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

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ABSTRACT

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

1. Introduction

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

Abbreviations: TCs, tetracyclines; TC, tetracycline; OTC, oxytetracycline; CTC, chlortetracycline; DC, doxycycline; MRL, maximum residue limit; HPLC, high performance liquid chromatography; UV, ultraviolet detection; DAD, diode-array detector; FL, fluorescence detection; MS, mass spectrometry; ESI, electrospray ionization source; Q-TOF-MS, quadrupole time-of-flight mass spectrometry; NICI, negative ion chemical ionization; UHPLC, ultra-high performance liquid chromatography; AOAC, Association of Official Analytical Chemists; FIA, flow injection analysis; CE, capillary electrophoresis; FASS-EMI, field-amplified sample stacking with electromigration injection; DPV, differential pulse voltammetry; CV, cyclic voltammetry; LC-PB-MS, liquid chromatography–particle beam-mass spectrometry; LLE, liquid–liquid extraction; SLE, solid–liquid extraction; SPE, solid-phase extraction; UAE, ultrasonic-assisted extraction; MAE, microwave-assisted extraction; PLE, pressurized liquid extraction; MSPE, magnetic solid phase extraction; MSPD, matrix solid-phase dispersion; SBSE, stir bar sorptive extraction; MIP-SPE, molecularly imprinted polymer solid-phase extraction; SPME, solid-phase microextraction; DSPME, dispersive solid-phase microextraction; LPME, liquid-phase microextraction; SDME, single drop microextraction; DLLME, dispersive liquid–liquid microextraction; HFSLM, hollow fiber-supported liquid membrane; HF-LPME, hollow fiber liquid phase microextraction; US-DLLME, ultrasound-assisted dispersive liquid–liquid microextraction; LOD, limit of detection; LOQ, limit of quantification; CCα, decision limit; CCβ, detection capability; RSD, relative standard deviation; HLB, hydrophilic-lipophilic-balanced; CTAB, cetyltrimethylammonium bromide; G-MWNTs, graphitized multiwalled carbon nanotubes; IL, ionic liquid; NOSM, non-organic solvent microextraction; PDMS, polydimethylsiloxane; MCR-ALS, multivariate curve resolution-alternative least squares; MIH, molecularly imprinted hydrogel; LWCC, liquid waveguide capillary cell; EDTA, ethylenediaminetetraacetic acid; TCA, trichloroacetic acid; TFA, trifluoroacetic acid; CAN, acetonitrile; HAc, glacial acetic acid; MeOH, methanol; ZIF-8, zeolite imidazolate framework-8

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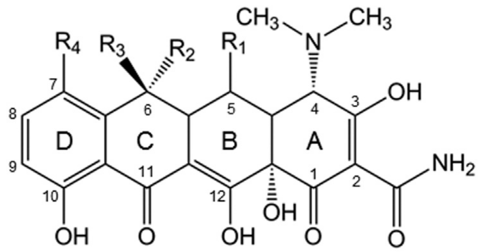

Compound	R_1	R_2	R_3	R_4
Tetracycline	H	CH_3	OH	H
Oxytetracycline	OH	CH_3	OH	H
Chlortetracycline	H	CH_3	OH	Cl
Doxycycline	OH	CH_3	H	H

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

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

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

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

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

The relationship between the use of antimicrobials in animal husbandry and antimicrobial resistance in humans has become a matter of great concern to public health. The reason being that the indiscriminate treatment of animals with veterinary antibiotics can turn their derived food products into sources for resistance to antibiotics in human species [8,12]. The discovery of new resistant strains of bacteria and other microorganisms that are becoming increasingly resistant over time has led to an increasing pressure on laboratories responsible for food safety. The laboratories are expected to monitor the use of veterinary pharmaceuticals and ensure food quality for human consumption [2,4].

1.1. Regulatory authorities

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

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

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

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

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

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