Metal organic frameworks as hybrid nanocomposites in drug delivery and biomedical applications.

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Nanoporous metal organic frameworks as hybrid polymer–metal composites for drug delivery and biomedical applications

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Metal organic frameworks (MOFs), porous hybrid polymer–metal composites at the nanoscale, are recent innovations in the field of chemistry; they are novel polymeric materials with diverse biomedical applications. MOFs are nanoporous materials, consisting of metal ions linked together by organic bridging ligands. The unique physical and chemical characteristics of MOFs have attracted wider attention from the scientific community, exploring their utility in the field of material science, biology, nanotechnology and drug delivery. The practical feasibility of MOFs is possible owing to their abilities for biodegradability, excellent porosity, high loading capacity, ease of surface modification, among others. In this regard, this review provides an account of various types of MOFs, their physiochemical characteristics and use in diverse disciplines of biomedical sciences – with special emphasis on drug delivery and theranostics. Moreover, this review also highlights the stability and toxicity issues of MOFs, along with their market potential for biomedical applications.

Introduction

Over the past few decades, research interest in the field of material chemistry for exploring the fundamental solid forms for diverse biomedical applications has been continuously increasing.

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In this regard, the quest for the synthesis of supramolecular structures has gained considerable impetus, leading to the generation of thousands of new chemical entities [1,2]. Metal organic frameworks (MOFs) are considered to be a new generation of hybrid material consisting of an organic and an inorganic component, behaving like a single entity with completely different physiochemical properties. Moreover, MOFs pose close structural similarity with metal coordination complexes, thus they have evolved as the new generation of coordination complex with a high degree of porosity and functionalization abilities [3]. Table 1 enlists the key structural differences between the coordination polymers and MOFs.

Generally, MOFs show a high degree of robustness in their framework structure with a highly bendable nature and they have the utmost flexibility for chemical modification during incorporation of metal ions with the organic linkers. A wide range of MOF structures are available with a high degree of versatility in their chemical composition, thus offering excellent surface modification (helpful in biomedicine applications), high surface area (for efficient loading of cargoes) and large pore sizes (that facilitate wrapping of various types of pharmaceuticals and theranostic agents) [3,4].

Upon close inspection of the structures of MOFs, they are high molecular weight supramolecular crystalline solid structures with well-defined geometry, wherein the inorganic component is connected to the organic part by struts [5]. The inorganic (polar) component can be a metal, transition metal or a group of metals, whereas the organic (nonpolar) component includes hybrid carbon materials. Several inorganic metals (e.g., iron, zeolite, silica, copper, etc.) and organic ligands (e.g., polycarboxylates, phosphonates, sulfonates, imidazolates, phenolates, etc.) have been investigated for preparing MOFs [6]. The detailed list of metal ions and organic linkers used for the synthesis of MOFs has been described in the literature [1,5].

The metal ligands are primarily categorized by their number and orientation of Lewis-base sites and combined with the organic linkers with well-defined geometries [6–9]. Further, the metal ions used in the MOFs can be typically mono-, di-, tri- or tetra-valent ligands [10]. The vast combination of inorganic metals and organic ligands tends to configure various molecular functionalities and architectures of MOFs with a wide variety of chemical and physical properties for diverse applications in medical and nonmedical fields. Because the applications of MOFs are abundant, this review endeavors to provide an insight into the biomedical application of MOFs in drug delivery, biosensing, imaging, chemical catalysis, gas storage, among others [5].

Structural classification of MOFs

Depending on the various stages of synthesis involved, MOFs are particularly classified as: (i) first generation (normal MOFs); (ii) second generation (functionalized MOFs); and (iii) third generation (smart MOFs). First-generation MOFs follow the basic architecture having an inorganic and organic moiety, second-generation MOFs possess surface modifications through chemical functionalities and third-generation MOFs contain biomolecules such as cations, drugs, bioactives, toxins and gases within their framework [11]. Moreover, MOFs can also be classified as flexible and rigid MOFs based on the robustness of the structural frameworks. Because certain MOFs can reversibly change their structural conformation in the presence of external stimuli, such as molecular inclusion, temperature or pressure, they are referred to as flexible MOFs. By contrast, rigid MOF frameworks do not have any change in the conformation in the presence of external stimuli [12].

On the basis of crystal structure arrangement, MOFs can be categorized into two types: crystalline and amorphous [13]. Crystalline MOFs possess an infinite arrangement of a highly regular solid porous framework. The frequently reproducing structures provide an uneven porous architecture of crystalline MOFs beneficial for physicochemical sorption characteristics; they also possess long-range order. By contrast, amorphous MOFs retain their basic building blocks and connectivity like the crystalline MOFs, except there is a long-range periodic arrangement order in their structural network [14].

Chemical approaches for the synthesis of MOFs

Synthesis of MOFs involves high-end chemical reactions between the inorganic and organic parts for attaining the desired structural network. Moreover, as far as the synthesis of MOFs is concerned, especially for biomedical applications, the chemistry needs to be thoroughly checked for assessing the safety of MOFs for biomedical applications [15]. Multiple synthesis methods have been reported to date for producing a variety of MOFs, where few of the widely employed approaches include hydro or solvothermal synthesis [16,17], microwave-assisted synthesis [18], mechanochemical synthesis [19], sonochemical synthesis [20], electrochemical synthesis [21], spray-drying, inverse emulsion and microfluidics-based synthesis [22], and many more. Each of the

TABLE 1

Differences between the coordination polymers and MOFs.

No.	Property	Coordination polymer	MOFs
1	Nature of joint SBU	Monatomic	Polyatomic
2	Framework pores	Charged, must contain counter ions	Neutral, can be empty
3	Formal bond valence	0	½
4	Estimated link energy (kJ/mol)	100–150	363
5	Bond break to excise SBU	4	12
6	Estimated energy to excise SBU/kJ/mol	400–600	2200

Abbreviations: MOF, metal organic framework; SBU, strategic building unit.

synthesis techniques has their own merits for producing MOFs with different physiochemical properties, functionalization and scale-up ability.

- Microwave-assisted synthesis: this method has been widely used in organic synthesis of MOFs. It has the advantage of a shorter reaction time for synthesis to produce the MOFs with high monodispersity, thus applicable in the industrial set-up [18].
- Spray-drying: considered as one of the advanced methods for synthesizing MOFs by aerosol casting, which tends to yield end-products with a highly crystalline appearance. The use of aerosol provides the advantage of producing MOFs with desired shapes and architectures [23].
- Microfluidic synthesis: this method has the advantage of producing MOFs with a desired hierarchy in a continuous manner to produce the monodispersed structures with a nanocrystalline and nanofiber appearance [24].
- Microemulsion synthesis: is suitable for particle shaping, allowing control over shape, size and polydispersity of the MOFs [25].
- Direct coupling synthesis: provides synthesis of MOFs by direct reaction between the metal ions with organic linkers [15].
- Electrospinning synthesis: this method is used for producing MOF formulations from the porous MOF polymer composites to produce the nanofibers. The detail has been discussed elsewhere in the MOF formulation section [15].
- Hydrothermal synthesis: this method is feasible in the organic synthesis of MOFs partially soluble in water at higher temperatures [17].
- Solvothermal synthesis: is useful for preparing the crystalline MOFs readily soluble in water [18].

Apart from these methods, the direct approach of synthesis of MOFs involves reaction between the precursor metals with the organic components (e.g., metal nitrates, sulfates or acetates) [10,13]. In general, during synthesis of MOFs, the process tends to get hampered by poor prediction of the network geometry and lack of proper penetration of the ligands into the coordination motifs for ring-opening polymerization and use of bulky ligands in different concentrations [8]. However, recent advances in the field have revealed developments in the morphology and geometry of MOFs for improving their porosity and surface characteristics by linking with organic ligands to provide rigid surfaces [26]. This generates ultra-porous MOF materials with surface-tunable properties, thus possessing high utility in drug delivery. Moreover, multivariate MOFs have emerged as powerful tools for changing the reactivity of the pores by creating catalytic sites, tending to provide multifold augmentation in their material properties for diverse biomedical applications [5,27].

Identification and characterization of MOFs

Owing to the wide diversity in the material characteristics of MOFs, their identification and characterization is considered to be highly challenging. Various instrumental techniques have been reported in the literature for characterizing different parameters of MOFs [14]. These include powder and thin film X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), X-ray, neutron total scattering and helium pycnometry as some of the commonly used techniques for characterization of the MOFs. PXRD is considered as an

evergreen invaluable technique in characterizing crystalline nature and phase purity of a wide range of MOFs, whereas FTIR and Raman spectroscopy tools are used for identifying the functional moieties for inferring the short-range ordering in the MOFs by tracking the vibrational modes within the functional groups across crystalline and amorphous products [10]. X-ray and neutron total scattering techniques are used to analyze scattering function for evaluating sorption sites in the MOFs along with unearthing information from Bragg and diffuse scattering. Helium pycnometry is used for measuring density of the crystalline and amorphous MOFs [14]. DSC is applied for identifying heat-induced amorphization of the MOFs. Apart from these, other techniques like pair-distribution function (PDF) analysis, excitation-attenuated fluorescence spectroscopy (EXAFS), X-ray-attenuated neutron emission scattering (XANES) and positron annihilation lifetime spectroscopy (PALS) are useful in characterizing the order of porous materials. These techniques are beneficial in identifying the nature of defects in the MOF structures [28]. Overall, these characterization techniques are also useful in unearthing other vital characteristics of the MOFs including porosity, density, bulk volume, pore size, topology, structural and constitutional properties along with thermal and mechanical stability [2,29].

Synthesis of variant MOFs
Crystalline MOFs
The MOF structures with crystalline appearance are synthesized by solvent-free methods [30]. Usually, metal acetate and organic proligands are mixed and ground in a ball mill, and subsequently the crystals are precipitated out by a salting-out mechanism. Solvent-free synthesis includes $Cu_3(BTC)_2$ MOFs synthesized via the hydrothermal approach [31]. Recently, the advancement in solvent-free preparation of MOF films and composites by chemical vapor deposition has produced end-products with a high yield [32]. These techniques have also been applied for the synthesis of ZIF-8 MOFs [33].

Amorphous MOFs
Like regular crystalline MOFs, amorphous MOFs contain analogous basic building blocks and lack long-range periodic order. Amorphous MOFs offer many exciting opportunities for practical application as novel functional materials for drug delivery applications [14,34]. These materials are simply defined as the network combinations containing inorganic nodes (clusters or metal ions) linked by the organic ligands (generally carboxylate or nitrogen-based functional groups). So far the literature reports have demonstrated the exploration of imidazole frameworks with various metals like zeolite, nickel, zinc, cobalt, copper, palladium, platinum, sodium, among others. The amorphous MOFs are prepared from the crystalline frameworks by applying a stress-like temperature and pressure [35]. The stress generated as a result of the application of energy causes deformation in the lattice geometry and increases amorphization in the structures. Recently, literature reports have revealed the application of the electric discharge method for collapsing the metal-binding carboxylate groups in the framework to produce the amorphous structures [14]. Moreover, the comminution approach using a ball mill has also been reported for producing amorphous MOFs. It has been observed that the degree of amorphization tends to impact drug delivery

applications for tailoring the release rates of the drugs. The recent application of amorphous MOFs has been reported by Orellana-Tavra et al. for delivering calcein using Zr-based UiO-66 MOF and observed superior drug release control for more than 30 days in relation to their crystalline counterpart with drug release control up to 2 days only [34].

Luminescent MOFs

These are the MOF variants particularly explored for their functional luminescence properties. The literature reports on luminescent MOFs have demonstrated they are well-suited as light-emitting devices for imaging applications [36]. The inherent high porosity and mesoporous nature of luminescent MOFs facilitate high loading capacity for the biological molecules like anticancer drugs or biogases into their pores. In addition, highly available functionality in luminescent MOFs in the form of open metal sites or functional Lewis basic and/or acidic sites on the linkers leads to opportunities that effectively control the interaction with biological systems and release into the environment [1,37].

Nano MOFs

Nanoscale structures of MOFs (typically known as nano MOFs) have now evolved as a new class of MOF with exciting applications. Nano MOFs display high surface area and unique size-dependent optical, luminescent, electrical and magnetic properties, as compared with conventional MOFs [38]. They exhibit a high degree of diversity in their composition, structure, properties and demonstrate high dispersibility and biocompatibility properties. These MOF structures are nano-sized or at times present in nanoparticulate structures. They can be synthesized by doping of inorganic nodes to alter the functional properties of MOFs without changing their coordination properties. Besides, the approach of tagging ligands with functional groups is also used as an alternative approach for chemical grafting of the drugs and biomolecules. This allows exploration of their specific applications in drug delivery and bioimaging for cancer treatment [39]. The nano MOFs are synthesized by two different strategies: by reducing the particle size by a top-down approach; or by synthesizing the nano-sized MOFs by a bottom-up approach. In this regard, the fundamental understanding of the growth mechanism and kinetics of nano MOFs tends to facilitate the development of various MOFs with nanoscale dimensions as versatile hybrid nanomaterials for biomedical applications [38]. In a typical approach for the synthesis of nano MOFs, the precursor solutions are mixed together to allow particle nucleation and growth. Further, nanoprecipitation was achieved for collecting MOF nanoparticles in the solvent system containing individual precursors remaining soluble within them. Nano MOFs provide an interesting opportunity for designing novel theranostic nanomedical devices. Della Roca et al. prepared nano MOFs loaded with cisplatin for tumor targeting and specifically achieved 75% loading in the $Pt(NH_3)_2Cl_2(succinate)_2$ MOFs with spherical morphology of $\sim$50–60 nm diameter [38].

Bio MOFs

Because MOFs are not considered to be highly biocompatible in nature owing to the lack of biodegradability, biocompatibility and toxicity associated with metal ligands and organic linkers, the idea of synthesizing biocompatible MOFs has gained lots of traction in the past few years. Attempts, therefore, have been made to bioengineer MOFs to produce bio MOFs. These can be synthesized by two different approaches such as trapping of biomolecules within the porous cavities of MOFs or by incorporating the biomolecules (e.g., drugs, toxins, gases, anionic or cationic ligands, organic ligands) within the MOF structure during the synthesis process [40,41]. Recently, a series of biomolecules has also been used to produce bio MOFs, including amino acids, peptides, nucleotides, cyclodextrins, etc. [42]. Like other MOF structures, bio MOFs possess diverse drug delivery and biomedical applications. A report by McKinlay et al. discussed the application of selection of biomolecules as linkers or bioactive metals as the inorganic counterparts for the synthesis of bio MOFs, where the developed MOFs have applications in bioimaging as a theranostic tool [40]. In an another report, the bio MOFs constructed from anionic metals have shown better absorption to the cationic drugs, eventually leading to high drug loading efficiency and controlled drug release profile from the pores of MOFs. Huxford et al. observed that cationic charge triggered drug release from the MOFs loaded with anionic drugs [43]. As far as the drug release is concerned from MOFs loaded with drug molecules in the porous cavity, the porosity of particles is considered as one of the rate-governing factors for controlling release rate of drugs. Ideally bio MOFs containing therapeutically active molecules as a part of the structural framework are usually synthesized with a minimum number of synthetic steps for attaining maximum drug payload by avoiding toxicity profiles. Furthermore, synthesis of bio MOFs depends on the selection of high quality and low toxic solvents to generate the MOFs with biodegradable and biocompatible natures. Coupling of drug molecules within the MOF includes drugs like bisphosphonates, cisplatin, vitamin B3, nicotinic acid and many more, and has been employed for bone repair, anticancer application and providing nutritional value for the purpose [41]. Moreover, the usage of metal ligands as a part of the MOF structure has lately been investigated. These include Ca, Mg, Ag, Zn and Fe as part of the MOF structure for potential applications in biomedicine.

Surface modification of MOFs

Functionalization of MOFs is a newer area of research for attaching therapeutic biomolecules on surfaces. Multiple strategies have been adopted for surface engineering of the MOFs with the help of polymers, biomolecules, ligands, among others. The surface modification of MOFs helps in improving their water dispersibility and stability, enhancement of drug loading, reducing plasma protein binding, avoiding uptake by the reticuloendothelial system and many more [43]. The coatings are used for improving the surface morphology of bio and nano MOFs for diverse therapeutic applications. Moreover, surface coating of MOFs also tends to alter the degradation pattern, thus modulating premature release of the loaded drug molecules in a controlled fashion. Fig. 1 illustrates the synthesis scheme of a nano MOF surface functionalized with silica and polymers.

Polymer-functionalized MOFs

This technique primarily includes modification of the MOF structure with a silica coating on the surface and/or encapsulation of the silica particles within the MOF framework [38]. The silica surface coating offers good biocompatibility, improved water
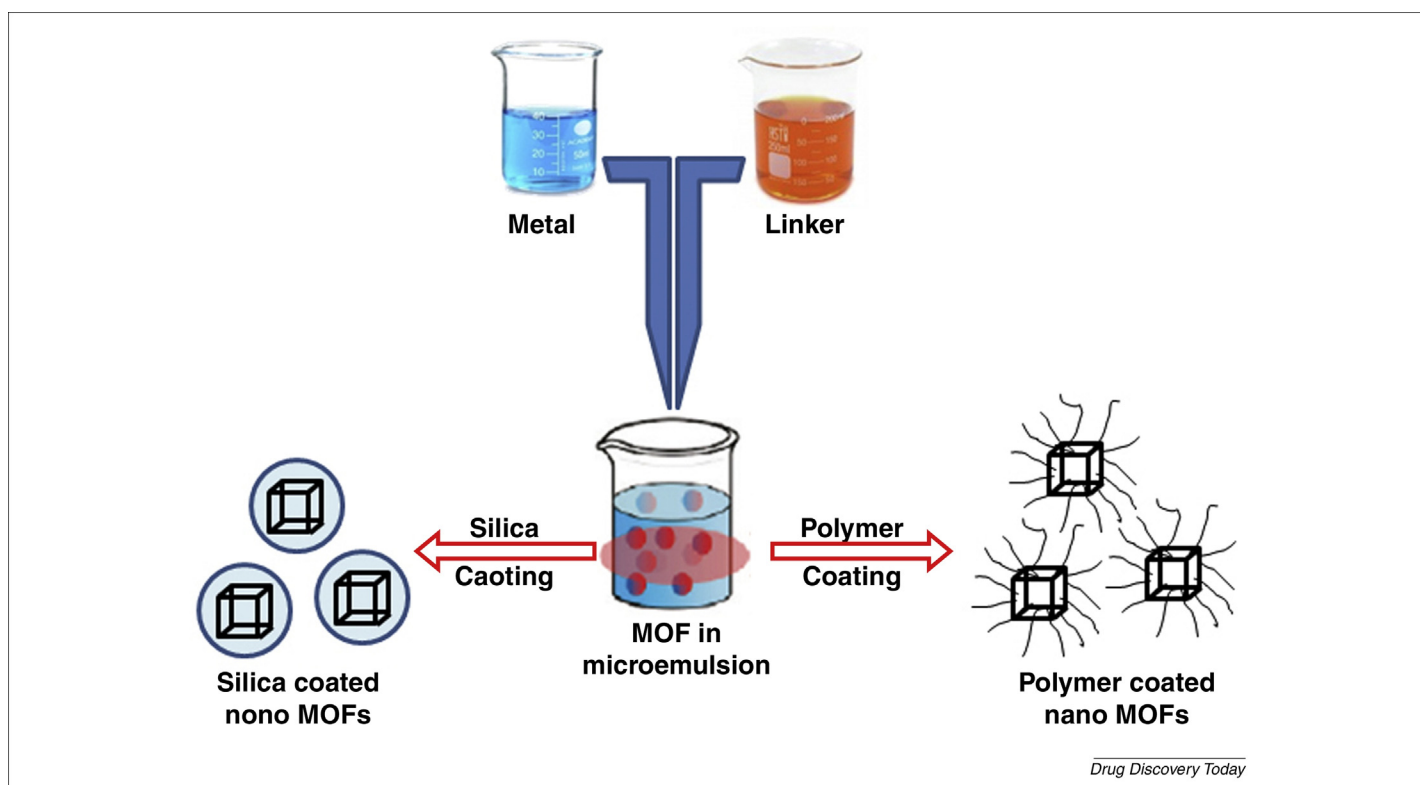
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FIGURE 1

Synthetic approaches for preparation of the functionalized nano MOFs.

dispersibility and ease of further functionalization owing to the presence of silyl groups on the silica surface [44]. Moreover, surface modifications with hydrophilic polymers like polyvinyl pyrroli-done also provide improvement in the water dispersibility. The polymer tends to bind with end groups of the MOFs at their vacant metal coordination sites via electrostatic attraction with the parti-cle surface, or covalent attachment with the bridging ligands for providing a shielding effect for the purpose [45]. The surface coating with silica or polymers is usually carried out during the synthesis of MOFs or post-synthesis of MOFs via a conjugation approach. Besides silica, other polymeric moieties have been employed for surface engineering of the nano MOFs. For instance, polysaccharides like dextran, fluorescein, biotin and chitosan are employed for attaining superior efficacy over the native MOF structures for improving solubility, cellular adhesion and contrast imaging [46]. The instance of polymer functionalization includes conjugation of thiol end groups of the polyvinyl pyrrolidone with the framework of $Gd_3þ$ MOFs. The polymer coating slows down the release of $Gd_3þ$ ions and helps in providing controlled release action to the framework structure [45]. Another example demon-strates the combined use of silica and polymer functionalization approaches to stabilize MOFs, which helps in augmenting the water solubility and dispersibility. Moreover, a literature report shows higher drug encapsulation efficiency for cisplatin and super-ior tumor targeting potential with silica-coated iron terephthalate MIL-101 nano MOFs [47].

PEG-functionalized MOFs

The approach of surface functionalization of MOFs with a PEG moiety tends to provide diverse benefits for biomedical applications, especially in solubility enhancement, tumor target-ing and diagnostic imaging. This includes surface coating of iron-carboxylate nano MOFs with PEG, where PEG coating provides controlled interaction of MOFs with the biological surface and prolongs the circulation half-life of loaded drug molecules in the circulation for several hours to days. Like other nanocarriers, nano MOFs also show 'stealth' imparted by the PEG molecules, which tends to circumvent uptake by the reticuloendothelial system.

Peptide-functionalized MOFs

The peptide functionalization on the MOF surface has been inves-tigated with fluorescence dyes for *in vitro* imaging and tumor targeting [48]. Recent instances of peptide functionalization in-clude MOFs coated with rhodamine, RGDfK and angiogenic pep-tides for targeting cancer cells [49].

Applications of MOFs

Applications of MOFs have been highlighted in Fig. 2, which indicates their diverse applications in drug delivery and biomedi-cal imaging.

Drug delivery system

MOFs have been extensively explored as drug delivery devices in the past decade for delivering loaded cargoes to desired sites. Although many carriers have been reported, MOFs garnered much attention owing to their porous structure containing voids, which provides high drug loading capacity and a controlled drug-release profile. A wide range of drug molecules with hydrophilic, hydro-phobic and amphiphilic natures can be encapsulated in the MOFs. Based on the loading approaches discussed earlier, drugs can be

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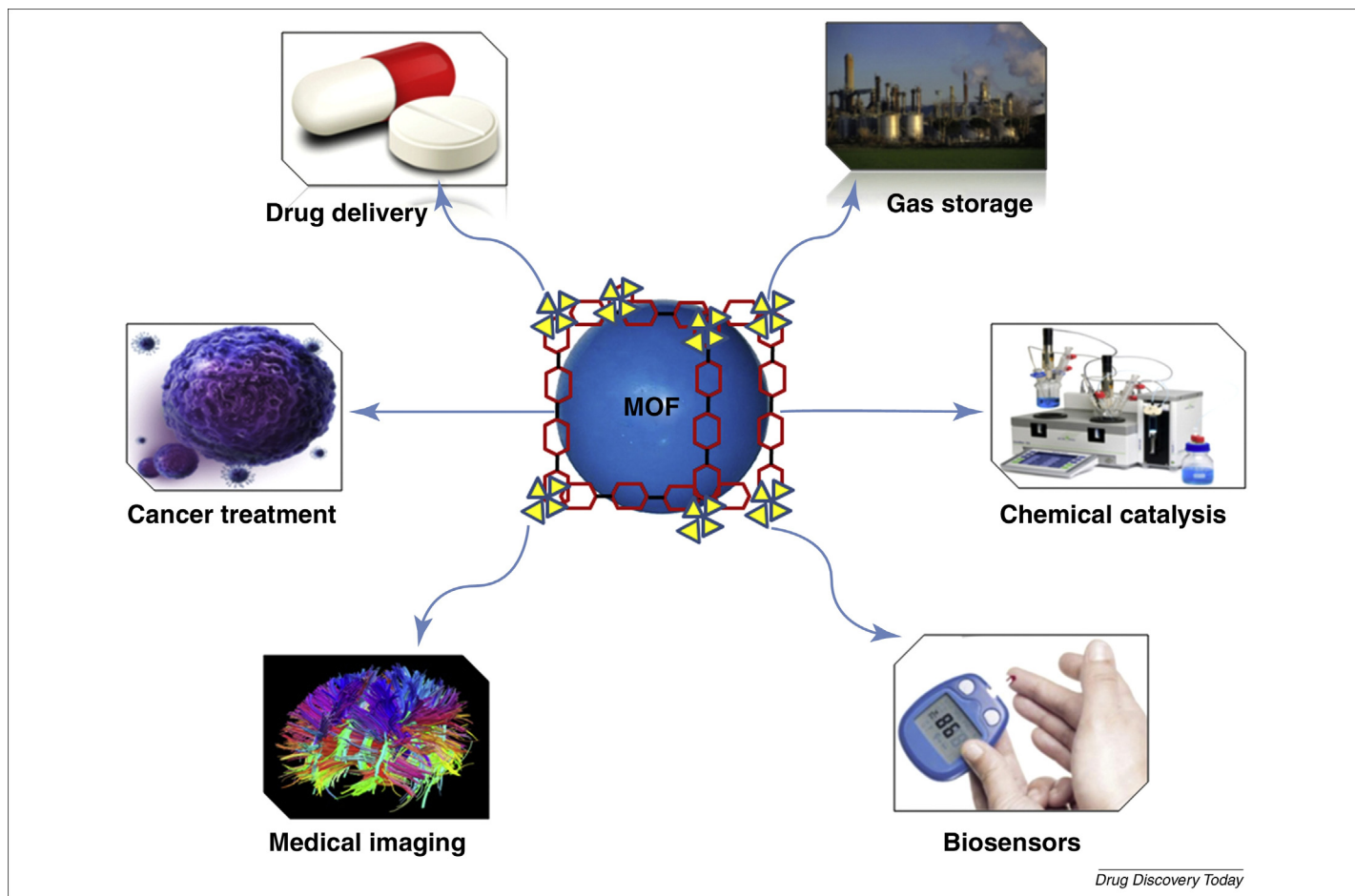
FIGURE 2

Overview of the biomedical applications of MOFs.

encapsulated in the MOF cavity and/or tethered with the framework structure [2,38,50]. Fig. 3 depicts the drug-loading in MOFs. The drug molecules functionalized by covalent conjugation with the MOFs provide higher ability for controlled drug release action over the drugs adsorbed in the cavity of MOFs [51,52]. Table 2 illustrates the applications of various MOFs in drug delivery and biomedical imaging.

Multiple factors tend to influence drug delivery applications of MOFs including the physiochemical properties of MOF materials and drug molecules (pore size, 3D arrangement), which allows fitting drugs inside the carrier molecules for efficient delivery to the desired site. Unlike other nanocarriers that tend to release the drug molecules with a burst effect, the drug release mechanism from MOFs includes slow and controlled liberation of the drugs by matrix degradation [53]. Iron-containing BioMIL-1 MOFs showed higher loading for nicotinic acid up to 75% as compared with the native MOF structures and exhibited controlled drug delivery [41]. Fig. 4 portrays the variable drug release profiles of metronidazole from Ni-CPO-27 and HUKUST-1 MOFs, where HUKUST-1 indicated pronounced controlled-release characteristics [54].

Apart from the direct drug delivery applications of MOFs, literature reports have demonstrated the development of various MOF formulations in the form of tablets, pills, films, patches, etc., for increasing their patient compliance [55]. These formulations have been reported in the literature for exploring their specific drug delivery applications. Besides these conventional formulations, utility of nanoparticle formulations of MOFs has lately been investigated for drug delivery applications. The details regarding various techniques employed for incorporating drugs and therapeutic agents into the MOF have been discussed above. The loading of drugs in MOFs is achieved *in situ* during the synthesis or post-synthesis phase. The approach of encapsulation of drug molecules involves noncovalent interactions, whereas functionalization involves covalent binding with the surface of MOFs. Combined use of these techniques has been practiced for attaining multimodal drug delivery and imaging with the help of MOF-based delivery systems [38]. Interestingly, the noncovalent approach has been found to possess high drug-loading capacity for MOFs, as is evident in the case of drugs like ibuprofen and cisplatin, with a controlled drug-release profile and lack of any burst effect [56]. Moreover, the use of mesoporous silica and zeolite in MOF structures has demonstrated robust frameworks with the advantage of lacking a burst-release effect [57].

Delivery of biomolecules
There are many applications of MOFs beyond drug delivery, thus they have gained wider attention in delivery of biological molecules like DNA, RNA, siRNA, etc. [2]. Recent instances of MOFs used for biomedical applications include utility of high porosity nano MOFs encapsulated with chemotherapeutic agents with
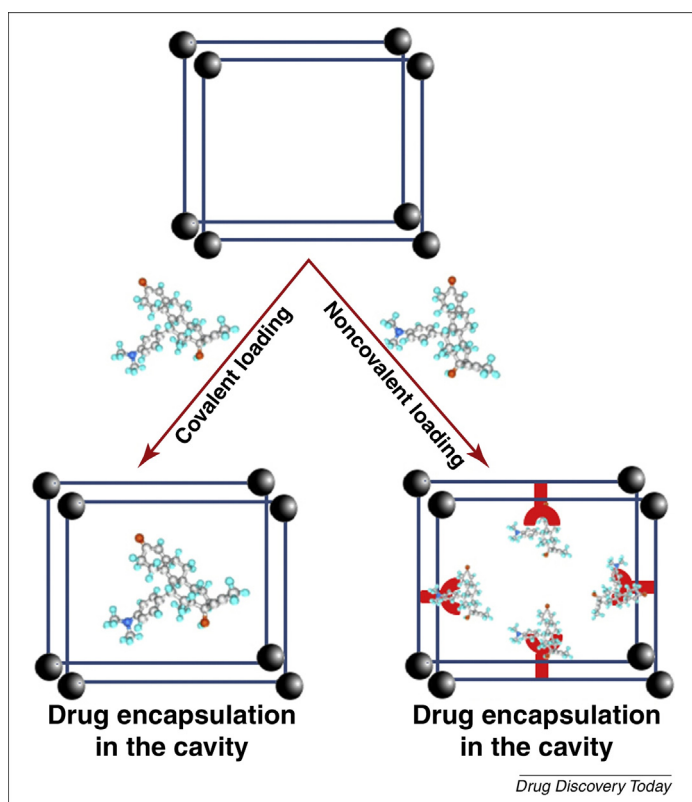
FIGURE 3

Drug loading strategies in MOFs, indicating characteristic differences between covalent and noncovalent drug loading mechanisms.

pooled multidrug-resistance (MDR) gene silencing siRNAs for action against drug-resistant ovarian cancer cells. In another case, the approach of delivering the prodrug of cisplatin by encapsulation within the MOF structure along with siRNA has been employed to provide improved anticancer action. In this context, not only do MOFs help in protecting the siRNA from ribonuclease degradation in the body but they also enhance cellular uptake and promote escape from endosomal enzymes for silencing MDR genes, leading eventually to enhanced chemotherapeutic efficacy [58]. Conjugation of MOFs with enzymes has been studied in the literature reports, where Cui *et al*. discussed the applications of MOFs for immobilization of CAL-B by conjugation on its surface [59].

Cancer therapy

Applications of MOFs in cancer therapy have been extensively explored for accomplishing desired targeted action for prolonged periods of time. Nano MOFs are highly useful in treating diverse human cancers [2]. Applications of Fe_3O_4-UiO66 MOFs for delivering an anticancer agent (i.e., doxorubicin) revealed improvement in the biopharmaceutical characteristics including controlled drug-release properties up to 40 days, superior anticancer activity in HeLa cells and significant reduction in the tumor volume (Fig. 5) [60]. Taylor and co-workers reported the use of Mn-containing nano MOFs [i.e., $Mn(1,4\text{-}BDC)(H_2O)_2$ and $Mn_3(BTC)_2(H_2O)_6$] coated with a silica shell for the delivery of RGDfK peptide; and rhodamine B dye revealed superior antiangiogenic properties on HT-29 cells by upregulation of the Rvβ3

integrin gene [61]. In another report, the utility of nano MOFs in ovarian cancer has been explored, where a combination of cisplatin and siRNA showed promising results in reducing growth of ovarian cancer cells during cellular cytotoxicity, uptake and apoptosis studies [62]. Likewise, the nano MOFs of Gd have shown enhanced anticancer activity against the FITZ-HAS endothelial sarcoma cell line model by increasing cellular apoptosis of Rvβ3 gene expression [63].

Intracellular trafficking

The role of MOFs in cellular trafficking has been investigated in the past few years. Because intracellular pH plays a vital part in regulating cellular functioning, the MOFs possess applications in modification of cellular vesicle trafficking, altering the metabolism and signaling process for the treatment of diseases [58]. In this regard, MOFs can be used for real-time sensing and monitoring of pH changes in the cells. Thus, MOFs have high importance in understanding physiological and pathological processes, and rational design of intracellular drug delivery systems. Instances of MOF usage in intracellular delivery include covalent conjugation of fluorescein isothiocyanate with UiO nano MOFs, which tends to guide the dye for efficient localization in the cells via pH-sensing properties and endocytosis [58]. This indicates nanosensor behavior of MOFs for efficient cellular trafficking of the drugs and other biomolecules.

Antibacterial properties

Antibacterial action has been observed with MOFs belonging to the M-CPO-27 family containing Mg, Cu, Fe, Mn, Co, Ni or Zn as metals and 2,5-dihydroxyterephthalate as the organic linker. Among these metals, MOFs containing Ni and Zn have shown promising antimicrobial activity [64]. The antibacterial properties of MOFs are attributed to the presence of metal ions, which easily internalize inside the bacterial cell wall and alter the synthesis of proteins. For instance, HKUST-1, MOF-199 and CuBTC MOFs have shown promising antibacterial action against *Escherichia coli*. The literature reports have also demonstrated that Ag-containing MOFs have proved to be the better antibacterial agents compared with conventional disinfecting agents with wide-spectrum action and lack of resistance over the plain Ag ions [65]. Moreover, the potential for delivering the antibacterial agent metronidazole has been illustrated in Fig. 4, where the Ni-CPO-27 MOF indicated drastic augmentation in the antibacterial activity of the drug against *Pseudomonas aeruginosa* and *Staphylococcus aureus* [54].

Photodynamic therapy

MOF applications in photodynamic therapy have been explored as an efficient technique for application against malignant cancer cells [1]. Because the mechanism of photodynamic therapy involves energy transfer from high to low energy light in the excited state, it generates reactive oxygen species (ROS) for inducing cellular apoptosis and localized destruction of the diseased tissues by minimal exposure to the healthy tissues [66]. For instance, chlorine-based nano MOFs (DBC-UiO) have demonstrated significantly improved photophysical properties over the porphyrin-based nano MOFs (DBP-UiO) owing to their crystallinity, stability and porosity properties, thus facilitating efficient apoptosis and immunogenic cell death against colon cancer [67]. Like-

TABLE 2

Select instances on the application of MOFs in drug delivery and imaging.

MOFs for drug delivery applications

No.	MOFs	Drugs	Key findings	Refs
1	ZrMOFs	PT, CPT	Drug-loaded MOFs exhibited better anticancer activity over free drug	[77]
2	UiO-66	5-FU	Delivery of light triggered release of 5-FU entrapped in UiO-66	[78]
3	ZIF-8	DOX	DOX@ZIF-8 system shows synergistic effect and higher cytotoxicity than free DOX	[79]
4	H3 BTC	DOX	Zn-BTC-DOX MOFs exhibited higher dissolution rate than the Fe-BTC-DOX composite	[80]
5	MIL-100	Gem-MP	MIL-100 nano MOFs showed drug loading up to ∼30 wt% compared with the amorphous systems	[81]
6	MIL-53, MIL-100	IBU	Improved anti-inflammatory activity as compared to the native MOFs	[82]
7	HKUST-1(Cu)	NIM	Enhanced drug loading up to 0.2 g per gram of MOFs and controlled drug release profile up to 11 days	[83]
8	MIL-53(Cr) MIL-53(Fe)	IBU	Exhibited slow release of drug under physiological conditions for 3 weeks with predictable zero-order kinetics	[82]
9	UiO-66(Zr)	CAF, IBU	Exhibited high drug payloads over other conventional porous solids	[84]
10	Zn(BDC)(H$_2$O)$_2$	NT recognition	Luminescent terbium (III) MOFs showed highly selective sensing properties against ATP, GTP and UTP	[85]
11	MIL-101(Fe)	ESCP	Demonstrated drug loading up to 13 wt% using silica-coated framework over plain frameworks	[86]
12	MIL-100(Fe)	DOX	Exhibited higher optical imaging and anticancer activity on HT-29 human colon adenocarcinoma cells in the form of nano MOFs	[82]
13	Zn(BIX)	CAM DAU	Higher encapsulation of the drug up to 21% and controlled drug release up to 8 h	[87]
14	ZIF-8(Zn)	5-FU	Remarkable improvement in the drug-loading capacity (660 mg/g of MOF) and pH-triggered controlled drug release property	[88]
15	MOF-1(Zn)	5-FU	Efficient delivery of 5-FU for drug delivery and imaging applications	[89]
16	MOF-15(Cu)	5-FU	Controlled drug release up to 24 h as compared to the plain drug suspension	[90]
17	CuBTC(Cu)	5-FU	Controlled drug release profile up to 48 h and enhanced anticancer action over the plain drug suspension	[91]
18	MIL-100(Fe)	CDV	Improvement in the drug loading up to 42% over other porous carriers	[82]
19		AZT-Tp	Sustained drug release characteristics under simulated pH conditions	[92]
20	MIL-101_NH$_2$(Fe)	CDV	Loading efficiency increased up to 42 wt% over other porous carriers	[82]
21	Fe$_3$O$_4$-UiO66	BSF, AZT-Tp, DOX, CDV	Enhanced drug loading for all the molecules and improvement in their bioefficacy	[51]
22	Fe-MIL-88A	Iron	Significant improvement in their enzyme-mimicking activity	[93]
23	Fe-MIL-88A	ART	High drug loading up to 848 mg/g and controlled release action owing to pH-responsive degradation mechanism	

MOFs for biomedical imaging

No.	MOF	Key findings	Refs
24	Gd(BTC)(H$_2$O)$_3$	MOFs increased the relaxivity measurement time for prolonging the duration of imaging	[94]
25	Fe$_3$O$_4$@IRMOF-3	Nano MOFs showed convenient imaging of the cancer cells (i.e., HeLa and NIH$_3$T$_3$ cell lines), whereas magnetic nano MOFs helped in MRI contrast imaging of the cancer cells	[95]
26	Mn$_3$(BTC)$_2$(H$_2$O)$_6$	Improvement in the target-specific MRI imaging	[96]
27	Gd(BHC)	Significant prolongation of the relaxivity time of the Gd-containing nano MOFs for better imaging applications	[97]
28	Tb(BTC)(H$_2$O)$_6$	Superior potential for imaging through MRI technique and prolongation in the duration of imaging time	[98]

Abbreviations: 5-FU, 5-fluorouracil; AA, ascorbic acid; ART, artemisinin; AZT-Tp, azidothymidine/zidovudine; BHC, benzenehexacarboylate; BSA, bovine serum albumin; BSF, busulfan; BTC, benzene-1,3,5-tricarboxylic acid; CAF, caffeine; CAM, camptothecin; CDV, cidofovir; CPT, cisplatin; DAU, daunomycin; DOX, doxorubicin; ESCP, ethoxysuccinato-cisplatin; Gem-MP, phosphated gemcitabine; HU, hydroxyurea; IBU, ibuprofen; NIM, nimesulide; NT, nucleotide; PTX, paclitaxel; MOF, metal organic framework; MRI, magnetic resonance imaging.
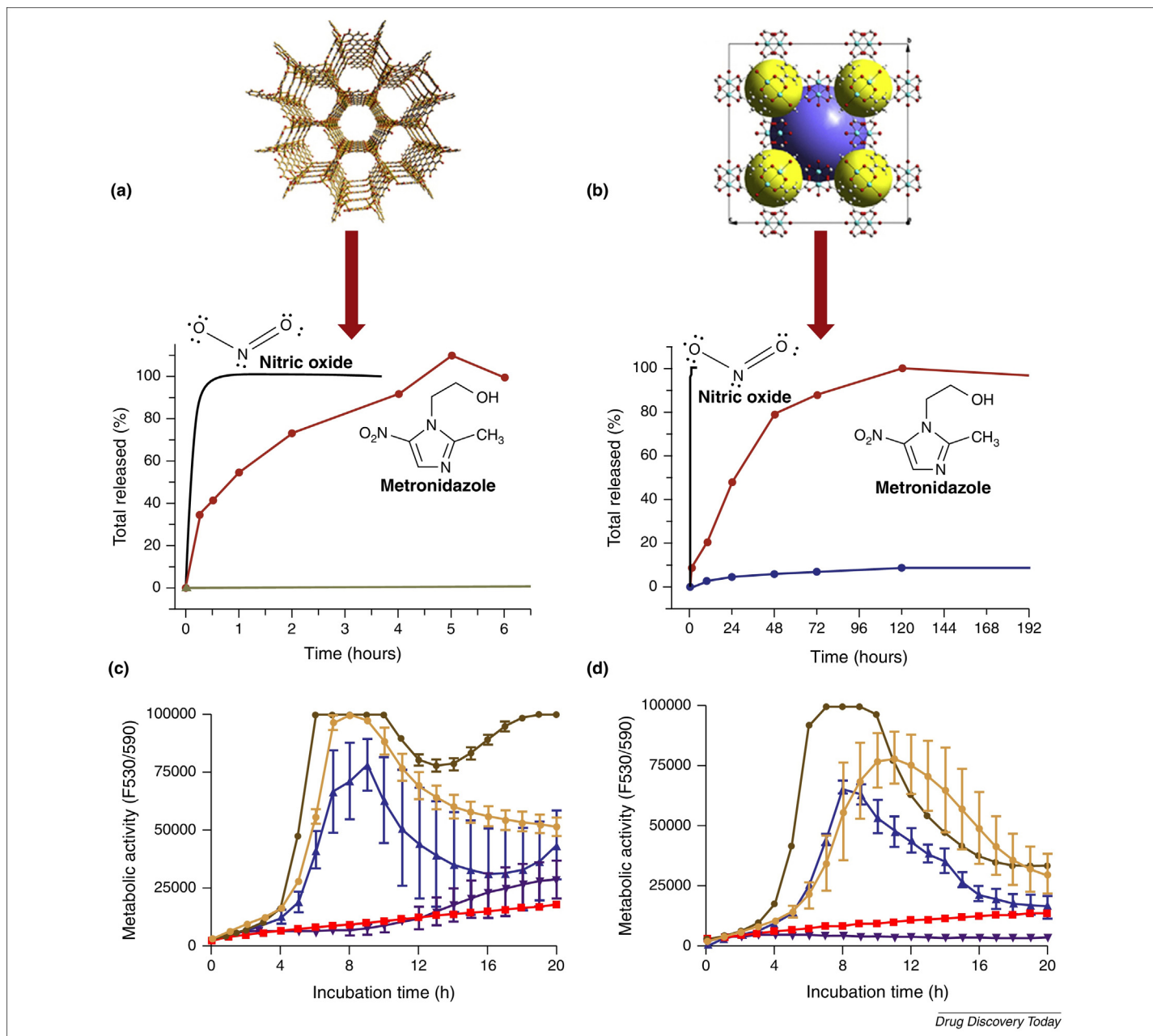
FIGURE 4

(a-b) *In vitro* drug release profiles of metronidazole from Ni-COP-27 and HUKUST-1 MOFs, *Key*: black line = NO release, red line = metronidazole release, green line = Ni release and blue line = Cu release; **(c-d)** Anti-bacterial activity of Ni-CPO-27 against planktonic *P. aeruginosa* and *S. aureus*, respectively. *Key*: brown line = growth control; blue = MOF only, orange = metronidazole-loaded MOF, purple = NO- and metronidazole-loaded MOF; and red line = antibiotic control. *Source*: Reproduced with permission from McKinlay [73], Copyright 2014 AIP Publishing.

wise, zirconium-based nano MOFs functionalized with BODIPY have shown efficient generation of ROS for killing cancer cells [68].

Gas storage

Storage of medical gases in the inert porous carriers is highly useful in biomedical applications. Extremely high surface area and pore volume facilitate storage of gases within the void space of the materials [69]. Examples of MOFs include M-CPO-27, which shows exceptional ability for the delivery of medial gases like nitric oxide and hydrogen sulfide. HKUST-1 MOFs have also been investigated

for their applicability in the storage and delivery of nitric oxide gas [70].

Biosensors

MOFs possess excellent utility in designing the biosensing devices as diagnostic tools for disease identification [27,71]. Magnetism, photostablity, light-sensing and luminescence are the vital properties of MOFs, making them capable of biosensing applications. Moreover, other useful characteristics of MOFs including channel size, specific coordination or H-bonding ability, and degree of
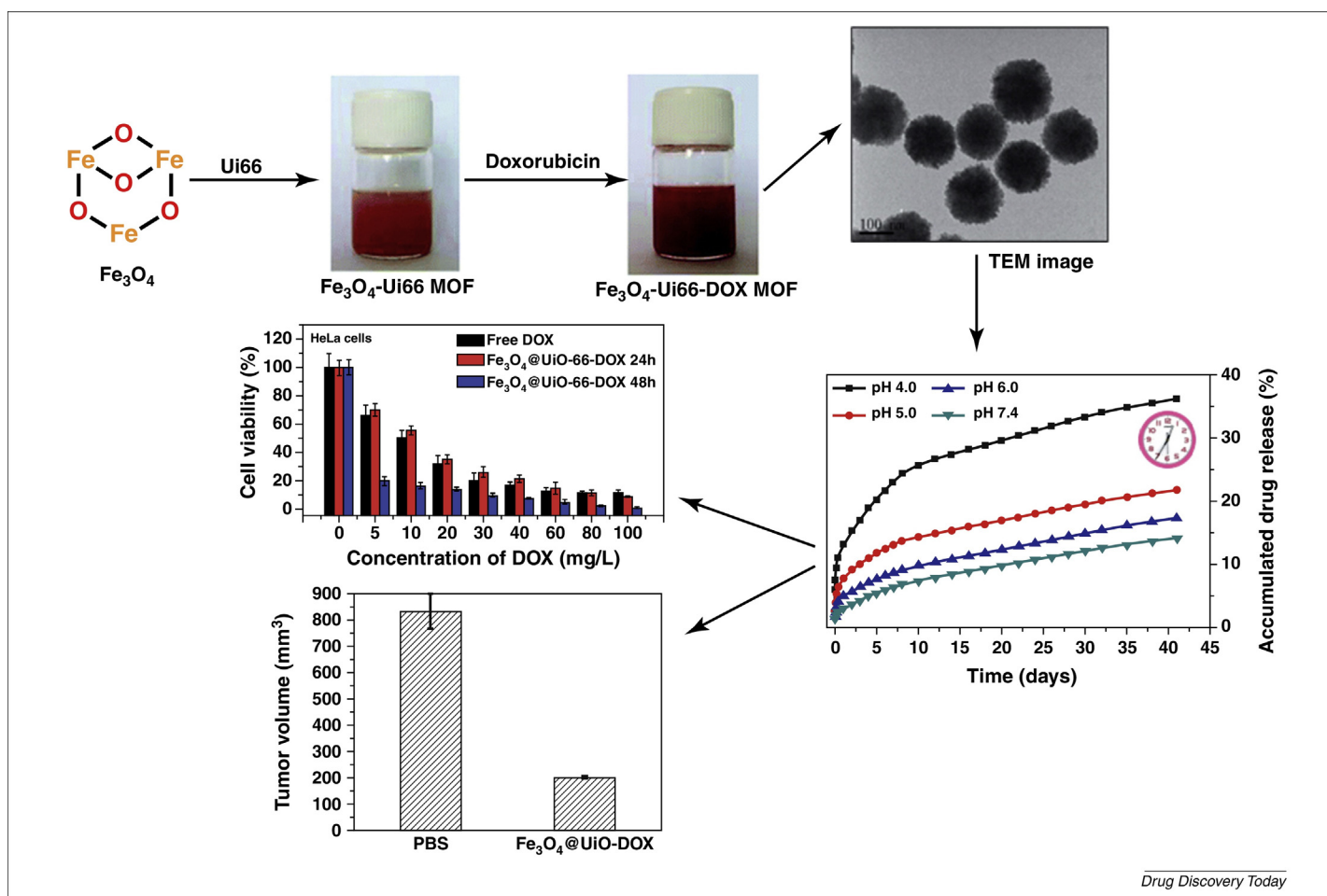
FIGURE 5

Scheme depicting the steps involved in the synthesis of Fe_3O_4-UiO66 MOFs loaded with doxorubicin along with the TEM image, *in vitro* drug release profile, cytotoxicity assay on HeLa cells and *in vivo* antitumor activity.
Source: Open access figure reproduced from Zhao [83], Copyright 2016 Royal Society of Chemistry.

chirality in the framework are considered to be influential on biosensing applications.

Chemical catalysis

Applications of MOFs in chemical catalysis have gained interest by facilitating chemical reactions like the Claisen–Schmidt reaction, cross-aldol condensation, ring-opening polymerization of epoxides, acetalization of aldehydes, acid-catalyzed selective hydrogenations, among others. Examples of some of the MOFs used for chemical catalysis include Fe(BTC), UiO-66(NH_2), $Cu_3(BTC)_2$, $Cu(NO_3)2$-$3H_2O$ and Al-MCM-41. Moreover, MOFs like Fe(BTC), $Cu_3(BTC)_2$, NHPI and NHPI/Fe(BTC) have now been used for oxidative catalysis of benzylic compounds, alcohols, thiols, cycloalkanes, amines and for waste treatment too [72].

Medical diagnosis

The application of carrier systems in the field of medical diagnosis involves their usage as the radiocontrast agents along with utilization of their fluorescent and photoluminescent properties for theranostic imaging [57]. Theranostic applications of MOFs were first discovered by Lin and co-workers by demonstrating the usage of nanoscale MOFs as contrast agents for medical imaging [73]. Because nano MOFs possess attractive features such as ability to accommodate diverse chemical moieties, they have special implications in the delivery of contrast imaging agents. Thus, MOFs have been extensively investigated for varied applications in medical imaging. Some of the instances of MOFs as imaging tools include usage of nanoscale MOFs containing lanthanide series elements for their excellent chemical or biofunctional behavior. It has been documented that surface modification of Gd nano MOFs with isopropyl acryl amide and methacrylate derivatives is suitable for attaining efficient medical imaging [49]. Further, surface modification of Gd MOFs with PEG has also shown superiority in the contrast-imaging properties. Gd-MOF-based theranostic devices containing functional polymer chains of glycine-arginine-glycine-aspartate-serine-NH_2 and O-methyl acrylate have also shown improved cellular imaging [44]. Likewise, the applications of amino-functionalized iron-carboxylate MOFs have been investigated as novel carriers for the delivery of Br-BODIPY for optical imaging [68]. Moreover, the unique luminescence and paramagnetic properties of MOFs are also known to be responsible for their radiocontrast effect and photostablity, long decay rates,

stokes shifts and narrow emission bands, thus making them suitable for magnetic resonance imaging (MRI) and computerized tomography (CT) scanning of vital body tissues and organs [60]. Gd-, Fe- and Mn-containing MOFs possess excellent properties as MRI contrast agents. Gd and Mn MOFs in their nano forms can better serve as contrast agents for MRI. Also literature reports have demonstrated application of microemulsion of Gd(BDC)1.5(H$_2$O)$_2$ and [Gd(1,2,4-BTC)-(H$_2$O)$_3$]H$_2$O MOFs with improved radiocontrast imaging properties [74].

Biodegradability and stability of MOFs

Because MOFs are primarily constructed form metal ions and organic linkers, their biocompatibility, biodegradability and stability are considered highly vital properties for biomedical and healthcare applications. MOFs, in this context, need to be thoroughly evaluated for these properties by considering their chemical compositions. Diverse *in vitro* and *in vivo* studies have been reported in the literature so far for evaluating the acceptance of MOFs. Instances of some of the MOFs with established biodegradability profiles include the series of iron carboxylate MOFs (e.g., MIL-88A, MIL-88B-4CH3, MIL-100, etc.) [2,41]. Biocompatibility of MOFs is characterized on the basis of selection of linker molecules (hydrophilic, hydrophobic, aliphatic and/or aromatic). Likewise, the stability of MOFs is also important for preventing hydrolytic cleavage of the covalent bonds between the metal and organic linker. Stability can be tested by subjecting MOFs under different simulated conditions like PBS and BSA, and evaluated for defects in the framework structure without any degradation products. Some of the examples of MOFs reported to be highly stable under simulated body conditions include MOF-5, M-CPO-27 and MIL-100. The degradation behavior and stability of MOFs basically depends on the crystalline structure, composition and particle size. Based on these properties, the degradation of MOFs can be modulated from a few days to many weeks. Moreover, before selecting a MOF for a given route of administration, it is advisable to determine its stability in water and other simulated body fluids.

Toxicity and safety considerations of MOFs

Compliance of MOFs for biomedical applications is a major challenge and it must be evaluated before their biomedical application. Toxicity of MOFs arises owing to the presence of metal ions and organic linkers. Careful selection of these components is highly essential along with the nature of organic solvents used during synthesis of MOFs. Because MOFs have wide diversity in their chemical composition and structure, it becomes highly difficult to summarize the toxicity profile of all the MOFs [43,75]. Principally, the metal ions used for synthesis of MOFs have their own toxicity and they accumulate in the body. Thus, the level of metal ions in MOFs must be kept within permissible limits for biological use. Ideally, metal cations with higher permissible limits for daily requirements in the body need to be selected for MOFs to avoid toxicity. Mg, Ca, Fe and Zn are some of the metals with established toxicity profiles that are considered to be safe for drug delivery and theranostic applications [50,51]. Beyond metals, the organic part of MOFs must also be biocompatible. Moreover, the approach of synthesizing bio MOFs is now more acceptable employing the biomolecules within the framework structure for altering the degradation behavior, improving biocompatibility and reducing toxicity. Lately, metal peptide frameworks have been reported in the literature as the novel 'bioinspired' materials with negligible toxicity over the MOFs [76]. Overall, cytotoxicity of MOFs is primarily evaluated with the help of cell lines. In the past few years, diverse reports have been published on toxicity evaluation of the MOFs including use of human promyelocytic leukemia (HL-60) cells for Zn(BIX) MOFs, MCF-7 cells, cervical cancer HeLa cells and human lung NCI-H446 cancer cells for Cu(PMB) MOFs, J774 and HeLa cells for MIL-100(Fe) nano MOFs with variable toxicity profiles for different types of MOFs.

Commercial viability of MOFs

The commercial production of MOFs has recently begun at BASF, Germany, which has underlined their market potential [40]. Despite the diverse biomedical applications of MOFs, the commercial applicability has yet to gain considerable importance. The major rate-limiting factor behind usage of MOFs includes their toxicity and lack of biodegradability. Thus, the market potential and commercial value of MOFs is still at the infancy stage. However, the exponential rise in patents and publications on biomedical applications of MOFs is a testimony to their wide acceptability in the research community, which will certainly increase their importance in the healthcare system.

Concluding remarks

The extensive research breakthroughs in MOFs for drug delivery and biomedical applications have further fueled their importance in the field. Although issues such as cost of synthesis, biodegradability, biocompatibility and toxicity are considerable and impact MOF applicability, the risk:benefit ratio is now considered to be favorable. The research focus needs to be switched to enable more-extensive evaluation of MOFs in biological systems through *in vitro* cell lines and molecular biology studies, as well as preclinical and clinical studies in animal and human models.

Conflicts of interest

The authors declare no conflicts of interest.

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