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Review

Climate friendly MOFs synthesis for drug delivery systems by integrating AI, intelligent manufacturing, and quantum solutions in industry 6.0 sustainable approach

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Since the Industrial Revolution, ecological damage, ecosystem disruption, and climate change acceleration have frequently resulted from human advancement at the price of the environment. Due to the rise in illnesses, Industry 6.0 calls for a renewed dedication to sustainability with latest technologies. Focused research and creative solutions are needed to achieve the UN Sustainable Development Goals (SDGs), especially 3, 9, 13, 14, 15, 17. A promising sustainable technology for enhancing healthcare while reducing environmental effect is Metal Organic Frameworks (MOFs). MOFs are perfect for drug administration because of their high surface areas, adjustable pore sizes, and remarkable drug-loading capacities. They are created by combining advanced artificial intelligence, intelligent manufacturing, and quantum computing. Researchers can create MOFs with functional groups or ligands that bind selectively to target cells or tissues, minimizing off-target effects, thanks to the distinct benefits that families like MIL, HKUST, UiO, and ZIF etc. offer for targeted drug delivery. Combining MOFs with other nanomaterials results in multipurpose systems that can handle challenging biomedical issues. Despite its promise, there are still issues with MOFs' possible toxicity and long-term stability in physiological settings. To advance their medicinal applications, these problems must be resolved. Researchers can increase the usefulness of MOFs in medicine by critically analysing these limitations and putting up creative alternatives. The creation of MOFs especially with advanced technologies (additive manufacturing etc.) for drug delivery is a prime example of how scientific advancement and environmental stewardship may coexist to provide healthcare solutions that are advantageous to both people and the environment.

Keywords: MOFs; drug delivery; SDGs; artificial intelligence; intelligent manufacturing; quantum computing.

Introduction

Humanity has made great strides since the start of the Industrial Revolution, but these developments have come at a high cost to the environment. Despite being progress-driven, the actions of earlier generations have caused significant environmental damage, upsetting ecosystems and hastening climate change. With the prevalence of diseases linked to climate change and environmental stressors on the rise, we are at a critical juncture where these cumulative effects are putting human health and biodiversity at greater danger.[1–7] Today, our duty goes beyond invention; it calls for a dedication to protecting life on Earth in all its manifestations. This necessitates coordinated research activities in line with the SDGs of the UN, especially those that address climate action (SDG 13), life on land (SDG 15), life below water (SDG 14), health and well-being (SDG 3), and responsible consumption and production (SDG 12). In this regard, investigating sustainable technologies like the use of MOFs in drug delivery, offers a chance to improve healthcare while reducing ecological impact, bringing our scientific endeavors into line with a larger vision of planetary resilience and health.[8–12] The most important field for mankind is drug delivery as biomedical and other fields come with vast changes like in small volumes how maximum drug can be carried out, how to minimize the prices as well as waste, how to manage stability of carrier, how to prevent unnecessary degradation. In medical and other fields improvement was required to change the entire field into a new field by making advancement in the drug delivery system. Drug delivery technologies has thus, not only enhanced the therapeutic efficacy and patient compliance but also reduced the toxicity.[13,14] Different materials are used for delivery of drugs to different parts of human body,[15] and these different materials like, nanoparticles which are highly biocompatible and easily encapsulate the drug,[16] and hydrogels which are highly biodegradable with tunable drug-releasing profile.[17]

Because of their special structural and functional characteristics, porous materials have long been employed in a variety of applications, such as medication delivery, gas storage, adsorption-based separation, and catalysis. These materials are adaptable for use in industrial, medicinal, and environmental settings due to their vast surface areas, adjustable pore diameters, and great chemical stability. Because of their special structural and functional characteristics, porous materials have long been employed

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in a variety of applications, such as medication delivery, gas storage, adsorption-based separation, and catalysis. These materials are adaptable for use in industrial, medicinal, and environmental settings due to their vast surface areas, adjustable pore diameters, and great chemical stability. Drug Delivery Systems (DDS) are made to deliver medicinal substances to certain bodily locations while regulating release rates and reducing adverse effects. For this aim, both organic and inorganic porous materials are taken into consideration; each has unique benefits and drawbacks. Because of their biocompatibility and biodegradability, organic porous materials such as porous polymers and organic frameworks are highly prized. At the nanoscale, however, obtaining consistent and well-defined porosity is a major challenge. Their usefulness in DDS is limited by variations in pore size and distribution, which can negatively impact drug loading and release kinetics. Covalent organic frameworks (COFs) and other porous organic frameworks show promise, although research is currently being done on their structural stability and synthesis repeatability.[18–20]

In contrast to their organic counterparts, inorganic porous materials provide more mechanical stability and precise pore control. Despite these benefits, their ability to load drugs is nevertheless limited, frequently as a result of very tiny pore sizes or their inability to chemically bind significant amounts of medicinal molecules. Layered double hydroxides (LDHs) are anionic clays that allow for regulated drug release due to their adjustable interlayer spacing. However, the total medication load they can hold is limited by their surface area, which normally ranges from 10 to 150 m^2/g. porous silicon is a strong contender for DDS due to its biodegradability and compatibility with biological systems. However, its surface area (200–800 m^2/g) and pore size (usually 5–50 nm) restrict its ability to load drugs, which presents a problem for applications that need larger therapeutic loads. Beyond DDS, porous materials are useful in several other domains. Materials such as zeolites and activated carbons are employed in adsorption-based separation to separate gases or liquids according to molecular size and interactions.[21,22] Zeolites' selective adsorption capabilities allow them to separate CO_2 from CH_4 with an efficiency of up to 85%. MOFs and porous carbons have remarkable capacities for gas storage; MOF-5 can store up to 10 mmoL/g of CO_2 at 1 bar, exceeding the capacity of conventional adsorbents. Because they act as supports for catalytic events, porous materials are extremely useful in catalysis. Mesoporous silica, such as SBA-15, is commonly utilized in hydrocracking and other catalytic processes because of its high surface areas, which allow for better dispersion of active sites. All the nanomaterials/materials used for the drug delivery purposes have limitations which includes, lack in diversity and variety of pore from micropores to mesopores, ultra-high surface area, tunability, excellency in drug loading and releasing capacity and stability. All these characteristics are present in MOFs which makes them ideal candidate for delivery of drugs.[23] The evolution of MOFs has advanced dramatically over time, as Fig. 1 illustrates (developed by different AI and editing technologies). MOFs have grown more sophisticated and adaptable in their uses, more porous, and have greater surface areas as a result of developments. Also, MOF synthesis in Industry 6.0 will heavily rely on 3D technology (additive manufacturing). This technology is a very successful, sustainable and economical method since it allows MOFs to be made in a variety of sizes and shapes with the highest porosity and surface area while minimizing material waste, net zero emission and lowering manufacturing costs.[24,25]

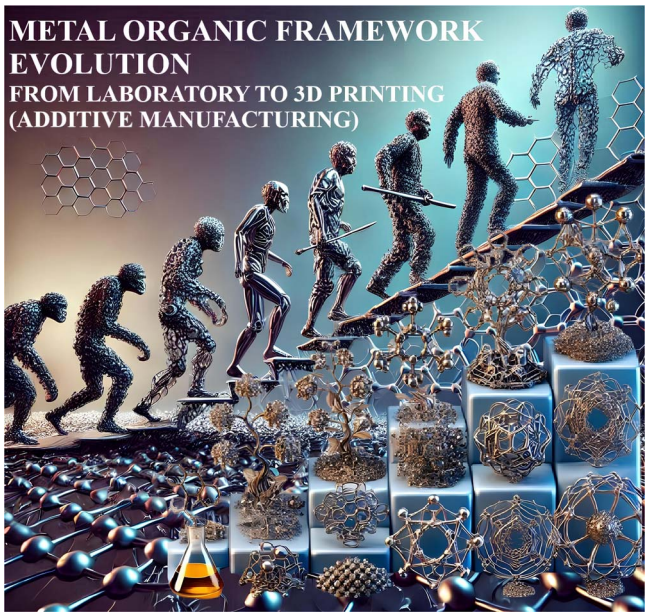

Fig. 1. Evolution of MOF with the passage of time.

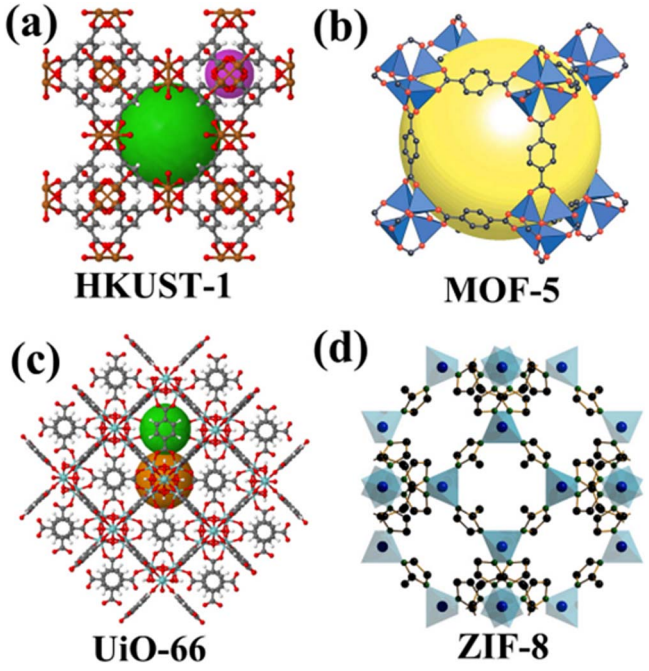

Fig. 2. Structure of different MOFs used in drug delivery.

Different types of MOFs are shown in Fig. 2.[26] MOFs consist of two main parts; one is metal ion and the other is organic ligand which are attached with each other in a polymeric manner. MOFs, a material with fine and solid characteristics showing wonders in many fields for its application like adsorption, electrochemical applications, gas storage, biosensing and drug delivery.[27,28] The functionality of MOFs depends on their distinct properties, and these are widely used as drug carriers now. The crown for its development goes to Ferey and its coworkers. This groundbreaking development is spreading widely in the field of medicine.[29] But there are main factors through which the structure and functionality of the MOFs are greatly affected like its mixing parameters, metal ligand ratio and its conditions like temperature, pressure, stirring etc.

There are different families that are under research and the first MIL family is discussed here which includes MIL-53, MIL-125, MIL-100, MIL-88B (Fe), MIL-125(Ti). These MOFs have porous surface, vast surface area, possess good resistance against water and heat. Above all, it possesses appreciable performance in drug delivery. Then HKUST family shows unique properties like larger surface area and higher porosities than MIL family and MOFs belong to this family have potential to work in drug delivery in efficient way. UiO family has MOF composites and nanoparticles which make them a controlled and steady drug loading and releasing due to its high thermal stability. The last one important family is ZIF family, which leaves behind all the previously discussed families because of its surface area, thermal stability, tunable pore size, and high drug loading capacity.[29] Because of its unique set of characteristics, the ZIF family of porous materials excels other families, which makes it especially useful for applications including drug delivery, gas storage, and catalysis. ZIFs' exceptional surface area, which frequently exceeds 2,000 m^2/g (ZIF-8, for example, has a BET surface area of about 1,630 m^2/g), offers a large amount of internal room for high drug loading capabilities, usually up to 40%–50% of their weight for some medications, such as doxorubicin. Their strong metal–ligand interaction between transition metals (such Zn and Co) and imidazolate linkers produces a sturdy tetrahedral framework similar to zeolites, which is responsible for their very porous structure. Another characteristic that sets ZIFs apart is their thermal stability; their breakdown temperatures frequently surpass 400 °C, which is far greater than those of many other MOFs and porous materials. Strong bonding and the imidazolate linkers' resistance to heat degradation are the causes of this high stability. Under extreme circumstances, ZIFs are guaranteed to maintain their structure and operation because to this thermal resistance. ZIFs' adjustable pore size, which can be between 2 and 30 nm. By altering the imidazolate linkers or adding functional groups, the framework's pore size and chemical environment can be changed, providing this flexibility. The material's selectivity and compatibility with different therapeutic compounds are improved by the ability to customize pore size and surface activity, which helps ensure effective drug delivery with regulated release profiles.[30–32] One novel aspect to emphasize could be the recent advancements in functionalizing MOFs for targeted drug delivery. This involves engineering MOFs with specific ligands or functional groups that can recognize and bind to target cells or tissues, enhancing drug delivery efficiency while minimizing off-target effects.[33]

These MOFs offer high drug loading capacity and controlled release, there may be concerns regarding their long-term stability in physiological conditions or potential toxicity. Some limitations and challenges associated with using MOFs as drug delivery carriers are that the MOFs may degrade or undergo structural changes over time when exposed to biological fluids or environments, potentially affecting their drug release kinetics and efficacy. Certain MOFs and their degradation products may exhibit cytotoxicity or induce immune responses in biological systems, raising concerns about their biocompatibility and safety for clinical applications. MOFs may encounter challenges related to their stability upon administration in vivo, such as premature drug release or clearance by the immune system, which could compromise their therapeutic effectiveness. Some MOFs may exhibit slow degradation rates or insufficient biodegradability, hindering their clearance from the body and leading to potential accumulation in tissues or organs. The synthesis of MOFs on a large scale with reproducible quality remains a challenge, impacting their feasibility for commercialization and clinical translation. The detailed discussion on drug delivery of MOF is in a separate section before conclusion.

Mil MOF family

These are the most studied and valuable MOFs that are under research for the advancement of the drug delivery application in many fields.[26] The MIL family includes MIL-68, MIL-67, MIL-53, MIL-88A, 88B, 88C, 88D, MIL-89, MIL-127, MIL-125, MIL-101, MIL-100.[34] Here we will discuss some examples related to this family MOFs in drug delivery systems.

Mil-101

It is the well-studied MOF and is produced by solvothermal method using chromium metal and terephthalic acid (T.P.A) as organic linkers. This MOF exhibited distinctive properties like ultra-porosity, large surface area, resistant to air water and heat, and good performance in drug delivery. It also showed MTN type (zeo type) crystal construction (diameter $= 2 \sim 3\ \mu m$). The SBUs is produced with metal chains and linker as terephthalic acid. There are two modes of huge spherical mesoporous cages[35] which is pentagonal and hexagonal. Thus, these large cages produced from pentagonal and hexagonal cages are capable of loading drugs easily. Adsorption of Ibuprofen by Cr-MIL-101 is a good example for explaining drug delivery which demonstrated 139% adsorption in SBF by MIL-101 (Cr) at 37 °C. This property enables this MOF as competitive material for drug delivery applications.[36]

An illustration of Ibuprofen can be taken as an example for the release of MIL-101. Research involving MIL-101 MOFs showed two stages of release ibuprofen. One is initial burst release and other is steady and persistent release. Rapid release from MIL-101 of an appropriate quantity of ibuprofen occurred at the start of experiment. Fast dissolution and diffusion of the drug from the large mesopores show the consequences of rapid release. External diffusion is eradicated by continuously stirring during the experiment. Primarily drug passing through megaspores showed the release mechanism,[35] and this phase of release rely on diffusion. There was sustained and slow release of ibuprofen then the release was continued for many hours, that is why this phase is called steady and persistent release. Ibuprofen molecules diffuse in the mesopores of MIL 101 easily because of its high diameter. The important factor is delivery rate of ibuprofen which was stimulated by both process diffusion and dissolution and the quality of ibuprofen that enters the MIL101 pores show saturated state.[37,38] Research showed that under the high level of loadings of ibuprofen and structure of MIL-101 remain intact. This makes the MIL-101 a potential candidate which is not only reliable but also a promising drug carrier because of two reasons stability and to control the release ability. From this study it was proved that the efficiency in loading and releasing of ibuprofen by MIL-101 followed by both process that is steady and controlled release by MIL-101 exhibited its pharmaceutical applications effectively.[38]

Mil-100

MIL-100 or $(Fe_3O_4\ (H_2O)_2OH(BTC)_2)$ have surface area and porosity to about 1.3 cm^3/gg and 2000 m^2/g respectively and produced from iron metal and BTC as organic linkers. The mesoporous cages that it contains, have a range between 25 and 29 A° and the range of the microporous window is 4.8 and 8.6 A°.[39] Ibuprofen and aspirin can be used as an example to find its drug loading capacity. Results showed that if both are used, drug loading ranges between 26.8 wt% and 22.4 wt% for ibuprofen and aspirin respectively. Low adsorption of MIL-100 (Fe) with comparison to MIL-100 (Cr) is

due to its small cages and there is only metal cluster is different between MIL-100 (Fe) and MIL-100 (Cr) MOFs.[40] For explanation and study of releasing kinetics 37 °C temperature was adjusted at continuous stirring, so that hydration can be stimulated and in one day MIL-100 releases 99% of ibuprofen and ~85% of aspirin. This is due to the large cage structure of MIL-100.[26]

Cancer is a disease with a less survival rate and almost all the anti-cancer agents cause toxicity in the body and their performance is poor when it comes to targeted delivery. For that purpose, various nano carriers were developed, and researchers deliver doxorubicin anticancer drug using MIL-100 (Fe). Different concentrations of this MOF were used and explained using TEM, SEM, and BET. The maximum loading capacity that was observed was ~19 mass% and this amount is higher than other nanoparticles used for this purpose. The difference between both MOFs is obvious because MIL-100 has small cages in its structure which makes the drug start loading at the larger cages than the smaller cages. MIL-101 has larger cages and ultra-high porosity so there are no void areas in the structure of MIL-101 that isn't filled by the drug. This makes MIL-101 more compatible for the drug loading as compared to MIL-100 as no area is left unloaded.[36,40]

MIL-88B (Fe)

Nontoxic and flexible characteristics make MIL-88B attractive for many applications especially drug delivery, because of having Fe metal which is regarded as bio element and present in living organism in different proteins and enzymes like hemoglobin and myoglobin. It is made up of 1, 4 –BDC as organic linker and iron metallic salt. Tian and his colleagues identified the crystalline surface of MIL-88B using crystal XRD. From all the calculations, it was clear that 194.6 mg/g drug loaded which makes this MOF superior from all. Further, when their cyto-toxicity was calculated, surprisingly the cell activity was fantastic and (below 15%) even at the higher value of drug loaded. This makes MIL-88B an excellent choice to be used either in a pH or responsive way or acidic tumor environment for the delivery of anti-cancer drug.[36] As MIL-88 has a porous surface and this characteristic of MIL-88 makes excellent choice to be used as drug carrier. It was observed that in case of ibuprofen, its drug loading capacity was 194.6 mg/g.[40] In case of MIL-88(Fe), releasing kinetics are just that according to need and pH-responsive method was used during the measuring of releasing kinetics.[40] Despite all the good characteristics of Fe-MOFs, some points still need under consideration like, how much dose of Fe^{3+} will be safe, what about in vivo pharmacokinetics, systematic toxicity etc.[34]

MIL-125 (Ti)

MIL-125 is a titanium-based MOF reported for the first time by Serre Sanchez et al. in 2009 using simple thermal dissolution which is very easy to synthesize and less toxic. They synthesized this MOF using 1, 4 benzoic acid and iso-proxy titanium by dissolving in DMF and methanol solvents having equal ratios. Further a crystalline powder is obtained, when the mixture is heated to 40 degrees. MIL-125 offers many structural benefits in drug packaging due to its tetragonal and octahedral cavity. Their wide usage included many fields like Sensing, Gas storage and Adsorption. Despite of its use in vast applications, it is widely used in adsorption, photocatalytic etc. modification strategies of MIL-125 (Ti) include metal ion doping calcination, structural control etc.[41] MIL-125 $–NH_2$, the amino form, can also be used as a drug carrier. Surprisingly if we load MIL-125-NH_2 as well as MIL-125 with chloroquine, the negative impact of CQ can also be eliminated. The most promising modification strategy is heterojunction because it effects various benefits like change separation, reduced rate of whole electron recombination and improved photocatalytic performance.[42]

Mil- 53

Chromium terephthalate is also extensively applied in various fields like drug delivery and can undergo reversible phase transition due to ores diameter of 1.3 mM. This MOF can also be used as a stimuli-responsive medication delivery system, can perform reversible structural shift as discolored by the use of various techniques like neutron powder diffraction.[43] In the case of iron and chromium-based MIL-53, 20% w/w ibuprofen was absorbed. Studies reveal that drug loading is not affected significantly by the types of metal used in the case of MIL MOFs.

All MIL MOFs are effectively used in drug delivery applications. Zero order kinetics was observed for MIL-53 due to slow delivery, which was because it finishes after 3 wk as reported by the SBF. Chromium and iron-based MOFs, MIL-53 eventually showed linear delivery.[43] Limited pathways for the synthesis of MIL-53 were considered to reduce synthesis time and increase the rate of production. The flexible nature of the MIL-53 enabled it to be used in different applications like adsorption, catalysis, and sensor and drug delivery. MIL-53 is highly porous which makes it a suitable choice for CO_2 adsorption. MIL-53 requires surface area modifications due to its limited applications in other fields. Its properties should also be regulated by grafting it with specific functional groups.[44]

HKUST-1 MOF family

HKUST-1, also known as MOF-199, has many distinctive properties like ultra-high volume of pore and ultra-high surface area and good chemical stability. It has BTC as organic linker and Cu metal in MOF and is called HKUST-1. Due to its distinctive nature and characteristic properties it acts as an excellent candidate that has the potential of great application in the gas separation, hydrogen storage and many other fields.[43] HKUST-1 has complex structure as it has both 3D framework and cubic structure. It comprises of many cages and channels that measure 9-by-9 inches. It shows vast application in drug loading and delivery, catalysis and gas separation. As it is considered very useful material due to its framework. (Cages and channels).[43,45] Impressive performance can be seen, when HKUST-1, was used in medication loading and releasing.[46] To get deeper inside knowledge of the loading and releasing of the HKUST-1 Chen and colleagues used three medicines. These three medicines were Ibuprofen (0.34 g per gram), Gualacol (0.38 g per gram), and Anethol (0.40 per gram). The results were astonishing as the specific drug loading for Ibuprofen and both MOFs was synthesized by Férey and colleagues.[46–48] The release time of the drug from HKUST-1 was also different. Ibuprofen was released over a period of 16 h and Anethol was released over a period of 22 h. Gualacol was released over a period of 10 h. Interesting fact, gotten from the results to that timing of drug release corrects the drug loading capacity, which demonstrates that the medicine which has higher loading doses shows longer release time from HKUST-1. Specific prospects will depend only on the ongoing research, technological advancement, evolving need of the pharmaceutical fields and medical fields. For the complex medical condition addressing drug loading and releasing becomes tough. Research work is going on the HKUST-1 for its optimal usage and its toxicity synthesis process must be well run for large scale manufacturing. Being a competitive candidate of MOFs, it is believed in the forth coming day

HKUST-1 will be used more in future. Controlled synthesis and post synthesis functionalization sometimes affect the release kinetics of HKUST-1 MOFs. Adjustment in the encapsulation strategy also controls the drug release. Sometimes this changes the method of drug loading, structure of MOF or function group to achieve sustained drug release.

UiO MOF FAMILY

Substantial research has been going on UiO MOFs. In 2008, the first UiO MOF was formed and published under the supervision of Karl Petrel at the University of Oslo. UiO MOFs are made up of Zn, Cu and Fe linked with terephthalic acid that is organic ligand. Because of its composition UiO MOFs have ultra-high porosity and well-ordered structure.[49] A well-known UiO MOF is UiO-66, UiO structure contains ZnO_6 octahedral structure, which have 1,4-BDC as linker and zinc metal. It has a 3D framework created by six coordinated octahedral ZnO_6 which is linked with terephthalic acid ligand. Each ligand is connected with four ZnO_6 Octahedral and each Octahedral ZnO_6 is linked to six ligands this comes up with the well-organized and tightly interrelated channels.[50] This interconnected network of UIO-66 showed its unique properties which includes high porosity ($0.6 \sim 1.2\ cm^3/g$), high thermal stability and higher surface area (1200–2,200 m^2/g). Its high porosity is because of its colossal empty areas in its structure. Tiny molecules like gases can easily be absorbed in these void areas. Its high surface area is because of the small channeling system having pore inside structure. Its high thermal stability is because of the strong covalent bond inside its structures. Its frequent encapsulation strategy involves drug loading, and these strategies have several methods to achieve instance covalent functionalization and impregnation. Drug that is being carried by UiO-66 includes anti-cancer drugs and anti-inflammatory drug. The loading of medicine was 450 mg/g for UiO-66 MOF for anti-cancer drugs for example doxorubicin. The contrast in these two drugs is highly visible just because of the difference in the size of the drug. Ibuprofen (206 g per mol) is smaller as compared to doxorubicin (molecular weight 544 g per mol). This result in the higher drug loading capacity for the doxorubicin as it will occupy more void spaces,[51] inside structure of UiO-66 as compared to Ibuprofen.

These are two stages for drugs to release normally by UiO-66. Initial burst sustained and steady release. After the loading of drug inside UiO-66, first few h or days is ingested, first stage occurs. This rapid stage as, at this point the amount of the drug was rapidly released from UiO-66 surface. This rapid release was attributed because of the difference in amount of drug present in interior and exterior of UiO-66 structure. It was under control more than the 1st stage. There are so many factors that effects the kinetics from MOF molecule, shape, porosity surface area of UiO-66 practical.[51,52] Because of its unique properties, it has vast application not only in drug delivery but also in other useful fields.[34] Thus, it can act as a potential candidate in drug delivery of tumor therapy.[26,53] Historical overview of UiO-66 explains it massive use in drug delivery but research has been going on which will make UiO-66 more popular in nanoscience and soon it will be meet the evolving challenges and problem related to UiO-66 MOF.

ZIF family

A crystalline structure formed because of the link between metal ion and organic ligand. ZIFs are porous material formed of Zn ions and 2-methylimidazole as organic linker having tetrahedral geometry and bond angle of M-IM-M is 140 degree.[38] Remarkable thermal stability, high surface area (BET 1630m^2/g) tunable porosity and shape, higher drug loading ability. Research has been going on into the different varieties of ZIF MOFs. But ZIF-8 for drug delivery system has shown positive results because of its unique behavior in drug loading. It makes ZIF-8 a potential candidate for medical field application not only in medical field but in many other fields. ZIF-8 has extensively being used like in catalyst adsorptions medication delivery.[54] Depending upon the size of ZIF-8, the appropriate amount of drug loads inside the structure. Thus, it can be modified into different shapes and lengths. ZIF-8 makes it feasible for macro-molecules like proteins and peptides (adsorption and attachment) and micro compounds like doxorubicin and methotrexate (encapsulation strategy) to be loaded inside empty space. ZIF-8 capacity of drug loading can be improved functionalization process, in which many functionalize the framework of MOF with specific functional groups.[55] Being stimuli responsive, ZIF-8 releasing kinetics is greatly affected. Just like UiO-66, ZIF-8 is stimuli responsive MOFs, which can only be activated by stimuli. After activation of physical structure and chemical composition of MOF is being altered intended to release the drug at certain point. Zn ions in ZIF-8 are primary reason of its being stimuli responsive MOF as Zn ions are pH sensative.[47,56] It consists of three phases to release drug. The structure of ZIF-8 is swollen, which is followed by degradation process which occurs because of external stimuli (example pH or temperature), results in the diffusing out of drug molecule from ZIF pores. In second step, distributing outside of pores of medicine spreading of drug molecule occurred once the structure of MOFs begins to collapse. Many factors are involved like porosity, size of drug molecules, gradient of drug molecules, concentration. At the last step, diffusing out from the MOF, the drug molecule interacts with the releasing medium which can be body fluid, buffer solution and factors release rate as well as drug stability for molecule are pH and temperature of release medium.

Comparison of drug delivery of different MOF families

MIL MOFs typically possess hefty surface areas and tunable pore sizes, allowing for efficient loading of drugs with varying sizes and physicochemical properties. This feature enables the encapsulation of a variety of molecules, which includes nucleic acids, proteins and smaller molecules. MIL MOFs offer a diverse range of structures and compositions, providing opportunities for tailored drug delivery systems. Surface modifications and functionalization can be employed to achieve specific targeting abilities and controlled release kinetics. Some MIL MOFs may exhibit inherent cytotoxicity or induce immune responses when introduced into biological systems. Evaluating the biocompatibility of MIL MOFs is crucial to ensuring their safe application for drug delivery. Stability Issues: Certain MIL MOFs may undergo degradation or structural changes in physiological environments, compromising their long-term stability and efficacy as drug carriers. Addressing stability concerns is essential for maintaining the integrity and performance of MIL-based drug delivery systems.[57,58]

ZIF MOFs are recognized for extraordinary thermal as well chemical constancy, making them promising candidates for drug delivery in harsh biological conditions. Their robustness ensures the integrity of drug-loaded ZIFs during storage and administration. Some ZIF MOFs exhibit pH-dependent drug release, wherein the acidic microenvironment of tumor tissues triggers the dissolution or disintegration of ZIFs surface, foremost controlled proclamation of encapsulated medicine. The narrow pore size

distribution of ZIFs may restrict the encapsulation of larger drug molecules or hinder the diffusion kinetics of loaded drugs within the MOF framework. Overcoming pore size limitations is crucial for optimizing drug loading capacity and release rates. Achieving precise control over ZIF synthesis parameters, such as reaction conditions and precursor selection, can be challenging. Furthermore, scaling up the production of ZIF-based drug delivery systems may encounter difficulties in maintaining batch-to-batch consistency and quality.[18,59]

Copper-based HKUST MOFs feature open metal sites and large pore sizes, facilitating high drug loading capacities and efficient encapsulation of therapeutics. This characteristic is advantageous for delivering a wide range of drugs, including hydrophobic compounds and biomolecules. HKUST MOFs can respond to peripheral stimulus like changes in heat or hydrogen ions concentration, or light, which enabled releasing of medicines at target sites within the body. Biocompatibility. The presence of copper ions in HKUST MOFs may raise concerns regarding potential toxicity and adverse effects in biological systems. Comprehensive evaluations of biocompatibility and long-term safety are necessary to assess the suitability of HKUST MOFs for clinical applications. HKUST MOFs may experience degradation or leaching of metal ions in physiological environments, compromising their structural integrity and drug release kinetics. Strategies to boost up stability of HKUST derived medicine carrying and releasing are essential for ensuring their efficacy and safety in vivo.[60,61]

UiO MOFs exhibit robust chemical stability, maintaining their structure and functionality in various biological and environmental conditions. This exceptional stability ensures the long-term integrity of drug-loaded UiO MOFs during storage and administration. UiO MOFs offer versatile pore structures that can be tailored to accommodate specific medicines and control releasing kinetics. Tunability in porosity as well as functionalities enable precise modulation of drug delivery systems for optimized therapeutic outcomes. Some UiO MOFs may feature relatively small pore sizes or narrow pore entrances, which can hinder the efficient diffusion of loaded drugs and affect release kinetics. Strategies to enhance pore accessibility and diffusion pathways are necessary to maximize the therapeutic efficacy of UiO-based drug delivery systems. Achieving precise surface functionalization of UiO MOFs for targeted medicine delivery applications may pose synthetic challenges and require sophisticated techniques. Strategies to streamline surface modification processes and ensure reproducibility are essential for advancing UiO-based drug delivery technologies.[62,63]

A novel structure with great potential for a range of scientific and industrial uses is the cobalt-based MOF (Fig. 3), $Co_2(OH)_2$(bbta).[64] Cobalt serves as the core metal ion in this MOF, which is coordinated with the bbta ligand (1H-benzo[d][1–3] triazole) and falls within the category of transition metal-based MOFs. The framework is a hydroxide-bridged MOF because the addition of hydroxyl groups (OH) emphasizes its open structure, which frequently improves catalytic or adsorption activities. Its repeated hexagonal pattern indicates that $Co_2(OH)_2$(bbta) has remarkable porosity. Because of this characteristic, it can be used for selective adsorption, catalysis, and gas storage. The framework's cobalt atoms are joined by organic ligands and hydroxyl bridges to form a strong three-dimensional network. In addition to stabilizing the framework, the hydroxide groups take part in a number of chemical reactions, including catalysis and hydrogen bonding. This MOF has diversity in terms of uses. It is perfect for gas adsorption and storage due to its high porosity

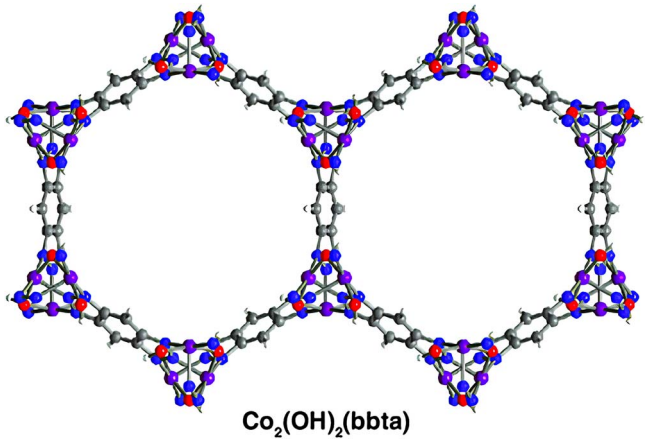

Fig. 3. Cobalt based MOF.

and stability, especially for gases like O_2, CO_2, and H_2. Its catalytic efficacy is increased by the exposed cobalt centers and hydroxide groups, which serve as active sites for redox reactions. This MOF's regulated pore diameters and structural stability may make it easier to employ in drug delivery systems with the right adjustments. The framework has coordinated hydroxyl groups and excellent porosity when activated. The structure changes slightly when oxygen is added, including the coordination environments and bond lengths (e.g. Co-O distances). The MOF's capacity for gas storage and catalysis is further improved by these modifications.[65,66]

$Co_2(OH)_2$(bbta) differs from other well-known MOFs like HKUST-1, MIL frameworks, and ZIFs in several ways depending on their core metal, ligands, structural characteristics, and applications. The core metal of HKUST-1 is copper (Cu^{2+}), whereas $Co_2(OH)_2$(bbta) is based on cobalt (Co^{2+}). The ligands also differ greatly; $Co_2(OH)_2$(bbta) uses a nitrogen-rich bbta ligand (1H-benzo[d][1,2,3]triazole), whereas HKUST-1 uses trimesic acid (benzene-1,3,5-tricarboxylic acid) as a carboxylate-based ligand. $Co_2(OH)_2$(bbta) has hydroxide bridges connecting cobalt atoms, which provide unique chemical reactivity, whereas HKUST-1 uses carboxylate coordination to generate paddlewheel units. Applications-wise, HKUST-1's large surface area makes it ideal for storing gases, especially CO_2 and CH_4. Utilizing the active centers of cobalt and hydroxide, $Co_2(OH)_2$(bbta) is better suited for catalytic and redox applications. $Co_2(OH)_2$(bbta) is based on divalent cobalt ions, whereas MIL MOFs usually use trivalent metal ions as Fe^{3+}, Cr^{3+}, or Al^{3+}. Their ligand selection also distinguishes them; whereas $Co_2(OH)_2$(bbta) integrates a nitrogen-based bbta ligand, creating a distinct coordination geometry, MIL frameworks employ carboxylate-based ligands such as terephthalate in MIL-53 or trimesic acid in MIL-101. In contrast to $Co_2(OH)_2$(bbta), which is more rigid because of the stabilizing impact of hydroxide bridges and cobalt's strong binding, MIL MOFs frequently display breathing behavior, which means that their pores can expand or contract in response to external stimuli. Whereas $Co_2(OH)_2$(bbta) is mainly designed for catalytic and reactive applications, MIL MOFs are excellent in gas adsorption and separation procedures. ZIFs, such as ZIF-8, have a distinct zeolite-like topology based on tetrahedral metal–ligand coordination, which contrasts with the framework of $Co_2(OH)_2$(bbta) that features hydroxide bridges and octahedral cobalt coordination. While ZIFs also use cobalt (or zinc) as the central metal, the imidazolate-based linkers (e.g. 2-methylimidazole in ZIF-8) result in tetrahedral coordination, unlike the triazole-based bbta

ligands in $Co_2(OH)_2$(bbta). Regarding thermal stability, ZIFs are known for their hydrophobic nature and exceptional thermal resilience. On the other hand, $Co_2(OH)_2$(bbta) is both thermally stable and hydrophilic due to its hydroxide bridges, making it particularly suitable for catalytic or adsorption processes in aqueous environments. The cobalt centers and hydroxide bridges in $Co_2(OH)_2$(bbta) make it particularly well-suited for applications needing strong catalytic activity and redox reactions, even though HKUST-1, MIL, and ZIF MOFs are well known for their general gas storage and separation capabilities. It differs from the other MOF families in both structure and use due to its unique ligand structure and bridging groups. Drug delivery may be possible using $Co_2(OH)_2$(bbta), but its applicability is dependent on certain structural and property-related parameters.[67–69]

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Each MOF family offers unique advantages and challenges for drug delivery applications, emphasizing the importance of considering specific design criteria, performance characteristics, and application requirements when selecting an appropriate MOF platform for therapeutic delivery. Addressing the identified challenges through innovative strategies and interdisciplinary collaborations will contribute to the advancement of next-generation MOF-based medicine carrying process with enhanced efficacy, safety, & clinical translatability.

MOFs are versatile materials with properties like high thermal stability and large BET (Brunauer–Emmett–Teller) surface areas, both of which are crucial for their practical applications. Thermal stability reflects a MOF's ability to maintain its structural integrity at elevated temperatures. MOFs such as UiO-66 and ZIF-8 exhibit exceptional thermal stability, with decomposition temperatures exceeding 500 °C and 400 °C, respectively. This makes them ideal for applications in industrial processes, such as high-temperature catalysis (e.g. hydrocarbon cracking), and gas storage systems, where structural robustness under varying conditions is essential. For biomedical uses, although extreme heat resistance is not directly required, thermal stability ensures material durability during sterilization and long-term storage.[70,71]

The total accessible surface available for adsorption or storage is represented by the high BET surface area, which is commonly expressed as m^2/g. For gases like CO_2, CH_4, and H_2, MOFs with surface areas greater than 1,500 m^2/g, such MOF-5 and ZIF-8, provide improved adsorption and storage capabilities. High surface areas in drug delivery devices improve therapeutic results by increasing drug loading capacities. In catalysis, more active sites are produced by a bigger surface area, increasing catalytic efficiency. However, the application determines whether a high BET surface area is relevant. MOF that excels in gas adsorption but has limited chemical stability and a high BET may not work well in water-based environments.[72,73]

UiO-66, which is exceptionally stable due to its strong Zr-O bonds and appropriate for both biomedical and industrial purposes, provide a concise summary of the practical implications of these features. ZIF-8's large surface area (~1,630 m^2/g) and hydrophobic nature make it ideal for pH-sensitive drug delivery and CO_2 storage. On the other hand, MOF-5 is less stable in humid environments but is better suited for gas storage due to its extraordinarily high surface area (~3,500 m^2/g). Since thermal stability and BET surface area have a direct impact on performance in drug delivery, catalysis, and environmental applications, it is essential to comprehend how these two parameters interact when choosing the right MOF for a certain application.[74,75] Because of their remarkable chemical stability and biocompatibility—two qualities essential to safe and efficient drug delivery—the UiO Series and ZIFs are among the best MOFs for biomedical applications. The structural flexibility of the MIL Series sets it apart from other pharmaceuticals and biomolecules, making it extremely adaptable to a wide range of medical uses. The PCN Series, on the other hand, is designed for photo-responsive drug delivery, a capability that is becoming more and more useful in advanced cancer therapies, especially in photodynamic treatments. Because of their inherent biocompatibility and biodegradability, which guarantee compatibility with biological systems while reducing side effects, bio-MOFs stand out as extremely promising for protein and gene delivery. The special ability of hybrid MOFs to combine several functions allows them to tackle difficult medical problems, such theragnostic, which is the integration of medicine delivery with diagnostics. This study offers a thorough summary of the characteristics, uses, and possibilities of several MOF families in the

medical domain (as mentioned in Table 1), emphasizing their unique benefits for particular biomedical applications.

Biomedical applications of MOF

Stability in physiological conditions

Chemical perspective

One important factor that determines how well MOFs operate in drug delivery is how stable they are under physiological settings. When exposed to aqueous environments, especially at physiological pH (about 7.4) or in slightly acidic settings (such as tumor microenvironments, pH 6.5–6.8), many MOFs undergo hydrolysis of their metal–ligand interactions. For example, because Zn-N bonds are prone to cleavage in water, particularly in acidic environments, zinc-based MOFs (such ZIF-8) are recognized for having comparatively reduced hydrolytic stability. Research has shown that in tumor-like acidic conditions or simulated stomach juice (pH ∼1.2), ZIF-8 suffers structural breakdown within 6–12 h, resulting in faster medication release rates. The hydrolysis of Cu-carboxylate bonds causes notable deterioration of copper-based MOFs, as HKUST-1, in biological fluids. For instance, HKUST-1's framework starts to disintegrate in 24 to 48 h after being exposed to phosphate-buffered saline (PBS) because phosphate ions attach to Cu centers in a competitive manner. This causes the surface area of HKUST-1 to drop from around 1,200 m^2/g to less than 300 m^2/g. However, because of their strong Zr-O bonds, zirconium-based MOFs (such UiO-66) have excellent hydrolytic stability and maintain their structural integrity even under extreme circumstances. According to reports, UiO-66 retains more than 90% of its crystallinity after 72 h in PBS, which makes it a good choice for applications that call for extended exposure to physiological fluids.[76,77]

Medical perspective

From a medical perspective, MOF instability in biological settings may result in early medication release, which might compromise the effectiveness of treatment. A "burst effect," which is characterized by an initial rapid release of the encapsulated drug, is frequently the result of premature release and can cause systemic toxicity or decreased drug availability at the target site. In contrast to the intended prolonged release over several days, more over 60% of the medication was released in the first 8 h in a phosphate-buffered medium in a study employing MIL-100 (Fe) loaded with doxorubicin. Because of the unchecked existence of free drug molecules, this instability not only lowers bioavailability but also raises the possibility of side effects such hepatotoxicity or nephrotoxicity. Certain MOFs' breakdown products, including metal ions or organic ligands, can have unfavorable systemic consequences. Cytotoxicity and oxidative stress in neighboring tissues have been linked to increased amounts of free Zn^{2+} ions from degraded ZIF-8 in vivo. Similarly, the production of reactive oxygen species (ROS), which can lead to inflammation and cellular damage, has been linked to copper ions that leach from HKUST-1. MOFs with stronger structures, as UiO-66, on the other hand, show far less degradation and very little production of harmful byproducts, guaranteeing safer profiles for medical applications.[78,79]

Recommendation to overcome

Improving the hydrolytic stability of MOFs is essential to reducing these difficulties. Stability can be considerably increased, and the burst effect can be decreased by utilizing surface functionalization techniques (e.g. PEGylation or coating with biocompatible polymers) and strong metal–ligand linkages, such as Zr-O or Al-O. It is possible to obtain regulated and localized drug release while reducing systemic toxicity by constructing MOFs with stimuli-responsive linkers that selectively degrade under particular conditions (such as pH or enzyme concentration). Thorough in vitro and in vivo stability experiments conducted under physiologically mimicked circumstances are necessary for clinical translation in order to confirm the safety and effectiveness of MOFs in biomedical applications.[80,81]

Potential toxicity

Chemical perspective

There are serious dangers to biological systems when MOFs release toxic metal ions or breakdown products. This is especially noticeable in MOFs made of chromium and copper, which are labile metals. Under physiological conditions, copper-based MOFs, such as HKUST-1, are known to breakdown and release Cu^{2+} ions in phosphate-buffered saline at concentrations more than 2 mg/L in less than 48 h. This quantity is higher than the 1.3 mg/L WHO acceptable limit for copper in drinking water, which raises concerns about oxidative stress and damage to lipids, proteins, and DNA, among other biological components. MIL-101(Cr) and other chromium-based MOFs may emit Cr^{3+} ions, which are necessary in minimal amounts but can be cytotoxic and genotoxic at high concentrations. Because of their interactions with cellular enzymes and DNA, Cr^{3+} ions can cause apoptosis in human fibroblasts at concentrations more than 1 mg/L. It's possible that the organic linkers utilized in MOFs, like imidazolate derivatives or terephthalic acid, increase toxicity. For example, some linkers can disrupt cellular signaling pathways when they metabolize into reactive intermediates in vivo. In one investigation, it was discovered that at concentrations as low as 50 μM, imidazolate-based linkers released from ZIF-8 could cause mitochondrial dysfunction in hepatocytes. Even though certain MOFs contain biocompatible ligands (such fumaric acid), this does not completely remove the possibility of toxicity from other breakdown products.[82,83]

Medical perspective

Medically speaking, materials based on MOFs have the potential to cause immunological reactions that result in inflammation or hypersensitivity reactions. MOF nanoparticles are frequently opsonized by plasma proteins upon intravenous injection, designating them for removal by the mononuclear phagocyte system (MPS). Systemic inflammation may result from this interaction's stimulation of the secretion of pro-inflammatory cytokines such tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). For instance, in mouse models, HKUST-1 nanoparticles have been demonstrated to increase IL-6 levels by 2.5 times in just 6 h after injection. Similarly, MOF particles, especially those with large surface charges, can trigger the complement system, causing hypersensitivity reactions that manifest as fever, hypotension, and rash. The lack of long-term toxicity studies on MOFs prevents them from being used in therapeutic settings. MOFs like MIL-100(Fe) are comparatively safer, exhibiting low acute toxicity in mouse models at dosages as high as 100 mg/kg. Concerns regarding long term toxicity are raised by the possible buildup of non-biodegradable MOFs in organs such as the kidneys, liver, or spleen. Even at subtherapeutic levels of 25 mg/kg, repeated administration of ZIF-8 over 14 days in rats led to a 30% rise in oxidative stress indicators in hepatic tissues.[84,85]

Recommendations to overcome

Researchers should give top priority to creating MOFs using metals that have low toxicity profiles, such aluminum or zirconium, and make sure that naturally biocompatible linkers

Table 1. Medical applications of different MOF families.

MOF Family	Central Metal Ions	Ligands	Key Features	Potential in Drug Delivery	Other Medical Applications
HKUST-1	Cu^{2+}	Benzene-1,3,5-tricarboxylate (BTC)	High surface area, moderate thermal stability, strong Cu-ligand bonds	Effective for loading hydrophilic drugs due to its polar framework, but limited for long-term stability in vivo	Gas adsorption for controlled O_2 delivery in therapeutic applications, imaging agents
UiO Series	Zr^{4+}, Hf^{4+}	Terephthalate (BDC)	High thermal/chemical stability, tunable porosity, biocompatible zirconium core	Widely used for sustained release of anticancer drugs and biomolecules (e.g. doxorubicin, proteins)	Imaging (as contrast agents), bio-imaging, and drug encapsulation
ZIFs	Zn^{2+}, Co^{2+}	Imidazolate derivatives	Zeolite-like topology, hydrophobic frameworks, high thermal stability	Redox-responsive drug delivery, pH-sensitive drug release in tumor microenvironments	Biosensors, oxygen delivery in ischemic tissues, and biocatalysis
MIL Series	Fe^{3+}, Cr^{3+}, Al^{3+}	Terephthalate, trimesic acid	Flexible framework (breathing effect), water stability in some types	Used for adsorbing and releasing water-soluble drugs, adaptable pore size for diverse drug molecules	Bio-catalysis, drug carriers for wound healing, and diagnostic agents
CAU Series	Al^{3+}	Amino-functionalized terephthalate	Highly stable, amino-functionalized for biomolecule interaction	Functionalized frameworks for enhanced drug adsorption and selective release	Antimicrobial coatings, enzyme immobilization
MOF-74	Mg^{2+}, Zn^{2+}, Ni^{2+}	2,5-Dihydroxyterephthalate	Open metal sites, high CO_2 adsorption capacity, tunable pore size	Effective for targeted drug delivery by exploiting the open coordination sites for specific biomolecule binding	Imaging agents for MRI, bio-catalysis for pharmaceutical synthesis
PCN Series	Zr^{4+}, Ti^{4+}	Terephthalate, porphyrin	Porphyrin-based light-harvesting, photosensitizing ability	Stimuli-responsive drug release using light or temperature, cancer photodynamic therapy (PDT)	Photo-imaging, PDT for cancer treatment, and nanotheranostics
Bio-MOFs	Ca^{2+}, Mg^{2+}, Zn^{2+}	Amino acids, nucleobases, or peptides	Biocompatible, derived from biomolecules, biodegradable	Ideal for protein and peptide delivery, excellent biocompatibility for gene delivery	Tissue engineering, bone regeneration scaffolds
Porous Silicon MOFs	Si^{4+}	Hybrid organic–inorganic linkers	Biodegradable, flexible pore size, highly tunable	Used for controlled drug release, especially hydrophobic drugs, due to flexibility in pore engineering	Antibacterial implants, long-term drug delivery in implants
Hybrid MOFs	Multiple metals	Mixed organic and inorganic ligands	Combined properties of two MOF families, adaptable chemistry	Multi-drug delivery systems for complex treatments (e.g. anticancer and anti-inflammatory drugs simultaneously)	Dual-functionality applications like drug delivery combined with imaging (theranostics)

are used in order to overcome these toxicity issues. Immune activation can be decreased and circulation times prolonged by functionalizing MOF surfaces with polymers such as PEG or zwitterionic coatings. To further guarantee safety, comprehensive in vivo investigations evaluating long-term toxicity, biodistribution, and clearance mechanisms are necessary. Safer clinical applications can be made possible by integrating cutting-edge imaging and analytical methods like ICP-MS and histopathology,

which can offer thorough insights into MOF degradation and toxicity profiles.[86,87]

Biodegradability and clearance

Chemical perspective

MOFs' long-term safety and effectiveness in biomedical applications are greatly impacted by their biodegradability. MOFs that degrade slowly or not at all are more likely to build up in tissues or organs, especially those with hydrophobic surfaces or big, inflexible structures. For instance, in simulated biological fluids, ZIF-8, a zinc-based MOF, only 30 to 40% of its structure breaks down over 72 h, indicating incomplete degradation under physiological pH (7.4) circumstances. The strong coordination between Zn^{2+} ions and imidazolate linkers, which inhibits hydrolysis, is the cause of this persistence. MOFs such as MIL-100(Fe) and UiO-66(Zr) show partial biodegradability because of the addition of more hydrophilic ligands or weaker coordinating bonds. Nevertheless, even for these MOFs, environmental variables like pH and the presence of chelating agents (such phosphate or citrate ions) have a significant impact on breakdown rates. In phosphate-buffered saline UiO-66 maintains more than 80% of its crystallinity after 72 h, suggesting a very moderate rate of deterioration. Due to its delayed biodegradability, MOF particles may not be completely cleared, which could result in long-term buildup and related hazards.[88,89]

Medical perspective

From a medical perspective, the buildup of MOFs in tissues presents significant hazards, including as long-term toxicity and disruption of regular organ processes. Due to their absorption by the mononuclear MPS, intravenously delivered MOF nanoparticles preferentially aggregate in the liver, spleen, and kidneys, according to studies conducted using rodent models. For example, a biodistribution study of MIL-101(Cr) in rats showed that only 15% of the dose was eliminated via renal excretion, with 60% of the dose remaining in the liver after 48 h. Because of the release of metal ions or unprocessed particles, this extended retention raises the risk of liver inflammation, fibrosis, or oxidative damage. The particle size of MOFs limits their renal clearance. The kidneys' glomeruli can only efficiently filter nanoparticles that are smaller than 5–6 nm. Larger MOFs (larger than 100 nm) frequently evade renal clearance in favor of slower and less effective hepatic metabolism. For example, it was discovered that ZIF-8 particles, which have an average size of around 120 nm, can remain in hepatic tissues for up to 14 days after being administered. This can lead to increased levels of liver enzymes, such as ALT and AST, which are indicators of hepatic stress.[90,91]

Recommendations to overcome

Researchers should concentrate on creating frameworks with stimuli-responsive linkers that break down more effectively in physiological settings in order to increase the biodegradability and clearance of MOFs. For example, tailored drug delivery can be facilitated while guaranteeing quick breakdown after administration via pH-sensitive MOFs that degrade in acidic environments, such as tumor microenvironments. Renal clearance and tissue accumulation can be improved by functionalizing particles (e.g. PEGylation) to increase surface hydrophilicity and decrease particle size. Thorough in vivo investigations are necessary to evaluate the long-term destiny of MOFs, considering their metabolism, excretion, and tissue accumulation potential. Remaining MOF materials in tissues and organs should be measured using methods like histological analysis and inductively coupled plasma mass spectrometry (ICP-MS). The safe and successful clinical translation of MOFs in biological applications will depend on overcoming these obstacles through creative design and exhaustive testing.[92,93]

Reproducibility and scalability

Chemical perspective

One of the biggest challenges in the industry is still creating MOFs with constant and desired characteristics, like consistent particle size, regulated porosity, and dependable surface functionalization. Batch-to-batch inconsistencies may result from variations in synthetic conditions, including temperature, pH, solvent ratios, and mixing parameters. For example, slight variations in temperature (±5 °C) or ligand-to-metal ratios during the solvothermal synthesis of UiO-66 can cause a 20 to 30% change in porosity and surface area. A UiO-66 sample with a surface area of 1,200 m^2/g can load up to 450 mg/g of doxorubicin, but a sample with reduced porosity (e.g. 900 m^2/g) may load less than 300 mg/g under the same conditions. These discrepancies have a direct impact on drug loading capacity and release kinetics. Since particle size affects biodistribution, cellular absorption, and clearance, achieving consistent particle size is also crucial. ZIF-8 nanoparticles produced with slightly varying rates of stirring can range in size from 80 nm to 150 nm. Inconsistent therapeutic results result from this size fluctuation, which also impacts the drug's release behaviour and encapsulation efficiency. To increase repeatability, sophisticated methods such as microfluidic synthesis have been investigated. These methods provide exact control over reaction conditions and achieve particle size variations within ±5 nm. Scalability is still a drawback for these approaches, though.[94,95]

Medical perspective

Scalability and reproducibility are essential in the medical setting to facilitate clinical translation and guarantee consistent therapeutic results. Changes in MOF characteristics can result in notable variations in drug release profiles, which may have an impact on safety and effectiveness. Batch-to-batch differences in porosity and particle size were blamed for inconsistent drug release rates (varying from 12 to 24 h for different batches) in a clinical experiment utilizing MIL-101(Cr) loaded with ibuprofen. Because organizations like the FDA demand rigorous adherence to quality standards and reproducibility in manufacturing, such disparities present difficulties for regulatory approval. Scalability is still another important obstacle. Due to their high energy requirements, lengthy reaction times, and challenges in maintaining consistent conditions, conventional solvothermal methods which are frequently employed for laboratory-scale synthesis are not readily transferable to industrial-scale production. Improved scalability was shown in a recent work on the continuous flow synthesis of MOFs, such as HKUST-1, which produced up to 500 g per day with consistent characteristics. Even with these refined techniques, surface functionalization at scale is still difficult to achieve since even small functionalization variations can change drug release patterns and targeting effectiveness.[96,97]

Recommendations to overcome

The use of sophisticated synthesis techniques, such as continuous flow reactors and mechanochemical processes, is necessary to addressing issues with repeatability and scalability. Larger-scale manufacturing of MOFs with consistent characteristics is made possible by continuous flow systems, which provide exact control over reaction settings. 95% repeatability in surface area (±50 m^2/g) and particle size (±10 nm) can be achieved using

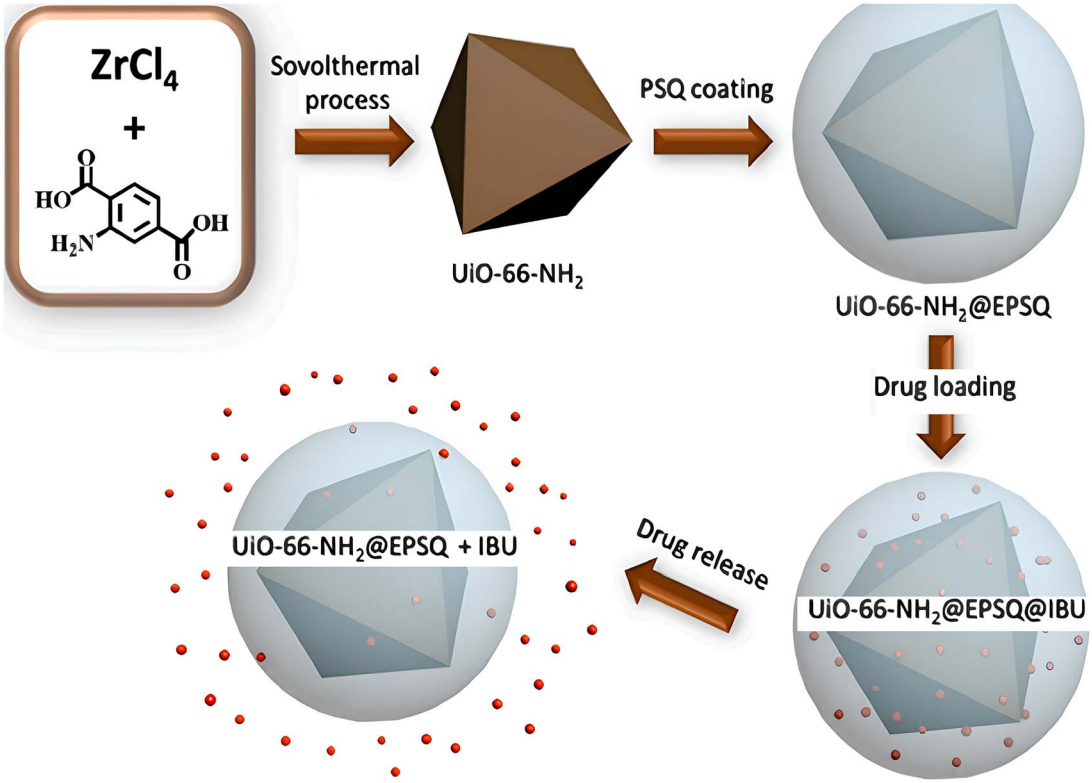

Fig. 4. Synthesis of UiO-66-NH_2@EPSQ MOF for drug delivery of medicine.

continuous flow synthesis of UiO-66 (fig. 4).[98,99] Batch consistency can be guaranteed by putting strong quality control procedures in place, such as real-time monitoring utilizing spectroscopic techniques (e.g. FTIR and XRD). Reproducibility will be further improved by creating standardized procedures for synthesis and post-synthesis changes, such as functionalization. Collaborations between academics and industry are essential for cost reduction and manufacturing process optimization to increase scalability. By resolving these problems, MOFs can move more quickly from lab research to clinical and commercial uses, guaranteeing dependable treatment results and regulatory compliance.[100,101]

Controlled release challenges

Chemical perspective

Because of their high porosity and adjustable architectures, MOFs are highly regarded as potential drug delivery vehicles. Controlling the release kinetics of medications encapsulated in MOFs is still quite difficult, though. Highly porous MOFs, including ZIF-8 and MIL-101(Cr), frequently show a quick initial release of the medication, which is known as the "burst effect." In PBS MIL-101(Cr) loaded with ibuprofen exhibits an initial burst release of more than 50% of the encapsulated medication within the first 6 h. Weak interactions between the drug and the MOF surface as well as the fact that pharmaceuticals are adsorbed on the outside of the surface rather than inside the pores are the reasons for this burst. The sluggish diffusion of pharmaceuticals from the MOF's core causes the release rate to frequently become suboptimal after the initial burst. The difficulties in attaining sustained release are demonstrated by ZIF-8, which shows a cumulative release of only 70% of encapsulated doxorubicin after 48 h at physiological pH. The MOF's pore size and functional groups, in addition to the size and charge of the drug molecules, are important factors in regulating release behavior. Even with attempts to functionalize MOF surfaces with stimuli-responsive groups (such as linkers that are sensitive to temperature or pH), it is still challenging to achieve exact control over the burst phase and sustained release.[102,103]

Medical perspective

The danger of systemic toxicity is further increased by the burst release of medications from MOFs, which can result in abnormally high initial drug concentrations in the bloodstream. High dosages of released chemotherapeutic drugs, like doxorubicin or cisplatin might have serious adverse consequences, including nephrotoxicity and cardiotoxicity. According to a study using HKUST-1 loaded with cisplatin, both malignant and healthy cells experienced rapid cytotoxic effects within the first 12 h, with 60% of the medication being released. For chronic illnesses that necessitate prolonged medication exposure at therapeutic levels, insufficient sustained release can make the therapy ineffective. UiO-66 loaded with methotrexate showed a plateau in drug release after 72 h, reaching just 50% of its targeted cumulative release in the treatment of osteosarcoma. This partial release reduces the treatment's therapeutic effectiveness and calls for larger dosages or more frequent administrations, both of which are impractical in clinical settings.[104,105]

Recommendations to overcome

There are several tactics that can be used to address these controlled release issues. First, by improving drug-MOF interactions and creating a barrier of protection, surface functionalization of MOFs with polymers such as PEG or stimuli-responsive ligands might lessen burst release. PEGylated UiO-66 showed a 20% decrease in doxorubicin burst release within the first 12 h, as opposed to 50% for untreated UiO-66. Second, early drug release can be avoided by adding gatekeeping mechanisms to the pore

openings, such as supramolecular assemblies or nanoparticles. ZIF-8 modified with cyclodextrin gates considerably lessened the burst impact by achieving a steady release of 80% doxorubicin over 96 h. Finally, balancing the drug molecules' adsorption and diffusion rates can be achieved by adjusting the synthesis parameters, such as pore size and surface area. These designs can be further improved by sophisticated computational modeling and real-time drug release profile monitoring utilizing spectroscopic techniques (such as UV/ visible or fluorescence spectroscopy). By resolving these issues, MOFs can be improved to deliver medications with the least amount of toxicity and the greatest amount of therapeutic benefit, opening the door for their wider use in clinical medicine.[106,107]

Functionalization and targeting

Chemical perspective

MOFs can be functionalized by altering their internal or external structure to enhance biocompatibility, targeting, or stimulus responsiveness. To add functional groups or ligands, this method frequently uses complex chemical processes including covalent grafting, non-covalent interactions, or post-synthetic alterations. MOFs are more stable in biological fluids and have lower immune clearance when PEG is attached to them (PEGylation. These changes do have a price, though; depending on the MOF type and the molecular weight of the polymer, PEGylation raises synthesis costs by 15 to 30%. Stimuli-responsive functionalization, such as incorporating pH-sensitive linkers, adds another layer of complexity. In UiO-66-based MOFs, the incorporation of acid-labile linkers allows the framework to degrade in acidic tumor environments (pH ∼6.5), releasing encapsulated drugs. UiO-66 functionalized with folic acid and a pH-sensitive moiety achieved a 3-fold increase in drug release at pH 6.5 compared to pH 7.4. However, these functionalization steps require multi-step syntheses and precise control over reaction conditions, increasing production time by approximately 25%–40%. Another level of complexity is added by stimuli-responsive functionalization, such as the use of pH-sensitive linkers. The addition of acid-labile linkers to UiO-66-based MOFs enables the framework to break down in acidic tumor settings (pH ∼6.5), releasing the medications that are contained. UiO-66 functionalized with folic acid and a pH-sensitive moiety increased drug release three times at pH 6.5 as opposed to pH 7.4. However, the manufacturing time is increased by about 25 to 40% due to the need for multi-step syntheses and exact control over reaction conditions for these functionalization processes.[108,109]

Medical perspective

Off-target effects in MOF-based drug delivery systems result from inadequate targeting, which lowers therapeutic efficacy and raises systemic toxicity. For instance, doxorubicin-carrying non-targeted MOFs may build up in healthy tissues and result in hepatotoxicity or cardiotoxicity. In contrast to ZIF-8 functionalized with RGD peptides (tumor-targeting ligands), which accumulated 60% of the injected dose in tumor tissues, ZIF-8 nanoparticles lacking particular targeting ligands distributed non-specifically, according to recent in vivo research. All MOF types do not have the same level of targeting effectiveness, even with sophisticated functionalization. Particle size, surface charge, and targeted ligand density are some of the variables that affect efficacy. For example, the increased permeability and retention (EPR) effect favors nanoparticles in the 10–100 nm range, making MOFs bigger than 200 nm less effective at penetrating tumor tissues. Furthermore, steric hindrance brought on by an increased ligand density can lower the binding efficiency of targeted MOFs. According to cellular uptake assays, excessive ligand attachment decreased targeting efficacy by 20% in a study employing MIL-101(Fe) functionalized with transferrin.[110,111]

Recommendations to overcome

Various tactics can be used to maximize targeting and functionalization. First, for improved specificity and controlled release, multi-functional MOFs can be made by combining stimuli-responsive components with targeted ligands, including peptides or antibodies. For instance, compared to unmodified UiO-66, a dual-functionalized UiO-66 that included both glutathione-sensitive linkers (for intracellular release) and folic acid (for tumor targeting) produced a 4-fold improvement in therapeutic index. Second, newer approaches such as bio-orthogonal processes and click chemistry provide accurate and effective ways to functionalize MOFs with the least number of adverse effects. When compared to conventional procedures, these strategies can reduce production complexity by 20 to 30%. Lastly, to confirm the targeting effectiveness and biocompatibility of functionalized MOFs, thorough in vitro and in vivo testing is necessary. Real-time information on the biodistribution and targeting effectiveness of MOFs can be obtained by sophisticated imaging methods including fluorescence imaging and positron emission tomography (PET). MOFs can be modified to produce better therapeutic results with fewer off-target effects by tackling these issues and utilizing creative functionalization techniques.[112,113]

Immune clearance

Chemical perspective

The reticuloendothelial system (RES) or mononuclear phagocyte system (MPS), which consists of the liver, spleen, and macrophages, is largely responsible for the immune system's quick recognition and removal of MOFs. This quick clearance is notably visible for larger MOF particles (greater than 200 nm in diameter) and those with surface charges that elicit opsonization, where plasma proteins bind to the particle surface, designating it for phagocytosis by immune cells. Macrophages significantly boost the uptake of ZIF-8 nanoparticles, which have a diameter of about 120 nm. This results in a shorter circulation time and improved clearance. According to trials where ZIF-8 was given intravenously to rats, this phenomenon causes a half-life of less than 2 h in vivo. Surface charge is essential for immunological clearance. The immune system is more likely to recognize positively charged MOFs, including HKUST-1, because they are more likely to interact with negatively charged cell membrane components. According to a study, macrophages absorbed ZIF-8 functionalized with positively charged amine groups 40% more readily than they did the same particles with neutral or negatively charged surfaces. The immune system's increased ability to recognize these particles shortens the time that they can deliver their encapsulated medication by speeding up their removal.[114,115]

Medical perspective

The bioavailability of MOF-drug complexes is greatly decreased by immune clearance, which limits their usefulness for targeted therapies or long-term treatments. In addition to shortening the therapeutic window, rapid clearance also makes it harder for MOFs to build up in target tissues like cancers. The immune system's removal of non-functionalized or non-targeted MOFs can jeopardize the effectiveness of cancer treatment, when prolonged drug release at the target site is crucial. Research

utilizing MIL-101(Fe) nanoparticles to administer doxorubicin in vivo revealed that unfunctionalized particles had a brief half-life, with over 70% of the injected dose being eliminated from the bloodstream in less than 12 h. This quick removal limited the particles' therapeutic effectiveness by preventing them from efficiently building up in tumor tissues. The decreased bioavailability brought on by immune clearance is especially troublesome for repeated or long-term treatments, such those for cancer or chronic illnesses. Larger dosage requirements may result from the faster clearance, raising the possibility of systemic toxicity. Patients who get intravenous injections of non-functionalized MOFs for medication delivery, for instance, could need larger dosages to make up for the rapid clearance, which could result in adverse consequences like fever, inflammation, or other immunological reactions.[116,117]

Recommendations to overcome

There are several ways to improve the circulation time and bioavailability of MOF-drug complexes in order to get around the problem of immune clearance. First, by blocking the immune system's ability to recognize MOFs, surface modification by PEGylation is a tried-and-true method to decrease opsonization and increase circulation time. It has been demonstrated that PEGylated MOFs, like PEGylated ZIF-8, decrease immune system recognition by around 60% and extend the circulation half-life to more than 24 h when compared to unmodified MOFs. Stealth coatings or biomimetic coatings, such as lipids or polysaccharides that can mimic cell membranes, are another intriguing tactic that can conceal the MOF surface from immune cells. When compared to bigger particles, smaller nanoparticles (less than 100 nm) typically exhibit better bioavailability and slower clearance rates. For instance, compared to particles larger than 100 nm, ZIF-8 particles with a diameter of 50 nm showed better pharmacokinetics and a 40% longer circulation time. Finally, adding targeted ligands, like peptides or antibodies, can decrease immune system recognition while simultaneously increasing MOF selectivity for the target region (tumors, for example). This strategy can reduce non-specific uptake while increasing the accumulation of drug-loaded MOFs at target locations. MOFs functionalized with antibodies or peptides that target cancer can bind to tumor cells selectively, improving drug delivery and minimizing off-target effects. By using these techniques, the problem of immune clearance can be lessened, resulting in longer-lasting therapeutic effects and better treatment results for MOF-based drug delivery systems.[118,119]

Smart technologies integration in MOF Synthesis

Modern technologies can greatly improve the efficacy and efficiency of MOFs in drug delivery applications.

Automated synthesis of MOFs using intelligent manufacturing techniques

The synthesis of biological and chemical MOFs/ COFs is being revolutionized using intelligent manufacturing techniques, such as 3D printing/ additive manufacturing as shown in fig. 5 (made with AI and other editing tools), automation and robotics, especially for drug delivery applications. Critical reaction parameters like temperature, pressure, mixing speed, and reactant concentrations can be precisely controlled by automated systems, producing MOFs of superior quality and improved reproducibility.[120]

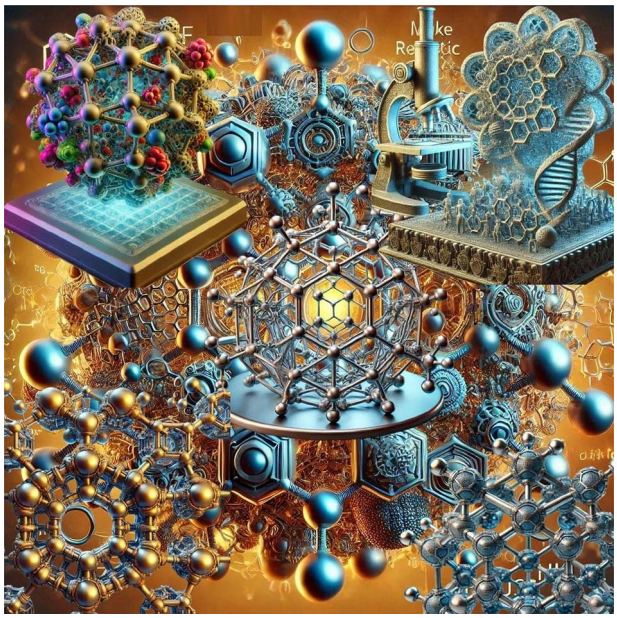

Fig. 5. Additive manufacturing (3D printing) technology to synthesize any type and shape of MOF.

Integration of automation and robotics

Automation lowers unpredictability and human error by enabling the execution of intricate synthetic processes with little assistance from humans. High-throughput robotic platforms, for instance, may manage several processes at once, optimizing solvents and metal-to-ligand ratios for the synthesis of MOFs. UiO-66 MOFs were synthesized using an automated microfluidic system that dynamically adjusted temperature and flow rates to achieve exact control over particle size (varying from 50 nm to 200 nm). In surface area measurements (1200–1,400 m^2/g), our approach outperformed conventional batch synthesis techniques with a 95% repeatability rate. In order to forecast the ideal reaction conditions for MOF synthesis, AI and ML are being used more and more. These models look for relationships between synthesis factors and material properties by analyzing big databases of experimental results. For instance, using input variables like temperature and solvent polarity, machine learning algorithms can forecast the pore size and drug loading capacity of MOFs. In a recent study, ZIF-8's BET surface area was 1,630 m^2/g, and AI-driven predictive models cut down on the time needed to determine the best synthesis conditions by 40%. To precisely control the production of MOFs, mathematical models are necessary for simulating reaction kinetics and thermodynamics. Consistent crystal development is ensured by real-time monitoring of synthesis conditions utilizing sophisticated sensors in conjunction with predictive algorithms. By preserving ideal pH and temperature gradients, these models have increased the yield of MIL-101(Cr) in automated setups from 75% to over 90%. More homogeneous MOF structures have been achieved by optimizing reactant mixing in continuous flow systems through the use of computational fluid dynamics (CFD). Automating MOF synthesis requires the combination of hardware innovations and robotics. Continuous flow reactors provide real-time reaction condition modifications thanks to real-time analytical instruments like FTIR and UV/ vis spectrophotometers. The industrial-scale production of HKUST-1 has shown that these systems are capable of producing up to 500 g/day of MOFs. By automating labor-intensive processes including material

collection, purification, and activation, robotics further improves scalability. MOFs made for drug delivery are guaranteed to satisfy strict quality requirements, such as consistent particle size and repeatable pore architectures, thanks to automated synthesis. Controlling medication loading and release profiles requires these attributes. When compared to MOFs made by hand, those made by automated methods demonstrated a 30% increase in drug encapsulation efficiency and a more stable release profile over a 72-h period. This is especially crucial for medical applications since variations in MOF characteristics can affect patient safety and treatment effectiveness.[121–123]

Although there are many benefits to combining automation and intelligent manufacturing, there are still issues with implementation complexity and expense. Significant investment is needed for advanced hardware and software infrastructure, such as robots and AI integration. Another constant difficulty is making sure automated systems work with a variety of MOF chemistries. The creation of modular systems that can adjust to various synthesis processes and the incorporation of quantum computing to model intricate reaction pathways with previously unheard-of accuracy are examples of future directions. In the creation of MOFs, automated synthesis via intelligent manufacturing signifies a paradigm shift. These systems promise to produce high-quality, repeatable MOFs at scale by utilizing interdisciplinary advancements in chemistry, engineering, artificial intelligence, and mathematics. This will enable them to reach their full potential in applications including drug delivery, gas storage, and catalysis.[124,125]

Real-time monitoring in MOF synthesis using IoT and smart sensors

An important development in intelligent manufacturing is the synthesis of MOFs using Internet of Things (IoT) devices and smart sensors. Key synthesis parameters including temperature, pressure, pH, and reactant concentration can be tracked by real-time monitoring devices, guaranteeing exact process control. These technologies improve the quality, reproducibility, and scalability of MOF manufacturing by allowing for the real-time optimization of reaction conditions through dynamic analysis of this data. During MOF synthesis, smart sensors are essential for continuously monitoring important for reaction parameters control. For MOFs like UiO-66, where a fluctuation of 5 °C can diminish porosity by 20%, temperature sensors, for instance, can precisely monitor reaction temperature up to ±0.01 °C. Like this, pH sensors can measure pH in real time while MIL-101(Cr) is being synthesized, guaranteeing constant crystallinity. A pH range of 4.5 to 5.0 is necessary to reach a surface area greater than 3,000 m^2/g. Solvothermal techniques where pressure control is essential can make use of pressure sensors. At 10–20 bar, pressure sensors remain stable since variations can interfere with crystal formation and cut yields by 15%–25%. IoT devices that are connected to these sensors collect and send the data for additional analysis. Smooth communication between sensors, controllers, and analytical software is made possible by IoT devices. In large-scale operations, IoT-enabled platforms may handle up to 1 GB of data per hour while gathering high-resolution data from several sensors. Deploying edge devices at manufacturing sites allows for local real-time decision-making, such as changing the heater settings or reactant flow rate in milliseconds. Additionally, data can be sent to cloud systems for global accessible and long-term storage, allowing for remote diagnosis and monitoring. By facilitating dynamic optimization, artificial intelligence considerably increases the value of real-time data. Incoming data is analyzed by AI algorithms to find abnormalities, forecast results, and suggest changes. For instance, even when input parameters fluctuate, machine learning models trained on historical synthesis data for HKUST-1 can predict ideal reaction conditions with 95% accuracy. In a recent example study, the variance in ZIF-8 particle size distribution was decreased to within ±5 nm by integrating AI and IoT in a continuous flow reactor, as opposed to ±20 nm using human approaches. Using dynamic changes, the yield increased by 30% while keeping the BET surface area at 1630 m^2/g.[126,127]

Reliable hardware infrastructure, such as IoT gateways, high-precision sensors, and processing units for data analysis, is necessary for the deployment of real-time monitoring systems. The cost of a modern temperature and pH sensor with wireless transmitters ranges from $300 to $500 per unit. While industrial IoT platforms like Siemens Mindsphere are utilized for large-scale manufacturing, devices like Arduino and Raspberry Pi modules provide affordable entry points for small-scale setups. Complex reaction modeling in AI-driven optimizations necessitates high-performance GPUs or quantum computers, especially for large-scale applications. Consistent manufacture of MOFs with characteristics suited for particular applications is ensured by real-time monitoring. For instance, maintaining exact pore diameters is crucial to regulating medication release rates in drug delivery.[128,129] Real-time pH and temperature monitoring during synthesis decreased drug loading capacity fluctuation to less than 5%, improving therapeutic efficacy, according to a study employing MIL-88B. These methods help with gas storage and catalysis in addition to drug delivery. For example, reaching adsorption capabilities of 10 mmol/g for CO_2 at 1 bar in gas adsorption tests requires maintaining a consistent pore size distribution in MOFs like MOF-5.

Even it is beneficial, real-time monitoring in MOF synthesis is not yet widely used due to several obstacles, including as the high upfront costs and the difficulty of combining various technologies. Future advancements could include AI-driven autonomous devices that can self-adjust without human assistance and the use of quantum sensors for previously unheard-of precision.[130,131] These developments could improve scalability and save costs by 20 to 30%, opening up MOFs for use in industrial and medicinal settings. An innovative method for MOF synthesis is provided by real-time monitoring through IoT and smart sensors.

Scalable production of MOFs using intelligent manufacturing

The capacity to scale up manufacturing of MOFs while preserving consistent quality is essential for their translation from laboratory research to industrial and therapeutic applications. Intelligent manufacturing offers creative answers to the problems related to scalable MOF synthesis by combining robots, machine learning (ML), sophisticated automation, and real-time monitoring. Intelligent manufacturing offers creative answers to the problems related to scalable MOF synthesis by combining robotics, ML, sophisticated automation, and real-time monitoring. Multiple MOF batches can be synthesized in simultaneously thanks to automation, which maximizes throughput while reducing human error. Continuous flow reactors, for example, are a crucial invention in the scaling up of MOF production. These technologies allow for continuous manufacturing as opposed to batch-by-batch synthesis since reactants pass through a reactor under carefully monitored conditions. Production of ZIF-8 has been shown to be possible in a continuous flow reactor with a yield of 500 g/day and more than 95% consistency in particle size and surface area (BET ~1,630 m^2/g). Compared to conventional batch processes, which

frequently yield just 50–100 g/day with high variability, this is a major improvement. Because AI dynamically optimizes reaction conditions, it is essential to the scale-up of MOF production. To forecast how factors like temperature, flow rate, and reactant concentration would affect product quality, machine learning systems examine enormous datasets. An AI-driven system enhanced the yield and crystal structure repeatability of MIL-101(Cr) by 30% by optimizing the reaction temperature to ±0.5 °C and pH to ±0.1. In therapeutic settings, where variations in MOF characteristics may affect drug encapsulation effectiveness and release profiles, this level of precision is essential.[125,132]

Scaling up the manufacture of MOFs requires mathematical models based on reaction kinetics and transport phenomena. By simulating the interactions between metal ions and organic ligands, these models forecast the prerequisites for consistent crystal formation. For the design of reactors used in large-scale MOF synthesis, computational fluid dynamics (CFD) is especially helpful. Optimal mixing speeds and temperature gradients were found in a CFD research on UiO-66 synthesis, which reduced defect formation in industrial-scale reactors by 20%. Automated mixers and modular continuous flow reactors are examples of advanced hardware solutions that provide reliable production at scale. Real-time analytical instruments such as dynamic light scattering (DLS) and Fourier-transform infrared (FTIR) spectroscopy are frequently installed in these reactors to track the quality of the output. For MOFs like UiO-66, where temperature changes can diminish surface area by up to 15%, it is crucial to maintain consistent temperatures within ±0.1 °C. Assure the crystallinity of pressure-sensitive MOFs like HKUST-1 by permitting solvothermal synthesis at pressures between 10 and 50 bar. Cost-effectiveness and quality must be balanced when scaling up MOF production. Through waste reduction and resource optimization, intelligent manufacturing lowers costs. For example, up to 80% of the organic solvents used can be recovered by solvent recycling systems in automated setups, which drastically lowers production costs. Compared to conventional techniques, the energy consumption of MOF synthesis has been reduced by 25% thanks to sophisticated energy-efficient reactors. For clinical applications, where vast quantities of MOFs are needed for drug delivery systems, scalable manufacture is very important. For instance, kilogram-scale batches are needed to support preclinical and clinical trials when making MIL-88B for sustained drug release. To meet regulatory standards, uniform medication loading and release are ensured by consistency in pore size and surface chemistry. Large-scale manufacturing makes it possible for MOFs to be utilized in industrial processes like gas storage and carbon capture in addition to healthcare. MOF-5 is being investigated for commercial-scale carbon sequestration projects due to its CO_2 adsorption capability of 10 mmol/g. The viability of large-scale applications has been demonstrated by the achievement of yields of 1 kg/day in the industrial production of MOF-5 employing continuous flow systems.[133,134]

Even with great progress, scaling without sacrificing MOFs' intricate architecture is still a difficulty. Continuous innovation is needed to address problems such reactor clogging, uneven crystallization, and high raw material costs. Future advancements could involve the creation of self-optimizing reactors that modify conditions on their own and the simulation of large-scale reaction pathways using quantum computing. By using green chemistry concepts, the scale-up procedure can become more environmentally friendly and in line with international initiatives to lessen its effects. The scalable production of MOFs is made possible by the strong framework that intelligent manufacturing offers. The effective transfer of MOFs from research to practical applications is ensured by this interdisciplinary technology combination. By evaluating patient data to customize MOF-based therapies that optimize drug release profiles according to specific patient demands, AI can support personalized drug delivery systems and enhance therapeutic outcomes. Through the analysis of extensive datasets of current materials, AI can help with the creation of innovative MOFs by forecasting new candidates with enhanced properties for certain drug delivery requirements. In material science, this method speeds up the discovery stage. The behavior of various MOF structures in drug delivery applications can be predicted using AI algorithms. To find the best metal–ligand combinations that improve drug loading and release patterns, machine learning algorithms can evaluate the data that is currently available. Researchers can learn how various alterations impact drug loading and release mechanisms by using quantum computing to conduct intricate molecular-level simulations of MOF interactions. The research cycle from concept to clinical application could be accelerated by using quantum computers' computing power to significantly cut down on the amount of time needed to predict novel MOF structures and how they interact with different medications. In order to improve the efficacy and safety profiles of MOFs, quantum algorithms may provide sophisticated optimization methods for creating MOFs with particular properties suited for targeted drug delivery.[135–137]

Challenges and future recommendations

To get precise outcomes in all kinds of biomedical applications, we need to use intelligent manufacturing approaches (automation AI integration and quantum computing). Industry 6.0 includes sustainable practices with human centric and customized working. Intelligent manufacturing-based industrial automation production (in Industry 4.0) lowers costs, however it is not directly environmentally friendly approach. It is strongly advised to conduct a life cycle assessment prior to beginning any further research work. Aligning our industrial production and research with sustainable development goals is the need of this era. Climate-resilient, customer-centric, fully automated systems that strive for net-zero carbon emissions, net-zero trash/ waste, and circular economy strategies should thus be the top priority of our academic and industrial research. It is also mandatory that GI (geographical indications) tagging be used with any country's resources and recognize biodiversity of specific nation before using in any biomedical and nonmedical industrial and lab scale applications.[138–143]

We have introduced a critical discussion on the limitations and challenges associated with using MOFs as medicine delivery carriers. MOFs offer high drug loading capacity and controlled release, there may be concerns regarding their long-term stability in physiological conditions or potential toxicity. Addressing these limitations and proposing strategies to overcome them would strengthen the manuscript's credibility and provide valuable insights for future research directions. MOFs may degrade or undergo structural changes over time when exposed to biological fluids or environments, potentially affecting their drug release kinetics and efficacy. Certain MOFs or their degradation products may exhibit cytotoxicity or induce immune responses in biological systems, raising concerns about their biocompatibility and safety for clinical applications. MOFs may encounter challenges related to their stability upon administration in vivo, such as premature drug release or clearance by the immune system, which could compromise their therapeutic effectiveness. Some MOFs may

exhibit slow degradation rates or insufficient biodegradability, hindering their clearance from the body and leading to potential accumulation in tissues or organs. The synthesis of MOFs on a large scale with reproducible quality remains a challenge, impacting their feasibility for commercialization and clinical translation. Ensuring that MOFs are biocompatible, and biodegradable is important for safe biomedical applications. There is a need for comprehensive studies to understand the interaction of MOFs with biological systems and to ensure that they do not elicit adverse immune responses. MOFs must maintain structural stability in the biological environment while also allowing for controlled drug release. Achieving the right balance between stability and release kinetics is challenging. The synthesis of MOFs on a large scale (industrial production) with consistent quality is essential for drug delivery and their daily life emergence. Reproducibility in synthesis is necessary for clinical translation especially on mass scale production. Targeted delivery and efficient uptake by cells are critical for effectiveness of MOF-based drug delivery systems. Strategies to enhance targeting and uptake are still under development. Drugs with respect to specific biological signals or environmental changes holds great potential for site-specific drug delivery. MOFs offer the possibility of enhanced penetration and distribution in tissues, which could improve the efficacy of drug delivery systems. MOFs could be used for combination therapy, where multiple therapeutic agents are delivered simultaneously to achieve synergistic effects, particularly in the treatment of complex diseases like cancer. MOFs are being investigated for tumor-targeted treatment, leveraging their modifiable structure and functionality to enhance targeting and reduce side effects.[144,145]

Conclusions

Since the Industrial Revolution, humanity has achieved great strides, but these achievements have come at a high cost to the environment. Significant ecological harm has been caused by the deeds of past generations, upsetting ecosystems and accelerating climate change. As a result, diseases associated with environmental stressors are on the rise, endangering both biodiversity and human health. Considering this circumstance, a renewed dedication to preserving life on Earth is required, with a focus on the necessity of coordinated research in line with the Sustainable Development Goals (SDGs) of the UN, especially those that deal with climate action, life on land and below water, health and well-being, and responsible consumption. Investigating sustainable technologies, like Metal–Organic Frameworks (MOFs) in medication delivery systems, is one exciting field of study. Because of its special qualities, such as their large surface area, adjustable pore diameters, and superior drug loading and release capabilities, MOFs have become the best options for drug administration. These substances are essential in biomedical applications because they can maximize therapeutic efficacy while reducing toxicity. Several MOF families including MIL, HKUST, UiO, and ZIF are potentially good, along with their traits and possible uses in drug delivery. The MIL Family is well-known for its substantial study and use in medication delivery systems. Higher porosities and greater surface areas are provided by the HKUST Family. High thermal stability is provided by the UiO Family for regulated medication loading and release. The ZIF family has remarkable drug loading capability and adjustable pore diameters. Functionalizing MOFs for targeted medication administration by modifying them with certain ligands that improve binding to target cells or tissues is another recent development. This method lessens off-target impacts while increasing delivery efficiency. Moreover, MOFs can be combined with other nanomaterials to create multifunctional systems that can solve challenging biomedical problems. Nonetheless, there are still problems with MOFs' long-term stability in physiological settings, possible toxicity, and biodegradability. To further their therapeutic applications, these constraints must be addressed. While examining the entire potential of MOFs in personalized medicine, the study highlights the significance of continued research to address these obstacles. Humanity has come a long way, but it now needs to concentrate on sustainable methods that safeguard the environment and human health. An example of how scientific progress can coexist with environmental responsibility is the creative application of MOFs in medicine delivery. We can clear the path for more efficient healthcare solutions that improve the health of the globe by tackling present constraints and encouraging interdisciplinary collaboration.

Author contributions

Maryam Akhtar (Writing), Hammad Majeed (Writing—original draft, Supervision, Conceptualization, Methodology, Editing, Software, visualization, Review), Tehreema Iftikhar (Writing, Supervision, Conceptualization, Methodology, Editing, Software, visualization, Review), Khalil Ahmad (Visualization).

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