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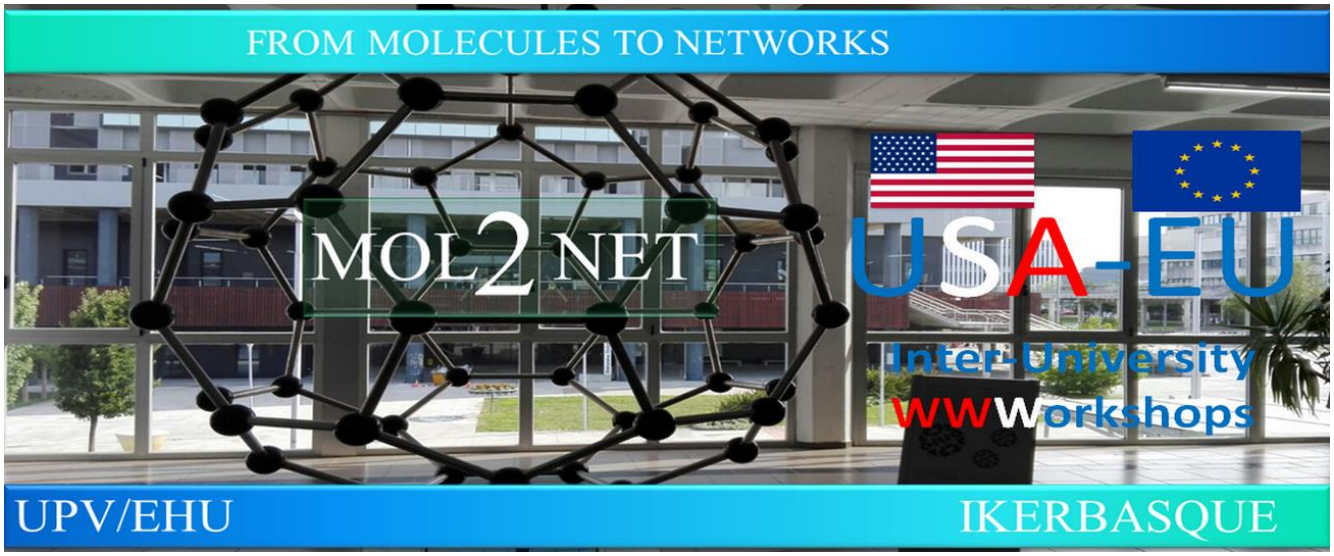


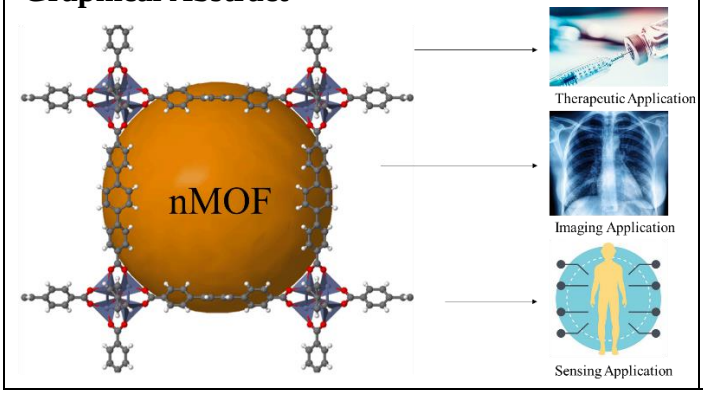
Review: Nanoscale Metal-Organic Frameworks for Therapeutic, Imaging, and Sensing Applications

Maitane Urgoiti Rodriguez [a], Arantzazu Letona Elizburu [a], Celia Elicegui Bravo [a], Harbil Bediaga Bañeres [a.b]

[a] Department of Organic and Inorganic Chemistry, University of Basque Country UPV/EHU, 48940, Leioa, Spain.

[b] Department of Physical Chemistry, University of Basque Country UPV/EHU, 48940, Leioa, Spain.

Graphical Abstract



Abstract.

In this work we carry out a short review of the fusion of nanotechnology and nanoscale MOFs (nMOFs) that have significant potential for biomedical applications. In addition to analyzing the therapeutic applications of its use in imaging and biosensors and the fundamental challenges and perspectives, we propose a series of improvements and future studies.

Introduction

The fusion of nanotechnology and MOFs has resulted in a promising new materials platform, nanoscale MOFs (nMOFs), with significant potential for biomedical applications. These nMOFs present unique opportunities for biomedical applications due to three major attributes of their structure. On the one hand, the high porosity and the long channels favor the loading inside the structures. On the other hand, there are many possibilities to functionalize MOFs with the selection and functionalization of SBUs. Finally, the stability of nMOFs in physiological environments, which allow the design of activated or controlled release nanocarriers, which is difficult to achieve with other nanoformulations.

Therapeutic applications

Regarding the therapeutic applications, non-covalent encapsulation is exposed through electrostatic interactions, π-π interactions between the hydrophobic drug and organic ligands and weak hydrophobic interactions between drugs. Cell uptake depends on pH, while drug release depends on the concentration of reducing agent, which is why the use of gatekeepers to reduce premature release is exposed. An example shown is the zeolitic structure of imidazole which provides an interesting encapsulation of charges due to its cavities and gradually decomposes under mild acidic conditions.

On the other hand, the therapeutic agents bind to the ligands by means of orthogonal conjugation, controllable triggers can be produced that are disconnected before certain chemical stimuli, and this binding can occur before the formation of nMOF or after, being the first the one that ensures the full loading and allows characterization of drug conjugates; but conjugation of the drug with the linkers reduces molecular symmetry and increases steric hindrance, impeding growth and crystallographic characterization. Direct incorporation of therapeutic agents can avoid problems with crystal growth when prefunctionalized ligands are used, providing high atomic economy leading to drug payloads. Most drugs or prodrugs do not possess the necessary coordination geometry or molecular rigidity; therefore, they are used to form amorphous coordination polymers at the nanoscale. It was shown that structurally intact nMOFs could function at the molecular level in vivo by taking advantage of the porous structures and the small dimension of the particles. Finally, biomolecules can be incorporated into SBUs, but only some metal centers can function directly as therapeutic agents, such as: Ag^{+}, Cu^{+}, Co^{2+} and Zn^{2+}.

Imaging and biosensing applications

In the last decade, nMOFs have been shown to be promising contrast agents for magnetic resonance imaging (MRI), X-ray computed tomography (CT), and PET by taking advantage of their metallic connection points or nodes. The incorporation of fluorophores into nMOF has also enabled the optical detection and imaging of physiologically significant species. The signals obtained from MRI can be used to contrast different tissues, distinguish lesions from healthy tissues, and build a map of the anatomical structures of the body. Currently, the most common contrast agents are Fe-based nMOFs (potential agents) and gadolinium small molecules. The latter have a fairly low sensitivity and occasionally cause nephrogenic systemic fibrosis in patients with severe renal failure. Since the binding of multiple gadolinium complexes has been shown to significantly increase relaxation, Gd-based nMOFs appear to be logical candidates as MRI contrast agents. On the other hand, the ability to encapsulate super paramagnetic nanoparticles in nMOF makes it possible to design nanocomposites as contrast agents.

X-ray computed tomography images provide a powerful diagnostic tool for 3D visualization of the internal structures of a scanned object based on X-ray attenuation. However, small molecular weight

contrast agents are required that they are currently used in the clinical setting. NMOFs have the potential to become computed tomography contrast agents because high atomic number elements (such as gold) can easily be incorporated into nMOF structures with extraordinarily high payloads.

Another application is optical imaging (OI). They are used in light illumination to obtain images of organs, tissues and cells based on the detection of ballistic or diffusive photons. It is minimally invasive to patients and highly sensitive, but the superficial penetration of light limits its clinical use. Furthermore, OI is compatible and complementary to other images and therapeutic modalities. In addition to the previously mentioned techniques, PET (Positron Emission Tomography) is used. Compared with other imaging techniques, PET imaging has superior detection sensitivity, deeper signal penetration, and better quantification ability. Imaging applications aside, it should be noted that the development of molecular sensors to probe physiological processes is a booming research area. Pathological disruptions or changes in physiological environments can cause changes in the concentrations and types of metabolites in cells. Therefore, the ability to detect and monitor these changes with specific and sensitive sensors will help diagnose diseases and reveal the underlying biology. NMOF-based sensors overcome the self-extinction and leaching problems of many small molecular biosensors to achieve high sensitivity, resolution, and precision in subcellular biosensitivity. Additionally, the ability to connect multiple functionalities to nMOF enables the design of Förster, radiometric, or multi-target resonance energy transfer sensors. When studying an nMOF for sensors, intracellular pH plays an important role in environmental physiology, regulating cellular functions and physiological activities. The dysregulation of this parameter in intracellular fluids is related to tumorigenesis and drug resistance.

Other aspects to take into account in sensors related to cellular metabolism and the physiological field are gaseous molecules (such as NO and H_2S) and metal ions. Although if the presence of these ions is in high concentrations it can be toxic and lethal, so it is important to detect them selectively. To this end, MOFs provide a platform for designing fluorescence quenching sensors, as energy/charge transfer between ligands and metal ions can lead to quenching of fluorescence. Furthermore, nucleic acid is also at the center of physiological regulation. Thus, in recent years, a number of nMOF-based nucleic acid sensors have emerged, most of which use quenching of fluorescence by binding nMOF to DNA detectors as a signal readout.

Fundamental challenges and perspectives

Taking into account the therapeutic, imaging and biosensing agents discussed above, the fundamental challenges and different perspectives will be addressed below in: controlled synthesis, biodistribution and biocompatibility/toxicity. In controlled synthesis, the most widely used method is solvothermal due to its versatility and applicability to a wide variety of MOFs. As far as particle size is concerned, it is an important parameter that indicates the biological fates and functions of nMOFs, since particle size strongly affects the biodistribution of systemically administered nMOF particles. The size and shape of the particles can also influence cell uptake. In addition to size, the modification of the surface of nMOF has been studied through the use of polymers (mainly PEG and its derivatives) and coatings with nucleic acids.

Based on the biodistribution of nMOFs, the main objective is the administration of nanoparticles to improve the pharmacokinetics (PK) of therapeutic and/or imaging agents. The size, shape, surface chemistry, and colloidal stability of the particles greatly affect the trafficking, removal, and tumor absorption of the nanoparticles. For nMOFs, their intrinsic crystallinity and stiffness often lead to very

well-defined shapes (cubes, rods, discs, etc.) for which sizes are more difficult to control than for conventional nanocarriers which tend to be spherical. Finally, the toxicity of nMOF is strongly correlated with the toxicity of the metal. Other factors such as the formation of new species, and the size / shape of the particles also influence toxicity.

Conclusions

NMOFs have distinct advantages over other nanoformulations in biomedical applications due to their intrinsic characteristics including high porosity, structural tuning / multifunctionality, and biocompatibility. Despite growing interest and impressive progress in this field, further studies are needed to address several key aspects of nMOFs (controlled synthesis, surface properties, pharmacokinetics and biodistribution, biocompatibility, toxicity, and therapeutic / imaging efficacy) before the biomedical applications of nMOFs can be fully validated for clinical use.

In the article studied, we believe that a large number of studies from different research groups are analyzed and this provides an overview of the applications that nMOFs may have in the clinical setting. However, the mention of all these works means that in-depth studies are not carried out on each one of them and that in most cases ideas are raised for future research. So we think it would be better to focus on an nMOF and make all kinds of processes and improvements in the most important factors of clinical use, including pharmacokinetics, toxicity and biocompatibility. In this way, different nMOFs can be investigated and those that do not have the appropriate properties can be ruled out. Furthermore, conclusions can be drawn and new nMOFs proposed and once the study of them is finished, they can be investigated in a similar way.

That said, from this article different studies can be proposed that could be carried out in the future with the aim of using nMOFs in the clinical setting. One of the most notable is the need to determine the reaction parameters for the synthesis of nMOFs, since today they are not optimized and this makes it difficult to predict and / or control their sizes and morphologies. Furthermore, the ignorance of the reaction conditions causes that the reproducibility of the synthesis of nMOFs is limited and therefore it is a question to be studied. It should be noted that if nMOFs are to be used in medical applications it is necessary to continue collecting data on biocompatibility and toxicity, two important parameters that must be controlled at all times. On the other hand, if nMOFs can be used in cancer-related immunotherapy, as discussed in the article, it would be advisable to continue exploring the immunological mechanisms behind their interactions with the tumor microenvironment and immune cells. Despite significant progress in surface modifications and active nMOF selection, accurate characterization of coating efficiency and stability remains an unsolved problem. Therefore, in vitro and in vivo studies are needed to realize the full potential of nMOF-based diagnostic and therapeutic agents. Finally, it can be mentioned that the biodistribution and the pharmacokinetic / pharmacodynamic parameters play a very important role in the performance of the nanocarrier and the release of the encapsulated drug. These parameters are not specified for routine administration studies, so we hope that more efforts will be made to define them.

In conclusion, we could say that nMOFs could be the future both in biomedicine and in the clinical field due to the properties and characteristics they present. However, it has been established that it is necessary to continue investigating and collecting all the possible information in order to be able to have the appropriate nMOFs.

References

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