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Review

Present state and applications of single drop microextraction for the determination of harmful organic compounds and pollutants

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Abstract

Single drop microextraction (SDME) nowadays earns an increasing attention by scientists due to its simplicity, low cost and the need for only common laboratory equipment. This microextraction technique combines sample cleanup and pre-concentration of analytes in one step. Furthermore, a significant reduction in the amount of organic solvents needed comparing to standard LLE techniques places SDME into the position of environmental friendly extraction techniques. SDME is a straightforward technique in which a micro-drop of solvent is suspended from the tip of a conventional micro-syringe and then it is in a direct contact with a sample solution in which it is immiscible or it could be suspended in the headspace above the sample. The paper overviews developments of the state-of-the-art SDME techniques for the extraction of harmful organic compound and pollutants from environmental, food and biological matrices. Key extraction parameters essential for SDME performance were described and discussed.

Introduction

The toxicity of pesticides and pollutants and their harmful environmental effects are attracting the attention of the society and interest in the identification and quantification of such compounds in various matrices have aroused. Thus, the importance is put on the development of the faster and selective analytical methodology, suitable for the determination of the low levels of these compounds. The limits of quantitation (LOQs) of pesticides and pollutants are usually in mg/L or below. Therefore, in order to accomplish the quantitation of these compounds in various samples, a pre-treatment step, extraction and pre-concentration step are required. Generally, when conventional liquid phase extraction is used, the preconcentration of the analytes is very small or not even obtained. A lot of research efforts have been focused on the development of combined sample preparation techniques, when conventional liquid phase extraction is in the combination with a proper liquid phase microextraction technique or sorptive based microextraction technique, in order to achieve additional preconcentration of the analytes. Contrary to this, in the case of the single drop microextraction (SDME) these two processes are performed in a single step (De Souza Pinheiro *et al.* 2011; Andraščíková *et al.* 2016).

Currently SDME has been increasingly used in the analysis of pesticides and other environmental

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pollutants in various matrices because it is simple, cheap, fast, effective and consuming only microliters of organic solvents per analysis. SDME technique is based on the principle of a distribution of analytes between a microdrop of the organic solvent and an aqueous phase or headspace phase above the solid/liquid sample. Using volume of sample in a milliliter scale and microliters of organic solvent leads to a high enrichment factor obtained. The SDME procedure using conventional microsyringe has the advantage of combining manipulation and injection of the sample into a single-step extraction and thus simplify the extraction process. However, some problems such as microdrop instability leading to the dislodgement of the drop or dislocation of the drop from the needle tip, and partial solvent loss caused by the high temperature and high solubility of the drop in the sample during extraction may reduce the repeatability of the method (Jeannot *et al.* 2010; Ramos 2012). Sampling repeatability requires the use of the proper syringe needle for the extraction. The use of the microdrop as a collector phase of analytes from the gaseous samples (Liu and Dasgupta 1995) and liquid samples (Liu and Dasgupta 1996) was described for the first time in the nineties of the 20th century. By the time, SDME has undergone many technical changes, and it is known in various modes.

Seven different modes of solvent microextraction that belong to the category of single drop microextraction are currently in use for various applications. The base classification of SDME modes is dividing into two sub-categories, two and three-phase techniques, which exist in equilibrium (Table 1). All modes are based on the principle of passing the analytes from the sample directly, or through the other phase (e.g. headspace) or mediator to the final extraction solvent having a volume in microliters (Ramos 2012). There are more advances to classify SDME, e.g. according to hydrodynamic features, static and dynamic modes of operation are distinguished (Alexovič *et al.* 2016).

Use of the extraction solvent, which is volatile, e.g. hexane or toluene, makes the application directly compatible with gas chromatography (Jeannot *et al.* 2010). Moreover, combinations of SDME with high performance liquid chromatography (HPLC) and capillary electrophoresis were reported (Amde *et al.* 2015; García-Vázquez *et al.* 2016; Yohannes *et al.* 2016).

Table 1. Overview of the SDME modes.

SDME mode	Acronym
Two-phases techniques	
direct immersion	DI-SDME
continuous flow microextraction	CFME
drop-to-drop microextraction	DDME
directly suspended droplet microextraction	DSDME
Three-phases techniques	
headspace	HS-SDME
liquid-liquid-liquid microextraction	LLLME
solvent-supported microextraction	SSME

SDME has become frequently used for the extraction of a broad scope of compounds for numerous analytical application due to the advantages as reviewed by more papers (Lamboropoulou *et al.* 2007; Jeannot *et al.* 2010; Jain and Verma 2011). In this review, the focus was given to the three main application areas of SDME for the extraction of the harmful organic compounds and pollutants in environmental, food and biological samples in the recent years.

Environmental samples

SDME has been used to extract a wide range of organic compounds from the environmental samples, mostly several types of water and soil. Overview of the applicability of SDME for environmental sample analysis is shown in the Table 2. SDME was an appropriate extraction technique for liquid samples such as tap water (Kaykhaii *et al.* 2005; Lamboropoulou et al. 2007; Yohannes *et al.* 2016), river water (Kaykhaii *et al.* 2005; Saraji and Bankhshi 2005; Ahmadi *et al.* 2006; De Souza Pinheiro *et al.* 2009; De Souza Pinheiro *et al.* 2011; Soares *et al.* 2014; Amde *et al.* 2015; Yohannes *et al.* 2016), lake water (Wu *et al.* 2008; Xie *et al.* 2014; Amde *et al.* 2015; Yohannes *et al.* 2016), surface water (Lopez-Blanco *et al.* 2003; Lamboropoulou et al. 2007; Santos *et al.* 2017), drinking water (Lopez-Blanco *et al.* 2003; Ahmadi *et al.* 2006; Carlos *et al.* 2013), effluent and influent water (Amde *et al.* 2015), ground water (Yohannes *et al.* 2016; Santos *et al.* 2017), water from the farm (Ahmadi *et al.* 2006),

sea water (Tian *et al.* 2014) and other water samples (Przyjazny and Kokosa 2002). Furthermore, SDME was applied for the extraction of the pesticides from the soil samples (Salemi *et al.* 2013; Williams *et al.* 2014; Soares *et al.* 2015).

Organic pollutants, such as pesticides (organochlorine pesticides (OCPs), organophosphorus pesticides (OPPs)), fungicides, aliphatic amines, volatile organic compounds, phenols, polyaromatic hydrocarbons (PAHs), nitro-PAHs and quinones extracted by SDME were mostly reported. Generally, two SDME modes were employed, DI and HS, nevertheless DI was preferably used due to the chemical properties of analyte and the type of the sample.

Special pre-treatment was not necessary for the majority of selected applications, except addition of NaCl to the sample for increasing the ionic strength by Lamboropoulou *et al.* (2007), Wu *et al.* (2007) and Yohannes *et al.* (2016), adjustment of pH to 2 – 6 reported by Saraji and Bankhshi (2005), and filtration in the case of surface and ground water (Santos *et al.* 2017). The volume of a sample varied in the range of 1 mL – 30 mL, the most commonly selected volume of the sample was 5 mL.

The pre-treatment of the solid samples was more difficult in comparison with water samples. Drying, sieving, ultrasonic extraction, sonication, centrifugation and final dilution with an appropriate solvent were used due to the matrix of the sample. The amount of sample was ranging from 2 g to 5 g (Salemi *et al.* 2013; Williams *et al.* 2014; Soares *et al.* 2015).

The selection of a suitable extraction solvent is a crucial step for SDME performance. According to the extracted analytes, mostly organic solvents differing in K_{ow} compatible with GC and HPLC were chosen, in order to obtain the highest extraction efficiency. Toluene, provided stable drop and avoided bubble formation during extraction according to vapour pressure lower than other solvents, was mostly used in direct immersion (DI) mode (Lamboropoulou et al. 2007; De Souza Pinheiro *et al.* 2009; De Souza Pinheiro *et al.* 2011; Tian *et al.* 2014; Santos *et al.* 2017). However, the bubble formation in the drop was required for the extraction of pesticides from lake water by Xie *et al.* (2014) by exposing the liquid-gas pendant drop (CPD) to the sample. The stability of the CPD was investigated by monitoring the formation of 1 μL organic droplets (toluene, chlorobenzene) containing different volumes of air bubble in a sample solution resulting in the better stability of the drop using chlorobenzene. A formation of a liquid-gas CPD was performed using a novel extraction assembly consisting of a 10 mm long quartz capillary, a funnel-like PMMA cap and a 5 mL microsyringe. The limitation of droplet instability in comparison with DI-SDME was overcome, larger microdrop size and higher stirring rates could be employed, as well as liquid-gas CPD has a potential to be fully automated by using a syringe pump (Xie *et al.* 2014). A 70- to 135-fold enrichment of pesticides was obtained. In comparison to a conventional SDME, improvement of the extraction efficiency could be ascribed by the increased surface area of the microdrop. The bubble in drop (BID) was studied by Williams *et al.* (2014) when chloroform was used as the extraction solvent. For the extraction of OCPs from tap and surface water, toluene and isooctane gave similar results for the majority of target analytes, but toluene was selected due to the selectivity and no significant loss of solvent during extraction (Lamboropoulou *et al.* 2007). The similar observation was reported for *n*-hexane that was selected due to its lower solubility in water, which increases the stability of the microdrop in comparison to the use of toluene. The analyte extraction was not significantly affected by the type of extraction solvent (*n*-hexane or toluene) (Soares *et al.* 2014). *n*-Hexane was suitable for the extraction of OCPs and pyrethroids from drinking water (Carlos *et al.* 2013), multiclass pesticides from water and soil (Soares *et al.* 2014; Soares *et al.* 2015).

For the extraction of the atrazine, desethyl-atrazine, desisopropyl-atrazine from the water samples, toluene, *n*-hexane, and cyclohexane were investigated, however, due to their low viscosity and density, the microdrop was not stable. Formation of the stable drop under the vigorous stirring and higher extraction efficiency was reached using 1-octanol as the extraction solvent (Yohannes *et al.* 2016). Solubility of the extraction solvent in water had a great effect for the extraction of 2 pesticides, α-endosulphane and β-endo-sulphane from water. *n*-Hexane didn't exhibit a good extractability of these compounds, because

Table 2. Applicability of SDME in environmental analysis.

Sample/Analyte	Sample volume (mass)/ Pre-treatment	SDME mode; Extraction solvent (volume); Volume of syringe; Extraction conditions; salt addition	Analytical technique	LOD (LOQ)	Recovery [%]/ Enrichment factor	Reference
River water/8 multiclass pesticides	30 mL	DI; *n*-hexane (1.6 µL); 10 µL: injected volume 1 µL; 30 min, 155 rpm, 17 °C; NaH_2PO_4	GC-ECD	5.9 – 58.9 ng/L	89.5 – 122.7/ 17 – 448	Soares *et al.* (2014)
Lake, river, effluent, influent water/chlorothalonil, kresoxim-methyl, famoxadone	10 mL	DI; 1-hexyl-3-methylimida-zolium-hexafluoro-phosphate (nanofluids) (10 µL); a syringe tip cap; 40 min, 500 rpm, 25 °C; After extraction the NP were removed by immersion of the drop into the Eppendorf vial + 100 µL of MeOH, sonification for 10 min, centrifugation at 7,000 rpm, 10 min. injected volume: 20 µL	HPLC-VWD	0.13 – 0.19 ng/mL	74.94 – 96.11/ 764 – 984	Amde *et al.* (2015)
Sea water/6 OPPs	4.5 mL	DI; toluene (3.5 µL); 5 µL; injected volume: 2.5 µL, rinsed: 8× acetone, 3× toluene, 10 min, 1,000 rpm, (pH= 6); –	GC-NPD	0.012 – 0.020 µg/L	70 – 107.5/ 2 – 189	Tian *et al.* (2014)
Lake water/fenpro-pathrin, bifentrin, chlorpyrifos, parathion-methyl	1 mL	CPD (DI); chlorobenzene (1 µL + 1 µL of air); 5 µL; 180 s, 700 rpm, 25 °C; –	GC-MS	0.05 – 0.10 µg/L	81 – 113/ 70 – 135	Xie *et al.* (2014)
Drinking water/14 pests (OCPs, pyrethroids)	10 mL	DI, *n*-hexane (1.6 µL); 10 µL; injected volume: 1 µL, 15 min, 380 rpm, 20 °C; –	GC-ECD	0.003 – 0.600 µg/L	71 – 107/ –	Carlos *et al.* (2013)
Lake, tap, river, ground water (4 types)/atrazine (ATZ), desethyl-atrazine (DEA), atrazine (ATZ), desethyl-atrazine (DEA), desisopropyl-atrazine (DIA)	5 mL (7.5 % NaCl (w/v), *aq*)	DI; 1-octanol (3 µL); 10 µL; rinsed: 3× MeOH, 20 min, 600 rpm; –	HPLC-DAD	ATZ: (0.01) DEA, DIA: (0.05) µg/L	65.6 – 96.3/ 90 – 120	Yohannes *et al.* (2016)

Table 2. Applicability of SDME in environmental analysis – continued.

River water/1.diemethoate, 2. methyl-parathion, 3. ethion, 4. permethrin	10 mL	DI; toluene (1 µL); 10 µL; 30 min, 300 rpm; –	GC-MS	0.05 – 0.38 (0.15 – 1.10) µg/L	76.2 – 107/ –	De Souza Pinheiro *et al.* (2011)
River water/ 1. λ-cyhalotrin, 2. methyl-parathion, 3.ethion, 4. Permethrin	10 mL	DI; toluene (1 µL); 10 µL; 30 min; 300 rpm; –	GC-FID	0.3 – 3.0 (0.9 – 9.0) µg/L	70 – 120/ 26 – 284	De Souza Pinheiro *et al.* (2011)
Water/benzene, toluene, ethylbenzene, xylene	20 mL	HS; 1-octanol (1 µL); 10 µL; rinsed: 10× 1-octanol, 6 min, 1,200 rpm, 23 °C; –	GC-FID	0.72 – 5.00 µg/L	–/–	Przyjazny and Kokosa (2002)
Tap and river water/ aliphatic amines	5 mL	HS; benzylalkohol + 2-butanone (IS) (1 µL); 5 µL; rinsed: 20× solvent; 15 min, 600 rpm, 50 °C; –	GC-FID	2.5 – 25.0 µg/L	–/–	Kaykhaii *et al.* (2005)
Farm, river, well water/ 13 OPPs	5 ml + TPP (IS)	DI; carbon tetrachloride (0.9 µL); 1 µL; rinsed: 10× solvent; 40 min, 1,300 rpm; –	GC-FPD	0.001 – 0.005 µg/L	91 – 104/ 540 – 830	Ahmadi *et al.* (2006)
Water/α-endosulfan, β-endosulfan	1.8 mL	DI; isooctane + lindan (IS) (1.5 µL); 10 µL; 20 min, 800 rpm, 22 °C; –	GC-ECD	0.01, 0.01 µg/L (resp.)	–/–	Lopez-Blanko *et al.* (2003)
River water/phenols	3 mL/pH adjusted to 2 – 6	DI; hexyl acetate (2.5 µL + 0,5 µL BSA); 10 µL; 15 min, 250 rpm; temperate after SDME extraction: 50 °C for 5 min in heating oven; –	GC-MS	4.0 – 61 ng/L	–/92 – 146	Saraji and Bankhshi (2005)
Tap and surface water/ 10 OPPs	5 mL (2.5 % NaCl (w/v))	DI; toluene (1.5 µL); 10 µL; 15 min, 800 rpm, r.t.; –	GC-MS	0.010 – 0.073 µg/L	80 – 112 /–	Lamboropoulou *et al.* (2007)
Surface and groundwater/ PAHs, nitro-PAHs, quinones	10 mL/filtration, cooling at 4 °C	DI; toluene (1 µL); 10 µL; 30 min, 200 rpm, rinsed 3× ACN + 3× solvent; –	GC-MS	0.01 – 0.03 0.25 – 1.07 6.96 – 468 µg/L (resp.)	36 – 152; 23 – 103; 48 – 134/108 – 175; 101 – 130; 97 – 154 (resp.)	Santos *et al.* (2017)

Table 2. Applicability of SDME in environmental analysis – continued.

Lake water, leafs/PAHs	Lake water 50 mL: filtration and addition of NaCl (0.2 g/mL) Leafs: 4 specific sample preparation procedures	HS; *β*-cyclodextrine (*aq*, 10 µL); rinsed: 5× solvent, 10 min, 1,000 rpm, 40 °C; NaCl (0.2 g/mL)	HPLC-FLD	0.004 – 0.247 ng/mL	94 – 110.5/ 18 – 53	Wu *et al.* (2007)
Soil/5 OPPs	2 g/dried, sieved, ultrasonic agitation, dilution by 2 mL water	HS; octanol (3 µL); 10 µL; rinsed: 6× MeOH, 3× toluene, ultrasound agitation, 30 min, 60 °C; –	GC-NPD	0.1 – 2.0 ng/g	—/ 1.4 – 12.7	Salemi *et al.* (2013)
Farm soil/atrazine, metachlor	2g/air-dried soil + 2 mL water, vortex + sonification (15 min), centrifugation (8.165 g), extraction with 1 mL of 10 % NaOH (*aq*) solution	BID (DI); chloroform (1 µL + 0.5 µL of air); 10 µL; 20 min, static; –	GC-MS	0.01; 0.02 µg/L (resp.)	97; 105/ – (resp)	Williams *et al.* (2014)
Soil/7 multiclass pesticides	4 g/SLE/LTP extraction: placing to the extraction medium 1:2 (4 mL water, 7.8 mL ACN+ 0.2 mL ethylacetate), agitation 1 min by Vortex, freezing -20 °C (3.5 h), collection of the supernatant, filtration, vaporization of organic phase by vacuum, dilution in 30 mL by MilliQ water	DI-SDME; *n*-hexane (1.6 µL); 10 µL; injected volume: 1 µL, 30 min 155 rpm, 17°C; –	GC-ECD	(0.188 – 0.590) µg/kg	67.2 – 122.5/ 3 – 93	Soares *et al.* (2015)

ACN: acetonitrile; BID: bubble in drop; BSA: *N,O*-Bis(trimethylsilyl)acetamide; CPD: compound pendant drop; DI: direct immersion; GC/ECD: gas chromatography-electron capture detector; GC/FID: gas chromatography-flame ionization detector; GC/FPD: gas chromatography-flame-photometric detector; GC/MS: gas chromatography-mass spectrometry; GC/NPD: GC with nitrogen-phosphorus detector; HPLC/DAD: high performance liquid chromatography-diode-array detector; HPLC/FLD: high performance liquid chromatography-fluorescence detector; HPLC/VWD: high performance liquid chromatography-variable wavelength detector; HS: headspace; OCPs: organochlorine pesticides; OPPs: organophosphorus pesticides; NP: nanoparticles; r. t.: room temperature; SDME-SLE/LTP: solid-liquid extraction with low temperature partitioning; –: data not given

it is more soluble in water in comparison to isooctane. Isooctane, being solvent of low polarity, provided higher extractive efficiency and reproducibility for both analytes (Lopez-Blanco *et al.* 2003). Extraction of the phenols from the river water by DI-SDME followed by in-syringe derivatization was investigated by Saraji and Bankhshi (2004). Several organic solvents in the broad range of polarity were investigated, resulted hexyl acetate being the most suitable for the extraction. Hexyl acetate provided the selective extraction of the phenols, in comparison to other solvent, when 4-nitrophenol was not extracted. Furthermore, the manipulation with hexyl acetate microdrop was acceptable without any stability problems during the extraction, however, chromatographic peak overlaps were observed (Saraji and Bankhshi 2004).

The volatile compounds were preferably extracted by using HS mode. Octanol, benzylalkohol and *β*-cyclodextrine were investigated as potential extraction solvents (Przyjazny and Kokosa 2002; Kaykhaii *et al.* 2005; Salemi *et al.* 2013). HS- SDME was found as an efficient technique for the extraction of the organic compounds such as benzene, toluene, ethylbenzene and xylenes from the water samples. Gas chromatography with flame ionization detector (GC-FID) was employed. For the highest extraction efficiency under the experimental conditions, solvents with a high boiling point and low vapour pressure were investigated, so as to minimize the evaporation of the microdrop during the extraction. 1-Octanol and *n*-hexadecane provided satisfactory extraction of the analytes. However, less impurities using *n*-hexadecane were interfering the analyte signal (Przyjazny and Kokosa 2002). The specific application of HS-SDME which was free of organic solvent was provided by Wu *et al.* (2007), when *β*-cyclodextrine was used as extraction solvent for PAHs from the lake water. Nanofluid (NF) prepared by dispersion of ZnO nanoparticles in 1-hexyl-3-methylimidazolium-hexafluorophosphate was reported as an extraction solvent for three fungicides in water. A syringe tip cap (obtained from 5 mL disposable syringe) was used as a holder of the microdrop instead of the syringe needle. The microdrop was immersed on the syringe tip cap by microsyringe and after the extraction, the microdrop was placed in an Eppendorf vial containing 100 μL methanol with the aim to remove nanoparticles. Nowadays, NFs earn an attention due to the frequent applications in many research directions. Replacing conventional solvent in liquid–liquid system by NPs can cause an increase of mass transfer coefficient and increase the efficiency of extraction as the main goal (Amde *et al.* 2015).

Volume of the drop is the next important factor for the efficient extraction. In general, increasing the drop volume results in the significant improvement of the extraction efficiency. However, when the microdrop volume increases further, the drop became unstable due to the gravity. The volume of the drop was in the range of 0.9 μL (Ahmadi *et al.* 2006) and 10 μL (Wu *et al.* 2007; Amde *et al.* 2015). Drop volume 1 μL was the most frequently applied, what can be explain by the found consensus between the volume, stability and extraction capacity of the drop (Kaykhaii *et al.* 2005; De Souza Pinheiro *et al.* 2009; De Souza Pinheiro *et al.* 2011; Williams *et al.* 2014; Xie *et al.* 2014; Santos *et al.* 2017). Sampling repeatability of the microdrop requires the use of the proper syringe needle for the extraction. Generally, 10 μL Hamilton syringe routinely used for GC was frequently used as a holder of the microdrop during the extraction process. The needle should have a minimum dead volume, for instance using a 1 μL microsyringe, no dead volume is occurred. The modification of needle tip, e.g. cones tip, or modified microsyringe causes increasing adhesion force between needle tip and drop, thereby increasing drop stability and achieving a high stirrer speed (up to 700 rpm for the cones tip and up to 1,700 rpm for the modified microsyringe) (Ahmadi *et al.* 2006). Furthermore, improved holding of the microdrop and larger extraction solvent volumes used for the extraction were reached by attaching a 2-mm long cone that was cut off from a 200 μL pipette tip onto the needle tip of a GC microsyringe (Tian *et al.* 2014). The similar approach was used for the modification of the HPLC syringe, which was supported by a part of the pipette tip, thus the larger microdrop was obtained (Wu *et al.* 2007). To avoid impurities, a rinse of the microsyringe before extraction was presented, mostly by the extraction solvent (Przyjazny and Kokosa 2002; Kaykhaii *et al.* 2005; Ahmadi *et al.* 2006; Wu *et al.* 2007;

Salemi *et al.* 2013; Tian *et al.* 2014; Yohannes *et al.* 2016; Santos *et al.* 2017).

Sample agitation is an important factor for the reduction of the extraction time. From the film theory of convective-diffusive mass transfer, the agitation of the sample solution enhances the extraction efficiency and reduce the extraction time, since the thickness of the stagnant film around the extracting phase (i.e. Nernst diffusion film) decreases with increasing stirring rate, and it results in faster extraction rate (Pena-Pereira *et al.* 2010). Magnetic stirring, mechanical vibration, continuous flow and syringe plunger motion are usually used for the sample agitation to increase the amount of convective mixing or interfacial contact area for the dynamic modes of SDME. The time required to reach equilibrium in SDME dependent on the type and degree of agitation, phase volumes, interfacial contact area and equilibrium distribution constant (Jeannot and Cantwell 1996; Jeannot *et al.* 2010). Magnetic stirring was applied for the majority of the applications, with the velocity range from 155 rpm (Soares *et al.* 2014) to 1,300 rpm (Ahmadi *et al.* 2006). High velocity of agitation was used for the HS mode, when the drop is not in the direct interaction with a sample. For the extraction of the atrazine and metachlor from soil, no stirring was used and the extraction was performed under static conditions (Williams *et al.* 2014). The positive effect of the ultrasound waves has been used in SDME for the OPPs extraction from the soil sample (Salemi *et al.* 2013).

For HS-SDME, the temperature is a key parameter to speed-up the rate of mass transfer of compounds from the sample to the headspace increasing the number and the amount of compounds of interest moved to the gas phase. Increased temperatures lead to the decrease of the extractant-headspace phase distribution constant and this results in the decrease of sensitivity of the method. Cooling of the extraction solvent, while the sample could be heated, is the promising solution of this problem. However, such an arrangement of experiment brings apparatus design complications, therefore, it is useful for ultra-trace analyses or for very volatile analytes with a low possibility to transfer to the headspace at ambient conditions (Jeannot *et al.* 2010). Extraction temperature was in the range from 17 °C (Soares *et al.* 2014) to 60 °C (Salemi *et al.* 2013).

The increase of the ionic strength of the water-based sample can affect the analyte transfer by the increase of the amount of salt to the aqueous phase (Wang *et al.* 2017). The majority of the publications were reported to be without salt addition.

Food samples

SDME extraction of the organic compounds from food samples is an important application field of SDME technique, it earns nowadays great interest proved by the published papers in recent years. Overview of papers reporting the analysis of various samples, such as tea (Liu *et al.* 2012; Wu *et al.* 2015), wine (Garbi *et al.* 2010; Perreira Dos Anjos *et al.* 2015), vegetables (Amrvrazi and Tsiropoulos 2009; Kin *et al.* 2009; Wu *et al.* 2016) and fruits (Perreira Dos Anjos *et al.* 2014; Pano-Farias *et al.* 2017) are summarized in the Table 3. All of them were targeted on the determination of the pesticides. No special pre-treatment was reported for liquid samples such as wine or coconut water, mainly conventional sonication, acidification, pH adjustment and centrifugation were used (Garbi *et al.* 2010; Perreira Dos Anjos *et al.* 2014; Perreira Dos Anjos *et al.* 2015). On the other hand, more difficult pre-treatment was required for solid samples prior to the extraction step (Amrvrazi and Tsiropoulos 2009; Kin *et al.* 2009; Liu *et al.* 2012; Wu *et al.* 2015; Wu *et al.* 2016; Pano-Farias *et al.* 2017). DI was the most occurred mode of SDME (Amrvrazi and Tsiropoulos 2009; Garbi *et al.* 2010; Perreira Dos Anjos *et al.* 2014; Perreira Dos Anjos *et al.* 2015; Pano-Farias *et al.* 2017). For the extraction of 8 pesticides from cucumber and strawberries, the HS mode was selected and its application was compared to headspace solid phase microextraction (HS-SPME) and solid phase extraction (SPE) (Kin *et al.* 2009). More complex apparatus was employed by Wu *et al.* (2015, 2016) for the dynamic microwave assisted extraction (DMAE) and dynamic microwave assisted extraction in combination with continuous flow microextraction (DMAE-CFME) of pesticides from tea (Wu *et al.* 2015) and cabbage, cauliflower, red cabbage and cucumber (Wu *et al.* 2016). Furthermore, DSDME using 100 µL isooctane for isolation of OCPs was used to analyze samples of tea by Liu *et al.* (2012).

Table 3. Applicability of SDME in food analysis.

Sample/Pesticides	Pre-treatment	SDME mode; Extractive solvent (volume); Volume of syringe; Extraction conditions; salt addition	Analytical technique	LOD (LOQ)	Recovery [%]/ Enrichment factor	Reference
Tea (4 types)/ 7 OPPs	Dried at 60 °C, powdered and sieved, 0.2 g is mixed with 1.0 g acidic alumina (dispersant), DMAE extraction with 25 % ethanol (*aq*); (flow rate 1.0 mL/min)	DMAE; carbon tetrachloride (5 µL); 10 µL; 230 W microwave irradiation, 10 min; –	GC-MS	0.4 – 1.7 (1.1 – 5.6) µg/kg	84.9 – 106.4/–	Wu *et al.* (2015)
Tea (bags, dry, drinks)/28 pesticides (OCPs, pyrethroids)	*Drinks:* dilution with ultrapure water (1:1, v/v); Bags: 2 g of sample + 100 mL boiled water (5 min), cooling, collection of supernatant; Dry tea: 0.5 g of sample + 10 mL of ACN + 0.05 g PSA, shaking 2 min, centrifugation 4,000 rpm, 5 min, collection of 1.5 mL aliquot, dilution with 3.5 mL ultrapure water	DSDME; isooctane (100 µL), taken volume: 10 µL; 10 µL; 15 min, 1,100 rpm; –	GC- ECD	0.04 – 1.00 µg/L	80.0 – 120.8/–	Liu *et al.* (2012)
Wine (white, $n = 15$ rosé $n = 4$)/ 18 multiclass pesticides	10 mL of sample, ultrasound bath for 5 min, acidification with HCl	DI; toluene (1 µL); 10 µL; rinsed: 6× MeOH, 3× toluene; 30 min, 200 rpm; –	GC-MS	0.10 – 4. 62 µg/L	13 – 161/–	Perreira Dos Anjos *et al.* (2015)
Wine/6 pesticides	4 mL/pH 3	DI; isooctane (2 µL); 10 µL; rinsed: 10× acetone 5× isooctane, 3 min, 180 rpm, 28 °C; –	GC-MS	0.003 – .045 (0.01 – 0.15) µg/L	–/46 – 192	Garbi *et al.* (2010)
Vegetables (cabbage, cauliflower, red cabbage, cucumber)/8 OPPs	2 g/Addition of 1.5 g of quartz sand (dispersant), 3 % NaCl (*aq*) as first extraction solvent	DMAE–CFME; toluene (2.5 µL); 10 µL; 10 min, microwaving 250 W; –	GC-MS	0.59 – 1.57 µg/kg	80.7 – 106.7/ –	Wu *et al.* (2016)
Coconut water/19 multiclass pesticides	1.5 mL aliquots of sample, centrifugation 5 min	DI; toluene (1 µL); 10 µL; 30 min, 200 rpm; –	GC-MS	0.10 – 0.88 (1.21 – 6.69) µg/L	27.9 – 160/ –	Perreira Dos Anjos *et al.* (2014)
Vegetables (cucumber and strawberries)/ 8 pesticides	Collection of 30 g from 100g of the sample, 1 h rest at room temperature, addition of 30 g distilled water, blending, homogenization, 5 mL (*aq*) sample	HS; toluene (1.5 µL); 10 µL; rinsed: 10× toluene, 15 min, 800 rpm; –	GC-ECD	0.02 – 1.00; (0.05 – 5.00) µg/L	76.7 – 104.0/ –	Kin *et al.* (2009)

Table 3. Applicability of SDME in food analysis – continued.

Vegetable (grapes and apples)/20 multiclass pesticides	500 g of sample: homogenization, selection of 2 g, addition of 25 mL solvent acetone/ water (10/90, v/v), homogenization (1 min, 13,000 rpm), centrifugation (1 min, 4,000 rpm), 10 min rest, collection of 7 mL of supernatant	DI; toluene (2 µL); 10 µL; rinsed: 10× toluene + IS, 25 min, 350 rpm; –	GC-NPD GC-µECD	0.8 – 30.0 0.03 – 5.38 µg/L	17.0 – 61.3/ 11 – 328	Amrvrazi and Tsiropoulos (2009)
Mango/multiclass pesticides	0.6 kg of fruit: washed, peeled, homogenized and transferred to the ark flask, stored at – 20 °C	DI; toluene (2 µL); 10 µL; rinsed:5× toluene; 30 min, 700 rpm, 45 °C; –	GC-MS	0.14 – 169.20 µg/kg	69 – 119/ 20 – 722	Pano-Farias *et al.* (2017)

ACN: acetonitrile; DMAE: dynamic microwave-assisted extraction; DSDME: direct suspended single drop microextraction; IS: internal standard; PSA: primary-secondary amine; other abbreviations see Table 2.

Table 4. Applicability of SDME in biological analysis.

Sample/Analytes	**Pre-treatment**	**SDME mode; Extraction solvent (volume); Volume of syringe; Extraction conditions; salt addition**	**Analytical technique**	**LOD (LOQ)**	**Recovery [%]/ Enrichment factor**	**Reference**
Male Swiss Albine mice/paraquat (Pq), maneb (Mb)	Animal treatment with Pq; (10 mg/kg) and Mb (30 mg/kg) dissolved in 0.9 % saline solution; sacrificing; collection of samples, 200 mg of sample: homogenized in 2 mL acidic water, signification 4 min, centrifugation 5 min at 10,000 rpm, collection of (*aq*) supernatant, dilution up to 15 mL of water, warmed up to 35 °C (1 min)	DI; 1-dodecanol (60 µL); –; WA agitation 50 s, freezing (few minutes), collection of solidified extraction phase, dilution with MeOH up to 200 µL; –	HPLC-MS/MS	Pq: 4.81 ng/g Mb: 9.12 ng/g	Pq: 92.62 – 96.70 Mb: 91.20 – 95.23 /Pq: 81 Mb: 114	Kumari *et al.* (2016)
Urine/chlorpyrifos, chlorpyrifos-oxon	Collection of urine, filtration through 0.45 µm pore-sized cellulose acetate filters. 5 mL of the sample was transferred to 20 mL vial with a stirring bar	DSDME; 2-dodecanol; 10 µL;70 °C, 40 min, after extraction freezing for 10 min, collection of the solidified solvent into the conical vial, removing of the residual water by centrifugation at 4,000 rpm for 3 min, injected volume: 7 µL; -	GC-MS	4.8 (CP) ng/L 3.8 (CPO) ng/L	100 (CP) 110 (CPO)/–	Pelit and Yengin (2014)

For effective extraction of the pesticides from the vegetable samples and stable drop in the continuous flow by DMAE-CFME, a variety of water-immiscible extraction solvents (*n*-hexane, cyclohexane, dichloromethane, chloroform, carbon tetrachloride, ethyl acetate, and toluene) were investigated, resulting dichloromethane and ethyl acetate as inappropriate for this mode. The major loose of these solvents was presented in the continuous sample flow arrangement. Toluene exhibited the most promising results of extraction efficiency for the majority of studied compounds (Wu *et al.* 2016). The wide scale of solvents, such as dichloromethane, chloroform, carbon tetrachloride, and chlorobenzene were examined for the extraction of the pesticides from the tea. An improved extraction chamber using as a holder of the microdrop was employed. The microdrop provided a sufficient stability in the flowing system and the microdrop transfer to analytical instruments by microsyringe after extraction was without loose of the extraction solvent. Carbon tetrachloride exhibited the highest extraction efficiency for most of the analytes, also the carbon tetrachloride extract was proved to be cleaner in comparison to other solvents. Chlorobenzene was not stable enough in the flow (Wu *et al.* 2015). Analyzing tea samples, cyclohexane drop immersed to the tea sample solution was not reproducible with low stability. Toluene was problematic as it extracted tea pigments and further cleaning was necessary. Isooctane showing the highest viscosity among studied solvents was selected as the final solvent for real-samples extraction, in addition, it formed stable microdrop (Liu *et al.* 2012). Microsyringe of the volume 10 μL was used in all of the mentioned applications and the drop of the sample was in the range of 1 μL and 10 μL. Especially, the volume 100 μL was used for the DSDME mode to measure the volume of the sample. Presence of the steady vortex was important for the formation of the microdrop (Liu *et al.* 2012). To avoid carry over effect, the rinse of the microsyringe was used mostly by the extraction solvent or polar organic solvents (Amrvrazi and Tsiropoulos 2009; Kin *et al.* 2009; Garbi *et al.* 2010; Perreira Dos Anjos *et al.* 2015; Pano-Farias *et al.* 2017).

The highest speed of the magnetic stirrer was used for the DSDME extraction, the stirring speed above 1,100 rpm causes instability and dissolution of the solvent microdrop (Liu *et al.* 2012). Low speed of magnetic stirrer was mostly used for the DI-SDME in the range of 180 – 700 rpm (Amrvrazi and Tsiropoulos 2009; Garbi *et al.* 2010; Perreira Dos Anjos *et al.* 2014; Perreira Dos Anjos *et al.* 2015; Pano-Farias *et al.* 2017) and microwave irradiation was employed for the DMAE (Wu *et al.* 2015) and DMAE-CFME (Wu *et al.* 2016).

The influence of microwave energy (100 – 350 W) on the extraction was studied. Implementation of the microwave-assisted extraction (MAE) prior to SDME simplify the pre-treatment process by the acceleration of the disruption of the vegetable cells under the high temperature. The high temperature improves the diffusion and mass transfer during extraction, and the dissolving capacity of extraction solvent at the same time, as well as, the target compounds dissolves faster. However, when high microwave power is used, it may cause the analyte degradation (Wu *et al.* 2016). No salt addition was reported in the published papers for food samples analysis.

Satisfactory recovery values in the acceptable limit (between 70 % and 120 %) were mostly reposted. Difficulties to extract some compounds were mostly explained by chemical properties of the analytes and by the interaction of the analytes with other compounds presented in the sample. Low values of recovery were reported for dursban (the pesticide) with recoveries in the interval of 13.2 % – 52.4 % (Perreira Dos Anjos *et al.* 2015), and for the pyrethroid insecticide λ-cyhalothrin (1.4 for grape and 1.5 for apple) (Amrvrazi and Tsiropoulos 2009). Permethrin I and permethrin II are compounds exhibiting higher affinity toward water phase, which is demonstrated by low partition coefficient, therefore, as a result, insufficient recovery rates were reported (39.4 % and 45.0 %, respectively). Thus, it is possible to notice a difficulty of the migration of these analytes from the aqueous sample to the organic solvent. Although a relatively high partition coefficient belonging to the pesticide endosulfane, a low recovery rate was reported (29.0 %), what was explained by the interaction with other matrix components comprising the coconut water. In general, extraction of the compounds with higher polarity such as OCPs, compared to other classes of compounds such as OPPs, is more difficult

hence they promote a higher affinity for water-based sample than for organic extractant (Perreira Dos Anjos *et al.* 2014).

Biological samples

Sample preparation step is essential for the isolation of analytes from complex biological matrices and has a great influence on their reliable and accurate determination. Suitable extraction technique is usually necessary because almost all biological samples are incompatible with the following chromatographic instrumentation, these samples exhibit complicated matrix for direct analysis, and components in the sample may interfere the signal acquisition. In addition, the analytes are present at concentration levels below the limit of detection of regular analytical methods (Ocaña-González *et al.* 2016). Biological samples contain proteins, salts, acids, bases, and various organic components with properties close to those of searched analytes.

In the recent years, applications of the SDME were aimed mostly to extraction of the several organic compounds in the biological samples such as fish (Botrel *et al.* 2017), urine and blood of the rats (Agrawal *et al.* 2007), human urine (Gao *et al.* 2011; García-Vasquéz *et al.* 2015), saliva (Timofeeva *et al.* 2016) and human blood serum (Shrivas and Patel 2009) (Table 4). The solidification of the extraction solvent in microliter scale after dispersive liquid-liquid microextraction for the extraction of drugs (Ebrahimzadeh *et al.* 2011; Ahmadi-Jouibari *et al.* 2014; Tehrani *et al.* 2014), medicaments (Ebrahimzadeh *et al.* 2013; Jia *et al.* 2013; Suh *et al.* 2014) was also reported.

A few papers were devoted to the extraction of pesticides, namely maneb (fungicide) and paraque (herbicide) in albine mice by Kumari *et al.* (2016) and chlorpyrifos and chlorpyrifos-oxon by Pelit and Yengin (2014).

1-Undecanol, 1-dodecanol, 2-dodecanol and *n*-hexadecane were investigated for the extraction of maneb and paraque from albine mice. Except *n*-hexadecane, all other solvents were found to recover comparably the same amount of targeted analytes. This maybe because all these solvents possess nearly similar affinity toward the targeted analytes. In this case, the solidification of the solvent drop was used, which offered manipulation with a microdrop without significant losing of extract. This approach was reported to be semi-automated and could be fully automated without varying from the original concept by the further modifications. Finally, 1-dodecanol was chosen to be used for further experiments, due to its peculiar characteristic of being easily solidified near room temperature. (Kumari *et al.* 2016).

In the case of urine, this matrix offers several advantages as it is very easy to obtain and specimen volume is not a limitation. Biomonitoring of the chlorpyrifos exposure in human urine was reported and 2-dodecanol as extraction solvent was selected due to the absence of the solvent peak presented in the same time as the analytes in the chromatogram in comparison with the other studied solvents. The extraction was performed using increased temperature, and no addition of the salt was presented. In this case, it was difficult to collect the organic phase due to the formation of smaller droplets of the solvent in the solution after addition of 0.5 g NaCl to 10.0 mL of the solution (Pelit and Yengin 2014).

Conclusions

SDME showed its suitability for the extraction of various type of analytes, which belongs to the wide group of harmful organic compounds and environmental pollutants from numerous types of samples. Applications of SDME for real samples analysis were sorted into 3 groups according to sample nature and summarized into the form of overview tables. As it was shown by the largest group of applications, SDME has the major utilization in the area of environmental samples analysis, then followed by food samples analysis.

Nowadays, there is an increasing frequency of publication devoted to the SDME for biological samples analysis. SDME offered the reach of high pre-concentration, clean final extract directly suitable for analysis, fast extraction and the simplicity of the process. It was shown, that the two most common SDME modes DI and HS have slightly different general fields of applicability, but they show their wide applicability for various matrices. DI-SDME was approved to be suitable mostly for the extraction of the nonpolar or moderately polar volatile and semivolatile analytes from relatively clean matrices, such as

water, using appropriate water immiscible solvents, due to the direct contact of the solvent with a water sample. Since volatile compounds are best pre-concentrated by headspace SDME. The selection of the working parameter was also established to be critical for the reaching satisfactory recoveries of the analytes and explained by numerous examples. In conclusion, miniaturized extraction methods such as SDME represent a new approach that is currently receiving a great deal of interest of researchers in the area of sample preparation methods for analytical purposes.

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