



Perspective Perspectives of Polymers in Forensic Analysis

Ana M. Díez-Pascual 回

Universidad de Alcalá, Facultad de Ciencias, Departamento de Química Analítica, Química Física e Ingeniería Química, Ctra. Madrid-Barcelona Km. 33.6, 28805 Alcalá de Henares, Madrid, Spain; am.diez@uah.es

Abstract: Polymeric materials have recently attracted a lot of attention due to their potential applications in many fields, ranging from biomedicine, the food industry and environmental monitoring to electronic, energy storage and sensing devices. Their versatility, functionalization capability, chemical/physical stability, reusability, long shelf-life, as well as good mechanical and thermal properties, also make them idoneous candidates for use in forensic sciences, which deal with the investigation of crimes, finding relations between evidence and criminals. In particular, molecularly imprinted polymers (MIPs), designed based on the principle of generating template-specific polymeric cavities fitted to the target molecules in the presence of selected chemicals via non-covalent or covalent interactions, are highly suitable for forensic analysis. In addition, their combination with other compounds such as carbon nanomaterials can provide composites with improved properties to be used in the analysis of illicit drugs, doping substances, biological agents, toxins and so forth. In this article, recent applications of polymeric materials in the field of forensic analysis are discussed. The goal is to summarize their current uses and put forth a projection of their potential as promising alternatives for standard competitors.

Keywords: polymeric materials; molecular imprinted polymer; forensic science; nanocomposites; illicit drugs; toxins

1. Introduction

The field of forensic science emerged due to the requirement for scientific techniques for identifying and investigating crimes. Forensic science is a multidisciplinary area of study that comprises many areas, including chemistry, biology, materials science, toxicology, geology, archeology, anthropology, astronomy, engineering, etc. All these subjects have different approaches to problem-solving and apply specific tools. Problem-solving in forensic analysis involves two stages [1]: Firstly, finding a piece of evidence or a questioned sample, and secondly, comparing it with a known (reference) material to provide the origin of the suspected sample. It typically examines the evidence found at the crime scene (i.e., hair, DNA, proteins, nails, paints, fibers, etc.) using certain analytical techniques. Polymerbased materials can make the investigation procedure quicker, more precise, sensitive and discriminatory. For instance, the combination with carbon nanomaterials such as fullerenes (C60), carbon nanotubes (CNTs), graphene (G) and its derivatives graphene oxide (GO) and reduced graphene oxide (rGO) offers innovative solutions to identify DNA from fingerprints, explosives and gunshot residues (GSR) [2], amongst others. Further, when integrated into sensors, they display advantageous features such as high sensitivity, precision and accuracy, easy handling, reduced cost, minimal sample requirement, simple integration into portable platforms and multifunctional capabilities. Their use could then aid to solve current problems forensic science is facing in terms of "in situ" detecting traces of analytes, which cannot be attained using conventional analytical techniques.

On the other hand, molecularly imprinted polymers (MIPs), due to their versatility, stability and recognition capabilities are perfect candidates for use in forensic sciences [3]. MIPs are based on the principle of making template-specific polymeric cavities fitted to target molecules in the presence of particular chemicals via non-covalent (hydrogen bond,



Citation: Díez-Pascual, A.M. Perspectives of Polymers in Forensic Analysis. *Macromol* **2023**, *3*, 108–119. https://doi.org/10.3390/ macromol3020008

Academic Editor: Dimitrios Bikiaris

Received: 13 August 2022 Revised: 28 March 2023 Accepted: 6 April 2023 Published: 10 April 2023



Copyright: © 2023 by the author. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). ionic and hydrophobic) or covalent interactions [4]. A cost-effective MIP guarantees high selectivity compared to antibodies, enzymes or aptamers with natural biological recognition units, and offers high stability and long-term reusability. MIPs can be synthesized under different formats (particles, monoliths and membranes) and sizes and can simultaneously have different properties such as magnetic, stimuli-responsive, fluorescence labeling, etc., which support their potential application in the field of forensic sciences [4,5].

In this article, current applications of polymeric materials in the field of forensic analysis are discussed. A systematic literature search has been performed over the last decade using core databases, and over 150 articles were found. Then, the most relevant publications were identified and clustered into groups related to target structures. The aim is to recapitulate their up-to-date uses and put forth a forecast of their potential as talented alternatives for current competitors.

2. Approaches of Polymer-Based Materials in Forensic Analysis

2.1. Detection of Illegal Drugs

A wide range of illicit and abused drugs are the focus of forensic cases. Some of the most common are described below with specific examples of how polymeric materials can be used for their detection. To make it easier for the readers, the main components of a chemical sensor and a brief explanation of the different types of chemical sensors and their principles are provided in the Supplementary Materials (Figures S1–S4).

Sedatives such as benzodiazepines and barbiturate sleeping drugs are among the most studied drugs [5]. Eberlin and coworkers [6] developed a method for direct extraction and quantification of benzodiazepines in human plasma by using MIPs, which is a versatile approach for producing selective binding sites in highly cross-linked synthetic polymers [7]. For this purpose, functional monomers were self-assembled around a "template" and then polymerized in the presence of crosslinkers. After template removal from the polymer, the imprinted cavities came out with chemical and physical recognition abilities to bind a target (Figure 1) [7]. Electrospray ionization mass spectrometry (ESI-MS) was used as the detection platform, leading to a linear calibration curve in the range of 10–250 μ g L⁻¹, with a limit of quantification (LOQ) lower than 10 μ g L⁻¹ and very good precision and repeatability for intra-day and inter-day measurements.

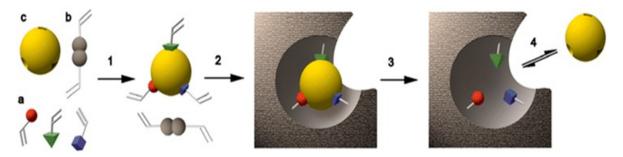


Figure 1. Representation of MIP synthesis: a: functional monomers; b: cross-linker; c: template molecule; 1: assembly of the prepolymerization complex; 2: polymerization; 3: extraction; 4: rebinding. Reprinted from ref. [7], copyright 2018, with permission from the American Chemical Society.

Anderson and coworkers [8] described the extraction of diazepam and other benzodiazepines from hair samples. They reported a high recovery of up to 93%, with a limit of detection (LOD) and LOQ of 0.09 and 0.14 ng/mg, respectively. Panahi et al. [9] developed an electrochemical sensor based on MIP-multiwalled carbon nanotube nanocomposites for the determination of midazolam, another benzodiazepine, in human urine samples and pharmaceutical formulations. The sensor showed high sensitivity and selectivity in the presence of other benzodiazepines. Ensafi and coworkers [10] also developed a novel electrochemical MIP-based sensor for the determination of lorazepam based on modified polypyrrole@sol-gel@gold nanoparticles/pencil graphite electrode and obtained a wide linear range of 0.02–2.00 μ g/mL. The same group [11] reported an MIP-based fluorescence detection approach to determine thioridazine (THZ), a sedative and antidepressant drug used in the treatment of psychiatric disorders such as schizophrenia. In this method, luminescent zinc oxide quantum dots were used to provide chemical stability and antimicrobial activity. The decrease in the emission intensity of the QDs by the MIP made THZ determination possible with an LQD of 0.43 nm L⁻¹.

Another class of drugs often studied are stimulants such as cocaine, amphetamine and methamphetamine. Gao and coworkers [12] used an aptamer with poly-cytosine (poly-C) DNA, a series of diblock DNA sequences containing between 0 and 30 cytosines, adsorbed on the surface of GO to detect cocaine. To avoid cocaine from nonspecific binding, a nonionic surfactant that may strongly interact with GO through its hydrocarbon lipophilic group was added, leading to a very low LOD of 2.45 pM.

De Wael et al. [13] prepared an electrode for the selective detection of cocaine using MIPs on the surface of Pd-decorated graphene. The MIPs were synthesized by cyclic voltammetry using p-aminobenzoic acid as a monomer and cocaine as a template, as depicted in Figure 2. Square-wave voltammetry was used to quantify cocaine, and a linear response was found in the range of 100–500 M, with an LOD of 50 M.



Figure 2. Synthesis of an electrochemical sensor for direct detection of cocaine based on MIPs electropolymerized onto electrodes with graphene-modified with Pd-NPs. Taken from ref. [13], copyright 2019, with permission from the Royal Society of Chemistry.

Muñoz et al. [14] developed a 3D-printed graphene–polylactic acid (PLA) electrode to measure low concentrations of cocaine. An LOD of 6 μ M was attained, with a linear concentration range between 20 and 100 μ M, and free from the interference of paracetamol, caffeine, phenacetin, lidocaine, benzocaine and levamisole, which are common adulterants found in seized drugs. This technique and electrode were previously used by the same group to measure phenolic compounds such as dopamine [15].

Madrakian et al. [16] proposed a new aptasensor based on a screen-printed carbon electrode (SPCE) modified with 3D magnetic rGO/polyaniline(PANI)/AuNPs for cocaine sensing. Under optimized conditions, cocaine was determined in a linear concentration range from 0.09 to 85 nM with an LOD of 0.029 nM. The proposed aptasensor was applied to determine cocaine in urine and human serum samples, leading to good results.

Chang et al. [17] prepared a simple and low-cost graphene-based sensor for methamphetamine detection via a one-step solvent-free fabrication method. The sensor was tested with real samples such as saliva and samples recovered from glass, stainless steel and plastic surfaces), and very high recoveries were attained, leading to an LOD of 0.3 g/mL, which corroborates its appropriateness for forensic investigations. Another selective electrochemical sensor for methamphetamine detection was designed by Ahmadi and coworkers [18], who used functionalized rGO. Initially, GO was reduced on the surface of a glass carbon electrode. Then, FeCl₃ was converted into Fe₃O₄ using NH₄OH, followed by polymerization in a mixture with pyrrole monomers, resulting in conductive PPy forming a shell around the Fe₃O₄. The core–shell nanoparticle suspension was then added dropwise to the surface of the rGO and left to dry. Urine and human blood serum were used as real samples for this study, and the LOD was found to be 1 nM with a linear range between 0.005 and 200 M.

Amphetamine-type stimulants, which are used as legally prescribed drugs in the treatment of attention deficit hyperactivity disorder or narcolepsy, have become the second most used drug after cannabis, exceeding the use of cocaine and heroin. Craniczkowska et al. [19] prepared MIP structures using bulk precipitation and electropolymerization methods to attach them to a surface gold electrode, and the developed approach was highly sensitive against methamphetamine, amphetamine, benzylmethyltketone and acetophenone.

Analgesics such as morphine, codeine and oxycodone have also been investigated. Koskinen and coworkers [20] combined an SWCNT network and a Nafion polymeric membrane for the selective detection of morphine (MO) and codeine (CO). SWCNT electrodes were manufactured via a dry transfer method and coated with Nafion. The applicability of the sensor was evaluated by the successful concurrent recognition of MO and CO in the presence of ascorbic acid (AA) and uric acid (UA), as well as in human plasma (Figure 3). With this SWCNT/Nafion electrode, two linear ranges of 0.05–1 and 1–10 μ M were found for MO and one linear range of 0.1–50 μ M for CO.

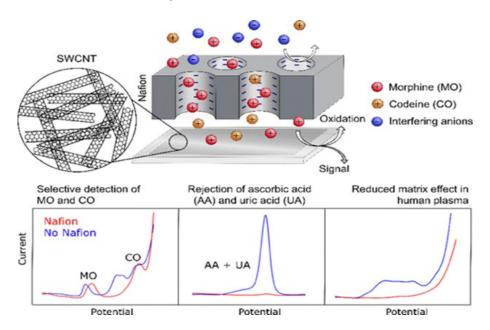


Figure 3. Top: Nafion-coated SWCNT electrode. Down: CV for SWCNT and SWCNT + Nafion electrodes. Reprinted from ref. [20] under an open access license.

The same group used the Nafion-coated SWCNT electrode to study the electrochemical behavior of oxycodone, a strong opioid frequently used as an analgesic, and its two main metabolites, noroxycodone and oxymorphone [21]. The electrode could selectively detect oxycodone in the presence of noroxycodone and oxymorphone, with a linear range of 0.5–10 μ M and an LOD of 85 nM. An MIP based on magnetic GO and carbon dots nanoparticles (MIP@MGO/CDs NPs) was also developed using ultrasonic-assisted dispersive solid-phase microextraction (UA-DSPME) to detect oxycodone [22]. The average recoveries of oxycodone in human urine samples were found to be in the range of 92.50 to 103.20%, with an LOD of 0.80 ng/mL and a linear range of 1–2000 ng/mL. Cannabinoids such as marijuana and hashish are the most commonly used illicit drugs. Moreda-Pineiro et al. [23,24] developed a micro-solid extractor for cannabinoid detection in order to analyze the plasma and urine of marijuana abusers by the combination of MIPs with an HPLC-MS/MS system. They reported that LOQ values for plasma and urine samples were in the ranges of 0.36–0.49 ng/L and 0.47–0.57 ng/L, respectively. The same group [25] developed a membrane-protected MIP micro-solid-phase extraction method to determine synthetic cathinones, new psychoactive substances known as "bath salts," that show severe effects compared to cocaine and methamphetamine. Unlike the natural cathinones, their structural differences make them invisible in the determination and monitoring of illicit drugs in forensic samples. In their study [24], ethylone and methcathinone were used as templates. The LOD values for penthylone, ethylone and 3-methylmethcathinone in real urine samples were found to be 0.072, 0.16 and 0.18 ppt, respectively.

Gonzalez-Rodriguez and coworkers [25] also developed water-compatible imprinted pills for cannabinoid extraction and detection in urine and oral fluid. The MIP was prepared using acrylamide as a monomer, ethylene glycol dimethacrylate as a cross-linker and catechin as a mimic template. They optimized the extraction performance by tuning the MIP composition and obtained a linear calibration in the ranges of 1–500 ng/mL and 0.75–500 ng/mL for urine and oral fluid, respectively. Quartz Crystal Microbalance (QCM) sensors modified with selective MIP layers also have the ability to recognize their target compounds. Akgönüllü et al. [26] developed a QCM sensor with a uniform surface for the determination of some cannabinoids in artificial saliva. For this purpose, MIP nanoparticles were deposited onto the surface of a chip under UV radiation after functionalization using piranha solution, leading to an LOD of 0.23 pg/mL. This type of sensor is very sensitive but has a lot of issues related to particle deposition problems and also the hazard of leaks. Interferences with molecules of similar mass may also bring errors. In addition, crystal thickness should be kept under control. L-Nicotine has also been used as a template molecule in MIP-QCM studies [27]. Bulk-polymerized L-nicotine MIPs for the detection of this drug in saliva and urine were used. The solutions were prepared using MAA as the monomer, EDMA as the cross-linker and L-nicotine as the template molecule, and then these solutions were polymerized at 60 $^{\circ}$ C for 72 h. The obtained polymers were ground, washed to remove the drug excess and then coated on a QCM electrode with PVC. MIPs were found to bind four times more L-nicotine than non-imprinted polymers in water and two times more in phosphate-buffered saline at pH 9. This study shows that L-nicotine could be detected directly in saliva and urine samples in the micromolar range.

Ketamine, initially used as an anesthetic, is known as a "club drug" in the markets since has hallucinogenic and euphoric potential. Fu et al. [28] applied ketamine imprinting on a thin layer of methacrylic acid (MAA) via UV-induced polymerization in the presence of a crosslinker on the surface of a metal–organic framework/graphene nanocomposite modified screen-imprinted electrode. The ratios between ketamine, MAA and crosslinker are critical parameters controlling the sensitivity. A low amount of monomer leads to poor imprinting, while high amounts produce too much crosslinking, resulting in inaccessible recognition and challenging template removal. With this technique, a very low LOD of 4.0×10^{-11} M was attained in 5 min, and the method provided highly selective against norketamine, methylene dioxymethamphetamine, methylamphetamine, dopamine and ascorbic acid.

It is important to note that the amount of novel psychoactive substances (NPS) has been growing exponentially over the last years; hence, new selective methods for their recognition are required. In this regard, engineering MIPs for the selective extraction and quantification of NPS is a very useful tool. For instance, Lowdon and coworkers [29] have developed novel MIPs for the detection of traces of methoxphenidine (MXP) and its regioisomers in complex samples. The MIPs were synthesized using 2-MXP as a template, styrene and MAA as functional monomers and varying amounts of crosslinker. Under optimal conditions, the maximum binding capacities of all MXP isomers were in the range of 170–190 µmol g⁻¹, as determined via HPLC coupled to UV detection. Forensic analysis approaches are also applicable for anti-doping purposes to determine doping with performance-enhancing drugs, stimulants, steroids, hormones and corticos-teroids. Ethirajan et al. [30] accomplished bulk and miniemulsion polymerization to yield colloidal particles, which were used for testosterone determination. They compared the performances of bulk and colloidal MIPs and found that the imprinting factor increased from 2.2 to 6.8 due to the smaller size, homogeneity and increased surface area of colloidal particles.

Erythropoietin (EPO) is the most important peptide hormone used as a blood-doping agent. It stimulates the growth of red blood cells; henceforth, athletes use EPO illicitly to improve their performance by promoting oxygen release to the tissues. Liu and coworkers [31] developed an MIP-based plasmonic immunosandwich assay for EPO recognition in human urine through surface-enhanced Raman scattering (SERS) measurements (Figure 4) and found an LOD of 29 fM in only 30 min analysis time. Han et al. [32] also developed an EPO sandwich-type immunosensor comprising fullerene (C60) functionalized with PAMAM and AuNPs. The resulting immunosensor had a linear response in the range of 0.01–80 mIU mL⁻¹ for EPO monitoring in human serum.

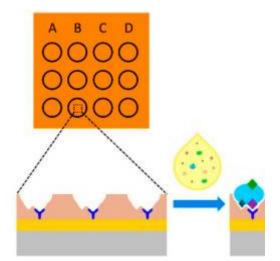


Figure 4. Schematic illustration of the MIP-based immunosandwich assay for determination of EPO. Reprinted from [31], copyright (2016), with permission from the American Chemical Society.

In the study of Lee et al. [33], the electropolymerization method was used to synthesize 17β -estradiol-imprinted (polyaniline-co-m-aminobenzenesulfonic acid) conductive film. The determined estradiol content in human cell serum was in the range of 18 to 73 ng L⁻¹, in the order of commercial kits, with good binding and recognition capability.

2.3. Detection of Toxins

A group of fungi metabolites are aflatoxin derivatives, including Aflatoxin B1 (AFB1) and fumonisin B1 (FB1), which are amongst the main mycotoxins. In particular, AFB1 is recorded as a group I carcinogen by the International Agency for Research on Cancer and is declared the most toxic mycotoxin due to its capability to bind with the DNA of cells, enhancing the hazard of liver cancer in humans [34]. The Food and Drug Administration (FDA) has fixed the limit of AFB1 at 300 ng mL⁻¹ [35]. Over years, due to the need to detect mycotoxins at very low concentrations, many electrochemical biosensors have been developed. Wang and coworkers [36] developed an aptasensing device for label-free determination of AFB1 by using a carbon-printed electrode coated with polydimethylsiloxane, leading to an LOD of 15 pg mL⁻¹ and a linear calibration in the range of 20 to 50 ng mL⁻¹. Bayram et al. [37] used poly(2-hydroxyethyl methacrylate) cryogel-based columns to im-

print aflatoxin for its quantification in hazelnuts, peanuts, figs and red pepper flakes, and very good results with high selectivity were obtained compared to commercial kits.

Gunasekaran and coworkers developed an electrochemical immunosensor for the selective and sensitive detection of two mycotoxins, FB1 and deoxynivalenol (DON) [38]. A screen-printed electrode was prepared and modified by gold NPs and a nanocomposite of polypyrrole and electrochemically reduced GO, leading to an LOD of 4.2 and 8.6 ppb for FB1 and DON, as well as linear ranges from 0.2 to 4.5 ppm and from 0.05 to 1.0 ppm, respectively.

Other toxins have been detected, such as okadaic acid (OA), a shellfish that is highly poisonous in humans, given that it causes the blocking of active sites of enzymes, resulting in the over-phosphorylation of proteins and gastrointestinal problems. Zhou et al. [39] developed an electrochemical biosensor comprising a screen-printed electrode modified with an electropolymerized polyaminophenol/CNT nanocomposite for enzyme immobilization. An LOD of 0.5 g L⁻¹ was attained with a linear range of 1–300 g L⁻¹.

Chloramphenicol is a cheap antibiotic commonly used in agriculture to increase food production and fight against many animal pathogens. However, high doses of this compound are toxic and induce clinical problems [40]. Shaheen et al. [41] used chloramphenicol imprinted networks to expand 2D bismuth nanosheets for chloramphenicol detection among thiamphenicol, florfenicol and clindamycin. High sensitivity was attained by making the binding sites more accessible via depositing a thick MIP layer on Bi₂WO₆ nanosheets. (Figure 5). The electrostatic interactions between the negatively charged oxygen atoms on the Bi₂WO₆ nanosheets and the carbonyl groups in the polymer mixture facilitated the formation of hydrogen bonds, resulting in better selectivity and sensitivity. An LOD of 0.74 μ M was attained, better than the previous literature [42,43].

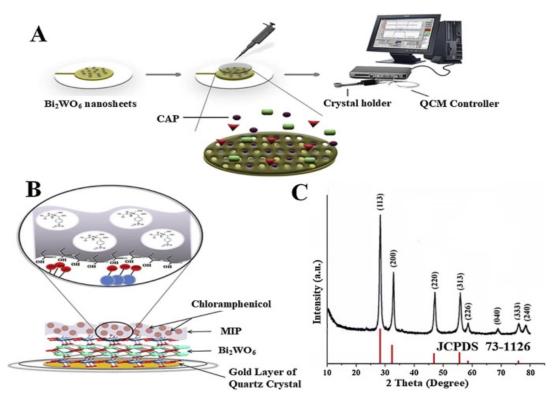


Figure 5. (A) MIP-based sensor for the detection of chloramphenicol. (B) Proposed mechanism for chloramphenicol, MIP and Bi_2WO_6 nanosheet interactions. (C) XRD of Bi_2WO_6 nanosheets. Reprinted from ref. [41], copyright 2020, with permission from Elsevier.

Lately, polymer-based materials have improved forensic investigation by speeding up forensic procedures and aiding in solving and preventing crimes. There are two primary challenges with forensic science applications: the complexity of the analyte(s) to be detected and/or the corresponding matrix and the fairly low concentration of the analyte(s) in this complex matrix. Therefore, the outstanding properties of polymers, such as chemical/physical stability, versatility, functionalization capability, chemical/physical stability and durability, as well as good mechanical and thermal properties, make them highly suitable candidates for use in forensic analysis. Further, when incorporated into sensoric platforms, they exhibit numerous advantages compared to conventional analytical sensors/biosensors, including better sensitivity, selectivity, improved precision and accuracy, lower cost and easier integration into portable devices. In particular, MIP-based materials have been the focus of numerous works for both sensing and sample preparation/preconcentration of forensic targets including drugs, doping substances, toxins and so forth, owing to their excellent compatibility with both of organic and aqueous media, long shelflife and outstanding recognition capabilities. Online pre-concentration, improved detection, enhanced selectivity and sensitivity, robustness, cost-efficiency, low limit of detection and quantification as well as ease of manufacture combined with a variety of synthesis approaches make MIP-based platforms a promising alternative for current commercial products with respect to the sensory applications. Nonetheless, despite MIP-based materials having a variety of applications in many different areas, the assessment of MIP-based sensors should be extended to the requirements of the forensic sciences. Some studies [44] have applied computational models for determining the composition of imprinting materials, which would allow the implementation of computationally designed systems to be used as efficient, time-saving and convenient tools for the determination of target analytes in forensics.

On the other hand, speed is one of the foremost decisive criteria in the detection/quantification of analytes in forensics sciences. In addition, the determination of multiple target analytes is one of the major challenges. Easier and more straightforward sample preparation protocols can speed up the rate of determination. Furthermore, if the results are comprehensible and robust, even by people who are not experts, reaching the end user will aid the conversion into commercial practice. In fact, for demanding applications such as preventing terrorist activities by monitoring gases evolving from explosives or toxic chemicals, novel disposable MIP sensors with portable products should be developed [45]. Furthermore, mobile systems integrating MIP sensors are crucial, owing to their environmental friendliness and accessibility.

One of the greatest challenges on electrochemical sensors with MIPs is the need to use redox markers. This can be solved by using electroactive polymeric materials and composites with stable and sensitive electrochemical properties versus the target analyte. In particular, nanocomposites comprising carbon nanomaterials such as fullerenes, quantum dots, carbon nanotubes, graphene and its derivatives graphene oxide and reduced graphene oxide are highly interesting in order to enhance the results of tracing, detection and analysis in forensic investigation. Carbon-based polymeric nanosensors have demonstrated improved performance compared with those without carbon nanomaterials in terms of selectivity, sensitivity and limit of detection. In addition, they are more sustainable. However, while significant advancement has been made in the arena of these multifunctional sensors, open questions and challenges still continue. On the nanomaterial preparation side, sensor-to-sensor variation is a big issue. To attain reproducibility, standardized methods for carbon nanomaterial synthesis are required, which is a key factor in determining device performance. Once the nanosensors are arranged, further characterization is needed to investigate the polymer-carbon nanomaterial interactions and to fully understand the sensing mechanisms and the parameters influencing device performance. To interpret the processes taking place between the analyte, the polymer and the carbon nanomaterials, theoretical modeling will be highly appreciated.

Regarding the polymer, particularly the MIP, specific molecular affinities in real biological fluids and complex matrices have to be increased in order to avoid interference effects. Therefore, novel MIP designs should be developed in this emerging and growing field. MIP sensors prepared using new hybrid nano- and conductive materials are imperative for the analysis of biological samples. Empiric estimation or molecular modeling are the two ways to find the optimal monomer/template/nanostructure ratio [46,47]. Theoretical calculation will also aid in the choice of the most suitable functional monomers to attain the best performance. Divergence of crosslinkers and the use of chemicals that can form different interactions at the same time will re-design the performance. In this direction, the field of multiple recognition has to be explored [48].

Another issue is the lack of commercial kits, despite the huge potential of these novel sensors and their compatibility with large-scale manufacturing for industrial applications [49]. This can be elucidated considering the unsurpassed advantage of antibodies, aptamers and other biomimetic materials in medical applications, where most of the money is invested [50]. In addition, numerous issues have been found regarding the integration of artificial recognition elements into transducers. It is essential to reduce the costs and simultaneously increase the mobility of detection systems. The synthesis of ligands to be used for the recognition of target analytes and the integration conditions should be matched with the mobility and the electronic components to be developed during the manufacturing phase. Nevertheless, the LODs attained with MIP-based sensors and their corresponding carbon-based composites are comparable or even higher compared to antibody-based methods [51]. Multifunctional MIP sensors provide great potential for high-end applications such as real-time analyte detection and wearable sensors and can complement traditional technologies. If MIPs are combined with cutting-edge technologies such as artificial intelligence, which will be the outcome of the desired practical solutions, they will be a sought-after material in commercialized kits undertaking detections in seconds.

4. Conclusions

In this review, a projection on the use of polymer-based materials in the related areas of forensic science has been provided. In particular, MIP-based materials and their combinations with nanostructures such as carbon nanomaterials for the detection of different target analytes including illicit drugs, toxins and biological agents have been highlighted. MIPs are beneficial over classical methods in terms of selectivity, sensitivity and sustainability. Moreover, easier application procedures and inexpensive production set-up will make them easier to handle. However, finding suitable functional monomers fitting the target molecules is still challenging. To conclude, polymeric-based materials are quickly and unceasingly growing platforms and their application in forensic science is yet in its infancy, demanding many novel designs.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/ 10.3390/macromol3020008/s1, Figure S1: Schematic representation of a chemical sensor and its main components. Figure S2: Schematic representation of an amperometric sensor with two electrodes. Figure S3: Schematic representation of an piezoelectric sensor. Figure S4: Schematic representation of static and dynamic quenching processes.

Funding: Financial support from the Community of Madrid within the framework of the Multi-year Agreement with the University of Alcalá in the line of action "Stimulus to Excellence for Permanent University Professors", Ref. EPU-INV/2020/012, is gratefully acknowledged.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The author declares no conflict of interest.

References

- Lodha, A.S.; Pandya, A.; Shukla, R.K. Nanotechnology: An applied and robust approach for forensic investigation. *Forensic Res. Criminol. Int. J.* 2016, 2, 00044.
- Diez Pascual, A.M. Carbon-Based Polymer Nanocomposites for High-Performance Applications II. *Polymers* 2022, 14, 870. [CrossRef] [PubMed]
- Chen, L.; Wang, X.; Lu, W.; Wu, X.; Li, J. Molecular imprinting: Perspectives and applications. *Chem. Soc. Rev.* 2016, 45, 2137–2211. [CrossRef]
- Díez-Pascual, A.M.; Cruz, D.L.; Redondo, A.L. Advanced Carbon-Based Polymeric Nanocomposites for Forensic Analysis. Polymers 2022, 14, 3598. [CrossRef]
- 5. Zhang, Y.; Wang, Q.; Zhao, X.; Ma, Y.; Zhang, H.; Pan, G. Molecularly Imprinted Nanomaterials with Stimuli Responsiveness for Applications in Biomedicine. *Molecules* **2023**, *28*, 918. [CrossRef] [PubMed]
- Figueiredo, E.C.; Sparrapan, R.; Sanvido, G.B.; Santos, M.G.; Arruda, M.A.; Eberlin, M.N. Quantitation of drugs via molecularly imprinted polymer solid phase extraction and electrospray ionization mass spectrometry: Benzodiazepines in human plasma. *Analyst* 2011, 136, 3753–3757. [CrossRef]
- Pan, J.; Chen, W.; Ma, Y.; Pan, G. Molecularly imprinted polymers as receptor mimics for selective recognition. *Chem. Soc. Rev.* 2018, 47, 5574–5587. [CrossRef]
- Anderson, R.A.; Ariffin, M.M.; Cormack, P.A.G.; Miller, E.I. Comparison of molecularly imprinted solid-phase extraction (MISPE) with classical solid-phase extraction (SPE) for the detection of benzodiazepines in post-mortem hair samples. *Forensic Sci. Int.* 2008, 174, 40–46. [CrossRef]
- 9. Panahi, Y.; Motaharian, A.; Hosseini, M.R.M.; Mehrpour, O. High sensitive and selective nano-molecularly imprinted polymer based electrochemical sensor for midazolam drug detection in pharmaceutical formulations and human urine samples. *Sens. Actuators B* **2018**, *273*, 1579–1586. [CrossRef]
- Rezaei, B.; Boroujeni, M.H.; Ensafi, A.A. A novel electrochemical nanocomposite imprinted sensor for the determination of lorazepam based on modified polypyrrole@sol-gel@gold nanoparticles/pencil graphite electrode. *Electrochim. Acta* 2014, 123, 332–339. [CrossRef]
- 11. Ensafi, A.A.; Zakery, M.; Rezaei, B. An optical sensor with specific binding sites for the detection of thioridazine hydrochloride based on ZnO-QDs coated with molecularly imprinted polymer. *Spectrochim. Acta Part A* **2019**, *206*, 460–465. [CrossRef] [PubMed]
- 12. Shi, H.; Xiang, W.; Liu, C.; Shi, H.; Zhou, Y.; Gao, L. Highly sensitive detection for cocaine using graphene oxide-aptamer based sensors in combination with tween 20. *Nanosci. Nanotechnol. Lett.* **2018**, *10*, 1707–1712. [CrossRef]
- 13. Florea, A.; Cowen, T.; Piletsky, S.; De Wael, K. Electrochemical sensing of cocaine in real samples based on electrodeposited biomimetic affinity ligands. *Analyst* **2019**, *144*, 4639–4646. [CrossRef] [PubMed]
- Rocha, R.G.; Ribeiro, J.S.; Santana, M.H.; Richter, E.M.; Muñoz, R.A. 3D-printing for forensic chemistry: Voltammetric determination of cocaine on additively manufactured graphene–polylactic acid electrodes. *Anal. Methods* 2021, 13, 1788–1794. [CrossRef]
- 15. Cardoso, R.M.; Mendonça, D.M.; Silva, W.P.; Silva, M.N.; Nossol, E.; da Silva, R.A.; Richter, E.M.; Muñoz, R.A. 3D printing for electroanalysis: From multiuse electrochemical cells to sensors. *Anal. Chim. Acta* **2018**, *1033*, 49–57. [CrossRef]
- 16. Hashemi, P.; Bagheri, H.; Afkhami, A.; Ardakani, Y.H.; Madrakian, T. Fabrication of a novel aptasensor based on three-dimensional reduced graphene oxide/polyaniline/gold nanoparticle composite as a novel platform for high sensitive and specific cocaine detection. *Anal. Chim. Acta* **2017**, *996*, 10–19. [CrossRef]
- 17. Saisahas, K.; Soleh, A.; Somsiri, S.; Senglan, P.; Promsuwan, K.; Saichanapan, J.; Kanatharana, P.; Thavarungkul, P.; Lee, K.; Chang, K.H. Electrochemical Sensor for Methamphetamine Detection Using Laser-Induced Porous Graphene Electrode. *Nanomaterials* **2022**, *12*, 73. [CrossRef]
- Riahifar, V.; Haghnazari, N.; Keshavarzi, F.; Ahmadi, E. A sensitive voltammetric sensor for methamphetamine determination based on modified glassy carbon electrode using Fe₃O₄@ poly pyrrole core-shell and graphene oxide. *Microchem. J.* 2021, 170, 106748. [CrossRef]
- 19. Granickowska, K.; PÜtz, M.; Hauser, F.M.; De Saeger, S.; Beloglazova, N.V. Capacitive sensing of N-formylamphetamine based on immobilized molecular imprinted polymers. *Biosens. Bioelectron.* **2017**, *92*, 741–747. [CrossRef]
- 20. Wester, N.; Mynttinen, E.; Etula, J.; Lilius, T.; Kalso, E.; Kauppinen, E.I.; Laurila, T.; Koskinen, J. Simultaneous detection of morphine and codeine in the presence of ascorbic acid and uric acid and in human plasma at nafion single-walled carbon nanotube thin-film electrode. *ACS Omega* **2019**, *4*, 17726–17734. [CrossRef]
- Mynttinen, E.; Wester, N.; Lilius, T.; Kalso, E.; Mikladal, B.; Varjos, I.; Sainio, S.; Jiang, H.; Kauppinen, E.I.; Koskinen, J. Electrochemical detection of oxycodone and its main metabolites with Nafion-coated single-walled carbon nanotube electrodes. *Anal. Chem.* 2020, *92*, 8218–8227. [CrossRef] [PubMed]
- 22. Ansari, S.; Masoum, S. A hybrid imprinted polymer based on magnetic graphene oxide and carbon dots for ultrasonic assisted dispersive solid-phase microextraction of oxycodone. *Microchem. J.* **2021**, *164*, 105988. [CrossRef]
- Sanchez-Gonzalez, J.; Salgueiro-Fernandez, R.; Cabarcos, P.; Bermejo, A.M.; Bermejo-Barrera, P.; Moreda-Pineiro, A. Cannabinoids assessment in plasma and urine by high performance liquid chromatography–tandem mass spectrometry after molecularly imprinted polymer microsolid-phase extraction. *Anal. Bioanal. Chem.* 2017, 409, 1207–1220. [CrossRef]

- 24. Sánchez-González, J.; Odoardi, S.; Bermejo, A.M.; Bermejo-Barrera, P.; Romolo, F.S.; Moreda-Piñeiro, A.; Strano-Rossi, S. Development of a micro-solid-phase extraction molecularly imprinted polymer technique for synthetic cannabinoids assessment in urine followed by liquid chromatography–tandem mass spectrometry. *J. Chromatogr. A* **2018**, 1550, 8–20. [CrossRef] [PubMed]
- Cela-Perez, M.C.; Bates, F.; Jimenez-Morigosa, C.; Lendoiro, E.; de Castro, A.; Cruz, A.; Lopez-Rivadullab, M.; Lopez-Vilarino, J.M.; Gonzalez-Rodriguez, M.V. Water-compatible imprinted pills for sensitive determination of cannabinoids in urine and oral fluid. J. Chromatogr. A 2016, 1429, 53–64. [CrossRef]
- Akgönüllü, S.; Battal, D.; Yalcin, M.S.; Yavuz, H.; Denizli, A. Rapid and sensitive detection of synthetic cannabinoids JWH-018, JWH-073 and their metabolites using molecularly imprinted polymer-coated QCM nanosensor in artificial saliva. *Microchem. J.* 2020, 153, 104454. [CrossRef]
- Alenus, J.; Ethirajan, A.; Horemans, F.; Weustenraed, A.; Csipai, P.; Gruber, J.; Peeters, M.; Cleij, T.J.; Wagner, P. Molecularly imprinted polymers as synthetic receptors for the QCM-D-based detection of l-nicotine in diluted saliva and urine samples. *Anal. Bioanal. Chem.* 2013, 405, 6479–6487. [CrossRef]
- Fu, K.; Zhang, R.; He, J.; Bai, H.; Zhang, G. Sensitive detection of ketamine with an electrochemical sensor based on UV-induced polymerized molecularly imprinted membranes at graphene and MOFs modified electrode. *Biosens. Bioelectron.* 2019, 143, 111636. [CrossRef]
- Lowdon, J.W.; Alkirkit, S.M.O.; Mewis, R.E.; Fulton, D.; Banks, C.E.; Sutcliffe, O.B.; Peeters, M. Engineering molecularly imprinted polymers (MIPs) for the selective extraction and quantification of the novel psychoactive substance (NPS) methoxphenidine and its regioisomers. *Analyst* 2018, 143, 2002–2007. [CrossRef]
- Kellens, E.; Bove, H.; Conradi, M.; D'Olieslaeger, L.; Wagner, P.; Landfester, K.; Ethirajan, A. Improved molecular imprinting based on colloidal particles made from miniemulsion: A case study on testosterone and its structural analogues. *Macromolecules* 2016, 49, 2559–2567. [CrossRef]
- Tu, X.; Muhammad, P.; Liu, J.; Ma, Y.; Wang, S.; Yin, D.; Liu, Z. Molecularly-imprinted polymer-based plasmonic immunosandwich assay for fast and ultrasensitive determination of trace glycoproteins in complex samples. *Anal. Chem.* 2016, *88*, 12363–12370. [CrossRef] [PubMed]
- 32. Han, J.; Zhuo, Y.; Chai, Y.Q.; Xiang, Y.; Yuan, R. New type of redox nanoprobe: C60-based nanomaterial and its application in electrochemical immunoassay for doping detection. *Anal. Chem.* **2015**, *87*, 1669–1675. [CrossRef] [PubMed]
- Lee, M.-H. Doping of transition metal dichalcogenides in molecularly imprinted conductive polymers for the ultrasensitive determination of 17-β estradiol in cell serum. *Biosens. Bioelectron.* 2020, *150*, 111901. [CrossRef] [PubMed]
- Chen, X.; Che, C.; Korolchuk, V.I.; Gan, F.; Pan, C.; Huang, K. Selenomethionine alleviates AFB1-induced damage in primary chicken hepatocytes by inhibiting CYP450 1A5 expression via upregulated SelW expression. *J. Agric. Food Chem.* 2017, 65, 2495–2502. [CrossRef]
- 35. Hu, Z.; Lustig, W.P.; Zhang, J.; Zheng, C.; Wang, H.; Teat, S.J.; Gong, Q.; Rudd, N.D.; Li, J. Efective detection of mycotoxins by a highly luminescent metal-organic framework. *J. Am. Chem. Soc.* **2015**, *137*, 16209–16215. [CrossRef]
- 36. Wang, C.; Qian, J.; An, K.; Ren, C.; Lu, X.; Hao, N.; Liu, Q.; Li, H.; Huang, X.; Wang, K. Fabrication of magnetically assembled aptasensing device for label-free determination of aflatoxin B1 based on EIS. *Biosens. Bioelectron.* **2018**, *108*, 69–75. [CrossRef]
- Bayram, E.; Yılmaz, E.; Uzun, L.; Say, R.; Denizli, A. Multiclonal plastic antibodies for selective aflatoxin extraction from food samples. *Food Chem.* 2017, 221, 829–837. [CrossRef]
- Lu, L.; Seenivasan, R.; Wang, Y.Z.; Yu, J.H.; Gunasekaran, S. An electrochemical immunosensor for rapid and sensitive detection of mycotoxins fumonisin B1 and deoxynivalenol. *Electrochim. Acta* 2016, 213, 89–97. [CrossRef]
- Zhou, J.; Qiu, X.; Su, K.; Xu, G.; Wang, P. Disposable poly(o-aminophenol)-carbon nanotubes modified screen print electrode-based enzyme sensor for electrochemical detection of marine toxin okadaic acid. Sens. Actuators B Chem. 2016, 235, 170–178. [CrossRef]
- Shendy, A.H.; Al-Ghobashy, M.A.; Gad Alla, S.A.; Lotfy, H.M. Development and validation of a modified QuEChERS protocol coupled to LC–MS/MS for simultaneous determination of multi-class antibiotic residues in honey. *Food Chem.* 2016, 190, 982–989. [CrossRef]
- 41. Shaheen, A. Design of heterostructured hybrids comprising ultrathin 2D bismuth tungstate nanosheets reinforced by chloramphenicol imprinted polymers used as biomimetic interfaces for mass-sensitive detection. *Colloids Surf. B Biointerfaces* **2020**, *188*, 110775. [CrossRef] [PubMed]
- 42. Cai, Q.; Zhang, L.; Zhao, P.; Lun, X.; Li, W.; Guo, Y.; Hou, X. A joint experimental-computational investigation: Metal organic framework as a vortex assisted dispersive micro-solid-phase extraction sorbent coupled with UPLC-MS/MS for the simultaneous determination of amphenicols and their metabolite in aquaculture water. *Microchem. J.* 2017, 130, 263–270.
- Munawar, A.; Tahir, M.A.; Shaheen, A.; Lieberzeit, P.A.; Khan, W.S.; Bajwa, S.Z. Investigating nanohybrid material based on 3D CNTs@Cu nanoparticle composite and imprinted polymer for highly selective detection of chloramphenicol. *J. Hazard. Mater.* 2018, 342, 96–106. [CrossRef] [PubMed]
- 44. Tabrizi, A.B.; Abdollahi, A. Determination of organothiophosphate insecticides in environmental water samples by a very simple and sensitive spectrofluorimetric method. *Bull. Environ. Contam. Toxicol.* **2015**, *95*, 536–541. [CrossRef]
- Ahmad, O.S.; Bedwell, T.S.; Esen, C.; Garcia-Cruz, A.; Piletsky, S.A. Molecularly imprinted polymers in electrochemical and optical sensors. *Trends Biotechnol.* 2019, 37, 294–309. [CrossRef] [PubMed]
- 46. Bates, F. Computational design of molecularly imprinted polymer for direct detection of melamine in milk. *Sep. Sci. Technol.* **2017**, 52, 1441–1453. [CrossRef]

- 47. Piletska, E.V.; Pink, D.; Karim, K.; Piletsky, S.A. Development of a computationally-designed polymeric adsorbent specific for mycotoxin patulin. *Analyst* 2017, 142, 4678–4683. [CrossRef]
- 48. Cao, Y.; Feng, T.; Xu, J.; Xue, C. Recent advances of molecularly imprinted polymer-based sensors in the detection of food safety hazard factors. *Biosens. Bioelectron.* **2019**, *141*, 111447. [CrossRef]
- 49. Uzun, L.; Turner, A.P. Molecularly-imprinted polymer sensors: Realising their potential. *Biosens. Bioelectron.* **2016**, *76*, 131–144. [CrossRef]
- 50. Luppa, P.; Junker, R. Point-of-Care Testing: Principles and Clinical Applications; Springer: Berlin/Heidelberg, Germany, 2018.
- Smolinska-Kempisty, K.; Guerreiro, A.; Canfarotta, F.; Cáceres, C.; Whitcombe, M.J.; Piletsky, S. A comparison of the performance of molecularly imprinted polymer nanoparticles for small molecule targets and antibodies in the ELISA format. *Sci. Rep.* 2016, *6*, 37638. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.