An overview of the main foodstuff sample preparation technologies for tetracycline residue determination

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ABSTRACT

Tetracyclines are widely used for both the treatment and prevention of diseases in animals as well as for the promotion of rapid animal growth and weight gain. This practice may result in trace amounts of these drugs in products of animal origin, such as milk and eggs, posing serious risks to human health. The presence of tetracycline residues in foods can lead to the transmission of antibiotic-resistant pathogenic bacteria through the food chain. In order to ensure food safety and avoid exposure to these substances, national and international regulatory agencies have established tolerance levels for authorized veterinary drugs, including tetracycline antimicrobials. In view of that, numerous sensitive and specific methods have been developed for the quantification of these compounds in different food matrices. One will note, however, that the determination of trace residues in foods such as milk and eggs often requires extensive sample extraction and preparation prior to conducting instrumental analysis. Sample pretreatment is usually the most complicated step in the analytical process and covers both cleaning and pre-concentration. Optimal sample preparation can reduce analysis time and sources of error, enhance sensitivity, apart from enabling unequivocal identification, confirmation and quantification of target analytes. The development and implementation of more environmentally friendly analytical procedures, which involve the use of less hazardous solvents and smaller sample sizes compared to traditional methods, is a rapidly increasing trend in analytical chemistry. This review seeks to provide an updated overview of the main trends in sample preparation for the determination of tetracycline residues in foodstuffs. The applicability of several extraction and clean-up techniques employed in the analysis of foodstuffs, especially milk and egg samples, is also thoroughly discussed.

1. Introduction

Tetracyclines (TCs) are a natural or semisynthetic group of antibiotics that exhibits antimicrobial activity against a wide range of gram-positive and gram-negative bacteria [1,2]. These antibiotics have been widely employed in human medicine for the treatment of infectious diseases [3]. The substances possess very similar chemical structures derived from a common core hydronaphtacene containing four fused

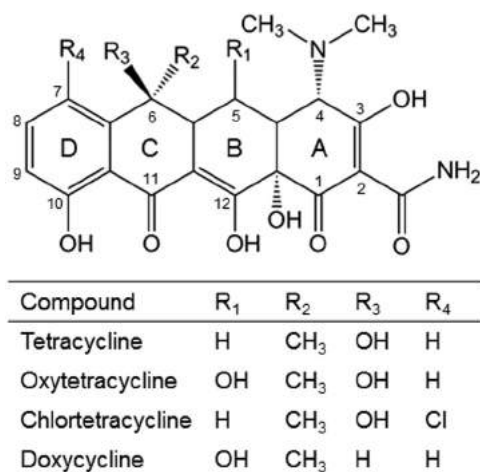| Compound	R_1	R_2	R_3	R_4
Tetracycline	H	CH_3	OH	H
Oxytetracycline	OH	CH_3	OH	H
Chlortetracycline	H	CH_3	OH	Cl
Doxycycline	OH	CH_3	H	H

Fig. 1. Chemical structure of the most commonly used tetracyclines.

rings. The common chemical structure of tetracyclines has three functional groups that influence the permeability of the molecule across biological membranes, thereby leading to the absorption of the tetracycline molecule by bacterial cells [4].

Tetracyclines are strong chelating agents, with the primary site of chelation being the 11, 12 B diketone system (Fig. 1). Chelation of a divalent metal ion to tetracyclines is essential for the antimicrobial activity of the antibiotic; such coordination is regarded very promising in the search for new compounds capable of reversing bacterial resistance [4,5]. The coordination of platinum with tetracycline and doxycycline via A ring yields compounds that are active against bacterial strains resistant to tetracycline and other antibiotics. By virtue of that, coordination compounds containing tetracyclines may be used in the future in clinical medicine for the treatment of cancer and other infectious diseases [5].

Due to their broad spectrum activity and low cost, tetracyclines are widely administered in food-producing animal husbandry for preventive and curative purposes [2,6]. These drugs are also employed as additives in animal feed aiming at promoting rapid animal growth and weight gain [1,7,8]. The rampant application of the drugs is currently regarded a serious problem for public health systems worldwide; this is largely because the widespread use of these substances induces an increase in infections caused by strains resistant to antimicrobial agents. In this sense, conditions hazardous to human and animal health are attributed to such practice, since most conventional treatments are rendered ineffective for antimicrobial clinical care [7,8]. Currently, there are eight marketed tetracyclines, with four of them being most commonly used in the veterinary prescription of antimicrobials [9]: tetracycline (TC), oxytetracycline (OTC), chlortetracycline (CTC) and doxycycline (DC) (Table 1).

Over the years, the indiscriminate use of tetracycline drugs in animal feed has raised huge concerns regarding the quality of food, including honey, meat, fish, milk and eggs, available to consumers [4,10,11]. The contamination of these types of foods with tetracycline residues poses risk to human health, having the potential of causing harmful effects on the population. Such deleterious consequences may range from possible allergic reactions, liver damage, teeth yellowing to gastrointestinal disturbances, among others. Another negative effect is that the consumption of foods contaminated with tetracycline residues is likely to induce the increase of pathogens resistant to antimicrobial agents [2].

The relationship between the use of antimicrobials in animal husbandry and antimicrobial resistance in humans has become a matter of great concern to public health. The reason being that the indiscriminate treatment of animals with veterinary antibiotics can turn their derived food products into sources for resistance to antibiotics in human species

[8,12]. The discovery of new resistant strains of bacteria and other microorganisms that are becoming increasingly resistant over time has led to an increasing pressure on laboratories responsible for food safety. The laboratories are expected to monitor the use of veterinary pharmaceuticals and ensure food quality for human consumption [2,4].

1.1. Regulatory authorities

An important area in the food sector is the management of food and nutrition safety. The role of the professionals in this area is to ensure access to quality basic food, in sufficient quantity, permanently and without compromising access to other essential needs based on healthy eating practices. Clearly, the relevance of the role played by the professionals in this area needs not be overemphasized. Their activities contribute to a dignified existence, in a comprehensive development context, of human beings [13,14]. Essentially, foodstuffs are required to be free from any form of contamination in order to ensure human safety.

To protect human health from the adverse effects of potentially dangerous antibiotics, several regulatory authorities have established tolerance levels or maximum residue limits (MRLs) for substances used as veterinary drugs in food-producing animals. MRLs have been defined by the European Community as the maximum concentration of residue of a veterinary product present in foodstuffs of animal origin, which may be ingested daily without posing any toxicological hazard to human health. In other words, MRLs are levels of a drug accepted by the community to be legally permitted or recognized as acceptable in food, and are expressed in $mg\,kg^{-1}$ or $\mu g\,kg^{-1}$ [11,12].

The Codex Alimentarius is a worldwide reference for consumers, food producers and processors, national food control agencies and other stakeholders in international food trade. The Codex Alimentarius food standards are internationally acknowledged as the best-established measures suitable for the protection of consumer health in addition to promoting fair practices in the food industry. Consumers can rely on the safety and quality of the food products they acquire while importers can rest assured that the food they order will meet their specifications [15,16].

Table 2 lists the MRLs established by Codex Alimentarius [17], European Union (EU) [18], Canada [19], People's Republic of China [20] and Brazil [21] with specific regulations for tetracycline (TC), oxytetracycline (OTC), and chlortetracycline (CTC) in some animal-derived food. In Brazil, tetracyclines are legally regulated in accordance with the National Plan for the Control of Residues and Contaminants (Plano Nacional de Controle de Resíduos e Contaminantes, PNCRC) [21]. These tolerance limits have been adopted for both individual tetracyclines and their combinations. For instance, in the case of bovine milk, the Brazilian regulation (PNCRC) [21] also includes doxycycline (DC) within the combination of these residues. When it comes to eggs, the European Union [18] and China [20] have relatively stricter regulations, with a tolerance limit of $200\,\mu g\,kg^{-1}$ for this class of compounds. Milk and eggs exhibit lower MRLs, as such, their quality control is, undoubtedly, of extreme importance.

The presence of tetracycline residues in animal-derived foods at levels above the legally tolerable limit indicates failure of compliance with good veterinary practices. This lack of compliance with established regulations renders the products unqualified and improper for human consumption. For these reasons, there is an unquestionable need for the stakeholders involved to set out effective and adequate means of monitoring and determining traces of these antibiotics in the most varied foodstuffs to help meet the requirements of regulatory agencies. Indeed, effective control of these residues is essential if we are to ensure a high degree of consumer protection.

Relevant data were obtained by searching through SciFinder and Scopus regarding the main methods for the analysis of honey, milk, eggs and animal tissues containing the term "tetracycline" in the title, abstract or keywords. The data indicate that since 1996 there has been

Table 1
Some chemical and physical properties of tetracycline antimicrobials (adapted from [4,57,138]).

Antimicrobial	Systematic name	Chemical structure	Acidity (pka)	Polarity (Log P)	Molecular mass (g/mol)
Tetracycline (TC)	4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene carboxamide		pK_{a1} 3.3 pK_{a2} 7.7 pK_{a3} 9.7	− 1.3	444.4
Oxytetracycline (OTC)	5-hydroxy-tetracycline		pK_{a1} 3.2 pK_{a2} 7.5 pK_{a3} 8.9	−3.6	460.4
Chlortetracycline (CTC)	7-chloro-tetracycline		pK_{a1} 4.5 pK_{a2} 7.8 pK_{a3} 9.8	−0.62	478.8
Doxycycline (DC)	6-deoxy-5-hydroxy-tetracycline		pK_{a1} 3.0 pK_{a2} 7.9 pK_{a3} 9.2	−1.9	444.4

Table 2
Maximum residue limits for tetracyclines in foods of animal origin.

Authority	Animal group	Target food	MRL ($\mu g\,kg^{-1}$)	Ref.
Codex Alimentarius	Poultry	Eggs	400	[17]
	Poultry	Muscle	200	
	Poultry	Liver	600	
	Cattle	Milk	100	
	Cattle and Swine	Muscle	200	
	Cattle and Swine	Liver	600	
	Fish	Muscle	200	
Canadian	Poultry	Eggs	400	[19]
	Poultry	Muscle	200	
	Poultry	Liver	600	
	Cattle	Milk	100	
	Cattle and Swine	Muscle	200	
	Cattle and Swine	Liver	600	
European Union	Poultry	Eggs	200	[18]
	Poultry, Cattle and Swine	Muscle	100	
	Poultry, Cattle and Swine	Liver	300	
	Cattle	Milk	100	
Chinese	Poultry	Eggs	200	[20]
	All Animal Source Foods	Muscle	100	
	All Animal Source Foods	Liver	300	
	Cattle and Lamb	Milk	100	
Brazilian (PNCRC)	Poultry	Eggs	–	[21]
	Poultry, Cattle and Swine	Muscle	200	
	Poultry, Cattle and Swine	Liver	–	
	Cattle	Milk	100	

Fig. 2. Different types of animal-origin foods studied which are used for detecting traces of tetracyclines.

their low cost and the fact that they are easily accessible to consumers. Milk and eggs are animal-origin foods that deserve careful attention. This is largely because their high nutritional value provides health benefits and are therefore highly consumed by humans. They are important sources of proteins, vitamins and minerals [22,23] and constitute fundamental components of the diet consumed in Brazil and other countries. The habitual human consumption of milk and eggs is important for maintaining a balanced and healthy diet. Hence, the presence of any contaminant in these foods is strictly not allowed [13,24].

The present review aims to investigate the main sample preparation techniques related to the analysis of tetracyline drugs in animal-derived foods, focusing on milk and egg matrices. This research will help identify aspects of residue extraction and sample clean-up that still require clarification. We will provide an overview of the parameters to consider for the development and implementation of a new food sample preparation method. To this end, 96 papers published between 1992 and 2017 have been thoroughly reviewed and are described below.

a steady increase in the number of scientific publications related to the determination of these veterinary drugs in foodstuffs. The review was conducted based on 96 articles published between 1992 and 2017. There has been an increasingly growing interest among scientists in studying tetracyclines, regarded an important research subject in food safety issues.

Fig. 2 shows the distribution of the selected publications according to the analyzed foodstuffs. As can be seen, milk (35%) and eggs (18%) are the most frequently studied food matrices; this is probably due to
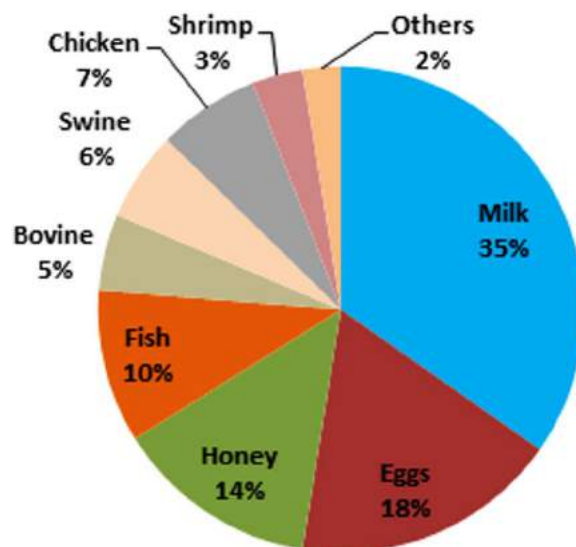
2. Analytical techniques

A wide range of analytical methods have been developed for the analysis of tetracyclines in food matrices. Among the techniques that merit mentioning include high performance liquid chromatography (HPLC) with ultraviolet (UV), fluorescence (FL), or mass spectrometry (MS) detection. In fact, the AOAC International recommends the use of HPLC with UV detection as the official method for the analysis of tetracycline residues in foods of animal origin, such as cow milk [25] and swine and bovine tissues [26].

Tetracyclines are highly polar, water soluble compounds that undergo chelation with metal ions [27]. They are weak bases with pKa values ranging from 3.2 to 9.8 (Table 1) and contain several chromophore groups. In view of that, tetracyclines exhibit an intensive absorption band in the ultraviolet region between 270 and 360 nm, in both acidic and neutral medium. UV and diode array (DAD) detectors are commonly used for the determination of this class of substances [5].

The mechanism by which tetracyclines are retained in chromatographic systems can be quite complex, in that these antibiotics present different functional groups. Reverse phase columns (C8 and C18) are commonly used for the chromatographic separation of these substances. The packing material allows tetracycline retention through the following mechanisms: ion pair formation, competition effects, active and inactive binding sites, ion exchange, interaction with silanol groups, among others [28,29].

Because of the high polarity nature of tetracyclines, mobile phases with high water content are widely applied in the performance of the chromatographic analyses [28]. Moreover, these substances can be adsorbed by the silanol groups through the reverse phase column, and tend to exhibit peaks with tail and low resolution. These problems can be overcome by adding oxalic acid in the mobile phase and using polystyrene-divinylbenzene columns. This explains the reason why mobile phase containing oxalic acid has been frequently reported in the literature on the analysis of tetracyclines in foods using HPLC technique since the late 80s. The mobile phase composition plays a very important role when it comes to the chromatographic behavior of tetracyclines [30].

Apart from HPLC, other techniques have also been employed toward the determination of tetracycline residues in food products. Fig. 3 shows the distribution of publications according to the analytical techniques applied. As mentioned above, among the target matrices, HPLC (69%) was found to be the most commonly used technique for the analysis of tetracyclines. This is probably because its varied detection systems provide high sensitivity and selectivity. Other techniques that have also been employed include spectrophotometry (9%), voltammetry (7%), capillary electrophoresis (6%), enzyme-linked
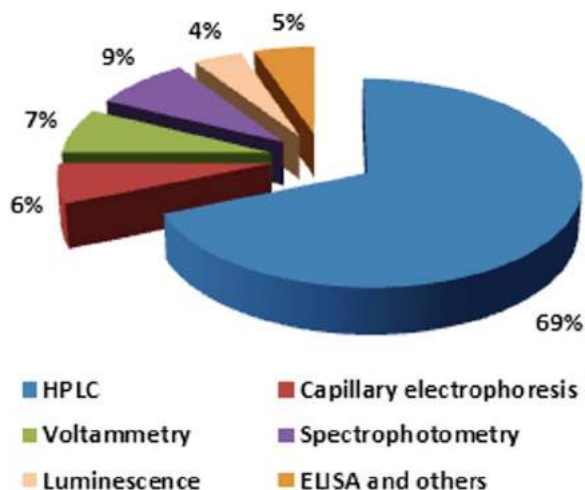
immunosorbent assay (ELISA) (5%), and luminescence (4%). A single work reported in the literature used Bragg diffraction red-shift for the determination of this group of substances. There have also been reports of studies that blended spectrophotometry and luminescence techniques with flow injection analysis.

Despite advances in the sensitivity of modern analytical instrumentation for the determination of trace contaminants in complex matrices, such as food, a rigorous sample pre-treatment is often required for extracting and isolating the target analytes from the food matrix, and thus, facilitate their determination [31].

A wide range of methods for the determination of tetracycline residues in food products have been reported in the literature. Most of these methods employed in the determination obtained low limits of detection and good extraction capacities because of the use of adequate sample preparation prior to instrumental analyses. However, a greater part of the methods lacks sufficient sensitivity needed for detecting residues in accordance with the maximum limits allowed; this makes them time-consuming besides involving laborious preconcentration procedures. Such procedures are often expensive and generally employ considerable volumes of organic solvents, resulting in the generation of large quantities of toxic waste that hinders proper treatment of solvents, while endangering human health and contributing to environmental pollution.

The choice of sample treatment depends largely on the complexity of the matrix as well as on the selected detection method. Highly sensitive detection methods require careful sample treatment steps; this is because, most often, sensitivity increases in both the target analytes and coextractives, generating unwanted matrix interferences in the analyses [31].

A powerful thrust for determining various chemical components with minimal or even no sample preparation was reached by direct analysis in real time (DART) mass spectrometry (MS) - an ambient ionization technique. This ionization approach is based on the fundamental principles of atmospheric pressure chemical ionization (APCI). Here, metastable species are generated from an excited helium gas stream. The species subsequently react with analytes to form gaseous ions [32–35]. The main parameters that are known to affect the ionization efficiency of DART include desorption temperature, gas type, gas flow rate, discharge energy and angular disposal of the sampler, among others [33,35].

The introduction of DART-MS accompanied by the rapid evolution of MS analyzers have led to the development of a simple and high-throughput frontier technology for rapid mass spectral analysis in situ of a large variety of samples. DART-MS allows one to analyze samples under atmospheric pressure. Furthermore, compounds that have been deposited or adsorbed onto surfaces or that are being desorbed thereof into the atmosphere can also be successfully analyzed with the aid of this technique [33,34].

Over the last decade, the application field of the DART-MS technique has seen extraordinary expansion. The technique has gained popularity among researchers and has been considered suitable for the following: olive oil authenticity assessment [36], pesticide monitoring on fruits [37] and vegetables [38], metabolite fingerprinting [39], plant seed characterization [40], clinical [35], pharmaceutical [41], forensic [42] and environmental [43] analyses, and for the detection of adulteration in foods such as milk [44] and honey [45].

In comparison with the traditional chromatography coupled to electrospray mass spectrometry, DART-MS presents improvements in terms of analysis time (in seconds) and operational simplicity [43]. Nonetheless, since there is no separation step prior to ionization in DART, these types of procedures must be carefully designed in order to avoid signal suppression, which when very pronounced may produce lower detection selectivity. This shortcoming (lack of separation step) renders the DART-MS technique more vulnerable to false (negative or positive) results [32]. In this context, both the efficiency of the sample treatment and the mass resolution are of extreme relevance for analysis

Fig. 3. Types of analytical techniques used for tetracycline determination in foodstuffs.

by the DART-MS technique [43].

Modern analytical strategies tend towards automatization and integration of sample preparation in the detection systems. These strategies are, most often, merged with chromatographic systems. Both solvent-minimized and solventless sample pretreatment techniques developed during the last decade are among the pillars of green analytical chemistry. The interest in this green approach is greatly driven by toxicological, environmental and economical concerns [31].

3. Sample preparation

Sample preparation is usually the most critical step in the development of methods for residue analysis. The type of treatment adopted depends on the matrix type, the method, and the chemical attributes of the analytes [10,46]. The typical steps involved in sample preparation include sampling, extraction, clean-up and concentration, followed by the final analysis. The sampling step is regarded the most important among them because an inadequate sampling can lead to erroneous results, regardless of whether the remaining steps in the analytical process have been flawless. Any portion or aliquot taken for analysis must be representative of the original bulk sample. For solid foodstuffs, proper crushing is recommendable to obtain smaller sample sizes. When conducting food composition analysis, smaller sample portions can be used. By contrast, for the determination of trace contaminants in food, relatively larger portions of sample are often required in order to obtain lower limits of detection. Irrespective of the selected sampling mechanism, sample homogenization is essential for chemical analysis [47].

Evidently, a large sample size requires more efficient extraction and clean-up techniques than a smaller one; hence, the economic costs of analysis are likely to increase [47]. Extraction methods are usually applied toward the isolation of residue contaminants from a representative sample, whereas clean-up methods are employed with the aim of separating co-extracted matrix components in order to obtain a more purified sample extract [31]. In analytical chemistry, these terms – extraction and clean-up – are commonly used interchangeably, and are often interdependent.

The extraction and clean-up methods for tetracycline residue analysis reported in the literature have been applied to a broad variety of matrices. Foodstuffs, such as milk and eggs, contain many interfering substances that need to be removed selectively. The difficulty encountered in the analysis of tetracycline antibiotics in this type of foods lies in the need to eliminate the main matrix components (e.g., lipids, proteins, vitamins, minerals, fats, and other nutritional and energy sources) that may interfere in the instrumental determination of the investigated compounds. This difficulty has led to the development of new strategies for the isolation and extraction of tetracycline residues from food matrices [10].

Table 3 summarizes the most relevant analytical applications regarding the determination of tetracycline drugs in different foodstuffs. The main techniques employed for the extraction and clean-up of tetracyclines from such matrices include solvent extraction (SE), solid-phase extraction (SPE), ultrasonic-assisted extraction (UAE), pressurized liquid extraction (PLE), magnetic solid-phase extraction (MSPE), matrix solid-phase dispersion (MSPD), molecularly imprinted polymer solid-phase extraction (MIP-SPE), and dispersive liquid–liquid microextraction (DLLME). Other less common techniques include hollow fiber liquid phase microextraction (HF-LPME) and dispersive solid-phase microextraction (DSPME). The advantages and limitations of these techniques are presented in Table 4.

The investigation conducted here showed that there are few methods capable of detecting traces of tetracyclines in animal-origin foods that do not include a prior sample treatment. This is probably due to the complexity of these matrices. Some authors have developed electrochemical methods using differential pulse voltammetry (DPV) [48] and cyclic voltammetry (CV) [49] for the analysis of milk matrix

without further sample treatment. Another work published in the literature involving the use of honey and milk samples reported to have obtained good linearity within the matrix application ranges. The authors achieved this result by diluting milk and honey samples in water and subsequently measuring the content through Bragg diffraction redshift [50]. Although these methods showed good results, some sample preparation is normally required prior to analysis so as to avoid matrix interference [12]. In fact, a report in the literature indicates that very low concentrations of these antibiotics in some food matrices were determined without performing sample clean-up, or with only a single prior step of protein precipitation [46].

3.1. Solvent extraction

Due to easy binding of the tetracyclines with proteins, the addition of strong acids and precipitating agents is highly recommended when it comes to extracting these compounds from food samples [28]. Deproteinization is a simple solvent extraction (SE) procedure commonly used to extract antibiotics from complex matrices. This off-line procedure is often necessary for the removal of matrix interferences in order to ensure good recoveries of analytes of interest [12].

Protein precipitation in milk and egg samples involves the use of organic solvents including acetonitrile [6,10,23,46,51], methanol [52–55] or acetone [56], as well as the combination of these solvents with acid compounds, such as trichloroacetic acid [46,57–61], trifluoroacetic acid [62,63], glacial acetic acid [64–66], succinic acid [67,68], citric acid [23,69], formic acid [54,70], or perchloric acid [71]. Other authors have used McIlvaine-EDTA [6,72–79], sodium citrate [10], oxalate [63], sodium succinate [80] and phosphate [81] buffers as deproteinizing agents for the treatment of these samples. Such processes are generally followed by some sample clean-up procedures.

Deproteinization of milk samples with 1% trichloroacetic acid solution without further clean-up procedure was reported to be sufficient for detecting tetracycline residues in remaining solution by spectrophotometry [46]. The acid treatment evaluated in that work yielded adequate recoveries (71.0–82.0%), considering the complexity of the milk matrix. Moreover, the authors obtained relatively lower limits of detection compared to other studies that employed complicated sample treatments [3,53] and expensive equipments [67,71].

Liquid–liquid extraction (LLE) is a separation process based on the different distribution (relative solubility) of the analytes in two immiscible liquid phases (usually water and an organic solvent); the process is controlled by partition equilibrium. The extraction of an analyte depends on the transfer of its mass from a first liquid phase to a second one; this is achieved by the differences in solubilities between the phases [47]. LLE is one of the most commonly used extraction techniques for the extraction of many organic compounds from a large variety of matrices, particularly aqueous samples.

Tetracycline antibiotics in milk samples have been determined by capillary electrophoresis using a clean-up/extraction procedure based on protein precipitation with trichloroacetic acid followed by liquid–liquid extraction with dichloromethane [58]. The method showed adequate sensitivity for the detection of residues and the recoveries obtained were within the allowed limits.

Solid–liquid extraction (SLE), also known as leaching process, is another technique employed in solvent extraction which has similar principles to those of LLE. The only difference is that in SLE analytes are extracted from solid samples. The SLE process occurs through the displacement of soluble substances, and analytes are extracted using a solvent. Owing to the interaction between the phases, the analytes can diffuse from the solid sample to the liquid phase, leading to the separation of the main components.

In general, the techniques described above involve the use of large quantities of organic solvents, which contribute significantly toward environmental pollution. Apart from their negative impact on the

Table 3
Analytical applications for tetracycline residue determination in foodstuffs.

Matrix	Sample preparation	Technique	Linear range	Sensitivity	Recovery (%)	Ref.
Milk	Protein precipitation with TCA and SPE	HPLC-ESI-MS/MS	50–500 µg L⁻¹	LOD 5.0–20 µg L⁻¹	90–101%	[57]
Honey	Pretreatment with McIlvaine buffer and Na₂EDTA, followed by SPE	HPLC-FL	25–500 µg kg⁻¹	LOQ 25 µg kg⁻¹	86–111%	[149]
Bovine muscle	Extraction with succinic acid and MeOH, followed by cleaning using MCAC and additional SPE step	HPLC-DAD	0–250 µg kg⁻¹	CCα 109–132 µg kg⁻¹; CCβ 118–164 µg kg⁻¹	91–104%	[150]
Fish muscle	Extraction with ACN and citrate buffer containing MgCl₂	HPLC-FL	5–100 µg L⁻¹	LOQ 0.15–1.5 µg kg⁻¹	60.6–84.3%	[151]
Milk	Magnesium hydroxide coprecipitation method	HPLC-DAD	25–200 µg kg⁻¹	LOD 3.0–8.5 µg kg⁻¹	96–105%	[152]
Lobster, duck, honey, and eggs	Pretreatment with McIlvaine buffer and MIP-SPE procedure	HPLC-ESI-MS/MS	–	LOD 0.1–0.3 µg kg⁻¹	94–103%	[99]
Fish tissue	Acid hydrolysis and protein precipitation with MeOH-TCA solution	HPLC-FL	75–3750 µg kg⁻¹	LOD 49–190 µg kg⁻¹	72–83%	[52]
Eggs	Pretreatment with ACN/TCA and IL-DLLME procedure	HPLC-DAD	5–1000 µg L⁻¹	LOD 2.0–12 µg kg⁻¹	58–95%	[145]
Honey	Solubilization with oxalate buffer and clean-up using SPE cartridges	HPLC-ESI-MS/MS	0–80 µg L⁻¹	–	≥95%	[153]
Milk	Pretreatment with McIlvaine buffer containing EDTA and SPE	HPLC-FL	12–300 µg kg⁻¹	LOD 5–35 µg kg⁻¹	68–110%	[3]
Swine muscle and kidney	Extraction with McIlvaine-EDTA buffer (pH 4.0), followed by SPE	HPLC-FL, LC-APCI-MS	100–1000 µg kg⁻¹	LOQ 50–100 µg kg⁻¹	71.0–86.7%	[154]
Milk	QuEChERS methodology based on extraction with ACN without sample clean-up	UHPLC-ESI-MS/MS	5–200 µg kg⁻¹	LOD 1–4 µg kg⁻¹	71–109%	[6]
Honey	Pretreatment with succinate buffer, followed by extraction using MCAC and purification via SPE	HPLC-ESI-MS/MS	50–2000 µg L⁻¹ / 5–300 µg L⁻¹	LOD 5–10 µg L⁻¹	52.7–69.0%	[155]
Milk	Protein precipitation with MeOH-TCA solution and SPE	HPLC-DAD	50–500 µg L⁻¹	LOD 20 µg L⁻¹	61–80%	[53]
Shrimp and milk	Acid hydrolysis and protein precipitation with HAc and H₃PO₄	HPLC-NiCl-PB-MS	30–80 µg L⁻¹	–	> 80%	[64]
Pork tissues	Sample extraction with succinic acid, followed by isolation using SPE column	Ion-pair HPLC-UV	–	LOQ 50–100 µg kg⁻¹	90–100%	[156]
Milk and shrimp	Sample extraction with succinic acid, followed by isolation using SPE column	HPLC-ESI-MS/MS	50–300 µg kg⁻¹	LOQ 50 µg kg⁻¹	75–95%	[67]
Honey	Samples treated with Na2EDTA–McIlvaine buffer (pH 4.0) before on-line C18-SPE-HPLC analysis	HPLC-UV	50–1000 µg kg⁻¹	LOD 5–12 µg kg⁻¹	92.1–96.1%	[157]
Bovine, pork, chicken, and lamb tissues	PLE using water as extractant, conducted at 70 °C and 1500 psi, followed by SPE	HPLC-ESI-MS/MS	5–10000 µg kg⁻¹	CCα 101–116 µg kg⁻¹; CCβ 112–130 µg kg⁻¹	89–99%	[158]
Milk and eggs	Pretreatment with Na₂EDTA followed by extraction using SPE cartridges	HPLC-ESI-MS/MS	25–400 µg L⁻¹	LOD 0.5–19.0 µg L⁻¹	72–102%	[95]
Butter, milk powder, egg and fish	SLE using formic acid in aqueous solution of Na₂EDTA-ACN-MeOH with additional UAE	HPLC-ESI-MS/MS	1–200 µg L⁻¹	LOQ 0.06–0.41 µg kg⁻¹	53–80%	[54]
Pork, chicken and bovine tissues	Extraction with TCA/ACN using ASE instrument	HPLC-UV	5–500 µg kg⁻¹	LOD 5–10 µg kg⁻¹	75.0–104.9%	[159]
Eggs	Pretreatment with sodium citrate buffer (pH 5) and liquid extraction using ACN	HPLC-ESI-MS/MS	20–400 µg kg⁻¹	LOQ 20 µg kg⁻¹	71–109%	[10]
Honey	Dissolution in citric acid buffer and absorption by an XAD-2 resin using column chromatography	HPLC-CL	1–800 µg L⁻¹	LOD 0.9–5.0 µg L⁻¹	92–122%	[160]
Eggs	Modified QuEChERS methodology and SPE using dispersive absorbents	HPLC-ESI-MS/MS	10–200 µg kg⁻¹	LOQ 1–20 µg kg⁻¹	81–94%	[111]
Bovine muscle	Pretreatment with citrate buffer and purification using SPE cartridges	HPLC-DAD	25–750 µg kg⁻¹	LOQ 25–40 µg kg⁻¹	98.7–103.3%	[161]
Eggs	Solvent extraction using ACN, citric acid (pH 4) and Na₂EDTA, followed by SPE	UHPLC-ESI-MS/MS	5–100 µg kg⁻¹	LOQ 0.1–0.4 µg kg⁻¹	58–82%	[13]
Honey	Dilution in water followed by SPE	HPLC-ESI-MS/MS	–	–	91–97%	[162]
Eggs	PLE using a mixture of ACN and a succinic acid buffer (pH 6.0) at 70 °C	UHPLC-ESI-MS/MS	100–300 µg kg⁻¹	CCβ 1.1–264 µg kg⁻¹	57–85%	[68]
Chicken and egg yolk	Extraction with TFA and oxalate buffer (pH 4), followed by SPE	HPLC-DAD	20–300 µg kg⁻¹	LOD 20–29 µg kg⁻¹	67–103%	[63]
Fish, shrimp and egg	PLE using TCA/MeOH conducted at 60 °C and 65 bar, without further clean-up	HPLC-UV	10–800 µg kg⁻¹	LOD 0.8–1.3 µg kg⁻¹	75–102%	[55]
Eggs	Adsorption using silica gel and elution with ACN, followed by online MIP-SPE procedure	HPLC-DAD	5–1000 µg kg⁻¹	LOD 11–15 µg kg⁻¹	91–107%	[100]
Eggs	Clean-up by on-line dialysis and on-line SPE using an extended ASTED system	HPLC-UV	50–600 µg kg⁻¹	LOD 5–40 µg kg⁻¹	90–97%	[114]
Honey, fish milk, lamb, and chicken	Pretreatment with ACN and sodium sulfate, and clean-up using HF-LPME procedure	HPLC-ESI-MS/MS	10–500 µg kg⁻¹	LOD 10–50 µg kg⁻¹	–	[138]
Eggs	Pretreatment with sodium succinate buffer and SPE	HPLC-DAD	–	LOD 11–27 µg kg⁻¹	45–55%	[80]
Eggs	Extraction based on QuEChERS methodology	HPLC-ESI-MS/MS	–	LOD 0.02–2.50 µg kg⁻¹	52–84%	[90]
Honey	Dissolution in Na₂EDTA (pH 4.0) and cleaning using SPE cartridges	HPLC-ESI-TOF-MS	–	CCβ 2.04–1316 µg kg⁻¹	73–91%	[163]
Eggs	Extraction using formic acid in ACN and EDTA and cleaning by SPE	HPLC-ESI-MS/MS	–	LOD 0.07–0.19 µg kg⁻¹	75–108%	[70]
Chicken and eggs	Magnetic separation using MIPs based on magnetite	HPLC-ESI-MS/MS	0.5–125 µg kg⁻¹	LOD 10.3–25.8 µg kg⁻¹	72.8–96.5%	[101]
Fish tissue	Extraction with a mixture of MeOH and ACN acidified with formic acid	HPLC-ESI-MS/MS	20–150 µg kg⁻¹	LOD 0.02–1.30 µg kg⁻¹	–	[164]
Eggs	Pretreatment with McIlvaine buffer containing EDTA, followed by SPE	HPLC-ESI-MS/MS	1.2–60 µg kg⁻¹	LOQ 0.5–10 µg kg⁻¹	83–110%	[72]
Animal tissues	Extraction with McIlvaine and phosphate buffers, followed by clean-up step based on SPE	UHPLC-ESI-MS/MS	0.5–500 µg kg⁻¹	LOD 0.61–10.34 µg kg⁻¹	58.4–80.4%	[81]
Honey and milk	Miniaturized SPE using chitosan-modified graphitized multiwalled carbon nanotubes	UHPLC-Q-TOF/MS	10–890 µg L⁻¹	LOD 1–5 µg kg⁻¹	81.5–101.4%	[95]
Chicken muscle	Extraction with ACN, citric acid and MgCl₂	HPLC-FL	10–300 µg kg⁻¹	LOD 0.08–1.12 µg kg⁻¹	65.0–79.2%	[165]
Milk and eggs	Extraction with HAc and clean-up using FIL-NOSM procedure	HPLC-UV	0.25–500 µg kg⁻¹	CCα 20–21 µg kg⁻¹; CCβ 49–50 µg kg⁻¹	94.1–102.1%	[66]
Honey	Extraction in EDTA-McIlvaine buffer, followed by SPE	HPLC-FL	50–200 µg kg⁻¹		86–95%	[166]

Table 3 (continued)

Matrix	Sample preparation	Technique	Linear range	Sensitivity	Recovery (%)	Ref.
Eggs and swine tissue	Pretreatment with ACN and TFA, followed by MIP-SPE procedure	HPLC-DAD	100–1000 µg L⁻¹	LOD 20–40 µg kg⁻¹	74–93%	[62]
Porcine muscle	Extraction with EDTA-McIlvaine buffer and TCA, followed by SPE	HPLC-DAD	–	–	50–70%	[167]
Milk and honey	Pretreatment with perchloric acid and clean-up using MIP-SPE procedure	HPLC-DAD	0.050–10 mg L⁻¹	LOD 10.2–18.8 µg L⁻¹	73.3–90.6%	[71]
Fish	Extraction with EDTA, m-H₃PO₄, HFBA and TCA, followed by SPE	HPLC-ESI-MS/MS	25–200 µg kg⁻¹	CCα 106–124 µg kg⁻¹	99–106%	[168]
Milk	Pretreatment using modified QuEChERS methodology followed by dispersive-SPME	HPLC-DAD	20–400 µg kg⁻¹	LOD 7.9–35.3 µg kg⁻¹	98.2–102.4%	[91]
Eggs, milk, and milk powder	Pretreatment with Na₂EDTA-McIlvaine buffer and UAE before on-line MIP-SPE-HPLC analysis	HPLC-UV	5–500 µg kg⁻¹	LOD 0.76–1.13 µg kg⁻¹	85.3–98.3%	[77]
Honey	Pretreatment with Na₂EDTA–McIlvaine buffer, followed by on-line C18-SPE-HPLC procedure	HPLC-UV	50–1000	LOD 5–12 µg kg⁻¹	84.2–120.6	[78]
Dry milk	Pretreatment with TCA and EDTA, followed by extraction with hexane	UHPLC-Q-TOF/MS	1–200 µg L⁻¹	LOD 0.1–0.5 µg L⁻¹	–	[169]
Chicken tissue	UAE using TCA and citrate buffer (pH 4.0), and purification by SPE	HPLC-DAD	50–5000 µg kg⁻¹	LOD 4.4–10 µg kg⁻¹; LOQ 10–27 µg kg⁻¹	68.8–92.4%	[170]
Milk	Pretreatment with McIlvaine buffer containing EDTA and clean-up using SPE cartridges	HPLC-FL	10–5000 µg kg⁻¹	LOD 2.2 µg kg⁻¹	75.3–82.5%	[75]
Bovine kidney	Pretreatment with McIlvaine buffer, and further HPLC analysis with on-line SPE	HPLC-ESI-MS/MS	100–1200 µg kg⁻¹	LOD 18–24 µg kg⁻¹; LOD 36–47 µg kg⁻¹	71–91%	[171]
Milk	Pretreatment with McIlvaine-EDTA buffer, followed by on-line HPLC using ZIF-8 as sorbent	HPLC-DAD	5–1000 µg L⁻¹	LOD 1.5–8.0 µg L⁻¹	70.3–81.4%	[76]
Fish	Extraction with MeOH/EDTA without any clean-up step	HPLC-ESI-MS/MS	10–1600 µg L⁻¹	LOD 12–16 µg kg⁻¹; LOQ 33–52 µg kg⁻¹	89–116%	[172]
Milk	Adjustment of pH to 7 by adding 0.1 mol L⁻¹ oxalic acid	HPLC-UV	5–300 µg kg⁻¹	LOD 3.2–7.1 µg kg⁻¹	95.2–106.2%	[113]
Bovine and swine tissues	Homogenization with water followed by centrifugation and ultrafiltration	HPLC-ESI-MS/MS	1–200 µg kg⁻¹	LOD 2 µg kg⁻¹	67.9–105.6%	[173]
Milk	Ultrasound-assisted MSPD extraction procedure	HPLC-DAD	0.5–20 µg mL⁻¹	LOQ 14.5–56.6 µg kg⁻¹	82–108%	[86]
Pig tissues	Pretreatment with sodium succinate solution and TCA, followed by SPE	HPLC-ESI-MS/MS	0–3000 µg kg⁻¹	LOD 0.5–4.5 µg L⁻¹	82.5–116.3%	[174]
Milk	Pretreatment with Na₂HPO₄ followed by HF-LPME	HPLC-UV	5–1000 µg L⁻¹	0.5–1.0 µg L⁻¹	50–64%	[139]
Veal muscle	Extraction with ACN and fat removal using hexane	HPLC-ESI-MS/MS	1–250 µg kg⁻¹	LOD 2–8 µg kg⁻¹	70–102%	[175]
Fish	Extraction with ACN in formic acid and subsequent cleaning using SPE cartridges	HPLC-ESI-MS/MS	–	LOD 0.062–0.39 µg kg⁻¹	93–102%	[176]
Milk	Protein precipitation using TCA followed by LLE combined with SPE	CE-DAD	1.0–200 µg mL⁻¹	LOD 12–29 µg L⁻¹	80.6–89.2%	[58]
Milk	MSPD procedure and elution with citric acid/MeOH	CE-UV	5–200 µg L⁻¹	LOD 74.5–80.8 µg L⁻¹; LOQ 4.3–5.9 µg kg⁻¹	94.2–99.8%	[69]
Fish	Pretreatment with Na₂EDTA, ACN and McIlvaine buffer (pH 4.0)	CE-UV	4–250 µg L⁻¹	LOD 2–9 µg L⁻¹	66–74%	[177]
Milk	MSPE procedure and elution with MeOH/HAc	CE-UV	2–10 µg mL⁻¹	LOD 0.78 µg mL⁻¹	89–105%	[102]
Milk	Pretreatment with TCA and clean-up using SPE cartridges	CE-UV	29.3–645 µg L⁻¹	LOD 7.1–14.9 µg L⁻¹	94–105%	[59]
Milk	Pretreatment with McIlvaine-EDTA solution and SPE, followed by FASS-EMI	CE-ESI-MS	0.1–100 µg L⁻¹	–	–	[73]
Milk	No sample treatment effected	CV	–	CCα 1 µg L⁻¹	–	[49]
Chicken and shrimp	Pretreatment with Na₂EDTA–McIlvaine buffer and subsequent SPE	AMP-FIA; CV	4.4–222.2 µg mL⁻¹	LOD 155.5–426.7 µg mL⁻¹	84.4–100.3%	[178]
Milk	Protein precipitation with 20% HAc solution	SWASV	44.4–888.8 µg L⁻¹	LOD 8.9 µg L⁻¹	–	[65]
Milk	Aqueous dilution at the ratio of 1:10	DPV	0.44–4444 µg L⁻¹	LOD 0.14 µg L⁻¹	92–106%	[179]
Milk	No further sample treatment effected	DPV	0.67–1555.4 µg L⁻¹	LOD 0.32 µg L⁻¹	93.1–103.8%	[48]
Honey and milk	Protein elimination by the addition of acetone	DPV	0.44–44.4 mg L⁻¹	LOD 35.5 µg L⁻¹	98–102%	[56]
Milk	Pretreatment with McIlvaine-EDTA and MSPE	DPV	0.5–90.0 ng L⁻¹	LOD 0.18 ng L⁻¹	92.1–105.5%	[79]
Fish	Extraction with EDTA-McIlvaine buffer and hexane-dichloromethane, followed by SPE	BL	0–500 µg kg⁻¹	LOD 5 µg kg⁻¹; LOQ 10 µg kg⁻¹	≥ 80%	[180]
Honey	Dilution with NaHCO₃–Na₂CO₃ buffer solution	ECL	4–400 µg L⁻¹	LOD 0.2 µg L⁻¹	87.5–115.0%	[181]
Honey	Dilution with water	CL-FIA	50–3000 µg L⁻¹; 500–7000 µg L⁻¹	LOD 2.0–4.9 µg L⁻¹; LOD 222–400 µg L⁻¹	89.2–106.6%	[182]
Fish	Trituration and later treatment with EDTA before on-line MIP-SPE-FIA	CL-FIA	4–400 µg L⁻¹	LOD 1 µg L⁻¹	97–106%	[105]
Honey and milk	Without further sample treatment	Bragg diffraction red-shift			–	[50]
Honey	Dilution with PBS-T and filtration using nitrocellulose membranes	ELISA	17.8–106.6 µg L⁻¹	LOD 0.4 µg L⁻¹	79–108%	[183]
Chicken	Dilution with PBS buffer (pH 7.2)	ELISA	1.15–38.9 µg L⁻¹	LOD 0.05 µg kg⁻¹	> 99%	[184]
Honey	Dilution with PBS-EDTA assay buffer (pH 7.2)	ELISA	25–1000 µg kg⁻¹	LOD 0.19 µg L⁻¹; LOQ 0.38 µg L⁻¹	95–101%	[185]
Honey	Dilution with phosphate buffered saline	ELISA	1.52–152 µg L⁻¹	LOD 0.02 µg kg⁻¹; LOQ 0.05 µg kg⁻¹	> 80%	[186]
Milk	Pretreatment with TCA and McIlvain buffer, and injection into an online SPE-FIA system	Spectrophotometry UV/VIS-FIA	0.2–1.0 µg mL⁻¹	LOD 0.08–0.1 µg mL⁻¹	86–109%	[74]
Milk	Pretreatment with McIlvaine buffer-EDTA solution and extraction using Florisil column	Spectrophotometry UV/VIS-FIA	3–10 µg mL⁻¹	LOD 0.38–1.55 µg mL⁻¹	82–106%	[187]

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Table 3 (*continued*)

Matrix	Sample preparation	Technique	Linear range	Sensitivity	Recovery (%)	Ref.
Milk	MSPE procedure and elution with HAc in MeOH	Spectrometry UV/VIS-FIA	30–600 µg L⁻¹	LOD 10 µg L⁻¹	91–97%,	[2]
Milk	Protein precipitation with TCA	Spectrometry UV/VIS-LWCC-FIA	50–400 µg L⁻¹	LOD 8.6–12.2 µg L⁻¹	71.0–82.3%	[46]
Egg supplements	Protein precipitation with ACN and TCA, followed by clean-up using US-DLLME procedure	Spectrometry UV/VIS-LWCC-FIA	30–600 µg L⁻¹	LOD 6.4–11.1 µg L⁻¹	85.7–96.4%	[51]
Milk	Pretreatment with TCA and MIH casting membranes are immersed into the pretreated samples	Spectrometry UV/VIS	0–4.4 µg mL⁻¹	–	100–106%	[61]
Honey and milk	Pretreatment with McIlvaine-EDTA buffer and extraction using Florisil column	Spectrometry UV/VIS-SIA	4.4–1777.8 µg mL⁻¹	LOD 2.2–3.5 µg mL⁻¹	99.6–100.2	[96]
Milk	Protein precipitation with TCA	Spectrophotometry FL	–	CCβ 25.9–124.4 µg L⁻¹	–	[60]

Key: LOD: limit of detection; LOQ: limit of quantification; CCα: decision limit; CCβ: detection capability; HPLC: high-performance liquid chromatography; UHPLC: ultra-high performance liquid chromatography; DAD: diode array detection; UV/VIS: ultraviolet/visible detection; FL: Fluorescence; AMP: amperometry; CL: chemiluminescence; ECL: electrochemiluminescence; BL: bioluminescence; ELISA: enzyme-linked immunosorbent assay; ESI: electrospray ionization; MS: mass spectrometry; Q-TOF/MS: quadrupole time-of-flight mass spectrometry; APCI: atmospheric pressure chemical ionization; MSPD: matrix solid-phase dispersion; IL-DLLME: ionic liquid-based dispersive liquid–liquid microextraction; Na₂EDTA: ethylenediaminetetraacetic acid disodium salt; TCA: trichloroacetic acid; TFA: trifluoroacetic acid; ACN: acetonitrile; HAc: glacial acetic acid; MeOH: methanol; HFBA: heptafluorobutyric acid; MCAC: metal chelate affinity chromatography; PBST: phosphate buffered saline; NICI: negative ion chemical ionization; PB: particle beam; LLE: liquid–liquid extraction; SLE: solid–liquid extraction; UAE: ultrasonic-assisted extraction; ASE: accelerated solvent extraction; PLE: pressurized liquid extraction; MIP-SPE: molecularly imprinted polymer solid-phase extraction; MSPE: magnetic solid phase extraction; FASS-EMI: field-amplified sample stacking with electromigration injection; CE: capillary electrophoresis; CV: cyclic voltammetry; SWASV: square wave anodic stripping voltammetry; DPV: differential pulse voltammetry; FIA: flow injection analysis; SIA: sequential injection analysis; HF-LPME: hollow fiber liquid phase microextraction; FIL-NOSM: functionalized ionic liquid-based non-organic solvent microextraction; MIH: molecularly imprinted hydrogel; LWCC: liquid waveguide capillary cell; US-DLLME: ultrasound-assisted dispersive liquid–liquid microextraction; SPME: solid-phase microextraction; ZIF-8: zeolite imidazolate framework-8.

environment, these techniques are, to a greater extent, expensive and laborious, and are also characterized by automation difficulty [82,83]. In view of that, attention has been devoted to the development and implementation of simpler and eco-friendlier extraction methodologies [84].

3.2. Ultrasound-assisted extraction

Ultrasound-assisted extraction (UAE) technique is a mechanism involving solvent extraction with the aid of ultrasound to enhance extraction efficiency. The technique consists of shaking and heating the sample during the extraction process. Like the microwave-assisted extraction (MAE), UAE was developed as an alternative to Soxhlet extraction. The merits of the UAE are that it is relatively faster and requires smaller amounts of solvent [47,85].

A point worthy of consideration when one seeks to obtain the maximum extraction efficiency and required selectivity in the employment of ultrasonication is the proper selection of the solvent type or solvent mixtures with water, with or without pH modification. Compared to other techniques, ultrasonification is more advantageous because the technique can be applied at room temperature, allowing the determination of thermolabile compounds. In addition, several extractions can be performed simultaneously and no expensive or specialized apparatus are required. One will note, however, that since the selectivity and enrichment capabilities of this technique are limited, further sample preparation steps are usually required to determine trace contaminants in foods [12,47,85]. By virtue of that, UAE is usually combined with other clean-up and/or preconcentration methodologies as an additional extraction process aiming at improving extraction efficiency.

A simple SLE procedure with 0.1% formic acid in aqueous solution of ethylenediaminetetraacetic acid (EDTA) 0.1% (w/v)–acetonitrile–methanol (1:1:1, v/v) was used for the extraction of tetracyclines from butter, fish tissue, milk powder and eggs [54]. An additional UAE step was, however, required to achieve recoveries within the 72–102% range by LC-MS/MS. The method was validated using matrix-matched calibration curves and the coefficient values determined indicated the absence of matrix effects.

Ultrasound-assisted matrix solid phase dispersion was applied for the determination of five tetracyclines using HPLC-DAD. This was the first attempt to apply matrix solid-phase dispersion combined with UAE for the preconcentration and clean-up of tetracycline residues from milk matrix. Interestingly, the process revealed high extraction yields [86]. Dispersive liquid–liquid microextraction has also been combined with UAE to isolate tetracyclines from egg supplement samples, followed by spectrophotometric determination using flow analysis. The additional ultrasonication step increased the method extraction capacity by approximately 6% [51]. These works, among others, have demonstrated the versatility of UAE when it comes to increasing tetracycline recovery in different foodstuffs by coupling with several sample extraction processes.

3.3. QuEChERS

QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and Safe) method was introduced by Anastassiades et al. for pesticide residue analysis in vegetables and fruits. During its development, great emphasis was placed on obtaining a dynamic procedure that could be applied in any laboratory, given the simplicity and flexibility of the steps. The original QuEChERS methodology involves initial extraction with acetonitrile, followed by liquid–liquid partitioning promoted by the addition of magnesium sulfate (MgSO₄) and sodium chloride (NaCl); and the supernatant is separated for further analysis. However, additional clean-up methodologies are commonly used for the removal of residual water and the isolation of analytes [87,88].

In QuEChERS procedures, salts are added to promote the salting out-effect, which is commonly observed in several multi-residue

Table 4
Detailed description of the advantages and drawbacks of selected sample preparation techniques for determination of tetracycline traces in food commodities.

Techniques	Advantages	Drawbacks	Refs.
SE	Simplicity and availability of a solvent variety that provides a wide range of solubility and selectivity High enrichment factors Good recoveries	Consumption of large volumes of samples and organic solvents, which causes disposal problems Partial extraction of samples with high affinity for water Concentration of solvent impurities together with the sample Possible formation of emulsions, which is time-consuming	[94,136]
UAE	Improved extraction efficiency from the choice of an appropriate solvent No specialized equipment is required Inexpensive procedure that allows several extractions simultaneously	Difficulty of automation and unsuitability for volatile analytes Sample clean-up or analyte preconcentration steps are generally required Extraction efficiency can be affected by the presence of water	[47]
QuEChERS	Robust method that presents simple, fast, and versatile steps Successful application in foods with different characteristics Compatible with several analytical techniques	Small amount of sample is obtained compared to other techniques Salt addition may cause spectral interferences in LWCC-based spectrophotometric techniques	[88]
SPE	Commercial availability of a broad variety of sorbents and simultaneous extraction of a wide range of organic analytes No formation of emulsions No decomposition of analytes sorbed onto the SPE cartridge Easy configuration for different extraction modes Automation possibility	Considerable solvent consumption Time-consuming and cumbersome technique Lack of selectivity Extraction efficiency may be affected by poor packing Batch-to-batch variation of the sorbents associated with low recovery and high matrix interferences Poor analyte fractionation	[16,94,136]
MIP-SPE	Cheap and easy preparation, and possibility of reuse High stability at extreme pHs and temperatures High analyte retention and improved selectivity Cleaner sample extracts	Selective extraction and clean-up limited to polar compounds Nonspecific hydrophobic interactions for application in aqueous media Sometimes low recoveries associated with lack of reproducibility	[92]
MSPE	Easy, fast and cheap handling Convenient phase separation by an external magnetic field High extraction efficiency and suitability for extraction of volume large samples Possibility of reusing magnetic adsorbents after an appropriate washing process	Complexity and difficulty in synthesizing the magnetic materials Large sorbent amount and solution volume necessary for elution	[2,112]
MSPD	Low solvent consumption and no need of multiple extractions Extraction selectivity can be achieved by packing a sorbent layer in the column bottom as an additional cleaning step	Difficulty of automation and usually a further cleaning step is required Extraction of many samples can be time-consuming	[16,47]
PLE	Automated sample handling Faster extraction times and reduced solvent consumption Elimination of the use of toxic solvents as extractants The use of high diffusion fluids improves the extraction process rate	Expensive equipment and limited sample amount to be extracted The use of higher temperature of the solvent may decrease extraction selectivity, besides affecting stability of thermo-labile compounds	[118,120]
SPME	Reduction of solvent consumption Sampling and extraction are performed in a single step Ability to examine smaller sample sizes	Variation of fiber coatings Low robustness Drag of matrix interferences affecting extraction of target analytes	[47]
DSPME	Simple, economic and easy procedure Rapid mass transfer and shorter equilibrium time Enhanced extraction capacity, reduced time and solvent consumption decrease	Salt addition may impair sorbent dispersion in sample solution High pH values can affect analyte desorption	[128] [130]
HF–LPME	High enrichment factors, relatively short extraction time, low cost of the extraction units and low consumption of toxic solvents Excellent sample clean-up that helps to prevent carry-over problems Addition of carrier agents in the sample facilitates the extraction of highly polar and hydrophilic compounds	Extraction time depends on analyte transfer through the SLM, limiting the process speed Need for commercially available equipment, which limits its application in routine laboratories Manual preparation of extraction units affects recovery precision and makes procedure automation difficult	[146]
DLLME	Easy handling, quickness and low cost Extraction occurs irrespective of time, and high preconcentration factors are achieved Considerable reduction or even elimination of hazardous solvent consumption via the use of IL as extracting solvents	Matrix effects can be observed as the analytes are not isolated from the soluble coextractives Automation difficulty due to the need to separate the phases	[85]

Table 4 (*continued*)

Techniques	Advantages	Drawbacks	Refs.
IL-mediated extraction	Low cost, ease of synthesis, and operational simplicity	Reactivity limited to certain reaction conditions and evidence of side reactions during the desired reactions	[66,125,188]
	High selectivity, precision and accuracy, and efficient sample clean-up	Incompatibility with ion-exchange columns	
	Application versatility	Glassware and steel parts can be damaged by the produced HF upon contact with fluoride-containing anions with moisture	
	Compatibility with varied analytical techniques	Some ILs show background interference in HPLC-UV analysis due to the strong absorption in the UV region	
	Organic solvent consumption elimination		
	Powerful solvents for chemical analysis		
	Environmentally friendly		

methods. Depending on the nature of the solvent used in the partitioning step, good recovery percentages for polar analytes can be obtained, since the presence of salts in the medium decreases the solubility of these compounds in aqueous phase. This stage is seen to be very convenient in the extraction with acetonitrile because it does not dilute the sample extract and allows the separation of the organic and aqueous phases. Furthermore, the step involving water removal provides a final extract of low polarity, thus facilitating the precipitation of polar co-extractives [88,89]. Since its inception, the method has been developed and modified, allowing the extraction of different compounds from several matrices.

A UHPLC–MS/MS multi-residue method for the selective determination of veterinary drugs in milk used a modified version of the QuEChERS methodology for sample preparation [10]. The extraction of pharmaceuticals, including doxycycline, was based on simple liquid extraction with acetonitrile without further clean-up step. Unlike the traditional method, acetic acid, Na$_2$EDTA and sodium acetate were also added to the extraction process. Fat removal and analyte extraction were performed in a single step devoid of the need for protein denaturalization before the extraction step. This type of modification is known as buffering QuEChERS. The use of UHPLC–MS/MS reduces analysis time and improves sensitivity and resolution. This technique allows the detection and quantification of several classes of veterinary drugs in less than 10 min.

The combination of LC-MS/MS technique with different modifications of the QuEChERS procedure has been studied for the simultaneous determination of residues of tetracyclines and other veterinary drugs in egg samples [11,90]. A work reported in the literature used formic acid in acetonitrile–water containing EDTA as the extraction solution, followed by the evaluation of eight different sample cleaning schemes. To date, the best results for tetracyclines were achieved using HybridSPE cartridges based on zirconia-coated silica. An additional cleaning with dispersive sorbents was, nonetheless, necessary to obtain recoveries above 80%. The latter step prolonged the time needed for sample preparation, providing clearer final extracts [11]. Other authors optimized a mixture of acetic acid in methanol–water as extracting solution. Two different clean-up procedures were tested for the removal of apolar substances and lipids from egg extracts; the procedures included dispersive-SPE using silica C18 and liquid–liquid extraction with n-hexane. The application of such procedures contributed toward the reduction of the matrix effect [90].

Dispersive solid-phase microextraction (DSPME) was also used as sample clean-up method following the application of the modified QuEChERS procedure for the analysis of tetracyclines in water and milk matrices using HPLC-DAD. Milk sample preparation was modified by adding 70–72% perchloric acid to the extracting mixture. Additionally, 14% NH$_4$OH solution was added to enable the alkalinization of the medium while analyte desorption was achieved using acetonitrile: perchloric acid: water mixture [91].

For the extraction of tetracycline via QuEChERS-like techniques, McIlvaine and/or EDTA buffer systems are often added to the extraction

mixture to prevent chelation of these compounds with metal ions such as Mg^{2+} and Ca^{2+}. EDTA acts as a competing chelating agent that facilitates the extraction of the analytes, thus paving the way towards obtaining high recoveries. In this sense, EDTA is commonly added to the extracting buffer and in many sample preparation steps. QuEChERS extraction is a fast and simple method that can be easily applied in routine laboratory [90,91].

3.4. Solid-phase extraction techniques

Solid-phase extraction (SPE) is one of the most widely employed extraction techniques in sample clean-up and preconcentration procedures; it is used for the determination of tetracyclines in complex matrices [4]. It is a separation technique that involves solid-liquid partition equilibrium and is based on the separation mechanisms of low pressure liquid chromatography. Here, the extracting phase is a solid sorbent [92]. The technique was introduced in the early 1970s and became commercially available in 1978 in the form of disposable cartridges. A wide array of sorbents that rely on different mechanisms for analyte extraction/retention can be found available on the market [12].

Fig. 4 illustrates a typical SPE procedure, which involves the following steps: sorbent activation, sample percolation/sorption of the analytes in the solid sorbent, elimination of the matrix interferences (clean-up), and elution and concentration of the analytes for subsequent analysis using the most appropriate technique. Conditioning the solid-phase materials entails passing organic solvents or water through the column so as to increase the effective surface area and reduce interferences. Sorbent drying is followed by the isolation and preconcentration of the analytes, which is accomplished by percolating the aqueous sample using a cartridge containing the sorbent. The analytes are initially retained for subsequent elution with another solvent in a collection tube [92]. The latter step is required owing to the disruption of the interactions between analytes and the solid-phase material; this step is accomplished by flushing small volumes of organic solvents, leading to desorption of the target analytes from the solid phase.

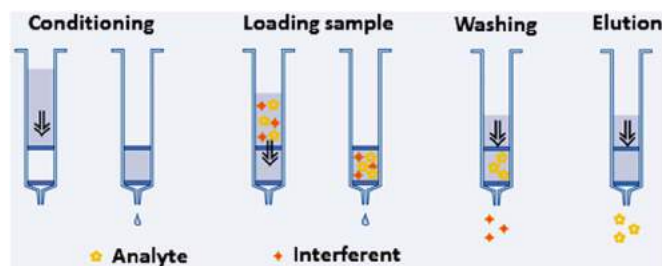**Fig. 4.** Typical four-step SPE procedure. Conditioning: moisturising of the solid phase with an organic solvent or water; Sample loading: sample is pressed or drawn through the solid phase to enrich the analytes on the sorbent, so that the interfering components are not retained; Washing: remaining interfering components are washed from the sorbent; Elution: analyte is removed from the sorbent by eluting with a suitable solvent.

3.4.1. Sorbent materials in SPE

Some of the parameters that ought to be considered when developing an SPE procedure include the choice of sorbent type and quantity, sample volume and solvent for cartridge activation, and elution of the analytes. Analyte characteristics, the nature of the matrix and its interferences should likewise be considered in the choice of sorbent [93].

There is a full range of reports in the literature describing the use of the SPE technique for the extraction of tetracycline residues from animal-derived foods [4], where OASIS HLB and C18 solid phases are found to be the most commonly used sorbents. OASIS HLB is a universal hydrophilic-lipophilic-balanced (HLB) polymeric reversed-phase sorbent that maintains its capability for greater retention owing to the fact that it is water-wettable. It is constituted by a specific ratio of two monomers, the hydrophilic N-vinylpyrrolidone and the lipophilic divinylbenzene. C18 is based on octadecylsilane bonded to irregularly shaped silica particles; this nonendcapped sorbent is strongly nonpolar and nonselective and provides reversed-phase binding of hydrophobic compounds. Van der Waals forces, nonpolar, or secondary interactions such as hydrogen bonding to silica silanols can be combined to obtain analyte retention. In general, all these syringe-barrel-type cartridges are designed for use with vacuum manifolds and automated SPE instruments [92,94].

OASIS HLB polymeric cartridges were used for the extraction of tetracyclines, sulphonamides and chloramphenicol from bovine milk for further determination by HPLC-DAD [53]. Sample preparation involved protein precipitation through the addition of McIlvaine buffer and trichloroacetic acid in methanol, which yielded good recovery of tetracyclines. LC-MS/M technique was used to quantify veterinary drug residues, including tetracyclines, in eggs after treatment with sodium succinate buffer, followed by clean-up using the same type of cartridges [80]. In the aforementioned study, tetracycline extraction efficiency was affected by the use of OASIS cartridges; as such, the obtained recovery values were below those established by legislation.

Different authors have also studied the extraction of tetracycline residues from bovine milk using C18 SPE cartridges, where further determination was carried out by capillary electrophoresis (CE) with UV [59] and MS [73] detection. Field-amplified sample stacking was applied to the CE-UV method; this resulted in lower detection limits and better recoveries compared to the CE-MS method. The result may be attributed to the relatively greater sensitivity and specificity of the MS detector. Furthermore, egg samples were treated with acetonitrile, citric acid and EDTA for the extraction of tetracyclines and other veterinary drugs using C18 and OASIS HLB cartridges [23]. Here, the SPE step was required since the extract was redissolved in the mobile phase and a dirty solution was obtained. It is worth noting that, it was, however, impossible to inject the dirty solution into the UHPLC–MS/MS system, despite the fact that it was filtered. While the recovery results obtained with both cartridges were found to be similar for most analytes, the use of OASIS HLB yielded higher values (over 60%) for tetracyclines.

By way of comparison, the use of OASIS HLB cartridges is highly recommended for the isolation and pre-concentration of tetracyclines from food samples such as milk and eggs. This is probably due to its stability pH values and in a broad spectrum of solvents, extraordinary retention of polar compounds, and a relative hydrophobic retention capacity found to be three-fold that of commonly used silica-based SPE sorbents-like C18 [92,94]. The number of articles published during the last two decades regarding tetracycline analysis in the study samples describing the use of OASIS HLB cartridges is much higher with respect to the use of C18 cartridges.

Carbograph 4 [95] and HybridSPE™ [11,55] cartridges and Li-Chrolut and Nexus SPE [63] cartridges have been used for cleaning animal-derived foods (milk, eggs and chicken tissue) in order to determine tetracycline residues by LC–MS/MS and HPLC-DAD, respectively. This class of antimicrobials and some veterinary medicinal products were also extracted and purified from milk samples using SPE columns based on Supelclean™ ENVI-Chrom P [64] and Florisil [96] sorbents aiming at determining drug residues by LC–PB-MS (liquid chromatography–particle beam-mass spectrometry) and spectrophotometry, respectively. All these works showed recovery and precision levels within acceptable limits according to the complexity of the food samples under analysis.

Remarkably, in spite of the drawbacks associated with SPE the importance of packing uniformity to avoid poor efficiency in complex matrices and the fact that the cartridges can only be used once, the technique has gained wider acceptance among researchers worldwide. This can be explained by the fact that the technique essentially prevents many of the problems associated with LLE, which include incomplete phase separations, low recoveries, the need for concentration of the extract and the use of expensive, breakable specialty glassware [94]. Some of the advantages associated with the use of SPE include less organic solvent usage, absence of foaming or emulsion problems, shorter sample preparation or minimal handling time which is tantamount to shorter analysis time, and clean sample extracts with high analyte recovery, even at low concentrations [92,97]. Furthermore, this technique presents ease of automation, extraction reproducibility, ability to increase analyte concentration in a selective manner and commercial availability of many SPE devices and sorbents, including the use of carbon-based nanomaterials [98], molecularly imprinted polymers (MIPs) [62,71,77,99,100], magnetic nanoparticles [2,79,101,102], among others.

3.4.1.1. Molecularly imprinted polymers.

Molecularly imprinted polymers (MIPs) are used as selective sorbent materials in traditional SPE; this has given rise to the molecularly imprinted polymer solid-phase extraction (MIP-SPE) method [103]. MIPs are synthesized via polymerization of a functional monomer and a cross-linker around a target analyte, which acts as a molecular template. Thus, template–monomer complexes are obtained between a chosen template molecule and a complementary functional monomer. Fig. 5 illustrates the exact constellation of this coordination, which allows us to distinguish the different types of molecular imprinting technologies from one another. After the templates are removed through washing, cleavage of chemical bonds, or ligand exchange, the binding sites remaining in the resultant MIP can specifically capture the template molecule and its structurally related molecules. This is rendered possible because the imprinted sites contain a three-dimensional network presenting pores with the geometry and position of the functional groups complementary to those of the templates [62,99,104,105]. In view of that, these tailor-made materials can exhibit high affinity and selectivity towards a given target or group of target molecules.

To produce MIPs with desirable properties, the preparation method should be appropriately selected. Generally, the mechanisms involving MIP preparation include free-radical polymerization and sol–gel processes. The most commonly used free-radical polymerization methodology is bulk polymerization; this involves mechanical grinding and sieving steps to obtain small particles. The process is tedious, time-consuming and needs a large amount of template molecules; as such, the obtained particles show a random shape and size. In an attempt to circumvent these shortcomings, more sophisticated and complex polymerization techniques have been proposed aiming at obtaining many different forms of MIPs, such as MIP particles, membranes, monoliths, and molecularly imprinted monolayers. Attractive polymerization methods for the preparation of MIP particles include suspension polymerization, emulsion polymerization, seed polymerization and precipitation polymerization [99,104].

Precipitation polymerization has emerged as a desirable and scalable approach for the production of high-quality, uniform, and spherical imprinted particles [106,107]. The feasibility of preparing highly selective molecularly imprinting polymers using this method has recently been demonstrated [108–111]. Although a large amount of
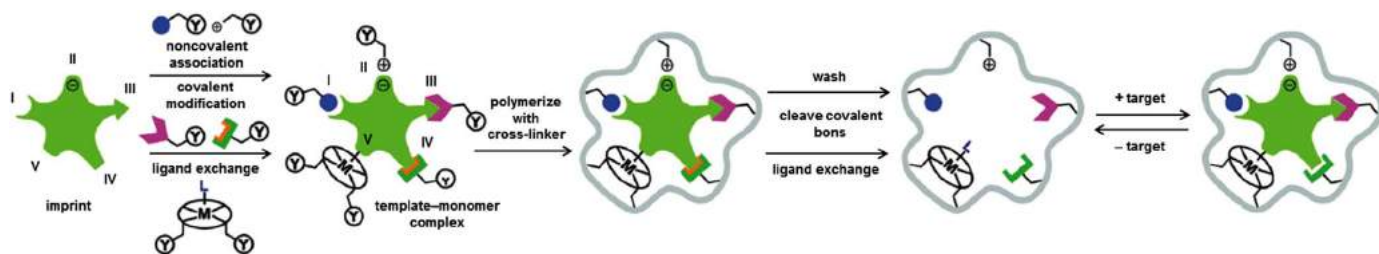
Fig. 5. General synthesis scheme for molecular imprinting technologies through noncovalent (I), electrostatic or ionic (II), covalent (III), semicovalent (IV), and metal center (V) interactions. An imprint molecule is combined with an appropriately selected functional monomer, via noncovalent, covalent, or ligand (L) to metal (M) interactions with complementary functional groups on the imprint. A template–monomer complex is formed, where the functional monomer is bound to the imprint molecule by hydrogen bonding or van der Waals interactions (I); by electrostatic or ionic interactions where the charges on the imprint and functional monomer may be reversed (II); through a covalent bond (III); through a covalent bond with a spacer (orange) (IV); or by ligand–metal or metal–ligand coordination (V). The functional monomer contains a functional group, Y, which undergoes a cross-linking reaction with an appropriate cross-linker (Reproduced from [104]).

template molecules is needed for the preparation process [99], precipitation polymerization has been the most outstanding method for the synthesis of MIPs focusing on the extraction of tetracycline residues from milk, eggs and other foods. Furthermore, by introducing the composite imprinting material strategy into sol–gel processes such as the preparation of nanomaterials and nanoimprinting, one is able to prepare MIPs with excellent interface characteristics and good electrical and optical properties. Clearly, this class of MIPs are more suitable for chemical or biological detection [104].

Several MIP-SPE methods combined with HPLC have been employed for determining tetracycline traces in food commodities. One of these methods made use of an imprinted polymer synthesized by precipitation polymerization for application in milk, egg and pork samples. Chlortetracycline was used as template molecule and methacrylic acid as functional monomer. Samples were initially treated with acetonitrile and trifluoroacetic acid [62]. The imprinted monolithic columns were also prepared via in situ molecular imprinting technique using tetracycline as the template. In this case, the functional monomer consisted of methacrylic acid and the cross-linker of ethylene glycol dimethacrylate. In addition, cyclohexanol and dodecanol were used as the mixed porogenic solvents. Thereafter, MIP-SPE coupled with C18 column was used to determine tetracyclines in milk and honey samples after treatment with $HClO_4$ solution [71]. Both methods were able to selectively extract the target substances.

A noteworthy application of molecular imprinting technique for selective tetracycline extraction in foodstuffs (duck, lobster, egg, and honey) was reported by Jing et al. [99]. The use of tetracycline as the template, methacrylic acid as a functional monomer, trimethylolpropane trimethylacrylate as a cross-linker, 2,2-azobisisobutyronitrile as a free radical initiator, and a methanol and acetonitrile mixture as solvent allowed the synthesis of new MIPs to be used as SPE sorbents. The synthesized MIP-SPE showed better clean-up efficiency and a higher recovery compared to the commercial sorbents C18 and Oasis HLB cartridges, respectively.

These results evidently demonstrate that the use of MIPs as sorbent materials contributes to a more efficient preconcentration of tetracycline residues and removal of the interfering compounds from food matrices. Their use enables a much more selective extraction of the target antibiotics than conventional SPE sorbents. Moreover, these restricted access materials are stable under harsh chemical conditions such as extreme pH, high pressure and high temperature, and can be reused dozens of times [104].

3.4.1.2. Magnetic sorbents. Magnetic solid phase extraction (MSPE) was developed during the past decade; it is a magnetically assisted chemical separation method that uses magnetic-nanoparticle-based support as absorbent material. This method shares the basic principles of the conventional SPE technique. Magnetic nanoparticles are superparamagnetic, i.e., they are attracted to a magnetic field, yet no residual magnetism is retained after field removal. Magnetic

sorbents are commonly prepared by organic or inorganic polymerization in the presence of magnetite [2,112].

An attractive property of this technique is that magnetic adsorbents can be isolated very quickly from the sample matrix by applying an external magnetic field, so that the superparamagnetic particles will not agglomerate upon the removal of the field. In this procedure, after the dispersion of magnetic support in the sample solution and formation of the suspension, the analytes adsorbed by the magnetic support are collected using a magnet without additional centrifugation or filtration. Finally, the analytes are consequently eluted from the recovered adsorbent and the extract is subjected to analysis [2,102]. An outstanding advantage of this technique lies in the possibility of improving the extraction performance by means of a high ratio between surface area and extraction phase volume.

In order to determine tetracycline residues by capillary electrophoresis, milk samples were prepared by MSPE using a paramagnetic, phenyl-functionalized silica adsorbent [102]. The magnetic phenyl silica adsorbents covered with previously synthesized magnetite were obtained via emulsion polymerization by varying the molar ratio of phenyltrimethylsilane and tetramethylorthosilicate; these adsorbents were evaluated in terms of their pH and degree of hydrophobicity for analyte retention.

MSPE based on magnetic silica-coated materials was also used for tetracycline preconcentration in milk samples [2]. The magnetic materials were synthesized by polymerization from previously prepared magnetite, tetramethoxysilane, Triton X-100 and cetyltrimethylammonium bromide (CTAB) using metanol as solvent. The method consisted of magnetic support dispersion onto untreated milk samples. The tetracyclines desorbed with acidified methanol from the magnetic support were determined simultaneously by spectrophotometic flow injection analysis.

Milk samples were also prepared by MSPE using b-cyclodextrin functionalized magnetic graphene oxide nanoparticles (b-CD-MGONPs) [79] and a laccaic acid-loaded magnetite nanocomposite [113] for the extraction and preconcentration of sought substances. The extracted tetracyclines were analyzed by differential pulse voltammetry and HPLC-UV, respectively. The evaluation of both extraction schemes showed that the electrochemical method was comparatively more sensitive, whereas the chromatographic method exhibited a better extraction performance.

The functionalization of MIPs with magnetic materials has also been used for the separation of tetracycline antibiotics from foods such as egg and chicken tissue samples. In the preparation of the magnetic MIPs, hydrophobic Fe_3O_4 magnetite was used as the magnetically susceptible component, oxytetracycline as the template molecule, methacrylic acid as the functional monomer, and styrene and divinylbenzene as the polymeric matrix components. Following the magnetic isolation and desorption of the analytes, the residues were detected and quantified by LC-MS/MS [101].

MSPE has attracted considerable attention in recent years because

of its biological applications in cell isolation, enzyme immobilization, protein separation, and analytical applications related to the pre-concentration of organic compounds from large volume samples, including food matrices [79,102]. Compared to conventional pretreatment methods, the magnetically assisted separation is easier, faster, cheaper and environmental friendlier [2]. Furthermore, MSPE overcomes the problem of column packing by simply using an external magnetic field [113]. This type of technology for complex sample preparation has aroused great interest, since it provides improved efficiency in the extraction of target analytes [112].

3.4.2. Automated SPE

Over the last years, on-line and automated SPE have gained a great deal of popularity and have been recommended for chemical analysis. Automated SPE systems include on-line SPE with measurement of the eluate and SPE with direct on-column measurement. In general, the analyte is retained by the solid support, and once eluted with an appropriate solvent, it can be measured in the eluate or directly using the support. Although the configuration of the latter is not very common in analytical chemistry, it provides good detection limits because of the avoidance of the dilution phenomenon involved in the elution process [92]. On the other hand, most on-line SPE protocols for the determination of tetracyclines in animal-derived foods consist of SPE columns coupled with one of the following: HPLC systems [76–78,100,114], spectrophotometric detectors [74] or chemiluminescence [105] detectors.

To date, HPLC coupled with sample pre-treatment using SPE has been the on-line configuration most frequently used for tetracycline analysis in foodstuffs. Tetracyclines were determined in egg and honey samples by coupling HPLC with on-line SPE using PLRP-S [114] and C18 [78] columns, respectively. In addition, on-line SPE based on MIP coupled to HPLC-UV has also been used to determine tetracycline antibiotic residues in egg samples [100], and egg, milk, and milk powder samples [77]. All tested sorbents showed sufficient sensitivity for residue detection in the target matrices, achieving good recoveries in each case.

Essentially, there has been a clear trend toward the use of automation techniques that merge sample pre-treatment using on-line SPE with liquid chromatography separation. The coupling technique improves the accuracy and reproducibility of the chromatographic method. Furthermore, the sensitivity of on-line SPE-HPLC method is much better, in that the whole sample extract is transferred to the analytical column. In conventional off-line techniques, only a small portion of the extract is injected [92].

Apart from the on-line HPLC-SPE procedures, tetracyclines have also been determined in fish samples by coupling MIP-SPE with chemiluminescence flow injection analysis (FIA). Here, polytetrafluoroethylene (PTFE) tubes were packed with MIP and were connected to the FIA system injection valve sampling loop. The chemiluminescence intensity was found to be linear in the application range of the sample. The combination of these procedures resulted in a new flow method capable of on-line extraction and determination of tetracycline residues in foods [105].

Another flow injection method worth mentioning is the one associated with on-line tetracycline preconcentration from milk using SPE and subsequent spectrophotometric determination [74]. The extraction minicolumn is packed with C18 sorbent material. After treatment with trichloroacetic acid and McIlvain buffer, the samples are injected into the flow system and the tetracyclines adsorbed on the C18 resin are desorbed by a stream of eluent (methanol-buffer solution, 40:60, v/v). Here, the tetracyclines are conducted to the detector flow cell through the eluent. The analytical frequency of the flow system of six samples per hour is found to be very low relative to other FIA methods that can analyze between 42 [31] and 52 [36] samples per hour.

Remarkably, on-line SPE is best recommended because it offers several advantages, including a reduction in the sample pretreatment time, and thus, an increase in the sample throughput. This technique allows automated conditioning, washing, and elution processes. In addition, it can reduce the risks of sample contamination, as well as analyte degradation and loss by evaporation. Cartridges used in on-line SPE can usually be reused; this helps to reduce the amount of solvent consumed and the costs involved in organic solvent waste disposal [92].

3.5. Matrix solid-phase dispersion

Matrix solid-phase dispersion (MSPD) is a widely applied sample preparation procedure for extracting/purifying analytes from a variety of solid, semi-solid or highly viscous foodstuffs [12]. This technique consists of mechanical blending of the matrix onto a solid support to promote its complete disruption, allowing the interactions of the sample matrix with a solid support bonded-phase and the subsequent extraction of target analytes using a suitable elution solvent. MSPD is primarily used due to its simplicity, flexibility, selectivity, and the possibility of performing extraction and clean-up in a single step, leading to a more rapid pre-treatment and lower solvent consumption [115–117].

Over the last decade, MSPD procedures have been little reported for the extraction of tetracyclines in foodstuffs. Interestingly, a matrix solid-phase dispersion-capillary electrophoresis (MSPD-CE) method was developed by Mu et al. for the simultaneous determination of tetracyclines in milk. The proposed MSPD proved to be a simple and effective method for sample pretreatment. In that work, several solid support materials were investigated; and silica with bonded C18 chains was selected as the best sorbent [69]. Other authors proposed ultrasound-assisted dispersive extraction of tetracycline residues from milk samples with the determination performed by HPLC-DAD. Among the tested sorbents, Bond Elut Plexa was found to be the most efficient for the extraction of the analytes as it presented the highest recovery. The reliability of the method was additionally checked by the analysis of a bovine milk certified reference material [86].

3.6. Pressurized liquid extraction

Pressurized liquid extraction (PLE) uses conventional solvents at elevated pressures and temperatures that do not reach their critical point to extract solid samples more quickly [118]. In general, a solid sample is packed into a stainless steel extraction cell and extracted with a suitable solvent under elevated temperature (40–200 °C) and pressure (500–3000 psi) conditions for short periods (5–15 min). Finally, the sample extract is purged into a collection vial with the aid of compressed gas [119]. The use of solvents at temperatures higher than their atmospheric boiling point improves solubility of the analyte. Furthermore, it also enhances the mass transfer properties of the analyte, which in turn improves the extraction yields due to improved sample wetting, better solvent penetration and higher diffusion rates [120,121].

A multiclass UHPLC–MS/MS method was developed and validated for the analysis of different antimicrobial agents in eggs by combining a PLE technique for target compound extraction. Tetracyclines were extracted using a 1:1 mixture of acetonitrile and a succinic acid buffer (pH 6.0) at 70 °C [68]. Liu et al. also reported to have used PLE to extract tetracyline drugs from egg, fish and shrimp samples with the aid of HPLC-UV for residue determination. The extraction procedure employed a trichloracetic acid/methanol mixture set at elevated temperature (60 °C) and pressure (65 bar) [55]. While both methods were effective in accomplishing their goal, the latter appears to have attained better results than the former when one considers the limits of detection and recovery values obtained in each case. Here, an opposite result was expected, since the HPLC–MS/MS technique is relatively more sensitive and specific compared to the HPLC-UV. Thus, a greater efficiency of PLE procedure is observed in the latter compared to the former.

3.7. Microextraction techniques

Microextraction techniques evolved from the classic sample preparation procedures and basically consist of the miniaturization of the latter. These techniques were developed to address the following concerns: limited selectivity, incompatibility with instrumental techniques, the need to extract analyte traces from a large number of samples, the quest for the reduction of costs and time of analyses and for minimizing the consumption of hazardous organic solvents that pose serious environmental and public health problem [122].

These techniques rely on quantitative yet non-exhaustive transfer of analytes through the equilibration of small portions of adsorbents or sorbents and large amounts of samples in direct or indirect contact [123]. Solid-phase microextraction (SPME) and liquid-phase microextraction (LPME) are microextraction techniques that have arisen as a response to the drawbacks faced by traditional techniques [122]. Each miniaturized technique for tetracycline extraction presents its peculiarities, which are described in detail below.

3.7.1. Solid-phase microextraction

Solid phase microextraction (SPME) is a solvent-free sample preparation technique and consists of the miniaturizacion of the traditional SPE technique. In SPME, the analytes are sorbed onto the surface of silica fiber coated with an appropriate stationary phase. This technique is controlled by partition equilibrium and may be applied to gaseous (headspace vapor), liquid and solid samples. While the extraction maximum sensitivity is obtained at the equilibrium point, it is not necessary to reach this point to obtain good results. Thus, the extractions can be performed for a defined period of time [47,124].

The basic procedure for SPME involves two essential steps. The first step involves the partitioning of analytes between the sample matrix and the sorbent coating. This step is followed by desorption of the analytes into the suitable instrument mobile phase for separation, usually performed by GC or HPLC. In SPME-GC analysis, the analytes are thermally desorbed into the injector of the chromatograph; this is generally restricted to volatile and thermally stable compounds. Moreover, sample matrix derivatization is required for some applications. In the case of SPME-HPLC, desorption is carried out in an appropriate interface using a static or dynamic mode. The interface consists of six-port injector with a special fiber desorption chamber installed in place of sample loop. Here, desorption is carried out by means of an organic solvent or mobile phase. This is attributed to the fact that thermal desorption at high temperature promotes the degradation of the polymer and incomplete desorption of many nonvolatile compounds from the fiber. Nevertheless, in-tube SPME devices are generally more suitable for LC automation [47,124,125].

SPME matched with GC has been widely applied for metabolite analysis in plant extracts, food, environmental and biological samples. Research and development for implementation of this microextraction technique have been conducted in biomedical, botanical, pharmaceutical and food sciences [126]. By contrast, a review conducted by Ridgway et al. summarizes some automated in-tube SPME applications combined with HPLC using diode array (DAD) and mass spectrometry (MS) detector for analysis of endocrine disruptors and heterocyclic amines, respectively, in different foods [47].

A miniaturized SPE method was used for the preconcentration of tetracycline antibiotics in honey and milk using extraction sorbent based on chitosan-modified graphitized multiwalled carbon nanotubes (G-MWNTs) [98]. The analytes were extracted by passing the samples directly through the cartridges, using chitosan-modified G-MWNTs as the solid sorbent and a mixture of acetonitrile/acetic acid as the eluent in miniaturized SPE. Some variables, such as the amount of sorbent, elution solutions, and carbon nanotube types, were optimized in this procedure. Residues were detected by ultra high performance liquid chromatography and quadrupole time-of-flight mass spectrometry (UHPLC-Q-TOF/MS). The new synthesized sorbent showed excellent recoveries and a relatively strong adsorption and enrichment capacity toward tetracyclines.

The applicability of SPME to a broader array of analytes and matrices has been expanded by devoting much attention and efforts in the engineering of new sorbent materials. In this sense, ionic liquids (ILs) can be structurally designed aiming at a selective extraction of target analytes based on unique molecular interactions according to their unique physico-chemical properties. Considerable benefits can be gained by exploring this feature for SPME experiments, since selective extractions can be achieved by adding certain substituents into the structural make-up of these compounds. Thus, the application of ionic liquids as innovative sorbent materials for SPME contributes toward expanding the field of research [125].

3.7.1.1. Dispersive solid-phase microextraction.
Dispersive solid-phase microextraction (DSPME) is based on a concept similar to those of SPME and stir bar sorptive extraction (SBSE) methodologies. Instead of the column-like format, dispersive solid-phase sorbent particles are used to trap analytes for analysis [127,128]. Like the other aforementioned techniques, SBSE is another sorptive technique developed with the aim of overcoming the limited extraction capacity of SPME fibers. A glass stirrer bar is coated with a potentially thick bonded absorbent layer (PDMS) meant to provide a large stationary phase surface area; this yields a higher phase ratio (50–250 times greater than that of SPME), resulting in a better extraction capacity and high recovery. The analytes are transferred from the bar by thermal desorption with the aid of gas chromatography, or solvent elution for liquid chromatography [47,129].

In DSPME, the extraction and enrichment of the analytes is accomplished with the addition of only a small amount of dispersive solid sorbent to sample solution. After extraction, the sorbents containing the retained analytes are settled by centrifugation or filtration. They are then washed with a small volume of solvent for analyte desorption, discarding most of the liquid followed by drying. In this type of procedure, the target analytes fully interact more easily with the adsorbents; hence, the adsorption capacities obtained in this method are higher than in conventional SPE. Since its discovery, DSPME has been recognized as a promising sample preparation technique, though it has been little implemented in food analyses [128].

DSPME in combination with HPLC-DAD was applied for tetracycline determination in water and milk samples [91]. Milk samples were prepared using a modified QuEChERS method. Several silica-based and polymeric sorbents were assessed in their adsorption capacities to preconcentrate the analytes in the dispersive format from aqueous or organic solutions. The effects of various experimental parameters on the performance of the method were also investigated. Silica-based sorbents functionalized with amine or carbonyl groups presented the highest tetracycline adsorption under organic environment. In this procedure, the analytes were adsorbed in a small amount of the optimized dispersive sorbent and subsequently desorbed with a small volume of desorption solution for further analysis by HPLC. The sorbent functionalization here showed better capabilities for trapping tetracyclines than those of polymeric sorbents in the dispersive format under solvent-enhanced environment [127].

DSPME is superior to traditional SPE in terms of enhanced recovery, extraction time-reduction, solvent consumption minimization and protocol simplicity. In addition, the performance of DSPME processes can be improved considerably by selecting sorbents according to their advantages such as the presence of reaction centers and a high surface area [130]. Thus, the application of novel reactive and non-toxic nanostructure adsorbents that ensure a high surface area and reactive centers can improve the extraction capacity of the method.

3.7.2. Liquid-phase microextraction

Liquid-phase microextraction (LPME) emerged from the need to apply small volumes of liquids for analytical extractions; it is, in

essence, a miniaturized implementation of conventional liquid-liquid extraction [131,132]. This technique is based on the distribution of analytes between a small amount of an appropriate solvent and an aqueous phase containing these analytes. Research in this field was initiated in 1996 with the use of organic droplets suspended from the tip of a microsyringe, and the technique was named single drop microextraction (SDME). Later on, the technology was refined by implementing the use of porous hollow fibers for the protection of the extraction liquids. This gave rise to the development of hollow fiber liquid phase microextraction (HF–LPME) in 1999. In 2006, Rezaee et al. developed the dispersive liquid–liquid microextraction (DLLME) which represented an advancement in miniaturized liquid–liquid extraction [133,134]. The last two techniques have gained prominence in the analysis of tetracycline residues in animal-derived foods.

3.7.2.1. Hollow fiber membrane microextraction. Hollow fiber liquid phase microextraction (HF–LPME), also known as hollow fiber-supported liquid membrane (HFSLM), is a technique that uses a porous hollow cylindrical fiber typically made of polypropylene to immobilize organic solvent in pores [133,135]. A membrane represents a selective barrier between a donor phase and an acceptor phase, through which a certain amount of mass can be transferred from one phase to another. The membrane supported separation occurs thanks to the capacity of the membrane to transport some components from the donor phase to the acceptor phase faster than in other techniques; this process is also referred to as permeation [136]. In this technique, the extraction takes place inside the lumen of the polypropylene porous hollow fiber, which contains the microvolume of the extracting liquid. This ensures that the extracting liquid is not in direct contact with the sample solution [85].

In practical terms, the pores of a porous hollow fiber are impregnated with an organic solvent to produce immobilization of the solvent into the pores of the hollow fiber. Thus, a thin layer of organic solvent is formed inside the wall of the hollow fiber. The next step consists of filling the lumen of the hollow fiber with microliters of an appropriate acceptor solution (aqueous or organic phase). Finally, the hollow fiber is immersed into the aqueous sample (donor phase) containing the compounds of interest, without direct contact between the acceptor phase and the sample. To expedite the extraction, the sample can be extensively heated, agitated or stirred. The analytes are then extracted from the aqueous sample (donor phase) through the organic layer on the walls of the hollow fiber and then placed into an acceptor phase inside the lumen of the hollow fiber [85,133,135]. Fig. 6 illustrates a general scheme of the HF-LPME procedure.

HF-LPME is controlled by partition equilibrium and may be employed both in two-phase or three-phase mode (Fig. 7), according to the type of acceptor phase and the characteristics of the analytes to be extracted. In two-phase systems, the acceptor solution is the same organic solvent immobilized in the hollow fiber pores. This mode is usually used to extract hydrophobic compounds, i.e., analytes with high solubility in an organic solvent immiscible with water. However, in a three-phase mode, the acceptor solution is another aqueous phase with controlled pH. This extraction mode is limited to basic or acidic analytes with ionizable functions. In this HF-LPME configuration, the analytes must be in their non-ionized form in the donor solution to facilitate their dissolution in the thin film of organic solvent contained in the hollow fiber pores. The analytes are, thus, transferred into the aqueous acceptor phase. The acceptor phase is composed of an acidic or alkaline aqueous solution and must have a pH value opposite to that of the donor phase to favor analyte ionization. In this sense, one is able to prevent the possibility of the analytes returning to the organic phase and thus to the donor solution, favoring their extraction. In this method, the pH adjustment plays a central role [85,133,135].

Among the parameters that can affect the extraction efficiency of HF-LPME include type of hollow fiber materials, type and volume of organic solvent, pH of donor and acceptor phases, extraction time,
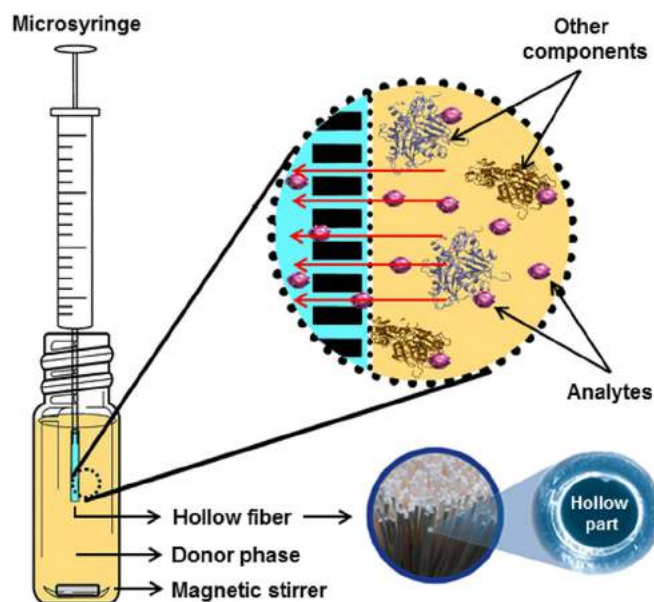

Fig. 6. Schematic illustration of the HF-LPME procedure.

temperature, stirring speed, and ion strength due to salt addition [135]. Carrier-mediated LPME is used as an active transport mode in order to promote the extraction of hydrophilic compounds from the donor aqueous phase into the organic phase [137]. The three-phase mode is the most commonly used configuration of HF-LPME because it is relatively easier to clean. In general, three-phase HF-LPME has been applied for the extraction and determination of analytes from complex matrices such as biological and food samples [138].

An efficient hollow fiber-based preconcentration method using carrier-mediated three-phase LPME prior to HPLC–UV was developed for simultaneous extraction and determination of tetracycline antibiotics from bovine milk, human plasma and water samples [139]. Milk samples are first pretreated with Na_2HPO_4. The effects of compositions of the aqueous sample and acceptor phase, type and volume of organic solvent, stirring rate and extraction time are evaluated in order to obtain high extraction efficiency. All the extractions are carried out using an Accurel Q3/2 polypropylene hollow fiber membrane. The carrier composed of a solution of 1-octanol containing 10% (w/v) of Aliquat-336 is immobilized in the pores of a hollow fiber. The aqueous acceptor phase, consisting of $0.1\ mol\ L^{-1}\ H_3PO_4$ and $1.0\ mol\ L^{-1}\ NaCl$ with pH = 1.6, is placed inside the lumen of the porous hollow fiber. The fiber is then immersed into the aqueous sample for subsequent tetracycline extraction. After this process, the aqueous extract obtained is directly injected into the HPLC system. The active transport mode of analytes allows a simple extraction setup with high clean-up effect and high enrichment factors as well as good precision.

Another technique that deserves mentioning is that proposed by Tajabadi et al. which combines HF-LPME with HPLC-DAD for the determination of tetracycline residues and other antibacterials in food samples [138]. Before the extraction procedure, all samples are adequately prepared to obtain an aqueous solution. The precipitation of proteins from milk sample is achieved by adding $K_3[Fe(CN)_6] \cdot 3H_2O$ and $Zn(CH_3COO)_2 \cdot 2H_2O$. The performance of the method is optimized by allowing the parameters to affect extraction using a Box-Behnken design under response surface methodology. HF is impregnated with 10% Aliquat-336 in 1-octanol to fill the pores with the solvent while the aqueous acceptor solution consisting of $1\ mol\ L^{-1}\ NaOH$ and NaCl is introduced into the lumen of the HF. Once the extraction procedure is completed, the analyte-enriched acceptor phase is analyzed using the HPLC instrument. The authors applied a multivariate curve resolution-alternative least squares (MCR-ALS) algorithm to solve the problem related to some overlapped peaks in multivariate second-order data of
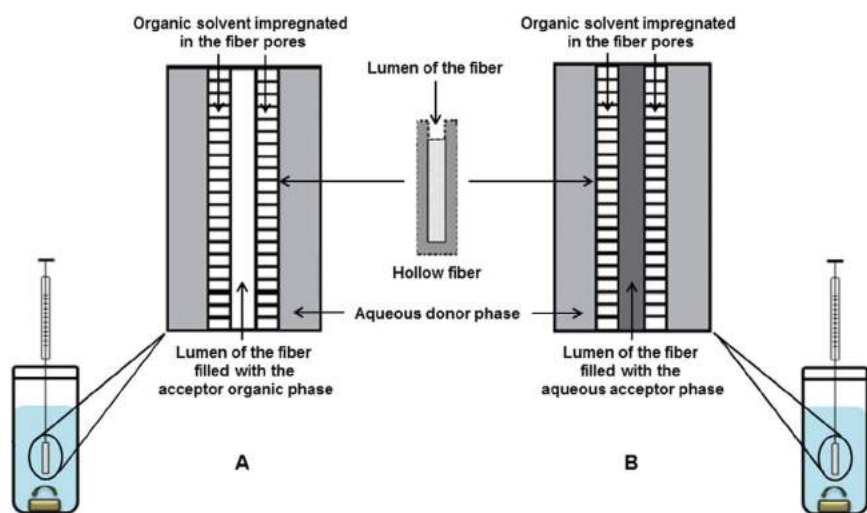
Fig. 7. Two-phase (A) and three-phase (B) systems involved in the HF-LPME technique.

HPLC-DAD. The applicability of the method was successfully confirmed by the extraction and determination of these drugs in milk, honey, fish and liver and muscles of lamb and chicken.

Based on the information presented in this section, one will find that the combination of HF-LPME with chromatographic systems proved successful for the extraction and detection of tetracyclines in food, biological and environmental samples. It should be noted that high enrichment factors, excellent sample clean-up within a short extraction time and low consumption of organic solvents are among the advantages of HF-LPME. In addition, the method allows the construction of different extraction units due to the high flexibility of the hollow fiber. Given the low cost of each extraction, the fiber can be used only once. This helps to avoid carry-over problems that is normally observed in other membrane extraction techniques [85,133,135].

3.7.2.2. Dispersive liquid–liquid microextraction. Dispersive liquid–liquid microextraction (DLLME) is a novel and powerful preconcentration technique that uses a ternary solvent system to separate the analytes of interest from the sample matrix [140]. The technique involves the dispersion of an extraction solvent (water-immiscible) and a disperser solvent (miscible with water and the extraction solvent) in an aqueous solution; this results in a large area of contact between the aqueous phase and the extraction solvent. In this way, a rapid transfer of analytes from the aqueous phase to the extractive phase occurs due to the partitioning process. By so doing, the extraction process quickly reaches the equilibrium state and it is independent of time [93]. In conventional mode, an appropriate mixture of extraction and disperser solvents is rapidly injected into an aqueous sample containing the analytes of interest. The mixture is then gently shaken to form a cloudy solution with microdroplets. In doing so, the analytes in the aqueous sample are rapidly extracted into the fine droplets of the extraction solvent due to the increase in the contact surface between both phases (aqueous and organic). The extraction phase is separated from the cloudy mixture by centrifugation and the enriched analytes in the sedimented phase are determined by the most appropriate analytical technique [51,140–142]. Fig. 8 provides a simplified diagram of the steps involved in the DLLME technique.

Ultrasound-assisted dispersive liquid–liquid microextraction (US-DLLME) was employed toward the development of a method for extracting tetracycline drugs from egg supplement samples [51]. Residues were rapidly determined by spectrophotometric FIA using a liquid waveguide capillary cell (LWCC) in-line with a controlled temperature heating bath. The samples were first treated with trichloroacetic acid to precipitate the proteins. Some factors affecting the extraction efficiency, such as the extraction solvent (μL), disperser solvent (μL), and sonication, extraction and centrifugation times, were optimized by
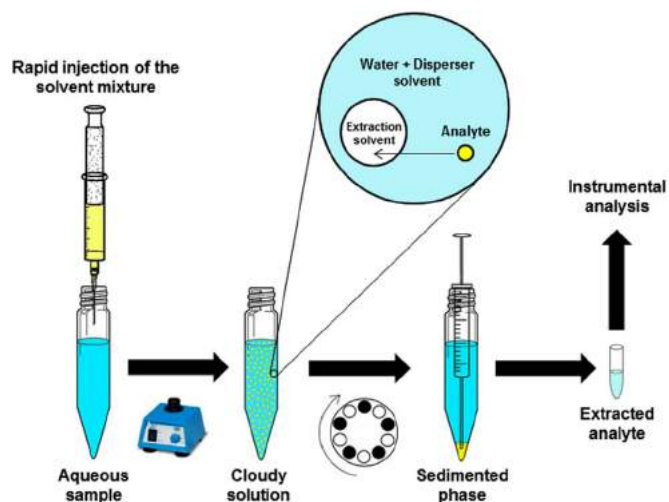

Fig. 8. Schematic diagram representing the steps involved in the DLLME technique.

multivariate analysis. Chloroform was found to be most effective for the extraction of individual tetracyclines. With regard to dispersive solvents, ethanol and acetonitrile exhibited the best overall recoveries probably due to better dispersion of the extraction solvent (chloroform) in the aqueous phase. Nevertheless, ethanol was chosen as the best dispersive solvent owing to the fact that it is a greener solvent and relatively less costly. It is worth pointing out that tetracycline recovery was reported to have improved by approximately 6% when the microextraction was assisted by ultrasound.

An obvious disadvantage of the traditional DLLME is that it requires the use of organic solvents such as extraction and dispersive solvents [143]. Ionic liquids (ILs) are organic salts consisting exclusively of organic cations paired with organic or inorganic anions. These liquids have been widely applied as possible "green solvents" in various fields of chemistry. The compounds often present melting points below or equal to 100 °C. The greatest importance of ionic liquids lies in the possibility of designing their chemical structure in such a way to produce the desired properties, including elevated thermal stability, low vapor pressure, tunable viscosity, and miscibility with other solvents, as well as the capability of undergoing numerous solvation interactions. In general, ILs are non-toxic and non-flammable, as such, they are considered less polluting to the atmosphere and less dangerous for the analysts compared to traditional organic solvents. As a result, ionic liquid-based microextraction techniques have been the focus of study during the last few years. The core objective of the use of these

techniques is to improve extraction and enrichment performance beyond those of the conventional sample preparation techniques [125,144].

In this context, Song et al. developed an ionic liquid-based dispersive liquid–liquid microextraction (IL-DLLME) procedure combined with HPLC aimed at determining tetracycline drugs in eggs [145]. Among the four ILs tested, 1-butyl-3-methylimidazolium hexafluorophosphate showed the best extraction performance. To optimize the microextraction procedure, several parameters found to influence the extraction efficiency (ionic liquid and its volume, disperser solvent and its volume, extraction and centrifugation time, pH and salt addition) were investigated.

More recently, a novel naphthoic acid-based ionic liquid was developed and optimized as a non-organic solvent for the microextraction of tetracycline antibiotics from milk and chicken eggs, followed by HPLC-UV determination [66]. In that work, the synthesized ionic liquid 1-butyl-3-methylimidazolium naphthoic acid salt ([C4MIM][NPA]) was used as extraction solvent while a conventional ionic liquid of 1-ethyl-3-methylimidazolium tetrafluoroborate ([C2MIM][BF4]) was employed as disperser solvent. The use of [C4MIM][NPA] in functionalized ionic liquid-based NOSM method led to an increase in extraction efficiency by more than 20%. It also modified the pH of the process because of its strong acidity, thus helping to rule out an additional pH adjustment step.

As with all other sample preparation techniques, there are certain constraints associated with DLLME. One of such limitations is the difficulty in automating the procedure by virtue of the need for phase separation steps. Moreover, the extracting solvent does not isolate the analytes from the soluble coextractives; this can cause errors in the quantification and affect the accuracy and precision of the results due to the matrix effect. The HF-LPME technique presents difficulty in analyzing highly polar and hydrophilic compounds. In view of that, it becomes necessary to add carrier agents in the sample that allow an increase in the permeability of these analytes in the hydrophobic membrane. Another current disadvantage of HF-LPME is the lack of commercially available equipment. The extraction units are usually cut to appropriate length and sealed using manual operation procedures, which affects the method precision. This shortcoming has imposed constraints on the application of HF-LPME in routine laboratories [85,146].

Despite the demerits associated with these techniques, their useful benefits have rendered them suitable for application in the extraction and preconcentration of various types of analytes in different matrices. Their utilization has contributed towards achieving high preconcentration factors. In general, LPME is simple, affordable, rapid, selective, and easy to operate, apart from yielding high recovery of the analytes. Its importance lies in the considerable reduction or even elimination of the toxic solvents used [133]. In sample preparation procedures developed in recent years, these common solvents are often replaced by ILs, which are gaining widespread recognition as novel solvents in chemistry. The wider preference of ILs over common solvents is attributed to the fact that the former are considered less polluting to the atmosphere and less hazardous to the user. Many researchers regard ILs as possible green solvents [147,148]. The implementation of environmentally safer separation processes plays an increasingly important role in the development of extraction technology.

4. Concluding remarks

This work presents an overview of recent advances in sample preparation technologies for the determination of tetracycline residues in foodstuffs, focusing on milk and egg matrices. We have thoroughly reviewed the main extraction and clean-up techniques that are currently applied in the field. Most articles in the literature espouse the need for carrying out sample treatment before the cleaning step. Few

methods were capable of detecting tetracycline residues in animal-derived foods without an appropriate sample treatment. This can be explained by the nature of complexity of food matrices.

Food analysis exhibits a clear trend toward the development of methods for determining a broad range of compounds in a single analysis step. Direct analysis in real time mass spectrometry (DART-MS) stands out among the discussed analytical techniques; this is by virtue of the fact that it allows the determination of both major and minor components in complex matrices with minimal or even no sample preparation. This rapid developing technique blended with the continuous advances in high resolution mass analyzers can fulfill the promise of a simple, rapid and high-throughput mass spectral analysis in situ of a large variety of samples. Nonetheless, from our investigation, we noted lack of scientific reports that shed light on the use of DART-MS schemes for tetracycline detection. While DART-MS is recognized as the best technique among the lots, one cannot ignore the fact that the lack of a separation step prior to ionization during the application of the technique can often result in very pronounced signal suppression and consequently lower detection selectivity. In this sense, sample treatment efficiency and mass resolution are key factors to consider when one chooses to perform analyses using DART-MS. Despite its limitations, DART-MS is regarded an emerging frontier technology for evaluating food authenticity and safety.

To date, sample preparation remains the crucial step for tetracycline drug determination in foodstuffs. The main efforts in this field have been directed toward the optimization of the preparation, extraction and clean-up steps, as well as the improvement of environmental compatibility of these procedures. Clearly, the development and application of new extraction approaches in the near future will undoubtedly help in routine monitoring, and will imply a drastic reduction of both work effort and time.

The isolation of tetracycline residues from food samples such as milk and egg is commonly aided by an organic solvent, usually acetonitrile or methanol, or by the combination of these solvents with acid compounds or buffer solutions. These extraction methods are often accompanied by cleaning steps for the separation of co-extracted matrix components aiming at obtaining a more purified sample extract for subsequent analysis using an appropriate technique.

Concerning the cleaning methods, SPE has become the most widely used approach for purification and preconcentration of these types of compounds in foods such as milk and eggs. This can be attributed to its simplicity, low cost, quickness, reduced time, low consumption of organic solvent, and availability of a wide range of sorbents. However, a major concern in the analysis of tetracyclines using traditional SPE sorbents lies in the tendency of the compounds to bind irreversibly to silanol groups contained in silica-based materials (C8, C18). These silanol groups either interact with the TC ketone groups or form chelate complexes with metal ions, which may result in low recovery yields during sample pre-treatment. Thus, these sorbents are prone to interferences by impurities in complex samples, and their cartridges are for single use only. Progress made in more efficient materials for SPE drives the trend towards more sensitive detection together with high sample throughput and less time devoted to sample clean-up.

Magnetically assisted chemical separation, which uses magnetite nano- or micron-sized particles coated with silica, has attracted great research interest in sample preparation over the last two decades. This technology has proved to be ideal for MSPE, in that silica shell presents reliable stability in aqueous media besides having a large surface area. The use of MSPE helps overcome the problem of column packing by simply using an external magnetic field.

Selective sorbents like MIPs are perhaps among the most innovative materials in the sample preparation field, even for the analysis of tetracyclines in foods. This molecular imprinting technology has drawn the attention of many researchers as an attractive alternative for the analysis of complex samples. The attractiveness of MIPs is attributed to their ability to selectively retain analytes and exclude macromolecules.

MIP-based sorbents can be used several times. These sorbents offer a much more selective analyte extraction than conventional SPE sorbents. The main problem here has to do with the selectivity of the analyte in the presence of the matrix interferents. Rigidity, physical robustness, resistance to elevated temperatures and pressures, and inertness towards acids, bases, metal ions and organic solvents are among the advantages of MIPs. The main drawbacks of these more selective sorbents are that they are expensive and less suitable for harsh environments.

The current trend toward miniaturization of sample preparation procedures has resulted in the development of several microextraction techniques. These techniques are characterized by low cost, high extraction efficiency, reduced solvent amount and ease of device automation. Besides that, they also allow a relatively straightforward adaptation of the methods for on-site analysis. Miniaturization and integration allow the shortening of the sample extraction route. They are likewise highly effective in saving analysis time and in improving reproducibility compared with the manual protocols. Admittedly, the introduction of automated techniques usually leads to a rise in costs. As reported in the present review, dispersive-SPME, HF–LPME, and DLLME are miniaturized extraction techniques developed from traditional SPE or LLE. These techniques have gained popularity in the analysis of tetracycline residues in foods, such as milk and eggs. The success of microextraction lies in the improved analytical performance that can be achieved when this kind of techniques is applied. In addition to that, several properties pertinent to microextraction indicate that these miniaturized techniques are within the framework of green chemistry.

Regarding the new solvents applied in extraction and microextraction methods, recent advances have been embedded on the employment of solvents with low toxicity, such as ionic liquids. We expect to see further development of these new solvents because their unique properties bring great versatility and possible green character for application in various chemistry fields. Furthermore, ionic liquids are compatible with a variety of instrumental techniques. The study of ionic liquids has become an increasingly growing and promising field of research that is devoted to eliminating the use of dangerous chemical products. The methods involving the use of these new "green" solvents along with the traditional miniaturization procedure, undoubtedly, contribute toward the reduction of harmful impacts of analytical activities.

Overall, to date, the number of different extraction and clean-up techniques and their application toward the determination of tetracycline residues has seen an overwhelming growth. Fundamentally, these techniques are developed aiming at improving compatibility with modern analytical instruments in addition to contributing toward the avoidance of the use of hazardous chemicals and allowing sampling and pretreatment of the most varied food products. Despite the existence of valuable studies in this area, there still remains the quest for developing sample preparation procedures that can be widely applied for analysis of tetracycline antibiotics in foodstuffs. Such procedures should also be capable of exhibiting suitable operational features, including simplicity, quickness, miniaturization, automation, costlessness and safety. The implementation of environmentally safer separation processes plays an increasingly important role in the development of extraction technology.

Acknowledgments

Conflicts of interest

The authors declare no conflicts of interest.

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