IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON MICROEXTRACTION TECHNIQUES AND ITS APPLICATIONS

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ABSTRACT: The review will attempt to provide an outline as well as a theoretical and practical grip of the use of microextraction study for drug analysis. Often only a small part of the initial analyte be extracted for analysis. The extraction regulation be set on by the partitioning of analyte between the sample matrix and the extraction phase. The higher the affinity the analyte possess for the extraction phase comparative to the sample matrix, greater the amount of analyte extracted. Microextraction techniques represent an important contribution to the improvement of sample preparation performance. Sample preparation be necessary for set apart desired components from complex matrices and greatly impact their reliable and accurate analysis. The role of sample preparation is to take out interferences and analyte assumption, change the analytes to suitable form for separation and detection. If an inappropriate sample preparation method has been working before the injection, the entire analytical process may be wasted. Because of low concentration levels of drug in plasma and the variety of the metabolites, the hand-pick extraction technique should be practically exhaustive. Solid-phase microextraction (SPME) is a current and essential sample preparation technique. Fibers and capillary tubes coated with an appropriate stationary phase are usually used for SPME, but alternative microextraction techniques are also used.

Keywords: Microextraction, Analyte, Efficiency, stationary phase, SPME, Affinity, Partitioning.

INTRODUCTION:

Microextraction is defined as an extraction technique where the volume of the extraction phase is very small in relation to the volume of the sample, and extraction of analytes is not exhaustive. In maximum cases only a small fragment of the initial analyte be extracted for study. The extraction efficiency be set on by the separate of analyte between the sample matrix and the extraction phase. The higher the affinity the analyte has for the extraction phase relative to the sample matrix, the greater the amount of analyte extracted [1] . Thus while the goal of microextraction is to extract based on equilibrium partitioning i.e. the goal is to extract as near as possible to 100% of the analytes from a sample [2].

Microextraction techniques represent an important contribution to the improvement of sample preparation performance, which especially addresses the issues of miniaturization, automation, onsite analysis, and time efficiency. Actually, different types of microextraction techniques were reported in literature a long time ago [3,4], but the field gained in significance with the invention of solid -phase microextraction (SPME) in 1990 [5], which later became commercially available.

During recent years, SPME has gained substantially in popularity, and from this point, several alternative approaches have been introduced, such as in-tube SPME designed primarily for high-performance liquid chromatography (HPLC) [6]. In parallel to the development of SPME, attention has also been directed to the utility of small volumes of liquids for analytical extractions, namely liquid-phase microextraction (LPME). This field was basically initiated in 1996 when the use of small droplets of organic solvents suspended from the tip of a micro-syringe was described for the first time HPLC [7,8], and this approach was subsequently refined by implementing the use of porous hollow fibers for protection of the extracting liquids [9].

Types of microextraction techniques [10]

1. Solid phase extraction (SPE)
2. Solid phase microextraction (SPME)
3. Liquid phase microextraction (LPME)
4. Molecularly imprinted polymers (MIP_S)
5. Turbulent flow chromatography (TFC)

1.*SOLID PHASE EXTRACTION*

Solid phase extraction (SPE) is an extraction procedure that utilize a solid phase and a liquid phase to segregate one, or one type, of analyte from a mixture. It is usually used to clean up a sample before using a chromatographic or other analytical method to quantify the amount of analytes in the sample [11].

Principles of solid-phase extraction [12]

1.Conditioning

Before extraction of analytes can start, the sorbent bed must be develop so that it will make cherished and effective surface communication with the liquid sample solution. Most commonly, process is achieve by passing a small volume of methanol or acetonitrile through the SPE ancestry tube. A few of this organic solvent is adsorbed on the surface of the sorbent fragments, making the surface further hydrophilic and thus more appropriate with a primarily aqueous sample solution. Without such therapy the surface of numerous common sorbents is hydrophobic and is badly wetted by the hydrophilic sample solution.

2.Adsorption

The liquid sample is passed through the packed SPE device with the aid of a gentle vacuum applied pressure or a pump. The flow rate should be reasonably constant. The flow rate and sorbent bed dimensions do depend on the particle size of the solid extractant.

3.Washing

The most common type of SPE is where organic analytes are extracted from an aqueous sample. The purpose of the washing step is to remove salts and other non-extracted material as completely as possible without eluting any of the appropriate wash solution, but some solutes may be partly keep retained by the SPE column and only slowly washed off by water alone. In such cases water containing 10-20% of organic solvent might be a better wash liquid. Of course, the wash solution must not carry a percentage of organic solvent high enough to wash out the sample analytes.

4.Elution

In the elution step the adsorbed analytes are eliminated from the solid extractant and are returned to a liquid phase that is fit for analytical estimation. Most commonly, the eluting phase is an organic liquid, while it is frequently possible to thermally remove analytes with the aid of a gas stream. It is normally better to choose an eluting solvent that is compatible with water, otherwise the effluent may carry two liquid phases. It is common practice to remove as much of the water is possible from the column just before the elution step. This can be accomplished by applying gentle vacuum for a few minutes or b passing compressed air or nitrogen through the column. Sometimes centrifugation is used to eliminate liquid from the column.

5.Normal phase

Normal phase SPE procedures typically involve a polar analyte, a mid- to nonpolar matrix phase. Recall of an analyte undergoing normal phase conditions be primarily because of interactions between polar functional groups of the analyte and polar groups on the sorbent surface.

6.Ion exchange

Electrostatic appeal of charged group on compound to a charged group on the sorbent's plane.

Mechanism of solid phase extraction process [13]

The most common procedures in SPE are based on van der Waals forces ("non-polar interactions"), hydrogen bonding, dipole-dipole forces ("polar" interactions) and cation-anion interactions ("ionic interactions).

Reversed phase involves a polar or rather polar sample matrix and a nonpolar immobilized phase. The analyte of attentiveness is often mid- to nonpolar. Retention of organic analytes from polar solutions onto these SPE materials is due firstly to the attractive forces between the carbon-hydrogen bonds during the analyte and functional groups on the sorbent surface. These nonpolar – nonpolar attractive forces exist commonly called van der Waals forces or dispersion forces. The nonpolar solvent, which can disturb the forces between the sorbent and compound, used to elute an adsorbed compound from a reversed phase SPE tube or disk.

A compound adsorbed by these mechanisms is eluted by passing a solvent that disrupts the binding mechanism, a solvent that is more polar than the sample's matrix.

Solid phase extraction process [14]

Step 1: Select the official SPE tube or Disk

- ✓ **Selecting SPE tube size**
  Criterion for the selection of SPE tube size is mentioned in table no.1
- ✓ **Selecting SPE disk size**
  Criterion for the selection of SPE disk size is mentioned in table no.2
- ✓ **Selecting an SPE tube: Bed weight Reversed phase, normal phase, and adsorption-type procedures**

The mass of the compounds to be extracted should not be more than 5% of the mass of the packing in the tube. In other words, if you are using a 100mg/1ml SPE tube, do not load more than 5mg of analytes.

Step 2: Condition the SPE tube or Disk

To state the SPE tube stuff, wash out with up to one tube-full of solvent before extracting the sample. For disks, use a volume of 5-10 ml.

Step 3: Add the sample

Precisely turn over the sample to the tube or reservoir, utilizing a volumetric pipette or micropipette. The trail must be in a form that is suitable with SPE.

Step 4: Wash the packing

If compounds are interest are retained on the packing, wash off unwanted, un-retained materials using the same solution in which the sample was dissolved, or another solution that will not remove the desired compounds. Usually no more than a tube volume of wash solution is needed, or 5-10ml for SPE disks.

Step 5: Elute the compounds of interest

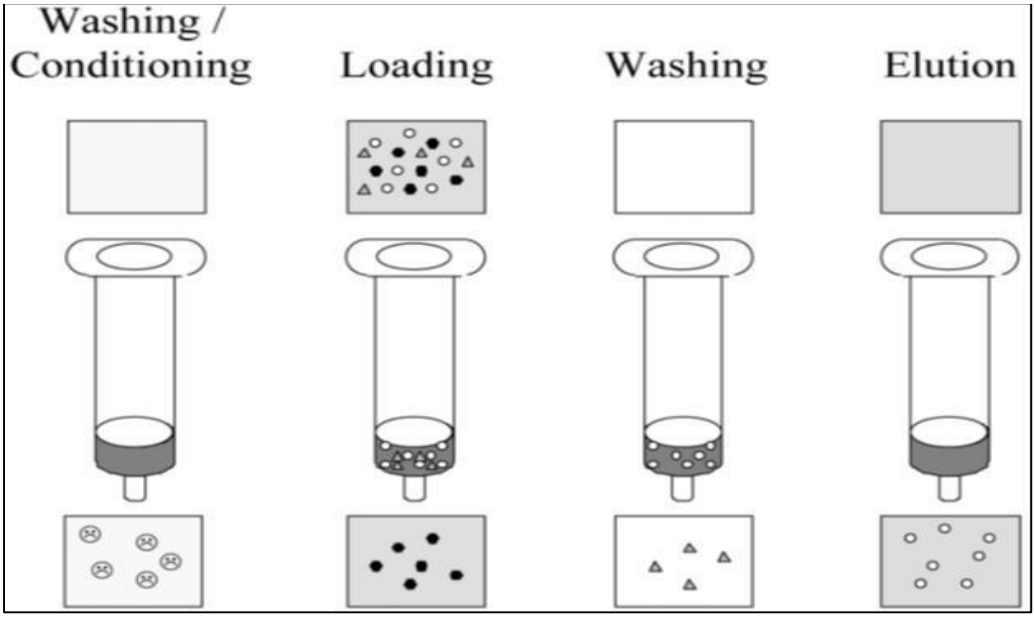
Rinse the packing with a small volume of a solution that removes compounds of interest, but leaves behind any impurities not removed in the wash step. Collect the eluate and further prepare as appropriate.

Table 1: Selecting SPE tube size

If your sample is	Use tube size
< 1ml	1ml
1ml to 250ml and the extraction speed is not critical	3ml
1ml to 250ml and a fast extraction procedure is required	6ml
10ml to 250ml and higher sample capacity is needed	12, 20, or 60ml
< 1 liter and extraction speed is not critical	12, 20, or 60ml

Table 2: Selecting SPE disk size

If your sample is	Use Disk size
100ml to 1 liter	47mm
>1 liter and higher sample capacity is needed	90mm



Steps of solid phase extraction process

Applications of SPE

- **Biological fluids**
  The compatibility of SPE coupled with HPLC has been reflected in growing popularity of SPE-HPLC on-line. A number of papers in the area of SPE-HPLC document that is a well established technique.
  e.g. determination of methylated arsenic species in human urine.
- **Waters**
  An interesting example of a simple combination of sample trapping with a non-separation analytical technique was presented by Ackerman et al. when they determined polycyclic aromatic hydro-carbons (PAH_S) isolated from water using SPE combined with a direct in-situ measurement by fluorescence. Various pollutants were determined in aqueous samples after SPE OR SPME.
- **Food, beverages and agricultural**
  The use of SPE in the determination of various chemicals in food has increased rapidly in the last decade and SPE methods have replaced many of the traditional methods of sample pretreatment. As an example, the bulk of lipid content of fats and oil in foods has complicated the analysis of pesticide residues as well as other chemical contaminants. The recent examples for food analysis for volatile flavor compounds show ongoing use of SPE-GC methods but especially an increase in the use of SPME-GC.
  Examples of the first type of analysis include trace-level determination of polar flavor compounds in butter by SPE with polymeric sorbent.
- **Air and gas**
  The analysis of air and gaseous samples can be subdivided into analysis of volatile compounds (VOCs) and of particulate matter (PM). The method classical SPE followed by GC analysis. The examples include the analysis of volatile hydro-carbons, volatile organic sulfur compounds.

2.SOLID PHASE MICROEXTRACTION (SPME) [21]

Microextraction techniques have been regarded as the most attractive for the pretreatment of complex sample matrices prior to chromatography and capillary electrophoretic processes because they enable rapid analysis at low operating costs and with no environmental pollution.

SPME is the most widely used technique. In tube SPME was developed primarily to extend SPME to high-through put applications and automated instrumentation. SBSE was developed to increase the sensitivity of SPME. Various new affinity SMPE sorbents, including immune sorbents and MIPs, have been used for the specific

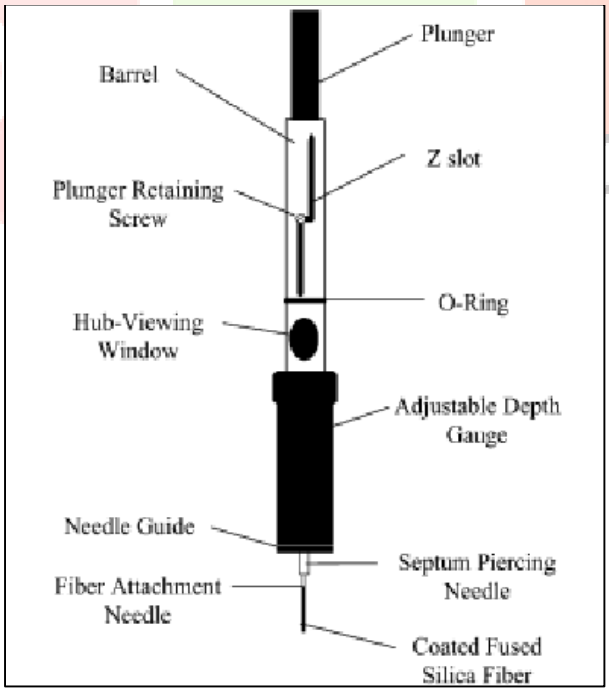
preparation of samples and are also described in this section. Other new microextraction techniques, such as liquid-liquid microextraction (liquid-phase[15] or single-drop[16] microextraction), solvent bar microextraction[17] and liquid membrane microextraction,[18] are not reviewed here, since they have been recently reviewed[19].

Another microextraction related technique is stir-bar sorptive extraction (SBSE) which is an extraction technique for enrichment of volatile and semi volatile organic compounds having high extraction efficiency compared to SPME but has longer extraction time. The technique has been applied effectively in environmental analysis mainly with gas chromatography-mass spectrometry (GC-MS). In addition, the SBSE technique was applied to some drugs in biological samples in combination with GC-MS [20].

Design of SPME device

SPME is a modified syringe-like instrument, having a small size and cylindrical shape, is connected to stainless-steel tubing that is used to provide additional mechanical strength to the fiber assembly for repeated sampling. This stainless-steel tubing is connected to a specially designed syringe-like instrument. The fused silica fiber is varnish with a comparatively thin film of several polymeric stationary phases.

The fiber gathering is reusable and replaceable. Small size and cylindrical geometry of fiber has some advantages such as uncomplicated placement of the sorbent fiber coating inside of a sample or headspace exceeding the sample to extract the analytes; also It can be easily placed in desorption camber of GC or interphase of the HPLC without any modification of GC or HPLC. Plunger movement and timing must be controlled carefully. It is extremely major for field sampling to avert loss of analyte throughout transport. To do this, the needle opening of SPME device.



SPME device

Working with SPME device

In the SPME mission, the fiber is earliest drawn within the syringe needle, then lowered into the vial by pressing the plunger. The fused silica fiber of suitable coating is pre-owned which is dependent upon the sort of analyte. Now the cleaned fiber coating is exposed to a sample matrix for a predetermined, fixed period, which results in

the adsorption of the analyte on the fiber coating. This extraction can be performed in two ways: 1) headspace SPME or HS-SPME where fiber is exposed in the vapor phase above a gaseous, liquid, or solid sample: 2) direct immersion DI-SPME, where the fiber is directly absorb in liquid samples.

Applications of SPME in various fields

- **Environmental applications**
  In the earlier developmental period the majority of applications were in environmental chemistry. Mostly organic compounds have been studied, and pesticides, herbicides and other biologically active compounds in aqueous samples [22].
- **Applications in food chemistry**
  Food analysis is main for the assessment of nutritional value, for quality control of fresh and fixed products and the monitoring of food additives and other poisonous contaminants. In general, flavor is delicate to compositional variations in the case of food (fruit, wine, etc.) [23].
- **Applications to biological fluids**
  Sample preparation is one of the most interpretative steps in the analysis of biological fluids and compounds in biological matrices [24].

Advantages of solid-phase microextraction

The main advantage of SPME is
Simplicity, rapidity, solvent elimination.

1. High sensitivity
2. Small sample volume
3. Low cost.

3.LIQUID PHASE MICROEXTRACTION (LPME)

Sample preparation can comprise cleanup policy for very dirty samples. This stair must also bring effective analytes to a satisfactory concentration level. LPME is a solvent-minimized sample pretreatment procedure of LLE, in which only several IL it of solvent are required to concentrate analytes from various samples rather than hundreds of ml needed in traditional LLE. It is compatible with capillary gas chromatography (GC), capillary electrophoresis (CE) and HPLC. In LPME, extraction normally takes place into a little quantity of a water-immiscible solvent (acceptor phase) from an aqueous sample containing analytes (donor phase).

Advantages

- It is rapid, simple, solvent free and sensitive method for the extraction of analytes;
- It is a simple, effective adsorption/desorption technique;
- It is compatible with analyte separation and detection by high-performance liquid chromatography with ultra violet detection (HPLC-UV);

Disadvantages

- Fiber breakage;
- Stripping of coatings;
- The bending of needles and their expense.

Types of liquid phase microextraction

It can be divided into three main categories

- Single-drop microextraction (SDME)
- Dispersive liquid-liquid microextraction (DLLME)
- Hollow-fiber microextraction (HF-LPME).

1. **Single-drop microextraction (SDME)**

SDME is the simplest mode of LPME, in which the extraction medium is a micro drop organic solvent at the tip of a micro syringe needle. After the extraction process, the organic drop is aspirated into the syringe and transferred for further analysis. SDME has been applied as a sample preparation technique to obtain acceptable analytical data. In addition, this technique has been shown to be applicable to real samples. However, SDME has also different limitations comprise the limited drop surface, instability of the micro drop, and consequently limitation of agitation slow kinetics. SDME can be done in the headspace (HS-SDME) or direct (DI-SDME) sampling modes.

SDME, usually typically 1-3 IL of an organic solvent at the tip of a micro syringe, has evolved from LPME.

In practice, two main approaches can be used to perform SDME;

a) Direct immersion (DI)-SDME

b) headspace (HS)-SDME

a) Direct immersion (DI)-SDME

In DI-SDME, a drop of a water-immiscible solvent is suspended directly from the tip of a micro syringe needle immersed in the aqueous sample.

b) Headspace (HD) -SDME

In HD-SDME, a drop of appropriate solvent is placed in the headspace of the sample solution or in a flowing air sample stream to extract volatile analytes.

Advantage

- A wide variety of solvents to choose from.

Disadvantage

- Removal and injection performed separately, using different apparatus.

2.Dispersive liquid-liquid microextraction (DLLME)

Dispersive liquid-liquid microextraction (DLLME) is another sample preparation technique derived from LPME, in which small volumes (µL) of an extraction solvent is used. DLLME is a powerful preparation technique based on the use of a ternary solvent system [25]. The extraction solvent is dispersed in the aqueous sample by getting help from the disperser and consequently forms micro droplets of the extractant, inside the aqueous sample, which enables a very fast extraction process. The enriched analytes can be analyzed by GC, due to the use of water-immiscible solvents in DLLME.

Advantages

- Simplicity of operation
- Rapidity
- Low cost
- High recovery
- High enrichment factor

- Very short extraction time (a few seconds).

3.Hollow-fiber microextraction (HF-LPME)

They used the basic principle of supported liquid membrane (SLM), for the first time, in simple, inexpensive, disposable extraction units for the liquid-liquid microextraction (LLLME) utilizing polypropylene HFs as the membrane.

The sample vial is filled with the aqueous sample. A short piece of a porous HF may be either a rod with a closed bottom or a u-shape where both ends are connected to guiding tubes. Prior to extraction, the HF is first dipped in the organic solvent for a few times to immobilize solvent in the pores, and excess solvent is removed. The solvent is immiscible with water to ensure that it remains within the pores during the extraction with no leakage to the aqueous sample.

This acceptor solution can be an organic solvent resulting in a two-phase extraction system, or the acceptor solution may be an acidic or alkaline aqueous solution, resulting in a three-phase extraction system.

Applications

- All LPME techniques can be utilized effectively for extraction of target analytes from various sample solutions.

4.MOLECULARLY IMPRINTED POLYMERS (MIPS)

Molecularly imprinted polymers (MIPs) are polymers prepared in presence of a template that serves as a mould for the formation of template complementary binding sites. Thus, MIP$_s$ can be programmed to recognize a large variety of target structures with antibody-like affinities MIP is based on the formation of a complex between an analyte and a functional monomer. In the presence of a large excess of a cross-linking agent, a three-dimensional polymer network is formed.

Applications of MIPS

- Their use as tailor-made separation materials.
- Their use in organic synthesis and enzyme technology as catalytically active polymers or enzyme mimics.
- As sensors in biosensor-like configurations.

5.TURBULENT FLOW CHROMATOGRAPHY (TFC)

Turbulent flow chromatography (TFC) is a technique that combines high-through put and high reproducibility by means of separating analytes from various matrices with reduced sample handling. The sample can be injected directly onto a narrow diameter column (0.5 or 1.0 mm) packed with large particles (30-60 m) at a high flow rate (higher than 1 ml min-1) helping creating a very high linear velocity inside the turbulent flow column. Under turbulent flow circumstances the improved mass move across the bulk mobile phase permit for all molecules to develop their radial distribution, however, under these state a laminar zone around the stationary phase particles still exists, where diffusional forces still dominate the mass transfer process [26]. It is extremely important to effectively avoid interferences from the matrix on the analysis of a contaminant.

Principal of TFC

Turbo flow methods are based on the direct injection of biological samples without previous extraction or treatment a column packed with large particles. Since 100% aqueous mobile buffers are used, the small analyte molecules are retained via diffusion into the particle pores, while the proteinaceous material is washed to waste. As the analytes are released from the turbo flow column they are transferred with the pumping solvent through the tee rotor -seal in the second valve and mixed with the pumping solvent from the analytical system.

Applications of TFC

- in food and environmental analysis.
- A solution that has gained wide use, particularly in the clinical field, to increase through put on such systems [27].

Microextraction techniques for forensic drug analysis in saliva

It involves qualitative and quantitative analysis of drugs of abuse and their metabolites in various complex biological matrices such as biological fluids and seized materials. Drugs of abuse such as opioids, cannabinoids, cocaine, amphetamines, hallucinogens and benzodiazepines are generally analyzed in biological fluids e.g. urine and plasma. While urine is efficient for investigation of metabolites, plasma reflects total concentration of drug [28].

Microextraction techniques {MTs} are basically miniaturized forms of extraction techniques where zero or microliters of extraction solvent and small amount of sample is used for extraction of target analytes.

Appeal of MTs for examination of drugs as to Abuse in Saliva Samples

- **Analysis of amphetamines**

  Amphetamines [AMP] are strong central nervous system stimulants. Amphetamine and methamphetamine [MAMP] are two prominent drugs of this class. Various substitutions in the structures of these two drugs have been made in order to limit their side effects and to maintain anorexic activity [29].

  The method was found to be sensitive enough and offered limit of detections of 5 and 0.5 ng/ml for AMP and MAMP, respectively [30].

Drugs of abuse	MTs	Detection technique	LOD
AMP & MAMP	DI-SPME	GC-MS	5 and 0.5 ng/ml
MDA, MDMA, MDEA & MBDB	HS-SPME	GC-MS	3.14, 1.19, 1.17& 1.92ng/mg
AMP, MAMP, MDA & MDMA	SVLE	GC-MS	1, 5, 2& 3ng/ml
AMP, MAMP, MDA, MDMA, MDEA	MEPS	LC-MS/MS	1,1,1,0.5,0.5 ng/ml
Δ9-THC, Δ8THC, CBD, CBN	DI-SPME	IT-GC-MS	1 ng/ml
THC, CBD, CBN	SPME	GC-MS	-
Δ9-THC	PMME	GC-MS	0.68ng/ml
THC	DI-SPME	GC-MS	3 ng/ml
Cocaine, EME, AEME	HFMSME	GC	11,12,28&6 ng/ml
Cocaine and Coca ethylene	DI-SPME	GC-MS	20& 5 ng/ml
Cocaine	HS-SPME	GC-MS	5 ng/ml
Cocaine, BZE, NCOC, and EME	MEPS	LC-MS/MS	0.3, 0.8, 0.5, & 1 ng/ml
Methadone and EDDP	DI-SPME	GC-MS	0.004, and 0.008µg/ml
Methadone	DLLME	HPLC-UV	25.12 ng/ml
Methadone, EDDP, BUP, NBUP	MEPS	LC-MS/MS	0.2,0.3,2&2 ng/ml
Morphine, and codeine	MEPS	LC-MS/MS	2,2& 0.8 ng/ml
6-MAM			
PCP, MES& psilocybin	µ-SPE	LC-MS/MS	0.1, 0.07& 1.2 ng/ml
MES& PCP	MEPS	LC-MS/MS	2& 0.2 ng/ml

AMP: Amphetamine; MAMP: Methamphetamine; MDA: Methylenedioxyamphetamine; MDMA: methylenedioxymethamphetamine; MDEA: methylenedioxymethamphetamine; MBDB:n-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine;DI-SPME:Directimmersion Solid-phase Microextraction; GC-MS: gas Chromatography-mass Spectrometry; HS-SPME: Head Space Solid-phase Microextraction; SVLE: Small Volume Microextraction; MEPS: Microextraction by packed sorbent; THC: Tetrahydrocannabinol; CBD: Cannabidiol; CBN: cannabinol; LC-MS/MS: liquid chromatography-tandem Mass spectrometry; IT-GC-MS: Ion trap GC-MS; EME: Ecgonine Methyl Ester; AEME: anhydroecgonine methyl ester HFMSME: Hollo Fiber

Membrane Solvent Microextraction; BZE: Benzyl ecgonine; NCOC: Norcocaine; EDDP: 2-ethylidine-3,3-diphenylpyrrolidine; HPLC-UV: High Performance Liquid Chromatography Ultraviolet Detection; BUP: Buprenorphine; NBUP: Norbuprenorphine; 6-MAM: 6-monoacetylmorphine; PCP: Phencyclidine; MES: Mescaline; µ-SPE: Micro Solid-Phase Extraction.

FUTURE TRENDS

Sample preparation in analytical toxicology is one of the most time consuming, tedious and error prone tasks. Traditional sample preparation techniques such as LLE and SPE are now being replaced with modern MTs owing to their simplicity, environment friendliness, rapidity, cost-effectiveness, extraction efficiencies, and sensitivity. Saliva has emerged as an alternative specimen for forensic drug analysis. Various MTs Such as SPME, MEPS, HFMSME, DLLME and µ-SPE have been applied for simultaneous determination of drugs of abuse in saliva samples. These MTs have also been coupled with various analytical instruments such as GC-MS, LC-MS/MS and HPLC.

Additionally, MTs may also be applied for analysis of other classes of drugs of abuse such as benzodiazepines, barbiturate and anti-depressants.

CONCLUSION

Solid phase extraction is a widely used sample preparation technique for isolation, concentration, clean-up and medium exchange. SPME is a system for extraction of organic compounds from gaseous, aqueous and solid matrices. All LPME methods can be utilized successfully for extraction of choose analytes from numerous sample solutions. Imprinted polymers are now well established as materials for molecular recognition, chromatographic separation, and analytical sample enrichment but their use as active biomedical devices is still in the early stages of development.

REFERENCES

1. ArthurCL, Pawliszyn J. Solid phase microextraction with thermal desorption using fused silica optical fibers. Anal. Chem. 1990; 62:2145.

2. Louch D, Motlagh S, Pawliszyn J. Anal. Chem. 1992; 64:1187.

3. Murray DAJ. Rapid microextraction procedure for analyses of trace amounts of organic compounds in water by gas chromatography and comparisons with microextraction methods. J. Chrom.1979;177:135– 140.

4. Thielen DR, Olsen G, Davis A, Bajor E, Stefanovski J, Chodkowski J. An evaluation of microextraction/capillary column gas chromatography for monitoring industrial outfalls. J. Chromatogr.Sci.1987;25:12–16.

5. Arthur CL, Pawliszyn J. Solid phase microextraction with thermal desorption using fused silica optical fibers. Anal. Chem. 1990; 62:2145–48.

6. Eisert R, Pawliszyn J. Automated in tube solid phase microextraction coupled to high performance liquid chromatography. Anal. Chem. 1997;69:3140- 47.

7. Liu H, Dasgupta PK. Analytical chemistry in a drop. Solvent extraction in a micro drop. Anal. Chem. 1996;68;1817-21.

8. Jeannot MA, Cantwell FF. Solvent microextraction into a single drop. Anal Chem. 1990;68;2236–40.

9. Pedersen-Bjergaard S, Rasmussen KE. Liquid-liquid microextraction for sample preparation of biological fluids prior to capillary electrophoresis. Anal.Chem.1999;71;2650–56.

10. Istvan B, Kiado B, Kezirat L. Modern analytical techniques in the pharmaceutical & bioanalysis.2011;3126-31.

11. Zwir-Ferenc A, Biziuk M. Solid Phase Extraction Technique – Trends, Opportunities and Applications. Polish J. of Environ. Stud.2006;15:677.

12. Urbe I, Ruana J. J. Chromatogr. 1998; 778:337.

13. Supelco Bulletin Guide to Solid Phase Extraction, Sigma-Aldrich Co 910;1998.

14. Sabikh, Jeannot R., Rondeaub. Multiresidue methods using solid phase extraction techniques for monitoring priority pesticides, including triazines and degradation products, in ground water. J. Chromatogr.2000;885:217.

15. Rasmussen KE, Bjergaard SP, Krogh M, Ugland HG, Gronhaug T.J. Chromatogr.2000;873:3.

16. Psillakis E, Kalogerakis N. Trends Anal. Chem. 2002; 21:53.

17. Jiang X, Lee HK. Anal. Chem.2004; 76:5591.

18. Jonsson OB, Nordlof U, Nilsson UL. Anal. Chem.2003;75;3174.

19. Kataoka H, Lord HL. In sampling and Sample Preparation for Field and Laboratory; Pawliszyn, J. Ed Elsevier 2002: 779.

20. E. Baltussen, F. David, H. Janssen, P. Sandra, and C. Cramers, "Stir bar sorptive extraction (SBSE), a novel extraction technique for aqueous samples: theory and principles," *Journal of Microcolumn Separations*, vol. 11, no. 10, pp. 737–747, 1999.

21. Kataoka H, Lord HL, Pawliszyn J. Application of solid phase microextraction in food analysis. J. of Chromatography2000;880:35–62.

22.Sarrion MN, Santos FJ, Galceran MT. J. Chromatogr.1999;839:159.

23. Vas G, Lorincz G. Acta Aliment.1999;28:95.

24. Imaizumi M, Saito Y, Hayashida M, Takeichi T, Wada H, Jinno K. J. Pharm. Biomed. Anal.2003 ;30:1801. ull.

25. Rezaee M, Assadi Y, Milani Hosseini MR, Aghaee E, Ahmadi F, Berijani S. Determination of organic compounds in water using dispersive liquid-liquid microextraction. J chromatogram. A. 2006; 1116:1-9.

26. Michopoulos F, Edge AM, Theodoridis G, Wilson ID. J. Sep. Sci.2010;33:1472.

27. 90. Berube M. Application note: 458, Thermo Scientific(www.thermo.com/appnotes).

28. Elmongly H, Rehin MA (2016) Saliva as an alternative specimen to plasma for drug bioanalysis: A review. Trends in Analytical Chemistry 83:70-79.

29. Cody JT (2005) Amphetamines: methods of forensic analysis. Handbook of Forensic Drug Analysis, Elsevier Academic Press, USA.

30.Yonamine M, Tawil N, Moreau RLDM, Silva OA (2003) Solid-phase micro-extraction-gas chromatography-mass spectrometry and headspace-gas chromatography of tetrahydrocannabinol, amphetamine, methamphetamine, cocaine and ethanol in saliva samples. J Chromatogr B Analyt Technol Biomed Life Sci 780(1):183-192.