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Bio-Inspired Metal-Organic Frameworks in the Pharmaceutical World: A Brief Review

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Abstract

One of the great challenges in the pharmaceutical industry is the search for more efficient and cost-effective ways to store and deliver existing drugs. Bio-inspired metal-organic frameworks (BioMOFs) are groundbreaking materials that have recently been explored for drug storage, delivery and controlled release as well as for applications in imaging and sensing for therapeutic and diagnostic. This review presents a brief overview on these materials, and by alluding to a few reported examples, it intends to clearly show the extremely important role that BioMOFs have been playing in the pharmaceutical field.

Keywords: BioMOFs, drugs, ZIFs, smart drug delivery

1. Introduction

The development of new solid forms of pharmaceuticals is of utmost importance in modern science as they present a single opportunity to modify the properties of active pharmaceutical ingredients (API) without interfering with its biological role. The influence of the crystal forms is very wide and diverse, changing not only the solid-state characteristics (density, habit, shape, colour, stability, melting point) but also properties that might affect their function (dissolution rate, solubility, stability to temperature and humidity, thermal properties, moisture uptake, bioavailability, pharmacokinetics) and even some industrial aspects of formulation (flowability, mixability, stress stability, granulation, encapsulation, tabletting). The combination of crystal engineering and supramolecular chemistry principles allows the design and synthesis of smartly designed drugs with tailor-made properties, keeping their pharmacological properties, and thus presenting major advantages, including reduced time for introduction in the market [1–6].
Consequently, the synthesis of new crystal forms evolved tremendously in the last decade, and the interest of pharmaceutical companies in the appearance/disappearance of new solid forms of APIs has vastly increased. Polymorphs, hydrates and salts of drugs are long-known forms with recognized impact in their properties. Cocrystals represent a more recent class of crystal forms that own particular scientific and regulatory advantages (FDA guidance is already available and cocrystals are now being commercialized as drugs in some countries). Many examples show their relevance in the pharmaceutical industry, most of them by enhancing stability, solubility and/or bioavailability of known drugs [7–20].

Likewise, nanoporous materials recently became of pertinent use in the medicinal and pharmaceutical fields for drug storage, delivery and controlled release in addition to applications in imaging and sensing for therapeutic and diagnostic [21–34]. Particularly, metal organic frameworks (MOFs) have generated large interest owing to their versatile architectures [35] and their promising applications not only in ion exchange, adsorption and gas storage [36–41], separation processes [42], heterogeneous catalysis [43, 44], polymerization reactions [45, 46], luminescence [47], non-linear optics [48] and magnetism [49], but also as drug carriers, systems for drug delivery [22, 23, 50, 51], contrast agents for magnetic resonance imaging (MRI) [21] and systems with potential use in other biomedical applications [23].

Up to now, drug delivery from porous solids has been achieved by encapsulation in mesoporous silicas or zeolites, methods that are strongly dependent on the pore size and on the host-guest interactions. Both hypotheses suffer from important drawbacks: low drug-storage capacity, too rapid delivery and solid degradation that brings toxicity concerns [23, 25, 26, 29, 52]. Extended metal-ligand networks with metal nodes and bridging organic ligands such as coordination networks, porous coordination networks (PCNs), porous coordination polymers (PCPs) and MOFs have attracted great attention in the last years [24, 25, 28, 53, 54]. Particularly, MOFs with biological-friendly composition emerged as new drug carriers capable of tackling these problems [21, 23, 25, 26, 28, 29, 55, 56].

In fact, MOFs are among the most exciting architectures in nanotechnology and are defined as hybrid self-assemblies of metal ions or metal clusters (coordination centres) and organic fragments (linkers). They exhibit some of the highest porosities known, turning them into ideal materials for capture, storage and/or delivery applications [21, 24–26, 29, 54, 57]. Compared to other nanocarriers, MOFs are candidates to extensive applications since they combine high pore volume with a regular porosity, and the presence of tuneable organic groups allows an easy modulation of the framework as well as of the pore size [22, 24–26].

The first families of MOFs considered as potential drug delivery systems were the coordination polymers from Oslo (CPO), such as CPO-27(Mg) [58] built up from magnesium coordination polymers, and the materials of Institute Lavoisier (MIL) [22]. Horcajada et al. [22, 23] prepared MIL-100 (with trimesic acid) and MIL-101 (with terephthalic acid) applied for the delivery of ibuprofen in the gastrointestinal tract, exhibiting high drug-storage capacity and a complete drug-controlled release under physiological conditions [22, 23]. Less toxic systems, using iron and more flexible MILs, are under study [25], and the first biodegradable therapeutic MOF, BioMIL-1, was reported by Miller et al. in 2010 [27]. The large breathing effect that MOFs can
attain is another particularly interesting feature for potential applications in drug delivery [54, 59, 52].

Zeolite-like MOFs (ZMOFs) are a unique subset of MOFs with exceptional characteristics arising from the periodic pore systems and distinctive cage-like cavities, in conjunction with modular intra- and/or extra-framework components [60–62]. Zeolitic imidazolate frameworks (ZIFs) are a special class of ZMOFs comprising imidazolate linkers and metal ions. ZIFs simultaneously have the following characteristics of MOFs and zeolites, combining the advantages of both: ultrahigh surface areas, unimodal micropores, high crystallinity, various functionalities and exceptional thermal and chemical stabilities, making them very promising for biomedical applications [63, 64]. Several studies describe the successful incorporation of anticancer drugs into ZIF-8 with positive results for the controlled pH-sensitive drug release and fluorescence imaging [65–69]. Also caffeine was already encapsulated into ZIF-8 showing a controlled release [70, 71].

The scope of this brief review focuses on presenting some aspects on the BioMOFs preparation, and a few examples of promising bioapplications of MOFs, including ZIFs.

2. Building bio-inspired MOFs

2.1. Design

The use of porous solids for biomedical applications requires a biological friendly composition, making compulsory the use of metals and linkers with acceptable toxicity [28].

When designing BioMOFs, the decision to exclude one linker and/or metal depends on several parameters: application, balance between risk and benefit, degradation kinetics, biodistribution, accumulation in tissues and organs as well as body excretion [21, 23, 25, 26, 28, 55, 56]. Both exogenous (not intervening in the body cycles) and endogenous (constitutive part of body composition) linkers have been used in MOF synthesis for drug delivery, with the first group having a higher prevalence [21, 25–29, 57]. It is also worth noting that if the therapeutic molecule is directly used as a linker, no large pores are required and the release of the drug molecule is achieved directly through the degradation of the solid, without any side effects arising from the release of a non-active ligand [26, 52].

Different methods have been explored to design BioMOFs, including ZMOFs, from which we highlight the molecular building block (MBB), supermolecular building block (SBB) and supermolecular building layer (SBL) approaches. Also, a brief allusion to the influence that computational simulations may have in building and studying BioMOFs is made.

2.1.1. Molecular building block (MBB), supermolecular building block (SBB) and supermolecular building layer (SBL) approaches

To construct a MOF, it is necessary to make a pre-selection of building blocks that would give the desired structural and geometrical information for a given underlying network—molec-
ular building block approach (MBB) [72]. The prerequisites for the successful implementation of this approach are (a) selection of an ideal blueprint net exclusive for the assembly of its corresponding basic building units and (b) isolation of the reaction conditions that allow the formation of the desired MOF. Simple MBBs based on simple organic ligands or polynuclear clusters are often limited in terms of connectivity [72]. To overcome this issue, two conceptual approaches were recently implemented to facilitate the design and deliberate construction of MOFs: supermolecular building block (SBB) and supermolecular building layer (SBL). These approaches allow the rational design of made-to-order MOFs [73].

The SBB approach consists of using metal-organic polyhedral (MOPs) as SBBs in building an MOF, presenting great potential to control the targeted framework. To obtain the desired topology, the MOP must have the correct geometrical information and peripheral points of extension (connectivity). The prerequisites for this approach are (a) a blueprint net with minimal edge transitivity, preferably singular, exclusive for the assembly of given building units, and not susceptible to self-interpenetration upon net expansion and/or decoration and (b) reaction conditions that allow the formation of the SBB in situ.

The SBL is based on the use of 2-periodic MOF layers (SBLs) as building blocks for the desired functional 3-periodic porous MOFs. This implies the chemical cross-linking of layers via accessible bridging sites on the layers, such as open metal sites or functionalized positions on the organic linker, whose judicious selection is mandatory. This approach, in principle, allows to predict MOFs with tuneable cavities, the endless expansion of confined space (as cavities and pores), and its modularity further permits an easy functionalization and introduction of additional functionalities [74] to aim specific applications. The prerequisites for this approach are (a) a blueprint net with minimal edge transitivity, rather singular, exclusive for the particular pillaring of the given building units and (b) the reaction conditions to allow the consistent formation of the SBL in situ.

2.1.2. Screening using simulations

Systematic studies relating MOF structures with their performance in drug delivery is crucial for the identification of promising structures. Molecular simulations are a mean that can be explored to seek for the optimal structure for a given application. The grand canonical Monte Carlo (GCMC) simulation is the preferred method for simulating adsorption in porous materials and for explaining and predicting new results. However, the simulation in the case of large guest molecules is difficult and that justifies the limited number of studies on drug-porous solid systems [75].

Fatouros et al. reported the use of molecular dynamics to study the diffusion properties of salbutamol and theophylline in the zeolite BEA, an indication that this method can be used for screening purposes on zeolite-drug systems [76].

Regarding MOFs, very few computational studies are reported and those are focused on one or more structures simultaneously, limiting the possibility of correlating drug delivery performance with structural features. A combined experimental and computational study of three MOFs for the drug delivery of 5-fluorouracil was recently presented, in which GCMC
simulations were used to investigate the interactions between the drug and the porous cage [77]. Density functional theory (DFT) calculations have been applied to identify the most favourable conformations and adsorption sites of ibuprofen and busulfan on MIL-53(Fe) [78]. Quantitative structure-activity relationship (QSAR) models were used to rationalize the experimental uptake of caffeine as model in a series of MIL-88B(Fe) materials with different functional moieties [79]. The energetics and dynamics of ibuprofen in MIL-101 were also studied recurring to simulated annealing followed by DFT of one single ibuprofen molecule to study the preferential adsorption sites [56].

Also worth mentioning an extensive study on GCMC simulations to screen a series of bio-compatible MOFs as carriers of ibuprofen has been reported. Simulations include microporous, mesoporous and nanoporous MOFs and have shown to be a successful pathway to predict the drug adsorption properties of porous adsorbents. Furthermore, this work proposes new tools that allow the study of new porous materials as potential drug carriers prior to experiment [75].

2.2. Synthesis

MOFs are still widely synthesized using solvo/hydrothermal techniques, the most common methods to obtain coordination networks [21, 25, 28, 29]. Nevertheless microemulsion synthesis [80] is also a typical method and interesting alternatives are being used based on environmental-friendly synthetic routes: ionothermal [81], microwave, ultrasound-assisted, and sonochemical synthesis [21, 25, 28], as well as mechanochemistry [82, 83]. The synthesis of this type of compounds has been reviewed several times [63, 84, 85] and therefore only brief details on each technique are presented herein.

The solvo/hydrothermal synthesis involves polar solvents under moderate to high pressures and temperatures. This method often requires toxic solvents such as DMF, and its use is limited by safety and time-consuming reasons. Alternative techniques allow higher efficiencies, have lower energy costs and have less impact in the environment [86].

Microemulsion synthesis is based on thermodynamically stable dispersions of two immiscible liquids in the presence of an emulsifier or surfactant (i.e., microemulsions). This technique confines the synthesis of MOFs to the nanoscale and offers the possibility of tuning the size. The disadvantages of the microemulsion approach include poor yields, reproducibility issues, usage of highly toxic surfactants and solvents that strongly limit biomedical applications and the possible decrease of the sorption capacity due to the combination of surfactants with highly porous structures [80, 86].

Ionothermal synthesis requires the use of green solvents such as ionic liquids and eutectic mixtures (a special type of ionic liquid) to obtain MOFs and it can be performed in open air. These solvents act both as solvents and templates to avoid the competition interactions between the solvent framework and the template framework that are present in the solvothermal methods [63, 81].

Microwave and ultrasound-assisted syntheses usually lead to the fast crystallization of MOFs and are considered green methods. In the case of microwaves, the heating involved in the
process favours a rapid and uniform nucleation process, which results into a more homogeneous particle size distribution. Regarding ultrasounds, it has shown to be a highly efficient method [86].

Sonochemical synthesis or sonocrystallization method not only promotes the nucleation process but also stimulates the homogeneity of the nucleation, what represents an advantage over the traditional solvothermal methods. This approach is prone for industrial applications due to its easy scale-up [63].

Mechanochemistry is a green, solvent-free and efficient strategy to build MOFs. It is based on the direct grinding of the linkers and the metal salts either in a mortar or in a ball mill, without recurring to solvent (neat grinding, NG) or recurring only to catalytic amounts of solvent to activate the process (liquid-assisted grinding, LAG). Alternatively, also catalytic amounts of ionic salts can be used to trigger the process (ion- and liquid-assisted grinding, ILAG). This is a simple method and the absence of solvent makes it very appealing to biomedical applications [63, 82, 83, 86].

2.3. Loading of drugs and other biomedically relevant compounds into MOFs

The loading of relevant molecules, such as imaging and therapeutic agents, into MOFs can be done directly during the MOF synthesis or in the postsynthesis.

The direct incorporation implies using those molecules directly to assemble the framework. This strategy also encloses the networks in which paramagnetic metal ions, such as Gd³⁺, Fe³⁺ and Mn²⁺, do not act only as the metal sites to connect the ligand but act also as magnetic resonance imaging contrast agents. High loadings of the relevant compounds can be achieved by this strategy; however, it is necessary to tune the morphology and physicochemical properties of these MOFs for each case and it is important to guarantee that there is no degradation of the compound during the synthesis [21].

The postsynthesis strategy requires high porosity and the active compound is incorporated within the MOF by noncovalent or covalent interactions. In the case of noncovalent loading, the process is reversible and therefore the drug release can be premature. On the other hand, the covalent loading creates a prodrug in which the drug release happens at the same time as the MOF degradation and thus it may be considered a more robust approach [87].

2.4. Surface modifications

The improved biomedical properties of MOFs also depend on the rational design of the surface. However, the task of changing the outer surface of the MOF without changing its characteristics is still very difficult. Ideally, MOFs should have a coating shell to confer stability to the material under the different physiological media, but it must be non-toxic and must not interfere with the pores [86]. There are two approaches to achieve the surface modifications: covalent and noncovalent attachments. The choice of the best method relies on the parameters and nature of the MOF, as well as on the nature of the molecule to be grafted [88]. To date only a few successful examples have been reported of which we highlight the following three.
A simple, fast and biofriendly method was reported for the use of heparin for the external functionalization of MIL-100(Fe), preserving all the properties of the MOF. The coating obtained by this method led to improved biological properties, such as reduced cell recognition, lack of complement activation and reactive oxygen species production [89].

The coating of MIL-101(Fe) with a thin film of silica resulted in the prevention of the rapid degradation of the MOF [87].

Another example of successful coating of MOFs concerns the use of phosphate-modified biocompatible cyclodextrins. This method was applied to MIL-100(Fe) and resulted in improved stability in body fluids without interfering with the MOFs properties [90].

3. Applications of BioMOFs: selected examples

The first biomedical applications of nanoscale MOFs were as delivery vehicles for imaging contrast agents and molecular therapeutics. However, the large amount of paramagnetic metal ions in these systems further allows their exploration for magnetic resonance imaging (MRI). [21]. Furthermore, BioMOFs are also being studied as materials for drug storage as well as controlled drug delivery and release. A few examples of such applications are briefly discussed and the details of the mentioned BioMOFs are presented in Table 1. For a matter of clarification, examples of different bio-inspired applications of ZIFs are given in the next section.

3.1. Exploring synergetic effects between metal and drug within a BioMOF

As previously mentioned, one of the best approaches to construct BioMOFs is the direct incorporation of therapeutically active molecules containing multiple complexing groups with biocompatible metal cations (Ca$^{2+}$, Ag$^{2+}$, Zn$^{2+}$, Fe$^{2/3+}$), and thus the delivery of the active compounds is accomplished via framework degradation [25, 91, 94–97]. Tamames-Tabar et al. recently discussed the possibility of directly introducing azelaic acid as linker and an endogenous low-toxicity transition metal cation (Zn$^{2+}$) [98]. Both linker and metal exhibit interesting antibacterial and dermatological properties for the dermatological treatment of several skin disorders and their combination results into a novel biocompatible and bioactive MOF, named BioMIL-5. It was synthesized by hydrothermal methods and its stability was assessed through tests in water and in bacteria broth at 37°C; also antibacterial activity studies against two Gram-positive bacteria *Staphylococcus aureus* and *Staphylococcus epidermidis* were conducted [91].

In the antibacterial activity studies, the MIC/MBC (MIC = minimal inhibitory concentration; MBC = minimal bactericidal concentration) values in *S. aureus* and *S. epidermidis* demonstrate that the antimicrobial activity of azelaic acid and Zn$^{2+}$ is maintained after the synthesis [91]. Regarding the stability tests, BioMIL-5 has shown to be stable in water and in bacterial culture medium, but especially in water, leading to the progressive release of both Zn$^{2+}$ and azelaic acid. Indeed, this progressive and slow release of the active Zn$^{2+}$ and azelaic acid in both media led to interesting and time-maintained antibacterial properties when used for 7 days against *S. epidermidis* [91]. The high stability demonstrated and the maintenance of its antibacterial
properties (Figure 1) turn BioMIL-5 into a promising candidate for future applications in the treatment of several skin disorders and in the cosmetic industry [91].

| BioMOF     | Metal  | Ligand            | Application                                      | Ref  |
|------------|--------|-------------------|--------------------------------------------------|------|
| BioMIL-5   | Zn$^{2+}$ | Azelaic acid      | Treatment of skin disorders                      | [93] |
| MIL-100    | Fe$^{3+}$ | Trimesic acid     | Drug delivery of ibuprofen                       | [22, 23] |
| MIL-101    | Fe$^{3+}$ | Terephthalic acid | Drug delivery of ibuprofen                       | [22, 23] |
| Bio-MOF-1  | Zn$^{2+}$ | Procainamide HCl  | Drug delivery of procainamide HCl                | [30] |
| MIL-53     | Fe$^{3+}$ | Terephthalic acid | Drug delivery of ibuprofen – “breathing effects” | [22] |
| CaZol nMOF | Ca$^{2+}$ | Zoledronic acid   | Drug delivery of Zol – targeted anticancer agent | [94] |
| IRMOF-3    | Zn$^{2+}$ | 2-Aminoterephthalic acid | Drug delivery of Paclitaxel – targeted anticancer agent and MRI applications | [95] |

Table 1. Details on the presented BioMOFs.
3.2. BioMOFs for the controlled drug delivery of ibuprofen

Bearing in mind that BioMOFs are envisaged as new tools for the controlled drug delivery [22, 19-23, 25, 26], Horcajada et al. prepared the first examples of MOFs for the delivery of ibuprofen in the gastrointestinal tract: MIL-100 (with trimesic acid) and MIL-101 (with terephthalic acid) [22, 56]. Ibuprofen was chosen as a model drug because it is a worldwide used pharmaceutical compound with analgesic and antipyretic features [56]. Both MOFs have large pores: MIL-100 contains pore diameters of 25–29 Å with pentagonal window openings of 4.8 Å, and hexagonal windows of 8.6 Å; MIL-101 contains 29–34 Å pore diameter with a large window opening of 12 Å for the pentagonal and 16 Å for the hexagonal windows. They exhibit a very high drug storage capacity: up to 0.35 g of ibuprofen per gram of porous solid for MIL-100 and 1.4 g of ibuprofen per gram of porous solid for MIL-101 [22, 23, 25, 56]. MIL-101 displays a higher loading capacity due to the fact that ibuprofen can fit in both pentagonal and hexagonal windows of MIL-101, but not into the smaller pentagonal window of MIL-100 [22, 23, 25]. This demonstrates the real importance of material’s pore size in drug loading [25, 50]. The kinetics of ibuprofen delivery to stimulated body fluid at 37°C was also studied, revealing a complete drug controlled release from 3 to 6 days [22, 23, 25].

3.3. Cation-triggered release of procainamide HCl from BioMOF-1

Another example of a BioMOF constructed by the direct incorporation of simple biomolecules and biocompatible metal cations in their structures is Bio-MOF-1 proposed by An et al. [30] Bio-MOF-1 is based on (i) adenine, a purine nucleobase, as a biomolecular ligand, (ii) a second ligand, biphenyldicarboxylic acid, which was used to promote the formation of larger accessible pores, and (iii) Zn$^{2+}$ as a biocompatible metal cation [30]. Bio-MOF-1 has shown to be stable and maintains its crystallinity for several weeks in biological buffers. Due to the intrinsic anionic nature of Bio-MOF-1, An et al. explored its potential use as a system for the storage and release of cationic drug molecules [30], more specifically the storage and release of procainamide HCl, an effective antiarrhythmic agent used to treat a variety of atrial and...
ventricular dysrhythmias with a short half-life in vivo making necessary its administration every 3–4 h [29, 30, 99]. Procainamide HCl was successfully encapsulated into the pores of Bio-MOF-1 through a cation exchange process and the complete loading (0.22 g/g material) was achieved after 15 days corresponding to approximately 2.5 procainamide molecules per formula unit residing in the pores and 1 procainamide molecule at the exterior surface [29, 30]. Due to the ionic interaction between procainamide and Bio-MOF-1, cationic drugs are triggered by cations and then released from the framework. Steady procainamide release was observed within 20 h and a complete release was observed after 72 h (Figure 2) [30].

![Figure 2](image)

**Figure 2.** (Left) Scheme depicting cation-triggered procainamide release from Bio-MOF-1; (right) procainamide release profiles from Bio-MOF-1 (blue—PBS buffer; red—deionised nanopure water) (image from An et al. [30]—Copyright © 2009, American Chemical Society).

### 3.4. Exploring the potentialities of the breathing effects on BioMOFs

Some MOFs can present structural flexibility or “breathing effects,” which allows them to modulate their pore size upon adsorption of organic molecules into the pores, while their crystallinity is maintained [22, 50, 54, 59]. One example of BioMOFs presenting a “breathing effect” is MIL-53 [22, 54, 100]. The structure of MIL-53 consists on terephatalate anions and trans-chains of metal (III) octahedra sharing OH groups and thus creating a 3D framework with one-dimensional pore channel systems [22, 100]. The capacity to expand its structure upon heating explains the “breathing effect” observed in MIL-53 (Figure 3) [22]. In this study, Horcajada et al. also observed that aluminium and chromium MIL-53lt (lt is low temperature) present a reversible pore opening involving atomic displacements by 5.2 Å upon dehydiration, whereas the iron analogue only open its pores during the adsorption molecules [101, 102]. This can be explained by the formation of hydrogen bonds between the water molecules and the inorganic hydrophilic parts of the pore. After approximately 3 weeks, a complete release of ibuprofen is observed, where 20 wt% of ibuprofen loading was achieved at high temperature (Figure 3) [22].

### 3.5. pH-responsive BioMOFs

An interesting example that shows the potential use of BioMOFs in biomedical applications is the recently disclosed work of Au et al. which is based on the reformulation of zoledronate (Zol) exploring nanotechnology to develop a new nanoscale MOF (nMOFs) formulation of Zol, turning a bone antiresorptive agent into an anticancer agent [92].
Zol is a third-generation nitrogen heterocycle containing bisphosphonate that is widely used as an antiresorptive agent for bone cancer metastasis. In the preclinical data, it was observed that bisphosphonates such as Zol have direct cytotoxic effects on cancer cells. However, such effect has not been firmly established in the clinical settings, what led Au et al. to develop a new bioreposable sub-100 nm diameter pH-responsive calcium zoledronate (CaZol) nMOF as a potential cytotoxic anticancer agent. Folate receptor (FR) is known to be overexpressed in tumours, and therefore folate (Fol) was incorporated as a target ligand into the CaZol nMOFs to facilitate tumour uptake. This study successfully demonstrated that the active-targeted CaZol nMOF possesses excellent chemical and colloidal stability on physiological conditions, encapsulating more Zol than other existing drug delivery systems. It further shows higher efficiency than small molecule Zol in inhibiting cell proliferation and inducing apoptosis in FR-overexpressing H460 non-small cell lung and PC3 prostate cancer cells in vitro. Au et al. also validated these results in vivo and observed that Fol-targeted CaZol nMOF proved to be an effective anticancer agent, increasing the direct antitumour activity of Zol by 80–85% [92].

3.6. Magnetic nanoscale MOF as potential anticancer drug delivery system, and imaging and MRI contrast agent

The combination of both imaging and therapeutic agents in the same MOF greatly facilitates the efficacy studies of theranostic nanoparticles. Having this in mind, Chowdhuri et al. developed a new magnetic nanoscale MOF (IRMOF-3) consisting of a MOF with encapsulated
Fe$_3$O$_4$ nanoparticles for targeted anticancer drug delivery with cell imaging and magnetic resonance imaging (MRI). More specifically, authors conjugated the magnetic nanoscale MOF with folic acid and labelled it with the fluorescent molecule rhodamine B isothiocyanate due to its fluorescent properties. These systems were then successfully loaded with the hydrophobic anticancer drug paclitaxel. The efficiency of this nMOF towards targeted drug delivery was evaluated using an in vitro cytotoxicity 5-diphenyltetrazolium bromide (MTT) assay and fluorescence microscopy, revealing that the loaded nMOF targeted and killed the cancer cells in a highly effective manner. Furthermore, they had also tested the effectiveness of MRI of this nMOF in vitro and observed a stronger T2-weighted MRI contrast towards the cancer cells, which proved the possible use of this system in imaging (Figure 4) [93].

Figure 4. (Left) in vitro T2-weighted spin-echo MR phantom images of magnetic nanoscale Fe$_3$O$_4$@IRMOF-3 and magnetic nanoscale Fe$_3$O$_4$@IRMOF-3/FA at different concentrations incubated in HeLa cells; (right) in vitro paclitaxel release from magnetic nanoscale Fe$_3$O$_4$@IRMOF-3/FA at different time intervals (images from Chowdhuri et al. [93]—Copyright © 2015, Royal Society of Chemistry).

4. Bio-inspired applications of ZIFs: selected examples

There are many applications for ZIFs, specifically ZIF-8 (Figure 5). However, this type of materials has largely been explored as a way to deliver anticancer drugs and other chemotherapeutics. Only a few relevant examples are mentioned herein.

Figure 5. (a) Synthesis of ZIF-8; (b) fragment of the crystal structure of ZIF-8 (images adapted from Katsenis et al. [103]—Copyright © 2015, Rights Managed by Nature Publishing Group); and (c) image generated for ZIF-8 in http://www.chemtube3d.com (University of Liverpool).
4.1. Slow release of the anti-cancer drug doxorubicin from ZIF-8

Zheng et al. successfully developed a simple one-pot synthesis of ZIFs that contain encapsulated organic molecules. One-pot synthesis is a new approach that combines MOF synthesis and molecule encapsulation in a one-pot process and that has been extremely used to overcome the drawbacks observed when using the two processes separately [104].

In this study, the doxorubicin: ZIF-8 complex, which aims to treat mucoepidermoid carcinoma of human lung, human colorectal adenocarcinoma (HT-29) and human promyelocytic leukaemia (HL-60) cell lines, exhibits lower toxicity than pure doxorubicin, probably due to the slow release of the drug that is achieved with this complex (Figure 6) [69, 104]. Furthermore, ZIF-8 crystals loaded with doxorubicin proved to be efficient pH-responsive drug delivery systems, in which the drug is released in a controlled manner at low pH (5.0–6.5). With this work, Zheng et al. opened a new opportunity to develop multifunctional materials for biomedical applications using this simple, scalable, and environment-friendly one-pot synthesis [104].

4.2. ZIF-8 as efficient pH-sensitive drug delivery

“Smart” drug delivery of anticancer drugs is being explored making use of pH-sensitive systems [65–68]. The interest in the use of a pH-responsive drug vehicle is due to the fact that they can reduce undesired drug release during transportation in blood circulation and improve the effective release of the drug in the tumour tissue or within tumour cells [105, 106].
Sun et al. evaluated the possibility to use ZIF-8 as a pH-responsive drug vehicle and they have demonstrated that ZIF-8 exhibits a remarkable loading capacity for the anticancer drug 5-fluorouracil (around 600 mg of 5 FU g\(^{-1}\) of desolvated ZIF-8) (Figure 7) [66]. Ren et al. further developed polyacrylic acid@ZIF-8 (PAA@ZIF-8) nanoparticles that exhibit ultrahigh doxorubicin loading capability (1.9 g doxorubicin/g nanoparticles) and that thus can be used as pH-dependent drug delivery vehicles [65].

**Figure 7.** (Left) Schematic illustration showing two approaches of the encapsulated 5-Fu released from ZIF-8 (C = grey, N = blue, O = red, F = light blue, Zn = green); (right) 5-Fu delivery (% 5-FU vs. t) from ZIF-8; the inset shows the release process from 0 to 24 h (images from Sun et al. [66]—Copyright © 2012, Royal Society of Chemistry).

Zhuang et al. successfully encapsulated small molecules, such as fluorescein and the anticancer drug camptothecin, in ZIF-8 nanospheres for drug delivery. In this study, the evaluation of fluorescein-encapsulated ZIF-8 in the MCF-7 breast cancer line demonstrated cell internalization and a minimal cytotoxicity. Furthermore, the pH-responsive dissociation of the ZIF-8
framework likely results in endosomal release of the small-molecule cargo proved that ZIF-8 can be an ideal drug delivery vehicle [68].

Another example of a pH-responsive drug vehicle using ZIF-8 is the work of Liu et al., who fabricate green fluorescent carbon nanodots@ZIF-8 (c-dots@ZIF-8 NPs). In this work, the authors observed that the nanoparticles synthesized exhibit green fluorescence and microporosity, characteristics that unveil its ability as potential platforms for simultaneous pH-responsive anticancer drug vehicle and fluorescence imaging in cancer cells (Figure 8). Moreover, the fluorescence intensity and size of c-dots@ZIF-8 NPs can be tuned by varying the amount of C-dots and the concentration of the precursors [67].

4.3. ZIFs as potential carriers to brain capillary endothelial cells

One extraordinary example of the biomedical applications of ZIFs is the recent work from Chiacchia et al. who synthesized and characterized nanospheres of biodegradable zinc-imidazolate polymers (ZIPs) as a delivery system into human brain endothelial cells, the main component of the blood-brain barrier (BBB) [107].

In this work, both biodegradable particles synthesized, RhB@ZIP and AuNP@ZIP, have shown to be able to encapsulate fluorophores and inorganic nanoparticles at the point of synthesis with extremely high loading efficiencies. Furthermore, these ZIP particles are non-cytotoxic, stable in cell culture medium and able to penetrate the hCME/D3 human cerebral microvascular endothelial cell line. This cell line is a well-established in vitro functional model for the human BBB, which expresses the same levels of transporters, cell-specific receptors and tight junction proteins found in healthy human brain microvessels [108, 109], to release their cargos within the cell cytoplasm (Figure 9) [107].

Figure 9. Synthesis and assembly of loaded ZIP particles and their uptake into human brain endothelial cells: (I) encapsulation process of cargo species into the ZIP matrices at the point of synthesis; (II) cross-section of the human cerebral microvasculature and cell-uptake of loaded ZIP particles by the isolated and immortalized human brain endothelial cell line (image from Chiacchia et al. [107]—Published by The Royal Society of Chemistry).
Nevertheless this work needs more studies related to the exact cellular uptake mechanism, clearance rate and blood-stream stability of the ZIP's, but this is a promising result in the use of ZIPs as a novel platform for brain-targeting treatments [107].

5. Final remarks

Bio-inspired metal-organic frameworks have already proven to have promising biomedical applications not only as drug delivery systems but also in magnetic resonance imaging (MRI), optical imaging and X-ray computed tomography (CT) imaging.

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References

[1] N. Blagden, S. J. Coles and D. J. Berry, CrystEngComm, 2014, 16, 5753–5761.
[2] M. D. Allendorf and V. Stavila, CrystEngComm, 2015, 17, 229–246.
[3] A. Mukherjee, Crystal Growth & Design, 2015, 15, 3076–3085.
[4] S. Satapathi, Inorganic Chemistry Communications, 2015, 56, 22–34.
[5] A. Delori, T. Friscic and W. Jones, CrystEngComm, 2012, 14, 2350–2362.
[6] K. Biradha, C.-Y. Su and J. J. Vittal, Crystal Growth & Design, 2011, 11, 875–886.
[7] S. Aitipamula, P. S. Chow and R. B. H. Tan, *Crystal Growth & Design*, 2014, 14, 6557–6569.

[8] N. K. Duggirala, A. J. Smith, L. Wojtas, R. D. Shytle and M. J. Zaworotko, *Crystal Growth & Design*, 2014, 14, 6135–6142.

[9] D. Maddileti, B. Swapna and A. Nangia, *Crystal Growth & Design*, 2014, 14, 2557–2570.

[10] D. P. Elder, R. Holm and H. L. de Diego, *International Journal of Pharmaceutics*, 2013, 453, 88–100.

[11] I. Tomaszewska, S. Karki, J. Shur, R. Price and N. Fotaki, *International Journal of Pharmaceutics*, 2013, 453, 380–388.

[12] C. Maheshwari, V. Andre, S. Reddy, L. Roy, T. Duarte and N. Rodriguez-Hornedo, *Crystengcomm*, 2012, 14, 4801–4811.

[13] V. Andre, A. Fernandes, P. P. Santos and M. T. Duarte, *Crystal Growth & Design*, 2011, 11, 2325–2334.

[14] V. Andre, D. Braga, F. Grepioni and M. T. Duarte, *Crystal Growth & Design*, 2009, 9, 5108–5116.

[15] V. Andre, L. Cunha-Silva, M. Teresa Duarte and P. P. Santos, *Crystal Growth & Design*, 2011, 11, 3703–3706.

[16] V. Andre, M. T. Duarte, D. Braga and F. Grepioni, *Crystal Growth & Design*, 2012, 12, 3082–3090.

[17] V. Andre, M. F. M. da Piedade and M. Teresa Duarte, *Crystengcomm*, 2012, 14, 5005–5014.

[18] V. Andre and M. T. Duarte, *Journal of Molecular Structure*, 2014, 1076, 238–243.

[19] K. J. Ardila-Fierro, V. Andre, D. Tan, M. T. Duarte, R. W. Lancaster, P. G. Karamertzanis and T. Friscic, *Crystal Growth & Design*, 2015, 15, 1492–1501.

[20] D. Braga, F. Grepioni, L. Maini, K. Rubini, M. Polito, R. Brescello, L. Cotarca, M. T. Duarte, V. Andre and M. F. M. Piedade, *New Journal of Chemistry*, 2008, 32, 1788–1795.

[21] J. Della Rocca, D. Liu and W. Lin, *Accounts of Chemical Research*, 2011, 44, 957–968.

[22] P. Horcajada, C. Serre, G. Maurin, N. A. Ramsahye, F. Balas, M. Vallet-Regi, M. Sebban, F. Taulelle and G. Ferey, *Journal of the American Chemical Society*, 2008, 130, 6774–6780.

[23] P. Horcajada, C. Serre, M. Vallet-Regi, M. Sebban, F. Taulelle and G. Ferey, *Angewandte Chemie-International Edition*, 2006, 45, 5974–5978.

[24] C. Janiak and J. K. Vieth, *New Journal of Chemistry*, 2010, 34, 2366–2388.

[25] S. Keskin and S. Kizilel, *Industrial & Engineering Chemistry Research*, 2011, 50, 1799–1812.
[26] A. C. McKinlay, R. E. Morris, P. Horcajada, G. Ferey, R. Gref, P. Couvreur and C. Serre, *Angewandte Chemie-International Edition*, 2010, 49, 6260–6266.

[27] S. R. Miller, D. Heurtaux, T. Baati, P. Horcajada, J.-M. Greneche and C. Serre, *Chemical Communications*, 2010, 46, 4526–4528.

[28] P. Horcajada, R. Gref, T. Baati, P. K. Allan, G. Maurin, P. Couvreur, G. Ferey, R. E. Morris and C. Serre, *Chemical Reviews*, 2012, 112, 1232–1268.

[29] C.-Y. Sun, C. Qin, X.-L. Wang and Z.-M. Su, *Expert Opinion on Drug Delivery*, 2013, 10, 89–101.

[30] J. Y. An, S. J. Geib and N. L. Rosi, *Journal of the American Chemical Society*, 2009, 131, 8376.

[31] Q.-L. Li, J.-P. Wang, W.-C. Liu, X.-Y. Zhuang, J.-Q. Liu, G.-L. Fan, B.-H. Li, W.-N. Lin and J.-H. Man, *Inorganic Chemistry Communications*, 2015, 55, 8–10.

[32] S. Li and F. Huo, *Nanoscale*, 2015, 7, 7482–7501.

[33] N. Motakef-Kazemi, S. A. Shojasadati and A. Morsali, *Microporous and Mesoporous Materials*, 2014, 186, 73–79.

[34] M. R. Ryder and J. C. Tan, *Materials Science and Technology*, 2014, 30, 1598–1612.

[35] M. O’Keeffe, *Chemical Society Reviews*, 2009, 38, 1215–1217.

[36] B. Xiao, P. S. Wheatley, X. Zhao, A. J. Fletcher, S. Fox, A. G. Rossi, I. L. Megson, S. Bordiga, L. Regli, K. M. Thomas and R. E. Morris, *Journal of the American Chemical Society*, 2007, 129, 1203–1209.

[37] J. Graetz, *Chemical Society Reviews*, 2009, 38, 73–82.

[38] M. Mueller, X. Zhang, Y. Wang and R. A. Fischer, *Chemical Communications*, 2009, 119–121.

[39] M. P. Suh, Y. E. Cheon and E. Y. Lee, *Coordination Chemistry Reviews*, 2008, 252, 1007–1026.

[40] S. S. Han, J. L. Mendoza-Cortes and W. A. Goddard, III, *Chemical Society Reviews*, 2009, 38, 1460–1476.

[41] T. Dueren, Y.-S. Bae and R. Q. Snurr, *Chemical Society Reviews*, 2009, 38, 1237–1247.

[42] S. Ma, D. Sun, M. Ambrogio, J. A. Fillinger, S. Parkin and H.-C. Zhou, *Journal of the American Chemical Society*, 2007, 129, 1858.

[43] D. Farrusseng, S. Aguado and C. Pinel, *Angewandte Chemie-International Edition*, 2009, 48, 7502–7513.

[44] J. Lee, O. K. Farha, J. Roberts, K. A. Scheidt, S. T. Nguyen and J. T. Hupp, *Chemical Society Reviews*, 2009, 38, 1450–1459.

[45] T. Uemura, N. Yanai and S. Kitagawa, *Chemical Society Reviews*, 2009, 38, 1228–1236.
[46] T. Uemura, Y. Ono, K. Kitagawa and S. Kitagawa, *Macromolecules*, 2008, 41, 87–94.
[47] M. D. Allendorf, C. A. Bauer, R. K. Bhakta and R. J. T. Houk, *Chemical Society Reviews*, 2009, 38, 1330–1352.
[48] O. R. Evans and W. B. Lin, *Accounts of Chemical Research*, 2002, 35, 511–522.
[49] M. Kurmoo, *Chemical Society Reviews*, 2009, 38, 1353–1379.
[50] G. Ferey, *Chemical Society Reviews*, 2008, 37, 191–214.
[51] F. Millange, N. Guillou, R. I. Walton, J.-M. Greneche, I. Margiolaki and G. Fereya, *Chemical Communications*, 2008, 39, 4732–4734.
[52] R. Kuroda, T. Sato and Y. Imai, *Crystengcomm*, 2008, 10, 1881–1890.
[53] B. Notash, N. Safari and H. R. Khavasi, *Crystengcomm*, 2012, 14, 6788–6796.
[54] G. Ferey and C. Serre, *Chemical Society Reviews*, 2009, 38, 1380–1399.
[55] J. An, S. J. Geib and N. L. Rosi, *Journal of the American Chemical Society*, 2009, 131, 8376.
[56] R. Babarao and J. Jiang, *Journal of Physical Chemistry C*, 2009, 113, 18287–18291.
[57] I. Imaz, M. Rubio-Martinez, J. An, I. Sole-Font, N. L. Rosi and D. Maspol, *Chemical Communications*, 2011, 47, 7287–7302.
[58] P. D. C. Dietzel, R. Blom and H. Fjellvag, *European Journal of Inorganic Chemistry*, 2008, 23 3624–3632.
[59] P. L. Llewellyn, G. Maurin, T. Devic, S. Loera-Serna, N. Rosenbach, C. Serre, S. Bourrelly, P. Horcajada, Y. Filinchuk and G. Ferey, *Journal of the American Chemical Society*, 2008, 130, 12808–12814.
[60] M. Eddaoudi, D. F. Sava, J. F. Eubank, K. Adil and V. Guillerm, *Chemical Society reviews*, 2015, 44, 228–249.
[61] T. D. Bennett, J. Sotelo, J.-C. Tan and S. A. Moggach, *Crystengcomm*, 2015, 17, 286–289.
[62] H. Su, F. Sun, J. Jia, H. He, A. Wang and G. Zhu, *Chemical Communications*, 2015, 51, 5774–5777.
[63] B. Chen, Z. Yang, Y. Zhu and Y. Xia, *Journal of Materials Chemistry A*, 2014, 2, 16811–16831.
[64] R. Li, X. Ren, J. Zhao, X. Feng, X. Jiang, X. Fan, Z. Lin, X. Li, C. Hu and B. Wang, *Journal of Materials Chemistry A*, 2014, 2, 2168–2173.
[65] H. Ren, L. Zhang, J. An, T. Wang, L. Li, X. Si, L. He, X. Wu, C. Wang and Z. Su, *Chemical Communications*, 2014, 50, 1000–1002.
[66] C.-Y. Sun, C. Qin, X.-L. Wang, G.-S. Yang, K.-Z. Shao, Y.-Q. Lan, Z.-M. Su, P. Huang, C.-G. Wang and E.-B. Wang, *Dalton Transactions*, 2012, 41, 6906–6909.
[67] L. He, T. Wang, J. An, X. Li, L. Zhang, L. Li, G. Li, X. Wu, Z. Su and C. Wang, CrystEngComm, 2014, 16, 3259–3263.

[68] J. Zhuang, C.-H. Kuo, L.-Y. Chou, D.-Y. Liu, E. Weerapana and C.-K. Tsung, ACS Nano, 2014, 8, 2812–2819.

[69] I. B. Vasconcelos, T. G. da Silva, G. C. G. Militao, T. A. Soares, N. M. Rodrigues, M. O. Rodrigues, N. B. da Costa, Jr., R. O. Freire and S. A. Junior, RSC Advances, 2012, 2, 9437–9442.

[70] L. Paseta, G. Potier, S. Abbott and J. Coronas, Organic & Biomolecular Chemistry, 2015, 13, 1724–1731.

[71] N. Liedana, A. Galve, C. Rubio, C. Tellez and J. Coronas, ACS Applied Materials & Interfaces, 2012, 4, 5016–5021.

[72] M. Eddaoudi, D. B. Moler, H. L. Li, B. L. Chen, T. M. Reineke, M. O’Keeffe and O. M. Yaghi, Accounts of Chemical Research, 2001, 34, 319–330.

[73] V. Guillerm, D. Kim, J. F. Eubank, R. Luebke, X. Liu, K. Adil, M. S. Lah and M. Eddaoudi, Chemical Society Reviews, 2014, 43, 6141–6172.

[74] J. F. Eubank, L. Wojaś, M. R. Hight, T. Bousquet, V. C. Kravtsov and M. Eddaoudi, Journal of the American Chemical Society, 2011, 133, 17532–17535.

[75] M. C. Bernini, D. Fairen-Jimenez, M. Pasinetti, A. J. Ramirez-Pastor and R. Q. Snurr, Journal of Materials Chemistry B, 2014, 2, 766–774.

[76] D. G. Fatouros, D. Douroumis, V. Nikolakis, S. Ntais, A. M. Moschovi, V. Trivedi, B. Khima, M. Roldo, H. Nazar and P. A. Cox, Journal of Materials Chemistry, 2011, 21, 7789–7794.

[77] J.-Q. Liu, X.-F. Li, C.-Y. Gu, J. C. S. da Silva, A. L. Barros, S. Alves-Jr, B.-H. Li, F. Ren, S. R. Batten and T. A. Soares, Dalton Transactions (Cambridge, England: 2003), 2015, 44, 19370–19382.

[78] T. Chalati, P. Horcajada, P. Couvreur, C. Serre, M. Ben Yahia, G. Maurin and R. Gref, Nanomedicine, 2011, 6, 1683–1695.

[79] C. Gaudin, D. Cunha, E. Ivanoff, P. Horcajada, G. Cheve, A. Yasri, O. Loget, C. Serre and G. Maurin, Microporous and Mesoporous Materials, 2012, 157, 124–130.

[80] S. Vaucher, M. Li and S. Mann, Angewandte Chemie-International Edition, 2000, 39, 1793.

[81] E. R. Parnham and R. E. Morris, Accounts of Chemical Research, 2007, 40, 1005–1013.

[82] A. Pichon, A. Lazuen-Garay and S. L. James, CrystEngComm, 2006, 8, 211–214.

[83] J. A. Perman, K. Dubois, F. Nouar, S. Zoccali, L. Wojaś, M. Eddaoudi, R. W. Larsen and M. J. Zaworotko, Crystal Growth & Design, 2009, 9, 5021–5023.
[84] W. Lin, W. J. Rieter and K. M. L. Taylor, *Angewandte Chemie-International Edition*, 2009, 48, 650–658.

[85] A. M. Spokoyny, D. Kim, A. Sumrein and C. A. Mirkin, *Chemical Society Reviews*, 2009, 38, 1218–1227.

[86] M. Gimenez-Marques, T. Hidalgo, C. Serre and P. Horcajada, *Coordination Chemistry Reviews*, 2016, 307, 342–360.

[87] K. M. L. Taylor-Pashow, J. Della Rocca, Z. Xie, S. Tran and W. Lin, *Journal of the American Chemical Society*, 2009, 131(40), 14261–14263.

[88] K. E. Sapsford, W. R. Algar, L. Berti, K. B. Gemmill, B. J. Casey, E. Oh, M. H. Stewart and I. L. Medintz, *Chemical Reviews*, 2013, 113, 1904–2074.

[89] E. Bellido, T. Hidalgo, M. V. Lozano, M. Guillevic, R. Simon-Vazquez, M. J. Santander-Ortega, A. Gonzalez-Fernandez, C. Serre, M. J. Alonso and P. Horcajada, *Advanced Healthcare Materials*, 2015, 4, 1246–1257.

[90] T. Loftsson and D. Duchene, *International Journal of Pharmaceutics*, 2007, 329, 1–11.

[91] C. Tamames-Tabar, E. Imbuluzqueta, N. Guillou, C. Serre, S. R. Miller, E. Elkaim, P. Horcajada and M. J. Blanco-Prieto, *CrystEngComm*, 2015, 17, 456–462.

[92] K. M. Au, A. Satterlee, Y. Z. Min, X. Tian, Y. S. Kim, J. M. Caster, L. Z. Zhang, T. Zhang, L. Huang and A. Z. Wang, *Biomaterials*, 2016, 82, 178–193.

[93] A. Ray Chowdhuri, D. Bhattacharya and S. K. Sahu, *Dalton Transactions*, 2016, 45, 2963–2973.

[94] T. V. Slenters, J. L. Sague, P. S. Brunetto, S. Zuber, A. Fleury, L. Mirolo, A. Y. Robin, M. Meuwly, O. Gordon, R. Landmann, A. U. Daniels and K. M. Fromm, *Materials*, 2010, 3, 3407–3429.

[95] S. R. Miller, E. Alvarez, L. Fradcourt, T. Devic, S. Wuttke, P. S. Wheatley, N. Steunou, C. Bonhomme, C. Gervais, D. Laurencin, R. E. Morris, A. Vimont, M. Daturi, P. Horcajada and C. Serre, *Chemical Communications*, 2013, 49, 7773–7775.

[96] E. Alvarez, A. G. Marquez, T. Devic, N. Steunou, C. Serre, C. Bonhomme, C. Gervais, I. Izquierdo-Barba, M. Vallet-Regi, D. Laurencin, F. Mauri and P. Horcajada, *CrystEngComm*, 2013, 15, 9899–9905.

[97] J. Della Rocca, D. Liu and W. Lin, *Nanomedicine*, 2012, 7, 303–305.

[98] L. M. Plum, L. Rink and H. Haase, *International Journal of Environmental Research and Public Health*, 2010, 7, 1342–1365.

[99] B. B. Yang, R. B. Abel, A. C. G. Uprichard, J. A. Smithers and S. T. Forgue, *Journal of Clinical Pharmacology*, 1996, 36, 623–633.
[100] C. Serre, F. Millange, C. Thouvenot, M. Nogues, G. Marsolier, D. Louer and G. Ferey, *Journal of the American Chemical Society*, 2002, 124, 13519–13526.

[101] T. R. Whitfield, X. Q. Wang, L. M. Liu and A. J. Jacobson, *Solid State Sciences*, 2005, 7, 1096–1103.

[102] T. Loiseau, C. Serre, C. Huguenard, G. Fink, F. Taulelle, M. Henry, T. Bataille and G. Ferey, *Chemistry – A European Journal*, 2004, 10, 1373–1382.

[103] A. D. Katsenis, A. Puskaric, V. Strukil, C. Mottillo, P. A. Julien, K. Uzarevic, P. Minh-Hao, D. Trong-On, S. A. J. Kimber, P. Lazic, O. Magdysyuk, R. E. Dinnebier, I. Halasz and T. Friscic, *Nature Communications*, 2015, 6, 6662.

[104] H. Zheng, Y. Zhang, L. Liu, W. Wan, P. Guo, A. M. Nystrom and X. Zou, *Journal of the American Chemical Society*, 2016, 138, 962–968.

[105] K. Engin, D. B. Leeper, J. R. Cater, A. J. Thistlethwaite, L. Tupchong and J. D. McFarlane, *International Journal of Hyperthermia*, 1995, 11, 211–216.

[106] M. Stubbs, P. M. J. McSheehy, J. R. Griffiths and C. L. Bashford, *Molecular Medicine Today*, 2000, 6, 15–19.

[107] M. Chiacchia, C. Cerutti, R. Gromnicova, K. Rietdorf, I. A. Romero and D. Bradshaw, *Journal of Materials Chemistry B*, 2015, 3, 9053–9059.

[108] B. B. Weksler, E. A. Subileau, N. Perriere, P. Charneau, K. Holloway, M. Leveque, H. Tricoire-Leignel, A. Nicotra, S. Bourdoulous, P. Turowski, D. K. Male, F. Roux, J. Greenwood, I. A. Romero and P. O. Couraud, *FASEB Journal*, 2005, 19, 1872.

[109] B. Weksler, I. A. Romero and P.-O. Couraud, *Fluids and Barriers of the CNS*, 2013, 10, 16.