The development of a sensor based on molecularly imprinted polymer nanoparticles (nanoMIPs) and electrochemical impedance spectroscopy (EIS) for the detection of trace levels of cocaine is described in this paper. NanoMIPs for cocaine detection, synthesized using a solid phase, were applied as the sensing element. The nanoMIPs were first characterized by Transmission Electron Microscopy (TEM) and Dynamic Light Scattering and found to be ~148.35 ± 24.69 nm in size, using TEM. The nanoMIPs were then covalently attached to gold screen-printed electrodes and a cocaine direct binding assay was developed and optimized, using EIS as the sensing principle. EIS was recorded at a potential of 0.12 V over the frequency range from 0.1 Hz to 50 kHz, with a modulation voltage of 10 mV. The nanoMIPs sensor was able to detect cocaine in a linear range between 100 pg mL\(^{-1}\) and 50 ng mL\(^{-1}\) (R\(^2\) = 0.984; p-value = 0.00001) and with a limit of detection of 0.24 ng mL\(^{-1}\) (0.70 nM). The sensor showed no cross-reactivity toward morphine and a negligible response toward levamisole after optimizing the sensor surface blocking and assay conditions. The developed sensor has the potential to offer a highly sensitive, portable and cost-effective method for cocaine detection.

Cocaine is classified as a central nervous system stimulant and is the most abused drug in the world, after cannabis. With over 655 tons detained yearly, cocaine is also one of the most seized illicit drugs worldwide \(^1\) and is one of the major recreational drugs illegally trafficked in European countries, where there are more than 17.5 million users \(^2\). Illicit-drugs-related crimes are of huge concern due to the burden on law enforcement agencies (LEAs) and healthcare systems, with associated social and economic problems.

To detect, control and manage drugs of abuse trafficking, LEAs make use of the powerful olfactory system of “sniffer dogs”. After an appropriate training, dogs are able to “smell and detect” very low concentrations (in the range of ppb) of illicit drugs concealed in various items, including packages and containers \(^3\)\(^4\). However, sniffer dogs can be prone to work fatigue and can be deceived by handlers \(^5\). Forensic chemistry can provide evidence on whether a suspected substance contains illegal drugs by means of reproducible scientific methods, thus providing unequivocal evidence of the drug-related offence \(^6\). Generally, suspected samples (either biological or environmental) are analyzed by presumptive and confirmatory tests. The former comes as rapid detection kits or devices, which are mainly screening tests indicating whether illegal drugs may be present or not \(^7\). Currently, onsite screening methods rely on Ion Mobility Spectroscopy (IMS) \(^8\), competitive inhibition immunoassay \(^9\) and colorimetric tests \(^10\). Nevertheless, these methods provide only qualitative or semi-quantitative results; they are prone to false-positive and negative results and many require trained personnel for operation. Confirmatory analyses are currently performed in accredited ISO 17025 laboratories, through several complex procedures and expensive analytical tools, such as GC–MS and LC-MS \(^10\).

Therefore, there is a need for new technologies that can provide fast screening tests with a high level of sensitivity and specificity. These technologies may speed up the investigative activities, thus reducing the false-positive/false-negative rate and, hence, confining the demand of confirmatory tests only on truly positive samples. Hence, the aim of this work was to develop a rapid and specific sensor able to detect cocaine at trace levels, to be used in diverse onsite testing scenarios, to tackle cocaine trafficking. While it is difficult to reproduce the complexity of the olfactory systems, electrochemical biosensors can offer an analogous way to transform the binding of the analyte to its sensing receptor into an electrical signal. Examples of electrochemical sensors for cocaine detection using aptamers or biomolecules have already been described in the literature \(^11\)\(^12\)\(^13\). Among all the electrochemical techniques available, in recent years, electrochemical impedance spectroscopy (EIS) has gained attention due to its ability of detecting
the target molecules at very low concentrations. Compared to amperometry and potentiometry, EIS is able to detect minimal changes at the sensor surface boundaries, thus leading to several advantages, such as a wide linear range, low limits of detection and direct assay mode. The method can also preserve the sample for further confirmatory analysis [14][15]. The basic principle behind EIS is the electrical impedance, which indicates the resistance that an electrical circuit presents to the flow of an alternating current (AC), generated by applying a small alternating voltage (AV) [16]. EIS can be performed with or without a redox probe (redox couple), such as potassium ferricyanide/ferrocyanide ([Fe(CN)]$_6^{3-/4-}$), added to the solution. When the redox probe is present, faradic current is gathered, thus leading to faradic EIS sensor. In this case, the resistance charge transfer (Rct) electrical element is usually affected by the events occurring at the electrode surface, such as the binding between a sensing receptor and its target [17].

In order to obtain a sensor suitable for onsite testing, it is highly desirable to employ stable and robust sensing elements. Previous works have demonstrated that the use of molecularly imprinted polymers in electrochemical sensing can result in robust, sensitive and specific diagnostic systems [18][19][20]. Particularly, molecularly imprinted nanoparticles (nanoMIPs), prepared using a solid phase, have shown to be a powerful and robust mimic of antibodies in sensors and assays [21][22][23], while providing convenient and animal-free synthesis. NanoMIPs have shown to be stable at a wide range of temperature and to possess a long shelf-life, with no need of refrigeration and preservation [22][24]. As such, nanoMIPs are the ideal receptor candidate for sensors that have to operate in unpredictable environmental conditions, which might contain denaturing agents and degrading enzymes capable of denaturing bio-derived receptors (protein, antibodies and aptamers).

Therefore, nanoMIPs and EIS were applied in this work for the first time to develop a highly sensitive and specific affinity sensor to detect traces of cocaine. The resulting nanoMIPs EIS sensor was able to detect cocaine in the low nM range, demonstrating potential application as a cheap and portable analytical tool to use in investigative activities of illicit drugs trafficking.

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