Universidade de São Paulo
Escola Superior de Agricultura "Luiz de Queiroz"

Microextração sólido-líquido para diotiocarbamatos em alimentos *in natura*

Fernanda Cristina de Oliveira Lopes Martins

Dissertação apresentada para obtenção do título de Mestra em Ciências. Área de concentração: Ciência e Tecnologia de Alimentos

Piracicaba
2022

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Engenheira de Alimentos

Microextração sólido-líquido para diotiocarbamatos em alimentos *in natura*

versão revisada de acordo com a resolução CoPGr 6018 de 2011

Orientadora:
Profa. Dra. **WANESSA MELCHERT MATTOS**

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1. Manebe 2. Microextração sólido-líquido 3. Alimentos 4. Espectroscopia de absorção atômica de chama I. Título

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À Fernanda Braga que é uma grande amiga, que desde o tempo do Colégio Tiradentes acreditou em mim e por estar do meu lado em todos os momentos.
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“Quando se sonha sozinho é apenas um sonho.
Quando se sonha juntos é o começo da realidade.”

Miguel de Cervantes

CONTENTS

RESUMO

Microextração sólido-líquido para diotiocarbamatos em alimentos *in natura*

Os ditiocarbamatos têm sido bastante empregados nas práticas agrícolas em razão da eficiência em evitar/controlar pragas, e também devido à baixa toxicidade e instabilidade quando comparados com outros pesticidas. Entretanto, esta classe pode proporcionar alguns efeitos adversos para a saúde humana, necessitando do controle em amostras de alimentos. Este trabalho foi dividido em dois capítulos, no primeiro, revisão bibliográfica detalhada foi realizada para as microextrações de fase sólida e líquida de pesticidas carbamatos e ditiocarbamatos em amostras de alimentos. Vantagens e desvantagens, aplicações, comparações com os métodos tradicionais de preparo de amostras e discussões dos parâmetros analíticos foram exploradas ao longo do texto. No segundo capítulo, foi desenvolvido laboratorialmente uma metodologia de microextração de manebe de alimentos *in natura*. Para tanto, foi explorada microextração sólido-líquido com determinação indireta de manebe por espectroscopia de absorção atômica de chama com injeção em fluxo. Resposta linear foi observada entre 0,9 a 20,0 µmol L^{-1} de manebe, boa repetibilidade (4,0%) e reprodutibilidade (3,4%), limites de quantificação (6,0 µmol L^{-1}) e detecção (0,20 µmol L^{-1}), abaixo do estabelecido pelos órgãos reguladores. A extração do manebe foi realizada com 685 µL da solução $1{,}0x10^{-3}$ mol L^{-1} de EDTA, e apresenta excelentes valores de recuperação de 86 a 103%. A metologia desenvolvida é uma alternativa ambientalmente amigável para a extração de manebe de amostras de alimentos (maçã, mamão e tomate) e não é influenciada pela degradação do composto alvo.

Palavras-chave: Manebe, Microextração sólido-líquido, Alimentos, Espectroscopia de absorção atômica de chama

ABSTRACT

Solid-liquid microextraction to dithiocarbamates in natura foods

Dithiocarbamates have been widely used in agricultural practices due to their efficiency in avoiding and/or controlling pests, and also by low toxicity and instability compared to other pesticides. Nonetheless, this class can provoke some adverse effects on human health, needing the determination of them in the food samples. This work was divided into two chapters, in the first, a detailed bibliographic review was made for solid-phase and liquid-phase microextractions of the carbamates and dithiocarbamates in food samples. The advantages, disadvantages, applications, comparations with traditional methods, and discussions of the analytical parameters were explored throughout it. In the second chapter, it was developed laboratory a microextraction methodology for the extraction of maneb natura foods. Therefore, it was explored the solid-liquid phase microextraction for maneb with posterior indirect determination by flow injection analysis-flame absorption atomic spectroscopy. The linear range was from 0.9 to 20.0 µmol L^{-1} of maneb, good repeatability (4.0%) and reproducibility (3.4%), detection (0.20 µmol L^{-1}), and quantification (6.0 µmol L^{-1}) limit, below of the established by regulatory agencies. The extraction of maneb was made using 685 µL of solution of the $1.0x10^{-3}$ mol L^{-1} of EDTA and showed excellent recovery from 86 to 103%. This microextraction demonstrated be an alternative environmentally friendly for the maneb extraction from foodstuffs (apple, papaya, and tomato), and it was not influenced by degradation of it.

Keywords: Maneb, Solid-liquid phase microextraction, Foods, Flame atomic absorption spectroscopic

FIGURE LIST

Chapter 1:

Chapter 2:

1. CONTEXTUALIZAÇÃO

Os ditiocarbamatos é uma classe bastante empregada nas práticas agrícolas em razão da baixa toxicidade e ampla aplicabilidade no controle de fungos e outras pragas. Além disto, esta classe é especial quando comparada com as outras devido ao emprego dos compostos na área industrial, práticas agrícolas e também na medicina. Isto ocorre por causa dos diferentes níveis de toxicidade, quando ingeridos inadequadamente acima da Nível Sem Efeitos Adversos Observáveis (NOAEL, do inglês No Observed Adverse Effect Level) podem provocar efeitos adversos à saúde humana. Agências regulamentadoras de cada país e o *Codex Alimentarius* estabelecem limites máximos de resíduos destes pesticidas em água e alimentos.

O desenvolvimento de metodologias para determinação dos ditiocarbamatos de forma seletiva e sensível é fundamental. No entanto, a composição das amostras podem influenciar diretamente no resultado analítico devido aos efeitos dos interferentes, sendo necessárias etapas de preparo de amostra, para minimizar/eliminar os efeitos de matriz. Estas etapas, geralmente, empregam grandes quantidades de solventes orgânicos e são muito morosas, promovendo erros sistemáticos e até mesmo contaminações. Alternativamente podem ser utilizadas na extração dos ditiocarmatos as microextrações de fase sólida e líquida, as quais são baseadas nas metodologias tradicionais de extração de fase sólida e extração líquido-líquido, respectivamente.

A dissertação apresentada é focada nos pesticidas ditiocarbamatos e em uma alternativa de extração ambientalmente mais amigável. O trabalho foi dividido em dois capítulos, no primeiro, revisão bibliográfica detalhada foi realizada para as microextrações de fase sólida e líquida para a extração de pesticidas carbamatos em amostras de alimentos. Vantagens e desvantagens, aplicações, comparações com os métodos tradicionais de preparo de amostras e discussões dos parâmetros analíticos foram exploradas ao longo do texto. No segundo capítulo, foi desenvolvido laboratorialmente uma metodologia de microextração de manebe de alimentos *in natura*. Para tanto, foi explorada microextração sólido-líquido com determinação indireta de manebe por espectroscopia de absorção atômica de chama com injeção em fluxo.

2. CURRENT OVERVIEW AND PERSPECTIVES IN ENVIRONMENTALLY FRIENDLY MICROEXTRACTIONS OF CARBAMATES AND DITHIOCARBAMATES[*]

Highlights:

- Only eight carbamates are permitted in the USA and EU.
- DLLME, HF-LPME, and SDME are widely employed in the extraction of carbamates and dithiocarbamates.
- Classification and timeline of the microextractions evolution used for extraction of them are shown.
- Different SPMEs were used in the extraction of the carbamates and dithiocarbamates.

Abstract

Carbamates and dithiocarbamates are two classes of pesticides widely employed in the agriculture practice to control and avoid pests and weeds, hence, the monitoring of the residue of those pesticides in different foodstuff samples is important. Thus, this review presents the classification, chemical structure, use, and toxicology of them. Moreover, it was shown the evolution of liquid- and solid-phase microextractions employed in the extraction of carbamates and dithiocarbamates in water and foodstuff samples. The classification, operation mode, and application of the microextractions of liquid-phase and solid-phase used in their extraction were discussed and related to the analytical parameters and guidelines of green analytical chemistry.

Keywords: Pesticides, Microextractions, Liquid-phase microextraction, Solid-phase microextraction, Foodstuff samples

2.1. General considerations

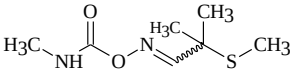
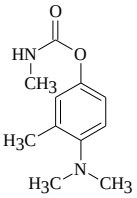
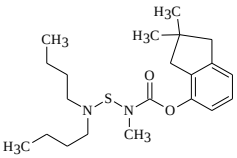
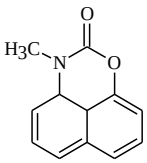
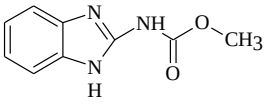
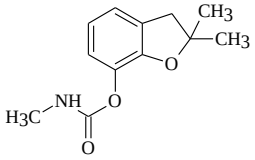
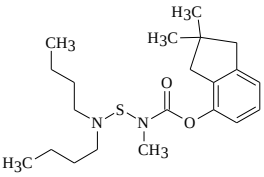
Several chemical compounds are employed in agricultural practice to eliminate and control diverse types of pests and weeds, which results in higher productivity with lower costs, and consequently increases profits. The pesticides can be classified into 9 classes according to their action function, and they can be divided into more specific groups based on their toxicity, chemical structure, and source. The most common classification is based on the chemical structure and gathers the compounds with similar physicochemical properties, such as organochlorines, organophosphates, carbamates, pyrethroids, bipyridyls, morpholines, triazines, and dithiocarbamates (Kaur et al., 2021; Reserved, 2011; Sharma et al., 2020).

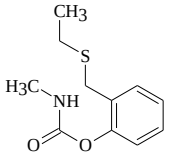
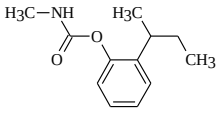
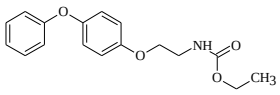
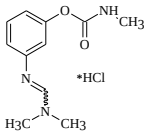
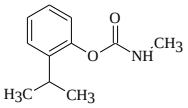
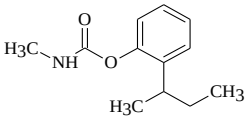
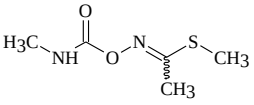
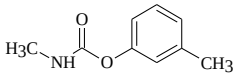
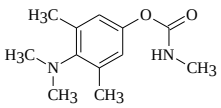
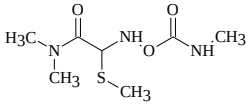
The carbamates are the most versatile class, which can be employed as an acaricide, insecticide, miticide, molluscicide, nematicide, and fungicide. These compounds have been employed since the 1960s in the control and prevention of diverse weeds and pests. Their mode of actuation is similar to the organophosphate class that inhibits the acetylcholinesterase enzyme and provides the overstimulation of the nervous system (Ghosh et al., 2015; Verma et al., 2021). However, carbamates toxicity is lower compared to organophosphate, due to its shorter half-life and reversible effects, moreover, their degradation can be accelerated by microbial degradation oxidation and hydrolysis of the compounds (Bhatt et al., 2021; Mishra et al., 2020, 2021). Thus,

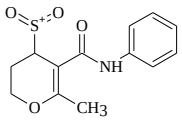
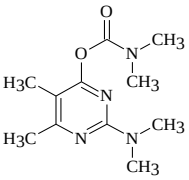
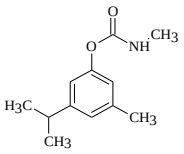
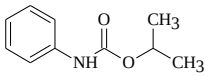
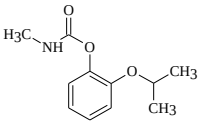
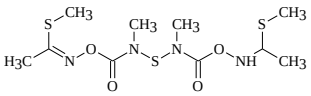
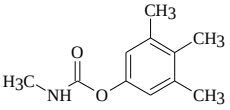
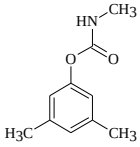
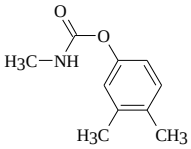
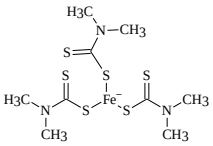
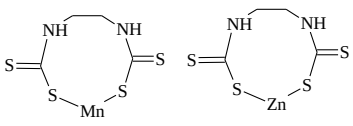
[*] This chapter composes is currently in press as: MARTINS, F. C. O. L., BATISTA, A. D., MELCHERT, W. R., **Current overview and perspectives in environmentally friendly microextractions of carbamates and dithiocarbamates.** In: Comprehensive review in food science and food safety.

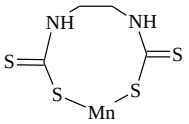
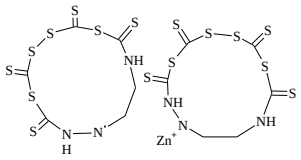
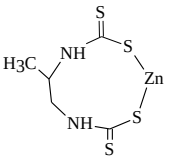
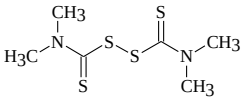
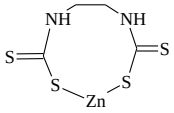
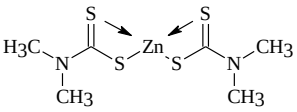
Table 1.1 is presented all the 27 carbamates with their respectively chemical structure, which present a carbamic acid (R-O-CO-NH-R') (Bleecker, 2008; R. C. Gupta, 2006; Horsak et al., 2005; Pang et al., 2020).

Table 1.1: The compounds of the classes of carbamates and dithiocarbamates with their chemical structures, use in agriculture, and maximum residue limit and toxic effect (Biscaldi et al., 1986; Cao et al., 2019; EPA, 1994a, 1994b, 1995, 1997, 1998, 2004b, 2004a, 2005b, 2005a; European Food Safety Authority, 2010; Food and Agriculture Organization of the United Nations World Health Organization et al., 2020; Pawan K. Gupta, 2018; R. C. Gupta, 2006; "Handbook of food toxicoloy," 2002; Janz, 2014; McCarroll et al., 2002; Padilla et al., 2007; Park et al., 2021; Rodgers, 2001; Sams et al., 2010; Shibamoto et al., 2004; Union, 2020; Zhu et al., 2019).

Class	Compounds	Structures	Use (MRL / mg kg^{-1})	Toxic effect
Carbamates	Aldicarb		Insecticides (0.01 – 0.5)	Sweating, headache, and nausea
	Aminocarb		Insecticide *(0.01)	Decrease humoral immune response to neutral and pathogenic antigens and increase the cytolysis of macrophages by virus
	Benfurocarb		Insecticide and nematicide *(0.01)	Miosis and suppressions of circulatory and autonomic nervous systems
	Carbaryl		Insecticide (0.02 – 170)	Pulmonary edema, effects in cardiovascular and respiratory systems, lacrimation, salivation, tremors, nausea, miosis, muscle incoordination, abdominal pain, profuse sweating, lassitude, vomiting, and cancer
	Carbendazim		Fungicide (0.05 – 20)	Teratogenic, mutagenic, degeneration of germinal tissue, aspermatogenesis and depressed caudal epididymitis weight
	Carbofuran		Acaricide, insecticide and nematocide (0.05 – 2)	Salivation, lacrimation, urinary incontinence, diarrhea, gastrointestinal cramping, and emesis
	Carbosulfan		Insecticide (0.05 – 0.3)	Eye and skin irritantig, and it is a dermal sensitizer. Salivation, lacrimation, ataxia, tremors, anogenital staining, diarrhoea

Croneton		Insecticite *(0.01)	Carcinogenicity, mutagenicity, or reproductive toxicity
Fenobucarb		Insecticide *(0.01)	Possible risk factor to cardiovascular and cerebrovascular systems
Fenoxycarb		Acaricide and insecticide *(0.01 – 3)	Decrease body weight gain and mean organ weight (liver and brain)
Formetanate		Insecticide, acaricide, and miticide *(0.01 – 4)	Inhibition in both brain and red blood cells
Isoprocarb		Insecticide *(0.01)	-
Methiocarb		Acaricide, insecticide and molluscicid e (0.04 – 2)	Inhibition of red blood cell and plasma cholinesterase
Methomyl		Insecticides (0.02 – 20)	Muscle weakness, dizziness, sweating, slight body discomfort, headache, salivation, nausea, vomiting, abdominal pain, diarrhea, contraction of the pupils with blurred vision, incoordination, muscle twitching, and slurred speech
Metolcarb		Acaricide and insecticide *(0.01)	Carcinogenic, teratogenic, and/or mutagenic
Mexacarbamate		Insecticide *(0.01)	-
Oxamyl		Insecticides , minicite and nematicide (0.01 – 0.04)	Malaise, osteoporosis, excessive sweating, nausea, abdominal pain, and miosis with unclear vision

	Oxycarboxin		Fungicide *(0.01 – 0.05)	Kidney: lesions of the renal tubules, chronic nephritis, progressive nephropathy. Bone/Parathyroids: Fibrous osteodystrophy of the femur/parathyroid hyperplasia. Hepatocellular carcinoma
	Pirimicarb		Aphicide *(0.01 – 5)	Inhibiting the enzyme acetylcholinesterase in nervous tissue
	Promecarb		Acaricide and insecticide *(0.01)	Skin causing a rash and itching, and damaging the liver and kidneys
	Propamocarb		Fungicide (0.01 – 100)	Non evidenced
	Propoxur		Insecticides *(0.05 – 1)	Carcinogenic
	Thiodicarb		Insecticide *(0.01 – 0.05)	Carcinogenic and neurotoxic
	Trimethacarb		Insecticide and molluscicide *(0.01)	Slight eye irritation
	XMC		Insecticide *(0.01)	-
	Xylylcarb		Insecticides *(0.01)	-
Dithiocarbamates	Ferbam		Fungicide *(0.01)	Slight eye or skin irritant, and weak dermal sensitizer, neurotoxicity, and toxic for liver, kidneys, and lungs
	Mancozeb		Fungicide *(0.05 – 25)	Poor gastrointestinal, transdermal absorption, itching, scratchy throat, sneezing, coughing, inflammation of the

			nose and throat, bronchitis, and high the risk of developing Parkinson's disease
Maneb		Fungicide *(0.05 – 25)	Skin irritation and sensitization (itching and mild erythema), teratogenicity, and high the risk of developing Parkinson's disease
Metiram		Fungicide *(0.05 – 25)	Carcinogenic, and endocrine effects
Propinebe		Fungicide *(0.05 – 25)	Carcinogenicity, teratogenicity, malfunction of the reproductive system, and abnormalities
Thiram		Fungicide *(0.1 – 2)	Neurotoxic effects (lethargy and reduced motor activity)
Zineb		Fungicide *(0.01)	Primary target organs appear to be the nervous system, liver, and thyroid, eye and skin irritation
Ziram		Fungicide *(0.05 – 25)	Neurodegenerative diseases such as Parkinson's

* Pesticides not allowed in EU and USA

The dithiocarbamates are fungicides chemically similar to the carbamates, where two oxygen are replaced by sulfurs resulting in the dithiocarbamic acid (R-S-CS-NH-R'), the degradation of them is influenced mainly by the medium pH, being that in alkaline pH can provoke their instability (Adeyemi et al., 2020; Riadi et al., 2010). This class is composed of 8 compounds, as shown in Table 1.1. These compounds were developed in the 1930s for applications during World War II as commercial fungicides for use in household products, in the treatment of ornamental plants, vegetables, crops, and seeds. Furthermore, some of these substances can have clinical applications, due to differences in the mode of actuation of biological activities of enzymes, proteins, and consequently, in their toxicity (Biscaldi et al., 1986; Janz, 2014; Reserved, 2011; Rubino et al., 2013; Szolar, 2007).

However, the use of dithiocarbamates and the majority of carbamates was prohibited by the Codex Alimentarius, European Union (EU), and the United States (USA) due to their toxic effects. Their chemical characteristics and toxicity are directly related to their chemical structure, which contains a carbamic or dithiocarbamic acid and two functional chains (R1 and R2), where could contain heteroatoms (manganese, zinc, iron), organic functions (ether, amine, thioether), and/or an aromatic ring (Biscaldi et al., 1986; Food and Agriculture Organization of the United Nations World Health Organization et al., 2020; Reserved, 2011; Union, 2020).

Some recent researches in in-vitro shown that carbamates and dithiocarbamates can provide reproductive, genotoxic, cytotoxic, toxic, and among other effects in animal and human cells, such as carbamates can cause inhibition of succinic dehydrogenase activity and cell viability in hamsters, already, in humans can provide apoptosis and necrosis to some cell. instability (Bhatt et al., 2021; Adeyemi et al., 2020; Mishra et al., 2020, 2021; Riadi et al., 2010). Table 1.1 shows the toxic effects for each carbamate and dithiocarbamates, which are provided by ingestion of inadequate concentration of carbamates and/or dithiocarbamates, such as in the central nervous system and thyroid, neuropathology, bone tumors, uterus, bladder, adrenal gland, kidney, and liver, among others. Hence, toxicity researches have established LD50 to carbamates and dithiocarbamates that are between 2.50 - 200 mg kg^{-1} and 18 - 4000 mg kg^{-1}, respectively (Biscaldi et al., 1986; Cao et al., 2019; EPA, 1994b, 1994a, 1995, 1997, 1998, 2004b, 2004a, 2005a, 2005b; European Food Safety Authority, 2010; Food and Agriculture Organization of the United Nations World Health Organization et al., 2020; Pawan K. Gupta, 2018; R. C. Gupta, 2006; “Handbook of food toxicology,” 2002; Janz, 2014; McCarroll et al., 2002; Mishra et al., 2021; Padilla et al., 2007; Park et al., 2021; Rodgers, 2001; Sams et al., 2010; Shibamoto et al., 2004; Union, 2020; Zhu et al., 2019).

Although, adequate concentrations of some dithiocarbamates and carbamates can be employed for pharmacological purposes at therapeutical concentrations. Thus, some carbamates can aid in ophthalmic disorders, muscle and anxiety tension, treatment of Parkinson's and Alzheimer’s disease, chemotherapy, and also as an antiretroviral drug against AIDS/HIV. While some dithiocarbamates can be used as antiseptics and antimycotics (Biscaldi et al., 1986; P. K. Gupta et al., 2007; “Handbook of food toxicology,” 2002; Kaul et al., 2021; Moretto et al., 2011). Their toxicity is closed related to their chemical structures, which consequently affects the establishment of the maximum residue level (MRL) by regulatory agencies in the raw materials and foodstuffs (Food and Agriculture Organization of the United Nations World Health Organization et al., 2020; Union, 2020).

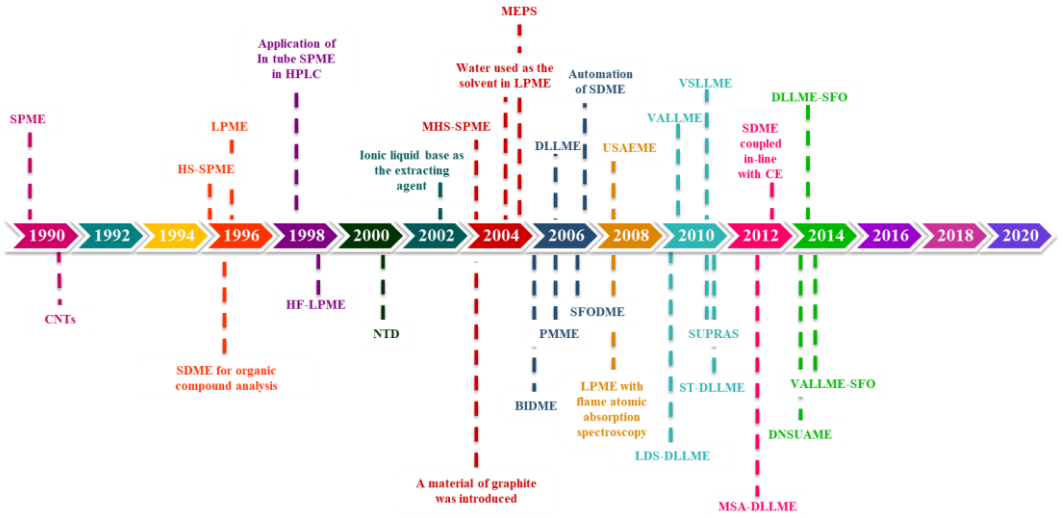
The residues control of the dithiocarbamates and carbamates in foodstuffs is carried out by different analytical techniques, such as spectroscopy (Chu et al., 2009; Gonzálvez et al., 2011; Przybylski et al., 2009), chromatography (Y. Chen et al., 2021; N. Li et al., 2015; Murillo Pulgarín et al., 2020; Xu et al., 2021), and electroanalytical (Gonçalves-Filho et al., 2020; Oliveira et al., 2020), which present different analytical performance, such as linear range, precision, accuracy, sensitivity, selectivity, robustness, analytical frequency, sample preparations, cost, and operationally (Christian et al., 2014; Harris, 2009; Martins et al., 2020; Skoog et al., 2014). However, the high complexity of foodstuff sample composition can hinder the accuracy of the analytical procedures, which makes necessary the use of sample preparation methodologies before instrumental analysis to remove potential interferents (Christian et al., 2014; Samsidar et al., 2018; Skoog et al., 2014). Additionally, the low concentration levels of these analytes in this kind of sample, make mandatory a preconcentration step, which can be performed concurrently with sample clean-up, depending on the chosen sample preparation technique (Christian et al., 2014; Mitra, 2004; Nasiri et al., 2020).

The sample preparation methodology is a crucial step in chemical analysis, which is responsible to remove potential interferents, preconcentrate the analyte, and put them into a solvent that is compatible with the chosen analytical technique. Nonetheless, this step is highly susceptible to errors related to analyte losses and contaminations. Moreover, some sample preparation methodologies are time-consuming and use relatively high quantities of organic solvents, which do not follow the guidelines of the Green Analytical Chemistry (GAC)

(Armenta et al., 2019; Jalili et al., 2020b; Kaur et al., 2021; W. Li et al., 2019; Ramos, 2020b; Tobiszewski et al., 2009; Vian et al., 2017).a.

2.2. Microextractions

The miniaturization of traditional sample preparation methodologies was proposed as an alternative to improve their performance and make them more environmentally friendly. Fig. 1.1 presents a timeline of the evolution of microextractions (ME) used in the determination of the carbamates and dithiocarbamates, where highlights the increasing use of MEs after the introduction of the Solid-Phase Microextraction (SPME). They were initially based on the miniaturization of traditional liquid-liquid and solid-phase extractions, which resulted in faster procedures with reduced consumption of solvents and samples, and consequently the minimization of waste generation, and still with the additional possibility of automation. These MEs were extensively explored in the last decades, especially due to their improved analytical performance combined with compliance with the GAC guidelines (de la Guardia et al., 2012; "Green Analytical Chemistry," 2011; Jalili et al., 2020b, 2021; Moreda-Piñeiro et al., 2019; Nunez et al., 2016).



SPME = Solid Phase Microextration; CNTs = Carbon Nanotubes; HS-SPME = Headspace Solid Phase Microextration; SDME = Single Drop Microextraction; LPME = Liquid-Phase Microextraction; HF-LPME = Hollow Fiber Liquid Phase Microextraction; NTD = Needle Trap Device; MHS-SPME = Multiple Headspace Solid-Phase Microextration; MEPS = Micro Extraction by Packed Sorbent; BIDME = Bubble-In-Drop Microextractions; DLLME = Dispersive Liquid-Liquid Microextraction; PMME = Polymer Monolith Microextraction; SFODME = Solidified Floating Organic Drop Microextraction; USAEME = Ultrasound-Assisted Emulsification Microextraction; LDS-DLLME = Low-Density Solvent Dispersive Liquid-Liquid Microextraction; VALLME = Vortex-Assisted Liquid-Liquid Microextraction; SUPRAS = Supramolecular Solvents; VSLLME = Vortex-Assisted Surfactant-Enhanced Emulsification Liquid-Liquid Microextraction; ST-DLLME = Solvent-Terminated Dispersive Liquid-Liquid Microextraction; CE = Capillary Electrophoresis; MSA-DLLME = Magnet Stirring Assisted Dispersive Liquid-Liquid Microextraction; DLLME-SFO = Dispersive Liquid-Liquid Microextraction based on Solidification of a Floating Organic Drop; DNSUAME = Dispersive Nano-Solid material-Ultrasound Assisted Microextraction; VALLME-SFO = Vortex Assisted Liquid-Liquid Microextraction based on Solidification of Floating Organic Droplet.

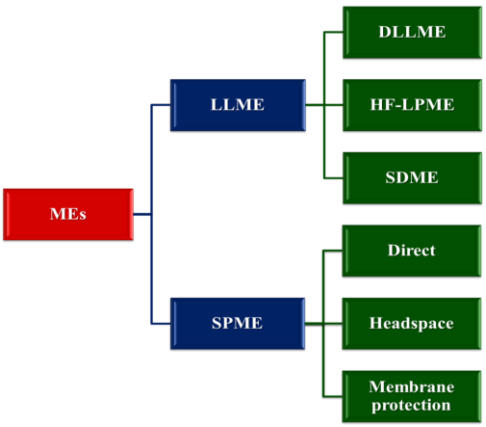
Figure 1.1: Timeline with the evolution of the microextractions.

The ability to perform sample clean-up, extraction, and preconcentration of the analytes is a remarkable characteristic of the MEs. Moreover, low sample and solvent consumption make them very popular

sample preparation methodologies tools, especially for organic analytes, and hence, they reached the analytical chemistry forefront in the last years. A suitable ME is selected according to the type of sample, analytes, and detection system, which can be modified to obtain better efficiency on the mass transference of the analyte from the sample to the extracting phase (Jalili et al., 2020b; Mitra, 2004; Moreda-Piñeiro et al., 2019; Samsidar et al., 2018).

These extraction methodologies are directly dependent on the composition of the sample, physicochemical, and physical properties of the analyte, solvents, and other extracting phases. Some properties of the solvents are responsible for the analyte transport between immiscible phases, such as vapor pressure, solubility, molecular weight, acid dissociation, and hydrophobicity. Furthermore, recent researches had developed new materials and solvents to improve the extraction efficiency of carbamates and dithiocarbamates (Abdel-Rehim, 2004; "Anal. Microextraction Tech.," 2017; Jalili et al., 2019, 2020b; Maciel et al., 2019; Ramos, 2020a; Venson et al., 2019).

The main classification of MEs is made according to the type of sample and extraction phase as presented in Fig. 1.2, which are based on liquid-phase extraction or solid-phase extraction, and they are called liquid-phase microextraction (LPME) and SPME, respectively. Thus, the LPME can employ two and/or three immiscible liquid phases, which can be aqueous and organic solvents. The SPME is based on the partition of the analytes between the sample and a solid phase, which is supported on a fused silica fiber. The MEs and their use in the determination of carbamates and dithiocarbamates are described in detail in the next sections, as well as and the last advances of those techniques ("Anal. Microextraction Tech.," 2017; da Silva Sousa et al., 2021; Ouyang et al., 2016; Pinto et al., 2010; Ramos, 2020b).



MEs = Microextractions; LLME = Liquid-phase microextractions; SPME = Solid-phase microextractions; DLLME = Dispersive liquid-liquid microextraction; HF-LPME = Hollow fiber-based liquid-phase microextraction; SDME = Single drop microextraction.

Figure 1.2: Classification of the microextractions.

2.3. Liquid-phase microextraction

The LPME is based on the miniaturization of the liquid-liquid extraction, which reduces significantly the volume of solvent and sample to a few microliters. Likewise, high enrichment factors can be achieved, due to the use of the low amount extraction solvent volumes. Moreover, they present additional remarkable advantages, such as low cost, affordability to any laboratory, reduction of wastes generation, and environmentally friendly.

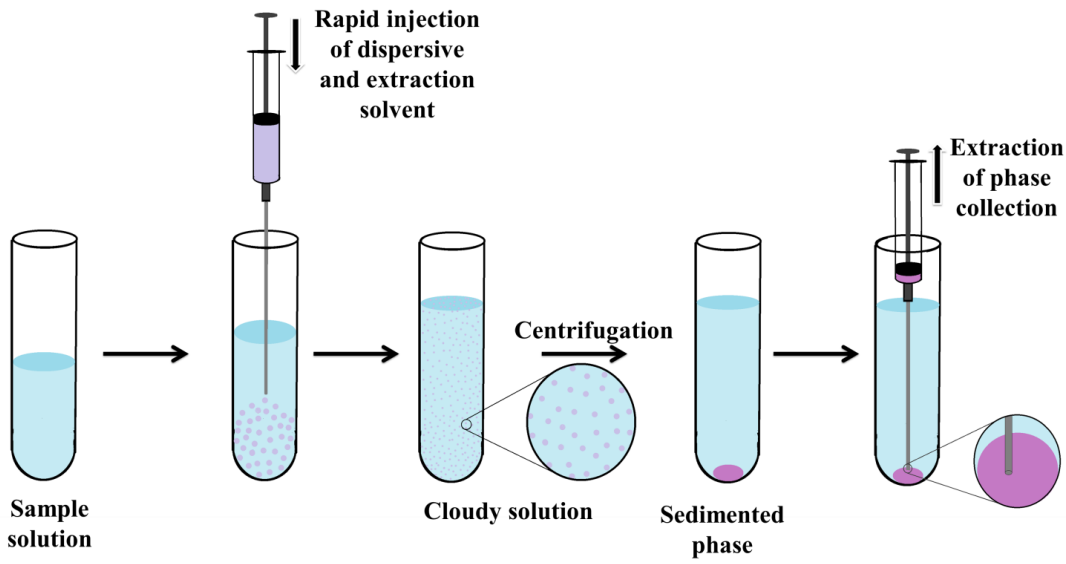
Thus, the LPME is classified according to their operation mode into dispersive liquid-liquid microextraction (DLLME), hollow fiber liquid-phase microextraction (HF-LPME), and single-drop microextraction (SDME) as presented in Fig. 1.2, which are detailed (Campillo et al., 2018; Moreda-Piñeiro et al., 2019; Pawliszyn, 2012b; Colin F. Poole, 2020; Ramos, 2020a; Rutkowska et al., 2019; Tobiszewski et al., 2009; Vian et al., 2017).

2.3.1. Dispersive liquid-liquid microextraction

The DLLME provides a high contact surface of fine droplets of extractant solvent and analytes. Hence, it is obtained a highly efficient extraction by the facilitated mass transference processes of carbamates and dithiocarbamates, resulting in a faster extraction procedure. This extraction derivated from the cloud-point extraction, and it has also some similarities with the classical homogeneous liquid-liquid extraction. The use of DLLME is a current trend in modern analytical chemistry, due to its high extraction efficiency, minimum requirements of sample and organic solvents, easy operation, low cost, and it fulfills the requirements of the GAC (Marcinkowska et al., 2019; Mousavi et al., 2018; Quigley et al., 2016; Rykowska et al., 2018; Sajid, 2018).

Thus, the DLLME usually requires an aqueous phase, disperser, and extractor solvents. A mixture of the extraction and the dispersive solvent is quickly injected into the sample solution. This mixture is shaken in order to obtain a cloudy solution. After centrifugation, organic and aqueous phases are separated, and the organic phase is collected and analyzed by a suitable analytical technique. The mass transference of the analyte from the sample solution to the extraction solvent occurs very quickly, due to the large surface area of the dispersive extraction solvent (Primel et al., 2017; Rutkowska et al., 2019; Sajid et al., 2018). These steps are illustrated in Fig. 1.3 (a). However, one disadvantage of the DLLME is associated with the chosen dispersive solvent, which can increase the solubility of the extraction solvent into the sample, hindering the extraction efficiency. The extraction time is defined as the interval around the steps of the injection at centrifugation of the mixtures (Mansour et al., 2018; Rutkowska et al., 2019; Trujillo-Rodríguez et al., 2013).

(a)



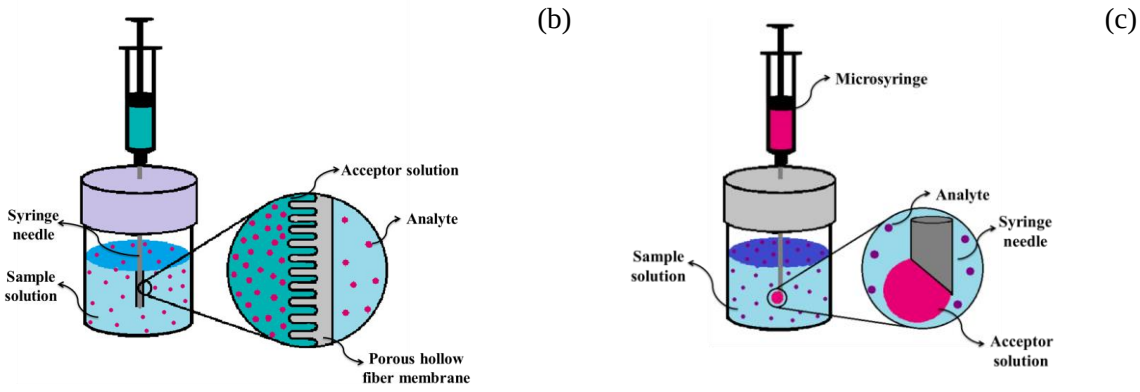


Figure 1.3: Schematic representation of (a) dispersive liquid-liquid microextraction, (b) hollow fiber-based liquid-phase microextraction, and (c) single-drop microextraction.

The choice of the extraction solvent is the most important parameter in the DLLME efficiency. Chlorobenzene, chloroform, tetrachloromethane, tetrachloroethylene, and carbon disulfide are the most employed extraction solvents, due to their low solubility in water and density. Beyond this, the volume of the extraction solvent volume is directly related to the enrichment factor, the lower the solvent volume, the higher the enrichment factor. Therefore, the extraction solvent volume must be low but still adequate for the analytical technique employed for analysis (Ahmad et al., 2015; Assadi et al., 2012; Fernández et al., 2014; Leong et al., 2014).

The dispersive solvent assists the extraction by the dispersion of the extractor solvent to generate fine droplets in the aqueous sample. For that, the dispersive solvent must present high miscibility in the aqueous phase and the extraction solvent (Colin F. Poole, 2020; Rutkowska et al., 2019). Ethanol, methanol, acetonitrile, and acetone are the most employed dispersive solvents. The dispersive solvent volume can directly affect the efficiency of extraction as it controls the dispersion degree into the aqueous phase. In this way, it changes in the volume of the dispersant solvent modifies affect the extraction efficiency, low volumes hinder the dispersion of the extraction solvent and high volumes increase the solubility of the analytes in an aqueous phase, and consequently, decreases the extraction efficiency (Ahmad et al., 2015; Assadi et al., 2012; Leong et al., 2014; Quigley et al., 2016; Rutkowska et al., 2019).

The DLLME is widely employed in the extraction of the dithiocarbamates in water and foodstuffs samples as presented in Table 1.2, due to the short extraction time, good recovery, the use of few microliters of organic solvents, and low detection limit (LD). So, this ME enabled the extraction of the dithiocarbamates below MRL with accuracy. Thus, Bodur et al. employed DLLME for extraction of propinebe in black tea and infant formulation using 0.3 mL of dichloromethane 0.30% (v/v) as extraction solvent, and ethanol as the dispersive solvent. Initially, the derivatization of propinebe was performed using potassium persulfate and potassium carbonate to obtain isothiocyanate, which was extracted by DLLME and analyzed by gas chromatography coupled with mass spectroscopy (Bodur et al., 2020).

Table 1.2: Microextraction methods for dithiocarbamates determination in the samples of water and foodstuffs.

Compounds	Samples	Sample Preparation	Solvent volume (mL)	Analytical technique	Extraction time (min)	LOD ($\mu g\ L^{-1}$)	Recovery (%)	Ref.
Maneb	River water	VALLME-SFO and DLLME-SFO	5 of NaCl 3.0% (m/v) (pH 7.0) and 0.10 of 1-dodecanol 0.33% (v/v), and 5 NaCl 4.0% (m/v) (pH 8.0), 0.10 of 1-dodecanol 33.33% (v/v) and methanol 0.26% (v/v)	LC-MS	1.58	0.025 - 0.377	80-106 and 69-98	(Asati et al., 2017)
Maneb, mancozebe, ziram	Grape, strawberry, carrot, lettuce, corn	VP-LPME	1 of EDTA 0.25 mol L^{-1} with NaOH 0.45 mol L^{-1} (pH 9–10)	IR	20	60 - 120	83 - 103	(Gonzálvez et al., 2011)
Nabam, thiram and zamethiphos	Tap water	SPME*	0.042 acetonitrile 70% (v/v)	HPLC-UV	30	1 - 10	95.5 - 99.5	(Aulakh et al., 2005)
Propineb	Black tea and infant formula	DLLME	0.3 of Dichloromethane 0.30% (v/v)	GC-MS	0.75	150	98–103	(Bodur et al., 2020)
Thiram	Tomato, cucumber and watermelon seeds	DLLME	1 of ethanolic potassium hydroxide, 5 of 0.01 mol L^{-1} copper (III), and 0.20 of 0.5 µg L^{-1} and carbon tetrachloride 2.00% (v/v)	UV/Vis	15	11.5	94.7-104.9	(Saadat Rastegarzadeh et al., 2013)
Zineb	River, tap and well water and soil	DLLME	5 of Robinson buffer with ascorbic acid and CTAB (pH = 10), 3 of carbon tetrachloride and ethanol 14.28% (v/v), and 0.9 $HAuCl_4$ 1.22×10^{-4} mol L^{-1}	UV/Vis	0.5	0.55	95.6–101.0	(Mohamadjafari et al., 2017)

*Direct extraction

Ref. = Reference; SPME = Solid Phase Micro Extration; HPLC-UV = High Performance Liquid Chromatography with Ultraviolet spectroscopy; VP-LPME =Vapor Phase Liquid Phase Micro Extration; IR = Infrared; DLLME = Dispersive Liquid-Liquid Micro Extration; UV/Vis = Ultraviolet- Visible spectroscopy; VALLME = Vortex-Assisted Liquid-Liquid Microextraction; SFO = Solidification of a Floating Organic; LC-MS = Liquid Chromatography with coupled to Mass Spectroscopy; GC-MS = Gas Chromatography coupled to Mass Spectroscopy.

Rastegarzadeh et al. employed DLLME to the extraction of thiram from tomato, cucumber, and watermelon seeds samples, using carbon tetrachloride as the extraction solvent without a dispersive solvent. A derivatization step was performed by the addition of ethanolic KOH to provide a colored yellow product, followed by the addition of copper (II) the increased the efficiency of the extraction, and consequently, the analytical signal obtained by ultraviolet-visible spectrophotometry (S. Rastegarzadeh et al., 2013).

Szarka et al. extracted 40 pesticides, including propham, chlorpropham, and pirimicarb, from neutraceutical drops and herbal alcoholic beverages by DLLME, using methanol and tetrachloroethane as a dispersive solvent and extraction solvent, respectively. The effect of salt addition was evaluated to facilitate target analytes extraction by the salting-out effect, however, its use provided a longer extraction time, and hence, 10% de NaCl was chosen for extractions. The determination and quantification of the pesticides were performed by gas chromatography-mass spectroscopy (Szarka et al., 2018).

Although DLLME presents remarkable advantages, some modifications have been presented to improve its performance for the determination of organic analytes in foodstuff samples. For example, the use of

ionic liquids as extraction solvents, which present tunable viscosity, negligible vapor pressure, miscibility in organic solvents and water, and high thermal and chemical stability. Therefore, among the DLLME modifications used for the determination of carbamates and dithiocarbamates are the solidification of floating organic drop-DLLME, molecularly imprinted polymer extraction-DLLME, and stir car sorptive extraction combined with DLLME, low toxic DLLME, and solvent terminated DLLME, ultrasound-assisted DLLME, and surfactant assisted-DLLME (Assadi et al., 2012; Leong et al., 2014; Quigley et al., 2016; Rutkowska et al., 2019; Trujillo-Rodríguez et al., 2013). Some works employing DLLME with or without modification for the extraction of carbamates in water and foodstuffs samples are presented in Table 1.3, which are widely employed because of their low LD and relative standard deviation (RSD), short extraction time, and good recovery. Furthermore, these MEs enabled the reduction of the use of organic solvents used in the extraction, and remotion of interferents from the matrix.

Table 1.3: Microextraction methods for carbamates determination in the samples of water and foodstuffs.

Analyte	Sample	Sample preparation	Extraction time(min)	Analytical technique	Precision (RSD, %)	LOD ($\mu g\ L^{-1}$)	Recovery (%)	Ref.
Aldicarb, benomyl, carbendazim, methomyl, asulam, aldicarb-sulfone, ethiofencarb-sulfoxide, carbofuran-3-hydroxy, carbaryl, carbofuran, propoxur, methiocarb, isoprocarb, ethiofencarb, promecarb, fenobucarb, pirimicarb-desmethyl, benthiocarb, diethofencarb, pirimicarb, fenoxycarb, napropamid, propamocarb, pyraclostrobin, and furathiocarb	Banana, tomato, and peach	VSLLME	34 (centrifugation, vortex and filtered)	MEC-TMS	5.0 – 11.0	0.7 - 1.4	81.0 – 104.0	(Moreno-González et al., 2015)
Aldicarbsulfoxide, Asulam, aldicarb-sulfone, oxamyl, methomyl, ethiofencarb-sulfone, pirimicarbdesmethyl, ethiofencarb-sulfoxide, methiocarbsulfoxide, carbofuran-3-hidroxy, cymoxanil, aldicarb, metolcarb, propoxur, carbofuran, carbaryl, ethiofencarb, thiodicarb, isoprocarb, fenobucarb, diethofencarb, methiocarb, promecarb, napropamid, and benthiocarb	Wine	UASEME	5 (sonification)	UHPLC-MS/MS	6.0	0.15 - 0.92	74.0 – 102.0	(Moreno-González et al., 2013)
Aminocarb, propham, chlorpropham, promecarb, carbofuran,	Tap, river and drain	BID	30 (extraction and stirring	GC-MS	3.34 - 7.53	0.02 - 0.04	81.7 - 99.0	(Chullasat et al., 2020)

pirimicarb, carbaryl, methiocarb	water		rate)					
Barban, carbaryl, chlorpropham, methiocarb, promecarb, propham	Tap, surface and well water, and wine	SPME*	12 (extraction)	HPLC–ESI-MS	2.1 – 4.2	0.01 - 1.2	-	(J. Wu et al., 2002)
Barban, carbaryl, propham, methiocarb, promecarb, chlorpropham	Natural water	SPME*	25 (extraction)	HPLC-UV	1.7 – 5.3	1.00 – 15.0	97.3 - 100.0	(Gou et al., 2000)
BAYGON, MTMC, MIPC and BPMC	Apple and lettuce	PEDOT-PIL/MWCNTs-SPME*	23 (extraction, centrifugation and thermal desorption)	GC-FID	4.7 – 7.8	0.0152 - 0.027	87.5 - 106.5	(M. Wu et al., 2016)
Bendiocarb and promecarb	Tap water, river water and mineral water	DNSUAME	11 (vortex and ultrasonic time)	HPLC-UV	5.5	0.0010 - 0.0015	91.4 - 98.7	(Khodadoust et al., 2013)
Benfuracarb, carbofuran, monuron, pirimicarb, monolinuron, diuron, diethofencarb, carbosulfan,	Orange, apple, cherry and strawberry	SPME*	30 (centrifugation and extraction)	LC-MS	1.0 - 17	5.00 – 50.0	1.0 – 79.0	(Sagratini et al., 2007)
Carbaryl and triazophos	River water, juice of apple, grape and peach	DLLME	15 (sample preparation)	HPLC-FLD	1.38 - 2.74	$1.23x10^{-5}$ – $1.60x10^{-5}$	80.4 - 117.9	(Fu et al., 2009)
Carbaryl, carbofuran, isocarbophos	Tea drinks	MSA-DLLME	5 (extraction)	HPLC-DAD	4.0 – 7.8	0.13 - 0.61	79.4 - 114.4	(Wang et al., 2013)
Carbaryl, metolcarb, carbofuran, pirimicarb, isoprocarb and diethofencarb	River, reservoir and well water	UASEME	8 (sonication and centrifugation)	HPLC-UV	3.2 - 4.8	0.1 - 0.3	81.0 - 97.5	(Q. Wu et al., 2010)
Carbaryl, metolcarb, isoprocarb, and diethofencarb	Pear and apple	G-HF-LPME	35 (centrifugation and extraction)	HPLC-UV/Vis	6.2 - 7.8	0.16 - 0.79	89.2 - 106.8	(X. Ma et al., 2014)
Carbaryl, pirimicarb, and isoprocarb	Cabbage, cucumber, spinach, celery, lettuce, rape, green been, carrot and eggplant	PMME	15.8 (extraction)	HPLC-DAD	2.06 - 6.36	0.285 - 2.06	70.4 - 98.5	(H. Ma et al., 2013)
Carbaryl, promecarb, carbofuran, propham, methiocarb and chlorpropham	River water	LDS-DLLME	7 (extraction and centrifugation)	GC-MS	5.3 - 9.2	0.01 - 0.1	87.9 - 108.3	(Guo et al., 2012)
Carbaryl, promecarb, propham, methiocarb, chlorpropham	River and tap water	LPME	20 (extraction)	GC-MS	4.86 - 7.81	0.2 - 0.8	83.0 - 121.3	(J. Zhang et al., 2006)
Carbaryl, propoxur, carbofuran, pirimicarb, 2,3,5-Trimetacarb, BDMC and carbaryl-d7	River and mineral water	SPME*	30 (extraction)	GC-MS	1.0 - 9.0	0.00004 – 0.0017	70.8 - 115.7	(Cavaliere et al., 2012)

Carbendazim, fipronil and picoxystrobin	River water	SUPRAS	5.5 (vortex stirring and centrifugation)	HPLC-DAD	1.65 – 6.53	0.23 - 0.45	93.5 - 110.0	(Scheel et al., 2020)
Carbofuran	Natural water	DLLME	A few seconds	HPLC-MS	1.9 - 9.1	–	62.7 - 120.0	(Caldas et al., 2010)
Carbofuran	Natural water	SPME*	45 (extraction and desorption)	HPLC-PAD	5.1 – 7.0	0.06 – 8.9	101.4	(López-Blanco et al., 2002)
Carbofuran, carbaryl, isoprocarb, diethofencarb and methiocarb	Apple	CNTs-SPME***	85 (extraction and desorption)	HPLC-DAD	2.24 – 7.30	0.0713 - 4.75	94.6 - 112.5	(Song et al., 2013)
Carbofuran, propoxur, metolcarb, isoprocarb, and fenobucarb	Spinach and Pakchoi	SPME*	43 (extraction and desorption)	GC–ToFMS	5.7–12.9	0.012 - 0.048	79.8 - 108.8	(Ai et al., 2015)
Carbofuran, tsumicide, isoprocarb, pirimicarb	Real water	ST-DLLME	10 (extraction)	GC-MS/MS	2.3 - 6.8	0.001 - 0.50	97.3 – 104.0	(H. Chen et al., 2010)
Chlorpropham, desmedipham, and phenmedipham	Wine, beer, apple juice and potato	VALLME	11.167 (centrifugation, self-separation of the phases and evapored)	HPLC - amperometric	5.73 -15.3	0.48 - 3.67	74.4 – 114.0	(Diuzheva et al., 2019)
Diethofencarb	Rain water and apple and peach juice	UASEME, USEAME and DLLME	22 (extraction, centrifugation, ultrasonic bath, centrifugation)	HPLC-DAD	3.6 – 8.0	0.01	88.0 – 117.0	(Cheng et al., 2011)
Ethyl carbamates	Wines	MEPS****	-	GC-MS	4.0 – 7.0	1.5	97.0 – 106.0	(Leça et al., 2014)
Ethyl carbamates	Beer and wines	HS-SPME**	60 (extraction)	GC-MS	4.3 – 8.6	3.0	92.8 – 97.5	(Y. Zhang et al., 2008)
Ethyl carbamates	Stone-fruit spirits	HS-SPME****	30 (extraction)	GC-MS/MS	4.3 – 8.2	30.0	-	(Lachenmeier et al., 2006)
Ethyl carbamates	Wine	HS-SPME**	25 (thermostatted and inserted in the headspace)	GC × GC – ToFMS	14.61 - 17.50	2.75 – 4.31	88.6 - 99.4	(Perestrelo et al., 2010)
Ethyl carbamates	Wine	MHS-SPME****	10 (extraction)	GC-FID	2.19	34.0	-	(Ye et al., 2011)
Ethyl carbamates	Bread	MHS-SPME**	1450.0 (mixture was hermetically kept and extraction)	GC-FID	1.60	41.0	92.5 - 103.4	(Ye et al., 2012)
Fenobucarb	Apple	SPME****	30 and 60 (extraction)	GC-MS	0.1 - 13.37	0.00792 - 0.158	80.0 - 105.0	(Abdulra'uf et al., 2013)
Metolcarb, carbaryl, isoprocarb, diethofencarb	River and reservoir water	μ-SPE*	70 (adsorption and desorption time)	HPLC-UV/Vis	1.8 – 8.3	2.27 - 3.26	83.9 - 108.8	(Zhou et al., 2015)
Pirimicarb	Wines	SPME*	43 (centrifugation and desorption)	MEKC-DAD	0.6 – 6.4	89.0 – 1690.0	90.0 - 107.0	(Ravelo-Pérez et al., 2008)
Propham, chlorpropham,	Nutraceutical drops and	DLLME	7 (extraction and	GC-MS	3 – 20	0.001 -	70.0 –	(Szarka et al.,

pirimicarb	herbal alcoholic beverages	centrifugation)	0.910	120.0	2018)

*Direct extraction

**Headspace extraction

***Extraction involving membrane protection

****Unclassifiable

LOD = Limit of Detection; Ref = Reference; BIDME = Bubble-In-Drop Microextraction; GC = Gas Chromatography; MS = Mass Spectroscopy; VALLME = Vortex-Assisted Liquid–Liquid Microextraction; HPLC = High Performance Liquid Chromatography; G-HF = Graphene Reinforced Hollow Fiber; LPME = Liquid-Phase Microextraction; UV/Vis = Ultraviolet–Visible Spectroscopy; SPME = Solid Phase Microextraction; ToFMS = Time-of-Flight Mass Spectrometry; PEDOT-PIL/MWCNTs = Poly (3,4-ethylene dioxy thiophene) derived from Poly(Ionic Liquid) Multi-Walled Carbon Nanotubes; FID = Flame ionization detector; CNTs = Carbon Nanotubes; DAD = Diode Array Detector; LDS = Low-Density Solvent; DLLME = Dispersive Liquid-Liquid Microextraction; UASEME = Ultrasound-Assisted Surfactant-Enhanced Emulsification Microextraction; ST = Solvent Terminated; VSLLME = Vortex-Assisted Surfactant-Enhanced-Emulsification Liquid-Liquid Microextraction; MEPS = Micro Extraction by Packed Sorbent; HS = Headspace; MSA = Magnetic Stirring-Assisted; MHS = Multiple Headspace; SUPRAS = Supramolecular Solvents; USEAME = Ultrasound-assisted surfactant-enhanced emulsification microextraction; PMME = Polymer Monolith Microextraction; DNSUAME = Dispersive Nano-Solid Material-Ultrasound Assisted Micro-Extraction; VP-LPME = Vapor Phase-Liquid Phase Microextraction; VALLME = Vortex-Assisted Liquid–Liquid Microextraction; SFO = Solidification of a floating organic .

Caldas et al. used DLLME for the extraction of carbofuran, clomazone, and tebuconazole. Carbon tetrachloride was used as an extraction solvent due to its compatibility with the analytes, the capacity to create a cloudy solution with the dispersive solvent, and good compatibility with the analytical technique. Acetonitrile was used as disperser solvent, as it increased the extraction efficiency. Moreover, the influence of pH on the extraction efficiency was evaluated by the addition of phosphoric acid, and pH 2.00 presented better extraction efficiency. The determination of the target compounds was realized by liquid chromatography coupled with tandem mass spectrometric detection (Caldas et al., 2010).

Cheng et al. extracted diethofencarb and pyrimethanil from water, apple, and peach juice employing ultrasound-assisted surfactant-enhanced emulsification microextraction, ultrasound-assisted emulsification microextraction, and DLLME. Thus, the authors verified that the ultrasound-assisted surfactant-enhanced emulsification microextraction had better recoveries than other MEs used in this work. Carbon tetrachloride was used as the extraction solvent. Thereby, the dispersion of the extractant was made only with the employment of ultrasound. High-performance liquid chromatography-mass spectroscopy was employed for the determination of diethofencarb and pyrimethanil with low detection limits, short extraction time, good recovery, precision, and accuracy (Cheng et al., 2011).

2.3.2. Hollow fiber liquid-phase microextraction

Hollow fiber liquid-phase microextraction (HF-LPME) employs a porous hollow fiber to aid the extraction of the carbamates and dithiocarbamates from the sample to the extraction phase, which does not get in direct contact with the sample solution, as it stays inside of the lumen of a porous polypropylene hollow fiber. The advantages of HF-LPME are the simplicity and the low-cost instrumentation, and also excellent automation potential. However, the main disadvantage of this ME is the high extraction times (from 15 min to 120 min) (Afshar Mogaddam et al., 2019; A Gjelstad et al., 2012; Khan et al., 2020; Kokosa, 2019; Płotka-Wasylka et al., 2016).

HF-LPME requires a supported liquid membrane that is formed in a few seconds by dipping the hollow fiber into an organic solvent, which penetrates hollow fiber pores bounding with a network of

polypropylene. The high porosity of the fiber results in a thin solvent film where the mass transference of analytes occurs from the aqueous sample to the film and posteriorly into solvent present in hollow fiber lumen, as shown in Figure 1.3 (b). This solvent, the so-called acceptor solution, can be organic or aqueous and must be immiscible with the supported liquid membrane promoting an extraction system of three phases. After extraction, the solution obtained with the analytes is removed by a microsyringe and analyzed by a suitable analytical technique (Chormey et al., 2020; Esrafili et al., 2018; A Gjelstad et al., 2012; Venson et al., 2019).

The kinetics of the extraction is directly related to the interaction of the analytes between the supported liquid membrane and donor phase, since the thickness of the fiber, solvent permeability, size of the pore of the fiber, and porosity can influence the equilibrium time and efficiency of extraction. Furthermore, the extraction kinetics also is influenced by ionic strength, since it can change characteristics of the ions, such as size, structure, hydration, charge density, and dielectric constant, by the effect of salting-out. Likewise, the presence of ion-pairing helps to avoid solvent leakage from the fiber and ionization of the analyte by increasing ionic strength (Afshar Mogaddam et al., 2019; A Gjelstad et al., 2012; Kokosa, 2019; Rutkowska et al., 2019; Salvatierra-stamp et al., 2018).

Better extraction efficiencies are obtained with higher porosity fibers due to quick mass transference between extraction solvent and sample solution. The selection of the organic solvent employed as the acceptor phase is based on the hydrophobic effect and dispersion forces for non-polar analytes and based on dipole-dipole or hydrogen-bonding interaction for polar analytes. The most common solvents are 1-heptanol, 1-octanol, 1-nonanol, and 1-undecanol, but some researchers use supramolecular solvents to substitute the organic solvent and suit the guidelines of GAC (Afshar Mogaddam et al., 2019; de la Guardia et al., 2012; A Gjelstad et al., 2012; Ramos, 2020b; Rutkowska et al., 2019; Vian et al., 2017).

The use of forced convection decreases the time to achieve the extraction equilibrium by the employ of ultrasound, vortexing, shaking, or stirring, but their use has to be carefully evaluated due to the possibility of damaging the fiber. Also, the temperature can modify the efficiency of mass transferences, hence its evaluation is an important parameter. Extraction time can be reduced by the use of electromembrane extraction, in which the analytes are extracted by an electrokinetic migration (“Anal. Microextraction Tech.,” 2017; Y. Chen et al., 2019; A Gjelstad et al., 2012; Khan et al., 2020).

HF-LPME can be classified in two-phase and three-phase systems, according to the polarity of the acceptor solution. Fig. 1.3 (b) illustrates the main steps of HF-LPME. The two-phase HF-LPME is performed by employing an organic acceptor solvent, which extracts the target analytes according to their solubility and immiscibility in water. Moreover, this ME can be used for the extraction and preconcentration of the carbamates and dithiocarbamates by headspace extraction and direct immersion extraction (Esrafili et al., 2018; A Gjelstad et al., 2012; Astrid Gjelstad, 2019).

Three-phase HF-LPME is performed using an alkaline or acid solution as the acceptor phase, and an organic solvent film between the acceptor phase and the sample solution, which can be classified in hollow fiber liquid-liquid-liquid phase microextraction and hollow fiber liquid-gas-liquid microextraction. However, this ME is limited by acidic and basic analytes with ionizable functions, because the efficiency of the extraction is directly related to these functions (A Gjelstad et al., 2012; Astrid Gjelstad, 2019; Khan et al., 2020; Salvatierra-stamp et al., 2018).

Ma et al. proposed the use of reinforced graphene HF-LPME for the extraction of metolcarb, carbamyl, isoprocarb, and diethofencarb in apple and pear samples. Methylene chloride, ethyl acetate, n-hexane, and 1-octanol were evaluated as acceptor phases according to compatibility with the fiber, low toxicity, high partition coefficient, good dispersion for grapheme, extraction time, and immiscible solution of the sample. 1-octanol presented the highest extraction efficiency with lower needed volume. The extraction was also improved by the addition of NaCl due to the salting-out effects. The extraction time was longer than DLLME. The combination of HF-LPME with high-performance liquid chromatography with a diode array detector enabled the determination of the carbamates in foodstuffs with good precision and detection limit (X. Ma et al., 2014).

Bedendo et al. used the HF-LPME to extract 18 pesticides, including carbendazim and carbofuran, from orange juice samples. Initially, it was added ammonium sulfate at pH 7.0 and toluene with ethyl acetate in the sample, where was fixed the fiber with a temperature constant of 25 °C and an extraction time of 35 min. Posteriorly, it was made desorption using methanol and acetone in an ultrasonic bath for 2 min. The extract obtained was injected liquid chromatography with tandem mass spectroscopy, which permitted the determination of the target pesticides in foodstuffs which had a good recovery, precision, LD, and RSD (Bedendo et al., 2012).

2.3.3. Single drop liquid phase microextraction

Single drop liquid-phase microextraction (SDME) is a nonexhaustive process with a reasonable extraction time and high preconcentration or enrichment factors. The solvent is carefully selected to facilitate the mass transference of the target compounds from sample solution to extraction solvent. This ME can achieve a high enrichment factor in a short time, thus it allows explore the liquid-phase extraction of the carbamates and dithiocarbamates (Afshar Mogaddam et al., 2019; Jain et al., 2020; Marcinkowska et al., 2019; Tang et al., 2018).

SDME only employs one drop of solvent that is hanging at a needle tip, resulting in a procedure with low cost, use of simple equipment, reduced sample consumption, wide applicability in polar and nonpolar compounds, and easy automatization. The ME is based on liquid extraction in two or three liquid phases, as presented in Fig. 1.3 (c). In the two-phase system, the extraction of the sample occurs from the sample solution to the organic solvent. While in the three-phase system the analytes are extracted from the sample solution to the organic solvent, and posteriorly, the analyte is transferred for an aqueous drop that is called back-extraction or single-drop liquid-liquid-liquid microextraction (Jain et al., 2020; Kokosa, 2019; Marcinkowska et al., 2019; Tang et al., 2018).

Dos Anjos et al. employed SDME to the extraction of 19 pesticides, including carbofuran, from coconut water. Toluene, cyclohexane, and isooctane were evaluated as extracting solvents, which presented good performance, however, toluene was chosen due to its low toxicity and compatibility with gas chromatography-mass spectrometry that was employed for separation and detection. The extraction equilibrium was reached in 30 min by most of the target analytes (Dos Anjos et al., 2014).

Nonetheless, some alterations were proposed in the SDME to make it more adequate to the guidelines of GAC, improve efficiency, and minimize the interferences from the samples. It is noteworthy the use of different solvents for extraction, their selection is based on the composition of the sample and the type of carbamates and dithiocarbamates analyzed. Some of these alterations avoid the use of toxic organic solvents and

use agitation of the sample to reduce the extraction time and improve efficiency. However, agitation can lead to the accidental formation of air bubbles, which can cause variation in the analyte extraction efficiency (Armenta et al., 2019; Chullasat et al., 2020; Jain et al., 2020; Kailasa et al., 2021; Marcinkowska et al., 2019).

In a specific case, the intentional incorporation of an air bubble larger than the drop size can improve the enrichment factor, recovery extraction, which is called a bubble in drop microextraction (BIDME). This SDME enabled the determination of the carbamates and dithiocarbamates, and it still allows automatization in the extraction steps, such as the generation of the solvent drop, insertion of an air bubble, drop reacquisition by the syringe, and injection into an analytical technique. However, BIDME is directly influenced by the size of the bubble due to the surface area of the drop, which can provide instability of the extraction (Chullasat et al., 2020; Jain et al., 2020; Marcinkowska et al., 2019; Williams et al., 2011; Xie et al., 2014).

Chullasat et al. employed the BIDME to the determination of propham, chlorpropham, promecarb, carbofuran, aminocarb, pirimicarb, carbaryl, and methiocarb in water samples. The extraction solvent was evaluated, and toluene and butylacetate were selected due to the better extraction time and recoveries. The ionic strength was evaluated by the addition of NaCl in different concentrations to modify the solubility of the polar analytes, and higher NaCl concentrations resulted in better extraction efficiency. The pH was set at 6.00, which provided higher extraction efficiency as the analytes are in their neutral form. Gas chromatography-mass spectroscopy was used to detect the carbamates (Chullasat et al., 2020).

2.4. Solid-phase microextraction

The SPME is based on the partitioning of the analytes between a coated extraction phase on fiber and a sample solution. This ME follows the guidelines of GAC, due to the minimum use of solvents, fast extraction time, and small sample volume comparing with solid-phase extraction. SPME presents additional advantages such as quickness, selectivity, reproducibility, and still, it enabled several configurations with the modification in the vessel walls, membrane, and fiber. Hence it is widely applied in the extraction of the carbamates and dithiocarbamates (Garrigues et al., 2020; Jalili et al., 2020a; Liu et al., 2020; Maciel et al., 2019; Ouyang et al., 2016; Pawliszyn, 2012a; Souza-Silva, Gionfriddo, et al., 2015; Souza-Silva, Jiang, et al., 2015).

SPME is classified according to the extraction mode, which are direct extraction, headspace extraction, and extraction with the use of membrane protection, as shown in Fig. 1.2. These MEs present easy operation, high efficiency on the preconcentration, and separation of target carbamates and dithiocarbamates, and they can be automated. Furthermore, new sorbent materials have been developed for the extraction of target analytes with different chemical properties, since the properties of the commercially available fibers are limited (“Anal. Microextraction Tech.,” 2017; Balasubramanian et al., 2011; Kataoka, 2021; Llompart et al., 2019; Ouyang et al., 2016; Pawliszyn, 2012b).

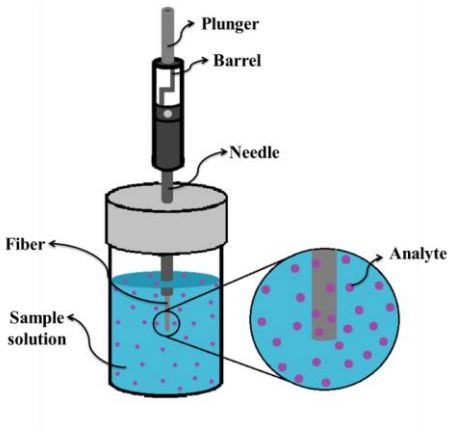
The main tools employed to improve the performance and selectivity of SPME are sol-gel technology, ionic liquids, and carbon nanotubes. Thus, sol-gel technology has been an interesting tool for the development of new sorbent materials for SPME as it enables different shapes, formats, compositions, and sizes. Moreover, the synthesis can be performed in extraordinarily mild conditions and the materials present several advantages, such as high permeability, large pore structures, and inexpensive preparation (Dugheri et al., 2021; Maciel et al., 2019; Mei et al., 2019; Paiva et al., 2021; Pawliszyn, 2012a, 2012b; Souza et al., 2021; Yavir et al., 2020).

Already, the ionic liquids have properties of solvation, immiscibility or miscibility with solvents, electrical conductivity, thermal stability, and low volatility, which make them a good alternative to modify SPME fibers and expand their applications. Ionic liquids can be used to modify the anion/cation composition and structure of the sorbent, which provokes different chemical interactions among analytes and sorbents. The use of polymeric ionic liquids was proposed due to their higher viscosity, which aids the coupling with some chromatography techniques that operate at higher temperatures (Mei et al., 2019; Pawliszyn, 2012a; Yavir et al., 2020).

Different configurations of carbon nanotubes are also used as sorbent phases in SPME, such as multi-walled carbon nanotubes and single-walled carbon nanotubes. These materials assist in the extraction of the ionic, nonpolar, and polar target compounds, due to their electronic and hydrophobic interactions and high ratios of surface-to-volume. Although carbon nanotubes possess advantages such as high durability and stability in different conditions, other carbonaceous sorbents have been presenting high performance as SPME sorbents. Graphene presented superior adsorption properties achieving low limits of detection, wide linear range, satisfactory reproducibility, high enrichment factors, long life spans, high mechanical strength, high affinity for organic compounds, thermal and chemical stability, and a high surface-to-weight ratio (Kataoka, 2021; Mei et al., 2019; Pawliszyn, 2012a; Souza et al., 2021; Souza Silva et al., 2013).

2.4.1. Direct extraction

Direct SPME is based on the insertion of the extraction fiber into the solution that contains the analytes and sample, where occur the mass transference of the target compounds from the sample to the extracting phase, as presented in Fig. 1.4 (a), so-called direct extraction. Since SPME is a non-exhaustive technique, analytes are not completely extracted from the sample and the extraction efficiency depends mostly on the velocity of agitation during the extraction. The sample solution composition and stirring influence the extraction equilibration times, due to alteration of the diffusion coefficient, and consequently, modifying the mass transference (“Anal. Microextraction Tech.,” 2017; Ouyang et al., 2016; Pawliszyn, 2012a; L. Zhang et al., 2018).



(a)

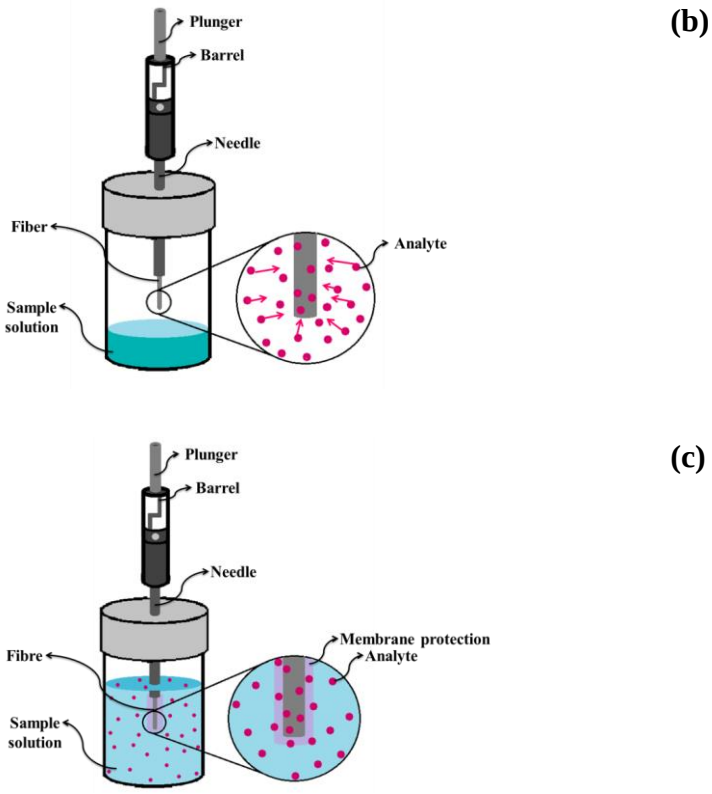


Figure 4: Schematic representation of solid-liquid microextraction of the type (a) direct, (b) headspace, and (c) membrane protection.

The mass transference is directly influenced by the boundary layer, due to the relation of the thickness of the sorbent phase with the rate of diffusion and convection of the target compounds from sample solution to extracting phase. The migration of the analytes is affected by the sample viscosity, agitation, and analyte diffusion coefficient. Nonetheless, the changes in the concentration of the carbamates and dithiocarbamates into the solution after some time results in the formation of a gradient concentration, where the interface has low concentration and slower flow of the analytes. Small molecules diffuse more deeply in the fiber providing stabilization, and consequently, reaching the state of equilibrium more quickly (Balasubramanian et al., 2011; Kataoka, 2021; Ouyang et al., 2016; Pawliszyn, 2012a).

Direct extraction is employed in the extraction of the carbamates in foodstuffs and water samples as can be visualized in Table 1.3, which have high extraction time (12 – 143 min), good precision, low DL, and good recovery. Thus, Ai et al. employed SPME for extraction of propoxur, metolcarb, isoprocarb, fenobucarb, and carbofuran in spinach and pakchoi, which initially were cut into small pieces followed by the addition of methanol. The organic extract was filtered and the analytes were extracted by direct SPME. The temperature was controlled to improve the efficiency of the extraction and decrease systemic errors. The identification and quantification of the carbamates were made by gas chromatography coupled to time-of-flight mass spectrometry (Ai et al., 2015).

Cavaliere et al. extracted propoxur, carbofuran, pirimicarb, carbaryl, and methiocarb from water samples using polydimethylsiloxane/divinylbenzene (PDMS/DVB) fiber, which was collocated by 45 min with 10% NaCl. The fiber was introduced in the injector, where occurred the desorbed at 270 °C for 6.5 min. The

determination of the five carbamates was made with gas chromatography-triple quadrupole mass spectrometry which selectivity, sensibility, accuracy, and precision (Cavaliere et al., 2012).

Ravelo-Pérez et al. employed poly(dimethylsiloxane)/divinylbenzene to extract and preconcentrate 11 pesticides, between them the pirimicarb, from red wines. Initially, the samples were filtered, and after this, it was added them sodium chloride. The pH of the solution obtained was adjusted 9.5 and collocated the SPME fiber under agitation at 900 rpm for 143 min to extract the pesticides quickly. The sample extract was obtained with the desorption using methanol under agitation at 1000 rpm for 13 min, which was evaporated at 250 bar and 40 °C and reconstituted by water and sodium tetraborate at pH 8.5. The sample extract was injected into the micellar electrokinetic chromatography coupled to DAD, enabling the determination of 11 pesticides with precision, accuracy, sensibility, and selectivity (Ravelo-Pérez et al., 2008).

Wu used SPME for the extraction of carbamates residues in apple and lettuce samples, which were previously cut into small pieces, followed by the addition of methanol in the nitrogen atmosphere. The residues were removed by centrifugation and the supernatant was used in the extraction. The fiber was direct immersed into the organic extract temperature-controlled at 40 °C for 20 min under magnetic agitation. The determination of the carbamates residues was realized employing gas chromatography coupled to flame ionization detector, which enabled low DL, good recovery, satisfactory RSD, and good linearity (M. Wu et al., 2016).

Direct extraction is also used in the extraction of the dithiocarbamates in water samples as is presented in Table 1.2. Aulakh et al. employed a polydimethylsiloxane fiber for the SPME of nabam, thiram, and azamethiphos from water samples. The influence of temperature on the extraction efficiency was evaluated, and higher temperatures provided the decrease in the extraction efficiency due to modification in the nabam solubility, and changes in the interaction between the analyte and fiber since it is an exothermic process. The extraction time and effect of salt addition were also evaluated, with the best time of adsorption and desorption at 30 min and 5 min, respectively, while the addition of NaCl enables a better performance because of the decrease of the pesticides solubility in the sample (Aulakh et al., 2005).

2.4.2. Headspace extraction

The use of headspace extraction in SPME can decrease the extraction time of carbamates and dithiocarbamates, due to the high constants of Henry's law, as presented in Fig. 4 (b). The mass transference is controlled by analytes diffusion presented in the sample solution through of boundary layer, moreover, the use of spray systems, purging, and agitation can facilitate the extraction of target compounds. Furthermore, the extraction of the compounds with low volatility can be facilitated by the heating of the solution, due to modification of the density gradients associated with temperature gradients, and consequently, the constant of Henry's law. Therefore, the extraction time can be decreased with the employ of efficient agitation and/or increase of temperature (Afshar Mogaddam et al., 2019; Lambropoulou et al., 2007; Paiva et al., 2021; Pawliszyn, 2012a).

Headspace extraction mode avoids adverse effects caused by the direct contact of the fiber with the sample, such as lower interference from the sample composition, such as high molecular weight, oily interferences, and presence of solids. This ME enables the modification of the sample solution without damaging the fiber and decreases the non-volatile interferences present in the sample. The number of analytes extracted by

direct SPME and headspace-SPME can have variation in the equilibrium concentration, because of several factors, such as volatility, vapor pressure. However, these MEs can show a significant difference in the recovery for many volatile analytes (Lambropoulou et al., 2007; Maciel et al., 2019; Ouyang et al., 2016; Paiva et al., 2021; Wilkes et al., 2000).

The headspace-SPME was employed in the extraction of the carbamates in foodstuffs and water samples as shown in Table 1.3, which have higher extraction time (25 – 1450 min) comparing with LPME, direct extraction, and extraction involving membrane protection, better precision, lower detection limits, and good recoveries. Ye et al. used headspace-SPME to extract ethyl carbamates in bread samples, which were toasted and crushed. The analytes were determined by gas chromatography with a flame ionization detection, that enabled satisfactory precision, linearity and detection limit, and good recovery (Ye et al., 2012).

Zhang et al. extract ethyl carbamate from wine, beer, and grape brandies using headspace-SPME. Initially, the sample was collocated in the glass vial with sodium chloride and internal standard under agitation. During 60 min was realized the modification of sampling temperature proving the equilibrium of the sample, posteriorly, the SPME fiber was inserted. When the extraction was finished the fiber was collocated into an injector of gas chromatography with mass spectrometry, where was made the determination of ethyl carbamates with sensibility, selectivity, precision, and accuracy (Y. Zhang et al., 2008).

Perestrelo et al. employed headspace-SPME for the extraction of ethyl carbamates from wines. The samples were mixed with 10% of NaCl solution that modified the ionic strength, and consequently, improved the efficiency of extraction. The temperature was controlled at 25 °C to improve the efficiency of the extraction and aids the extraction of the target carbamates. Moreover, it was used constant magnetic stirring to facilitate the mass transference, but the extraction time was 60 min. The analytes were analyzed by gas chromatography coupled to time-of-flight mass spectrometry (Perestrelo et al., 2010).

2.4.3. Extraction involving membrane protection

The membrane protection can be employed to protect the fiber against interferences, the presence of solids, and modification of the sample, such as extremes of basic and acid pH. Thus, the use of these membranes can aid in the extraction of the carbamates and dithiocarbamates with low volatility, being an alternative to headspace-SPME. The type of membrane material can improve the selectivity of the extraction. However, this microextraction modality requires a high extraction time due to the slower extraction kinetic compared to the direct extraction. The thickness of the membrane is directly related to the velocity of mass transference, and proportional to the extraction time (“Anal. Microextraction Tech.,” 2017; Maciel et al., 2019; Pawliszyn, 2012a).

Song et al. used carbon nanotubes-reinforced hollow fiber SPME for the determination of carbofuran, carbaryl, isoprocarb, diethofencarb, and methiocarb in apples, which were initially cleaned, peeled, cored, cut, and homogenized. A fraction of the sample was mixed with water and NaCl, and the pH was adjusted to 5.50 and the mixture was shaken for 15 min. After resting for 4 h at room temperature, the obtained solution was used in the extraction step. A high-pressure liquid chromatography with a diode array was used for the determination of them with good analytical parameters (Song et al., 2013).

Therefore, the LPMEs and SPMEs need lower samples, solvents, sample preparation steps, and extraction time than official methodologies for carbamates and dithiocarbamates as was shown in the previous

sections. The carbamates official methodology extraction is a liquid-liquid extraction, which uses ethanol and petroleum ether and it has several steps of the extraction and filtration of the sample extract (Onley et al., 1971). Thus, comparing with the LPMEs enable that are less laborious, propitious systematic errors because of minimization of the extraction steps, and they have more selectivity.

The dithiocarbamates official methodology is acid digestion, which provides a decomposition of all dithiocarbamates with a hot acid solution generating CS_2, and so, they can be aspirated by lead acetate traps to remove enables interferents and CS_2 fixed in the KOH-methanol (Bontoyan, 1963). Furthermore, the employed of the LPME and SPME is more selectivity due to the separation of the other organic compounds present in the food samples, and also between dithiocarbamates that can provoke a matrix effect, moreover, acid digestion needs a more qualified analyst than MEs, and it can have a higher risk operational.

2.5. Perspectives

This review presented discussions about the carbamates and dithiocarbamates employed in the agriculture practice, which present different toxicity degrees. Some of them are prohibited in the United States and the European Union, hence, the control of the concentration of carbamates and dithiocarbamates in the foodstuffs and water is necessary to ensure population health. Nonetheless, the complexity of the sample composition can provide the matrix effect, why the sample preparation steps aid in the application of analytical techniques in complex samples by removing interferences and improving the sensibility and selectivity of the methodology. Furthermore, new researchers have made the miniaturization of the traditional methods to decrease the solvent and sample used and minimizing the damage in the analyses, such as analyte losses and contamination causing systematic errors.

The MEs are employed in the extraction of the carbamates and dithiocarbamates from complex samples to achieve better analytical parameters in the chemical analyses. However, few publications are dedicated to this subject. The use of these techniques enables the minimization of the interferences concentration during the realization of the analyses, and consequently, matrix effects and some systematic errors. Furthermore, the MEs decrease the amount of required solvent and sample quantities, extraction time, and waste generation. Their modifications permitted more applicability in the samples and extraction of several target compounds simultaneously without losing selectivity.

The LPME is more used for the extraction of carbamates and dithiocarbamates, due to its easy operation, use of small amounts of solvent and sample, and short extraction time. These MEs are classified according to their operation mode into DLLME, HF-LPME, and SDME. Their extraction efficiency is directly related to the chemical affinity of extraction solvent with the analyte, during the mass transference of target compounds from sample to solvent. The DLLME and HF-LPME were more employed in the extraction of carbamates and dithiocarbamates. However, SDME was not yet employed for the extraction of dithiocarbamates and was poorly explored for the extraction of carbamates. Therefore, these MEs still have a lot to be explored in the determination of the carbamates and dithiocarbamates, such as employed deuteric and ionic liquids like solvents, and the use of SDME for dithiocarbamates.

Likewise, the SPME was extensively employed for the extraction of carbamates and dithiocarbamates, due to its easy operation and the use of small amounts of solvent and sample. These MEs are classified according

to the extraction mode, that is a direct extraction, a headspace extraction, and extraction with the use of membrane protection. The mass transference in these MEs occurs from a sample to a solid phase. SPME is more employed for the extraction of carbamates and poorly explored for the extraction of dithiocarbamates. Thus, this SPME still can be explored in the utilization of new sorbents materials and/or with the coupled to ultrasound and microwave to the determination of the carbamates and dithiocarbamates.

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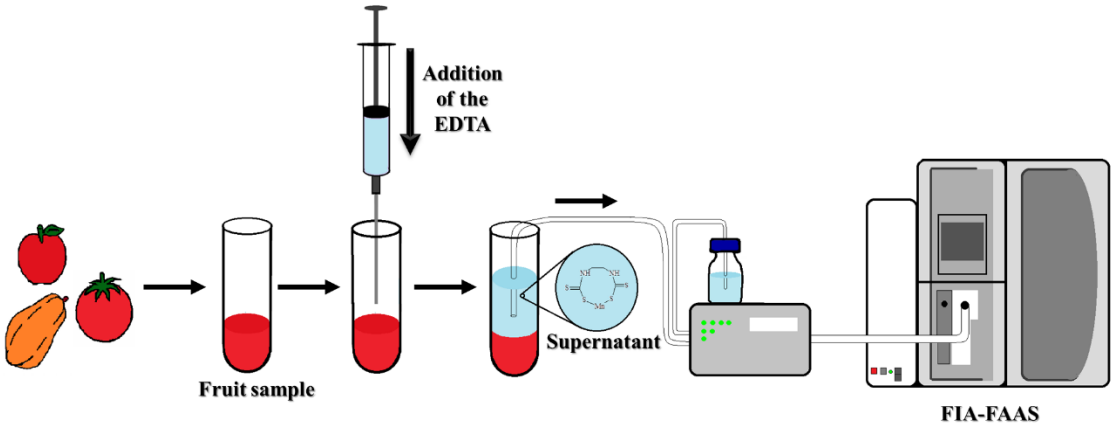
3. ENVIRONMENTALLY FRIENDLY AND NOVEL SOLID-LIQUID PHASE MICROEXTRACTION OF MANEB IN FOODSTUFFS[†]

Graphic abstract:



Highlights:

- Indirect determination of the maneb using FIA-FAAS
- Microextraction of the maneb in the foodstuffs without organic solvent
- Factorial designs optimization of the extraction provided efficient extractions
- Easy SLPME for extraction of the maneb from foodstuffs samples

Abstract

The dithiocarbamates class has been widely used in agriculture practice because of lower toxicology and instability than other classes of pesticides. Among them, the maneb had been used in the production of diverse fruits and vegetables, but its high ingestion can provoke adverse effects on human health. This work used the Solid-Liquid Phase Microextraction (SLPME) for extraction of the maneb in foods sample with posterior determination by Flow injection analysis-Flame Absorption Atomic Spectroscopy (FIA-FAAS). Curve analytical had a linear range from 0.9 to 20.0 µmol L^{-1} maneb (A = 5.9x10^{-4} C (µmol L^{-1}) + 6.9x10^{-4}), good repeatability (4.0%) and reproducibility (3.4%), quantification (6.0 µmol L^{-1}) and detection (0.20 µmol L^{-1}) limit, which was above of the established by regulatory agencies. The extraction of the maneb was performed using 685 µL of the solution of the 1.0x10^{-3} mol L^{-1} of EDTA, and it has excellent recovery values from 86 to 103 %. Therefore, the developed SLPME demonstrated an alternative environmentally friendly for the maneb extraction from foods samples (apple, papaya, and tomato).

Keywords: Pesticides, Microextractions, Liquid-phase microextraction, Solid-phase microextraction, Foodstuff samples.

3.1. Introduction

[†] This chapter is currently under review
MARTINS, F. C. O. L., MELCHER, W. R., Environmentally friendly and novel solid-liquid phase microextraction of maneb in foodstuffs.

In agricultural practices are largely used some compounds to control and eliminate diverse types of fungi, and still, increase the production profits. Among fungicides, the dithiocarbamates class has been widely employed in different agricultural productions, due to its lower toxicology and instability than carbamates and organophosphates, and high efficiency [1–3]. In Brazil, maneb (manganese(II) ethane-1,2-diyldicarbamodithioate) has been used in the production of fruits and vegetables [4]. However, recent researches have shown that high ingestion of them can provoke the development of Parkinson's disease, teratogenicity, and skin irritation and sensitization (itching and mild erythema) [5,6].

In reason of its toxicity, the regulatory agencies have established the maximum residue level (MRL) of the maneb in the raw materials and foodstuffs. Brazilian Health Regulatory Agency (ANVISA) and European Union (EU) permit from 0.1 to 10.0 mg kg-1 and from 0.05 to 25.0 mg kg-1 of maneb, respectively [4,7]. Hence it is necessary the realization of the residue control of the maneb in foods, which can be made using different analytical techniques, such as chromatography, electroanalytical, and spectroscopy [5,8–11].

Flame atomic absorption spectroscopy (FAAS) has been employed in the indirect determination of the maneb with other dithiocarbamates in food samples using a step of the sample digestion, due to high sampling rate, differentiation among dithiocarbamates through metal analysis, and robustness [10,12]. However, the FAAS need of high amount of sample, hence, the flow injection analysis can aid in the decrease of the reagent and sample consumption, ease in their application, and minimization of the waste generated [13,14].

Nonetheless, the composition of the food sample can provide a matrix effect, being necessary the achievement of the sample preparation steps to remove the potential interferents, and consequently, improve the accuracy of the methodology [15,16]. The miniaturization of extraction methods has been an alternative to the official methodology, liquid-liquid extraction, and solid-phase extraction of dithiocarbamates, which need of high among of the solvents and steps [5]. The official method of the dithiocarbamates is acid digestion to generate CS2 by decomposition of all dithiocarbamates using a hot acid solution [17]. The microextractions decrease the errors from contaminations and analytes losses, solvent volume employed, and extraction time, which followed the guidelines of the Green Analytical Chemistry (GAC) [18,19].

The use of some variations of the liquid phase microextraction (LPME) has been used in the extraction of the dithiocarbamates due to an increase in the selectivity of the methodology. Moreover, the employment of the LPME has some advantages, such as low cost, reduction of solvent and sample volume used, affordability to any laboratory, and being environmentally friendly [5,18,20]. Besides this, the main goal of this work was the development of a methodology according to guidelines of GAC using the solid-liquid phase microextraction (SLPME) in the extraction of the maneb in natura foodstuff samples (apple, tomato, and papaya) coupled to determination by FIA-FAAS.

3.2. Experimental

3.2.1. Materials and reagents

Spectroscopic analyses were performed in a Fast Sequential Atomic Absorption Spectrometer FS230 from Varian, coupled to SpectraA, also from Varian. A system with a lab-made commutator injector peristaltic, Tygon tubes, and pump with 5 channels (Ismatec) was used before the nebulizer. The pH of the solutions was adjusted using a pHmeter from Quimis, model Q400RS. The dispersing of the extractant throughout the sample was made using an orbital shaker from Quimis, model Q225M, vortex agitator from Vortex-Genie 2, model SI-0266, and/or ultrasonic bath from Quimis, model Q335D2. To accelerate the separation of phases was used a centrifuge from Quimis, model Q222TM2.

All solutions were made using ultrapure deionized water (18 µS cm-1) (Merck Millipore, model: Synergy® Water Purification System) and reagents with high analytical purity (Sigma-Aldrich). The stock solution was made by dissolving 2.00 mg of the maneb, from Sigma-Aldrich (CAS 12427-38-2), in 25.0 mL of solution $2.50x10^{-3}$ mol L^{-1} of ethylenediaminetetraacetic acid (EDTA). The solution of 1.00% of nitric acid (v/v) was used as a carrier fluid in the FIA-FAAS.

3.2.2. Optimization flow injection analysis-flame atomic absorption spectroscopy

FIA-FAAS experiments were performed using a manganese (Mn) hollow cathode lamp and according to instrumental parameters that were recommended by the manufacturer for Mn, which were a wavelength of 279.9 nm, spectral and pass of 0.2 nm, lamp current of 5.0 mA, and a flame of air and acetylene (13.5 and 2.00 L min^{-1}, respectively). Initially, the sample loop was optimized from 10 to 80 µL with a capillary (0.8 mm i.d.,) considering the repeatability and area of the peak obtained.

3.2.3. Analytical parameters

Following the experimental optimization, the analytical curves were made using solutions with different concentrations of the maneb from $9.10x10^{-7}$ to $20.00x10^{-6}$ mol L^{-1} in triplicate. It was calculated of the detection (DL) and quantification limits (QL) using the slope of the straight line of the average analytical curve (s), standard deviation (Sb) of the 11 absorbances signal of the blank solution in $1.00x10^{-3}$ mol L^{-1} of the EDTA, according to the recommendation of the IUPAC [21].

The reproducibility (interday precision) and repeatability (intraday precision) experiments were used to evaluate the precision of the methodology, which used $8.00x10^{-6}$ mol L^{-1} of the maneb in $1.00x10^{-3}$ mol L^{-1} of EDTA. The reproducibility experiments were made using five spectroscopic analyses, in different solutions and different days. The repeatability experiments were realized employing 11 spectroscopic analyses, on the same day and in the same maneb solution. It was calculated the relative standard deviations (RSD) for the reproducibility and repeatability using a standard deviation of the mean area peak absorbance value obtained [22].

3.2.4. Optimization of solid-liquid phase microextraction procedure

In all experiments were made using the sample without doped and sample doped with 20 µL of stock solution of the $301.5x10^{-6}$ mol L^{-1} of maneb. These samples were used in the evaluation of the chemical and physical experimental parameters (concentration and volume of the extractor solution, mass of the sample, mode and times of the agitation and speed and time of the centrifugation). The supernatant obtained in each extraction was analyzed by FIA-FAAS, and the optimization of the physical and chemical parameters was made considering the percentage of the absorbance obtained from the analytical standard and tomato sample.

The extractor solutions of the EDTA from $1.00x10^{-4}$ to $1.00x10^{-2}$ mol L^{-1} were evaluated in the extraction of the maneb with the 200 mg of the sample, agitation of the orbital shaker of 200 rpm at 20 min, and centrifugation of 4000 rpm at 20 min. Posteriorly, the optimization of the dispersing of the extractant throughout the sample was made evaluating the orbital shaker, vortex agitator and/or ultrasonic bath during 20 min with 200 mg of the sample doped, 400 µL of extractor solutions of $1.00x10^{-3}$ mol L^{-1} of EDTA, and centrifugation of 4000 rpm at 20 min.

Physical experimental parameters were optimized using factorial designs (screenings) of 2^{5-1}. So, it evaluated the sample mass from 100 to 300 mg, extractor solution volume from 400 to 1000 µL, agitation time from 10 to 30 min, centrifuge speed from 1000 to 4000 rpm, and time from 10 to 30 min. Subsequently, the factorial designs (2^4) with five central and axial points, where was evaluated the sample mass from 100 to 500 mg, extractor solution volume from 400 to 1200 µL, agitation time from 10 to 50 min, centrifuge speed from 1000 to 4000 rpm, as presented in Table 2.1.

Table 2.1: 2^4 factorial designs proposed with five central points and axial points.

Parameters	**Levels**				
	-2	**-1**	**0**	**+1**	**+2**
Sample mass (mg)	100	200	300	400	500
Extractor solution volume (µL)	400	600	800	1000	1200
Agitation time (min)	10	20	30	40	50
Centrifugation speed (rpm)	1000	1750	2500	3250	4000

3.2.5. Evaluation of the effect of concomitant species

The interference effects on the maneb determination were evaluated with the addition of nickel ($1.70x10^{-4}$ mol L^{-1}), iron ($4.48x10^{-5}$ mol L^{-1}), and phosphate ($3.23x10^{-5}$ mol L^{-1}) in the solution $8.80x10^{-6}$ mol L^{-1} of the maneb, according to the recuperation of the dithiocarbamates.

3.2.6. Application

The natura foods (tomato, apple, and papaya) were obtained at a supermarket located in Piracicaba city, São Paulo state, Brazil, and all samples were frozen for later use. All samples used in this work were initially prepared according to the proposed methodology, and all samples were doped with 20 µL of stock solution of the $226.1x10^{-6}$, $301.5x10^{-6}$, or $386.8x10^{-6}$ mol L^{-1} of maneb. The efficiency of the extraction was

evaluated by recuperation of the maneb in the sample. Posteriorly, the effect of matrix and nebulization was evaluated by analytical curves into the sample extract. These curves were built using 500 µL of the sample extractor and 500 µL a solution of the $1.00x10^{-3}$ mol L^{-1} of EDTA at pH 9.50 in different concentrations of the maneb from $9.10x10^{-7}$ to $20.00x10^{-6}$ mol L^{-1}, in triplicate and compared in the analytical curve of the standard.

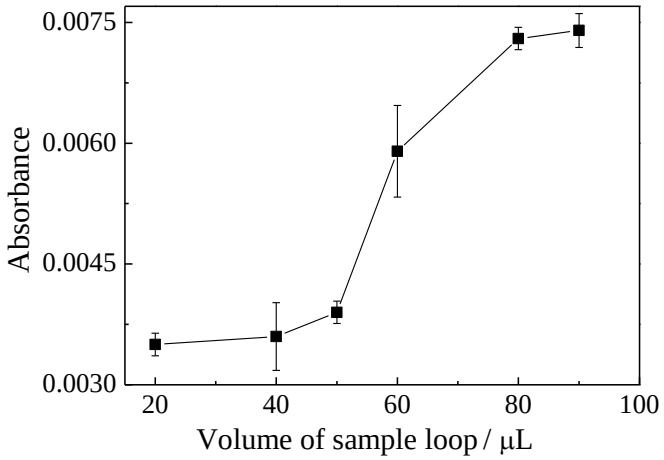
3.3. Results and discussion

3.3.1. Optimization of the flow injection analysis-flame absorption atomic spectroscopy

The analytical signal of the Mn with maneb in the FIA-FAAS, employing a wavelength of 279.9 nm, spectral and pass of 0.2 nm, lamp current of 5.0 mA was evaluated to verify the similarity. So, it was observed by the ratio between the slopes of the analytical curves of Mn ($A = + 1.23x10^{-2}$ C (µmol L^{-1}) – $1.38x10^{-3}$) and maneb ($A = + 1.15x10^{-2}$ C (µmol L^{-1}) – $9.72x10^{-4}$) that did not have a significant difference. Subsequently, the parameters of the FIA-FAAS were optimized, such as carrier, sample loop, and flow rate.

The carrier was evaluated ultrapure deionized water and a solution of 1.00% of nitric acid (v/v) with a flow rate of 7.50 mL min^{-1}, which was adequate with the flow of the FAAS nebulizer. In both mediums was observed good repeatability (3.72 and 2.45%, respectively) and sensibility, but the use of nitric acid assisted in the cleaning and avoided the memory effect during the analysis, which was chosen as the carrier. The optimization of the volume of the sample loop was performed from 10 to 90 µL of the solution of the $4.00x10^{-6}$ mol L^{-1} of maneb. Thus, this optimization allows observing that the absorbance increase until 80 µL, which had higher signal analytical and lower RSD, Fig. 2.1.

Figure 2.1: Variation of the volume of the sample loop from 10 to 90 µL with a capillary (0.8 mm i.d.,) using carrier fluid of 1.00% of nitric acid (v/v) with a flow rate of 7.50 mL min^{-1}, and solution of $4.00x10^{-6}$ mol L^{-6} of maneb. Error bars correspond to the standard deviation (n = 3).



3.3.2. Analytical parameters

The use of the FIA-FAAS with the experimental (volume of the sample loop of 80 μL, carrier of 1.00% of nitric acid (v/v) with a flow rate of 7.50 mL min^{-1}) and spectroscopic (wavelength of 279.9 nm, spectral and pass of 0.2 nm, lamp current of 5.0 mA) optimized parameters enable the construction of the analytical curves from $9.10x10^{-7}$ to $20.0x10^{-6}$ mol L^{-1}, as described in the Experimental Section. The average analytical curve was expressed as $A = 5.9x10^{-4}$ C (μg L^{-1}) + $6.9x10^{-4}$ (r=0.998). The reproducibility, repeatability, DL, and QL were 3.39%, 4.07%, $1.97x10^{-7}$ mol L^{-1}, and $5.98x10^{-6}$ mol L^{-1}, respectively.

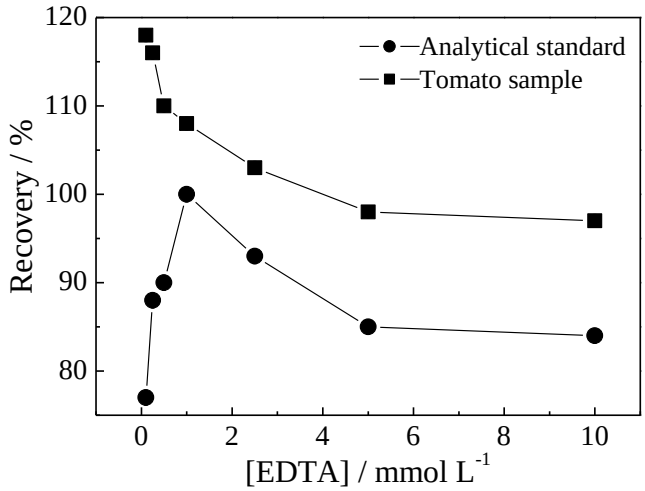
3.3.3. Optimization of the solid-liquid phase extraction

The solubility of the maneb in the organic solvent is very low. Hence, the extraction of this dithiocarbamate in the foodstuffs samples was made with the solution of the EDTA, which provided the interaction of the Mn present in the chemical structure of the maneb generating a complex. The formation of this complex can avoid the combination of other metal cations with the maneb that can decrease interferents and the formation of insoluble substances [10,27,28]. Nonetheless, the formation and stability of this complex need solution with a pH above 6.00, for this, the extractor solution of EDTA used had a pH of 9.50.

3.3.3.1. The concentration of the EDTA

The concentration of the EDTA of the extractor solution was evaluated from $1.00x10^{-4}$ to $10.0x10^{-3}$ mol L^{-1} to improve the efficiency of the extraction and decrease the interference effects, as can be visualized in Fig. 2.2. The concentrations of the EDTA bellow of $1.00x10^{-3}$ mol L^{-1} showed a high difference between the percentage of the analytical signal obtained of the analytical standard and tomato sample. Demonstrating that had a decrease in the sensibility in low concentration of the EDTA and an increase in the effects matrix.

Figure 2.2: Variation of the concentration of extractor solution from $1.00x10^{-4}$ to $10.0x10^{-3}$ mol L^{-1} of the EDTA using SLPME (200 mg of the sample, which was doped with 20 µL of stock solution of 301.5 µmol L^{-1} of maneb, extractor volume of 400 µL, centrifuge speed of 4000 rpm and time of 20 min, and agitation time of 20 min) with FIA-FAAS (volume of the sample loop of 80 µL, carrier fluid of 1.00% of nitric acid (v/v) with a flow rate of 7.50 mL min^{-1}). Error bars correspond to the standard deviation (n = 3).



The concentration of the EDTA above of $1.00x10^{-3}$ mol L^{-1} presented a decrease in the analytical signal, where can have a higher consumption energic and generation of the intermediate species (carbon monoxide and dioxide) promoving spectral interference [29]. Therefore, the concentration of extractor solution chosen was of the $1.00x10^{-3}$ mol L^{-1} of EDTA had a similar percentage between results obtained by extracted and standard.

3.3.3.2. Mode of agitation

The optimization of the dispersing of the extractant throughout the sample was performed to improve the extraction efficiency and decrease the matrix effect employing the orbital shaker, vortex agitator, and/or ultrasonic bath, as described in the Experimental Section. Therefore, the recoveries obtained for the orbital shaker, vortex agitator, and ultrasonic bath were 131.4 ± 4.00, 144.2 ± 9.05, and 170.7 ± 2.44%, respectively. Hence, it was chosen the orbital shaker because its use did not degrade the analytical standard of the maneb, and it had better recovery among them.

3.3.3.3. Factorial designs

The optimization physical experimental parameters were realized using 2^{5-1} factorial designs (screenings) as described in the Experimental Section, to optimize the sample mass, extractor solution volume,

centrifugation speed and time, and agitation time. Thus, it was observed that did not have significant differences in the centrifugation time between 10 and 30 min. Therefore, the centrifugation time of 10 min was chosen to develop a faster procedure.

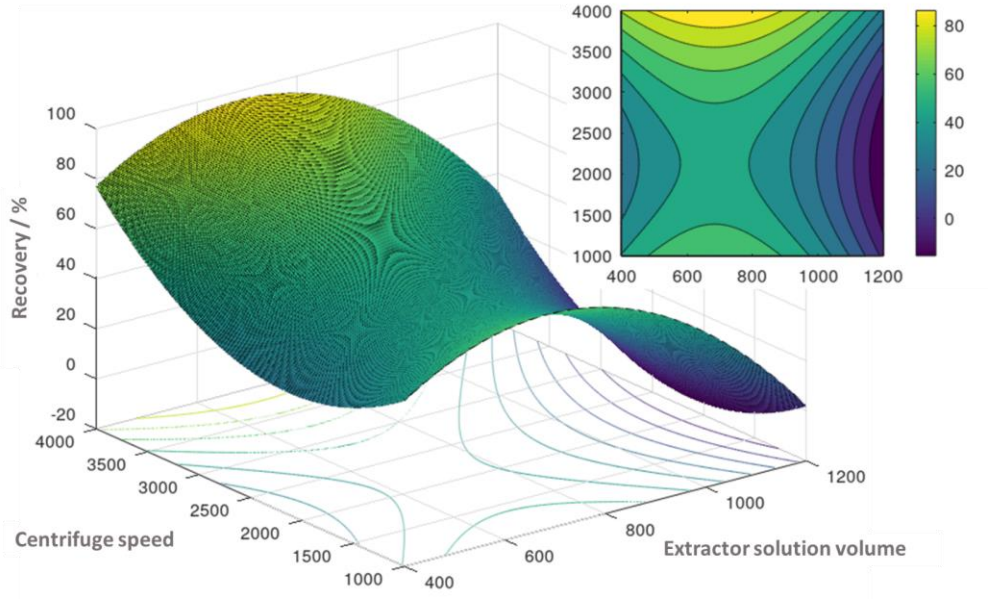
Posteriorly, the 2^4 factorial designs with five central and axial points were made of mode randomized order, as described in the Experimental Section, to decrease errors. The conditions were sample mass (x_1) from 100 to 500 mg, extractor solution volume (x_2) from 400 to 1200 µL, agitation time (x_3) from 10 to 50 min, and centrifuge speed (x_4) from 1000 to 4000 rpm. The F test was made to evaluate pure error, lack of fit and used to the residue and regression.

The results obtained demonstrate a lack of adjustment was < 1 and experimental data were correlated demonstrating that the proposed model can be acceptable. Besides this, an empirical relationship between the variables and response was expressed by the following fitting second-order polynomials Eq. 1. Using the significant coefficients (centrifuge speed and extractor solution volume) was obtained a response surface, as presented in Fig. 2.3, and quadratic regression model, which can be expressed as:

$$Response = 46.92 - 11.07x_2 + 7.69x_4 - 9.59x_2^2 + 7.74x_4^2 \quad \text{Equation 1}$$

This model was in accordance with recent researches that have demonstrated that the quadratic terms can influence directly extraction efficiency [30,31].

Figure 2.3: Response surface and level curves for optimization of the centrifuge speed and volume of the extractor solution of the SLPME.



Optimum conditions were 200 mg of the sample, which was doped with 20 µL of stock solution of the $301.5x10^{-6}$ mol L^{-1} of maneb, extractor volume of 685 µL, centrifuge speed of 4000 rpm and time of 10 min, and agitation time of 10 min, which had recovery in the tomato of 91.24 ± 7.91%, that demonstrated the extraction efficiency.

3.3.4. Effect of concomitant

The effect of concomitant species was evaluated for metals that could influence the determination by FAAS as iron, nickel, and phosphate because they can interact with the manganese creating um compounds most thermally stable. Besides this, the solutions of $8.80x10^{-6}$ mol L^{-1} of maneb in a solution of $1.00x10^{-3}$ mol L^{-1} of EDTA containing $1.70x10^{-4}$ mol L^{-1} of nickel, $4.48x10^{-5}$ mol $L^{-1}$of iron, and $3.23x10^{-5}$ mol L^{-1} of phosphate was used. The analytical signals were evaluated to those obtained without the presence of interfering metals. Thus, the metals presented a signal variation lower than 5.0%, not interfering in the proposed methodology.

3.3.5. Optimization of the solid-liquid phase extraction

The solubility of the maneb in the organic solvent is very low. Hence, the extraction of this dithiocarbamate in the foodstuffs samples was made with the solution of the EDTA, which provided the interaction of the Mn present in the chemical structure of the maneb generating a complex. The formation of this complex can avoid the combination of other metal cations with the maneb that can decrease interferents and the formation of insoluble substances [10,27,28]. Nonetheless, the formation and stability of this complex need solution with a pH above 6.00, for this, the extractor solution of EDTA used had a pH of 9.50.

3.3.6. Application

The proposed methodology was applied in apples, papayas, and tomatoes samples. The extractions in the samples were performed as the proposed methodology employing SLPME, in order to extract the maneb from complex samples and decrease the matrix effect. Subsequently, the supernatant was analyzed by FIA-FAAS and determined the concentration found ($[Maneb]_{found}$) and recovery percentages (%R), as shown in Table 2.2.

Table 2.2: Addiction-recovery extraction of maneb using SLPME in natura food samples. Standard deviation corresponds to analysis in triplicate (n = 3).

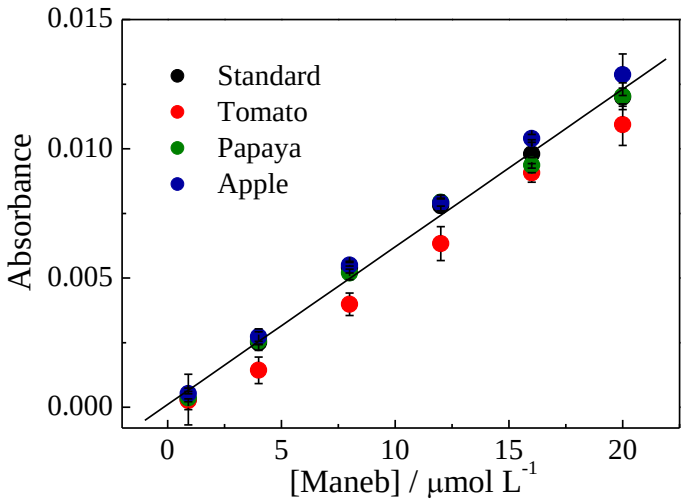
Foodstuff sample	Maneb (μmol L^{-1})					
	Spiked	**Found**	**Recovery (%)**	**Spiked**	**Found**	**Recovery (%)**
Apple 1	6.60	5.76±0.34	87.21	11.00	10.33±0.46	93.95
Apple 2	6.60	6.85±0.52	103.80	11.00	10.53±0.46	95.76

Apple 3	6.60	5.95±1.08	90.22	11.00	10.04±0.46	91.23
Apple 4	6.60	6.45±0.62	97.72	11.00	10.53±0.34	95.76
Papaya 1	6.	6.85±0.30	103.80	11.00	10.63±0.62	96.66
Papaya 2	6.60	6.85±1.03	103.80	11.00	10.73±0.90	97.57
Papaya 3	6.60	6.25±0.30	94.75	11.00	10.14±0.52	92.14
Papaya 4	6.60	6.35±0.17	96.26	11.00	10.24±0.35	93.04
Tomato 1	6.60	6.56±0.49	99.38	11.00	9.47±0.49	86.09
Tomato 2	6.60	6.13±0.65	92.84	11.00	11.09±1.04	100.08
Tomato 3	6.60	6.56±1.14	99.38	11.00	10.97±0.65	99.82
Tomato 4	6.60	6.56±0.37	99.38	11.00	10.66±0.32	96.88

The %R calculated proposed methodology was from 86.09 to 103.80 % for samples of apple, papaya, and tomato. Therefore, comparing the values of the %R obtained with the acceptable from 70 to 120% for recovery percentages, it was demonstrated that the SLPME development for extraction of the maneb in food samples is applicable in food samples.

Moreover, the analytical curves into sample extracts were built under experimental conditions of the SLPME and FIA-FAAS are presented in Fig. 2.4. They were made employing 500 µL of sample extracts and 500 µL a solution of the $1.00x10^{-3}$ mol L^{-1} of EDTA at pH 9.50 in different concentrations of the maneb, as described in the Experimental Section. Demonstrating that did not have matrix and nebulization effects in the presence of the sample chemical composition of apple, papaya, and tomato, due to the slopes of the curves in the sample and the analytical standard being very similar.

Figure 2.4: Analytical curves obtained to maneb in the range concentration from $9.101x10^{-7}$ mol L^{-1} to $20.00x10^{-6}$ mol L^{-1} in a solution of $1.00x10^{-3}$ mol L^{-1} of EDTA at pH 9.50, and apple, papaya, and tomato sample, and using SLPME (200 mg of the sample, extractor volume of 685 µL, centrifuge speed of 4000 rpm and time of 10 min, and agitation time of 10 min) with FIA-FAAS (volume of the sample loop of 80 µL, carrier fluid of 1.00% of nitric acid (v/v) with a flow rate of 7.50 mL min^{-1}).



It was perceived that analytical parameters obtained demonstrated a high sampling rate, good precision, low extraction time, a small volume of the extractor solution and sample, and environmentally extractor solution. This way, it was compared the proposed SLPME with other extraction methods used to maneb, which employed a high among of extractor solution and/or organic solvents, as presented in Table 2.3.

Table 2.3: Analytical parameters of some extraction methods for the maneb determination in natura food samples.

Extraction type	Sample	Sample preparation time (min)	Extractor solvent (mL)	Eco-scale	Determination method	Determination time (min)	Linear response ($mg\ L^{-1}$)	DL ($mg\ L^{-1}$)	Ref.
LLE	Apple	35	6 of EDTA	92	HPLC-MS	2.5	33.0 – 2000	0.01	[8]
LLE	Rice, potato, crecked wheat, and river water	50	25 of dimethylsulfoxide	87	UV-Vis	15	0.067 – 1.067	2.2	[9]
LLE	Tomato	6	3 acetonitrile–dichloromethane–chloroform (1:1:1)	84	LC-UV	11	0.1 – 5.0	0.45	[25]
LLE	Grain, tomato, and cabbage	60	30 of dimethylsulfoxide	87	UV/Vis	-	0.125 – 4.8	0.08 – 2.4	[33]
VALLME-SFO or DLLME-SFO	River water	3 or 9.58	5 of NaCl 3.0% (m/v) (pH 7.0) and 0.10 of 1-dodecanol 0.33% (v/v), or 5 NaCl 4.0% (m/v) (pH 8.0), 0.10 of 1-dodecanol 33.33% (v/v) and methanol	88	LC-MS	3	0.0005 – 0.50 or 0.001 – 1.00	0.025 – 0.377	[34]

			0.26% (v/v)						
VP-LPME	Grape, strawberry, and corn	20	1 of EDTA 0.25 mol L^{-1} with NaOH 0.45 mol L^{-1} (pH 9–10) and tin (II) chloride dihydrate acid	89	IR	-	0.006 – 0.120	-	[35]
LPME	Apple, papaya, and tomato	20	0.400 of EDTA 1.00 mmol L^{-1} (pH 9.50)	94	FIA-FAAS	0.33	0.242 – 53.1	0.0504	This work

DL = Detection Limit LLE = Liquid-Liquid Extraction; HPLC-MS = High Performance Liquid Chromatography; UV-Vis = Ultraviolet–Visible Spectroscopy; LC = Liquid Cromatography; UV =Ultraviolet Spectroscpy; VALLME-SFO = Vortex Assisted Liquid-Liquid Microextraction Based on Solidification of Floating Organic Droplet; DLLME-SFO = Dispersive Liquid-Liquid Microextraction Based on Solidification of Floating Organic Drople; VP-LPME = Vapour Phase Liquid-Phase Microextraction; IR = Infrared Spectroscopy; SLPME = Solid-liquid phase microextraction; FIA-FAAS = Flow Injection Analysis Flame Atomic Absorption Spectroscopy.

The developed methodology does not use organic solvent in the extraction process and the consumption of the extractor solution was decreased by approximately 98% compared with the LLE that used dimethylsulfoxide [9,33]. The sample preparation time was similar with LLE [8] and VP-LPME [35] but 40% smaller compared to with LLE that employed dimethylsulfoxide as extractor solvent. The Analytical Eco-Scale was calculated for the works published of extractions of the maneb and proposed methodology, which demonstrated that is most environmentally friendly due to a score calculated of 94. While the other methodologies had a score between 84 – 92 because used organic solvents and several steps of the sample preparations, as presented in Table 3 [32].

Furthermore, this extraction enabled the indirect determination of the maneb by FIA-FAAS, where had DL below of the established by regulatory agencies (0.1 to 10.0 mg kg^{-1} of food) and very quick analysis (0.33 min). Therefore, the proposed methodology presented suitable applicability in the extraction and determination of the maneb in the apple, papaya, and tomato samples, with excellent recuperations, robustness, precision, accuracy, and still, it was greener than those previously reported.

3.4. Conclusion

The novel of this work is the use of the solid-liquid phase microextraction with flow injection analysis-flame atomic absorption spectroscopy in the determination of the maneb from natura food samples. It was not employed organic solvent in the extraction of the dithiocarbamate. The steps of the sample preparation were decreasing, and consequently, there were minimized systematic errors, reduced the time and cost of the analysis.

Furthermore, the solid-liquid phase microextraction used a lower amount of extractor solution and sample than other methods reported in the literature, and also, it had quickness, efficiency in the extraction, and simplicity in the sample preparation. Hence, this microextraction can be an alternative environmentally friendly to the extraction of the maneb from foods samples (apple, papaya, and tomato).

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4. CONCLUSÃO GERAL

Os ditiocarbamatos são bastante empregados nas práticas agrícolas no Brasil, mesmo apresentando altos níveis de toxicidade e sendo proibidos na União Europeia e nos Estados Unidos. A determinação em amotras de alimentos e água é fundamental para controlar a concentração dos pesticidas ditiocarbamatos. No entanto, estas amostras possuem alto grau de complexidade podendo interferir nas análises, necessitando da realização de etapas de preparo de amostra para aumentar a sensibilidade e seletividade. Assim, nesta dissertação foi mostrado as principais microextrações de fase sólida e líquida empregadas nas extrações de ditiocarbamatos, as aplicações, vantagens, desvantagens e os parâmetros analíticos das metodologias de análises.

O desenvolvido de uma metodologia de microextração sólido-líquida, rápida, simples e de baixo custo de manebe de amostras de alimentos foi realizado. Algumas vantagens foram alcançadas como os resultados analíticos não serem influenciados pela degração do pesticida, a alta frequência analítica, e a não utilização de solvente orgânico, conferindo uma metodologia amigável ao meio ambiente e ao ser humano. Além disto, excelentes valores de precisão, exatidão e sensibilidade foram estimados, os quais foram avaliados de acordo com repetibilidade (4,0%), reprodutibilidade (3,4%), recuperação (86 - 103 %) e limite de detecção (0,20 μmol L^{-1}).