPLC)、毛细管电泳 (CE) 离线或在线联用, 易实现自动化。但是诸如液滴的表面积和体积受限、溶剂挥发性、液滴稳定性不足、重复性差等缺点也很明显[9,10]。研究人员不断尝试克服SDME技术存在的缺点。Mehravar等[11]在利用基于深共晶溶剂 (deep eutectic solvent, DES) 的HS-SDME方法分析水样中多环芳烃的过程中使用钟形管作为载体, 能够显著提高微滴的稳定性,可在更高的萃取温度和搅拌速度下实现高效快速萃取。Yildirim等[12]将DI-SDME与HPLC仪器在线联用, 用于富集测定环境水样中的氟喹诺酮类药物。使用Lab in syringe技术, 实现了样品处理与分析自动化, 通过在液滴内部产生小气泡使液滴膨胀, 增加界面面积, 提高萃取性能。与传统方法比具备富集时间短, 程序简单且萃取富集因子高等优势。Song等[13]利用SDME联合GC方法测定尿液中苯丙胺和甲基苯丙胺时引入电场增强的手段, 通过电场加速目标分析物从样品溶液到有机溶剂液滴的传质, 显著改善了因萃取时间过长液滴不稳定影响萃取效率的问题。Mafra等[14]建立了用磁性离子液体 (magnetic ionic liquid, MIL) 作为萃取相的SDME结合HPLC方法测定环境水样中尼泊金甲酯等7种内分泌干扰化合物, 使用96孔板系统显著缩短分析时间、实现高通量分析并提高再现性。MIL作为萃取剂可以形成更大体积的液滴, 显著增强微滴的稳定性[15]。

1.2　SDME在生物样品预处理中的应用

在各种LPME技术中, SDME出现最早且最简单有效, 能与GC、HPLC等各种分析方法联用。虽然已有替代技术出现, 但其在农药成分、疾病标志物、抗抑郁药及抗生素等药物成分的富集分析中仍有不少应用, 应用最多的生物样本是尿液样本。

Tang等[16]开发了一种磁三相SDME用于高灵敏的核酸定量检测。该方法以200 μL十二烷作为有机相置于含有DNA/Fe_3O_4网络的水样上方, 6.0 μL的3,3′,5,5′-四甲基联苯胺 (TMB)-H_2O_2混合溶液作为萃取溶剂液滴附着在磁棒下端浸入有机相中进行萃取, 分析物的富集速度可提高至数秒 (6 s)。磁提取的应用可最小化背景信号, 避免基质效应并显著增强检测信号强度, 能获得较低的LOD, 较以往报道方法不需要分离步骤, 可显著降低成本, 已成功应用于肝细胞癌患者真实血清样本中miRNA-122和HBA-T (乙肝病毒DNA片段) 等生物标记物的检测, 具有作为高通量核酸检测平台的较大潜力。Mafra等[17]将平行单液滴微萃取与HPLC-DAD结合用于监测人尿液样本中戊唑醇等四种农药成分。选取 $[P_{6,6,6,14}^{+}]_2[MnCl_4^{2-}]$ 作为萃取剂, 以尿液稀释10倍、提取130 min为最佳萃取条件, 加盐量对分析结果没有显著影响。该方法获得了较好的精密度和准确度, 目标分析物的LOD为7.5 μg·L^{-1}, LOQ为25 μg·L^{-1}, 相对回收率为70%～122%, 富集因子在4～15之间, 与传统SDME方法相比提供了更高的分析通量和较好的液滴稳定性, 可以作为生物样本中农药测定的有效方法。Purgat等[18]使用SDME结合

毛细管区带电泳法测定人尿中同型半胱氨酸硫内酯(HTL)。该方法以0.2 mol·L^{-1}磷酸盐缓冲液 (pH 8.2) 和甲醇稀释的尿液样本作为供体相, 将40 μL的氯仿放置于供体水相表面作为有机相, 4.5 mmol·L^{-1}磷酸溶液作为受体相, 通过毛细管电泳系统在线SDME方式对尿液样本进行液−液−液萃取。最佳条件下HTL的LOQ和LOD分别为50和25 nmol·L^{-1}, 回收率在96.4%～101.9%之间, 准确度为96%～110%, 与已报道的方法相比具有全自动和耗时短的优势, 且重复性好、操作简便、经济环保, 可以应用于HTL相关的人类病理生理学研究。

2 分散液−液微萃取技术及应用

2.1 基本原理与影响因素

Assadi和Rezaee等[19]在2006年提出了一种小型化的液−液萃取技术—DLLME, 并成功将其应用于水中有机化合物的测定。DLLME系统是一种由水相(供体相)、分散剂和萃取剂 (受体相) 组成的三元组分溶剂体系, 基本流程见图2, 用注射器将萃取剂与分散剂混合物快速注入样本溶液, 使原本与水相不混溶的萃取剂 (受体相) 在分散溶剂的作用下形成微小的液滴, 高度增加萃取相与水相之间的接触交换表面积, 快速达到平衡, 实现待分析物从供体相转移到受体相的高效萃取过程, 在较短的时间内能够获得较高的回收率和富集系数[12,19-21]。

常见的影响DLLME萃取效率的因素包括萃取溶剂和分散溶剂的种类及体积、萃取时间、辅助分散的方式和时间、离心速度及时间、样品溶液pH值、盐效应和离子效应等[22]。其中最关键的是萃取溶剂和分散溶剂的选择。分散溶剂一般要求与待测样本溶液和萃取溶剂均能混溶, 常用的分散溶剂包括甲醇、乙醇、丙酮、乙腈、异丙醇等[23]。萃取溶剂主要选择对目标化合物具有良好萃取能力和色谱行为的有机溶剂, 氯仿、二氯甲烷、甲苯、乙腈、二氯乙烷等都是经典DLLME中常用的萃取剂[24, 25]。Fischer等[26]开发了一种DLLME结合GC-MS/MS的方法同时测定尿液中的UV-327及其代谢物, 用来评估其潜在的人体暴露。使用40 μL BSA/TMCS衍生化。对DLLME中分散剂及萃取剂的类型和体积、样品溶液的pH值、盐添加量和涡旋时间进行了优化。在CH_2Cl_2、$CHCl_3$和CCl_4等3种常用萃取溶剂以及乙腈、丙酮、甲醇、乙醇和异丙醇5种常用分散溶剂中确定$CHCl_3$和异丙醇分别作为最佳的萃取和分散溶剂; 考察不同体积$CHCl_3$ (100～450 μL) 与异丙醇(400～1 000 μL) 对萃取效果的影响后确定400 μL氯仿和700 μL异丙醇效果最好; 在涡旋时间0、10、30、60、120和180 s中确定涡旋30 s可获得最佳萃取效率。其他条件优化为控制样品pH < 2, 添加5% NaCl。

总体来讲, DLLME具有萃取速度快、富集系数高、有机溶剂使用少、操作简便和成本低等特点[22], 还可同时提取和衍生分析物, 对于气相色谱法分析高极性化合物很有帮助, 因此在生物样品分析中具有广泛的应用[27]。但是目前为止绝大部分DLLME仍需使用有机溶剂作为萃取或分散溶剂, 较难实现高通量和自动化, 无法避免操作误差, 在一定程度上限制了DLLME的推广应用。

2.2 辅助分散方法

近年来, 诸如超声波、涡旋、微波和空气等辅助分散的方式逐渐被引入DLLME中并广泛使用。这些辅助分散方式能进一步减少有机溶剂的使用, 有效提高萃取速度和效率[28]。根据其辅助分散手段不同可以将DLLME分为超声辅助分散液−液微萃取 (ultrasound-assisted dispersive liquid-liquid microextraction, UA-DLLME)、空气辅助分散液−液微萃取 (air-assisted dispersive liquid-liquid microextraction, AA-DLLME) 和涡旋辅助分散液−液微萃取 (vortex-assisted dispersive liquid-liquid microextraction, VA-DLLME) 等模式。Rahmani等[29]比较AA、VA和UA三种DLLME方法对水样中痕量苯、甲苯等成分分析结果发现, 三种辅助模式均可不使用分散溶剂, 萃取溶剂分别通过气泡、涡旋和超声波的辅助作用实现较好的分散, 进一步减少有机溶剂的使用。不同辅助模式DLLME在生物样品预处理中的应用比较见表1[26,30-47]。

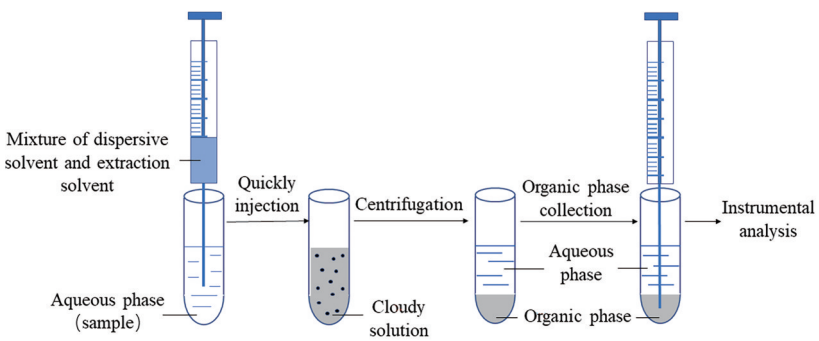

Figure 2 Basic process of conventional dispersive liquid-liquid microextraction (DLLME)

Table 1 Application of different auxiliary modes of DLLME in the analysis of biological samples. ACN: Acetonitrile; UV-328: 2-(2*H*-Benzotriazol-2-yl)-4,6-di-tert-pentylphenol; EAC: Ethyl acetate; UV-327: 2-(5-Chloro-benzotriazol-2-yl)-4,6-di-(*tert*-butyl) phenol; TAP: Thiamphenicol; CAP: Chloramphenicol; FF: Florfenicol; 1,2-DBE: 1,2-Dibromoethane; NTs: Neurotransmitters; DP: Donor phase; AP: Acceptor phase; UA: Ultrasound-assisted; VA: Vortex-assisted; AA: Air-assisted; MSA: Manual-shaking-assisted

Extraction method	Matrix	Analyte	Extraction solvent	Dispersive solvent	Extraction condition	Enrichment factor	Analysis method	LOD/ng·mL^{-1}	LOQ/ng·mL^{-1}	Ref.
Classical	Plasma	Efavirenz	$CHCl_3$ (100 μL)	ACN (1 200 μL)	–	–	GC-MS	8	27	[30]
DLLME	Human blood	UV-328 and its metabolites	CH_2Cl_2 (900 μL)	ACN (800 μL)	2% NaCl	–	GC-MS/MS	0.1	0.2–0.4	[31]
	Blood/urine	New psychoactive substances	$CHCl_3$: 100 μL (urine), 200 μL (blood)	MeOH: 250 μL (urine), 500 μL (blood)	NaCl: 4 mg (urine), 10 mg (blood)	–	GC-MS	1–10, 50 (amphetamine)	2–50	[32]
	Urine	10 mycotoxins	EAC (100 μL)	ACN (1 000 μL)	0.3 g NaCl	–	GC-MS/MS	0.12–4.00	0.25–8.00	[33]
	Urine	TAP, FF, CAP	4-Methyl-2-pentanone (1 000 μL)	MeOH (1 200 μL)	0.9 g NaCl	–	LC-QTOF-MS	0.029 (TAP), 0.006 (FF), 0.003 (CAP)	0.098 (TAP), 0.021 (FF), 0.009 (CAP)	[34]
	Urine	5 cocaine adulterants	$CHCl_3$ (800 μL)	ACN (300 μL)	pH = 12, NaCl (15%, *m/v*)	–	RP-HPLC	–	180	[35]
	Urine	UV-327 and its metabolisms	$CHCl_3$ (400 μL)	Isopropanol (700 μL)	pH < 2, NaCl (5%, *v/v*)	–	GC-MS/MS	0.05–0.10	0.15–0.31	[26]
	Urine	Diazinon	Toluene (310 μL)	MeOH (800 μL)	NaCl (1 %, *w/v*)	–	HPLC-DAD	150	450	[36]
	Urine	Rimantadine	$CHCl_3$ (100 μL)	ACN (800 μL)	pH = 10.5	58	LC-PCD	0.5	1.8	[37]
UA-DLLME	Plasma	Malondialdehyde	1,2-DBE (80 μL)	ACN (750 μL)	pH = 4, NaCl (5.0 %, *w/v*)	–	GC-FID	0.75	2.48	[38]
	Human plasma	Empagliflozinda, pagliflozin, canagliflozin	1-Dodecanol (100 μL)	MeOH (1 000 μL)	pH = 7, sonication (3 min)	19–50	HPLC-DAD	0.37–1.66	1.1–3.5	[39]
	Urine	Synthetic cannabinoids and their metabolites	$CHCl_3$ (150 μL)	–	0.1 g NaCl, sonication (5 min)	–	GC-MS	1–5	5	[40]
	Plasma/urine	Fluoxetine and norfluoxetine enantiomers	$C_2H_2Cl_4$ (50 μL)	Acetone (200 μL)	pH = 11.5	2 000–3 000	FASS-CE	0.06–0.80	0.2–3.0	[41]
	Urine	Amino acids, monoamine NTs and their metabolites	4-Bromoanisole (80 μL)	ACN (150 μL)	pH = 9.5, sonication (1 min)	–	UHPLC-MS/MS	0.000 1–0.010 0 nmol·L^{-1}	0.5–2.0 nmol·L^{-1}	[42]
VA-DLLME	Urine	Nicotine, cotinine	$CHCl_3$ (1 400 μL)	MeOH (200 μL)	pH = 9.7, vortex (48 s)	–	GC-MS/MS	0.33 (nicotine) 0.34 (cotinine)	1.09 (nicotine) 1.10 (cotinine)	[43]
	Plasma	Nateglinide	1-Octanol (30 μL)	MeOH (200 μL)	pH = 2.5, vortex (2 min)	330	HPLC-UV	15	–	[44]
AA-DLLME	Plasma	Metronidazole, linezolid, meropenem, piperacillin and ciprofloxacin, *etc.*	1-Dodecanol (30 μL)	MeOH (50 μL)	pH = 7, NaCl (4%, *w/v*)	87–121	UHPLC-PDA	1–80	5–250	[45]
	Plasma	Amitriptyline, doxepin	Toluene (40 μL)	–	pH = 10; DP∶AP = 150∶1, 12 (air injection)	Amitriptyline: 82, doxepin: 111	GC-FID	2	20	[46]
MSA-DLLME	Plasma	Zaltoprofen	$C_2H_4Cl_2$ (220 μL)	ACN (900 μL)	NaCl (3.75%, *w/v*), 13 s (manual oscillation)	18	HPLC-UV	0.03	0.09	[47]

2.2.1 AA-DLLME AA-DLLME中样品溶液与萃取溶剂的混合物通过细针吸入注射器, 反复抽拉实现空气辅助混合。Ferrone等[45]以低密度的1-十二醇作为萃取剂, 建立了基于悬浮固化有机液滴 (solidified floating organic droplet, SFO)的AA-DLLME-SFO方法结合UHPLC-PDA同时定量测定人血浆中的甲硝唑、美罗培南、环丙沙星、利奈唑胺和哌拉西林等成分。该过程未使用分散剂, 利用10 mL玻璃注射器反复快速地抽吸与注射作为空气辅助使体系快速平衡分散形成浑浊溶液。考察了萃取周期对萃取效率的影响, 在抽拉1～10次中确定空气辅助抽拉8次时重复性和回收率均最好, 该步骤可在不到1 min内完成, 能够实现简便、快速、有效地萃取。

2.2.2 VA-DLLME VA-DLLME使用涡旋搅拌器分散样品溶液中的有机相。Hammad等[44]用VA-DLLME与HPLC-UV结合的方法对血浆中那格列奈进行预富集和测定。以20 μL 1-辛醇为萃取溶剂, 200 μL甲醇为分散溶剂, 对涡旋时间进行优化, 结果显示在0.5～2.5 min内涡旋2 min可达到最优效果, 涡旋时间小于2 min会导致萃取相的不完全分散, 大于2 min则会使萃取相在水中溶解度增加。

2.2.3 UA-DLLME 超声波是DLLME中最有效和应用最多的辅助分散手段, 超声过程中产生的瞬态空化使得萃取相破碎形成纳米或者微米级别的液滴并快速分散到样品溶液中形成浑浊的溶液, 在没有分散剂的情况下能有效增加两相的接触, 促进乳化, 加速传质过程, 快速达到平衡并提高萃取效率, 减少甚至取代甲醇、丙酮和乙腈等分散剂的使用。但是过度的超声也会导致分析物的降解[27,48]。Mercieca等[49]建立了UA-DLLME结合GC/MS的方法快速测定血液和尿液中的合成大麻素及其代谢物。此过程中仅使用150 μL氯仿作为萃取溶剂, 通过超声2 min辅助混溶, 该过程未使用分散溶剂。

2.3 新型DLLME溶剂与材料

近年来, 新型绿色替代溶剂和材料, 诸如离子液体 (ionic liquid, IL)[40]、DES[50]、低密度溶剂 (low density solvent, LDES)[51]、超分子溶剂 (supramolecular solvent, SUPRAS)[52]、表面活性剂溶剂[53]、低转变温度混合物溶剂 (low transition temperature mixture, LTTM)[54,55]和可切换溶剂[56]等不断涌出并在DLLME中发挥重要作用。表2[40,48,51,52,54,55,57-76]归纳了基于新型绿色萃取剂的DLLME应用于生物样品前处理的部分实例。

2.3.1 离子液体 IL是由不对称的阳离子和阴离子组成的熔融盐, 熔点多低于100 ℃, 具有多种物理性质和多重溶剂化能力。选择合适的阳离子和阴离子能够调整IL的黏度、密度、疏水和亲水性, 通过不同化学基团的结合可以选择性与某些分析物相互作用, 因而可以用作萃取溶剂[77,78]。相比传统有机溶剂, IL具有可回收、高热稳定性、特定溶解能力、离子导电性、室温下的低蒸气压等显著优势[79]。对IL改进后又衍生出MIL、表面活性离子液体 (SAIL)等新型萃取剂。Kong等[72]建立了一种基于SAIL的DLLME方法, 结合HPLC法同步测定人血浆中4种脂溶性维生素和6种类胡萝卜素, 使用 $[C_{16}MIM][PF_6]$ 作为萃取剂, 最优条件下LOD为0.002～0.076 μg·mL^{-1}。该方法可在IL相 (萃取相) 中自组装形成易溶的纳米液晶结构, 减少有毒溶剂的消耗, 实现了高效地提取和直接注入萃取层。

2.3.2 深共晶溶剂 虽然IL与传统有机溶剂相比已具备明显优势, 但仍具有一定的毒性和不良降解性。近年来, DES因为与IL特性类似越来越受关注[80]。DES是两种物质通过氢键相互作用形成的熔点远低于每种组分的共晶混合物, 通常由无毒、易获得、廉价的可持续化合物合成, 具备一定的生物相容性和生物降解性。DES中含有大量的不对称离子, 这些离子的晶格能较低, 因此有较低的熔点[81]。其物理化学性质可通过改变结构中氢键受体 (hydrogen bond acceptor, HBA)与氢键供体 (hydrogen bond donor, HBD) 的比例调节[82]。常见的DES主要有四种类型: ① 季铵盐与金属卤化物的组合; ② 季铵盐与水合金属卤化物的组成; ③ 季铵盐与HBD (酰胺、羧酸和醇等) 的组成; ④ 金属氯化物与HBD (酰胺、羧酸和醇等) 的组合。其中前两种主要合成亲水性的DES, 后两种主要合成疏水性的深共晶溶剂 (hydrophobic deep eutectic solvent, HDES)[83,84]。LPME中的DES多使用氯化胆碱与酚 (氯酚、苯酚等)混合制备[85]。水会改变DES的结构特性, 使其在水相中显著溶解, 因此不能用于水相样品的提取, 而HDES却可用于水相样品, 这进一步扩大了DES在DLLME中的应用[86]。大多数HDES是离子型的。通常以长链季铵盐作为HBA与长链醇、长链脂肪酸或小有机分子 (薄荷醇、百里酚、有机酸等) 等HBD合成HDES。与氯化胆碱等短链铵盐相比, 长链铵盐作为HBA具有更大的疏水性[87]。HDES的黏度在萃取过程中起着重要的作用[88], 黏度越低越利于其分散和分析物的传质, 萃取效率越高, 因此, 低黏度HDES的进一步开发与应用值得关注。

最近出现的天然深共晶溶剂[89]由糖、糖醇、多元醇、有机酸碱和氨基酸等天然化合物通过氢键相互作用以特定摩尔比组成, 相比于IL和传统的DES, 其天然来源使其更加符合绿色化学发展需要, 值得进一步关注[90]。LTTM是一种与DES相似的溶剂, 其区别在

Table 2 Application of novel green extractant DLLME in biological sample analysis. EAC: Ethyl acetate; BZD: Benzodiazepines; TBABr: Tetrabuthylammonium bromide; NFV: Nelfinavir; NVP: Nevirapine; EFV: Efavirenz; CPC: Cetylpyridinium chloride; DMT: *N*,*N*-Dimethyltryptamine; HRM: Harmine; HRL: Harmaline; THH: Tetrahydroarmine; MYOAC: Methyltrioctylammonium chloride; MENTH: Menthol; PAA: Phenylacetic acid; ACN: Acetonitrile; THF: Tetrahydrofuran; α-CD: α-Cyclodextrin; CBZ: Carbamazepine; CPC: Cetylpyridinium chloride; Ses: Sesamol; IL: Ionic liquid; UA: Ultrasound-assisted; DES: Deep eutectic solvent; SFO: Solidified floating organic droplet; HDES: Hydrophobic deep eutectic solvent; VA: Vortex-assisted; LDES: Low density solvent; SPE: Solid phase extraction; UABE: Ultrasound assisted back extraction; SUPRAS: Supramolecular solvent; RM: Reverse micelle; DSS: Double-solvent supramolecular; SAIL: Surface active ionic liquid; LTTM: Low transition temperature mixture; CA: Cyclodextrin-assisted; MIL: Magnetic ionic liquid; EO: Essential oil

Extraction method	Matrix	Analyte	Extraction solvent	Dispersive solvent	Extraction condition	Enrichment factor	Analysis method	LOD/ng·mL^{-1}	LOQ/ng·mL^{-1}	Ref.
IL-DLLME	Plasma	Atenolol, metoprolol, propranolol	[BMIM]PF_6 (100 μL)	MeOH (300 μL)	pH = 10	313−330	HPLC-DAD	0.002 6−0.003 0	0.008 9−0.009 9	[40]
IL-DLLME	Blood	BZDs and BZD-like hypnotics	[BMIM]PF_6 (60 μL)	−	pH = 8	−	LC-MS/MS	0.003−4.740	2−50	[57]
IL-DLLME	Blood	Antidepressants	[BMIM]PF_6 (60 μL)	−	pH = 3	−	LC-MS/MS	0.78−2.14, 35.15 (trazodone)	10, 250 (trazodone)	[58]
IL-DLLME	Plasma/urine	Lamotrigine, CBZ	[C_8MIM]PF_6 (30 μL)	MeOH (100 μL)	pH = 10, NaCl (1.0%, *w*/*v*)	Lamotrigine: 26 (blood), 19 (urine); CBZ: 35 (blood), 27 (urine)	HPLC-DAD	Lamotrigine: 50 (blood), 70 (urine); CBZ: 20 (blood), 40 (urine)	Lamotrigine: 170 (blood), 300 (urine); CBZ: 70 (blood), 100 (urine)	[59]
IL-UA-DLLME	Plasma	15 NTs	[BMIM]PF_6 (117 μL)	ACN (350 μL)	pH = 7	−	LC-MS/MS	0.028−0.978	−	[60]
IL- UA-DLLME	Urine	Underivatized NTs	[BMIM]PF_6 (150 μL)	ACN (400 μL)	Sonication (4.3 min)	−	HILIC-UHPLC-QTRAP®/MS^2	0.05−4.88	0.12−11.24	[61]
IL-DLLME	Urine	*Trans*, *trans*-muconic acid	[$P_{14,6,6,6}$]Cl (40 μL)	−	pH > 4, NaCl (1.62%)	197−202	HPLC-UV	11	32−10 000	[62]
DES-UA-DLLME	Urine/plasma	Erythrosine (E127)	TBABr∶1-octanol (1∶2, molar ratio) (200 μL)	−	pH = 7	40	UV-VIS	3.75	11.30	[48]
DES-SFO-DLLME	Urine/plasma	Pesticides	MENTH∶PAA (3∶1, molar ratio) (41 μL)	−	NaCl (5%, *w*/*v*)	379−485 (urine) 158−194 (plasma)	GC-MS	0.002−0.017 (urine), 0.004−0.036 (plasma)	0.007−0.059 (urine), 0.013−0.121 (plasma)	[63]
HDES-VA-DLLME	Plasma	Vincristine	MTOAC∶*n*-butanol (1∶3, molar ratio) (80 μL)	−	pH = 10.5	110.5	HPLC-UV	0.02	0.06	[64]
LDES-DLLME	Serum	25-OH-vitamin D_3	1-Octanol (80 μL)	MeOH (650 μL)	pH = 4.5	180	Rp-HPLC	0.6	1.9	[51]
DLLME-SFO	Blood	Deferasirox	1-Undecanol∶1-decanol (2∶5, *v*/*v*) (40 μL)	−	pH = 5.5	147	HPLC-UV	0.06	0.20	[65]

Continued

Extraction method	Matrix	Analyte	Extraction solvent	Dispersive solvent	Extraction condition	Enrichment factor	Analysis method	LOD/ng·mL^{-1}	LOQ/ng·mL^{-1}	Ref.
SPE-DLLME-SFO	Human plasma	NFV, NVP, EFV	1-Undecanol (52.4 μL)	MeOH (200 μL)	pH = 6.9, NaCl (20%, *w*/*v*)	459−1 507	HPLC-UV	0.03−0.07	0.10−0.25	[66]
DLLME-SFO-UABE	Urine	Suvorexant	1-Undecanol (20 μL)	ACN (200 μL)	−	−	UPLC-MS/MS	0.1	0.27	[67]
UA-LDES-DLLME	Urine	10 new psychoactive piperazine derivatives	*n*-Hexane (100 μL)	−	pH = 12	−	GC-MS/MS	0.3−2.0	10	[68]
UA-DLLME-SFO	Serum	Tetracycline	1-Undecanol (90 μL)	MeOH (300 μL)	pH = 6	125−137	HPLC-UV	0.002 0	0.003 9	[69]
SUPRAS-DLLME	Serum	Aucubin	Pentanol (1 000 μL)	THF (4 000 μL)	SUPRAS (200 μL); vortex (2.5 min)	−	UPLC-MS/MS	1	3	[52]
RM-DLLME	Human plasma	5 TA_2 of teicoplanin	CPC:*n*-hexanol (15 mmol·L^{-1}) (80 μL)	−	pH = 11	228−347	HPLC-UV	502.5−3 015.0	837.5−5 025.0	[70]
DSS-DLLME	Human plasma	Methotrexate	1-Undecanol∶1-dodecanol (1∶2, *v*/*v*) (45 μL)	−	pH = 5	152	HPLC-UV	0.03	0.10	[71]
SAIL-DLLME	Human serum	Four fat soluble vitamins; six carotenes	$[C_{16}MIM]PF_6$ (0.04 mmol)	EAC (100 μL)	−	0.24−3.7	RP-HPLC-PDA	2−76	−	[72]
LTTM-DLLME	Urine	14 illicit drugs	Choline chloride∶Ses (1∶3, molar ratio) (100 μL)	EAC (400 μL)	pH = 9	17.7−29.1	HPLC-MS	0.006−0.072	0.01−0.37	[54]
LTTM-DLLME	Urine	Pesticides	Choline chloride∶Ses (1∶3, molar ratio) (100 μL)	EAC (400 μL)	NaCl (50 mg·mL^{-1})	17.7−28.5	LC-MS	−	0.02−0.76	[55]
CA-DLLME	Urine	CBZ, chlorbazine	$CHCl_3$ (100 μL)	α-CD (0.4 mmol·L^{-1})	−	CBZ: 175, chlorbazine: 196	MEKC	CBZ: 0.6, chlorbazine: 0.5	−	[73]
MIL-DLLME	Urine	Multiclass compound	$[P_{6,6,6,14}^{+}]_2[MnCl_4^{2-}]$ (20 mg)	MeOH (20 μL)	pH = 2	6−16	HPLC-DAD	3.0−7.5	10−25	[74]
VA-HDES-ferrofluid-DLLME	Urine/plasma	Doxycycline	Ferrofluids (150 μL)	−	pH = 3, NaCl (6%, *w*/*v*)	83.61	HPLC-UV	3.6	8.5	[75]
VA-EO-DLLME	Human plasma	DMT and β-carbolines (HRM, HRL, THH)	Eucalyptus globulus essential oil (80 μL)	−	Borate buffer pH = 9.8 (100 μL)	−	UHPLC-MS/MS	≤1	1−2	[76]

于其没有熔点或冰点, 而是显示出玻璃化转变。因此在制备和使用LTTM作为DLLME的萃取剂之前, 需要利用差示扫描量热法等对化合物进行表征, 以确定其为LTTM而非DES[91,92]。

Mohebbi等[93]采用DLLME结合GC-MS的方法测定尿液中的三环类药物, 该方法使用极少量的DES (薄荷醇-癸酸) 代替传统有毒溶剂, 使用去离子水作为分散溶剂, 较经典DLLME方法更加安全、绿色。Golpayegani等[64]以甲基三辛基氯化铵与正丁醇 (摩尔比 1∶3) 组成的HDES作为DLLME的萃取剂, 结合HPLC-UV方法测定白血病儿童血浆中的长春新碱, 提取效率高于以往方法, 适用于复杂生物样品中不同微量药物的测定。

2.3.3　低密度溶剂　经典的DLLME中萃取剂一般密度比水高, 离心后沉淀于管底以便进行相分离, 但是这些溶剂多为氯化溶剂一类有毒溶剂, 而正辛醇等低密度溶剂一般具有较低的毒性且与分析仪器有较好的相容性, 可以作为DLLME的萃取剂。但是萃取完成后低密度溶剂的有机相一般以浮滴的形式存在于水面上方, 不容易收集, 因此设计出类似长颈或窄颈容器等用于收集低密度有机相, 然而到目前为止最简便的方法还是使用带有针头的注射器[94]。Leong等[95]在2008年基于LDES开发出了DLLME-SFO的方法, 使用毒性小、密度比水低的萃取剂, 离心后悬浮在萃取管的顶部, 有机液滴在冰水浴中凝固收集, 而后在室温下融化进行分析。DLLME-SFO萃取溶剂要求在分散溶剂中能高度溶解但是在水相中溶解度低、对目标分析物具有高萃取能力、高纯度和室温附近的熔点, 常选用1-十一醇、1-十二醇 (十二烷醇) 和正癸醇等低密度溶剂[69]。到目前为止, 该方法在生物液体样本中应用不多, 主要是由于DLLME-SFO最终有机相与基于质谱的检测系统不兼容。为了解决这一问题, Canales等[96]提出了新的替代方法, 即在DLLME后再进行超声辅助反萃取, 而后进行LC-MS/MS分析。Iqbal等[67]则首次成功将超声辅助反萃取与DLLME结合应用于生物样本分析, 与UPLC-MS/MS联用分析测定人尿液中的suvorexant。

2.3.4　液态磁性材料　液态磁性材料最近在微萃取技术中的应用比较广泛, 主要有MIL和磁流体。MIL具有与传统IL相似的理化性质, 同时能够在磁场作用下表现出强烈的响应。MIL通常由一类对外部磁场有强烈响应的化合物组成, 在DLLME中使用可以消除传统的离心步骤。由于MIL可以磁分离并且易于回收, 因此被认为比传统IL更环保[97, 98]。磁流体是磁性纳米粒子持续悬浮在载体溶剂中形成的一种高度均匀的磁性胶体系统, 有助于物质的快速积累, 相分离速度更快。在磁流体中, 通过使用聚合物或表面活性剂覆盖磁芯形成一个排斥层, 可以避免聚集体的形成及沉降[99]。Alipanahpour等[75]使用以Fe_3O_4磁性纳米材料与HDES混合制备的铁磁流体相作为绿色萃取剂的DLLME与HPLC-UV结合的方法对尿液、血浆和牛奶样品中的多西环素 (DOC) 进行富集分析。该方法中HDES能够在磁性纳米颗粒的侧面提供屏蔽层来阻止纳米颗粒的聚集, 增强磁流体的稳定性。涡旋辅助则用于改善铁磁流体在溶液中的分散, 增加分析物的传质。最后使用磁铁将有机相和水相分离, 减少了离心的步骤, 能够明显缩短提取时间。与其他多西环素分析方法相比具有更低的LOD, 可用于真实生物样品中DOC的提取。

2.4　DLLME在生物样品预处理中的应用

目前DLLME方法在生物样本前处理中的应用除多见的精神疾病类药物、抗生素、毒品等以外, 还包括抗病毒与肿瘤化疗药物、中药活性成分、食品与环境致病物、营养素、真菌毒素、神经递质等化学成分、药物成分和生物标志物的体内浓度监测和代谢研究等, 血液和尿液样本以及HPLC和GC等分析方法均有较多联用。

Rahimi等[69]建立了UA-DLLME-SFO与HPLC联用的方法分析环境和血清样本中的盐酸四环素。用0.2 mol·L^{-1}磷酸盐缓冲液调节样本pH = 6, 以90 μL 1-十一烯醇作为萃取剂和300 μL甲醇作为分散剂, 超声15 min后离心, 萃取相于冰水浴中凝固分离后在室温下融化进行分析。优化后盐酸四环素的富集因子在125～137之间, 线性范围为0.005～3 mg·L^{-1}, LOD为0.002 mg·L^{-1}, RSD在2.7%～3.2%之间 (n = 5)。该方法具有良好的提取回收率, 线性范围优于其他报道, LOD接近或低于其他研究, 有机溶剂使用体积更小。Zhou等[61]建立了UA-IL-DLLME结合超高效液相色谱-三重四级杆线性离子阱串联质谱方法研究轻度认知障碍和轻中度痴呆患者尿液样本中的神经递质。150 μL [BMIM]PF_6和400 μL乙腈分别作为萃取溶剂和分散溶剂, 在307 W超声功率下超声4.3 min, 搅拌4.8 min。最优条件下, 15种神经递质的LOD在0.05～4.88 ng·mL^{-1}之间, LLOQ在0.12～11.24 ng·mL^{-1}之间, 提取回收率 (n = 3) 为72.67%～125.43%, R^2均大于0.991 7, 方法可用于研究不同临床生物液中神经递质。

3　中空纤维液相微萃取技术及应用

3.1　HF-LPME原理及装置

1999年, Pedersen-Bjergaard等[100]建立了HF-LPME方法, 有效克服SDME技术中微滴不稳定的问题。

HF-LPME技术具有溶剂消耗少和样品处理时间短等优势, 而且多孔的中空纤维壁孔可以阻止生物大分子物质进入, 减少复杂基质对于检测的影响。HF-LPME主要分为两相模式和三相模式 (图3), 三相模式克服了两相模式由于受体溶液在供体溶液中的溶解度高而萃取效果不佳的缺点, 不需要进一步的清理程序即可实现很大的选择性。HF-LPME一般使用聚丙烯等多孔的中空纤维作为液膜的支撑, 在中空纤维内部以不溶于水的有机溶剂形成的支撑液膜 (supported liquid membrane, SLM) 作为萃取界面。在两相模式中, 有机溶剂作为支撑液膜的同时也是受体相, 而三相模式则在中空纤维的内腔充满与SLM不混溶的受体相 (通常为水相)。提取时, 将纤维插入样品中, 分析物从供体水相 (通过SLM) 提取到管腔的受体相溶液中, 而后富集处理并检测。由于受体相可以是有机溶剂或者水溶液, 所以HF-LPME适配灵活, 可与大多数色谱、电泳、分子和原子光谱分析以及电化学分析仪器兼容[101]。

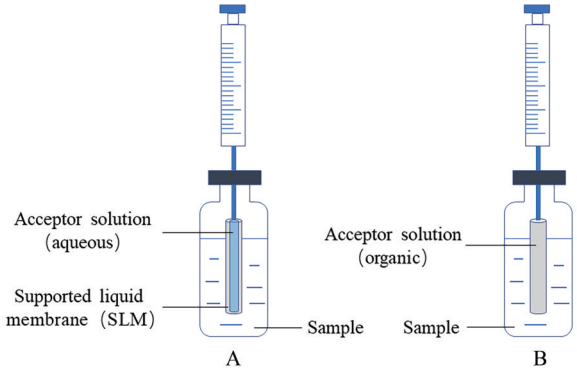

Figure 3 Two main modes of hollow-fiber liquid-phase microextraction (HF-LPME) A: Three phase HF-LPME B: Two phase HF-LPME

3.2 新型膜基介导的液相微萃取技术

3.2.1 电膜萃取 (electromembrane extraction, EME)

EME技术最早在2006年引入[102], 使用包含水不溶性溶剂的SLM从水性介质中提取带电物质, 是HF-LPME的发展和延伸。与HF-LPME通过扩散萃取不同, EME萃取的动力是一个电场, 因而具备快速和选择性好的优势, 特别是对于复杂基质的分析。EME萃取过程通过调节pH值来电离分析物, 并在电场的作用下使分析物从水样中转移到固定在聚合物载体孔中的有机溶剂薄层[103]。最近几年关于EME的大量研究聚焦于SLM的修饰和优化上, 采用纳米材料修饰[104]和新型琼脂糖凝胶膜的应用[105]等均在很大程度上改善了常规EME的萃取效率、稳定性和选择性问题。同时由于EME具有高度的灵活性和适应性, 也有学者研究开发了不同的微流控形式的EME技术, 具有独特的应用前景[106]。

3.2.2 溶剂棒微萃取 (solvent bar microextraction, SBME)

为了进一步简化和改进HF-LPME技术萃取程序, 避免中空纤维固定支架对萃取的限制, 2004年, Jiang和Lee等[107]在HF-LPME基础上开发出一种替代方法——SBME。SBME使用一小段两端闭合的中空纤维在供体相中搅拌进行萃取, 此过程不需要支撑, 因此溶剂棒可以自由移动, 极大地增强了分析物的相转移能力, 可获得更短的萃取时间和更高的预浓缩因子[108,109]。与HF-LPME类似, SBME同样具有两相和三相两种模式。对SBME进行优化改造后又开发出溶剂/双溶剂搅拌棒微萃取[110,111]、旋转溶剂棒微萃取[112]等自动化高效萃取装置并成功应用于生物样品分析中。Li等[113]使用超分子溶剂六氟异丙烷醇建立了磁性搅拌棒液相微萃取方法, 使萃取相对极性范围广泛的小分子成分进行高效萃取回收的同时能够有效排除蛋白质、多糖等大分子物质的干扰, 该方法已成功应用于人血清中非甾体抗炎药的分析测定。

3.3 在生物样品分析中的应用

HF-LPME等膜基微萃取技术与SDME和DLLME相比与血液等复杂生物基质的兼容性更好, 能进一步避免复杂基质中干扰杂质对受体相分析的影响。不足在于需要部分专用设备, 要求较其他方法更高。文献报道中除关于血液和尿液样品中农药、非甾体抗炎药、精神活性物质等药物成分的测定外, 也可与微流控装置相结合, 单独或同时测定生物样本中酸/碱性药物[114], 还可用于肝脏等类器官衍生药物代谢物的分离测定研究[115]。

Kiani等[116]将SBME与HPLC-UV结合, 用于富集和测定血、尿等生物样品中的痕量长春新碱。选择正辛醇作为SLM, 将长春新碱先提取到SLM中, 而后反萃取到水相受体相中。预处理过程需分别调节供体相和受体相pH为10.7和3.1, 在51 ℃下萃取60 min以获得最佳萃取效率。长春新碱的富集因子为98.5, LOD和LOQ分别为0.015和0.05 mg·L^{-1}。该方法为首次从生物样品中微萃取长春新碱, 较传统HF-LPME方法具有更好的萃取效率和速度。Bai等[117]以5 mmol·L^{-1}表面活性剂DPPC溶解在正辛醇中形成的反胶束作萃取相, 将HF-LPME与HPLC结合用于测定生物基质中罗替戈汀的含量。将血浆样品稀释25倍并调节pH为6。用荧光法对所形成的反脂质胶束进行表征, 中空纤维片螺纹固定在磁性搅拌棒上, 加入15% NaCl以降低罗替戈汀的溶解度, 促进其分配到萃取相。反胶束作为表面活性剂聚集体, 对于不同类型和性质的分析物具

Table 3 Comparison of three modes of liquid-phase microextraction (LPME) technologies. SDME: Single-drop microextraction; HF-LPME: Hollow-fiber liquid-phase microextraction; SLM: Supported liquid membrane; NSAIDs: Non-steroidal anti-inflammatory drugs

Mode	Basic principle	Advantage	Disadvantage	Application	Ref.
SDME	Single organic droplet is used as extraction media to extract the analytes by direct immersion in the sample or by standing in the headspace of the sample.	① High enrichment factor; ② low organic solvent consumption; ③ good compatibility with analytical instruments; ④ low cost; ⑤ easy automation.	① Restricted droplet surface area and volume; ② organic solvent volatilization; ③ lack of stability; ④ poor reproducibility.	Determination of antibiotics, psychoactive drugs, NSAIDs, pesticides, biomarkers and other components in biological samples such as blood and urine.	[4−6,10, 13,17,18]
DLLME	Extraction solvent is rapidly dispersed into the sample solution by dispersion solvent or auxiliary dispersion mode to form an emulsion, which is stratified after centrifugation and separated for instrumental analysis.	① Wide selection of extraction solvents; ② auxiliary dispersion; ③ fast extraction speed; ④ less use of organic solvents; ⑤ easy to operate; ⑥ economy, *etc*.	① Extraction phase is easily contaminated by complex sample matrices; ② still requires the use of toxic organic solvents; ③ low automation; ④ easily affected by human operation.	*In vivo* detection and metabolite studies of drugs, chemicals, endogenous components, food and environmental pathogens, active ingredients of traditional Chinese medicine, nutrients, disease markers, *etc*.	[21,22, 25−76]
HF-LPME	SLM formed by porous hollow fiber (a carrier), used as the extraction interface. There are two modes: ① two-phase HF-LPME, SLM as the extraction phase; ② three-phase HF-LPME, there is a receptor phase (mostly aqueous) along with the sample solution and SLM (organic phase).	① Wide range of application; ② not easily contaminated by complex matrices; ③ good stability; ④ compatible with most analytical instruments (acceptor phase can be aqueous).	① Slower extraction speed than DLLME; ② requires special equipment.	Single or simultaneous determination of acidic/alkaline drugs in biological samples; study on metabolites of organoid derived drugs (such as liver organoid).	[101−115]

有良好的溶剂化能力, 可以用于蛋白质纯化分离, 在HF-LPME中有较好的富集效果。罗替戈汀的LLOQ为2 ng·mL^{-1}, 富集因子达到126, 可用于有关药代动力学研究。

4　小结与展望

SDME、DLLME和HF-LPME作为LPME中应用最多的三种主要模式, 至今仍在不断地改进与优化。SDME技术最简单有效, 但是萃取速度慢、液滴不稳定等问题突出, HF-LPME技术能够显著改善SDME稳定性的问题, 但是萃取速度仍然较慢, EME和SBME等新型膜基液相微萃取技术可以显著提高萃取速度。相较而言DLLME技术具有简便、快速、经济、环保的特点, 但对于血液等复杂样品的处理不够理想, 容易被基质成分污染。总体来看, 这三种方法各有特点又互为补充 (表3[4-6,10,13,17,18,21,22,25-76,101-115]), 在生物样本预处理中需要充分结合分析要求、待分析物性质、样品基质等因素综合考量确定处理方法。此外, 还有糖诱导的液相微萃取、挥发油基液相微萃取、平行人工液膜萃取等众多新方法。

LPME在生物药物分析领域正逐步克服液−液萃取或固相萃取等传统样品前处理方法有机溶剂消耗大、操作复杂且耗时的缺陷, 尤其适用于血液、组织和尿液等生物基质中痕量药物的分析, 使用微量 (微升级) 溶剂即可快速、高效地萃取和富集待分析物, 在满足各种分析仪器要求的同时大大提高样品分析的速度、灵敏度和准确性[118]。

LPME距离理想的样品预处理方法尚有发展空间。主要表现在以下几个方面: ① LPME处理后的样品与分析仪器的兼容有局限, 适用范围较窄, 重现性不够好; ② 操作步骤需进一步简化, 样品预处理速度有待提高。一些LPME技术仍需数十分钟甚至数小时, 距离法医毒物分析、临床TDM监测等快速分析的实际要求仍有一定差距; ③ 人为参与少、高通量自动化分析且重复性好的LPME技术仍有待开发; ④ 具有良好选择性和广泛适用性的新型绿色溶剂仍需进一步寻找。今后可整合SPME等其他样品预处理技术优势, 继续从天然绿色无毒可降解溶剂着手, 进一步提高LPME方法的速度、效率和重现性, 着力开发能够商业化的高通量全自动样品预处理设备, 实现生物样品成分的准确快速分析。

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