Selective and Sensitive Electrochemical Sensor for Aflatoxin M1 with a Molybdenum Disulfide Quantum Dot/Metal–Organic Framework Nanocomposite

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ABSTRACT: Aflatoxins are the hepatotoxic secondary metabolites which are highly carcinogenic and known to cause several adverse effects on human health. The present study reports a simple, sensitive, and novel electrochemical sensor for aflatoxin M1 (AFM1). The sensor has been fabricated by modifying the screen-printed carbon electrodes with a functional nanocomposite of molybdenum disulfide (MoS2) quantum dots (QDs) and a zirconium-based metal–organic framework (MOF), that is, UiO-66-NH2. The MoS2/UiO-66-modified electrodes were decorated with the AFM1-specific monoclonal antibodies and then investigated for the electrochemical detection of AFM1. Based on the electrochemical impedance spectroscopy analysis, it was possible to detect AFM1 in the concentration range of 0.2–10 ng mL\(^{-1}\) with a limit of detection of 0.06 ng mL\(^{-1}\). The realization of an excellent sensing performance can be attributed to the electroactivity of MoS2 QDs and the large surface to volume area achieved by the addition of the MOF. The presence of UiO-66-NH2 is also useful to attain readily available amine functionality for the robust interfacing of antibodies. The performance of the developed sensor has also been validated by detecting AFM1 in the spiked milk samples.

1. INTRODUCTION

Aflatoxins (AFs) are mycotoxins produced as the highly toxic metabolites by different fungi, such as Fusarium, Aspergillus, and Penicillium. AFs particularly AFB1, AFB2, and AFG1 are known to be carcinogenic, mutagenic, and teratogenic. They are known to inflict several health risks in humans.1 AF M1 (AFM1) is the hydroxylated form of AFB1. It is mainly secreted in the milk of mammals that consume AFB1-contaminated feed.2 The consumption of the AFM1-contaminated food (e.g., milk and dairy products) can lead to severe health problems including decreased immune response, reduced functioning of the liver, and increased susceptibility to infections.3 AFM1 has been qualified as a group I carcinogen by the International Agency for Research on Cancer. Due to its hepatotoxicity and potential carcinogenicity, different regulatory agencies have regulated maximum permissible levels for AFM1 in milk, ranging from 0.025 to 0.5 μg L\(^{-1}\).4 Therefore, the monitoring of AFM1 in food has become essential to protect consumers from its dangers and ensure the safety of the food products.

Conventional methods, such as thin-layer chromatography, high-performance liquid chromatography (HPLC)-fluorescent detection, liquid chromatography–tandem mass spectrometry (LC–MS/MS), and LC/atmospheric pressure chemical ionization MS, have been commonly used for the detection of AFM1.5 In addition to these, immunoassays such as enzyme-linked immunosorbent assay have also been developed.6 Nevertheless, the biosensors for AF bear a special significance as they can satisfy the demands of rapid, cost-effective, point-of-care, portable, and sensitive analytical systems for AFM1. The use of nanomaterials in the development of biosensors has gained tremendous importance.7 As potential food safety monitoring tools, the electrochemical sensors are projected as valuable tools to determine various biological/ecological parameters as well as monitor diverse inorganic and organic pollutants. Due to the features of fast detection rates, low cost, high sensitivity, and easy adaptability, the electrochemical sensors have also gained considerable attention for the quantitative detection of AF.8 In recent years, most of such developments were based on the use of nanomaterials and their composites, such as ZnS quantum dots (QDs), AuNP/CuCoPBA, NH2–Co-MOF, and so forth.9 The use of nanomaterials in electrochemical detection...
platforms offers high conductivity and strong binding interactions with the receptors. The above-mentioned sensors have been reported with quick response time, simplicity, high specificity, and better portability to facilitate the detection of AF. The common transducer mechanisms used in the conventional electrochemical sensors follow amperometric, voltammetric, impedimetric, potentiometric, and conductometric approaches.

Among the different advanced functional materials being explored for the development of electrochemical biosensors, molybdenum disulfide (MoS2) and metal–organic frameworks (MOFs) have established their unique reputations.10 The nanoforms of MoS2 offer the advantages of both direct and indirect band gap properties, and they have been advocated highly useful in electrochemical and optical sensors.11 In particular, the MoS2 QDs are easier to synthesize with better control on the shape and morphology.11b,c,12 Their addition to other matrices like MOFs can deliver the realization of interesting composite films with fascinating chemical and physical properties, for example, a high surface area, desirable film conductivity due to the filler effect, and readily available functionality for required bioconjugations.13 Such composite thin films can be explored for the development of novel electrochemical sensors.14

The present research work, for the first time, explores the use of a MoS2/ MOF composite for the development of an electrochemical biosensor for the detection of AFM1. Due to many desirable platform properties, as listed above, we have been able to realize an outstanding sensor performance delivering the quantification of AFM1 over a wide concentration range and with a low limit of detection (LOD). The sensor has also worked excellently for the analysis of spiked milk samples.

2. EXPERIMENTAL SECTION

2.1. Materials and Characterization Tools. AFM1 and its monoclonal antibody were purchased from Sigma-Aldrich, India, and Abcam, India, respectively. Zirconium chloride (ZrCl4), 2-aminoterephthalic acid (NH2BDC), ferric chloride hexahydrate (FeCl3·6H2O), ammonium molybdate tetrahydrate, L-cysteine, and other solvents were also purchased from Sigma-Aldrich, India, and Abcam, India, respectively. Zirconium chloride (ZrCl4), 2-aminoterephthalic acid (NH2BDC), ferric chloride hexahydrate (FeCl3·6H2O), ammonium molybdate tetrahydrate, L-cysteine is oxidized to L-cystine (a disulfide dimer). They combine to form the MoS2 product.

2.2. Microwave-Assisted Synthesis of MoS2 QDs. 0.5 g of sodium molybdate tetrahydrate and 0.25 g of l-cysteine were added into 50 mL of deionized water.15 The mixture was stirred to dissolve the precursors and then transferred into a microwave vial (G-30 vial). The microwave-assisted synthesis was carried out at 20 W for 20 min, maintaining a pressure of 6.5 bar. After the reaction, the solution was allowed to cool down to room temperature (RT, 25 ± 2 °C). After centrifugation for 60 min at 7000 rpm, a light yellow supernatant containing MoS2 QDs was obtained. For purification, the prepared QDs were treated with dichloromethane, followed by a filtration step using a 0.22 μm microporous membrane. The purified bright-yellow-colored QD solution was stored at 4 °C.

During the microwave-assisted synthesis, the crystal lattices generate unsaturated Mo atoms at the edge. At the same time, l-cysteine is oxidized to l-cystine (a disulfide dimer). They combine to form the MoS2 product.

2.3. Synthesis of the MoS2/UIO-66-NH2 Composite. The UiO-66-NH2 MOF was synthesized accordingly to a previously reported solvothermal procedure with minor modifications.16 0.2 g of ZrCl4 was dissolved (ultrasonication, 30 min) in 20 mL of a solvent mixture (HCl/DMF, 1:5, v/v). Similarly, 0.016 g of NH2-BDC was dissolved in 20 mL of DMF. The above metal and ligand solutions were then mixed and left to react overnight in a Teflon-lined autoclave placed in a heated oven (80 °C). The formed product was collected and washed with DMF and ethanol, followed by vacuum drying for 12 h (80 °C). The formation of the MoS2/UIO-66-NH2 composite was also processed as per the above method, with an additional step of addition of 20 μL of MoS2 QDs in the metal ion solution before mixing it with the ligand solution and starting the solvothermal reaction.

2.4. Preparation of the Antibody/MoS2/UIO-66-NH2 Sensor. 1 mg of the MoS2/UIO-66-NH2 sample was dispersed in 1 mL of deionized water through ultrasonication for 15 min. 10 μL of the prepared suspension was then drop-cast on the working area of the SPCE. The modified electrode was then left to dry at 80 °C in a vacuum oven. Next, 10 μL of the antibody solution (1 μg/mL) and 20 μL of a mixture of ethylcarboxyamine hydrochloride (EDC)/N-hydroxysuccinimide (NHS) (0.05 M each) in 0.1 M MES buffer were introduced onto the modified screen-printed electrode (SPE) and left to incubate for 2 h. The nonspecific binding sites were then blocked by the standard bovine serum albumin treatment method. Finally, the prepared biosensor was washed with PBS buffer and stored under refrigerated conditions (4 °C). Several batches of the antibody (Ab)/MoS2/UIO-66-NH2 bioelectrodes were prepared using the above method and employed for the quantification of the AFM1 analyte.

For quantification of AFM1, 10 μL of the sample analyte was introduced onto the sensor surface, and the antigen–antibody interaction was allowed to take place for 10 min, unless specified. The sensor was then washed with PBS buffer and investigated for its electrochemical response. All the different experiments have been performed in triplicate at pH 7 at RT, and the average values are reported.

2.5. Analysis of Spiked Milk Samples. Some milk samples were spiked with known concentrations (i.e., 0.2, 0.5, 1, 2, 5, and 10 ng mL−1) of AFM1. The spiked samples were centrifuged for 20 min to remove their fat content before 2.5% sodium hypochlorite and 0.25 N sodium hydroxide for 30 min.
3. RESULTS AND DISCUSSION

3.1. Morphological and Structural Studies. The morphological investigations of the UiO-66-NH₂ and MoS₂/UiO-66-NH₂-modified SPEs have been made using electron microscopies, as shown in Figure 1. The scanning electron microscopy (SEM) image of the UiO-66-NH₂/SPEs shows the coverage of the glassy carbon electrode (GCE) with MOF crystal with a size of around 250–300 nm (Figure 1A). Such a morphology of the synthesized MOF agrees well with the literature report. The SEM image of the MoS₂/UiO-66-NH₂ composite over the SPEs is shown in Figure 1B. The particle size of the composite has become slightly larger than that of the MOF alone, and the particles are also relatively more homogeneous in shape. The structural analysis of the MoS₂ QDs and MoS₂/UiO-66-NH₂ composites was done with transmission electron microscopy (TEM) imaging (Figure 1C). The synthesized MoS₂ QDs are spherically sized with a diameter of around 6–8 nm. The TEM image of the MoS₂/UiO-66-NH₂ composite does not reveal the presence of QDs on the surface. It can be assumed that the QDs were entrapped within the MOF particles. The same has been confirmed by energy-dispersive X-ray spectrometry-based elemental analysis. This analysis confirms the presence of both Zr (from UiO-66-NH₂) and Mo (from MoS₂ QDs) along with carbon, oxygen, and nitrogen contents (Figure 2).

Figure 1. (A,B) SEM images of UiO-66-NH₂ and MoS₂/UiO-66-NH₂ composites deposited over the SPE, respectively; (C,D) TEM images of MoS₂ QDs and MoS₂/UiO-66-NH₂, respectively.

Figure 2. (A) Elemental mapping of different metals in MoS₂/UiO-66-NH₂, shown in different colors; (B) relative percentage distribution of different metals in MoS₂/UiO-66-NH₂.
3.2. Electrochemical Studies and the Detection of AFM1 Using Ab/MoS2/UiO-66-NH2.

3.2.1. Cyclic Voltammetry Studies.

The electrochemical experiments were carried out with a three-electrode system wherein Ag/AgCl, the Pt wire, and SPEs were taken as reference, auxiliary, and working electrodes, respectively. The electrochemical impedance spectroscopy (EIS) experiments were performed in the frequency range of $0.1 \times 10^5$ Hz with a perturbation potential of 5 mV.

The Ab/MoS2/UiO-66-NH2 immunosensor electrodes were characterized by cyclic voltammetry (CV) measurements. Figure 4A shows the CV curves of the electrode during different stages of its preparation. The well-defined oxidation and reduction peaks are observed for the bare SPE owing to the electron transfer between the electrode and electrolyte solution. The intensity (extent of current values) decreases to some extent after the modification of the SPE with the MoS2/UiO-66-NH2 composite. The immobilization of antibodies on the surface caused a further decrease in the redox peak current values, which is expected as the protein layer acts as a barrier for the surface charge transfer and also restricts the diffusion of the redox couple in the bulk electrode. A change in the peak-to-peak separation between the cathodic and anodic signals is another indicator of the fact that the electron-transfer kinetics is influenced. The introduction of the counter analyte, that is, AFM1, also results in a further decrease in the peak currents as the antigen–antibody (Ab-AFM1) complex forms and reduces the conductivity of the electrode surface. The CV studies have provided useful confirmation on the successful step-by-step modification of the SPE.

3.2.2. EIS-Based Bioassay Development for AFM1.

EIS is an extremely useful electrochemical technique for the development of sensitive biosensors. EIS characteristics of the electrodes are recorded in the form of Nyquist plots. Nyquist plots recorded during different stages of sensor development are shown in Figure 4B. For the bare SPE, the value of $R_c$ is estimated to be 1.58 kΩ, which increases to 3.31 kΩ after its modification with the UiO-66-NH2/MoS2 composite. The attachment of antibodies further increases...
the $R_x$ value to 4.21 kΩ, which is attributed to the formation of a less conducting protein layer. Once the Ab/MoS$_2$/UiO-66-NH$_2$/SPE is used for the analysis of AFM1, $R_x$ of the system increases again (e.g., 9.54 kΩ for 2 ng mL$^{-1}$ AFM1) because of the formation of the antigen–antibody complex over the surface of the electrode. The antigen–antibody complex acts as a kinetic barrier for the charge transfer and hence results in an increase in the $R_x$ values directly in proportion to the concentration of the antigen being analyzed. As such, the EIS results are also in accordance with the CV results.

The detection of AFM1 (0.2, 1, 2, 5, and 10 ng mL$^{-1}$) with the Ab/MoS$_2$/UiO-66-NH$_2$/SPE biosensor has been investigated in detail by the EIS technique. Nyquist plots obtained for these studies are shown in Figure 5A. The values of $R_x$ have shown a regular increment as the concentration of AFM1 was increased from 0.2 to 10 ng mL$^{-1}$. The highest concentration of AFM1 (10 ng mL$^{-1}$) is characterized with a $R_x$ value of 27.1 kΩ. The calibration curve, depicting the dependence of $R_x$ values as a function of AFM1 concentration, is shown in Figure 5B. Under the experimental conditions for the development of the Ab/MoS$_2$/UiO-66-NH$_2$/SPE biosensor, the present system delivers an excellent linear profile ($R^2 = 0.99$) for a concentration range of 1–10 ng mL$^{-1}$ AFM1. The detection limit of the biosensor is estimated as 0.06 ng mL$^{-1}$ (LOD = 3 $σ/m$, where $σ$ = standard deviation of the blank sample and $m$ = slope of the curve). The limit of quantification (LOQ) has also been calculated by the formula “LOQ = 10 ($σ/m$)” and found to be 0.49 ng mL$^{-1}$.

A comparison of the performance of the Ab/MoS$_2$/UiO-66-NH$_2$/SPE biosensor with other recently reported similar electrochemical sensors is summarized in Table 1. Clearly, the Ab/MoS$_2$/UiO-66-NH$_2$/SPE biosensor has exhibited excellent performance in terms of the LOD. Its design is also simple, which can be easily translated into a cost-effective disposable option.

### 3.2.3. Selectivity of the Immunosenor

The selectivity of the Ab/MoS$_2$/UiO-66-NH$_2$/SPE biosensor has been tested against some common food contaminants, such as toxins (zearalenone), pesticides (atrazine, methyl parathion), a heavy metal (Pb$^{2+}$), and bacteria (Escherichia coli). The experimental conditions were kept identical in all these selectivity studies. As shown in Figure 6, the biosensor did not exhibit any significant $R_x$ response against the nonspecific analytes, and the signal was close to the baseline (blank) reading. A response (change in the $R_x$ value) was observed only for the AFM1 analyte. These results clearly show the selective response of the Ab/MoS$_2$/UiO-66-NH$_2$/SPE biosensor toward AFM1.

### 3.2.4. Application of the Ab/MoS$_2$/UiO-66-NH$_2$/SPE Biosensor for the Detection of AFM1 in Spiked Milk Samples

The quantification of AFM1 in the spiked milk samples was tested using the Ab/MoS$_2$/UiO-66-NH$_2$/SPE biosensor. The results are presented in Table 2. The biosensor was added to milk samples spiked with different concentrations of AFM1, and the $R_x$ values were recorded. The data were analyzed using the linear regression model, and the LOD and LOQ were calculated. The results showed that the biosensor was able to detect AFM1 at concentrations as low as 0.06 ng mL$^{-1}$ (LOD) and 0.49 ng mL$^{-1}$ (LOQ), respectively.
samples was established by the HPLC technique. For this, 10 mL of the spiked milk sample was diluted with 100 mL of ultrapure water and then filtered through a 0.45 μm filter paper. It was then centrifuged at 8000 rpm for 20 min to separate out the fat before introducing the sample (aliquots of 10 μL) into the HPLC column. The analysis was performed using a C18 column (Thermo Fisher 120, 50 mm × 2.1 mm × 5 μm). An eluent mixture of acetonitrile: water (35:65) was used as the mobile phase gradient. The flow rate during the analysis was maintained to 1 mL min⁻¹. For detection, the signal from the UV–vis detector at 362 nm wavelength was measured. The collected chromatograms are shown in Figure 7. The retention time of AFM1 was at 1.39 min, and the blank sample did not show any interference. The HPLC-verified samples were then tested with the Ab/MoS2/UiO-66-NH2/SPE biosensor.

The Ab/MoS2/UiO-66-NH2/SPE biosensor was used to detect AFM1 in spiked milk samples to verify its practical utility. The aliquots, collected after the centrifugation of the spiked milk samples, were introduced over the working area of the sensor and left to incubate for 5 min. The electrode was then gently washed with water and studied for its EIS characteristics using the [Fe(CN)₆]³₋/⁴₋ redox probe. The recorded values of Rct were converted into the concentration values using the calibration curves, as shown in Figure 8 (y = 1.28 + 0.252x). The Rct values from this study match well with the data collected with the standard buffer solutions. Therefore, the Ab/MoS2/UiO-66-NH2/SPE biosensor for AFM1 has a clear potential to be used for practical applications. The concentrations of the AFM1 analyte in the spiked milk samples were also validated with a reference HPLC method. The HPLC-based data also corroborated the excellent performance of the Ab/MoS2/UiO-66-NH2/SPE biosensor toward the detection of AFM1.

In recent years, the utility of QDs, for example, graphene and MoS2 nanosheets, for the development of electrochemical biosensors has been well recognized. These nanomaterials facilitate better electrocatalytic activities and high surface areas. The integration of MoS2 QDs with MOFs provides multiple advantages as far as the biosensor preparation is concerned. First, the MoS2/UiO-66-NH2 composite ensures a high surface area to the transducer material which is important to achieve an efficient immobilization of the antibodies. Furthermore, UiO-66-NH2 brings the readily available –NH₂ functionality which minimizes the application of chemical treatment to the transducer material. In addition to this, the presence of a...
porous MOF allows the diffusion of the analyte within the sensor surface. This leads to a better signal stability and sensor reproducibility.

4. CONCLUSIONS
In the present study, the MoS2 QDs have been incorporated within a UiO-66-NH2 matrix to prepare a novel functional composite. MoS2 QDs have a high theoretical capacity, a good electrochemical activity, and a superior chemical stability. MOFs, as such, do not possess enough electrochemical activity due to the presence of coordinate bonding between the metal and the linker. The SPEs of MOFs exhibit a high resistivity and consequently also exhibit a high value of charge transfer resistance. The MoS2/UiO-66-NH2 composite has the necessary electrochemical activity, high surface area, and amine functionality which advocate its application for the development of electrochemical biosensors. The antibody-conjugated MoS2/UiO-66-NH2 has been used to prepare an SPE biosensor for the detection of AFM1 using CV and EIS. The analytical performance of the biosensor is established in terms of its high sensitivity, low LOD (0.06 ng mL−1), wide detection range (0.2–10 ng mL−1), and specificity. In addition, the practicality of the sensor is further established by analyzing the detection of AFM1 in some spiked milk samples. This approach can also be extended for the detection of other AFs such as AFB1.

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Notes
The authors declare no competing financial interest.

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