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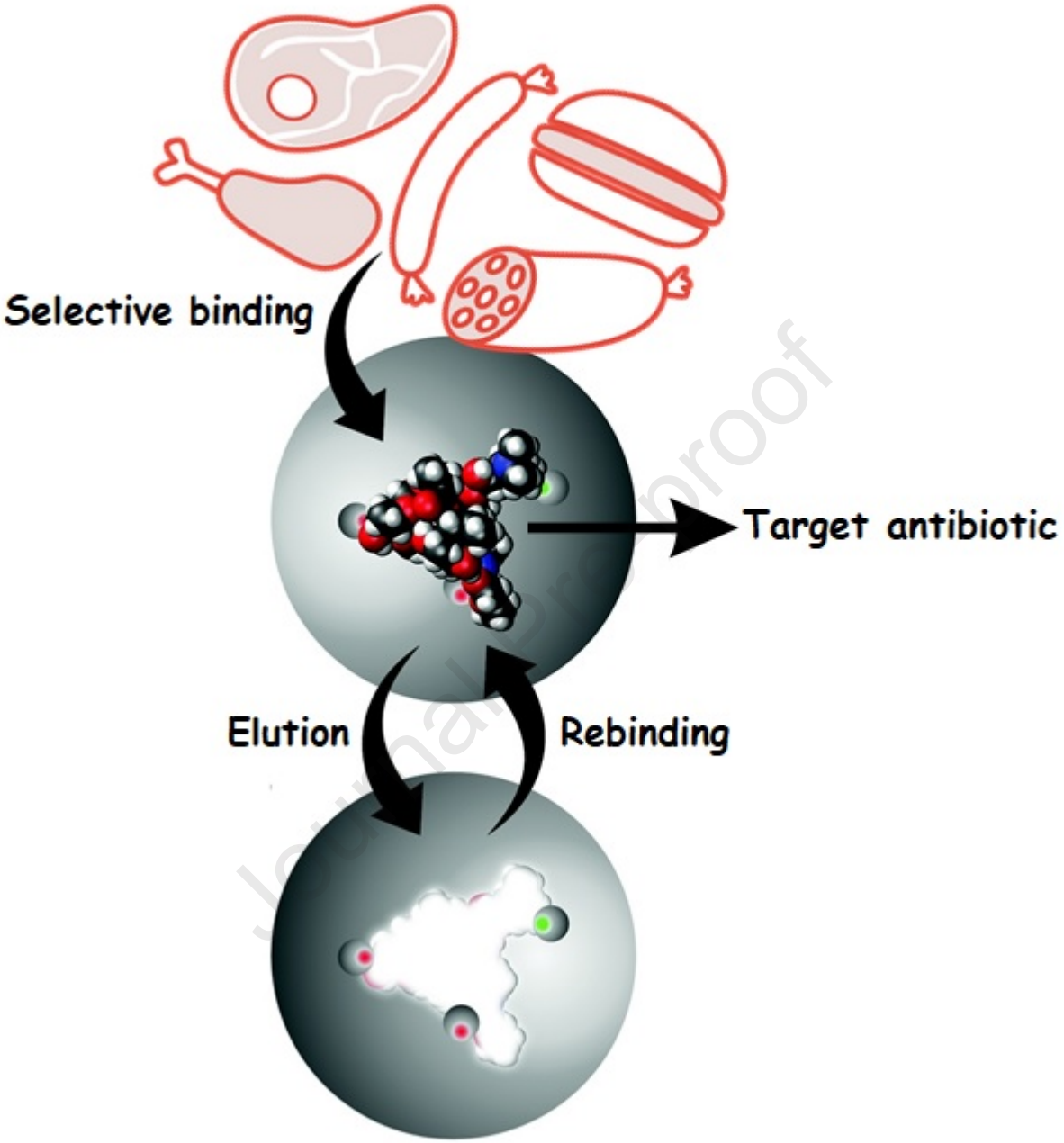

MIP-based extraction techniques for the determination of antibiotic residues in edible meat samples: design, performance & recent developments

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Abstract

Misusing or overusing antibiotics in livestock and poultry can result in the accumulation of mentioned drugs in the animal meat. Consequently, its consumption by humans and therefore increasing the risks of antibiotic resistance emergences. In order to decrease these risks, constant monitoring of the meat samples is necessary. Therefore, the concentration of antibiotics needs to be lower than maximum residue limits. As meat is a complex matrix, sample preparation is a mandatory step in the analysis. Molecularly imprinted polymers are one of the extensively studied tools in this aspect. These polymers exhibited great affinity and selectivity towards the target compound/s.

In this work, a collection of studies from 2017 – 2021 is reviewed. Inclusion criteria were formed around papers incorporating molecularly imprinted polymers as a means of extraction or detection of antibiotics in meat samples. This review represents different synthesis methods of these polymers and their applications in the extraction and determination of antibiotics from meat samples. It also demonstrates the advantages, gaps and weakness of these systems in the food chemistry field. It can also act as a guide for the design and development of novel polymer-based analytical methods for food applications. Throughout this review, the methods for determination of antibiotic residues in food samples using conventional and novel MIP based techniques are discussed, by coupling MIPs with other analytical techniques, Limit of detection and quantification and recovery rates will improve significantly, which results in designing of platforms in food chemistry analysis with higher efficacy.

Keywords: Molecularly imprinted polymers, Antibiotics, Meat samples, Determination, Extraction

1. Introduction

Nowadays, in a worldwide fairing, food excellence and protection attract more consideration for administration and users. A broad series of chemical substances in food products have proven to cause direct or indirect unfavorable effects on human health. (Delatour et al., 2018) More common chemical substances harmful to human health are plant toxins, mycotoxins (Alshannaq & Yu, 2017), and antibiotic residues. A wide variety of antibiotic classes such as Tetracycline, Fluoroquinolones, Phenicols, Sulfonamides, Aminoglycosides, Cephalosporins, and Macrolides are used in livestock farming. (Ramatla et al., 2017) Generally, Antibiotics are approved to be used for treating or preventing animal diseases. The American Veterinary Medical Association (AVMA) affirmed that antibiotics are one of the most important equipment that veterinarians use to support both human's and animal's health. (AVMA, 2019a)

On the other hand, significant amounts of antibiotic residues in animal food products probably worsen the immunological reactions and negatively affect gastrointestinal microflora.(Ramatla et al., 2017)

The animal health community, in cooperation with the food and drug administration (FDA) and the AVMA, innovated the manner antibiotics are used on U.S farms.(AVMA, 2019b) New revisions from January 1, 2017, readjusted the uses of antibiotics in animal farming and the need for increased veterinary surveillance to confirm a reasonable use of antibiotics. (AVMA, 2019c) Due to the critical effects of antibiotic residues in food, international organizations, such as Codex Alimentarius Commission (FAO/WHO, 2018) and the European Union (European Medicines Agency, 2018), have provided maximum residue limits (MRLs) of antibiotics in veterinary-related food (Table S1) (Supporting Info I)

Table S1.

Meat, an important veterinary-related product, has a complex matrix of various components. Based on the type (beef, fish, pork, chicken, etc.) It includes water (in the range from 72% to 75%), fats (in the range from 5% to 25%), nitrogen components (21% include proteins and nonprotein nitrogenous compounds). his wide range of compounds within meats makes it difficult to select one specific analytical method.(Laskowski et al., 2018) That is why it's necessary to apply sample preparation techniques to remove unwanted components from the meat tissue that can eliminate these interactions. Among such techniques, one can point to solid-phase extraction (SPE), solid-phase microextraction (SPME), dispersive solid-phase extraction

(DSPE), dispersive solid-phase microextraction (DSPME). Coupled with HPLC, MASS, UV or electrochemical and photoelectrochemical sensors, it is possible to evaluate the effectiveness of extraction and determination of target compounds. However, each of these methods has its limitations and disadvantages. For example, The main disadvantage of traditional SPE is that high amounts of adsorbent are required or, the disadvantages of DSPE and DSMPE methods are the need for filtration and centrifugation.

The history of molecularly imprinted polymers (MIPs) dates back to the 1930s. (Polyakov, 1931) Molecular imprinting is a technique to create cavities and receptors for a target compound by constructing selective recognition sites in a highly cross-linked polymeric structure. Typically, a template such as an ion or molecule is introduced in the polymerization matrices to facilitate interactions, such as hydrogen bonds, Van der Waals forces, hydrophobic and electrostatic to form the spatial arrangements of functional monomers and recognition sites (BelBruno, 2019). The polymerization process of functional monomers and cross-linkers can fix the spatial arrangement in which the template conformation and configuration get preserved as cavities. Sterical and chemical cavities (imprints) formed in the polymer network will be left partly or completely via the subsequent removal of the template to rebind the analyte. (Janczura et al., 2021) The template can be the same as the analyte or a dummy template with a similar structure and functional groups when the final molecule is sensitive to one or some of the aspects of the process (e.g., Heating) (Du et al., 2013; Vasapollo et al., 2011; Wen et al., 2012). A crucial choice in polymerization is the selection of functional monomers, as these molecules need to have a strong interaction with the template molecule in the pre-polymerization step. In the case of the non-covalent method, these interactions are commonly Hydrogen bond donation and acceptance.(Golker et al., 2013; Guć & Schroeder, 2017).

Cross-linkers are rigidifying agents, and fix the functional monomers around the template; therefore, the shape of cavities and the position of functional groups in the polymer stays the same even after the removal of the template. The cross-linker is vital because it dictates the flexibility and rigidity of the polymer. (Janczura et al., 2021).

On the other hand, initiators are necessary for the start of the chemical process of polymerization. The most commonly used reaction is free-radical based ones in which the polymerization starts with the cleavage of the initiator's azo or peroxide bonds due to sufficient thermal or UV photonic activation energies. Free radical forms created through this process

attack the functional monomer or the crosslinker's vinyl groups due to their electrophilic properties. Azoisobutylnitrile (AIBN) is the predominant free radical polymerization initiator. (Janczura et al., 2021; Mijangos et al., 2006)

Porogen is the solvent that works as the dispersion medium for the components of the polymerization process. Commonly used porogen include Dimethyl sulfoxide (DMSO), Acetonitrile (ACN), Chloroform, N,N-Dimethylformamide (DMF), and Toluene. (Esfandyari-Manesh et al., 2011; Gladis & Rao, 2004) Table 1 shows the composition and preparation techniques of various MIPs towards different antibiotics reported in the literature.

Table 1

Due to their excellent affinity and selectivity towards the template or template-like molecules, MIPs can be successfully applied in solid-phase sample preparation techniques via replacing conventional solid-phase with molecularly imprinted solid-phase.(Bitas & Samanidou, 2018; Hatamabadi et al., 2020) Utilizing MIPs has significantly improved the efficiency of extraction techniques and resulted in new and powerful extraction approaches such as molecularly imprinted solid-phase extraction (MISPE) (Keçili et al. 2020; Kupai et al., 2017; J. Chen et al., 2019; Heravizadeh et al., 2019, Keçili et al., 2019; Hussain and Keçili, 2019; Keçili and Hussain 2018; Keçili and Denizli 2021), dispersive molecularly imprinted solid-phase extraction (D-MISPE) (Büyüktiryaki et al., 2020; Alenazi et al., 2016; Sierra & Morante-Zarcero, 2018), molecularly imprinted matrix solid-phase dispersion (MI-MSPD)(Wen et al., 2012; Yan et al., 2007), molecularly imprinted solid-phase microextraction (MISPME)(Ansari & Karimi, 2017), and EC-sensor based MIPs (Mostafiz et al., 2021). The two most important advantages of MIPs are their selectivity and stability at high temperatures, different pressures, and pHs (Sadegh et al., 2021; Alipanahpour Dil et al., 2021). This method can extract the target analytes more efficiently from the solution in the imprinting process. Other advantages are physical strength and resistance to high pressure and heat. (Murphy, 2009)

On the other hand, there are some challenges and limitations MIPs during the polymerization process. One of the significant disadvantages is template bleeding which occurs when not all template molecules are effciently removed from the polymeris structure. In this case, some templates remain in the polymeric structure that causes to interference with the actual result. One way to prevent this from happening is using an analog (usually the isotopic form of the

molecule). Another drawback is the preparation of polymers with the unoptimized ratio of template to functional monomer. If the ratio is either high or low, it leads to nonspecific adsorption, which results in inaccurate analysis. (Murphy, 2009) Also, In many cases, the synthetic route of MIPs contains materials that are very damaging to the environment. Sometimes the formation of an appropriate product involves several repetitions ending in an enormous amount of solid and liquid waste materials. (Madikizela et al., 2018)

These techniques have also been extensively utilized in food analysis. A general insight into different synthesis methods had been previously presented. (Villa et al., 2021) Some of these examples include using MIP hydrogels to extract insecticides from green pepper and cinnamon samples, (J. K. Ma et al., 2018) magnetic core-shell MIPs in the extraction of pigments from onion and apple samples (Asfaram et al., 2018) and phytochemicals from fruit samples, (Alipanahpour Dil et al., 2020)Paper based MIP immunosorbent assay for detection of carbaryl insecticide from cabbage and rice, (Zhang et al., 2015) QD based core-shell MIP for the detection of malachite green from fish. (Lin et al., 2019) These were few examples of wide and vary forms of MIPs in the field of food science.

On the other hand, danger of chemical pollutions pushes the scientific world towards newer aspects of chemical synthesis such as green chemistry. Gałuszka and co-workers introduced 12 principles of green analytical chemistry. Minimizing the consumption of toxic reagents and solvent as well as the reducing energy and decreasing the generated wastes are main components of these principles (Gałuszka et al., 2013) Some features of MIPs such as their reusability, green functional monomers (i.e.ionic liquids) etc. are in accord with principles of green chemistry.(Madikizela et al., 2018)

This paper specifically focuses on the applications of MIPs in the detection, extraction and quantification of various antibiotics in meat samples. Figure 1 represents the schematic depiction of the synthesis and the application of MIPs in the extraction of antibiotics from meat samples**.**

Figure 1

2. Application of MIPs in the detection and determination of antibiotics in meat samples

2.1. Antibiotics and their classification

There are various methods for the classification of antibiotics based on the mechanism of their action, origins and chemical structure. In this paper, the division of antibiotics based on their chemical structure is discussed due to importance of chemical structure of the template for MIP synthesis (Kurylowicz et al., 1975). Various types of antibiotics are briefly described in the following:

Beta – lactams: One of the oldest antibiotics discovered by mankind, Beta – lactams are used for inhibition of bacterial cell wall synthesis by penicillin binding protein. If chosen as a template, due to susceptibility of the iconic beta – lactam ring, 6-aminopenicillanic acid (6-APA) and 7-aminocephalosporanic acid (7-ACA) to degradation, it will requires more specific conditions for MIP synthesis. (Kuru et al., 2020; Yin et al., 2010).

Sulfonamides: Due to similarity of structure to PABA, sulfonamides perform their role by mimicking PABA and inhibiting bacterial Dihydropteroate synthesis, prevents the folic acid synthesis and therefore blocking of the bacterial nucleic acid synthesis, and causing a bacteriostatic result. The chemical structure of sulfonamides makes them a suitable template for MIP synthesis, the functional sites can construct hydrogen bonds (Amine and Sulfonamide) or pi-pi interaction (aromatic ring) bonds with functional monomers, resulting a suitable complex of template – functional monomer and therefore more effective MIPs. (L. Chen et al., 2015)

Aminoglycosides: Containing a core structure of aminocyclitol linking to one or more amino sugars by glycoside bonds. The hydrophilic sites of aminoglycosides, make the molecule more soluble in polar solvents and can cause complications for MIP synthesis due to radical scavenging of polar solvents such as water or ethanol, although these sites can build effective hydrogen bonds with the functional monomer if chosen as a template. (Z. Zhang et al., 2020)

Macrolides: Macrocyclic lactones of different ring sizes attached to one or more deoxy-sugar or amino-sugar residues, in contrast to aminoglycosides , macrolides are more hydrophobic and

freely soluble in chloroform or acetone and also contain functional groups able to build hydrogen bonds with the functional monomers if chosen as a template. (Song et al., 2018)

Fluoroquinolones: Synthetic analogues of nalidixic acid , the quinolone structure consist of a bicyclic system containing a carboxyl group of the core structure which can build hydrogen bonds with the functional monomers. Fluoroquinolones have various chemical properties therefor vary in MIP synthesis conditions. (Gómez-Pineda & Quiroa-Montalván, 2016)

Tetracyclines: have basic chemical structure consisting of tetracyclic naphthacene carboximide ring, the dimethyl amine substitution is essential for antibacterial effect, and is capable of building donor hydrogen bonds with the functional monomers if chosen as a template for MIP synthesis. (Cai & Gupta, 2004)

Phenicols : First fully synthetic antibiotic, chloramphenicol is commonly used in treatment of various infections, and thus a target for trace in analyte samples. The chemical structure of Chloramphenicol has multiple sites for interaction with the functional monomers in MIP synthesis, and has acceptable solubility in solvents such as chloroform. (Xie et al., 2020)

2.2. Beta-lactams

Beta-lactams are a class of antibiotics that have a reactive beta-lactam ring system. Generally, there are five types of ring systems. Panel, penam, carbapenem, cephem, and monobactam ring forms. (Fernandes et al., 2013) The availability of 6-aminopenicillanic acid (6-APA) and 7-aminocephalosporanic acid (7-ACA) have enabled the formation of hundreds of synthetic and semi-synthetic beta-lactam antibiotics. Potency, the spectrum of effectiveness, and pharmacokinetics of beta-lactams can differ based on substitutions on 6-APA and 7-ACA. (Fernandes et al., 2013; Fr/`ere et al., 1988) Generally, Cephalosporins have a base structure of 7-ACA, which can be divided into five categories based on chemical structure: Cephalosporins, cephamycins , oxa-1-cephems, carba-1-cephems, and miscellaneous. (Page, 2007)

On the other hand, penicillins are natural beta-lactams produced by *Penicillium chrysogenum*, and semi-synthetic beta-lactams such as methicillin, cloxacillin, ampicillin, carbenicillin, ticarcillin, azlocillin, piperacillin, and temocillin. (Rolinson & Geddes, 2007). In a crucial

research (Du et al., 2018), Du and colleagues designed and prepared molecularly imprinted membranes (MIMs) for the determination of cloxacillin in shrimp samples. For this purpose, polyvinylidene fluoride-based MIMs towards the target compound cloxacillin were prepared by using MAA, ethylene glycol dimethacrylate (EGDMA) and cloxacillin as the functional monomer, cross-linker and template compound, respectively. The achieved results indicated that MIMs demonstrated high permeability, fast adsorption rate and excellent adsorption capacity for cloxacillin. The highest capacity of MIMs was obtained as 3.93 μmol g^{-1}, and the adsorption equilibrium was achieved in 30 min. In addition, adsorption mechanism was also investigated and the Freundlich adsorption model and pseudo second order model were suitable for the description of the static and kinetics of MIMs, respectively. Compared to the other reported studies in the literature, the developed low-cost, effective and selective molecular imprinting-based extraction approach in this study could be a great alternative for the efficient extraction of various antibiotics such as cloxacillin in food samples.

In an interesting research carried out by Cheng *et al.* (Cheng et al., 2021), ceftiofur sodium was successfully extracted from chicken, pork, beef and milk samples by using MIPs. In their research, MIPs towards ceftiofur sodium were designed and developed. For this purpose, 1-allyl-3-vinylimidazolium bromide and 2-acrylamide-2-methylpropanesulfonicacid were used as functional monomers and water was chosen as the environmentally-friendly progenic solvent. The obtained results displayed that the developed MIPs exhibited excellent affinity and selectivity towards the target antibiotic ceftiofur sodium. Under the optimized conditions, the detection limit was found as 0.0015 mg L^{-1} and the achieved great recovery values were in the range between 0.005 and 1.0 mg L^{-1}. In addition, recovery values using the same MIPs were still higher than 95% after 20 cycles which is very crucial to reduce the cost of the extraction process.

Chen and co-workers reported the development of magnetic core-shell MIPs for the efficient extraction of cephalexin from pork and milk samples. (S. Chen et al., 2019). For this purpose, selective MIP shell was prepared on the surface of magnetic Fe_3O_4 nanoparticles using acrylamide and EGDMA as the functional monomer and cross-linker, respectively. The obtained results confirmed that the prepared magnetic core-shell MIPs can be effectively applied for the extraction of the target compound cephalexin from pork and milk samples. The detection limit

was obtained as 5.00 µg kg^{-1} and the achieved great recovery values were in the range from 85.5 % to 94.0 %. The researchers concluded that magnetic separation combined with molecular imprinting technology has great potential to open a intriguing window for the effextive extraction of the target compound/s in complex matrices such as food samples. This approach provides easy collection and fast separation without using tedious sample preparation steps such as filtration or centrifugation.

2.3. Sulfonamides

Sulfonamides (SAs) are sulfanilic acid (p-aminobenzenesulfonic acid) derivatives which are used for human and animal diseases for decades. SAs, as bacteriostatic agents, exhibit great activity against gram-negative and gram-positive bacteria and microorganisms such as agents of malaria and toxoplasmosis. (Baran et al., 2011) SAs precursor is p-aminobenzenesulfonamide, first synthesized in 1908 and vastly used as an intermediate in producing dyes. G. Domagk first recognized the antibacterial effects of SAs in 1935. Due to SAs mechanism, which blocks the synthesis of dihydrofolic acid, only microorganisms that synthesize their own dihydrofolic acid are susceptible to SAs (Dmitrienko et al., 2014). SAs are prevalent veterinary drugs for prophylactic and therapeutic purposes. This extensive application is caused by broad-spectrum activity, low costs of SAs, and notable efficacy as growth enhancers. SAs also have been used as a food supplement for the weight gaining of food-producing animals and feed efficiency. (Parab & Amritkar, 2012) However, long-term use of SAs can increase the antimicrobial resistance risk and causes deleterious environmental and ecological hazards, even at low concentrations. According to this, health organizations have set limitations for the presence of SAs in the edible tissue of animals. (Baran et al., 2011)

On the other hand, MIPs were also successfully applied for the sensitive detection of SAs in meat samples. For example, in an interesting work peformed by Zhao Bin Li and colleagues, (Zhao Bin Li et al., 2019) an effective MIP-based chemiluminescence sensor was designed and fabricated using a dummy-template (sulfabenz) for the sensitive detection of 15 SAs in chicken and pork samples. In this work, computational simulation was applied before the preparation of MIP and conformational similarities of SAs with the sulfabenz was investigated to explain the interaction mechanism. It was also demonstrated that the 3D conformation and molecular size of

the template have a crucial role in the ability of polymer recognition. The results indicated that the developed MIP-based chemiluminescence sensor can successfully and sensitively recognize the target SAs with excellent detection limits varied in the range between 1.0 and 12 pg mL^{-1}. In addition, detection process was completed within 30 min. The developed sensor has great potential for the routine screening of SAs in meat samples.

Zhao *et al*. reported the design and preparation of water-compatible MIPs for the extraction of six SAs in animal-derived food products and water samples (Zhao et al., 2018). For this purpose, and MAA was chosen as the functional monomer and MIP particles were synthesized with surface grafted-poly (2-hydroxyethyl methacrylate) (pHEMA). The achieved detection limit values were in the range from 0.02 μg L^{-1} to 0.1 μg L^{-1}. One of the crucial aspects of the prepared MIPs is their greenness. Because they are water-compatible and extraction process avoided consumption of toxic organic solvents. Therefore, the developed MIP-based extraction method can beconsidered as a promising and environmentally-friendly approach for the sensitive detection of SAs in food samples.

In another important study (Peng et al., 2017), Peng *et al.* designed and prepared MIP microspheres to introduce an enzyme-linked immunoassay (MIP-ELISA) for the sensitive detection of the detection of sulfamethazine residue in swine muscle samples. In their study, the MIP microspheres were prepared by applying precipitation polymerization technique using sulfamethazine as the template. Then, the prepared MIP microspheres were coated in the inner surface of the 96-well plate. The efficiency of the developed MIP-ELISA system was investigated based on the direct competition between free sulfamethazine residue and horseradish peroxidase (HRP)-labelled sulfamethazine residue. The quantification and detection limit values were found as 20.4 and 6.8 μg kg^{-1}, respectively. This interesting study was the first report in the literature which is on the design and fabrication of MIP-based ELISA system for the sensitive detection of sulfamethazine residue in real samples.

Li and co-workers reported the preparation of a MIP-based photonic crystal sensor for the sensitive detection of sulfaguanidine in fish samples (L. Li et al., 2019). In their study, the researchers used MAA and EGDMA as the functional monomer and cross-linker, respectively. The achieved results exhibited that the developed MIP-based photonic crystal sensor showed excellent selectivity and sensitivity towards sulfaguanidine in fish samples. The sensing process

was completed within very short time (5 min) and the detection limit was obtained as 2.8×10^{-10} mol L^{-1}.

In a crucial research carried out by Sun and colleagues (Sun et al., 2019), a MIP-based electrochemical sensor for the sensitive detection of sulfamerazine in chicken and pork samples. In this research, in the first step, amino-functionalized multiwalled carbon nanotubes (MWCNTs), covalent organic frameworks (COF) and MoS_2 nanosheets were efficiently deposited the glassy carbon electrode (GCE). In the next step, MIP membrane was prepared on the previously modified GCE via electrochemical polymerization technique. The developed MIP-based electrochemical sensor showed great reproducibility and selectivity towards sulfamerazine. The detection limit was achieved as 1.1×10^{-7} mol L^{-1}. The developed strategy reported in this research enables a framework for the rational design and fabrication of electrochemical sensor systems towards more target compounds in food samples.

2.4. Tetracyclines

One of the most used groups of antibiotics in veterinary medicine is tetracyclines (TCs). Due to their extensive use, various methods have been developed to determine and quantify their amount in animal-derived food regarding MLRs. (Gavilán et al., 2016; Kanda et al., 2008; Salama et al., 2011) TCs was first isolated from actinomycetes soil bacteria in the 1940s. The second and third generations of TCs were semisynthetic analogs with enhanced efficacy against TC-resistant bacteria and pharmacokinetics. (M. L. Nelson & Levy, 2011) Studies show that protein synthesis inhibition via binding to the ribosomal 30S subunit is TCs primary mode of action. (Chopra & Roberts, 2001; Miller et al., 1971) The application of TCs in livestock farming has resulted in several TC-resistance in bacteria (Martins da Costa et al., 2007) On the other hand, TCs presence in food can develop allergies in animal-derived food consumers. (Alipour et al., 2020) TCs, as the name indicates, consists of four rings that other chemical groups are attached to the upper or lower side of rings. (Askari Rizvi, 2018; Fuoco, 2012) TCs exhibit also chelating activity, and they can bind to metallic cations of elements such as iron, calcium, aluminum, and magnesium. (Grenier et al., 2000; Neuvonen, 1976)

In a study conducted by Yang *et al.* (J. Yang et al., 2018), efficient recognition of tetracycline in fish samples was carried out by using the developed MIP-based fluorescent nanosensor. In this study, (3-Aminopropyl) triethoxysilane and tetraethyl orthosilicate were used as the functional monomer and cross-linker, respectively. MIPs were coated on the surface of carbon quantum dots. The results confirmed that the response of the developed MIP-based fluorescent nanosensor towards the target tetracycline was linear in the range between 0.1 and 50 μmol L^{-1} with a quite low detection limit (9 nmol L^{-1}).

In another work reported by Lu and co-workers (Lu et al., 2020), a nanofiber based on MIP was designed and prepared for the SPME of tetracycline residues in fish, chicken and milk samples. For this purpose, MIP nanofiber was synthesized on the surface of stainless steel wire and successfully used for the effective extraction of the target tetracycline residues. In this study, the highest extraction capacity of the MIP-based nanofiber was achieved as 2.35 μg g^{-1} and the obtained detection limits were in the range from 0.38 to 0.72 μg kg^{-1}.

He and colleagues reported the design and development of MIP-based carbon nanocomposite towards tetracycline residues in fish, chicken and milk samples (He et al., 2019). In their work, the researchers prepared hydrophilic MIP having great selectivity using a carbon nanocomposite composed of graphene oxide (GO) and carbon nanotube (CNT) applying a green synthesis technique of freeze-drying. The achieved results displayed that the developed MIP-based carbon nanocomposite can be successfully employef for the effective extraction of tetracycline residues in real samples. High recovery values were obtained in the range between 85.58 % and 116.87 %. The achieved detection limit was 0.127 μg kg^{-1}.

In a work performed by Ma *et al.* (N. Ma et al., 2020), a nanopolymer composed of MIP and metal-organic framework (MOF) was prepared for the determination of 7 tetracyclines in chicken muscle samples. The prepared MIP/MOF-based nanocomposite was efficiently used for the extraction of the target tetracyclines in real samples. The results indicated that the prepared nanocomposite showed great extraction capacity in the range between 2200 and 3000 ng mg^{-1}. The achieved detection and quantification values were in the range from 0.2 to 0.6 ng g^{-1} and 0.5 to 2.0 ng g^{-1}. This recent study was the first report on the development of MIP-MOF

nanocomposite–based adsorbent for the efficient extraction of tetracycline residues in poultry products.

2.5. Fluoroquinolones

Fluoroquinolones (FQs) are broad-spectrum antibacterial agents and are commonly used in respiratory and gastrointestinal infections. The antibacterial mechanism of Quinolones is by inhibition of two key enzymes in the bacterial DNA replication process, DNA gyrase and topoisomerase IV. ((Fàbrega et al., 2009; Mizuki et al., 1996)

FQs are 1,8-Naphthyridine or quinolone derivatives with 3-carboxylate and 4-carbonyl groups. These groups are considered essential for antibacterial activity. On the other hand, FQs such as norfloxacin and ofloxacin contain a piperazinyl group attached to C-7. (Ezelarab et al., 2018; Park et al., 2002) Generally, FQs are amylose compounds. Therefore, their ionization extent, which affects their physicochemical and biological properties, depends on pH. (Blokhina et al., 2016) Earlier studies have shown that FQs exhibit photochemical behavior and can undergo photochemical decomposition. (Detzer & Huber, 1975; Polishchuk et al., 2008)

In 1951, the United States FDA approved the use of animal feeds as growth promoters in addition to their former therapeutic applications. (Jones & Ricke, 2003) Although the use of FQs is not essential for food animal production, they are used in food-producing animal feeds. (Collignon, 2005; Hao et al., 2014) However, it has been reported that the presence of FQ in animal feeds correlates to Campylobacter antibiotic-resistant infections in humans. (Iovine & Blaser, 2004) In 2005 United States FDA banned the use of enrofloxacin in the poultry food cycle, which resulted in a diminished rate of drug-resistant Campylobacter infections in the following years. (J. M. Nelson et al., 2007)

As mentioned, excessive content of FQ residues in food sources has harmful effects on community health. Hence many studies have tried to develop accurate and efficient methods for extraction and analysis of FQ residues in meat such as Solid-phase extraction, QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and Safe), Stir Bar Sorptive Extraction (SBSE), immunoaffinity column, HPLC, LC-MS/MS, TLC, ELISA, Colorimetric assay. (Barreto et al., 2017; Fan et al., 2015; C. Li et al., 2008; Lucatello et al., 2015; Pena et al., 2010; Ramatla et al., 2017; Silfrany et al., 2013) A recent study reported a selective method for the extraction and quantification of ciprofloxacin in fish meat. This method embedded ciprofloxacin and

Eu(DBM)3Phen, a Fluorescent sensor, in polystyrene MIP microparticles to receive quenched fluorescent signals from tris(dibenzoylmethane)(1,10-phenanthroline)europium(III) (Eu(DBM)3Phen) when ciprofloxacin is encaged in the MIP. This phenomenon does not occur with other FQs. (Zhuanying Li et al., 2019)

Tang and co-workers prepared magnetic MIPs by coating the surface of the magnetic upconversion particles (MUCPs) with enrofloxacin imprinted polymers. They assembled Fe_3O_4 nanoparticles and MIPs on NaYF4:Yb3+, Er3+ upconversion particles layer-by-layer. These MUCPs@MIP probes were successfully used for the detection of enrofloxacin and other four FQs in fish samples. The detection mechanism was based on the fluorescent quenching. A significant decrease in fluorescent intensity was obtained when the target compound bound to the prepared MIPs. Compared to the obtained results from a HPLC-based method, the developed MIP-based extraction method exhibited no significant difference (Figure 2). (Tang et al., 2018)

Figure 2

In an interesting work carried out by Yuphintharakun and colleagues (Yuphintharakun et al., 2018), a novel MIP-based nanocomposite optosensor was developed by embedding CdTe quantum dots and carboxylic acid functionalized-MWCNTs into a ciprofloxacin imprinted polymer (Figure 3). For this purpose, 3-aminopropylethoxysilane and tetraethoxysilane were used as the functional monomer and cross-linker, respectively. The developed MIP-based nanocomposite optosensor exhibited great specificity, sensitivity and affinity towards ciprofloxacin. The achieved detection limit was very low (0.066 $\mu g\ L^{-1}$).

Figure 3

Zhu and co-workers recently developed a ciprofloxacin MIP using a green polymerization technique (Zhu et al., 2019) (Figure 4). They used a mixture of a functional monomer, 2-hydroxyethyl methacrylate (2-HEMA), and an ionic liquid, 1-allyl-3-vinylimidazole chloride (AVIM-Cl), as a bifunctional monomer. The prepared green MIP was successfully employed for the effective extraction of ciprofloxacin in water, soil and pork samples. The obtained recovery values were in the range between 87.33% and 102.50%. It has been concluded that the developed MIP-based extraction approach with green aspects has great potential for the sensitive

recognition and extraction of trace quinolones in complex samples such as food and environmental matrices.

Figure 4

A study was conducted on the design and preparation of silica-based MIP for the detection of lomefloxacin. The analysis was based on the fluorescent emission of QDs, which its intensity would decrease after rebinding to the analyte. The selectivity of this MIP probe was carefully investigated and the results exhibited that the developed MIP probe is highly selective towards the target lomefloxacin compared to other fluoroquinolone antibiotics. (Orachorn & Bunkoed, 2019)

Sarafloxacin is a discontinued antibiotic which due to its discontinuation could be a subject of abuse in poultry. Therefore, its determination is of importance. A polydopamine/MIP nanocomposite fluorescent probe developed for sarafloxacin detection showed that these probes are efficient, rapid, and cost-effective. (Chaowana & Bunkoed, 2019)

A fluorescent-based MIP probe was examined for the determination of norfloxacin, and it was shown that these types of sensors could be effectively used in the determination of norfloxacin. (Bunkoed et al., 2020)

2.6. Macrolides

Macrolides (MLs) are broad-spectrum bacteriostatic antibacterial agents that are mostly prescribed in various types of infections and are used as an alternative drug of choice in most cases. (Leekha et al., 2011) They inhibit the translation process and Protein Synthesis by targeting the 50s ribosomal subunit. (Katz & Ashley, 2005; Vázquez-Laslop & Mankin, 2018)

The chemical structure of MLs consists of 8-38 membered-ring macrolactone attached to one or more sugars and commonly substituted by hydroxyl and alkyl groups, (Mazzei et al., 1993; Stepanić et al., 2012) Making them significantly larger and more complex than other antibiotics. Therefore most common rules and models, such as Lipinski's rule of 5 and the model for predicting ADMET do not correlate with the physicochemical and pharmacokinetics of MLs. (Stepanić et al., 2012) Generally, MLs are degraded in low pH environments and have low aqueous solubility; therefore, they have poor oral bioavailability. (Fohner et al., 2017; Stepanić et al., 2012)The Acid-sensitivity of MLs can be reduced by modification of reactive sites. For

example, Clarithromycin, an analog of Erythromycin, has a C-6 methoxy substitution, resulting in a more Acid-Stable substance. (Asaka et al., 2005; Hardy et al., 1992)

Continuous exposure to MLs due to their presence in human food may cause bacterial resistance, such as resistance to S.pneumoniae. (Roberts, 2004) Therefore, the quantification of MLs in human food supplies is a necessity to control the exposure to MLs. (García-Mayor et al., 2012; Piatkowska et al., 2016) As previous studies suggested, methods such as SPE and MSPD can be used for the extraction and analysis of MLs. On the other hand, MIPs are efficient platforms for extracting analytes from different forms of matrixes. (Vasapollo et al., 2011) Thus, in 2018, ML class-specific Solid-phase extraction MIPs (MIP-SPE) were synthesized and followed by LC-MS/MS to develop a simple, sensitive, and reproducible quantification of MLs method. (Song et al., 2018) In 2019 a team of Chinese scientists developed a molecularly imprinted monolithic extraction column (MIMC). It was capable of detecting and quantifying six MLs in chicken, pork, and beef samples with assuring recoveries. The polymerization process was performed inside a 200 µL micropipette tip, and roxithromycin was used as the dummy template. MAA, acrylamide (AM), HEMA, and 4-vinyl pyridine (4-VP) in different functional monomer/template ratios were investigated in this study, and MAA with a functional monomer/template ratio of 4:1 was selected. Cross-reactivity studies showed that roxithromycin imprinted polymers are class-selective for macrolides. These MIPs also provided better durability and analyte retention capability than conventional methods like C18 and HLB cartridges. (Song et al., 2019)

2.7. Chloramphenicol and florfenicol

Chloramphenicol (CAP) was first obtained from Streptomyces venezuelae in 1947. It is a broad-spectrum antibacterial agent in the treatment of various types of infections, such as H. influenza infections, E. coli infections. (Feder et al., 1981) It prevents protein synthesis by binding to the peptidyltransferase domain at the 50S subunit of the bacterial ribosome. (Weintraub, 1953)

CAP has two chiral carbon atoms, which leads to four possible stereoisomers. each of these isomers has been synthesized and biologically evaluated. The two erythro isomers are proven to be biologically inactive (Brock, 1961) CAP administration has notable difficulties; it cannot be used in the IV route of administration due to its low aqueous solubility and instability (it hydrolyzes to glycol easily and also is inactivated via intravenous administration) (Leopold et al.,

1950) nor through the oral route, because it is extremely bitter. (Feder et al., 1981; Lv et al., 2006)

Although CAP is an effective broad-spectrum antimicrobial agent through the past decades of use, it has shown significant side effects and hematologic disorders z. (Rosenbach et al., 1960; Scott et al., 1965) such as aplastic anemia (Rheingold & Spurling, 1952), gray baby syndrome (Krasinski et al., 1982), and idiopathic bone marrow aplasia. (Rosenbach et al., 1960)

Nowadays, CAP is used for treatment and protection against pathogenic agents such as Escherichia spp. And Salmonella spp.; therefore, this drug is mainly incorporated in food-producing animals. Unfortunately, the presence of CAP residue in livestock products has been reported by numerous studies. (Darwish et al., 2013; Kolosova et al., 2000; T. L. Li et al., 2002; Nicolich et al., 2006; Settepani, 1984; Tajik et al., 2010; L. Wang et al., 2010) Consequently, the chemical residue may enter the food chain and cause significant problems such as antibiotic resistance and previously mentioned hematologic disorders. (Berendsen et al., 2010)

In a study reported by Jia *et al.* (Jia et al., 2019) a sensitive and novel method for CAP quantification in pork, fish, and chicken samples by MIPs was introduced. They coated MIP particles in 96-well microplates and used as a ELISA-based chemiluminescence sensor towards CAP. In their study, 4-nitrotoluene (NT) was ushosen as a dummy template for the preparation of highly selective MIP for the target antibiotic CAP. The achieved results indicated that the developed MIP-based sensor displayed great affinity and senrivity for CAP with a very low detection limit (5.0 pg g^{-1}). The recovery values were obtained in the range from 71.5% to 94.4%. In addition, the detection process was completed within 20 min.

In 2018, a MIP-based sensing system was designed and fabricated for on-site monitoring of CAP based on carbon screen-printed electrodes modified with MIPs placed on the surface of the electrodes during electro-polymerization. The sensing mechanism of the fabricated system was based on the evaluation of changes in electron transfer properties of a redox probe [Fe(CN)6]3-/[Fe(CN)6]4- and was able to detect CAP in concentrations down to 10nM. This method was quick and accurate and had the potentials for manufacture and commercialization. (Cardoso et al., 2018).

Jia and co-workers reported a rapid, sensitive, and cost-effective MIP-based sensor for the sensitive detection of CAP in meat samples and the chemiluminescence resonance energy transfer (CERT) phenomenon. They prepared selective MIP layer on the surface of magnetic graphene particles (MIM@MG) and used these nanocomposites along with the CERT strategy for extraction and detection of CAP. Briefly, the CERT mechanism occurs in the presence of the analyte. CERT inhibition results in chemiluminescence intensity raising and light emission. The limit of detection (LOD) for this method is significantly lower than LC-MS/MS method, the chemiluminescence signal assay could be obtained within 10 min, and the MIM@MG composites have good reusability. (Jia, He, et al., 2019)

Li and co-workers prepared magnetic MIPs for the effective recognition and extraction of CAP in pork samples. (Li et al., 2018) For this purpose, the surface of the magnetic Fe_3O_4 nanoparticles was coated with the selective MIP layer towards the target compound CAP. MAA and AM were chosen as the functional monomers. The achieved results showed that the developed magnetic MIPs exhibited high extraction behaviour for CAP with a maximum adsorption capacity up to 42.60 mg g^{-1}. In this work, the obtained detection limit was 10 μg L^{-1}.

2.8. Aminoglycosides

Aminoglycosides (AGs) are natural or semisynthetic antibiotics. They are structurally similar to carbohydrates, containing more than one amino sugars connected to a hexose core. AGs are wide-spectrum, potent, and concentration-dependent antibiotics that have a bactericidal effect on both gram-negative and some gram-positive bacteria by inhibiting protein synthesis and causing misread of the genetic code. (Ackerman et al., 1984; Krause et al., 2016) These mistranslated proteins can facilitate AG entrance by incorporating into the membrane and creating channels that permit the influx of antibiotics. (Davis, 1987) On the other hand, AGs are positively charged, and they can bind to negatively charged molecules on bacterial membranes, such as phospholipids, and enter the bacteria. AG uptake is mediated by active electron transport, making them active ingredients on aerobic bacteria. (Krause et al., 2016) Due to the importance of monitoring the residue levels of AGs as veterinary medicines for treatment, prevention of diseases, and promoting growth, several methods were introduced to detect and determine the AG residues in animal-derived foods. (Arsand et al., 2016; Tao et al., 2012)

In a study reported in 2017(Yang et al., 2017), eleven AGs were analyzed in pork samples by the HILIC-MS/MS and MISPE method of extraction. In this study, SupelMIP® SPE-Aminoglycoside cartridges were purchased from Sigma-Aldrich . The achieved detection and quantification limit values were in the range from 2–30 μg kg^{-1} and 7–100 μg kg^{-1}, respectively.

2.9. Miscellaneous antibiotics

In 2017, a MIP-based biosensor towards lincomycin was designed and fabricated was conjugated with aptamers to fabricate a MIP biosensor using electropolymerization. Through this process, MIP was prepared through electropolymerization of Carbon-dots-tagged DNA aptamers mixed with lincomycin as template and ortho-aminophenol as the foundation for the assembly of aptamers and MIP on the gold modified electrode. The change of the ECL signal indicated the presence of lincomycin. Due to the bounding of lincomycin and DNA aptamers and the MIP, the ECL signal decreased; therefore, a dual method for lincomycin analysis was developed. (S. Li et al., 2017)

In 2019, a novel reusable coordination imprinted polymer (CIP) was developed for the detection and determination of flumequine residues in fish samples. In this work, CIP monolithic column doped with silanized graphene oxide was prepared using flumequine-Zn^{2+} as the template. Itaconic acid and 4-VP were chosen as functional monomers and EGDMA was used as the cross-linker. The prepared imprinted polymer showed excellent affinity and selectivity for flumequine The detection limit and recovery values were achieved as 0.32 ng g^{-1} and 95.2%, respectively. (Zhai et al., 2019). In addition, reusability studies confirmed that the developed imprinted polymer can be used twenty times without significantly losing its recognition efficiency which is very crucial to reduce the cost of the detection process.

On the other hand, Wang *et al.* developed a MIP-based system for the sensitive and rapid detection of 20 antibiotics (eight FQs, eight SAs, and four TCs) in pork samples. (G. N. Wang et al., 2017). They used sulfabenzamide, pipemidic acid and chlortetracycline as the templates for SAs, FQs, and tetracyclines, respectively. MAA and EGDMA were chosen as the functional monomer and cross-linker, respectively. In this study, the achieved detection limits were in the range between 0.5 and 3.0 ng g^{-1} while the recovery values were obtained in the range from 74.5% to 102.7%. The authors concluded that the developed sensitive, fast and specific MIP-based sensing system can be successfully employed for the effective monitoring of the residues

of FQs, SAs and TCs in animal derived food samples. Table S2 shows the summary of information about Wang's MMIP.

Table S2

Various MIP-based extraction techniques for different antibiotics in meat samples is shown in Table 2.

Table 2

3. Prospect and future trends

Molecular imprinting technology can be considered as a powerful tool in the implementation of selective extraction, separation and purification of analytes in complex samples to unprecedented levels and offering highly selective analytical methods. Furthermore, by smart modifications and improvement of polymerization techniques, MIPs can promote current sample-preparation techniques and the direct coupling with the detection system will introduce very simple, sensitive and selective analytical methods with potential applicability in different fields and healthcare systems.

This review provides the various MIP-based extraction approaches towards antibiotics in meat samples and demonstrates the gaps, strengths and weaknesses of MIPs in the analysis of antibiotics in meat samples based on their classes including beta-lactams, sulfonamides, tetracyclines, fluoroquinolones, macrolides, chloramphenicol, aminoglycosides in meat samples such as shrimp, chicken, beef, pork, liver and fish.

Different formats of MIPs including bulk, micro and nanoparticles, core-shell particles, fibers considering the polymerization ingredients have been summarized and the application of developed MIPs in validated analytical methods with adaptability of MIPs to almost any separation and analytical techniques has been highlighted.

Although scientists are still a long route from design and fabrication of novel sensing and extraction platforms based on molecular imprinting technology that fulfill all the requirements of high sensitivity, selectivity, reusability, accuracy and stability under harsh conditions, the recent

and interesting applications described in this review allows envisaging the development of new generation MIP-based sensor systems for food applications.

It is strongly believe that so much effort put on the development of MIP-based extraction systems will also provide to the development of cheap, environmentall-friendly and rapid analytical approaches and the feasibility of compact and more integrated systems by reducing the required volume of solvents, generated waste, time, energy as well as portability, automation and on-site application possibility. In addition, there is still outlook for the progresses of novel MIPs and expanding their applications in different fields such as beverage, food, environmental and bioanalysis. In this regard, refinement of the applications of MIPs in sample-preparation techniques and their combination with different analytical methods will offer new, simple, rapid, and selective analytical and hopefully commercialized techniques in the near future.

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Table 1. Composition and preparation techniques of various MIPs towards different antibiotics

Template	MIP synthesis	Functional Monomer	Crosslinkher	Porogen	Template/monomer/crosslinker Mole ratio	References
Cloxacillin	Photopolymerization	MAA	EGDMA	DMF	1:06:20	(Du et al., 2018)
ceftiofur sodium	Surface Polymerization	[VAIM]Br, AMPS	MBA	Water	1:06:20	(Cheng et al., 2021)
cephalexin	Suspension polymerization	AA	EGDMA	Acetonitrile	1:04:20	(Chen et al., 2019)
Sulfabenz	Bulk polymerization	MAA	EGDMA	Methanol	1:06:20	(Zhao Bin Li et al., 2019)
sulfadiazine	RAFT-RPP	MAA	DVB	Acetonitrile: Methanol 4:1	1:04:20	(X. Zhao et al., 2018)
Sulfamerazine	Electrochemical polymerization	p-ABA	N.A	0.01 M HCl	N.A	(Sun, Xu, et al., 2019)
sulfamethazine	Precipitation polymerization	MAA, 4-VP, AM	EGDMA	Acetonitrile	1:12:20	(Peng et al., 2017)
sulfaguanidine	MIP photonic crystals	MAA	EGDMA	Methanol	1:10:4	(L. Li et al., 2019)
Minocycline	MOF Surface polymerization	MAA, AA, BIS	TEMED	Water	N.M.	(Ma et al., 2020)
Tetracycline	Bulk Co-polymerization	MAA,HEMA	EGDMA	Acetonitrie, Methanol	1:04:25	(Lu et al., 2020)
Tetracycline	Freeze drying	MAA,HEMA	EGDMA,γ-MAPS	Water	1:16:32	(He et al., 2019)
Tetracycline	reverse microemulsion polymerization	APTES	TEOS	Cyclohexane, n-hexanol,	1:03:15	(J. Yang et al., 2018)

lomefloxacin	Sol Gel polymerization	APTES	TEOS	Water	1:06:20	(Orachorn & Bunkoed, 2019)
Ciprofloxacin	Bulk (embedded in polystyrene microparticles)	MAA	EGDMA	Acetonitrile:Methanol:triethylamine 40:10:1 V/V	1:04:20	(Zhuanying Li et al., 2019)
sarafloxacin	Sol Gel polymerization	APTES	TEOS	water	1:08:20	(Chaowana & Bunkoed, 2019)
Enrofloxacin	Core Shell Magnetic Particles	MAA	EGDMA	Dichloromethane	1:04:20	(Tang et al., 2018)
Norfloxacin	Copolymerization	APTES	TEOS	water, ethanol	1:51:15	(Bunkoed et al., 2020)
Ciprofloxacin	sol-gel copolymerization (MWCNT-QD nanocomposite)	APTES	TEOS	Deionized water	1:08:20	(Yuphintharakun et al., 2018)
Ciprofloxacin	Bulk (Green polymerization)	AVIM-Cl, 2-HEMA 2:1	N,N'-methylenediacrylamide	Water	1:06:20	(Zhu et al., 2019)
Diflocxacin & Ofloxacin 1:1	Polymer Coated stir bar	MAA	EGDMA	Chloroform	1:6:30 & 1:3:15	(K. Yang et al., 2017)
Roxithromycin	*in situ* polymerized Monolithic columns	MAA	EGDMA	Toluene:dodecanol 1:6 V/V	1:04:20	(X. Song et al., 2019)
4-nitrotoluene	Bulk	MAA	EGDMA	Chloroform	1:04:20	(Jia, Huang, et al., 2019)

Chloramphenicol	Surface Imprinted Electrochemical Electrodes	EBT	4-AMP	Acetonitrile		(Ana et al., 2018)
Nitrobenzene	Imprinted microsphere on the surface of magnetic graphene	MAA	DVB	Toluene:Acetonitril 1:3 V/V	1:04:30	(Jia, He, et al., 2019)
Chloramphenicol	Magnetic Core-Shell Particles	MAA, AM	EGDMA	Ethanol+0.1g PVA	1:05:06	(Zengwei Li et al., 2018)
N.M.	N.M.	N.M.	N.M.	N.M.	N.M.	(B. Yang et al., 2017)
lincomycin	Electropolymerization on Au-GO-EC	Aptamer	o-Aminophenol	PBS	N.M.	(S. Li et al., 2017)
Flumequin-Zn2+	in situ polymerization SGO-CIP	ITA, 4-VP	EGDMA	Methanol: Water 85:15 V/V	1:04:30	(Zhai et al., 2019)

Abbriviaations: 4-AMP: 4-Aminothiophenol; 4-VP: 4-Vinylpyridine; AA: Acrylic acid; AM: Acrylamide; AMPS: 2-acrylamide-2-methylpropanesul- fonic acid; APTES: (3-Aminopropyl)triethoxysilane; Au-GO: goldnanoparticle-functionalized graphene oxide; AVIM-Cl: 1-allyl-3-vinylimidazole chloride; BIS : N,N-methylenebisacrylamide; BMIMBF4: 1-Butyl-3-methylimidazolium tetrafluoroborate; CD: Cyclodextrin; DEAEM: 2-(Diethylamino)ethyl methacrylate; DMF: N;N-Dimethylformamide; DMSO: Dimethyl sulfoxide; DVB: Divinylbenzene; EBT: Eriochrome black T; EGDMA: Ethylene Glycol Dimethacrylate; GDMA: Glycerol 1; 3-dimethacrylate; GMA: Glycidyl methacrylate; HEMA: hydroxyethyl methacrylate; ITA: Itaconic acid; MAA: Methacrylic acid; MBA: N,N'-methylenebisacrylamide; MIP: Molecularly imprinted polymer; MMA: Methyl methacrylate; MOF: Metal organic framework; MWNT: Multi-walled carbon nanotube; N.M.: not mentioned; p-ABA: Para-aminobenzoic acid; PBS: Phosphate-Buffered Saline; QD: Quantum dot; RAFT: reversible addition-fragmentation chain; RPP: reflux precipitation polymerization; TEMED: N,N,N,N-tetramethylethylenediamine; TEOS: Tetraethyl orthosilicate); TEPA: Tetraethylenepentamine pentahydrochloride; TFMAA: 2-(Trifluoromethyl)acrylic acid; THF: Tetrahydrofuran; TRIM: 1-[2-(Trifluoromethyl)phenyl]imidazole; [VAIM]Br: 1-allyl-3-vinylimidazolium bromide.

Table 2. Various MIP-based extraction techniques for different antibiotics in meat samples

Analyte	Matrix	Extraction technique	LOD[a]	LOQ[a]	Linear range[a]	Recovery %	RSD %	Imprinting factor[b]	Reference
Cloxacillin	shrimp	MIM-HPLC UV	0.03 µg/g	0.10 µg/g	0.50–500.00 µg/g	76.0-84.3	2.4 - 9.0	2.7	(Du et al., 2018)
ceftiofur sodium	chicken, pork, beef	MIP SPE - HPLC UV	0.0015 mg/L	0.0050 mg/L	0.0050 – 1.0000 mg/L	91.9–106.8	< 8.5	2.16	(Cheng et al., 2021)
cephalexin	Pork	Magnetic MIP - HPLC UV	5 µg/L	N.M	20 –5000 µg/L	85.5 - 91.3	1.2 - 2.1	2.34	(Chen et al., 2019)
sulfadiazine	Pork and Chicken	Batch MIP SPE[c]-Chemiluminescence sensor	1.0 pg/ml	N.M.	1.0-12.0 pg/ml	78.6 - 95.6	5.9 - 9.6	4.5	(Zhao Bin Li et al., 2019)
sulfamethoxazole			3.0 pg/ml			74.8 - 95.3	6.4 - 10.7	4	
Sulfadimethoxine			12.0 pg/ml			84.7 - 92.4	5.8 - 9.3	1.5	
sulfamethazine			5.0 pg/ml			72.7 - 85.2	7.2 - 12	3.1	
sulfamonomethoxine			8.0 pg/ml			76.9 - 94.5	7.4 - 14.3	2.1	
sulfamerazine			6.0 pg/ml			79.4 - 94.6	6.2 - 13.5	3.5	
sulfametizole			4.0 pg/ml			79.2 - 95.4	6.5 - 9.6	4.3	
sulfamethozypyridazine			7.0 pg/ml			76.1 - 92.5	7.2 - 11.6	3.2	
sulfadoxine			10.0 pg/ml			75.8 - 97.5	6.9 - 13.4	1.5	

sulfamethoxydiazine			7.0 pg/ml			80.4 - 96.4	7.6 - 11.3	2.9	
sulfapyridine			1.0 pg/ml			86.2 - 94.6	5.8 - 13.2	4.6	
salfalene			9.0 pg/ml			77.2 - 94.5	7.3 - 12.6	2.8	
sulfathiazole			1.0 pg/ml			79.5 - 94.1	5.6 - 9.4	3.9	
sulfisoxazole			5.0 pg/ml			78.2 - 94.5	6.2 - 12.4	3.4	
sulfadiazine	beef, chicken, pork, and liver	Batch MIP SPE-HPLC-MS/MS	0.05 µg/L	0.20 µg/L	1.00 - 2500.00 µg/L	83.94 - 92.26	2.59 - 2.82	2.52	(X. Zhao et al., 2018)
sulfathiazole			0.04 µg/L	0.07 µg/L		82.48 - 96.40	1.27 - 2.49	2.06	
sulfamerazine			0.05 µg/L	0.50 µg/L		103.71 - 105.53	3.57 - 5.04	1.76	
sulfisoxazole			0.02 µg/L	0.05 µg/L		63.65 - 74.77	0.72 - 3.75	1.9	
sulfamethoxydiazine			0.10 µg/L	0.50 µg/L		86.09 - 100.95	2.47 - 2.92	1.86	
sulfadoxine			0.02 µg/L	0.03 µg/L		80.29 - 93.88	0.08 - 0.86	1.77	
Sulfamerazine	Pork, Chicken	MWCN GCE MIP - EC Sensor	0.11 µMol/L	N.M	0.30 - 200.00 µMol/ L	86 - 102	<5	1	(Sun, Xu, et al., 2019)
sulfamethazine	swine muscle	Off-line MIP SPE-ELISA like sensor	N.M.	N.M.	100-3200 µg/L	89.6 - 101.4	1.7 - 4.3	2.68	(Peng et al., 2017)
sulfaguanidine	fish	MIP Film-photonic crystal sensor	0.28 nmol/L	N.M.	10.00-1000000.00 nmol/L	88.5 - 114.1	N.M.	N.M.	(L. Li et al., 2019)

Minocycclin	chicken muscle	MIP-MOF-DSPME-UPLC	0.6 ng/ mL	2.0 ng/ mL	2.0- 200.0 ng/ mL	72.5 92.3	5.1 - 9.8	N.M	(Ma et al., 2020)
chlortetracycline			0.4 ng/ mL	1.0 ng/ mL	1.0- 200.0 ng/ mL	69.6 - 84.7	5.2 - 8.6		
tetracycline			0.2 ng/ mL	0.5 ng/ mL	0.5 - 200.0 ng/ mL	73.2 -94.7	5.7 - 9.4		
oxytetracycline			0.2 ng/ mL	0.5 ng/ mL	0.5 - 200.0 ng/ mL	84.7 - 94.6	6.8 - 11.6		
demeclocycline (DMC),			0.4 ng/ mL	1.0 ng/ mL	1.0- 200.0 ng/ mL	72.8 - 87.6	6.8 - 9.4		
doxycycline			0.6 ng/ mL	2.0 ng/ mL	2.0- 200.0 ng/ mL	71.3 - 89.4	5.8 - 9.4		
Methacycline			0.4 ng/ mL	1.0 ng/ mL	1.0- 200.0 ng/ mL	71.0 -84.8	7.0 - 10.1		
Tetracycline	Chicken , Fish	MIP SPME Fiber - HPLC UV	0.38 - 0.72 µg/kg	1.14 - 2.56 µg/kg	5.00– 1000.00 µg/L	81.2 - 97.8	1.3 - 5.4	3.24	(Lu et al., 2020)
Oxytetracycline						79.8 - 92.1	1.2 - 7.0	1.73	
Tetracycline	Chicken , Fish	MISPE - HPLC UV	0.127 µg/kg	0.423 µg/kg	0.062 - 0.615 µg/kg	83.39 - 114.01	1.46 - 7.71	N.M	(He et al., 2019)
Oxytetracycline			0.127 µg/kg	0.423 µg/kg		85.58- 106.40	1.34 - 8.92		
doxycycline			0.122 µg/kg	0.407 µg/kg		86.34 - 104.2	1.32 - 9.54		
Tetracycline	fish	Batch MIP SPE-Flourscent based sensor	9 nmol/L	N.M.	100 - 1000 and 1000 - 50000 nmol/L	98.4-103.1	less than 6.0	N.M.	(J. Yang et al., 2018)

lomefloxacin	Chicken	QD MIP - Flourscent optosensor	0.07 µg/L	0.22 µg/L	0.10–50.00 µg/L	81.5 -97.8	1.8 - 6.5	16.7	(Orachorn & Bunkoed, 2019)
Ciprofloxacin	Fish meat	SLE-Fluorescent sensor (Eu(DBM)3Phen)	0.092 µg/L	0.310 µg/L	0.500 - 100.000 µg/L	85.37 - 86.56	2.21 - 3.87	2.5	(Zhuanying Li et al., 2019)
Enrofloxacin	Fish meat	SLE-Upconversion Fluorescent Probe	0.000250 nmol/L	N.M	1.03 - 280.00 nmol/L	91.5 - 105	0.71 - 3.18	1.35	(Tang et al., 2018)
Fleroxacin			0.000406 nmol/L		1.69 - 220.00 nmol/L	90.33 - 107.35	0.24 - 1.27	N.M.	
levofloxacin			0.00147 nmol/L		6.92 - 280.00 nmol/L	95.8 - 108.43	1.04 - 5.53		
Ciprofloxacin			0.00124 nmol/L		7.54 - 300.00 nmol/L	97.3 - 102.9	1.18 - 2.66		
Enoxacin			0.00112 nmol/L		3.90 - 250.00 nmol/L	102.59 - 105	1.63 - 4.24		
norfloxacin	Chicken meat	MIP- flourscent optosensor	0.35 µg/L	1.18 µg/L	1.00 – 100.00 µg/L	95.2 - 99.3	1.1 - 5.3	68.7	(Chaowana & Bunkoed, 2019)
Ciprofloxacin	Chicken muscle	SLE-QD Fluorescent Probe	0.066 µg/L	N.M	0.100 - 1.000 µg/L and 1.000 - 100.000 µg/L	82.6-98.4	less than 8	17.67, 4.28	(Yuphintharakun et al., 2018)
Ciprofloxacin	Pork	Batch MIP SPE-HPLC UV	0.11 µg/L	0.29 µg/L	0.29 - 147000.00 µg/L	89.33-94.67	3.99 - 9.52	presented in Chart	(Zhu et al., 2019)
Ofloxacin	Chicken -Pork-Fish	MIP SBSE-HPLC UV	0.2 ng/mL	0.6 ng/mL	1.0-1000.0 ng/mL	74.6 - 86.3	4.5 - 9.2	9.2	(K. Yang et al., 2017)

Ciprofloxacin			0.3 ng/mL	0.7 ng/mL	1.0-1000.0 ng/mL	75.8 - 91.6	4.9 - 9.5	8.6	
Pefloxacin			0.2 ng/mL	0.5 ng/mL	1.0-1000.0 ng/mL	71.5 - 94.5	4.9 - 8.8	9.5	
Lomefloxacin			0.2 ng/mL	0.5 ng/mL	1.0-1000.0 ng/mL	76.4 - 97.4	4.4 - 9.4	8.9	
Enrofloxacin			0.1 ng/mL	0.4 ng/mL	1.0-1000.0 ng/mL	67.4 - 86.4	5.2 - 9.6	9.3	
Sarafloxacin			0.2 ng/mL	0.5 ng/mL	1.0-1000.0 ng/mL	81.4 - 99	4.8 - 9	8.8	
Danofloxacin			0.3 ng/mL	0.9 ng/mL	1.0-1000.0 ng/mL	69.4 - 84.7	5.4 - 9.8	8.9	
Marbofloxacin			0.2 ng/mL	0.6 ng/mL	1.0-1000.0 ng/mL	72.9 - 88.1	5.8 - 9.1	9	
Difloxacin			0.1 ng/mL	0.4 ng/mL	1.0-1000.0 ng/mL	82.5 - 98.2	4.8 - 9.2	9.4	
ofloxacin			0.11 µg/L	0.36 µg/L	0.50 - 20.00 µg/L	73.5 - 93.2	2.4 - 7.2	N.M.	
norfloxacin			0.016 µg/L	0.054 µg/L	0.200 - 10.000 µg/L	65.3 - 89.6	1.6 - 6.5	N.M.	
ciprofloxacin			0.044 µg/L	0.140 µg/L	0.200 - 10.000 µg/L	85.3 - 114.9	1.8 - 6.6	N.M.	
enrofloxacin			0.057 µg/L	0.190 µg/L	0.200 - 20.000 µg/L	83.3 - 107.4	1.6 - 7.0	N.M.	

sarafloxacin	Chicken	MIP - spectrofluorimetry	0.05 µg/L	0.15 µg/L	0.10 – 15.00 µg/L	82.8–99.1	0.6–2.4	8.18	(Bunkoed et al., 2020)
Erythromycin	chicken, pork, beef	Off-line MIP SPE-LC-MS/MS	0.5 µg/kg	2.0 µg/kg	1.0 - 100.0 µg/kg	76.8 - 86.1	1.7 - 10.4	single analyte*: 2.3	(X. Song et al., 2019)
								multiple analyte: 2.1	
Clarithromycin			0.5 µg/kg	2.0 µg/kg		80.2 - 89.7	0.7 - 9.8	single analyte: 2.6	
								multiple analyte: 2.3	
Tulathromycin			1.0 µg/kg	5.0 µg/kg		75.8 - 81.2	1.2 - 8.3	single analyte: 1.6	
								multiple analyte: 1.4	
Azithromycin			0.5 µg/kg	2.0 µg/kg		78.4 - 91.7	1.4 - 8.2	single analyte: 1.7	
								multiple analyte: 1.8	
Spiramycin			1.0 µg/kg	5.0 µg/kg		78.2-87.6	1.1 - 8.9	single analyte: 2	
								multiple analyte: 1.8	

Tilmicosin			0.5 µg/kg	2.0 µg/kg		78.2 - 91.8	1.5 - 8.1	single analyte: 1.8 multiple analyte: 1.6	
Chloramphenicol	Pork, Fish, Chicken	Batch MIP SPE-ELISA like sensor	0.005 ng/ml	N.M	N.M	79.5 - 97.6	5.4 - 13.0	N.M	(Jia, Huang, et al., 2019)
Chloramphenicol	Fish	MIP-Electrochemical sensor	0.54 nmol/L	N.M	1.00 nM-100000.00 nmol/L	N.M	N.M	N.M.	(Ana et al., 2018)
Chloramphenicol	Pork, Chicken, Fish	Magnetic MIP Microsphere-CRET	2.0 pg/ml	N.M	10.0 - 100000.0 pg/ml	75.5 - 97.3	5.2 - 12	N.M	(Jia, He, et al., 2019)
Chloramphenicol	Pork	Magnetic MIP Batch SPE-HPLC UV	10 µg/L	N.M	20 - 10000 µg/L	95.31 - 99.32	1.21 - 2.6	2.935	(Zengwei Li et al., 2018)
Streptomycin	Pork	SupelMIP-HPLC MS/MS	5 µg/kg	17 µg/kg	17 - 1500 µg/kg	87.3 - 92.7	SD: 3.6 - 9.6	N.M.	(B. Yang et al., 2017)
Dihydrostreptomycin			4 µg/kg	13 µg/kg	13 - 1500 µg/kg	87.2 - 94.6	5.3 - 10.4	N.M.	
Kanamycin			11 µg/kg	36 µg/kg	36 - 1500 µg/kg	83.4 - 91.3	4.9 - 6.7	N.M.	
Gentamicin C1a			6 µg/kg	20 µg/kg	20 - 1500 µg/kg	82.4 - 89.6	3.9 - 7.4	N.M.	
Spectinomycin			3 µg/kg	10 µg/kg	10 - 1500 µg/kg	82.3 - 92.1	4.6 - 7.2	N.M.	
Amikacin			12 µg/kg	40 µg/kg	40 - 1500 µg/kg	84.4 - 90.8	4.4 - 7.0	N.M.	
Tobramycin			11 µg/kg	36 µg/kg	36 - 1500 µg/kg	82.6 - 91.7	3.7 - 8.3	N.M.	

Sisomicin			7 μg/kg	23 μg/kg	23 - 1500 μg/kg	74.3 - 82.2	5.6 - 8.2	N.M.	
Paromomycin			30 μg/kg	100 μg/kg	100 - 2500 μg/kg	72.9 - 84.7	4.9 - 8.3	N.M.	
Netilmicin			8 μg/kg	27 μg/kg	27 - 1500 μg/kg	76.4 - 82.6	4.3 - 9.9	N.M.	
Hygromycin			10 μg/kg	34 μg/kg	34 - 1500 μg/kg	77.4 - 87.5	3.7 - 7.0	N.M.	
Lincomycin	Chicken	MIP-ECL Electrode	0.16 pmol/L	N.M.	5.00 - 1000.00 pmol/L	89.9 - 104.5	2.58 - 4.33	N.M.	(S. Li et al., 2017)
	Duck								
	Curcian								
	Pork								
	Crab								
	Beef								
	Mutton								
Flumequin	Fish	SGO-CIP-SPE / HPLC FLD	0.32 ng/g	N.M.	25.00 - 2000.00 ng/mL	80.6 - 95.2	3.8 - 5.9	N.M.	(Zhai et al., 2019)

Table 2. Information of the validation of detection and determination methods.

list of abbriviations: CIP: Coordination imprinted polymer; CL: Chemiluminescence; d-μ-SPE: Dispersive micro-solid phase extraction; FI: Flow Injection; FLD: Fluorescence detector; HPLC: High-performance liquid chromatography; LC: Liquid chromatography; LOD: Limit of detection; LOQ: Limit of quantification; MIM: Molecularly imprinted membrane; MIMSPD: Molecularly imprinted matrix solidphase dispersion; MIP: Molecularly imprinted polymer; MS/MS: Tandem mass spectrometry; N.M.: Not mentioned; QD: Quantum dot; RSD: Relative standard deviation; SBSE Stir Bar Sorptive Extraction; SGO: Silanized graphene oxide; SLE: Solid-liquid extraction; SPME: Solid-phase microextraction; UCNP: Upconverting nanoparticle; UFLC: Ultra-fast liquid chromatograph; UV: Ultraviolet.

a: In some studies LOD, LOD, and linearity range was reported based on the weight of meet (the values are reported per g or kg).

b: In this column, N.M. is when either the imprinting factor wasn't mentioned at all or it wasn't mentioned in an quantitative manner

c: Batch MIP SPE: Batch SPE refers to practice of mixing particles with a solution containing the template

d: Off-line MIP SPE: Off-line SPE refers to practice of using MIP Packed cartridges and analyzing the eluent afterwards

e: On-line MIP SPE: On-line SPE refers to practice of using MIP column which are directly coupled with analytical instrument

Figures

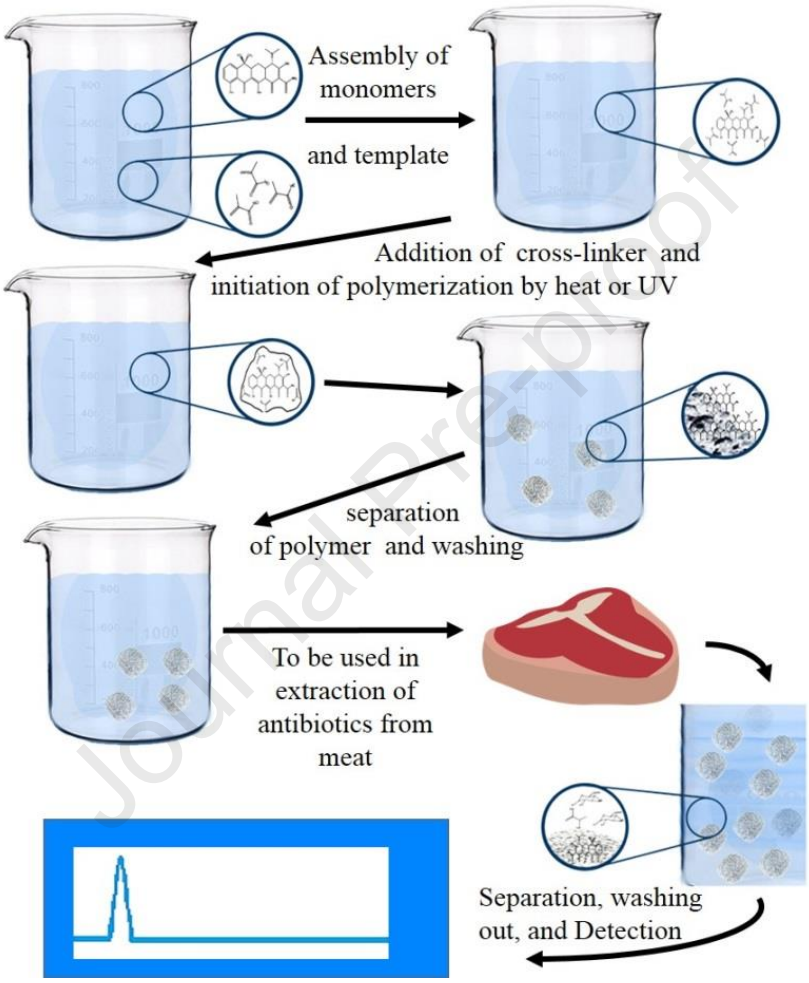

Figure 1. Synthesis and application of molecularly imprinted polymers in detection of antibiotics in meat samples.

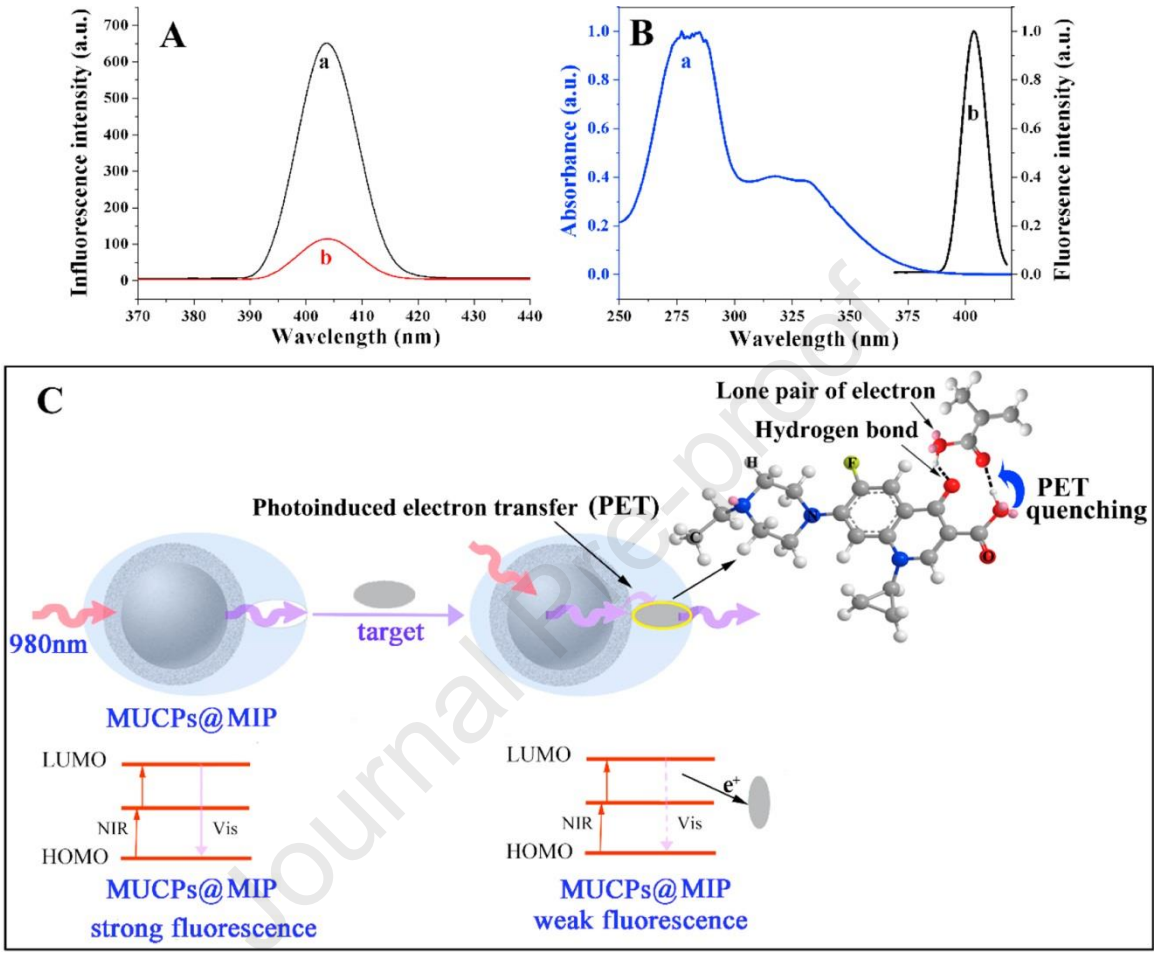

Figure 2. Fluorescence spectra (A) of MUCPs@MIP after (spectrum a) and before (spectrum b) the removal of template molecule; the fluorescence spectrum of MUCPs@MIP (Bb) and UV –vis absorption spectrum of ENR (Ba); the schematic diagram of fluorescence quenching mechanism (C). Reprinted with permission (Tang et al., 2018)

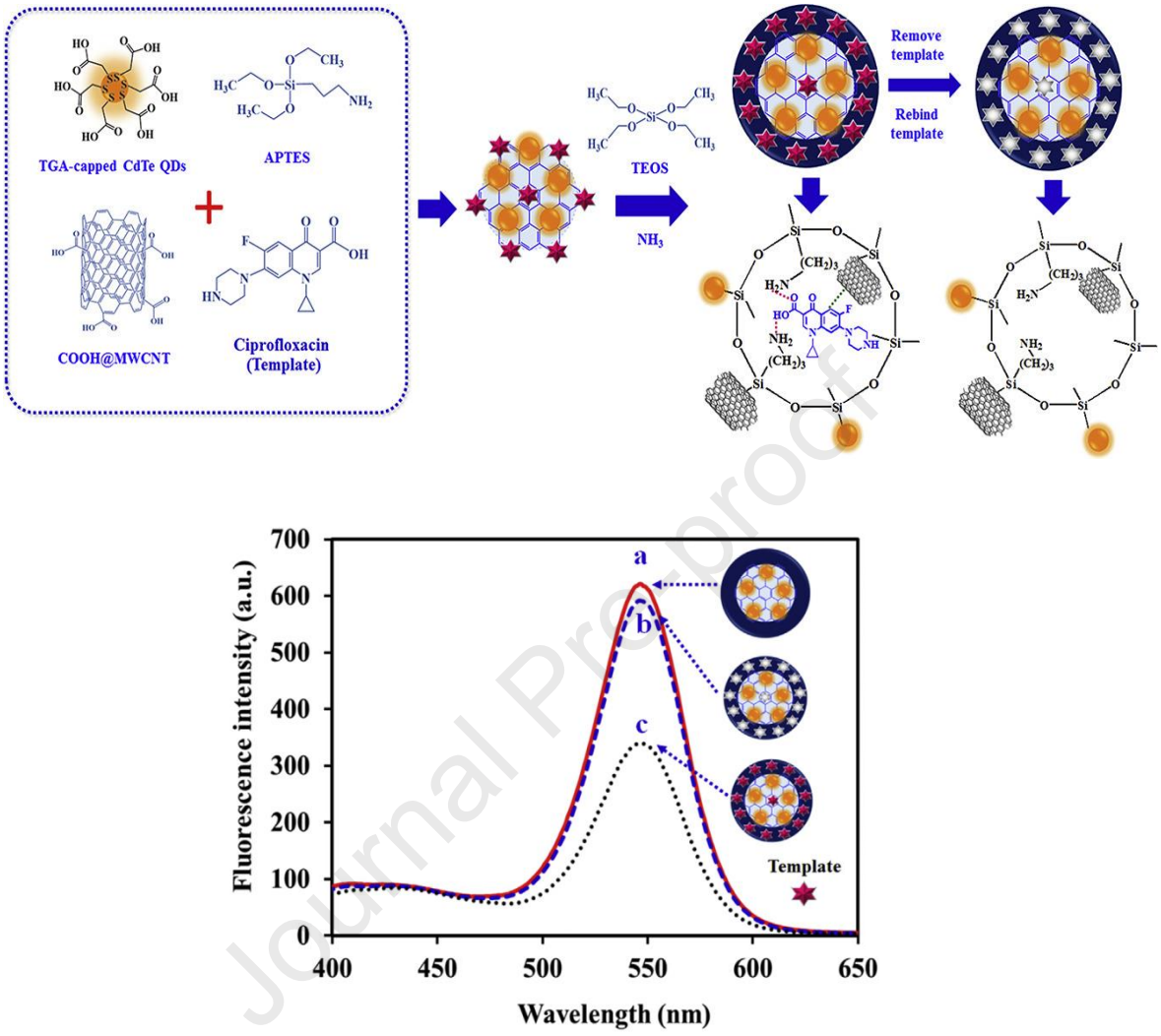

Figure 3. The synthesis of nanocomposite COOH@MWCNT-MIP-QDs optosensors for the specific recognition of ciprofloxacin and its fluorescence spectra. Reprinted with permission (Yuphintharakun et al., 2018)

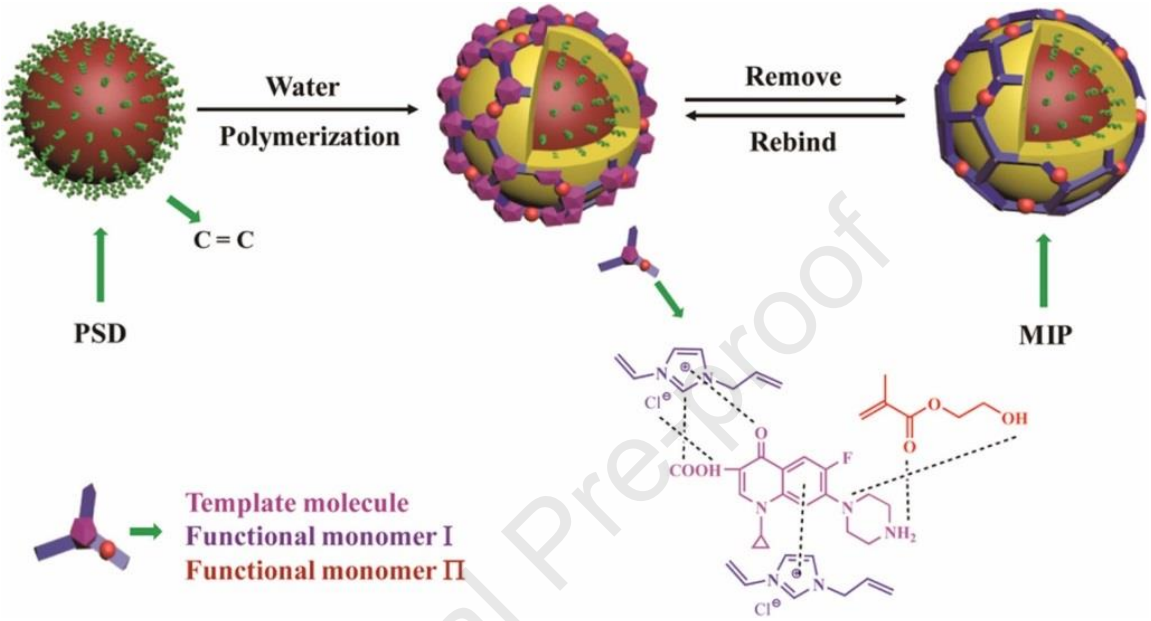

Figure 4. Schematic illustration of the synthetic route of the ciproflxacin imprinted polymer . Reprinted with permission.(Zhu et al., 2019)

Highlights

- Molecularly imprinted polymers (MIPs) can be successfully used for food applications.
- MIPs are powerful materials in sample-preparation techniques.
- The analysis of antibiotics in meat samples can be efficiently achieved by using MIPs.
- MIPs have potential to direct coupling with the detection systems.

Declaration of Interest Statement

All Authors declare no conflict interest.