

Advances in Liquid Phase Microextraction for Trace Analysis: A Review

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ABSTRACT:Real samples which are subjected to analysis by a chromatographic technique, such as high performance liquid chromatography or gas chromatography, present two major challenges that determine the success of analysis and identification. First, the analytes are only present in traces, typically down to a few microgram per litre or kg of sample, and when injected as such the analytes peak result into insufficient sensitivity. Secondly, the sample matrix is too complicated, and as such, the situation would yield a complex chromatogram. Thus, the analyte enrichment and injection solution cleanup are important steps in chromatographic analysis. This review article discusses four liquid-liquid extraction based techniques, viz., single drop microextraction, salt-assisted liquid-liquid microextraction, hollow fibre liquid-phase extraction, and dispersive liquid-liquid microextraction which have gained popularity in recent literature. Each method is evaluated with respect to its working, optimization, advantages and future aspects.

KEYWORDS:single drop microextraction, salt-assisted liquid-liquid microextraction, hollow fibre liquid-phase extraction, dispersive liquid-liquid microextraction.

I. INTRODUCTION

Measurements based on analytical chemistry are important and critical to the success of agriculture, chemical industries, food and drink processing, defence industries, pharmaceuticals, textile, etc. Such measurements safeguard health, safety and the quality of the products, and cover a wide range of concentration from major constituents of materials down to contaminants present at parts per billion or below [1]. The European Union requires the detection of many organic compounds typically at level of $1-3 \mu\text{g L}^{-1}$ in surface water and at $0.1 \mu\text{g L}^{-1}$ in drinking water [2]. There are usually two distinct situations found in analytical measurements. In clinical or forensic analysis there may be only small portion of sample for use but the concentration of analytes may be high. On the other hand, sample available for environmental analysis is plentiful but the concentration of analyte is very low. Hence, despite technological advances in GC-MS and LC-MS most instruments cannot handle real samples directly. As a result a sample preparation step is commonly involved in an analytical procedure. The main aim of sample preparation is to clean up, isolate, concentrate the analytes of interest, while rendering them in a form that is compatible with the analytical system via phase transfer or derivatization of analyte to show a good separation behaviour and detectability of analytes.

Sample preparation frequently involves generation of large amount of toxic waste. The most commonly used classical liquid-liquid extraction (LLE), also known as solvent extraction (Fig. 1), has long been a method of choice for extracting compounds from their aqueous phase to another water immiscible phases such as chloro-solvents, which are required in large amounts and are toxic to the environment and public health [3]. Necessity to evaporate the extract increases the chances of analytes loss either through vapourization or decomposition. Pre-concentration by evaporation is time consuming and labour intensive and reduces the sample throughput. Moreover, emulsion formation, unfavourable partition equilibria, slow phase transfer and production of large volume of waste are other drawbacks of this technique. Thus, classical LLE is an eco-unfriendly approach. The available literature mentions that 10 atoms of chlorine can destroy upto one million ozone molecules [4].

The sample preparation method can be performed on-line or off-line [5-8]. Obviously, each approach has its own advantages and disadvantages. Off-line approaches are generally the best choice. However, if a procedure is intended to be used frequently and for rather a large number of (similar) samples, then setting up an automated system can be worth the efforts. Development and automation of analytical technologies have also been in focus. Automation will reduce both labour and costs can improve the quality of data, increase sample throughput, and improve

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productivity of personnel and analytical instrumentation. By setting up a (semi-) automated on-line method, the elimination of analyte losses and the introduction of the whole amount of the preconcentrated analyte into the separation-plus-detection unit will improve both the sensitivity and repeatability of the analyses. A note of warning should be added; contrary to what is often believed, (automated) on-line procedures require the presence of skilled personnel, especially when further development or extension of setting up an on-line system also requires a higher level of 'analytical thinking' compared with off-line designs. The on-line approach is the best choice if aggressive chemicals and/or exotic conditions have to be used.

Enormous efforts have been devoted in the last two decades to the development of faster, safer and more environment friendly techniques for sample extraction and clean-up, prior to instrumental analysis [9,10]. Miniaturization of sample preparation has resulted in portability of the system, and method efficiency such as reduced cost per analysis, high speed at which optimum sample throughput could be obtained, and minimum or no waste production [11]. The proper selection of pre-treatment procedure depends on several aspects which include (i) the concentration levels of analytes of interest and the interfering matrix compounds, and (ii) characteristics of the analytes such as their volatility, thermostability, reactivity and polarity, and their difference with regard to these characteristics with matrix constituents.

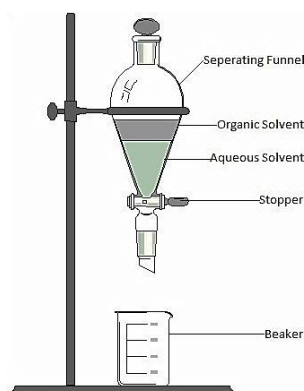


Fig. 1. A typical assembly used for classical liquid-liquid extraction (LLE).

II. SINGLE DROP MICROEXTRACTION (SDME)

Recent studies have shown that microdroplet processes are distinctly accelerated compared to the corresponding bulk-phase operations[12]. This raises the question whether all analytical processes can be sped up by this means. For greater preconcentration it is important to increase the fraction of analyte component extracted by using a small phase ratio (V_o/V_a). When LLE is performed in a classical mode (in a separatory funnel) it is necessary to disperse drops of one phase into the other by agitation in order to facilitate mass transport and thereafter to allow coalescence and phase separation. This mode of operation introduces some practical problems. For one thing, it is not possible to work with phase ratio (V_o/V_a) smaller than about 0.01 which militates against a high preconcentration ratio. Other inconveniences are unfavourable partition equilibria, formation of emulsions, necessity to use large volume of solvents and difficulty in disposal of waste [13]. This is a particular problem for samples of natural origin such as urine and vegetable extracts, which contain surface-active agents that adsorb at the liquid-liquid interface to produce emulsions. Another disadvantage of the classical mode is the relatively large amount of waste organic solvent that is generated.

A newly developed protocol, which overcomes the problems of solvent evaporation in liquid-liquid extraction, and solid-phase extraction [14]; and fibre degradation in solventless method of solid-phase microextraction [15], is solvent microextraction. It is based on the traditional LLE technique but involve only a few microlitres of organic solvent as extractant contained at the end of a PTFE rod [16]. This system required two discrete parts--the first for extraction and the second for injection. A microdrop liquid extraction system was described for trace amounts of analytes, which was subsequently identified by *in situ* UV/vis detection[17]. Subsequently, another approach termed as

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Vol. 6, Issue 8, August 2017

dynamic liquid-phase microextraction used the microsyringe as a separatory funnel [18]. Later, a simpler kind of microextraction system was introduced using a single microlitre-volume drop called single drop microextraction (SDME) [19].

2.1 SDME WORKING

In SDME, the analytes are distributed between the bulk aqueous phase and a microdrop of organic solvent, suspended directly at tip of a microsyringe needle that is immersed in a stirred aqueous sample solution (Fig. 2). After a certain time, when sufficient amounts of analytes are transferred into the organic extractor, the microdrop is retracted into the microsyringe, and subsequently injected into the chromatographic system. Since drop volumes are in the microlitre to picolitre range the phase ratio, V_o/V_a , is always very small [20,21].

An important additional feature of SDME is the integration of extractions and injection in microsyringe, making it possible to employ this miniaturised medium for extraction as well as an injection device for GC. Apart from being inexpensive, SDME requires only common laboratory equipment and does not suffer from carry-over between extractions that may be experienced using SPME[22-25].

2.2 MODES OF SDME

Two basic types of extraction can be performed using SDME, direct extraction and headspace configuration. In the direct extraction mode, the solvent microdrop is inserted into the sample and the analytes are transported directly from the sample matrix to the extracting drop. To facilitate rapid extraction, some level of agitation is required to transport analytes from the bulk of the solution to the vicinity of the extracting drop. For gaseous samples, natural convection of air is sufficient to facilitate rapid equilibration. For aqueous matrices, more efficient agitation techniques, such as fast sample flow, vial movement, stirring or sonication is required. These conditions are necessary to reduce the effect caused by the “depletion zone” produced close to the drop as a result of fluid shielding and slow diffusion coefficient of analytes in liquid matrices.

Direct or immersed SDME suffers from some major disadvantages, such as the method can only be useful for liquid samples; only water-immiscible solvents are applicable in this method; it is a suitable method for extraction of non-polar and moderately polar analytes; also high molecular mass and other non-volatile interfaces which are extracted by the microdrop; matrix has an important effect on extraction process. These drawbacks can be eliminated if microdrop is used in the headspace of solution. In headspace-SDME (HS-SDME) (Fig. 2), extraction of analytes occurs via suspending a microlitre drop of a proper solvent from the tip of a microsyringe that is located in the headspace of a stirred aqueous sample solution thermostated at a given temperature for a pre-set extraction time [26-29]. The drop remained at the tip of the microsyringe throughout the extraction period and then was retracted back into the needle and injected into analytical instrument (GC/LC) or placed on the pedestal for spectrophotometric measurements for the identification and quantification of the extracted analytes.

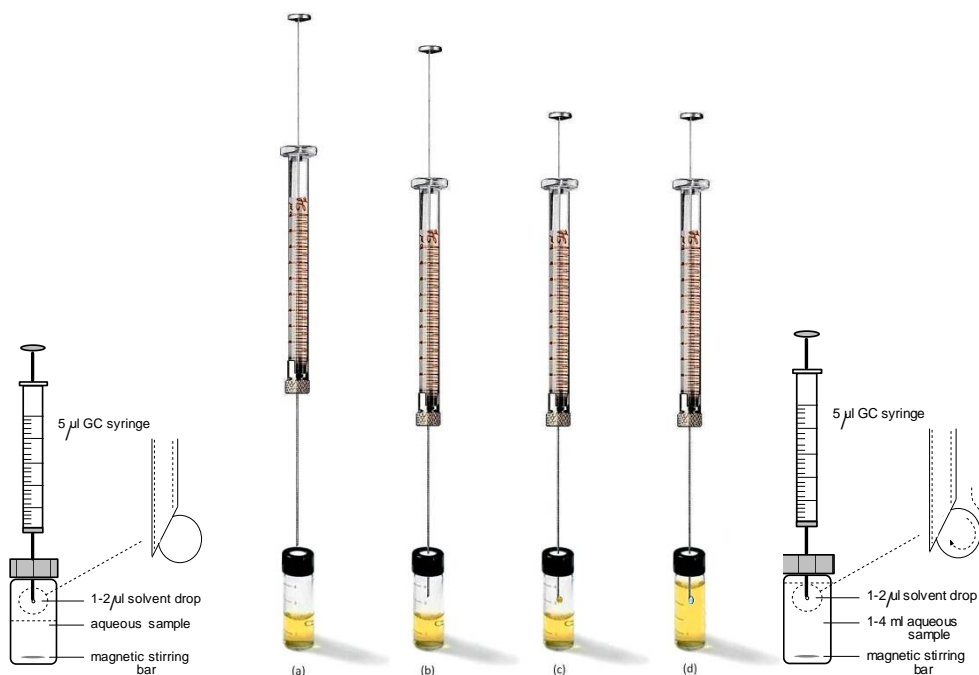


Fig. 2. Single drop microextraction. Left panel, typical device for single drop microextraction showing a 1-2 μL drop of the organic phase suspended from the tip of a microsyringe needle and positioned in the headspace of the sample. Middle panel, (a) vial filled with sample and a syringe ready for SDME, (b) vial septum pierced by needle of syringe to begin SDME, (c) drop suspended at the tip of syringe above the sample solution (HS-SDME), (d) drop suspended inside the aqueous sample (DI-SDME). Right panel, enlarged view of the needle tip with the pendent drop is shown. The dashed arrow outside the drop indicates local convection in the stirred aqueous phase and the dashed arrow inside the drop indicates circulation in the microdrop that is induced by momentum transfer from the aqueous phase.

2.3 OPTIMIZING SDME

For SDME there are several parameters to control optimum performance including the nature of solvent used as extractant, temperature of microdrop and sample solution, stirring rate, ionic strength, microdrop and aqueous solution volumes and extraction time.

Nature of microdrop solvent. The choice of an appropriate solvent is essential for SDME method. The extraction solvent has to meet three requirements: to have low volatility in order to be stable during the extraction period, to extract analytes well and to be separated from the analyte peaks in the chromatogram. The extracting solvents that have been used for SDME are listed in Table 4. A wide range of solvents and polarities is possible. For headspace sampling, the boiling point of the solvent should be high to avoid significant evaporation during sampling. Developing new solvents is one of the key aspects in Green Chemistry in order to reduce the intensity of anthropogenic activities related to analytical laboratories. A range of new and more eco-friendly media have been employed as extractant phases. These media, besides being less hazardous, provide shorter extraction times, simplicity, low cost, better selectivity in some cases [30]. Solvents compatible for diverse analytical techniques are listed in Table 5.

To compare the solvent selectivity for the extraction and in-drop derivatized of carbonyl compounds into its corresponding 2,4-dinitrophenylhydrazones, three solvents were tried, butanol, ethylene glycol and propanol (Fig. 3). Apparently, ethylene glycol, as the extraction solvent, shows higher extraction efficiency in comparison with other solvent because of the high polarity and dipole-dipole interactions with 2,4-dinitrophenylhydrazones [31]. Solvent exchange after SDME has been employed for elimination of interfering matrix effects of saliva and caffeine metabolites, such as theophylline, theobromine and paraxanthine [32].

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Vol. 6, Issue 8, August 2017

Table 4. Extracting solvents for SDME

Liquid immersion SDME		Headspace SDME	
Solvent	Boiling point, °C	Solvent	Boiling point, °C
n-Hexane	69	n-Octane	125
n-Octane	125	n-Decane	174
Isooctane	116	Tetradecane	246
Cyclohexane	81	n-Hexadecane	287
n-Hexadecane	287	Toluene	110
Benzene	80	o-Xylene	144
Toluene	110	Cyclohexane	81
Chlorobenzene	132	1-Octanol	195
Chloroform	61	Ethylene glycol	197
Anisole	154	Diethyl phthalate	298
Acetophenone	202	Anisole	154
Diisopropyl ether	68	1-Butanol	117
n-Butyl acetate	126	Benzyl alcohol	206

This was despite the fact that, due to the safety consideration and the green chemistry involved, water can also be employed as a suitable extraction solvent. It should be noted that because of the exothermic behaviour of the dissolution of the headspace vapours in microdrop solvent, the use of a water micro-drops are also expected to result in a considerable pre-concentration of the analyte, under the experimental conditions employed. It is noteworthy that, since the use of water as solvent may damage the stationary phase of the GC columns, it would be safer to use with LC and microspectrophotometry instead of GC for sample analysis [33].

Table 5. Single drop microextracting solvent compatibility for different analytical techniques.

SDME solvents		
NanoDrop Spectrophotometry	HPLC	GC
Water Toluene Acetophenone Cyclohexane Benzene Chlorobenzene Anisole	Water Ethylene glycol 1-Butanol 1-Propanol Iso-propanol 1-Pentanol Ethyl acetate	Toluene Anisole Acetophenone Benzene n-Octane n-Decane Cyclohexane

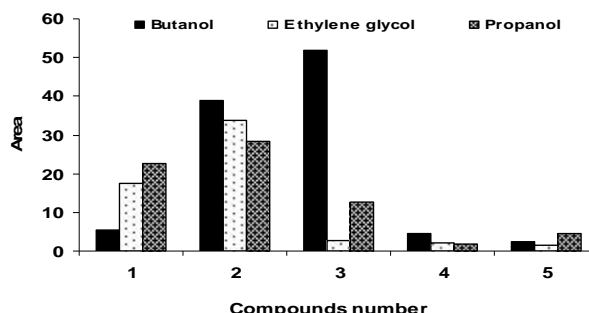


Fig.3. Effect of solvent polarity on the extraction and in-drop derivatization of carbonyl compounds as their 2,4-dinitrophenylhydrazones. Analyte identification; 1=formaldehyde, 2=acetone, 3=methyl ethyl ketone, 4=benzaldehyde, 5=cyclohexanone [31].

Microdrop volume. In SDME the volume of the organic drop does not remain constant during the process because no solvent is completely immiscible with water so that there will be some dissolution of the organic phase in the aqueous phase (and the reverse). However, a slight decrease in drop volume is acceptable because it will occur to

the same extant for the standard as for the sample and its effect will cancel out. An increase in the volume of the microdrop (up to 3 μL) resulted in a sharp enhancement in the extraction efficiency of the system. However, at larger volumes (i.e. $>3 \mu\text{L}$), the microdrop revealed the great tendency to fall down from the tip of the microsyringe. Thus, generally 1 or 2 μL drop size was chosen as the optimized volume. Effect of drop volume of 1-butanol on the HS-extraction and derivatization of carbonyl compounds (1 mg L^{-1}) into their respective 2,4-dinitrophenylhydrazones has been shown in Fig. 4[34].

Exposure time. Solvent microextraction is not an exhaustive extraction method and analytes are partitioned between the bulk aqueous phase and organic microdrop. The total amount of analytes transferred in the drop reaches its maximum when equilibrium between the two immiscible phases is established. For quantitative analysis, it is not necessary for the analytes to have reached equilibrium, only to allow sufficient mass transfer into the drop and exact reproducible time. To avoid incidents of drop loss or dissolution generally 10-20 min extraction time was adopted, even though analytes had not reached equilibrium at this time point.

The effect of equilibration time for thiols, derivatized to thiolate ion, in deionized water and extracted into toluene drop as ion pair with tetraoctyl ammonium bromide and the variation of the absorbance was studied as a function of exposure time (Fig. 5) [13].

The analytical signal increased quickly with sampling time in the range of 5-15 min, and after 15 min the rate of increase slowed down. It can be seen, however, that equilibrium had not been reached even after 25 min. An extraction time of 15 min was selected as reasonable compromise between enrichment factor and analysis time.

Ionic strength. Addition of salt to the sample may have several effects on extraction. More commonly, the presence of salt increases the ionic strength of the solution and affects the solubility of organic analytes. For SDME, the effect of salt was previously studied for the extraction of mixture of nitroaromatic explosives [35]. The results revealed that the presence of salt significantly decreases the extraction efficiency.

Thus the effect of sodium chloride concentration (from 0 to 1 g) was investigated for 10 mg L^{-1} of periodate reacted with norephridine and extraction efficiency was monitored. The results showed decrease in extraction efficiency with increase in ionic strength for the targeted analyte as shown in Fig. 6. A possible explanation for this observation may be that apart from salting-out effect, the sodium chloride dissolved in aqueous solution may have reduced the rate of diffusion of the targeted analyte into the drop. This means that with increased salt concentration the diffusion of analytes towards the organic drop becomes more and more difficult thus extraction efficiency was decreases [35,36].

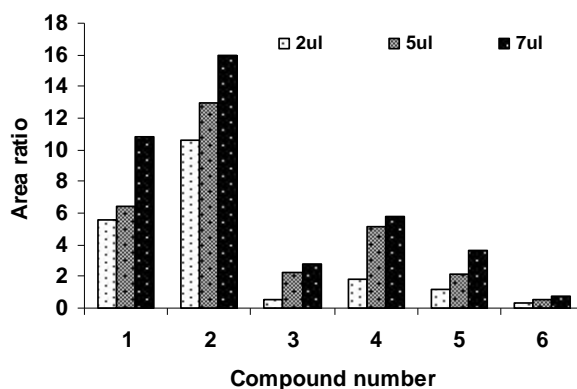


Fig. 4. Effect of volume of 1-butanol drop for SDME and derivatization of 1 mg L^{-1} of carbonyl compounds at $40 \text{ }^\circ\text{C}$, 10 min equilibration time, 750 mg L^{-1} 2,4-DNPH and 10 mg L^{-1} IS. Analyte identification, 1=formaldehyde, 2=acetone, 3=methylethyl ketone, 4=benzaldehyde, 5=cyclohexanone [31].

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Vol. 6, Issue 8, August 2017

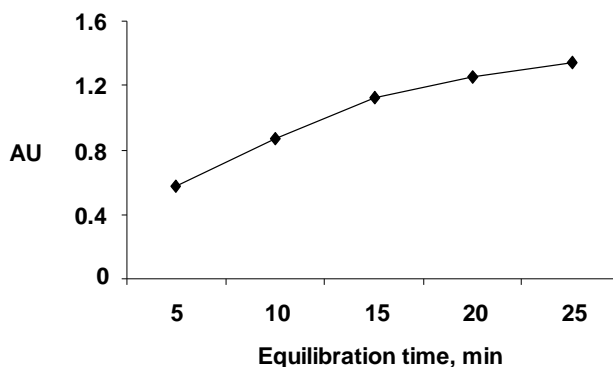


Fig.5. Effect of time on SDME of 80 µM cysteine as its thiolate ion using 2 µL toluene containing 0.5 M tetraoctyl ammonium bromide as ion pair reagent.

In case of HS-SDME as the solubility of an analyte increases in a given sample, the partition coefficient increases and the headspace sensitivity is reduced. In this situation, altering the sample matrix will have a significance effect on the partition coefficient. Thus, addition of salt to water will reduce the solubility of polar compounds in the water and increase the sensitivity of headspace analysis [37,38]. For this purpose, the ionic strength of solutions was modified by addition of 0 to 1 g of sodium chloride in the sample spiked with 1 mg L⁻¹ of periodate and treated with norephrine. Plot of peak area versus amount of sodium chloride has been shown in Fig. 7[39]. According to the curve, it is clear that the addition of salt promoted the transport of analytes to the headspace and hence to the extracting drop. For this the sample solution must be saturated from the salt and 1 g of sodium chloride is sufficient for this. This can be explaining by the fact that water molecules form hydration spheres around the salt ions. These hydration spheres reduce the concentration of water available to dissolve analyte molecule; hence it is expected that this will drive additional analytes into the extraction phase [40].

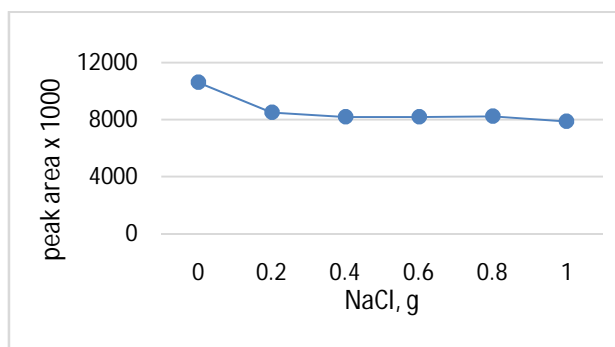


Fig. 6. Effect of salt addition on the SDME of benzaldehyde; equilibration time 20 min; solvent 1.5 µl of toluene.

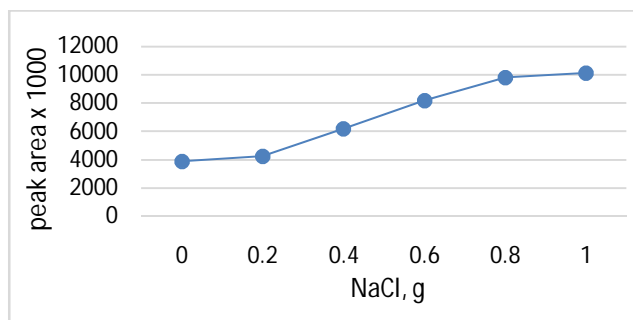


Fig. 7. Effect of salt addition on the HS-SDME of benzaldehyde; equilibration time 20 min; and solvent 1.5 μ L of toluene.

2.4 ADVANTAGES AND LIMITATIONS OF SDME

For sample preparation prior to an analytical measurement, SDME is more suitable than the other extraction methods, which are previously discussed because of its relative simplicity and much smaller organic solvent consumption. Techniques in which the single drop is in contact with a convected (i.e. stirred or flowing) aqueous sample solution appear usually to be preferable to those in which the aqueous solution is not convected because of the large value of kinetic rate control is usually in the aqueous phase. For reproducibility, the conditions of convection and temperature should be fairly well controlled. Single drop-LPME techniques in which the analyte components in the organic drop are determined by injection into an instrument with the capability of resolving and simultaneously determining multiple components are more suitable for sample preparation than are those techniques in which in situ analyses are performed. This is because most samples contain several to many components and the in situ measurements, such as absorption and fluorescence spectroscopy and electrochemistry, are not capable of simultaneous analyses and also are subjected to interference from non-analyte components that are present in the sample. Formation of air bubble in the solvent drop is accidental problem that vitiates the precision. However, significant improvements to microdrop extractions of triazine pesticides has been realized by the intentional incorporation of air bubble into the solvent microdroplet used in SDME. The increase in extraction is attributed partly to greater droplet surface area resulting from the air bubble being incorporated into the solvent droplet as opposed to it sitting thereon and partly to thin film phenomena [41].

In this context, ways and means of accomplishing the injection of part or the entire sample organic drop into a chromatographic column, an electrophoresis capillary or an atomic or mass spectrometer are important consideration. Transfer of the drop from a capillary was also identified [42]. The transfer of small volumes of solution into capillary liquid chromatographic columns, capillary electrophoresis columns and for GC-flame photometric detection is an area of active research and development [43,44].

2.5 FUTURE ASPECTS OF SDME

Since the drop to be analyzed after SDME is composed of a water-immiscible organic solvent it is readily compatible with direct injection in gas chromatography, normal phase liquid chromatography, mass spectrometry and atomic spectrometry. However the sample volume needed in conventional spectrophotometry is usually larger than which is used in SDME, thus hampered the compatibility of SDME with spectrophotometry. In recent years much development has been driven by a need to perform rapid measurement on small scale sample volumes. One such invention is NanoDrop, a fibre-optic-based micro-spectrophotometer which is equipped to accommodate sample volumes as small as 1 μ L for absorbance measurement with high accuracy and reproducibility[13], and thus made it possible to couple SDME with direct spectrophotometric detection. Similarly the use of water immiscible solvents in SDME had become a bottleneck for its compatibility with RPLC where mainly aqueous carrier fluid is used. But with the recent use of water miscible solvents in HS-SDME made it possible to couple SDME with RPLC. For now these two coupled systems are new in the field of analytical method development. SDME with in-drop derivatization and online coupling with capillary electrophoresis has also been described recently[45]. The results had shown that there is a great potential to develop fast, eco-friendly, sensitive, selective and cost effective method using these techniques.

International Journal of Innovative Research in Science, Engineering and Technology

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Vol. 6, Issue 8, August 2017

SDME has been applied for organic compounds of a wide range of volatility using the same solvent drop in direct immersion mode and then in the headspace [46]. Solidified floating organic drop microextraction (SFODME) is also a new form of SDME [47], and its combination with electrothermal vaporization (ETV)-inductively coupled plasma mass spectrometry (ICP-MS) was developed for the determination of trace heavy metals in environmental water samples with sodium diethyldithiocarbamate (DDTC) as both chelating reagent in SFODME and chemical modifier in ETV [48].

III. SALT-ASSISTED LIQUID-LIQUID MICROEXTRACTION (SALLME)

The major drawback with SDME is the use of non-polar, water miscible organic solvents which due to their low dielectric constant give relatively poor extraction for very polar or highly charged solutes even when used in immersion mode. More polar compounds are frequently water miscible and thus cannot be used in immersion mode.

It has long been known that the addition of an inorganic salt into a mixture of water and a water-miscible organic solvent causes a separation of the solvent from the mixture and the formation of a two-phase system [49]. Sometimes this phenomenon is referred to as “salt-induced phase separation”. Observations of this “salting-out” phenomenon were made for a number of water-miscible organics such as acetone, methanol, ethanol, and acetonitrile [50]. Different salts and different salt concentrations will cause different degrees of phase separation. The high-polarity, water-miscible solvents used in salting-out systems have been investigated for extraction or concentration of many analytes that cannot be extracted by conventional LLE methods. This salting out often occurs at high salt concentrations. In some cases, the “salting-out” (or perhaps better termed “sugaring out”) effect also can be achieved with high concentrations of saccharides [51].

Although the salting-out phenomenon has been known for many years, some systematic studies have been carried out to help choose the optimum solvent systems and salt additives. The salting out of acetone from water was investigated as a solvent-extraction system for metal chelates [52,53]. A solvent system was developed for enhancing the sensitivity of flame emission and atomic absorption spectrometry measurements of metal ions extracted as their chelates into the acetone phase in the absence of water. The investigations included seventy-nine salting-out agents, and of those found for this water-acetone system, calcium chloride, magnesium chloride, and sucrose were most effective. Salting out extraction has been used for the preconcentration of neutral to polar organics from water. In fact, the U.S. Environmental Protection Agency method 8330A for the isolation of nitroaromatic and nitramine explosives from water at the nanogram-per-litre level is based upon a salting-out extraction method [54].

Several mechanisms have been proposed for the effects of electrolytes on the salting out of water-miscible solvents. For example, some electrolytes have been classified as having either salting-out or salting-in effects and ranked according to their salting strength. Most theories concerned with the salting-out effect have used salting-out coefficient (Setschenow constant) defined as $k_s = 1/m(\log S_0/S)$, where S_0 and S are the solubilities of the organic solvent in water and electrolyte solution of molality m , respectively [55,56].

3.1 WORKING OF SALLME

The typical steps involved in SALLME are illustrated in Fig. 8. The aqueous sample is mixed with a water miscible solvent and shaken. Thereafter, adequate amount of a suitable salt is added to saturate the solution when the water miscible solvent separates out on standing. The separation is also speeded up by centrifugation. A portion of the organic solvent is used for analysis.

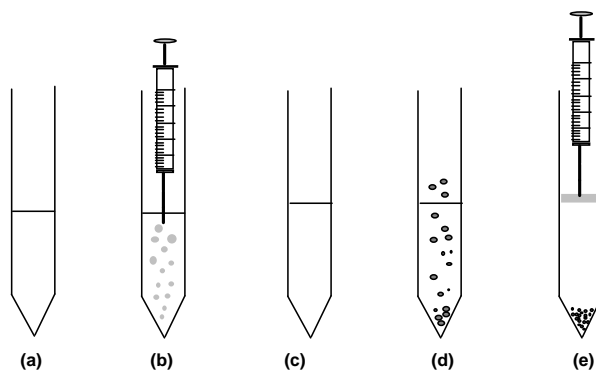


Fig.8. Typical stages involved in SALLME, (a) aqueous reaction mixture, (b) addition of water miscible organic solvent, (c) homogeneous reaction mixture, (d) addition of salt to saturate the solution, and (e) phase separation.

3.2 OPTIMIZING SALLME

For SALLME there are several parameters to control optimum performance including nature of solvent used as extractant, nature and amount of salt used for phase separation, organic and aqueous phase volumes and extraction time.

Selection of hydrophilic organic solvent. The choice of an appropriate solvent is essential for the homogeneous SALLME. The extraction solvent must be stable at the extraction period and to extract analytes well after the phase separation by adding salt. The solvent selectivity was compared for the extraction of allyl isothiocyanate derivatives of tricyclic antidepressant drugs (TCAs); amoxapine and nortriptyline[57]. For this purpose three solvents were tried, acetonitrile, acetone and 2-propanol (Fig. 9). Apparently, acetonitrile, as the extraction solvent, showed better extraction efficiency in comparison to other solvent possibly because of its high polarity that was suitable for polar analytes. A similar effect of organic solvent was recorded for extraction of 2,4-dinitrophenylhydrazones (Fig. 10)[58].

For clear phase-separation of water-acetone, water-acetonitrile and water-2-propanol mixtures containing 4.5 ml of water and 0.5 ml of water-miscible organic solvent, respectively 2.1, 2.8 and 3.4 g of ammonium sulphate were required to be added. The volume of organic solvent rich phase/water rich phase after separation were 0.3 mL/5.8 mL, 0.15 mL/5.3 mL and 0.4 mL/6.0 mL, respectively.

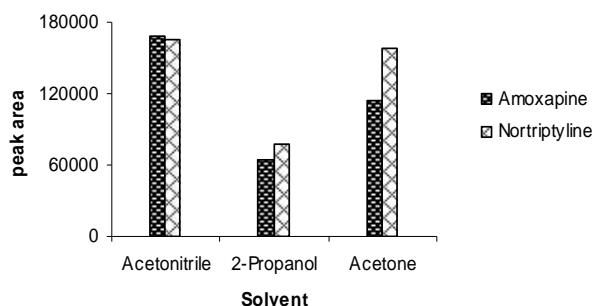


Fig. 9. Effect of organic solvents for SALLME of allyl isothiocyanate derivatives of 2 mg L⁻¹ of each TCAs. The initial volume of aqueous phase and organic solvent was 4.5 and 0.5 mL, respectively. The separated organic phase analyzed by HPLC. AFS, 0.16.

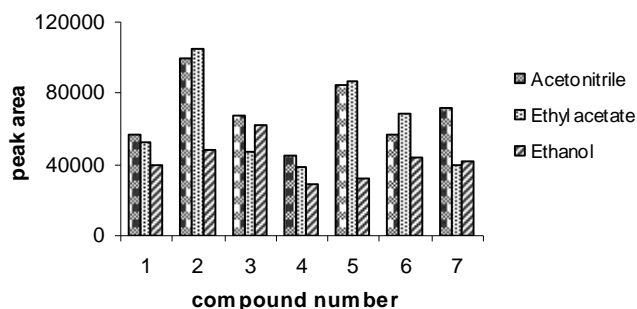


Fig. 10. Effect of organic solvents for SALLME of 2,4-dinitrophenylhydrazones of 2 mg L^{-1} of each carbonyl compounds. The initial volume of aqueous phase and organic solvent was 4.5 and 0.5 mL, respectively. The separated organic phase analyzed by HPLC. Peak identification, 1 = formaldehyde, 2 = furfural, 3 = acetone, 4 = ethylmethyl ketone, 5 = benzaldehyde, 6 = iso-propylmethyl ketone and 7 = cyclohexanone.

Optimization of solvent volume. In the proposed technique, the volume of the water soluble organic solvent does not remain constant after extraction because hydrophilic solvents have some solubility with water after adding excess of inorganic salt. (no hydrophilic solvent is completely immiscible with water). Effect of solvent volume on the extraction of hydrazones of carbonyl compounds in 5 mL sample volume shown in Fig. 11.

Selection of salt. A relatively simple theory has been used to explain salting-out phenomena, postulating removal of one solvent via solvation processes, i.e., salt effect theory. This theory can be applied only to ionic compounds assumes that the more polar of the two solvents, e.g., water, preferentially congregates around the salt because of electrostatic attraction, leading to non ideal behaviour and positive deviation from Raoult's law. Thus, the vapour pressure above the aqueous phase is increased and the escaping tendency of the second solvent is increased with the result that its solubility in the first solvent is decreased.

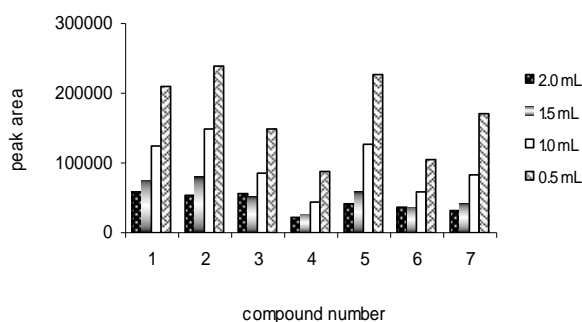


Fig. 11. Effect of volume of extracting organic solvent, acetonitrile, used in the SALLME of 2,4-dinitrophenylhydrazones of 1 mg L^{-1} of each carbonyl compound. Peaks identification as in Fig. 21.

3.3 MERITS AND FUTURE ASPECTS OF SALLME

SALLME integrates sampling, extraction and cleanup in a single step. Quick phase separation, rapid partition equilibrium, minimum amount and less toxicity of extracting solvent, and compatibility of extract with subsequent analysis by HPLC are advantages of SALLME. Furthermore, this method has benefit of its simplicity, high sensitivity, short preconcentration time and freedom from memory effects. SALLME is more suitable for HPLC owing to the use of water-miscible extraction solvents[59,60]. The apparent limitation of this extraction technique is occurrence of fair amounts of salt in the extract which restricts its prospective use in GC, and possible precipitation in injector or column in HPLC. SALLME has great potential for its future application in chromatography and other methods of analysis where extraction plays an important role in sample preparation. This technique completely replaces toxic halo-solvents,

and a wide range of water-miscible solvents and inorganic salts are available to suit the extraction, and its automation has been demonstrated [61].

IV. HOLLOW FIBRE LIQUID-PHASE MICROEXTRACTION (HFLPME)

Another approach to extraction on the microlitre scale based on supported liquid membrane (SLM) has been introduced using a porous hollow fibre membrane filled with an acceptor solution in order to improve solvent stability [62,63]. In hollow fibre membrane liquid-phase microextraction (LPME), target analytes are extracted from aqueous samples and into a supported liquid membrane (SLM) sustained in the pores in the wall of a small porous hollow fibre, and further into an acceptor phase present inside the lumen of the hollow fibre. The acceptor phase can be organic, providing a two-phase extraction system compatible with capillary gas chromatography, or the acceptor phase can be aqueous resulting in a three-phase system compatible with high-performance liquid chromatography or capillary electrophoresis. In SLM using hollow fibre membrane, the organic solvent is impregnated and/or contained within the lumen of the porous hollow fibre as an extracting phase into where the analyte is extracted. This LPME is based on the use of single, low-cost, disposable, porous, hollow fibres made of polypropylene. The micro-extract is contained within the lumen of a porous hollow fibre, so the micro-extract is not in direct contact with the sample solution. As a result, samples may be stirred or vibrated vigorously without any loss of the micro-extract. Thus HFLPME is more robust and reliable alternative for LPME. In addition, the equipment needed is very simple and inexpensive [64].

4.1 WORKING OF HFLPME

The experimental set-up can be easily improvised in the laboratory (Fig. 12). In this system the acceptor solution is contained in a piece of porous polypropylene hollow fibre [65]. The fibre is sealed at one end by singeing with flame, and filled from another end with 15-25 μL of the acceptor solution, such as octanol, and was subsequently immersed in an aqueous sample where partitioning of the analytes occurs. Since the extracting solvent is confined in the lumen, the sample solution can be stirred without significant loss of solvent. After extraction, the acceptor solution was retracted from the lumen into the Hamilton syringe and analysed directly by chromatographic techniques.

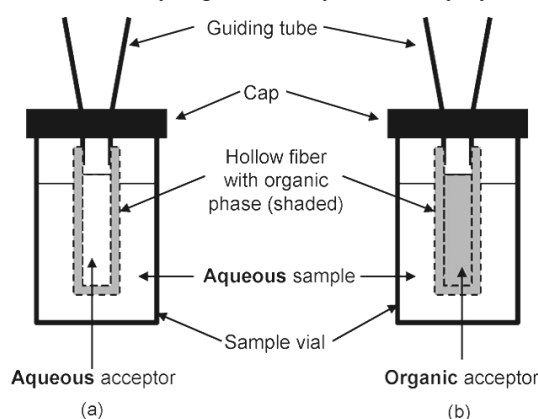


Fig. 12. Typical device for hollow fibre microextraction, (a) three and (b) two phase LPME.

One essential advantage of the hollow fibre technique is the relatively high enrichment factors, which can even be achieved with small sample and solvent volumes. This is attributable to the favourable geometric dimensions of the hollow fibre these includes length of the fibre, inner diameter, which determines the volume of the extracting solvent and other dimensions like the wall thickness, average pore size and percent porosity determines the clean-up and extraction efficiency. Thus high preconcentration factors obviously make hollow fibre extraction especially attractive for water analysis [66]. Due to the high enrichment factor the injection of 1 μL of the extract is usually sufficient to secure the required sensitivity. Large volume injections [67] often entailing the pollution of the liner and capillary column as well as additional optimization efforts are not required. But additionally a large volume (up to 20 μl) of extraction solvent can be used as opposed to only 1–2 μl with the hanging drop. This improves the rate and efficiency of analyte transfer across the membrane [68]. Because hollow fibres are inexpensive, the fibres are not reused to eliminate the potential for carryover. This type of hollow fibres has been used for analysis of several drugs in

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Website: www.ijirset.com

Vol. 6, Issue 8, August 2017

biometrics, and pesticides in water demonstrating good sample clean-up, high preconcentration factors and low detection limits [69-79]. These reports have all used protocols with relatively long extraction times (30-45 min) that limit sample throughput, however, much shorter extraction time (3 min) has also been used.

4.2 OPTIMIZING HFLPME

The internal diameter (ID) of the hollow fibre is typically 600-1200 μm , but fibres with ID of 330 μm have also been used. The former dimensions are appropriate for acceptor-solution volumes of 5-25 μL , and for applications with sample volumes in the range 0.5-4 mL. In designing the technical set-up, it is important to have a large surface area of the fibre in contact with the sample solution and a short diffusion distance to the fibre, in order to govern high extraction speed. Wall thickness of 200 μm seems to be standard among commercial fibres. Values below 200 μm , may result in poor mechanical stability, while values above this, may result in extended extraction times and reduced recoveries because of increases in volume and the thickness of the organic phase.

When selecting a suitable solvent, two factors need to be taken into account. First of all, for enrichment to be effective, the analytes should be well soluble in the solvent used. Another factor is the appropriate viscosity of the solvent applied to avoid diffusion through the porous hollow fibre membrane into the aqueous phase. The organic solvent used within the pores of the hollow fibre has to satisfy certain criteria, such as, it should be immiscible with water to prevent leakage; it should be strongly immobilized in the pores of the hollow fibre to prevent leakage; and it should provide an appropriate extraction selectivity to provide high extraction recoveries. To study solvent suitability pure as well as mixtures of different extracting solvents were studied like *n*-octanol, and *n*-octanol mixed with butyl acetate or dihexyl ether [80] were used as acceptor solution. The application of octanol for the extraction of 11-nor- Δ^9 -tetrahydrocannabinol-9-carboxylic acid [81] and chloroform for the extraction of cocaine and its metabolites [82] has also been described, although in these cases enrichment times of only 10 and 3 min, respectively, were used because of the leakage of the solvent. The sensitivity of this method was reported to be in the $\mu\text{g/L}$ range. To determine the bioactive analytes in this study, several organic solvents such as *n*-octanol, butyl acetate, dihexyl ether, *n*-alkanes (C_8 – C_{11}), xylene, mesitylene and *tert*-butylbenzene were tested for usage with the hollow fibre technique. All the other solvents except *n*-octanol displayed greater leakage, and so only shorter extraction times could be applied. Due to the time dependence of the extraction yields in this case, lower enrichment factors have to be expected.

4.3 ADVANTAGES AND LIMITATIONS OF HFLPME

HFLPME provides high extraction recoveries, high enrichment and excellent sample clean-up with extraction times of 15-45 min. The technique is compatible with a broad range of samples including plasma, whole blood, urine, saliva, breast milk, tap water, surface water, pond water seawater, and soil slurries. In addition, since the method may be operated as a two- or three-phase system or as a system based on active transport, a broad range of analytes may be extracted with the same type of equipment. Other benefits of the hollow fibre technique are its low cost, the possibility of automation, and its simple handling, which requires only a negligible amount of material. Moreover dynamic extraction can also be performed using hollow fibre membrane extraction [83]. Furthermore, the automation facility should be underlined. After extraction, the sample vial can be placed directly into a GC autosampler. Using appropriate injection guides, the technique can be used with all commercial autosampler systems.

4.4 FUTURE ASPECTS OF HFLPME

The investigations reveal the potential of hollow fibre extraction as a simple but nevertheless effective tool in water analysis. Its advantages make automatic hollow fibre enrichment especially suitable for screening analysis. Moreover, given appropriate sample volumes the technique is also a useful tool for trace analyses. Indeed, the usage of *n*-octanol with a boiling point of 178.5°C has consequences for the subsequent GC-MS analysis. To accomplish tailing-free peaks, an initial column temperature of at least 120°C is necessary. Hence only compounds with boiling points above 250°C can be determined reproducibly in this way. Further investigations are required for the use of solvents other than octanol. One way of keeping more suitable solvents in the fibre is probably to immobilize stationary phases within the pores of the hollow fibre. This could also improve selectivity for several classes of substances. A new development involved two-phase hollow fiber-liquid microextraction based on reverse micelle as sensitive and efficient method for the extraction of quercetin in human plasma, onion and tomato samples [84]. The extraction is based on the solubilization of analyte in the aqueous core of the reverse micelle of cetyltrimethyl ammonium bromide, which are

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Website: www.ijirset.com

Vol. 6, Issue 8, August 2017

present in the organic phase and are used as acceptor phase in hollow fiber-liquid phase microextraction. In still another method, the derivatized acrylamide (2,3-dibromopropionamide) was extracted from the aqueous sample into a thin layer of an organic solvent sustained in pores of a porous hollow fiber. Then, it was back-extracted using a small volume of organic acceptor solution located inside the lumen of the hollow fiber [85]. Further investigations regarding the modification of the hollow fibres used are necessary for the utilization of GC common solvents.

V. DISPERSIVE LIQUID-LIQUID MICROEXTRACTION (DLLME)

DLLME is a modified solvent extraction method in which acceptor-to-donor phase ratio is greatly reduced as compared with other methods. Here, an appropriate mixture of extraction and disperser solvents is rapidly injected by syringe into an aqueous sample containing the analytes of interest [86-88]. DLLME employs a mixture of high-density solvent (extraction) and water-miscible, polar solvent (disperser). Acetone, methanol and acetonitrile can be used as dispersers, whereas chlorinated solvents such as chlorobenzene, carbon tetrachloride and tetrachloroethylene are useful as extractants [89-92]. In practice, the extractant solvent represents only 1-3% of the total volume of the extraction mixture so that a cloudy solution forms, resulting from the formation and dispersion of fine droplets of the extraction solvent, and thus a large surface area available for extraction. After centrifugation, the fine droplets of extractant settle at the bottom of the centrifuge tube, and a portion of microextract is used for analysis.

5.1 WORKING OF DLLME

Dispersive LLME is a miniaturized sample pre-treatment technique based on ternary component solvent systems and salting-out phenomenon similar to SALLME. The main difference between these two techniques is that in SALLME, the mixture of solvents first produce a homogeneous solution and then the phase separation is induced by addition of salt, while in DLLME the phase separation is accomplished instantly by adding rapidly the mixture of disperser and extraction solvents into the aqueous solution. The cloudy solution results from the formation of fine droplets of water-immiscible extraction solvent. The cloudy solution is centrifuged and the fine droplets sediment in the tube [86-88]. The determination of analytes in sedimented phase can be performed by a range of analytical methods. By this procedure, any component in the solution, either directly as such [89-93] or after derivatization [94,95], interacts with the fine droplets of extraction solvent.

5.2 OPTIMIZING DLLME

There are a few variables that need optimization before application to real samples [96]. The selection of organic solvent for DLLME plays an important role in the success of microextraction. It should be able to form a cloudy solution in water with the help of dispersion solvent. Also it should be immiscible with aqueous phase (sample solution), and should show high extraction efficiency and selectivity. Chloroform, chlorobenzene and carbon tetrachloride have been employed so far. In batch method, organic solvents are selected on the basis of their higher density over water. This facilitates sedimentation upon centrifugation. The volume of solvent phase need also to be optimized, since higher volume would decrease enrichment factor. The solvent should also have good gas chromatographic properties. Most methods use solvents of density higher than water, and there is always a difficulty in withdrawing an aliquot of microextract for analysis. The problem is pronounced when ionic liquid based solvent is used for extraction [97]. Use of a narrow glass tube has been recommended to assist collection of extract using solvents lighter than water [98].

5.3 ADVANTAGES AND LIMITATIONS OF DLLME

Simplicity, rapidity, low sample volume, low cost, high recovery, high enrichment factor and reduction of laboratory waste are some advantages of DLLME, and the technique has been applied to the determination of trace organic compounds [86-98] and metal ion complexes [99-103]. A variety of analytical techniques such as GC, HPLC, fibre-optic spectrophotometry and atomic absorption spectrometry can be used for the analysis of microextract. Since DLLME does not involve evaporation step, the sample processing time is reduced. The amount of organic solvent(s) used is very small. Since only one operational step is involved, problem of contamination and loss of analytes do not occur, and further since each extraction uses fresh portions of solvent(s), cross-contamination does not take place. Comparative studies between DLLME and conventional liquid extraction demonstrated that the methods exhibit similar

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Website: www.ijirset.com

Vol. 6, Issue 8, August 2017

performance in terms of analyte recovery and precision. However, the detection limits obtained are better in DLLME, and this observation is due to high enrichment factor attained in this technique. Factors that affect the DLLME include selection of a suitable extraction solvent, dispersing solvent, ratio of their volumes, and extraction time. It is important to optimize all these factors in order to obtain good performance in DLLME. Contrary to other methods of extraction such as SPME and SDME, where extraction by both sample solution immersion or placement in the headspace is feasible, the DLLME cannot be used for headspace extraction. Owing to extraction by volatile hydrophobic solvents, DLLME is more suitable for GC. Evaporation of extraction and reconstitution of analytes in polar solvents enables use of HPLC, but during this process there are chances of analytes loss and decomposition, and the whole method becomes lengthy.

5.4 FUTURE ASPECTS OF DLLME

Most of the reported methods using DLLME have aimed to extract analytes from relatively simple matrix, but in future the technique could be tested for complex matrices as well. Broadening of the range of extraction solvents is another area that would increase the efficacy of the method. Application for determination of multi-elements using their pre-complexation, and hyphenation of miniaturized on-line DLLME systems with various detection techniques especially ICP-AES or ICP-MS would be an exciting area of research. Automation of the technique involving either solvent switching [104] or oxidative back-extraction [105] have been reported. An interesting application involved solidification of aqueous phase that assisted the micro-volume of the extract [106].

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Vol. 6, Issue 8, August 2017

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