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Review article

An investigation of affecting factors on MOF characteristics for biomedical applications: A systematic review

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ABSTRACT

Metal-organic frameworks (MOFs) are a fascinating class of crystalline porous materials composed of metal ions and organic ligands. Due to their attractive properties, MOFs can potentially offer biomedical field applications, such as drug delivery and imaging. This study aimed to systematically identify the affecting factors on the MOF characteristics and their effects on structural and biological characteristics. An electronic search was performed in four databases containing PubMed, Scopus, Web of Science, and Embase, using the relevant keywords. After analyzing the studies, 20 eligible studies were included in this review. As a result, various factors such as additives and organic ligand can influence the size and structure of MOFs. Additives are materials that can compete with ligand and may affect the nucleation and growth processes and, consequently, particle size. The nature and structure of ligand are influential in determining the size and structure of MOF. Moreover, synthesis parameters like the reaction time and initial reagents ratio are critical factors that should be optimized to regulate the size and structure. Of note is that the nature of the ligand and using a suitable additive can control the porosity of MOF. The more extended ligands aid in forming large pores. The choice of metallic nodes and organic ligand, and the MOF concentration are important factors since they can determine toxicity and biocompatibility of the final structure. The physicochemical properties of MOFs, such as hydrophobicity, affect the toxicity of nanoparticles. An increase in hydrophobicity causes increased toxicity of MOF. The biodegradability of MOF, as another property, depends on the organic ligand and metal ion and environmental conditions like pH. Photocleavable ligands can be served for controlled degradation of MOFs. Generally, by optimizing these affecting factors, MOFs with desirable properties will be obtained for biomedical applications.

1. Introduction

Generally, agents being applied for therapeutic purposes come up with typical limitations such as low bioavailability, high side effects, and rapid clearance from the body. To address these problems, nanoparticle-based systems are potential candidates due to their small size, high surface area, increased drug loading, improved pharmacokinetics and biocompatibility [1, 2]. Moreover, nanoparticles provide a non-invasive platform with long-term observation for bioimaging and diagnostic purposes [3]. Nanoparticles can be applied as contrast agents because of their small size and high sensitivity. Also, nanoparticles can be conjugated with targeting ligand or incorporated with suitable functional agents for bioimaging application [4]. As a result, various types of nanoparticles, such as polymeric nanoparticles, polymeric micelles, liposomes, magnetic nanoparticles, and dendrimers, have been developed in this regard. Each nanomaterial demonstrates advantages and disadvantages related to toxicity, stability, drug loading capacity, and other properties [5]. In this context, nanoscale metal-organic frameworks

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(NMOFs) are a fascinating class of crystalline porous materials composed of various metal ions and organic linkers. MOF characteristics such as high porosity, high surface area, large pore size, biodegradability, biocompatibility, and versatile functionality for post-synthetic modifications make them promising alternatives in many applications [6, 7, 8], such as gas storage, catalysis, magnetism, sensing, separation, and so on [9, 10, 11]. Recently, their biomedical applications, including drug delivery and bioimaging, have garnered increasing attention [12]. MOFs in biomedical applications can trap biomolecules into their cavities or incorporated them during synthesis [13]. Because of their large surface area, high porosity, and tailorable characteristics, NMOFs can be used as carriers for targeting specific sites of the body and controlled release of the drugs [6, 7]. Recently, the development of NMOFs has shown successes in cancer-targeted therapy [14]. Today, functionalization of inner and outer surfaces of MOFs has been made reliable systems for diagnosis and treatment applications [15].

Furthermore, NMOFs have been receiving much attention in imaging applications [16]; for example, MOFs could be used in magnetic resonance (MR) and optical imaging by incorporating paramagnetic metal ions and luminescence-based materials, respectively [17].

Although MOFs have many advantages in biomedical applications, there are some challenges in their clinical applications. For example, the accumulation of MOFs in the body due to the heavy metals used in their structures and difficulties in the controlling of drug loading and release can be counted as the challenge, though many studies have been recently performed to solve these issues [14].

MOFs have a series of requirements to be used as nanocarriers for drug delivery and imaging, such as biodegradability for low accumulation in the body, biocompatibility, and low toxicity, which rely on composition and structure, controlled release property, and high drug loading efficiency depending on size and porosity [5]. Thus, the structural and biological properties of NMOFs, including particle size, morphology, porosity, biocompatibility, and biodegradability, are influential factors in biomedical applications, which should be considered [18, 19, 20, 21, 22, 23].

The size of particles is considered as one of the most critical physicochemical properties of MOFs regarding their biological applications as it makes direct impacts on their biocompatibility, biodistribution, circulatory lifetime, and in vivo excretion [18]. Thus, controlling the particle size is essential in biological studies. In one approach, additives are used as a growth inhibitor in the synthesis process to postpone the growth process and reduce the size. The properties of inhibitors are related to the precursors as the competition between ligand and inhibitor in the reaction results in slowing down the crystal growth process and reducing the size of MOF nanoparticles [24]. Morphology, another essential feature of MOFs, depends on various factors. The versatility of metal nodes and organic ligands makes it possible to tune compositions and structures of MOFs [28]. The metal ions and organic ligands with different magnetic, optical, and electronic properties can be chosen for specific applications of MOFs. Overall, the flexibility of MOFs presents a platform to control size and morphology [25]. High porosity and large surface area as the most desirable characteristics of MOFs are essential for various applications, including drug delivery and imaging. One of the methods used for forming and tuning MOFs with large pores is the elongation of the ligand length [26]. Furthermore, some additives can manipulate pores size by involving in the structure of MOFs [27]. Biocompatibility is another property of MOFs that must be considered in biomedical applications [22]. The biocompatible system refers to materials or systems that are not toxic, injurious, causing physiologically reactive or immunological reactions. Appropriate metal ions and ligands must be selected to reach the low toxicity of NMOFs. The physicochemical properties of MOFs also influence the biocompatibility of these systems [18]. The biodegradability of MOFs in the biological system is another important feature that should be taken into account. The nature of metal and ligand affect the biodegradation of MOFs in biological applications. For instance, a photocleavable ligand can be used for the controlled degradation of MOF, triggered by light or temperature [28, 29].

Design and fabrication of desired MOFs with regular pores, desirable size and composition, high surface area, high biocompatibility, and acceptable biodegradability require a good knowledge of various factors which influence their properties. Since some characteristics of MOFs are determinant in biomedical applications, the effect of various factors on these properties must be considered. Although there are researches in the literature that addresses the influence of few elements on the characteristics of MOF, to the best of our knowledge, there is no perfect compilation of influential parameters on characteristics of MOFs. Thus, this review was conducted to identify and summarize the effects of essential factors on MOF characteristics.

2. Method

An electronic search was performed in four databases, including PubMed, Scopus, Web of Science, and Embase. In the search strategy, words relevant to MOF and characteristics were searched at the title. Also, the most critical properties of MOFs were searched in the title. Finally, words related to biomedical applications of MOFs were searched at the title and abstract level. The search was not limited to specific years. The search query used in the PubMed database is indicated in Table 1. In other databases, similar structures were formed.

Inclusion Criteria

1. Matching with the search strategy
2. The results include properties of MOFs with the investigation a factor effect on property
3. Published in the English language

Exclusion Criteria

1. Reviews
2. The studies reported the properties of MOF as characterization results and didn't investigate the effects of specific factors on the properties

2.1. Screening process

All articles were imported to EndNote software. Then duplicate records were removed. Two independent researchers investigated the title and abstract of the papers.

2.2. Analysis

Reported information, including article titles, authors, years, MOF types, effective factors, reported characteristics, and major results, were extracted from the obtained included papers and tabulated. In the next step, each characteristic and the effective factors were visualized using an effect-cause diagram. The review was written based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [30].

3. Results and discussion

In this paper, the effects of various factors on key properties of MOFs for drug delivery and imaging applications were reviewed. The process of study is displayed in Figure 1; 20 papers were included, and the included papers are presented in Table 2. The characteristics of MOFs and the effects of different factors on them are shown in Figure 2.

The relationship of factors that influence the MOF structural properties and biological activity drawn from Table 2 is represented in Figure 2. Applications of MOFs in the biomedical field, including imaging and drug delivery, are shown at the top. The performance of MOFs in

Table 1. PubMed search query.

Search terms	
1.	MOF[Title] OR MOFs[Title]
2.	("Metal organic"[Title] AND framework*[Title])
3.	1 OR 2
4.	properties [Title] OR characteristics[Title]
5.	size[Title] OR surface[Title]
6.	morphology[Title] OR shape[Title]
7.	porosity[Title] OR biodegradability[Title] OR degradation[Title]
8.	toxicity[Title] OR biocompatibility[Title]
9.	4 OR 5 OR 6 OR 7 OR 8
10.	delivery[Title/Abstract] OR imaging[Title/Abstract] OR biomed*[Title/Abstract]
11.	3 AND 9 AND 10

these applications depends on the structural properties and biological activities, as shown in the figure. Finally, the affecting factors of each property are shown at the bottom.

3.1. Structural properties

3.1.1. Size

Particle size is a critical attribute of MOFs in biomedical applications, especially in the administration route and incorporating MOFs with other compounds [46]. Also, particle size has a significant effect on toxicity, biodistribution, and lifetime of particles in the body [18]. The size of nanocarriers impacts on cellular uptake and intracellular transporting in controlled drug delivery [27]. Hence, optimizing the particle size is an essential step for biomedical applications of MOFs [24]. The nanoparticles are more practical in biomedical applications, though their toxicological effects on the body are undetermined. There are not sufficient observations about the specific relationship between the impact of size and toxicity [48]. Generally, it has been reported that particles with a size larger than 200 nm have toxicity and are removed by macrophages, which results in reduced delivery efficiency [49].

Suitable additives can control the particle size of MOFs in the reaction. Also, by modulating the nucleation and growth process, synthesis methods and experimental parameters effectively influence the size of crystals [45, 46]. The size of MOF particles can be controlled by optimizing the synthesis parameters, such as tuning the initial concentration of precursors and adding the co-modulators or capping ligands to the synthesis medium [27, 40, 45, 46].

Synthesis parameters can determine the final particle size of MOFs. Abazari et al. reported morphology and size-controllable synthesis of Zn-based MOFs. The process was performed by the sonication method through optimizing synthesis parameters (sonication time, initial reagent concentrations, irradiation frequency, and molar ratios of reagents). In the mentioned process, with increasing the concentration of reagents and reaction time, the nanoparticles became agglomerated. In this study, the optimal sonication time achieved in the research was stated to be 60 min, which resulted in increased uniformity in nanoparticle size. Also, the higher concentration of the reagents caused the greater mean diameter. Moreover, in 30 kHz irradiation frequency, aggregation was decreased, but in higher irradiation frequency (60 kHz), the size of the obtained nanostructures and aggregation was increased. Also, pyridine and acetic acid were applied as modulators, and these compounds illustrated a chemical structure similar to the ligand. Using pyridine and acetic acid in a 50:50 ratio resulted in uniform particles. Scanning Electron Microscopy (SEM) images of MOFs in two different irradiation frequencies are shown in Figure 3 [38].

Moreover, the ultrasonication method is a practical approach to control the crystallization process. Ultrasound irradiation is a feasible technique that can increase mass transfer and accelerate molecular diffusion to reduce particle size [46]. Also, controlling the synthesis conditions like temperature is vital in regulating particle size and size distribution. In this study, the hydrothermal/solvothermal route was used to manage the particle size. The particle size and size distribution are essential for their pulmonary drug delivery application since the uniformity of size is critical for enhancing the chemical and physical properties. Cyclodextrin-MOF (CD-MOF) was produced under 50 °C with

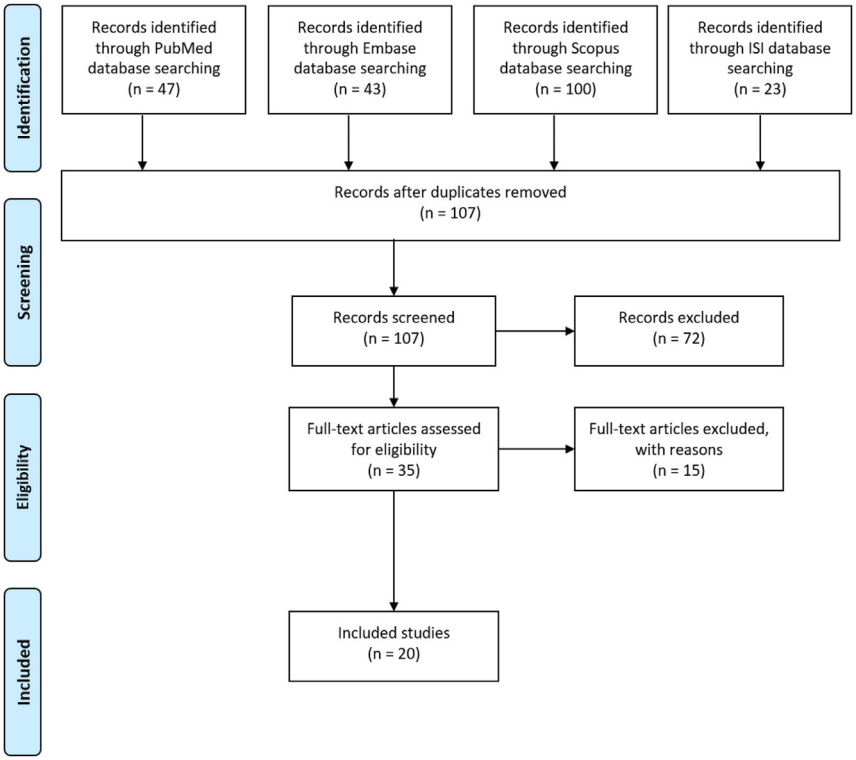

Figure 1. Flow chart of the study selection process based on PRISMA.

Table 2. Reviewed papers: The effect of various factors on the major characteristics of MOFs.

Article title	Author, year	MOF type	Effective factors	Reported characteristics	Outcomes
Metal-organic framework structures of Cu(II) with pyridine-2,6-dicarboxylate and different spacers: Identification of a metal-bound acyclic water tetramer	Sujit K. Ghosh et al., [31], 2004	Cu(pdc) MOF (Metal: Cu, Ligand: pyridine-2,6-dicarboxylate)	Type of spacer	Morphology	The various spacer can be placed within the ligand structure and affect the final structure and morphology of MOF. Pyridine-2,6-dicarboxylate as a ligand with different spacers could prepare a stable Cu(II)-based MOF under the hydrothermal process. Generally, the pyridine-2,6-dicarboxylic acid ligand with various N-heterocycles spacers reacted with $Cu(NO_3)_2.6H_2O$ under the hydrothermal conditions and formed different structures of MOF depending on the spacer nature.
Synthesis of Gadolinium Nanoscale MetalOrganic Framework with Hydrotropes: Manipulation of Particle Size and Magnetic Resonance Imaging Capability	Wilasinee Hatakeyama et al., [32], 2011	Gd-MOF: (Metal: Gd, Ligand: BDC (Benzenedicarboxylate))	Type and concentration of Hydrotrope	Particle size and morphology	Hydrotrope is a compound with hydrophobic and hydrophilic properties, which can change an oil-in-water micelle's rigidity. Gd-MOF was synthesized via a reverse microemulsion method, and then the effect of type and concentration of hydrotropes (NaSal, 5-mSalAc, SalAc) on the nanoparticle shape and size were investigated. The addition of all three hydrotropes provided an increased length of particles with an increased concentration of hydrotropes. The width of particles may be increased or decreased. Also, all hydrotrope compounds convert the structure of MOF to a worm-like form.
Chiral nanoporous Metal-Organic Frameworks with high porosity as materials for drug delivery	Chun-Yi Sun et al., [33], 2011	MOF (Metal: Zn, Ligand: 5,5′,5″ -(1,3,5-triazine-2,4,6-triyl) tris(azanediyl) triisophthalate (TATAT))	Ligand	Porosity	TATAT [(5,5′,5″-(1,3,5-triazine-2,4,6-triyl) tris(azanediyl)triisophthalate)] as a hexadentate ligand could be used in the MOF structure, which could produce a highly porous structure of MOF because of its extended structure.
In vitro biocompatibility of mesoporous metal (III; Fe, Al, Cr) trimesate MOF nanocarriers	Romain Grall et al., [34], 2015	MIL-100 NPs (Metal: Al, Cr, Fe, Ligand: 1,3,5-benzene tricarboxylic acid)	Metal ion	Biocompatibility	Metal ions can affect the biocompatibility of MOF; thus, the effect of metal ions was investigated by comparing the toxicity of three MOFs with different cations, including Fe, Al, and Cr, in various cell lines. The metal ion may influence the cells by producing reactive oxygen species (ROS) or could aid in ROS's neutralization. MIL100(Fe, Al, Cr) NPs didn't show in vitro cell toxicity in the p53 wild type cell lines But MIL100-Fe could induce toxicity in the hepatocarcinoma cell line.
Structural and degradation studies of a biocompatible Zn-L-tartrate metal-organic framework	Ana Palǒić et al., [35], 2014	Zn-L-tartrate MOF (Metal: Zn, Ligand: L-tartaric acid)	The pH of media in the aqueous phase and SBF	Biodegradability	The degradation of Zn-L-tartarate MOF was studied in the aqueous phase in various pH (pH = 1–7) and in the simulated body fluid (pH = 7.4) through evaluation of the released Zn ion. The results demonstrated that 60% of Zn was released in acidic conditions after 6 h. Also, as the solution's pH was increased, the rate of degradation decreased.
Synthesis, culture medium stability, and in vitro and in vivo Zebrafish Embryo toxicity of Metal-Organic Framework nanoparticles	Angels Ruyra et al., [36], 2015	MIL-100 MIL-101 MOF-5 MOF-74 ZIF-7 ZIF-8 Uio-66-NH2 Uio-67	Metal and ligand	Biocompatibility	In vitro and in vivo toxicity of different MOFs composed of various metals and ligands against two human cell lines and in zebrafish embryos were investigated. There was a high correlation between the in vitro and in vivo toxicity results. Nano MgMOF-74 had minor toxicity in vitro and in vivo. The results showed that the degradation process of MOFs in solution produced metal ions that strongly determined the toxicity of MOFs.
Controllable porosity conversion of metal-organic frameworks composed of natural ingredients for drug delivery	Jiang Liu et al., [20], 2017	CD-MOF-1 ($CsC_{42}H_{71}O_{36}$) and CD-MOF-2 ($Cs_3C_{84}H_{133}O_{70}$) (Metal: cesium, β-CD as building blocks, With template agent)	Size of the template agent	Porosity	Different template agents were applied to the preparation of CD-MOFs (γ-cyclodextrin metal-organic frameworks) through a template-induced strategy. The size of template agents showed notable effects on the porosity of CD-MOFs. Overall, the template agent unit existence and length could affect the crystallization process and porosity of CD-MOF-1 and CD-MOF-2. This approach can help the development of more CD-MOFs in biomedical applications.
Exploring the geometric, magnetic, and electronic properties of Hofmann MOFs for drug delivery	Mandal, B. et al., [37], 2017	Bimetallic Hofmann MOF (Metal: Fe and Co with Ni, Ligands: pyrazine and 4,4′-bipyridine)	Ligand and metal	Morphology	Bimetallic Hofmann MOFs demonstrated a porous crystalline structure and high loading capacity. The unit cell of Ni–Fe MOF showed a square shape. The lattice dimensions were changed by replacing metal ions with Pt due to the increasing size of metal ions and increasing metal-ligand bond length.

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Table 2 (*continued*)

Article title	Author, year	MOF type	Effective factors	Reported characteristics	Outcomes
					Also, Mn and Co caused tetrahedral geometry. Ni and Fe preferred a square planar geometry. In addition, the bidentate ligand, such as pyrazine and bipyridine, transformed the structure into three-dimensional (3D). Thus, ligand and metal could affect the morphology of MOF.
Morphology- and size-controlled synthesis of a metal-organic framework under ultrasound irradiation: an efficient carrier for pH-responsive release of anti-cancer drugs and their applicability for adsorption of amoxicillin from aqueous solution	Reza Abazari et al., [38], 2018	Zn(II)-based MOF: (Metal: Zn, Ligand: H_3BTCTB and 4,4′-BPDC carboxylate)	Synthesis parameters such as time, initial materials concentration, irradiation frequency, and the molar ratio of reagents	Particle size and morphology	The synthesis parameters such as sonication time, reagent concentration, irradiation frequency, and the molar ratio of reagents were optimized in the synthesis process. The optimum sonication time was obtained as 60 min. The higher reagent concentration caused the less regularity of the shape and greater mean diameter. Also, irradiation frequency has affected the structure of particles. Pyridine and acetic acid were applied as modulators, and these compounds had a chemical structure similar to that of the linker. Pyridine and acetic acid were used in the 50:50 ratio in the mixture and produced a uniform size and shape. So, the synthesis parameters could alter the size and morphology of MOF nanoparticles.
On-demand degradation of Metal−Organic Framework based on photocleavable Dianthracene-based ligand	Guillaume Collet et al., [28], 2018	CD-MOF-161(Metal: ytterbium, Ligand:9-anthracenecarboxylic acid dimer)	Ligand	Biodegradability	The nature of the ligand could aid in the biodegradation of MOF. A photocleavable MOF was synthesized for controlled degradation using organic ligand with light-responsive nature under light exposure at a wavelength less than 300 nm or at high temperature (160 °C). In CD-MOF-161, a photocleavable dianthracene-based ligand was used for controlled degradation of this MOF, triggered by light or temperature.
The effect of size and aspect ratio of Fe-MIL-88B–NH2 metal-organic frameworks on their relaxivity and contrast enhancement properties in MRI: in vitro and in vivo studies	Sadegh Dehghani et al., [39], 2018	MILs (Metal: Fe, Ligand: 2-aminoterephthalic acids)	Initial materials ratio (CH_3COOH/Fe^{+3} ratio)	Particle size	MILs were synthesized in different sizes using different CH_3COOH/Fe^{+3} ratios. Acetic acid could affect the nucleation and crystallization of MILs. The higher acid concentration caused a lower degree of carboxylic linker deprotonation, and the nucleation and growth rate of crystals were decreased, and larger MIL was formed.
Size and surface controllable metal-organic frameworks (MOFs) for fluorescence imaging and cancer therapy	Xuechuan Gao et al., [40], 2018	UIO-66-NH_2 (Metal: Zn, Ligand: 2-amino terephthalic acid)	Concentration of Additives	Particle size and morphology	The size and shape of UIO-66-NH_2 could be controlled by variation of benzoic acid concentration as an additive. When the additive concentrations decreased, the sizes of the UIO-66-NH_2 diminished from 200 to 20 nm. Also, the shape of the particles was changed from cubic to spherical.
Biocompatibility characteristics of the metal-organic framework ZIF-8 for therapeutical applications	Marcus Hoop et al., [41], 2018	ZIF-8 (Metal: Zn, Ligand:2-methyl imidazole)	The concentration of MOF (Related to effect of metal ion)	Biocompatibility	Biocompatibility of ZIF-8 with different concentrations was assessed in six cell lines representing various parts of the body. It was concluded that ZIF-8 concentrations above 30 μg mL^{-1} cause high toxicity. These results can be attributed to the release of zinc ions into the cell lines. So, low ZIF-8 concentrations (‘30 μg mL^{-1}) showed a biocompatible system.
Degradation paths of manganese-based MOF materials in a model oxidative environment: a computational study	Elena V. Khramenkova et al., [42], 2018	Mn-BTC MOF (Metal: Mn, Ligand: benzene-1,3,5-tricarboxylate)	Ligand and metal	Biodegradability	Oxidative transformation of the Mn centers causes controlled degradation of Mn-based MOFs under high levels of oxidants that may be formed in pathogenic tissues. The results showed good stability of the Mn-carboxylate structure against direct hydrolysis, but oxidation facilitated the hydrolysis of coordination bonds. This phenomenon depends on the nature of ligand and metal as well as the construction of MOF. Degradation by environmental conditions is a good idea for designing triggered and targeted drug delivery systems.
Controlled nucleation and controlled growth for size predicable synthesis of nanoscale Metal-Organic Frameworks	Xiao-Gang Wang et al., [43], 2018	HKUST-1 MOF (Metal: Cu, Ligand: 1,3,5-benzenetricarboxylate)	Control of nucleation and growth	Particle size	An appropriate approach was developed for the controlled synthesis of MOFs with small and uniform sizes. In this method, the size was adjusted by controlling the nucleation and growth of crystals. This strategy is based on the separation of nucleation and growth process by preserving the degree of supersaturation below the degree of nucleation and higher than the

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Table 2 (*continued*)

Article title	Author, year	MOF type	Effective factors	Reported characteristics	Outcomes
(MOFs): A general and scalable approach					degree of growth. Controlling the supersaturation degree of reactions was performed by a syringe pump to deliver metal and ligand solutions separately with a controlled feed rate along with stirring.
Nanoscale Zr-based MOFs with tailorable size and introduced mesopore for protein delivery	Zhe Wang et al., [27], 2018	Uio-66 (Metal: Zr, Ligand: 1,4-benzenedicarboxylate)	Type of additives	Particle size and porosity	The size of nanocarriers has noteworthy effects on cellular uptake and intracellular transporting in controlled drug delivery systems. In the synthesis of UiO-66 MOF, monocarboxylic acids and organic bases can be served as a modulator for control pore size and particle size. In this study, dodecanoic acid (DA) and triethylamine (TEA) were applied as a comodulator to control particle size and porous structure. Then the modulator was removed to the formation of the structural defects and excess pore space.
Nanoporous CD-MOF particles with uniform and inhalable size for pulmonary delivery of budesonide	Xiaoxiao Hu et al., [44], 2019	γ-cyclodextrin metal-organic framework (CD-MOF)	Synthesis conditions (temperature, solvent, additive)	Particle size	The hydrothermal/solvothermal method could control the particle size. For example, this approach was employed to produce CD-MOF. Also, using a capping agent and controlling incubation time can regulate the particle size of CD-MOFs. Finally, CD-MOF crystals with a controlled size of 1–5μm (with most of the particles in the range of 2–3μm) were correctly prepared for inhalation administration.
Direct imaging of tunable crystal surface structures of MOF MIL101 using high-resolution electron microscopy	Xinghua Li et al., [45], 2019	MIL-101 (Metal: Cr, Ligand: benzene dicarboxylate)	Type of additive	Particle size and morphology	The different inorganic and organic additives can control the crystallization process and modify the particle size. Different MIL-101(Cr) could be synthesized using HF (hydrofluoric acid), acetic acid (Ac), or without additive (NA); . The results demonstrated that all three MOFs exhibit an octahedral crystal shape but showed different crystal sizes. But, the precise mechanism of these phenomena is unclear and requires more investigations.
Size-control and surface modification of flexible Metal-Organic Framework MIL-53(Fe) by polyethyleneglycol for 5- Fluorouracil anticancer drug delivery	Hoai Phuong Nguyen Thi et al., [46], 2019	MIL-53 (Metal: Fe, Ligand: benzene dicarboxylate)	Synthesis method and capping ligand	Particle size and morphology	The crystal growth of MOFs can be controlled using the monovalent capping ligand such as polyethyleneglycol (PEG). For instance, the flexible MIL-53 was prepared with PEG aid using an ultrasonication approach, and the particle size of MIL-53 was precisely controlled using PEG. The results showed that PEG had a significant effect on the shape and size of MIL-53. Besides, ultrasonication is a feasible method that can intensify mass transfer and accelerate molecular diffusion to reduce particle size. So, this method is a helpful approach to control crystallization.
Toxicity screening of two prevalent metal-organic frameworks for therapeutic use in human lung epithelial cells	Wagner, A. et al., [47], 2019	MIL-160 (Metal: Al, Ligand: 5-furandicarboxylic acid) ZIF-8 (Metal: Zn, Ligand: 2-methyl imidazole)	Physicochemical properties (Particle size, structure, and hydrophobicity)	Biocompatibility	The toxicity of two MOFs (MIL-160 and ZIF-8) with different physicochemical properties was investigated to evaluate the effect of structural properties on the overall toxicity of biological systems. The toxicity differences between these two MOFs are due to their different characteristics like hydrophobicity, size, metal ion, and structure. This paper emphasized the value of the toxicological studies of MOFs before biological applications.

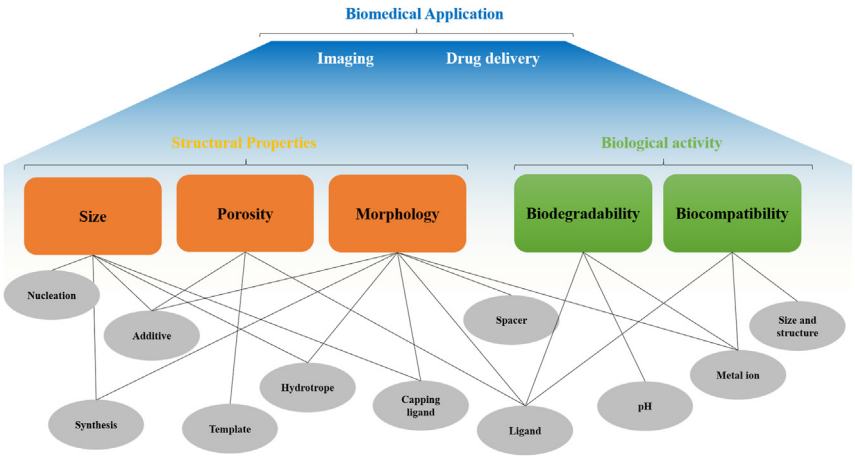

Figure 2. Summary of affecting factors on metal-organic framework characteristics.

pre-addition of methanol to the aqueous solution of γ-CD and KOH. The reaction of γ-CD with KOH and vapor diffusion of methanol at room temperature resulted in the fabrication of MOF particles with a size of 200–400 μm. The modified preparation process of MOFs made smaller particles with a 1–10 μm using cetyltrimethyl ammonium bromide as a capping agent. Also, the synthesis of CD-MOFs with a smaller size than 40 μm needed a long incubation time of about 24–32 h. Therefore, having this in mind and by a solvothermal method in temperature of 50 °C, Hu and coworkers could prepare porous CD-MOF crystals with uniform and proper size (with most of the particles in the range of 2–3 μm) for pulmonary drug delivery and inhalation administration [44].

Various inorganic and organic additives can also be utilized to control particle size by modification of crystallization. Gao et al. demonstrated that the addition of different amounts of benzoic acid as an additive to the reaction helps to regulate particle size. By decreasing the concentration of benzoic acid, the size of UIO-66-NH_2 crystals has been reduced. Also, the shapes were converted from cube to sphere. These results are shown in Figure 4. Generally, the smaller particle size shows long in vivo circulation time. However, UIO-66-NH_2 with a size of 20 nm demonstrated aggregations. As a result, a particle size of 50 nm was chosen as a drug carrier [40].

Hydrofluoric acid (HF) and acetic acid could be utilized as additives for synthesizing MIL-101 MOF particles. Li et al. study indicated that the presence of these additives could influence the size of particles. Different MIL-101(Cr) could be synthesized using HF (hydrofluoric acid), acetic acid (Ac), or without additive (NA). The results demonstrated that all three MOFs have an octahedral crystal shape despite the different crystal sizes: MIL-101-HF (700–800 nm) > MIL-101-NA (350–450 nm) > MIL101-Ac (150–250 nm). These additives may manipulate the crystallization process for controlling the crystal size. However, the chemistry and mechanism of these phenomena are unclear and require more investigations to realize the mechanisms behind them [45].

Besides, the size of Zr-based MOF particles was shown to be controlled by adding dodecanoic acid (DA) and triethylamine (TEA) as a co-modulator. In the synthesis of UIO-66 MOF, monocarboxylic acids and organic bases can be served as a modulator to control particle size. Thi, H.P. et al. demonstrated that TEA could be applied as a modulator of the nucleation process to control the particle size. It was stated that TEA could reduce the nucleation time of crystallization by accelerating the deprotonation of the BDC (Benzenedicarboxylate) ligand to obtain smaller particles [27]. In addition, Thi et al. reported that capping ligands can be applied to control the particle size of MOFs. Monovalent capping ligands such as polyethyleneglycol (PEG) could be used to synthesize MIL-53 by sonication method and precisely tune the size of particles. While the preparation of MIL-53 without the presence of PEG resulted in the crystals with an average size of 500 nm, the synthesis with PEG produced small MIL-53(Fe)-PEG, with homogeneous particles and an average diameter of 400 nm. In conclusion, there is an inverse relationship between the concentration of PEG and the size of the crystals. This phenomenon is due to the effects of PEG on the nucleation process of MIL-53, which means that the bonding of the hydroxyl of PEG on the surface of MIL-53 could control the nucleation and growth process.

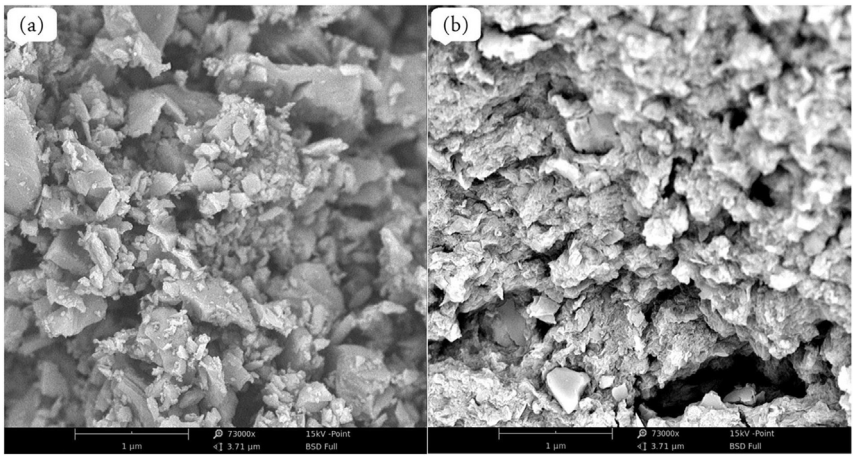

Figure 3. SEM images of MOF structure prepared by a sonochemical process in two irradiation frequency a) 30kHz and b) 60kHz (Adapted with permission from [38]).

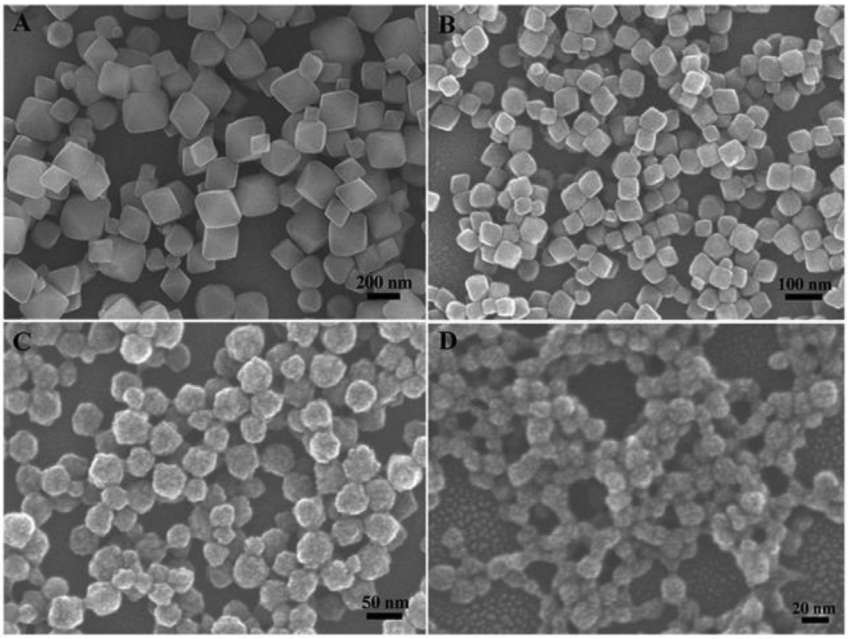

Figure 4. SEM images of UIO-66-NH_2 structure with a particle size of 200 nm–20 nm prepared with different amounts of benzoic acid: A) 0.76 g, B) 0.38 g, C) 0.19 g, and D) 0.095 g (Adapted with permission from [40]).

Besides, ultrasonication is another feasible method to control the crystallization process by intensifying mass transfer and accelerating molecular diffusion to reduce the particle size. Figure 5 illustrates the effect of the PEG concentration on the particle size of MIL-53 [46].

Furthermore, the results revealed that smaller and monodispersed particles could be obtained by separating the nucleation and growth process. Usually, the critical supersaturation degree of nucleation (S_n) is higher than the degree of growth (S_g). If the supersaturation degree in a growth process is lower than S_n and higher than S_g, the nucleation during growth is stopped. Hence, the final particle size is reduced, and more uniform nanoparticles will be obtained. In a study carried out by Wang et al., the supersaturation degree of reactions was controlled through a syringe pump to enter metal and ligand solutions separately at a specific feed rate into the reaction along with stirring [43].

Hydrotropes are compounds with both hydrophobic and hydrophilic properties that can alter the rigidity of an oil-in-water micelle. These compounds, as additives in the reaction, can influence the particle size and structure. Hatakeyama et al. applied three different hydrotropes, i.e., sodium salicylate (NaSal), 5-methylsalicylic acid (5-mSalAc), and salicylic acid (SalAc), in the preparation of Gd-MOF particles through reverse microemulsion process. By increasing the concentration of NaSal, the length of the MOF structure was raised, and the diameter was decreased. 5-mSalAc brought about a large decrease in width and increase in length. Also, SalAc caused elongated structures and increased the lengths and widths of structure with increasing concentration [32].

Dehghani et al. demonstrated that MILs MOF could be synthesized in different sizes using various initial reagent ratios (CH_3COOH/Fe^{+3}). Acetic acid was shown to influence the nucleation and crystallization

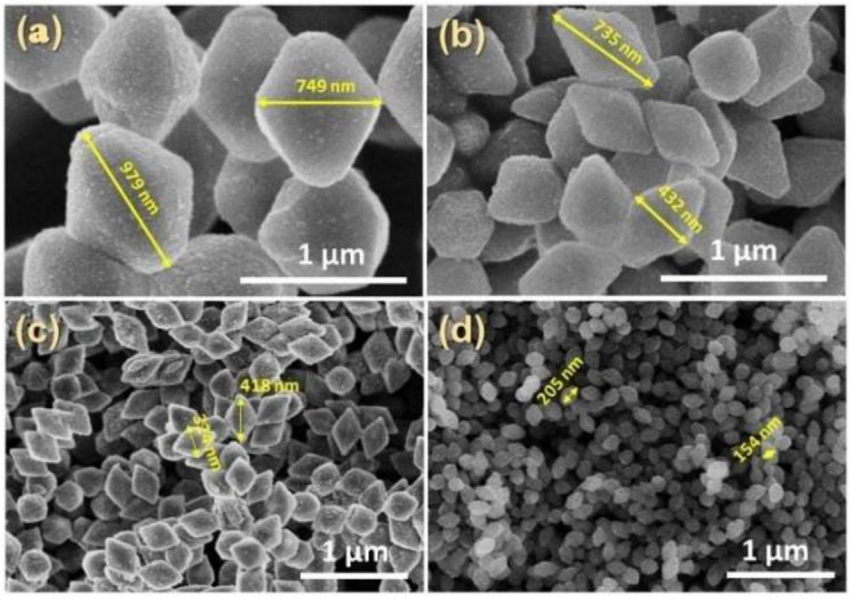

Figure 5. SEM images of MIL-53 with PEG volume of a) 10 ml b) 20ml c) 40 ml d) 60ml. (Adapted with permission from [46]).

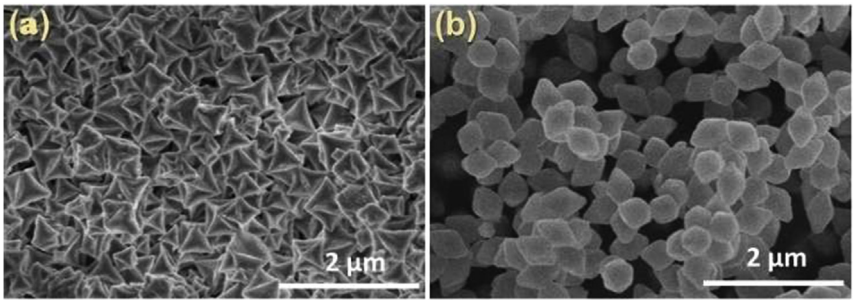

Figure 6. SEM images of MIL-53 a) without and b) with PEG assistance (Adapted with permission from [46]).

process of MILs. The higher concentration of acetic acid results in a lower degree of carboxylic linker deprotonation, and the rate of nucleation and growth of crystals was decreased, then larger MIL was formed [39].

3.1.2. Morphology

The structure and morphology of MOF particles are other critical factors in determining their final properties. As an illustration, the morphology of nanoparticles can be attributed to their properties, such as toxicity in biological applications [19]. Also, the structure and morphology of nanoparticles can influence the interaction of nanoparticles with biological fluids and interfaces and, finally, on the performance of nanoparticles in the body [50]. The surface morphology of MOFs can be investigated using SEM and FESEM (field emission scanning electron microscope) methods, and the inner structure of particles can be studied using TEM (transmission electron microscopy) [13]. Morphology can be adjusted by using different spacers in the MOF structure [31], changing the type of ligands and the metal ions [37], controlling the synthesis parameters [38], as well as utilizing various additives in the reaction [32, 40, 45].

The versatility of metal nodes and organic linkers makes it possible to efficiently tune compositions and structures of MOFs [51]. Different organic ligands with various shapes and sizes can be applied to control the structure and functionality for specific applications. So, the selection of metals and ligands can contribute to determining the structure and morphology of MOFs. Although organic units have predetermined shapes and geometry, their flexibility often influences the final architecture [51, 52]. The metal ions and organic ligands with different magnetic, optical, and electronic properties can be chosen for various applications. Overall, the flexibility of MOFs presents a platform to control the size and morphology [25].

The metal ion size and the metal-ligand bond length are essential parameters in the overall structure of MOF particles. Also, the structure and coordination numbers of ligands are effective in the structure of MOF. In Mandal et al. study, bimetallic Hofmann MOF with two ligands

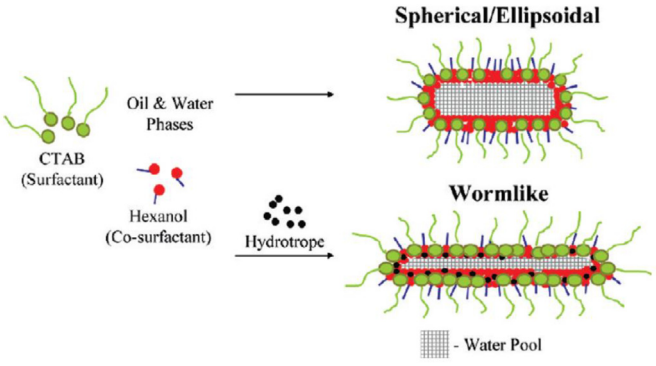

Figure 7. Role of hydrotrope on the structure in a reverse microemulsion process (Adapted with permission from [32] Copyright (2020) American Chemical Society).

(pyrazine and 4,4′ -bipyridine) and metal ions including Fe and Co in combination with Ni was designed. These MOFs had a porous crystalline structure with a high loading capacity. Ni–Fe MOF exhibited a unit cell with a square shape. The lattice dimensions in this MOF were changed by replacing metal ion with Pt due to the increasing size of metal ion and increasing metal-ligand bond length. The result revealed that Mn and Co preferred tetrahedral geometry, and Ni and Fe preferred a square planar geometry. Also, the bidentate ligand, such as pyrazine and bipyridine, transformed the structure into three-dimensional construction [37].

Moreover, a spacer, as a co-ligand, can influence the structure and morphology of MOFs. Ghosh. et al. used pyridine-2,6-dicarboxylate ligand with three spacers in the MOF structure, and three different morphology were observed. The results demonstrated that this ligand with additional spacers could prepare stable Cu(II)-based MOF by hydrothermal process. The MOF structure with spacer 1 (4,4′-bipyridine) provided a dimeric Cu(II) structure with the asymmetric unit. One Cu was pentacoordinated with geometry of square pyramidal, and the second Cu is hexacoordinated with tetragonal geometry. This compound contains spacer 1 showed a triclinic crystal system. In using spacer 2 (pyrazine), the pyrazine spacer bound the two Cu, formed a dimer, and showed a tetragonal symmetry around each Cu(II). Using spacer 3 (pyridine), one pyridine and two bridging carboxylate O atoms showed tetragonal coordination. Compounds 2 and 3 displayed monoclinic crystal systems. In short, the pyridine-2,6-dicarboxylic acid ligand reacted with $Cu(NO_3)_2.6H_2O$ under hydrothermal route with various N-heterocycles as spacers and formed 1D, 2D, or 3D structures of MOFs depending on the spacer nature. Meanwhile, 4,4′-bipyridine spacer formed a 2D network in which every alternate Cu(II) ion is coordinated to an acyclic tetrameric water cluster in the chain [31].

Additionally, the MOF crystal growth can be controlled using monovalent capping ligands such as polyethyleneglycol (PEG). Nguyen Thi, H.P. et al. prepared MIL-53 in the presence of PEG using the ultrasonication method. In the synthesis without PEG, the obtained MIL-53 octahedron crystals were irregular, while synthesis with PEG resulted in the MIL-53(Fe)-PEG with well-distribution and homogeneous particles and hexagonal bipyramidal morphology. The results demonstrated that PEG has a remarkable effect on the shape and structure of MIL-53. The morphology of MIL-53 with or without PEG was evaluated by SEM, which is shown in Figure 6 [46].

Optimization of synthesis parameters, like reaction time, reagents concentration, irradiation frequency, and molar ratios of reagents, could control the structure and morphology of MOF particles. Abazari et al. obtained the optimum time equal to 60 min in sonication synthesis of Zn-based MOF particles, after which the prepared nanoparticles showed more uniformity in the morphology. While by increasing the concentration of reagents, the regularity in the shape of the nanoparticles was reduced. Also, in the irradiation frequency of 30 kHz, the structure was plate-like, and particles became more uniform than 60kHz (Figure 3). In addition, pyridine and acetic acid were applied as modulators. These compounds were used in a 50:50 ratio which could cause a uniform shape [38].

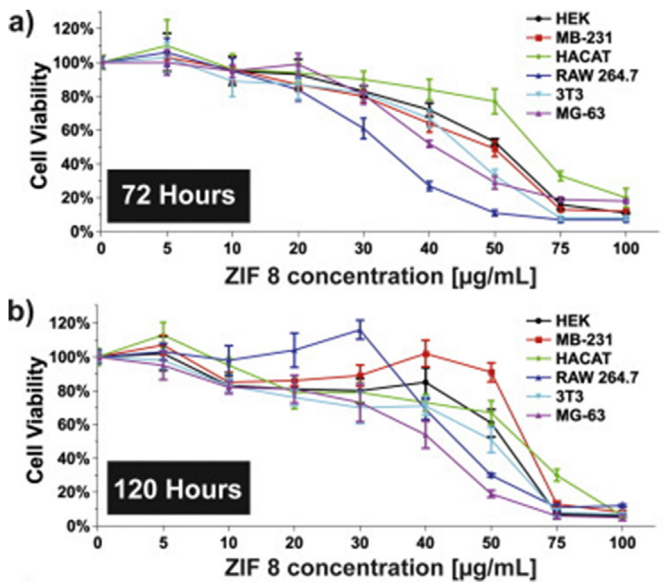

Figure 8. Cell viability of various cell lines after (a) 72 h and (b) 120 h in different concentration of ZIF-8 (Adapted with permission from [41]).

As stated in the previous section, hydrotropes are able to act on the size and structure of obtained MOFs. Hatakeyama et al. utilized sodium salicylate (NaSal), 5-methylsalicylic acid (5-mSalAc), and salicylic acid (SalAc), as hydrotropes in the synthesis of Gd-based nanoscale MOF particles. Increasing concentration of all three hydrotropes yielded increased lengths of particles, and the width may be increased or decreased. By increasing the concentration of NaSal, the particles were transitioned from spherical to a worm-like structure. By adding the 5-mSalAc, enhanced elongation to worm-like structure, and a remarkable decrease in the width of nanoparticles have resulted while the length of nanoparticles was increased. Besides, the addition of SalAc caused elongated structures with worm-like structures. As the results revealed, there is a direct relationship between the concentration of SalAc and the increase in the size of the obtained structures. The general effect of hydrotrope on the obtained structures is shown in Figure 7 [32].

As mentioned previously, the various inorganic and organic additives can be utilized to modulate the crystallization process and control MOF structure. Li, X.H. et al. applied hydrofluoric acid and acetic acid as additives for synthesizing the MIL-101(Cr). The results showed no significant changes in the morphology of the prepared MOFs with and without additives. However, MIL-101(Cr) particles with different sizes were obtained in the presence and absence of the additives [45]. Another additive used in the fabrication of the Uio-66-NH_2 MOF structure is benzoic acid. The results obtained from the structural characterization revealed that by decreasing the concentrations of benzoic acid as an additive, the structure of particles was transformed from cubic to spherical [40].

3.1.3. Porosity

Porosity, including the size and shape of the pores, has a notable effect on the loading capacity and drug release rate in the biological environment [20]. The construction of MOFs with large pores could be obtained through elongation of the length of the ligands. So, the nature of the ligand is a determinant factor in MOF porosity [26]. Furthermore, some additives can regulate pore size by involving in the structure of MOFs [27]. The porosity and pore size of MOFs can be controlled by various factors, such as type of ligand, size of template agent, and additives [20, 27, 33].

Monocarboxylic acids and organic bases are served as modulators to control the pore size. In the study conducted by Wang, Z. et al., dodecanoic acid (DA) was used as a competitive ligand to creating large pores. This carboxylic acid could coordinate with the metal centers. Then modulator could be removed to form the structural defects and excess pore space [27].

Also, the structure of the ligand is an influential factor in MOF porosity. Ligand with a more extended structure causes large pores in MOF. In Sun, C.Y. et al. study, TATAT(5,5′,5″-(1,3,5-triazine-2,4,6-triyl) tris(azanediyl)triisophthalate) was used as a hexadentate ligand. TATAT could form large pores in MOF structure due to its extended structure rather than other carboxylic ligands such as BTC (1,3,5-benzenetricarboxylate), BTB (4,4′,4″-benzene-1,3,5-triyl-tribenzoate), and TATB (TATB = 4,4 ′,4″s-triazine2,4,6-triyltribenzoic). Besides, the TATAT ligand illustrated multiple metal and hydrogen binding sites which can provide the possibility of host-guest interactions. This MOF with high porosity demonstrated high loading efficiency and slow release of the drug [33].

Various template agents could be applied in the production of CD-MOFs. Liu, J. et al. used 1,2,3-triazole-4,5-dicarboxylic acid (H_3tzdc), methyl benzene sulfonic acid (TsOH), or an ibuprofen molecule (IBU) as template agents in CD-MOFs. The size of the template agents had effects on the porosity and crystallization process of the CD-MOFs. H_3tzdc with a size of less than 5Å and TsOH and ibuprofen bigger than 6Å were utilized, and they produced different channel arrays of CDs. Overall, the existence and length of the template agent unit showed an effect on the crystallization process and porosity of CD-MOF-1 ($CsC_{42}H_{71}O_{36}$) and CD-MOF-2 ($Cs_3C_{84}H_{133}O_{70}$) [20].

3.2. Biological activity

3.2.1. Biocompatibility

In addition to the mentioned characteristics, biocompatibility and toxicity of MOFs must also be considered in their biomedical applications [22] to ensure not being toxic, injurious, or causing physiologically reactive and immunological reactions [18]. Indeed, MOF biocompatibility is affected by the type of metal and ligand used in MOF structure. MOF physicochemical properties such as particle size, structure, and hydrophobicity can also be effective on MOF biocompatibility [34, 36, 47].

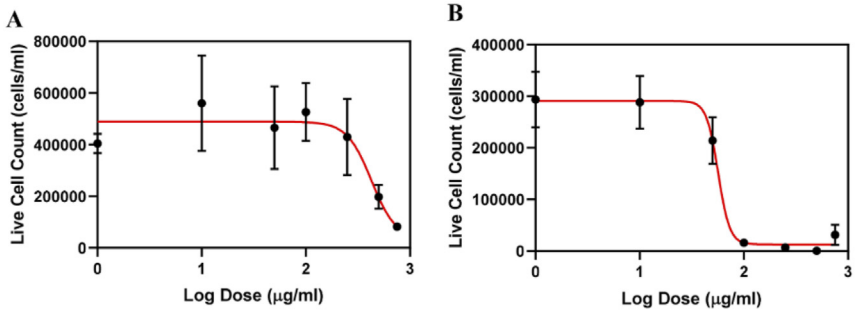

Figure 9. Dose-response curves of BEAS-2B cells in confronting with A) MIL-160 and B) ZIF-8 (Adapted with permission from [47]).

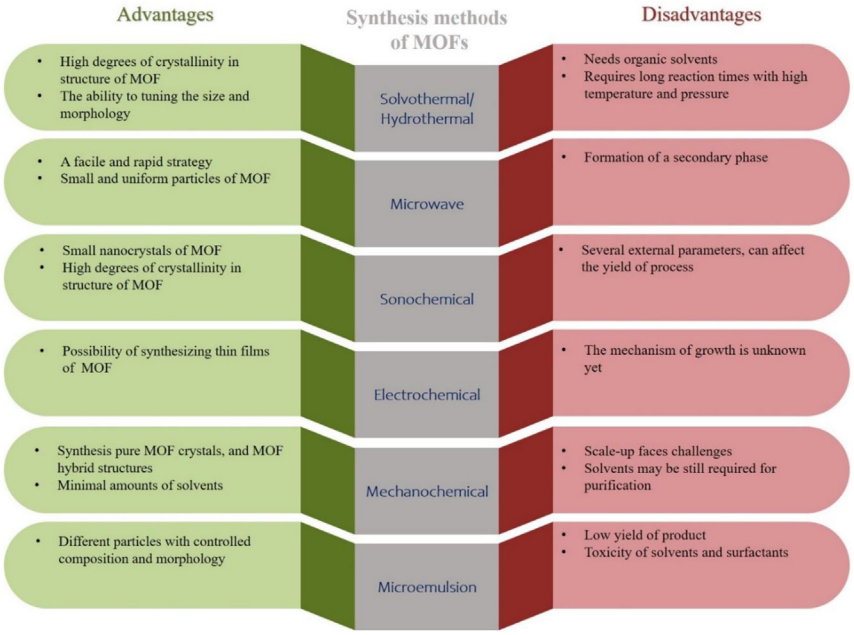

Figure 10. Synthesis approaches of MOFs with advantages and disadvantages.

The biocompatibility of MOFs can be evaluated by in vitro and in vivo toxicity screening. The type of metal ion in the MOF structure is a critical factor in determining its toxicity since it can be released after the degradation of MOF and causes toxicity. In research conducted by Grall, R. et al., the impact of metal type was evaluated by comparing the toxicity of different MOFs using various cations, including Fe, Al, and Cr. The results showed that MIL100 (Fe, Al, Cr) NPs didn't exert in vitro cell toxicity in the p53 wild-type cell lines (A549 and calu-3 (lung) and HepG2 (liver)) while MIL100-Fe caused toxicity in the hepatocarcinoma cell line. In vitro toxicity was evaluated to understand the mechanisms of MIL-100 toxicity and the cation release role. The nature of the released metal ion could damage the cells by producing reactive oxygen species (ROS), or metal ions can help to neutralize ROS [34].

As another study of the effects of metal ion and organic ligand on the toxicity, Ruyra, A. et al. evaluated in vitro and in vivo toxicity of different MOFs composed of various metals and ligands against HepG2 and MCF7 human cell lines and zebrafish embryos. There was a high correlation between the in vitro and in vivo toxicity results. Nano MgMOF-74 had minor toxicity in vitro and in vivo. The results showed that degradation of MOFs in solution produced metal ions that strongly could determine the toxicity of these MOFs [36].

Various investigations have revealed that particle toxicity of MOFs is dose-dependent, which means that different MOF concentrations affect biocompatibility. For example, as illustrated in Figure 8, the concentration of ZIF-8 below 30 μg mL^{-1} exhibited biocompatibility in cell lines. These results can be attributed to the release of Zn ions into the cells. Increased Zn^{2+} correlates with an increase in ROS generation, and ROS could arrest the cell cycle and activated apoptosis in all evaluated cell lines [41].

MOF physicochemical properties such as particle size, structure, and hydrophobicity of MOFs are pivotal factors that influence biocompatibility. In a study by Wagner, A. et al., the toxicity of two MOFs (MIL-160 and ZIF-8) with different physicochemical properties was compared. MIL-160 had a cube-like morphology containing distinguished edges and points, while ZIF-8 showed a flower-like morphology with softer edges. Both MOFs showed homogenous sizes, 8–10 μm for MIL-160 and 1–2 μm for ZIF-8. Smaller particles had higher surface area along with higher degrees of toxicity. Also, MIL-160 demonstrated a morphology with sharper edges than ZIF-8 and could damage cells. Also, hydrophobicity could play essential roles in the interaction of nanoparticles with biological systems. In this study, MIL-160 had a hydrophilic framework, and ZIF-8 had a hydrophobic framework. By increasing the Log P of MOF, the degree of toxicity was increased. This result showed that an increase in hydrophobicity induced higher toxicity of MOFs. In addition to physicochemical properties, zinc in the ZIF-8 structure was shown to have a higher level of toxicity than other metals like iron. The differences in toxicity between these two MOFs are due to their different characteristics. These outcomes are shown in Figure 9. This study demonstrated the importance of screening toxicity before biomedical applications of MOFs [47].

3.2.2. *Biodegradability*

Biodegradable nanoparticles provide significant advantages in biomedical applications. These nanoparticles make a controlled release system with good stability in the circulation system. These nanomaterials can also offer non-toxic and non-immunogen systems with prolonged circulation due to avoidance of the reticuloendothelial system [53]. The biodegradability of MOF depends on the type of ligands and metals used in the MOF structure and environmental conditions like pH [28, 35, 42].

Environmental conditions such as pH and oxidative agents are influential factors on the degradation path of MOFs. Paloic, A. et al. performed a degradation study on biocompatible Zn-L-tartrate MOF in acidic conditions in various pH (pH = 1–7) and the simulated body fluid (pH = 7.4). The results indicated that 60% of Zn ion was released in acidic conditions, and as the pH of the solution was increased, the rate of degradation decreased [35].

The oxidative conditions can aid the hydrolysis of the coordination bond between ligand and metal and induce degradation. This phenomenon depends on the nature of ligand and metal as well as the structure of MOF. Khramenkova et al. reported oxidative transformations of the Mn, which can lead to controlled degradation of Mn-based MOFs under high levels of oxidants. Oxidants may be produced in pathogenic tissues. The results revealed the excellent stability of the Mn-carboxylate structure against direct hydrolysis. However, oxidation helped in the hydrolysis of the coordination bonds. Degradation through environmental conditions is a suitable platform for targeted and triggered drug delivery [42].

In addition, the type of ligand is a valuable parameter in biodegradation. For example, Collet, G. et al. indicated that using an organic ligand with light-responsive property can help to control the MOF degradation in specific wavelengths and temperatures. In CD-MOF-161, a

photocleavable dianthracene-based ligand was used for controlled degradation, which can be triggered by light (wavelength less than 300 nm) or high temperature (160 °C) [28].

Overall, in this paper, influential factors on MOF characteristics were investigated. Size, structure and morphology, porosity, biocompatibility, and biodegradability were mentioned as structural and biological properties of MOFs, and as stated, various factors could affect these characteristics. In the reviewed articles, the factors that affect the features of MOFs have been investigated. Since MOF optimized properties are essential in all their applications, especially in their efficacy in biomedical applications, it was decided to summarize the factors that affect these properties in a review article. Although it seems that some influential factors on their characteristics, such as stability, and acute and chronic toxicity, have not been well studied still. Considering the investigated characteristics and optimizing the effectual parameters, it is possible to reach suitable properties of MOFs that can improve the efficiency of MOFs in biological applications.

Regarding findings, particle size is a critical attribute of MOFs in biomedical applications, significantly affecting toxicity, biodistribution, lifetime, cellular uptake, and intracellular transportation of particles in the body. Similarly, it was reported [25] that the main variables in the MOF preparation, such as composition, metal ion and ligand, additives, temperature, solvent, and synthesis procedure, could modulate the MOF particle size and morphology of MOFs. It was concluded that controlling the size and morphology can help to improve the MOFs and their potential efficiency.

It was expressed that the morphologies and structures of nanoparticles can lead to the emergence of various nanoparticle properties such as toxicity, nanoparticle interaction with biological fluids and interfaces, and finally, nanoparticle performance, especially in biological applications. In this regard, Allendorf and Stavila reviewed the structure-function relationship in MOFs. They reported that the possibility of precise MOF structure design led to predicting and achieving MOF desirable characteristics. However, the diversity in structures and chemical bonds of MOFs makes it challenging to determine a definitive relationship between experiments and theory [54].

As mentioned above, biocompatibility of MOFs must be considered, especially in biomedical applications. This feature can be affected by MOF physicochemical properties such as particle size and structure. Li and coworkers investigated effectual parameters on the biocompatibility of MOFs and finally reported that physicochemical properties like particle size and surface properties could affect biocompatibility. Also, they mentioned that selection of safe metal ions and ligands might provide biocompatible MOFs for biomedical applications. The result of their review was that a better understanding of the relationship between different factors and biocompatibility aids for making proper nanoparticles; however, there is no clear theory yet, due to the complexities of toxicology and the variety of practical factors [18].

Size, structure, and many other physicochemical properties of MOFs could be adjusted by selecting the synthesis method and controlling the synthesis parameters. Various synthetic approaches of MOFs with advantages and disadvantages have been reported in Figure 10. Solvothermal/hydrothermal techniques are a convenient route for synthesizing the MOFs, in which reactions proceed at high temperatures and pressure. The advantages of these methods can be counted as a high degree of crystallinity in MOF structure and the ability to tune MOF size and shape. However, this technique requires a long reaction time with high pressure and temperature and needs organic solvents [55, 56, 57]. As another method, microwave-assisted synthesis is a facile and rapid synthesis that produces small and uniform particles. Still, there may be a secondary-phase formation as a problem during the process [58, 59]. In the following procedure, sonochemical synthesis, although small nanocrystals with a degree of crystallinity are gained, this process is affected by several external parameters [60, 61]. In addition to these methods, electrochemical synthesis possesses the ability to synthesize MOF thin film. However, this approach mechanism is remained relatively unknown yet [62]. Mechanochemical synthesis of MOF is another strategy with the ability to synthesize pure crystals and hybrids of MOFs with the minor use of solvents. However, it may require solvent for the purification process, and scale-up faces challenges [63]. Finally, although microemulsion strategy can produce different MOF particles with controlled composition and morphology, a low yield of product and the toxicity of solvent and surfactant are challenges of this approach [64].

MOFs synthesized by suitable strategy with desired properties led to different biomedical applications, as mentioned earlier. Also MOFs with tunable characteristics could be applied in separation [65, 66, 67], catalysis [68, 69, 70], sensing [71, 72, 73, 74, 75, 76, 77], and storage [78, 79, 80, 81].

4. Conclusion and future prospects

As a class of highly porous materials, metal-organic frameworks are considered promising carriers for drug or imaging agent delivery. Based on these applications, characteristics of MOFs are critical in biological systems, and investigation of the effective factors on these properties seems to be essential. In this review, we assessed the correlation between various effective parameters and characteristics of MOFs. Metal ions and organic ligands, additives, synthesis strategy, and several other factors affect the properties of MOFs. Accordingly, the consideration of these potent parameters has a critical role in improving biomedical applications of MOFs. In general, there is a need for investigating multiple parameters in each study by changing a factor while keeping others constant and repeating this process for all parameters.

In the future, controlling the properties of MOFs through adjustment of influential factors can help in the development of MOFs regarding their applications and performance. Hence, achieving desirable properties of MOFs can improve efficacy for precise drug delivery and imaging. This improvement motivates ongoing studies to expand MOFs for biomedical applications. Besides, further research on the characteristics of MOFs and influential factors is still required. It is also suggested to conduct future investigations on developing practical models and computerized tools to analyze MOFs synthesis conditions that help scientists optimize the conditions and other effective factors.

Declarations

Author contribution statement

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

[1] F. Alexis, et al., Factors affecting the clearance and biodistribution of polymeric nanoparticles, Mol. Pharm. 5 (4) (2008) 505–515.
[2] W.R. Sanhai, et al., Seven challenges for nanomedicine, Nat. Nanotechnol. 3 (5) (2008) 242.
[3] P. Padmanabhan, et al., Nanoparticles in practice for molecular-imaging applications: an overview, Acta Biomater. 41 (2016) 1–16.
[4] S. Siddique, J.C. Chow, Application of nanomaterials in biomedical imaging and cancer therapy, Nanomaterials 10 (9) (2020) 1700.
[5] I. Christodoulou, C. Serre, R. Gref, Chapter 21 - metal-organic frameworks for drug delivery: degradation mechanism and in vivo fate, in: M. Mozafari (Ed.), Metal-Organic Frameworks for Biomedical Applications, Woodhead Publishing, 2020, pp. 467–489.
[6] W.J. Rieter, et al., Nanoscale metal– organic frameworks as potential multimodal contrast enhancing agents, J. Am. Chem. Soc. 128 (28) (2006) 9024–9025.
[7] W.J. Rieter, K.M. Taylor, W. Lin, Surface modification and functionalization of nanoscale metal-organic frameworks for controlled release and luminescence sensing, J. Am. Chem. Soc. 129 (32) (2007) 9852–9853.
[8] X.-G. Wang, et al., A multifunctional metal–organic framework based tumor targeting drug delivery system for cancer therapy, Nanoscale 7 (38) (2015) 16061–16070.
[9] B.F. Hoskins, R. Robson, Infinite polymeric frameworks consisting of three dimensionally linked rod-like segments, J. Am. Chem. Soc. 111 (15) (1989) 5962–5964.
[10] Q. Zhua, Q. Xu, Metal–organic framework composites, Chem. Soc. Rev. 43 (16) (2014) 5468–5512.
[11] W. Xia, et al., Metal–organic frameworks and their derived nanostructures for electrochemical energy storage and conversion, Energy Environ. Sci. 8 (7) (2015) 1837–1866.
[12] P. Horcajada, et al., Metal–organic frameworks in biomedicine, Chem. Rev. 112 (2) (2011) 1232–1268.
[13] A. Samui, S.K. Sahu, Chapter 13 - characterizations of MOFs for biomedical application, in: M. Mozafari (Ed.), Metal-Organic Frameworks for Biomedical Applications, Woodhead Publishing, 2020, pp. 277–295.
[14] B.A. Lakshmi, S. Kim, Current and emerging applications of nanostructured metal–organic frameworks in cancer-targeted theranostics, Mater. Sci. Eng. C 105 (2019) 110091.
[15] J. Qiu, et al., Chapter 20 - carbohydrates in metal organic frameworks: supramolecular assembly and surface modification for biomedical applications, in: M. Mozafari (Ed.), Metal-Organic Frameworks for Biomedical Applications, Woodhead Publishing, 2020, pp. 445–465.
[16] W. Cai, et al., Gold nanorods@metal-organic framework core-shell nanostructure as contrast agent for photoacoustic imaging and its biocompatibility, J. Alloys Compd. 748 (2018) 193–198.
[17] W. Cai, et al., Metal–organic framework-based nanomedicine platforms for drug delivery and molecular imaging, Small 11 (37) (2015) 4806–4822.
[18] S. Li, L. Tan, X. Meng, Nanoscale metal-organic frameworks: synthesis, biocompatibility, imaging applications, and thermal and dynamic therapy of tumors, Adv. Funct. Mater. 30 (13) (2020) 1908924.
[19] V. Raman, et al., Synthesis of Co3O4 nanoparticles with block and sphere morphology, and investigation into the influence of morphology on biological toxicity, Exp. Ther. Med. 11 (2) (2016) 553–560.
[20] J. Liu, et al., Controllable porosity conversion of metal-organic frameworks composed of natural ingredients for drug delivery, Chem. Commun. (Camb) 53 (55) (2017) 7804–7807.
[21] G. Zhao, et al., Bimetallic zeolitic imidazolate framework as an intrinsic two-photon fluorescence and pH-responsive MR imaging agent, ACS Omega 3 (8) (2018) 9790–9797.
[22] D.F. Williams, On the mechanisms of biocompatibility, Biomaterials 29 (20) (2008) 2941–2953.
[23] M.V. Paula, et al., Metal organic frameworks for selective degradation of amoxicillin in biomedical wastes, J. Braz. Chem. Soc. 29 (10) (2018) 2127–2136.
[24] P. Horcajada, et al., Colloidal route for preparing optical thin films of nanoporous metal–organic frameworks, Adv. Mater. 21 (19) (2009) 1931–1935.
[25] B. Liu, et al., Recent advances in controlled modification of the size and morphology of metal-organic frameworks, Nano Res. 11 (9) (2018) 4441–4467.
[26] H. Deng, et al., Large-pore apertures in a series of metal-organic frameworks, Science 336 (6084) (2012) 1018–1023.
[27] Z. Wang, et al., Nanoscale Zr-based MOFs with tailorable size and introduced mesopore for protein delivery, Adv. Funct. Mater. 28 (16) (2018).
[28] G. Collet, et al., On-demand degradation of metal-organic framework based on photocleavable dianthracene-based ligand, J. Am. Chem. Soc. 140 (34) (2018) 10820–10828.
[29] G. Collet, et al., On-demand degradation of metal–organic framework based on photocleavable dianthracene-based ligand, J. Am. Chem. Soc. 140 (34) (2018) 10820–10828.
[30] D. Moher, et al., Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement 4 (1) (2015) 1.
[31] S.K. Ghosh, J. Ribas, P.K. Bharadwaj, Metal-organic framework structures of Cu(II) with pyridine-2,6- dicarboxylate and different spacers: identification of a metal bound acyclic water tetramer, CrystEngComm 6 (2004) 250–256.
[32] W. Hatakeyama, et al., Synthesis of gadolinium nanoscale metal-organic framework with hydrotropes: manipulation of particle size and magnetic resonance imaging capability, ACS Appl. Mater. Interfaces 3 (5) (2011) 1502–1510.
[33] C.Y. Sun, et al., Chiral nanoporous metal-organic frameworks with high porosity as materials for drug delivery, Adv. Mater. 23 (47) (2011) 5629–5632.
[34] R. Grall, et al., In vitro biocompatibility of mesoporous metal (III; Fe, Al, Cr) trimesate MOF nanocarriers, J. Mater. Chem. B 3 (42) (2015) 8279–8292.
[35] A. Palčić, et al., Structural and degradation studies of a biocompatible Zn-L-tartrate metal-organic framework, J. Solid State Chem. 225 (2015) 59–64.
[36] A. Ruyra, et al., Synthesis, culture medium stability, and in vitro and in vivo zebrafish embryo toxicity of metal-organic framework nanoparticles, Chem. Eur J. 21 (6) (2015) 2508–2518.
[37] B. Mandal, J.S. Chung, S.G. Kang, Exploring the geometric, magnetic and electronic properties of Hofmann MOFs for drug delivery, Phys. Chem. Chem. Phys. 19 (46) (2017) 31316–31324.
[38] R. Abazari, et al., Morphology- and size-controlled synthesis of a metal-organic framework under ultrasound irradiation: an efficient carrier for pH responsive release of anti-cancer drugs and their applicability for adsorption of amoxicillin from aqueous solution, Ultrason. Sonochem. 42 (2018) 594–608.
[39] S. Dehghani, et al., The effect of size and aspect ratio of Fe-MIL-88B-NH2 metal-organic frameworks on their relaxivity and contrast enhancement properties in MRI: in vitro and in vivo studies, J. Nanoparticle Res. 20 (10) (2018).
[40] X.C. Gao, et al., Size and surface controllable metal-organic frameworks (MOFs) for fluorescence imaging and cancer therapy, Nanoscale 10 (13) (2018) 6205–6211.
[41] M. Hoop, et al., Biocompatibility characteristics of the metal organic framework ZIF-8 for therapeutical applications, Appl. Mater. Today 11 (2018) 13–21.
[42] E.V. Khramenkova, et al., Degradation paths of manganese-based MOF materials in a model oxidative environment: a computational study, Phys. Chem. Chem. Phys. 20 (32) (2018) 20785–20795.
[43] X.G. Wang, et al., Controlled nucleation and controlled growth for size predicable synthesis of nanoscale metal-organic frameworks (MOFs): a general and scalable approach, Angew Chem. Int. Ed. Engl. 57 (26) (2018) 7836–7840.
[44] X.X. Hu, et al., Nanoporous CD-MOF particles with uniform and inhalable size for pulmonary delivery of budesonide, Int. J. Pharm. 564 (2019) 153–161.
[45] X.H. Li, et al., Direct imaging of tunable crystal surface structures of MOF MIL-101 using high-resolution electron microscopy, J. Am. Chem. Soc. 141 (30) (2019) 12021–12028.
[46] H.P. Nguyen Thi, et al., Size-control and surface modification of flexible metal-organic framework MIL-53(Fe) by polyethyleneglycol for 5- fluorouracil anticancer drug delivery, ChemistrySelect 4 (8) (2019) 2333–2338.
[47] A. Wagner, et al., Toxicity screening of two prevalent metal organic frameworks for therapeutic use in human lung epithelial cells, Int. J. Nanomed. 14 (2019) 7583–7591.
[48] N. Feliu, B. Fadeel, Nanotoxicology: no small matter, Nanoscale 2 (12) (2010) 2514–2520.
[49] E. Blanco, H. Shen, M. Ferrari, Principles of nanoparticle design for overcoming biological barriers to drug delivery, Nat. Biotechnol. 33 (9) (2015) 941.
[50] R. Ridolfo, et al., Exploring the impact of morphology on the properties of biodegradable nanoparticles and their diffusion in complex biological medium, Biomacromolecules 22 (1) (2021) 126–133.
[51] C. Dey, et al., Crystalline metal-Organic frameworks (MOFs): synthesis, structure and function, Acta Crystallogr. B: Struct. Sci. Crystal Eng. Mater. 70 (1) (2014) 3–10.
[52] L. Jiao, et al., Metal–organic frameworks: structures and functional applications, Mater. Today 27 (2019) 43–68.
[53] S. Su, P.M. Kang, Systemic review of biodegradable nanomaterials in nanomedicine, Nanomaterials 10 (4) (2020) 656.
[54] M.D. Allendorf, V. Stavila, Crystal engineering, structure-function relationships, and the future of metal-organic frameworks, CrystEngComm 17 (2) (2015) 229–246.
[55] S. Zhang, et al., Metal-organic framework-based nanomaterials for biomedical applications, Chin. Chem. Lett. 31 (5) (2020) 1060–1070.
[56] O. Yaghi, H. Li, Hydrothermal synthesis of a metal-organic framework containing large rectangular channels, J. Am. Chem. Soc. 117 (41) (1995) 10401–10402.
[57] X. Cheng, et al., Size-and morphology-controlled NH2-MIL-53 (Al) prepared in DMFwater mixed solvents (Dalton Transactions (2014), Dalton Trans. 43 (33) (2014).
[58] C. Chen, et al., Microwave-assisted rapid synthesis of well-shaped MOF-74 (Ni) for CO2 efficient capture, Inorg. Chem. 58 (4) (2019) 2717–2728.
[59] R.F. Mendes, J. Rocha, F.A. Almeida Paz, Chapter 8 - microwave synthesis of metal-organic frameworks, in: M. Mozafari (Ed.), Metal-Organic Frameworks for Biomedical Applications, Woodhead Publishing, 2020, pp. 159–176.
[60] H.-Y. Cho, et al., High yield 1-L scale synthesis of ZIF-8 via a sonochemical route, Microporous Mesoporous Mater. 169 (2013) 180–184.
[61] C. Vaitsis, G. Sourkouni, C. Argirusis, Chapter 11 - sonochemical synthesis of MOFs, in: M. Mozafari (Ed.), Metal-Organic Frameworks for Biomedical Applications, Woodhead Publishing, 2020, pp. 223–244.
[62] H. Al-Kutubi, et al., Electrosynthesis of metal–organic frameworks: challenges and opportunities, ChemElectroChem 2 (4) (2015) 462–474.
[63] S. Tanaka, Chapter 10 - mechanochemical synthesis of MOFs, in: M. Mozafari (Ed.), Metal-Organic Frameworks for Biomedical Applications, Woodhead Publishing, 2020, pp. 197–222.
[64] W. Zheng, et al., Controllable preparation of nanoscale metal–organic frameworks by ionic liquid microemulsions, Ind. Eng. Chem. Res. 56 (20) (2017) 5899–5905.
[65] J. Pei, et al., Current Status of microporous metal–organic frameworks for hydrocarbon separations, Metal-Organic Framework (2020) 305–338.
[66] Y. Peng, et al., A water-stable cyano-functionalized metal-organic framework as an efficient adsorbent of uranyl ion, Mater. Res. Express 6 (12) (2019) 125505.

[67] J.-W. Zhang, et al., Microporous rod metal–organic frameworks with diverse Zn/Cd–triazolate ribbons as secondary building units for CO 2 uptake and selective adsorption of hydrocarbons, Dalton Trans. 46 (3) (2017) 836–844.
[68] Ikreedeegh, R.R. and M. Tahir, A critical review in recent developments of metal-organic-frameworks (MOFs) with band engineering alteration for photocatalytic CO2 reduction to solar fuels. J. CO_2 Utilization. 43: p. 101381.
[69] M. Ramyashree, et al., Metal-organic framework-based photocatalysts for carbon dioxide reduction to methanol: a review on progress and application, J. CO_2 Utilization (2020) 101374.
[70] D. Adekoya, M. Tahir, N.A.S. Amin, Recent trends in photocatalytic materials for reduction of carbon dioxide to methanol, Renew. Sustain. Energy Rev. 116 (2019) 109389.
[71] J.N. Hao, B. Yan, Determination of urinary 1-hydroxypyrene for biomonitoring of human exposure to polycyclic aromatic hydrocarbons carcinogens by a lanthanide-functionalized metal-organic framework sensor, Adv. Funct. Mater. 27 (6) (2017) 1603856.
[72] Z. Hu, et al., Effective detection of mycotoxins by a highly luminescent metal–organic framework, J. Am. Chem. Soc. 137 (51) (2015) 16209–16215.
[73] S. Wang, et al., Functionalization of microporous lanthanide-based metal–organic frameworks by dicarboxylate ligands with methyl-substituted thieno [2, 3-b] thiophene groups: sensing activities and magnetic properties, Inorg. Chem. 55 (11) (2016) 5139–5151.
[74] D.I. Osman, et al., Nucleic acids biosensors based on metal-organic framework (MOF): paving the way to clinical laboratory diagnosis, Biosens. Bioelectron. 141 (2019) 111451.
[75] S.M. Sheta, et al., A novel HCV electrochemical biosensor based on a polyaniline@Ni-MOF nanocomposite, Dalton Trans. 49 (26) (2020) 8918–8926.
[76] M. Alhaddad, S.M. Sheta, Dual naked-eye and optical chemosensor for morphine detection in biological real samples based on Cr(III) metal–organic framework nanoparticles, ACS Omega 5 (43) (2020) 28296–28304.
[77] E. Asadian, S. Shahrokhian, A.I. Zad, Highly sensitive nonenzymetic glucose sensing platform based on MOF-derived NiCo LDH nanosheets/graphene nanoribbons composite, J. Electroanal. Chem. 808 (2018) 114–123.
[78] Y. Ye, et al., A microporous metal–organic framework with naphthalene diimide groups for high methane storage, Dalton Trans. 49 (12) (2020) 3658–3661.
[79] W. Fan, et al., Fine-tuning the pore environment of the microporous Cu-MOF for high propylene storage and efficient separation of light hydrocarbons, ACS Cent. Sci. 5 (7) (2019) 1261–1268.
[80] M. Dinca, et al., Hydrogen storage in a microporous metal− organic framework with exposed Mn2+ coordination sites, J. Am. Chem. Soc. 128 (51) (2006) 16876–16883.
[81] H.-M. Wen, et al., A microporous metal–organic framework with lewis basic nitrogen sites for high C2H2 storage and significantly enhanced C2H2/CO2 separation at ambient conditions, Inorg. Chem. 55 (15) (2016) 7214–7218.