Enhancing electrode sensitivity for detection of antibiotic contamination in water using functionalized magnetic nanoparticles

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Abstract

Portable electrochemical sensors for the detection of antibiotic (AB) contamination are gaining interest as point of care devices and as in-field analytical sensors. In that respect, the low cost and high sensitivity of the sensors is a major benefit. In this study, a low-cost indicator electrode was designed against neomycin (NEO), gatifloxacin (GAT) and sulfathiazole sodium (STNa) as examples of ABs with high probability of contaminating animal feed/water. Ionophore functionalized magnetic nanoparticles were incorporated into the electrode structure to enhance its performance. The detector was able to discriminate (within 10 s) AB clean from AB contaminated water in ranges of 10^{-3} – 10^{-8} M, of 10^{-2} – 10^{-8} M, and of 10^{-2} – 10^{-13} M for NEO, GAT and STNa, respectively. The developed electrodes can be fabricated at low cost; with promising fast and high sensitivity for the detection of AB contamination in water.

Keywords Antibiotic contamination · Electrode · Antibiotic resistance

Abbreviations

AB	Antibiotic
NEO	Neomycin
GAT	Gatifloxacin
STNa	Sulfathiazole sodium
IUA	Irrational use of antibiotics:
USDA	US Department of Agriculture
DI	De-ionized
THF	Tetrahydrofuran
cPVC	Carboxylated polyvinylchloride
DOP	Dioctyl phthalate
β -CD	β -Cyclodextrin
OA	Oleic acid

1 Background

Irrational use of antibiotics (IUA) is a global concern. One form of IUA is the use of antibiotics (ABs) in animal husbandries as growth promoters or for prophylaxis against bacterial infection [1]. This may take place by adding the ABs to the cattle feed or their drinking water [2] or by directly injecting/infusing the animals with ABs [1]. Another form of IUA is their use in aquacultures for a similar purposes [3]. This practice is banned by many governments but this is not easily acceptable by farmers and those working in farming industries [4]. For instance, the US department of agriculture (USDA) had rejected the WHO recommendations to cease the use of ABs in animal feed [5]. This IUA in agriculture and aquaculture hugely contributes to developing bacterial resistance and spreading of antibiotic-resistant infections in humans [1]. This is due to the possibility of the ABs disposal into the surrounding environment compartments such as

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surface waters and soil, or by being a direct source of resistant bacterial strains [6]. It is alarming that, despite the awareness on developing bacterial resistance due to excessive use of ABs, there is a global warning that the use of ABs in livestock is estimated to increase from 63 to 67% in the period between 2010 and 2030 [7]. Another important source of ABs contamination in the environment is their disposal from healthcare facilities [8]. Against this background, there is a continuous demand on portable sensing devices for detecting ABs in environment. To this end, the device should be portable, require minimal technical experience to operate, and provide excellent sensitivity. Multiplexing, i.e., the ability to monitor several ABs of AB classes in one test, and low cost are also appreciated.

Literature review revealed several multi-residue screening assays for the determination of ABs in water. Most of these methods rely on the state of the art LC–MS/MS based techniques [9–13]. These assays offer excellent reliability, precision, and accuracy but they require extensive sample preparation procedures for sample clean-up and concentration and must be operated by well trained technicians. In addition to that, the running cost of LC–MS/MS methods is inherently high and it cannot be moved to application sites which adds a burden of sample transfer to central laboratories [14, 15]. Other laboratory based methods include electrophoresis [16–20] and enzyme assay (ELISA) [21, 22].

Electrochemical sensors are gaining interest as portable alternatives for in-field analysis, especially those utilizing nanoparticles for providing a large surface area for interaction which enhances the electrochemical sensitivity [23–25]. In this respect, immuno-sensor based devices have been described [26, 27]. These antibody-based alternatives are highly specific but being a biological product the repeatability of mass production and the product stability are compromised [28]. Other reports have investigated the aptamer-based sensors for the detection of ABs [29–34]. These methods are attractive in terms of cost where the preparation expenses of aptamers are relatively reasonable as well as their durability but their design requires special expertise that is not always available [35].

The use of non-biologically conjugated nanoparticles may be a good solution. They can be reproducibly synthesized at low cost. Meanwhile, they will retain appropriate stability. Literature survey revealed few non-biological electrochemistry-based sensors for the determination of neomycin (NEO) [36, 37], gatifloxacin (GAT) [38–40] and sulfathiazole sodium (STNa) [41]. The aim of this study was to enhance the sensitivity of non-biologically based electrochemical methods for the three drugs by introducing surface-modified magnetic nanoparticles into the electrode inner solution.

2 Methods

FeCl_3 , FeSO_4 and ammonia solution (25%) were obtained from Al-Gomhoreya for Chemical Industries in Cairo, Egypt. Reference standards for NEO (purity: 99.89%), GAT (purity: 99.95%) and STNa (purity: 99.99%) were generously supplied from National Organization for Drug Quality Control and Research (NODQCAR). De-ionized (DI) water was produced in house by a Milli-Q system (Milford, Connecticut, USA). A Jenway pH/mV/ °C meter 3505 by Barloworld Scientific Ltd, (Staffordshire, UK) equipped with an Aldrich Ag/AgCl, double junction glass reference electrode (Z113107; Sigma Aldrich, St. Louis; USA) was used for the measurement. A JEM-2100Plus transmission electron microscope (Jeol, MA; USA) was used.

2.1 Synthesis and surface modification of the nanoparticles

The thermal co-precipitation method was adopted for the preparation of magnetic iron nanoparticles (MNPs) using FeCl_3 , FeSO_4 and ammonia (25%) [42, 43]. Briefly, 1.1 g of FeCl_3 and 0.6 g of FeSO_4 were weighed and dissolved in de-ionized water (33 mL). The solution was heated at 70°C for 15 min with stirring [42, 43]. Fifteen mL of ammonia solution (25%) was added until a black precipitate was formed (magnetite Fe_3O_4) and collected by an external magnet. The shape and size of the prepared MNPs were examined. One drop of the suspension was spread on the carbon grid and left to dry. The dried spot was then observed under a transmission electron microscope at electron acceleration voltage of 80 kV. MNPs were surface-coated with oleic acid (OA) as described in [44] to prepare OA-MNPs. Alternatively, 2-hydroxyl- β -cyclodextrin-coated MNPs (2 β -CD-MNP) were prepared by dispersing MNPs into tetrahydrofuran (THF; 1 mL) containing a mixture of carboxylated polyvinylchloride (cPVC; 0.2 g), dioctyl phthalate (DOP; 35 μL) and β -cyclodextrin (β -CD; 0.1 g) and left to dry in air while spread on glass sheet [45].

2.2 Synthesis of the membrane and electrode assembling

The membrane was synthesized by mixing 0.04 g β -CD, 0.2 g of cPVC, and 35 μL of DOP in a total volume of 5.6 mL THF. The mixture was allowed to dry in air on a glass sheet until a flexible membrane was obtained [45, 46].

The conventional automatic pipette blue-tip (1 mL) was used as a case for the electrode. Briefly, the tip was wetted with THF and placed on a previously cut membrane sheet which was slightly larger in diameter (1 mm) than

the tip opening. THF was allowed to dry to fix the membrane on the blue tip opening. The electrode inner solution was filled into the tip (MNP suspension and equimolar solution of KCl and the tested drug solution; 100 μL of each). A silver wire connected to the potentiometer was inserted carefully into the mini electrode cavity and the upper wider opening of the blue tip was closed by a parafilm to prevent contamination. The electrode was soaked in a solution of the target analyte for conditioning before use. Figure 1 illustrates the setup of the electrode. The electrochemical cell was assembled using the designed electrode as an indicator electrode and Ag/AgCl, double junction glass as a reference electrode both connected by copper wire to the Jenway pH/mV/ $^{\circ}\text{C}$ meter for measurement (Cell assembly: Ag/membrane/test solution//KCl salt bridge//Ag/AgCl).

2.3 Potentiometric measurement

Measurement was performed by dipping the reference and indicator electrodes in the working solution of the tested drugs and recording the change in electromotive force (emf) over the ranges 1×10^{-3} – 1×10^{-8} , 1×10^{-2} – 1×10^{-13} , 1×10^{-2} – 1×10^{-8} for NEO, STNa and GAT, respectively. Electrodes were allowed to equilibrate

under stirring. Measurements was performed at neutral conditions (pH 7; 25 $^{\circ}\text{C}$) with washing in distilled water in between. The potential difference (mV) between the indicator electrode and the reference electrode was recorded. The durability of the electrode was investigated by monitoring its ability to detect AB contamination over 3 days.

2.4 Evaluation of response time

The electrode response time is the time required to reach a stable electrochemical signal. The stable electrochemical signal was recorded and the time to reach the stable signal was determined. This was based on recording a stable reading with average RSD < 4%.

2.5 Method optimization

Limit of detection (LOD); the limit of detection was experimentally tested as the concentration below which the analytical response is not detected. In this experiment, serial dilutions (10-fold) of the stock solution were prepared and tested as working solutions (10^{-3} – 10^{-8} M, 10^{-2} – 10^{-8} M 10^{-2} – 10^{-13} M for NEO, STNa, and GAT, respectively). The measurement was performed by dipping the electrode in the working solution of the tested drugs with washing in

Fig. 1 An illustration of the proposed electrode setup

distilled water in between. Potential difference (mV) was recorded and the concentration at which no detectable change in emf was observed was considered the LOD [47].

Selectivity; the selectivity of the test was determined for validating the proposed detection assay by observing signal change in blank sample at variable pH values (6, 7, 8). The experiment was extended to be applied in tap water to resemble the animal drinking water [48].

3 Results

Synthesis of nanoparticles: MNPs were synthesized by the thermal co-precipitation method. The synthesized nanoparticles were negatively charged (-18 mV), spherical in shape and of an average size of $5\text{--}15$ nm as evident from their transmission electron microscope image (Fig. 2) [44]. The synthesized particles were subsequently surface-coated with the lipophilic OA or β -CD [49].

3.1 Indicator electrode performance

Aminoglycosides (NEO): The electrode inner solution composed of OA-MNPs, a stock solution of NEO (1×10^{-3} M) and KCl (1×10^{-3} M) was able to detect a potential difference on contact with blank samples (tap water) and samples containing variable concentrations of NEO. By using this mini-electrode, tap water recorded a potential difference of 58 mV with RSD less than 2% ($n = 3$). NEO solutions of variable concentrations ($10^{-3}\text{--}10^{-8}$ M) recorded a potential

difference of $124\text{--}66$ mV. The measurements were stable where the RSD did not exceed 4% for all concentration when measurements were repeated in triplicate.

Sulfonamides (STNa): Good detection capabilities were obtained on using OA-MNPs, a variation in potential difference was observed between blank samples (tap water; 320 mV) and samples spiked with STNa in range of $10^{-2}\text{--}0\text{--}10^{-13}$ M which recorded a potential difference of $1808\text{--}515$ mV.

Fluoroquinolones (GAT): The inner filling solution contained 2β -CD-MNP along with the GAT stock solution (10^{-2} M) and the KCl (10^{-2} M). This setup recorded a potential difference of 178 mV for tap water while a potential difference of $149\text{--}100$ mV was measured in GAT-contaminated water over the concentration $10^{-2}\text{--}10^{-8}$ M. The electrode signal was stable with RSD not exceeding 3% for all measurements ($n = 3$).

The average response time to reach stable analytical signal was found to be 10 s. After those 10 s, the electrode signal reached an equilibration state where a stable signal was observed with RSD found to be ranging from 1 to 4% for NEO, $0.2\text{--}3\%$ for STNa, and $0.4\text{--}2\%$ for GAT. Although the electrode was designed to be disposable, it was capable of detecting AB contamination over 3 days which indicate the durability of the electrode.

3.2 Method optimization

Limit of detection: Limit of detection was found to be 10^{-8} , 10^{-13} and 10^{-8} M for NEO, STNa and GAT, respectively.

Indicator selectivity: The selectivity was tested as the absence of analytical signals in blank sample (distilled and tap water). No analytical signal was observed in both cases (even at variable pH values) which indicates the selectivity of the indicator electrode.

4 Discussion

Numerous reports have indicated the irrational use of these antibiotics in animal husbandries and aquatic cultures for prophylaxis against infectious diseases and as growth promoters [50]. For instance aminoglycosides were reported to be irrationally used in 18% of poultry farms in Ghana [51]. In the same context, sulfonamides were reported to be used in 53% of farms in Cameroon [52] and the fluoroquinolones (the class to which GAT belongs) was reported to be used in 57 and 11% of farms in Cameroon and Ghana, respectively [51, 52].

In this study, a simple and low-cost mini-indicator electrode with excellent sensitivity was designed for the detection of NEO, STNa, and GAT. The indicator electrode is

Fig. 2 A transmission electron microscope image of the magnetic iron nanoparticles

designed to give an indication on the presence or absence of antibiotics in water samples in field. For this purpose, the electrode was designed to act as a disposable sensor which mandates a low-cost fabrication. To this end, the electrode casing was chosen as the disposable pipette tip. The tip was filled by the inner solution for each drug and closed from one end by the electrode membrane while from the other end a Parafilm® was used to seal the mini-electrode and prevent evaporation of its components. The design of the electrode is presented in Fig. 1.

cPVC was recruited as a membrane support material. This selection is based on its improved adhesive property over the non-functionalized PVC based supports [53]. In addition to that the carboxyl function group tends to support the ionophore mediated selectivity and counteract the reduction of selectivity which may be induced by the charged membrane additives. This probably via acting as an inherent ion exchanger [53–55].

β -CD was used as an ionophore through which the ABs diffuse across the concentration gradient. β -CD is oligosaccharide composed of six glucose units arranged to form a hydrophobic inner cavity and a hydrophilic outer side. The drug can be included in a host guest complex in the β -CD nano-sized cavities which acts as a molecular recognition and inclusion complexation site [56]. Those sites acts as molecular receptors which form hydrogen bonds, hydrophobic interactions and Van der Waals forces within their hydrophobic cavity to support the cooperative binding processes with the analyte [57–59]. The molecular recognition of β -CD is dependent predominantly on hydrogen bonding and its orientation in the β -CD molecule [56, 60, 61].

The electrodes performance (analytical signal) is based on generating a potential difference (mV) across the membrane as a result of selective permeability and exchange of the analyte between the indicator electrode inner solution (reference solution) and the sample solution through the ionophore which are pores embedded into the membrane (Fig. 1) [61]. These ionophores, which show size and usually binding selectivity to the analyte, contribute along with the inner solution to the selectivity of the membrane [62].

Our literature review revealed that polymer membranes fortified with lipophilic ion exchangers exhibit large and reproducible potentiometric responses toward poly-ions, specifically those of biomedical relevance [63]. Furthermore, the lipophilic ions can reduce resistance and cease the counter ion effect [53]. More importantly, the lipophilic additives, specifically anionic ones, are reported to enhance the selectivity to nitrogen-containing organic bases [64]. Specifically OA was previously reported to act as a lipophilic additive in lidocaine selective electrodes [65]. In this context, the OA conjugation on the MNP surface may act as an ion-exchanger with enhanced

availability and exposure for interaction. This is primarily due to the large surface area of magnetic nanoparticles and secondly due to the proper dispersion of the nanoparticles being in a colloidal state. These two factors together may contribute to the availability of reaction sites for ion-exchange process which in turn is expected to enhance electrode sensitivity [66]. Being magnetic enables its collection from the matrix by an external magnet whenever a leakage occur [67]. Based on this, OA-MNPs were incorporated in the design of the mini-indicator. The particles were in-house synthesized by the thermal co-precipitation method and subsequently coated with OA. In doing this, we benefited from the large surface area the nanoparticles has to offer as well as the lipophilicity as imparted by the OA which enhance the potentiometric response of poly-ions and selectively interacts with NEO [66].

The electrode was challenged to record potential difference between AB-clean and AB-contaminated samples. For sensing NEO, the electrode inner solution was composed of OA-MNPs, a stock solution of NEO and KCl. The electrode was able to detect a potential difference on contact with blank samples (tap water) and variable concentrations of NEO in range of 10^{-3} – 10^{-8} M. This may be explained by the reported selective interaction and complex formation between Fatty acids, including OA, and aminoglycosides, specifically NEO [68, 69]. This is in addition to the possible electrostatic interaction between poly-amines of NEO and the fatty acid [70, 71]. In the same context, for detecting STNa (which was recruited as a representative of sulfonamide antibiotics), good detection capabilities were obtained on using OA-MNPs for detecting STNa in range 10^{-2} – 10^{-13} M. This may be explained by the inherent ability of STNa to interact with carboxylic acids via its amine groups [72].

In case of using the OA-MNP in the inner solution of the electrode for sensing GAT, no response was observed. This may be explained by the chemical structure of GAT which has carboxylic acid moiety attached to it, preventing its interaction with fatty acids. Previous research has shown that β -CD can form an inclusion complex with GAT and thereby enhance its electrochemical detection [61]. This may be explained by the possible hydrogen bonding interaction between the hydroxyl groups of 2β -CD and the carboxylate and ketone moiety of GAT [38]. These findings had encouraged us to coat MNP with β -CD. Accordingly, the filling solution was changed from containing OA-MNP to contain 2β -CD-MNP along with the GAT stock solution and the KCl. On doing this, the indicator electrode was able to detect a potential difference on changing the GAT concentration in the range of 10^{-2} – 10^{-8} M.

It is important to mention that the AB contaminants can be present in extremely minute concentrations. At such low contaminant levels, the electrochemical response to

varying concentration becomes progressively less. This implies more closely spaced calibration points to evaluate the concentration. Yet, the percentage error per mV on the calculated concentration will be progressively higher as the slope reduces. It is also important to mention that the deviation from the Nernstian slope is likely to happen in the presence of counter ions, ionophores or at very low concentrations [73]. In that sense, the detection of the presence of AB contamination will be a more useful application than its quantitation [74]. A proposed flow-chart for application is presented in Fig. 3. Where the electrode can give a preliminary insight into the cleanliness of water sample as compared to tap water and spiked AB samples (which are considered as a reference standard for our application). This detection is based on a potential difference between the clean and contaminated sample. Only suspected contaminated samples can be transferred to central laboratories for confirmation and quantitation purposes. This is expected to reduce the work-flow on the central laboratories. The designed simple electrodes exhibit fast sensing dynamics where a stable potential difference can be recorded after 10 s. Finally, the performance of the proposed electrode was compared with a reference

method and results are tabulated in Table 1. This is in terms of application range, LOD and the response time. The proposed electrodes had a larger application range, a lower limit of detection and a faster response time than those reported in literature [36, 38, 41].

5 Conclusions

In this study, a cheap and simple indicator electrode with preliminary capabilities for discriminating AB-clean and AB-contaminated water samples was fabricated. The electrode is only based on micropipette tips as a casing and a tiny in-house made selective membrane. Meanwhile, the electrode filling is also not expensive where it is based on functionalized MNP which can be easily synthesized in-house. The electrode showed promising preliminary response for detecting the presence of NEO, STNa, or GAT provided the corresponding inner filling solution is added. Furthermore, the detection dynamics of the electrode is fast where it reaches a stable potential difference record in few seconds.

Fig. 3 A flow-chart for application of the propose electrode

Table 1 Comparison of the proposed method with the previously reported sensors

	NEO		STNa		GAT	
	Proposed assay ^a	Reference method [36]	Proposed assay ^b	Reference method [41]	Proposed assay ^b	Reference method [38]
Limit of detection (M)	1×10^{-8}	7.63×10^{-9}	1×10^{-13}	4.0×10^{-8}	1×10^{-8}	2×10^{-5}
Range	1×10^{-3} – 1×10^{-8}	7×10^{-6} – 9×10^{-9}	1×10^{-2} – 1×10^{-13}	9.7×10^{-8} – 5.0×10^{-5}	1×10^{-2} – 1×10^{-8}	5×10^{-5} – 150×10^{-5}
Response time (S)	10	800	10	11	10	–

^aWider response range and a shorter response time were achieved

^bWider response range and enhanced sensitivity were achieved

The proposed electrode can be easily transferred to a (potential) AB application site such as farms and animal husbandries for the determination of AB contaminants in animal drinking water. This is a characteristic which represents a clear prerequisite for in-field analytical techniques and cannot be conveyed by laboratory based instruments. The test is intended to give an indication on the presence of AB contaminants and will direct the analysts to perform more targeted LC–MS/MS based assays in a central laboratory facility. Such procedure is expected to reduce the work-flow and analysis cost on central laboratories and have a positive impact on the screening potentials and capabilities of the authorities. In addition to that, the preparation of the electrode is rather simple and of low cost. It does not require special expertise for preparation like those required for aptasensor-based electrodes. Also, being a non-biological product, their stability does not represent a technical problem, like with immune-sensors. The proposed electrode exhibits a favorable analytical performance over previously reported non-biologically based ones. It exhibits a faster response, improved sensitivity and a wider application range where the LOD is 1×10^{-8} , 1×10^{-13} and 1×10^{-8} for NEO, STNa and GAT, respectively [36, 38, 41]. In conclusion, the designed electrode shows preliminary capabilities to generate fast signal in the presence or absence of AB contamination in the sample at a remarkably high sensitivity (10^{-8} or even 10^{-13} M, depending on the target molecule) and at very low cost. Future studies include further optimization and investigation of the electrode applicability and selectivity towards various organic molecules including members of the same AB class.

Authors contributions FF carried out the experimental studies via synthesis of the particles, assembling the mini-electrode, carried out the analytical measurements. WN conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials Data are included in the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Consent for publication Authors and their institutes approve the publication of the data by Springer.

References

- Landers TF et al (2012) A review of antibiotic use in food animals: perspective, policy, and potential. Public Health Rep (Washington, D.C.: 1974) 127(1):4–22
- Food and Drug Administration (2013) Phasing out certain antibiotic use in farm animals. <https://www.fda.gov/consumers/consumer-updates/phasing-out-certain-antibiotic-use-farm-animals>
- Serrano PH (2005) Responsible use of antibiotics in aquaculture. Food & Agriculture Org, Rome
- Wallinga D, Burch DG (2013) Does adding routine antibiotics to animal feed pose a serious risk to human health? BMJ 347:f4214
- Heinzerling L (2013) The FDA's continuing incapacity on livestock antibiotics. Stan Envtl LJ 33:325
- Salaheen S et al (2019) Antimicrobial resistance among Escherichia coli isolated from veal calf operations in Pennsylvania. Foodborne Pathogens Dis 16(1):74–80
- Price LB, Koch BJ, Hungate BA (2015) Ominous projections for global antibiotic use in food-animal production. Proc Natl Acad Sci 112(18):5554–5555
- Jha RR et al (2017) Ultrasound-assisted emulsification microextraction based on a solidified floating organic droplet for the rapid determination of 19 antibiotics as environmental pollutants in hospital drainage and Gomti river water. J Sep Sci 40(13):2694–2702
- Ngumba E et al (2016) A multiresidue analytical method for trace level determination of antibiotics and antiretroviral drugs in wastewater and surface water using SPE-LC-MS/MS and matrix-matched standards. Anal Methods 8(37):6720–6729
- Chitescu CL et al (2015) High sensitive multiresidue analysis of pharmaceuticals and antifungals in surface water using U-HPLC-Q-Exactive Orbitrap HRMS. Application to the Danube river basin on the Romanian territory. Sci Total Environ 532:501–511

11. Gusmaroli L, Insa S, Petrovic M (2018) Development of an online SPE-UHPLC-MS/MS method for the multiresidue analysis of the 17 compounds from the EU "Watch list". *Anal Bioanal Chem* 410(17):4165–4176
12. Gao J et al (2016) Multiclass method for the quantification of 92 veterinary antimicrobial drugs in livestock excreta, wastewater, and surface water by liquid chromatography with tandem mass spectrometry. *J Sep Sci* 39(21):4086–4095
13. Qian M et al (2019) A high-throughput screening method for determination of multi-antibiotics in animal feed. *J Sep Sci* 42:2968–2976
14. Mohapatra S, Padhye LP, Mukherji S (2018) Challenges in detection of antibiotics in wastewater matrix. In: *Environmental contaminants*. Springer, pp 3–20
15. Kim C et al (2018) A review of analytical procedures for the simultaneous determination of medically important veterinary antibiotics in environmental water: sample preparation, liquid chromatography, and mass spectrometry. *J Environ Manag* 217:629–645
16. Dai T et al (2017) Determination of sulfonamide residues in food by capillary zone electrophoresis with on-line chemiluminescence detection based on an Ag(III) complex. *Int J Mol Sci* 18(6):1286
17. Jang MG, Jang MD, Park JH (2017) Doxycycline as a new chiral selector in capillary electrophoresis. *J Chromatogr A* 1508:176–181
18. Ji H et al (2017) Sensitive determination of sulfonamides in environmental water by capillary electrophoresis coupled with both silvering detection window and in-capillary optical fiber light-emitting diode-induced fluorescence detector. *Electrophoresis* 38(3–4):452–459
19. Moreno-González D et al (2017) Evaluation of a multiresidue capillary electrophoresis-quadrupole-time-of-flight mass spectrometry method for the determination of antibiotics in milk samples. *J Chromatogr A* 1510:100–107
20. Wang Y et al (2017) Novel label-free and high-throughput microchip electrophoresis platform for multiplex antibiotic residues detection based on aptamer probes and target catalyzed hairpin assembly for signal amplification. *Biosens Bioelectron* 97:100–106
21. Kong D et al (2017) Development of ic-ELISA and lateral-flow immunochromatographic assay strip for the detection of vancomycin in raw milk and animal feed. *Food Agric Immunol* 28(3):414–426
22. Tang S-P et al (2017) A pseudo-ELISA based on molecularly imprinted nanoparticles for detection of gentamicin in real samples. *Anal Methods* 9(19):2853–2858
23. Munteanu F-D et al (2018) Detection of antibiotics and evaluation of antibacterial activity with screen-printed electrodes. *Sensors (Basel, Switzerland)* 18(3):901
24. Zhu C et al (2015) Electrochemical sensors and biosensors based on nanomaterials and nanostructures. *Anal Chem* 87(1):230–249
25. Li N-N et al (2015) Fe₃O₄@ZrO₂ magnetic nanoparticles as a new electrode material for sensitive determination of organophosphorus agents. *Anal Methods* 7(12):5053–5059
26. Pollap A, Kochana J (2019) Electrochemical immunosensors for antibiotic detection. *Biosensors* 9(2):61
27. Zhang Z et al (2019) A competitive immunosensor for ultra-sensitive detection of sulphonamides from environmental waters using silver nanoparticles decorated single-walled carbon nanohorns as labels. *Chemosphere* 225:282–287
28. Mishra G, Sharma V, Mishra R (2018) Electrochemical aptasensors for food and environmental safeguarding: a review. *Biosensors* 8(2):28
29. Zhou N et al (2015) A label-free electrochemical aptasensor for the detection of kanamycin in milk. *Anal Methods* 7(5):1991–1996
30. Wang M et al (2018) Electrochemical biosensing based on protein-directed carbon nanospheres embedded with SnO_x and TiO₂ nanocrystals for sensitive detection of tobramycin. *Biosens Bioelectron* 99:176–185
31. Ghanbari K, Roushani M (2018) A novel electrochemical aptasensor for highly sensitive and quantitative detection of the streptomycin antibiotic. *Bioelectrochemistry* 120:43–48
32. Aghajari R, Azadbakht A (2018) Amplified detection of streptomycin using aptamer-conjugated palladium nanoparticles decorated on chitosan-carbon nanotube. *Anal Biochem* 547:57–65
33. Roushani M, Ghanbari K (2018) A novel aptasensor based on gold nanorods/ZnS QDs-modified electrode for evaluation of streptomycin antibiotic. *Anal Methods* 10(43):5197–5204
34. Sharma A et al (2017) Disposable and portable aptamer functionalized impedimetric sensor for detection of kanamycin residue in milk sample. *Sens Actuators B Chem* 245:507–515
35. Groher F, Suess B (2016) In vitro selection of antibiotic-binding aptamers. *Methods* 106:42–50
36. Lian W et al (2013) Electrochemical sensor using neomycin-imprinted film as recognition element based on chitosan-silver nanoparticles/graphene-multiwalled carbon nanotubes composites modified electrode. *Biosens Bioelectron* 44:70–76
37. Hamnca S et al (2017) Electrochemical determination of neomycin and norfloxacin at a novel polymer nanocomposite electrode in aqueous solution. *Anal Lett* 50(12):1887–1896
38. Jiang Z, Li G, Zhang M (2016) Electrochemical sensor based on electro-polymerization of β -cyclodextrin and reduced-graphene oxide on glassy carbon electrode for determination of gatifloxacin. *Sens Actuators B Chem* 228:59–65
39. Zhang F et al (2013) Simultaneous determination of ofloxacin and gatifloxacin on cysteine acid modified electrode in the presence of sodium dodecyl benzene sulfonate. *Bioelectrochemistry* 89:42–49
40. Radi A-E et al (2010) Electrochemical determination of gatifloxacin, moxifloxacin and sparfloxacin fluoroquinolonic antibiotics on glassy carbon electrode in pharmaceutical formulations. *Drug Test Anal* 2(8):397–400
41. Msagati TAM, Ngila JC (2002) Voltammetric detection of sulfonamides at a poly(3-methylthiophene) electrode. *Talanta* 58(3):605–610
42. Liu ZL et al (2004) Synthesis and characterization of ultrafine well-dispersed magnetic nanoparticles. *J Magn Magn Mater* 283(2–3):258–262
43. Axéll T et al (1996) Oral white lesions with special reference to precancerous and tobacco-related lesions: conclusions of an international symposium held in Uppsala, Sweden, May 18–21 1994. *J Oral Pathol Med* 25(2):49–54
44. Shebl RI, Farouk F, Azzazy HME-S (2017) Effect of surface charge and hydrophobicity modulation on the antibacterial and antibiofilm potential of magnetic iron nanoparticles. *J Nanomater*. <https://doi.org/10.1155/2017/3528295>
45. El-Kosasy AM et al (2014) A novel potentiometric detection strategy for the determination of amlodipine besylate based on functionalized particles. *Electroanalysis* 26(5):1031–1038
46. Abd El-Rahman MK et al (2015) Novel strategy for online monitoring of the degradation kinetics of propantheline bromide via a calixarene-based ion-selective electrode. *Talanta* 132:52–58
47. Guideline, I.H.T. (2005) Validation of analytical procedures: text and methodology Q2 (R1). In: *International conference on harmonization*, Geneva, Switzerland
48. Tohda K et al (2001) Studies on the matched potential method for determining the selectivity coefficients of ion-selective

- electrodes based on neutral ionophores: experimental and theoretical verification. *Anal Sci* 17(6):733–743
49. Kakhki RM (2015) Application of magnetic nanoparticles modified with cyclodextrins as efficient adsorbents in separation systems. *J Incl Phenom Macrocycl Chem* 82(3–4):301–310
50. Quaik S et al (2019) Veterinary antibiotics in animal manure and manure laden soil: scenario and challenges in Asian countries. *J King Saud Univ Sci*. <https://doi.org/10.1016/j.jksus.2019.11.015>
51. Boamah VE et al (2016) Practices and factors influencing the use of antibiotics in selected poultry farms in Ghana. *J Antimicrob Agents*. <https://doi.org/10.4172/Antimicro.1000120>
52. Kamini MG et al (2016) Antimicrobial usage in the chicken farming in Yaoundé, Cameroon: a cross-sectional study. *Int J Food Contam* 3(1):10
53. Ma S, Chaniotakis N, Meyerhoff ME (1988) Response properties of ion-selective polymeric membrane electrodes prepared with aminated and carboxylated poly(vinyl chloride). *Anal Chem* 60(20):2293–2299
54. Pechenkina I, Mikhelson K (2015) Materials for the ionophore-based membranes for ion-selective electrodes: problems and achievements. *Russ J Electrochem* 51(2):93–102
55. Cosofret VV, Buck RP, Erdosy M (1994) Carboxylated poly(vinyl chloride) as a substrate for ion sensors: effects of native ion exchange on responses. *Anal Chem* 66(21):3592–3599
56. Zhang H et al (2012) Molecular recognition in different environments: β -cyclodextrin dimer formation in organic solvents. *J Phys Chem B* 116(42):12684–12693
57. Basha MA et al (2017) Novel potentiometric application for the determination of amprolium HCl in its single and combined dosage form and in chicken liver. *Chin Chem Lett* 28(3):612–618
58. Barr L et al (2004) Cyclodextrin molecular reactors. *J Incl Phenom Macrocycl Chem* 50(1–2):19–24
59. El-Kosasy AM et al (2011) Comparative study of 2-hydroxy propyl beta cyclodextrin and calixarene as ionophores in potentiometric ion-selective electrodes for neostigmine bromide. *Talanta* 85(2):913–918
60. Szente L, Szemán J (2013) Cyclodextrins in analytical chemistry: host–guest type molecular recognition. *Anal Chem* 85(17):8024–8030
61. Madhusudana Reddy T, Sreedhar M, Jayarama Reddy S (2003) Electrochemical determination of sparfloxacin in pharmaceutical formulations and urine samples using a β -cyclodextrin modified carbon paste electrode. *Anal Lett* 36(7):1365–1379
62. Hu J, Stein A, Bühlmann P (2016) Rational design of all-solid-state ion-selective electrodes and reference electrodes. *TrAC Trends Anal Chem* 76:102–114
63. Meyerhoff ME et al (1996) Peer reviewed: polyion-sensitive membrane electrodes for biomedical analysis. *Anal Chem* 68(5):168A–175A
64. Petrukhin OM et al (2001) The effect of lipophilic anionic additives on detection limits of ion-selective electrodes based on ionophores with phosphoryl complexing groups. *Sens Actuators B Chem* 76(1):653–659
65. Giahi M, Pournaghdy M, Rakhshae R (2009) A new lidocaine-selective membrane electrode based on its sulfathiazole ion-pair. *J Anal Chem* 64(2):195–200
66. Song DA et al (2010) Potentiometric detection of polyions based on functionalized magnetic nanoparticles. *Chin Chem Lett* 21(11):1378–1381
67. Wang H et al (2012) β -Cyclodextrin/ Fe_3O_4 hybrid magnetic nano-composite modified glassy carbon electrode for tryptophan sensing. *Sens Actuators B Chem* 163(1):171–178
68. Thompson G, MacMahon M, Claes P (1970) Precipitation by neomycin compounds of fatty acid and cholesterol from mixed micellar solutions. *Eur J Clin Investig* 1(1):40–47
69. Lacy RW (1968) Binding of neomycin and analogues by fatty acids in vitro. *J Clin Pathol* 21(5):564–566
70. Furda I (1983) Aminopolysaccharides-their potential as dietary fiber. ACS Publications
71. Thompson GR et al (1971) Action of neomycin on the intraluminal phase of lipid absorption. *J Clin Investig* 50(2):319–323
72. Koike R et al (2014) Structural determination of a novel polymorph of sulfathiazole–oxalic acid complex in powder form by solid-state NMR spectroscopy on the basis of crystallographic structure of another polymorph. *Cryst Growth Des* 14(9):4510–4518
73. Javanbakht M, Akbari-Adergani B (2012) Chapter 11—Molecularly imprinted polymer-based potentiometric sensors for the determination of drugs in pharmaceutical, biological, and environmental samples. In: Li S et al (eds) *Molecularly imprinted sensors*. Elsevier, Amsterdam, pp 247–273
74. Rundle CC (2000) A beginners guide to ion-selective electrode measurements. En ligne]. Disponible sur: <http://www.nico2000.net/Book/Guide1.html>. Consulté le: 14 Sept 2013

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