Chapter VI

Conclusion and Future Prospects

1. Major shortcomings of MOFs in sensor development

Despite their high specific surface area and high porosity, the traditional MOFs possess drawbacks when used as opto-electrochemical sensors. Here, some of the challenges related to MOFs and new approaches to improve their performance in commercial prospects are discussed as follows.

I) **Low electrical conductivity:** The potential of conventional MOFs as electrode materials in electrochemical sensors for practical applications is severely constrained by their weak electrical conductivity and low electron carrier mobility**.** To address this issue, various approaches and tactics have been used to generate MOF materials with remarkable electrical conductivity and high carrier mobility[1,2]. For example, to create conductive MOF materials, MOF-based nanocomposites have been produced with carbon-based materials (graphene, carbon dots, SWNTs, etc.) and various metallic/metal oxide nanostructures (AuNPs, AgNPs, Fe_3O_4, CuO, etc.) to make novel nanohybrid systems[3–5]. In addition, redox-active linkers, conductive metal nodes, and conducting molecules are doped or encapsulated with the MOFs[6].

II) **Poor analyte specificity:** The selectivity for a single analyte is lacking in conventional MOF-based sensors, irrespective of the transduction mechanism. However, several approaches have been recently developed to boost the selectivity of MOFs for the recognition of specific analytes. These include the development of functional MOFs or combining MOFs with specific recognition molecules such as aptamers, antibodies, enzymes, molecularly imprinted polymers (MIP), and bioconjugation pairs[7–9]. Such conjugative fabrication strategies can be adopted to enhance MOF-based sensor specificity towards analytes.

III) **Instability of MOFs:** Although many MOFs contain divalent metals had outstanding porosity, their instability prevents them from being used in extreme conditions with moisture, water, or that in the acidic or basic media. As a result, the stability issue is now being addressed by the scientific community to produce more robust framework structures so as to enable further use and commercialisation of such developed sensors. The catalytic roles of MOFs in a sensing matrix are often hampered by chemical and thermal instability along with blockage of metal sites by the linkers[10]. Most of the MOFs use carboxylate linkers for the framework structures which are usually considered hard bases. So, instead of using divalent metal ions, usage of high-valence metal ions results in the formation of stable MOFs. These MOFs have proven to show exceptional stability in highly humid environments as well as in extreme pH conditions [11,12]. In addition to this, adding hydrophilic groups to the organic linkers may also enhance the structural integrity of MOFs.

IV) **Toxicity and lack of biocompatibility of MOFs:** For most of the conventional MOF materials, the synthesis pathways include toxic solvent systems such as DMF due to the compromised solubility of the precursors. These render to the low biocompatibility of the MOF-based materials. However, in recent times greener synthetic approaches are being adopted where biocompatible solvents are being used or solvent-less synthesis is being performed as already discussed in the **Section 3**. Additionally, the modulation of the MOF size into nano-MOF (nMOF) has been proven to drastically decrease the cytotoxicity of MOF making them suitable for biosensor applications[13].

V) **Low limit of detection:** The major hindrance towards commercialization of MOF-based biosensors lies in their poor LOD which makes them commercially non-viable. For surfaces involving MOF as a sensor matrix component, high LOD is unsuitable for some analytes existing in trace concentrations within real samples[14]. This thereby defies the sole purpose of sensor development where most nanomaterial-based advanced commercial sensors work in the range of picomolar and femtomolar concentrations. The remedial approach would be development nanohybrids comprising of MOFs and high-performance nanostructures that assist in improved electron transfer at the probe-analyte interface.

VI) **Processability:** Being an overlooked problem in MOFs, this arises due to the inherent nature of powdered reticular materials that restricts their application in unprocessed form at bulk[15]. The steps involved in MOF processing and thereby application-based commercial synthesis complexities makes its usage less viable in upscaling of these materials.

2. Conclusions and Future Prospects

Phenomenal progress has been seen recently in the field of biomolecular detection using MOFs. They have been profoundly integrated in detection systems for their usage in different transducer environments ranging from mechanical, optical, electrochemical to opto-electrochemical hybrids.

The **first chapter** highlights the literature review on introduction of biosensors, its types, different transduction systems and the role of nanomaterials. It then converges to our material of interest, i.e., MOFs where we discuss about different unique properties ranging from mechanical to catalytic to opto-electronic ones. Then, the different methods that can be employed for their synthesis have been discussed such as dry-gel conversion, diffusion, electrochemical, solvothermal, mechanochemical, microwave-assisted, sonochemical and ionothermal synthesis. Based on various literatures, it has been found for all above listed methods that each one has certain restricted usage with some of them involving high energy consumption, unconventional equipment or lengthy reaction period. From some methods it was inferred that use of unwanted anions, with the introduction of metal salts, makes the process control cumbersome and increases cost of production considerably. For methods like solvothermal the advantage lies in rendering chemical and structural stability along with morphological symmetry to the developed MOF structure whereas, the challenge is in optimizing of temperature conditions for desirable morphological characteristics. Methods like electrochemical synthesis are a fast, clean, cost-effective method favourable for fabrication of films rather than particles with an associated advantage of lesser errors since are devoid of human interventions. However, it can be concluded that the choice of method for MOF fabrication entirely depends upon one's choice of material and its further applicability. We have elaborately discussed on several biosensing strategies involving MOFs-based sensing matrices for detection of free radicals, metal ions, small and macro molecules and cells.

MOFs, though not being good conductors, are still extensively being used in electrochemical sensing methods due to their other merits like high surface area which imparts greater chelation with metal ions like Au^{3+}, Pd^{2+}. These metals not only improve their conductivity rather also widen their usage as nanozymes or catalysts. More research should be promoted in this field on doping MOFs with electroactive species to widen their applicability in this area. MOFs involving d-block metal centres like Cu and Co have been widely used in such case without the need for extensive doping too due to their inherent catalytic properties. This opens new window for label-free biosensors with excellent repeatability and low LOD values. The luminescence characteristics of MOFs can also be accredited to the excitation of direct organic ligands causing ligand-to-ligand charge transfer (LLCT). Lanthanum-based MOFs involving mostly Eu^{3+} are now trending as MOFs hence such systems can be implemented fluorescence-based diagnostics in future. MOFs have also been known to possess commendable ECL activity with distinct emission peaks. The luminescence can be generated by the metal center (antenna effect) where a ligand-to-metal or vice-versa charge transfer can lead to luminescence. Emission MOFs need to be researched more for their usage as theranostic agents with improvement in their *in vivo* compatibility. Future work should be directed towards exploring and engineering MOF platforms for attachment of functional molecules which can act as moieties for macromolecular sensing without using sophisticated and multistep functionalization methods. Additional efforts are also required for use of these systems in miniaturized platforms and point-of-care diagnostics.

The **second segment of the chapter** talks about the evolutionary progress that has been reported in recent times for detection of biomarkers using MOFs. They have been explored vividly and integrated strategically in sensing matrices within a range of transduction environments. The article focusses only over the electrochemical transduction systems on MOF-based disease diagnosis tools where the segregation of study is primarily done on the basis of multiple diseases. Each disease segment has been briefed with recent advances in MOF-based probe fabrication strategies involving elaborate discussions on sensor fabrication and sensing parameters. It has been found that the selection of MOFs in specific sensing applications relies primarily on the suitability of the metal center. Ni, Co and Cu based MOFs have been opted more in recent past due to their proven catalytic potential and electroactive properties. Bimetallic MOFs and their use in sensor matrices are evolving as a new prospect where relatively simpler probe fabrication can generate enhanced signal amplification which was being previously achieved through incorporation of multiple matrix layers. Ni-Co bimetallic MOFs are the prominent ones in the category, however, more research in the field of other bimetallic MOFs with different metal centers can further be developed. MOFs, though being not very good conductors, are enormously being used in electrochemical transduction matrices by virtue of their high surface area which endows them with greater chelation ability with other metal ions. An attempt towards bimetallic MOFs and their further doping with electroactive species can be another exciting area for research. The authors ponder if trimetallic MOFs could also be an option in near future. Also, a range of MOF synthesis approaches discussed in all segments of the article are suggestive of a notion that solvothermal still remains the most adopted method. However, its major challenge would still be elimination of toxic synthetic solvents like DMF and methanol by the greener ones, decreasing dependency on high temperature conditions. Sustainable MOF synthesis methods like microwave-assisted or dry-gel conversion methods are rare in reports when it comes to development of biosensors. Label-free detection is another promising aspect of MOFs that is being heavily explored. Direct functionalization of MOF surface with target specific molecules could envision future work for development of miniaturized platforms and point-of-care diagnostics. However, the commercial bottleneck would still be the development of envisioned MOF-based POCTs due to challenges arising from high cost, scattered literature and knowledge gap on sustainable MOF development strategies. The major drawbacks in the commercial prospects of these materials are compromised conductivity, poor analyte specificity, instability in a range of solvents, toxicity leading to poor biocompatibility and low detection limits which need to be tackled. For diseases included in the article, a lot of progress has been done which have been tabulated in each section. The future work could be directed towards similar diagnostic solutions for other disease categories too like pulmonary disorders which the authors could not find much reports on.

In the **second** chapter, a novel 3D AuND/Ni-MOF/Hyd nanohybrid sensor surface was developed which was precisely directed towards the non-enzymatic sensing of hydrogen peroxide. The electrodeposition variables were keenly optimized for construction of the matrix with superior analytical performance. The addition of successive layers developed into an interesting hybrid module with enormous surface area and charge transfer characteristics favoring sensing applications. The nanohybrid sensing probe displayed a commendable response time of 5.02 ± 0.42 seconds, attributing to its excellent sensitivity towards H_2O_2 determination within the detection range of 1 x 10^{-8} and 1 x 10^{-15} M and a LOD of 0.34 (±0.05) x 10^{-15} M.

The **third** chapter focusses on the development of a novel sandwich sensing probe for monitoring a physiologically significant vitamin (FA) through electrochemical route. The sandwich probe was fabricated by optimization of process parameters to replace existing tedious MOF synthesis process by a simpler electrochemical approach, followed by its conjugation with Au nanostructures above and beneath it. The calibration study yielded a linear slope within a FA concentration range of 1 x 10^{-11} and 1 x 10^{-3} M and a LOD of 0.48 ± 0.02 x 10^{-11} M. The engineered sensor probe displayed a commendable response time of less than 2.1 seconds, attributing to its excellent sensitivity towards FA determination.

In the **next** study (chapter 4), a novel approach was adopted to fabricate Co-MOF at a low potential in a short fabrication time, as low as 600 seconds. The developed Co-MOF was then assembled as a crucial component within a sensing matrix by stacking over a Ni-MOF surface. The surface was further conjugated with AuNP to engineer the final sensing probe as GCE/Ni-MOF/Co-MOF/AuNP. This is the first report of its kind where such a stacked MOF-based platform has been deployed for NO_2^- sensing purpose along with a smartphone interface giving real-time qualitative and quantitative concentration outputs using only current as an input.

The **last** chapter discloses the method for development of a bimetallic MOF based nanocomposite (GCE/Co/Mo MOF) through the electrochemical route for the electro-catalytic oxidation and thereby sensing of UA. The sensor was capable of detecting UA in the detection range of 1 x 10^{-2} to 1 x 10^{-9} M. The future prospects of the study could also be integration of the proposed matrix in wearable and patch-based sensors which would however require advance analyses involving the toxicity aspects of these materials.

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