Consideration of Metal Organic Frameworks for Respiratory Delivery†

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Abstract

Metal organic frameworks (MOFs) have garnered increased attention over the past 20 years. Due to their porosity, high surface area, and nearly limitless customization and tunability MOFs have been designed for applications ranging from gas storage and separation to catalysis to sensing to biomedical engineering. Within the latter category, MOFs offer an appealing function for drug delivery as they can be loaded with multiple therapeutic moieties tailored to target specific disorders with triggered and controlled release characteristics. However, there is an unmet need to assess their viability for pulmonary treatment via inhalation. Targeting pulmonary disorders including infectious diseases by delivering medication directly to the lungs attacks the primary site of infection rather than relying on systemic distribution. The inherent advantage of this strategy is maximizing local lung concentrations of the drug. An introduction to inhaled therapies is provided here as a preamble to a brief summary of the current development state of MOF drug delivery systems. This review is intended to highlight the relative disparity between research toward MOFs as pulmonary drug delivery vehicles compared to other delivery platforms. Prospective biomedical applications for inhalable MOFs are also discussed.

Keywords: metal organic frameworks, aerosol, coordination polymer, pulmonary delivery, dry powders

1. Introduction

Inhalation therapies continue to be important treatments for several pulmonary diseases including asthma, cystic fibrosis (CF), and chronic obstructive pulmonary disorder (COPD). Aerosol delivery can achieve a high local drug concentration in the lungs while minimizing systemic exposure, thus potentially resulting toxicity and patient adherence, generating promise as a therapeutic strategy for other pulmonary diseases and infections such as tuberculosis (TB). Metal organic frameworks (MOFs) are emerging drug delivery tools. MOFs offer, in addition to drug delivery, the inclusion of metals, presenting multiple therapeutic moieties tailored to target specific disorders with triggered and controlled release characteristics.

Metals have a long history of being utilized to treat various ailments. Cu has been used for treating pulmonary disorders, sanitizing water, and treating wounds (Borkow G. and Gabbay J., 2005; Grass G. et al., 2011; Ladomersky E. and Petris M.J., 2015). Eye ailments were treated with Zn compounds (Giachi G. et al., 2013). The Chinese had used gold to manage many disorders (Huaizhi Z. and Yuantao N., 2001). However, it was not until the 20th century that metals began to be better understood and utilized by the medical community.

As medicine has progressed into modern times and the essential biological processes associated with metals are known, the applications taking advantage of unique traits of metal (particularly transition metal) complexes as diagnostic, treatment, and preventative medicinal components have opened up. Since the relatively recent discovery of the anticancer Pt-based complex cisplatin in the mid-20th century (Lippert B., 1999; Rosenberg B. et al., 1969), the use of metals in medicine is largely centered on anticancer activity (Franz K.J. and Metzler-Nolte N., 2019; Ndagi U. et al., 2017), though there are other promising applications. Ag, Co, and Cu have antibacterial and antiviral uses (Borkow G. and Gabbay J., 2005; Chang E.L. et al., 2010; Clement J.L. and Jarrett P.S., 1994; Zhao G. and Stevens S.E., Jr., 1998), Ti and Ti-alloys are used for prosthetics and implants (Zhao L. et al., 2009), and Cu, Rh, Ru, and Zn have been explored for anti-malarial efficacy (Navarro M. et al., 2005; 2010; Sánchez-Delgado R.A. et al., 1996). The nano-biotechnology research field has blossomed in recent decades: silver nanoparticles (Ag NPs) have
became popular as bactericidal (Baker C. et al., 2005; Martínez-Castañón G.-A. et al., 2008) and anticancer agents (Foldbjerg R. et al., 2011; Ong C. et al., 2013) while gold nanoparticles (Au NPs) have shown promise in a wide variety of applications from imaging to drug delivery (Giljohann D.A. et al., 2010; Murphy C.J. et al., 2008). There are many comprehensive reviews detailing the use of metals in medicine (Dabrowiak J.C., 2017; Guo Z. and Sadler P.J., 1999; Lemire J.A. et al., 2013; Medici S. et al., 2015) and the inclusion of metals in biomedical research is expanding from its arguable origins in the 1960s (Franz K.J. and Metzler-Nolte N., 2019).

An intriguing 21st century approach to implementing metals in medicine is the use of metal organic frameworks (MOFs). The extensive interest in MOFs over the past two decades has garnered interest from a variety of disciplines including the medical community. There is an immense amount of customization available to a researcher when considering MOFs as a drug delivery platform: elevated porosity for drug encapsulation, unique drug and metal combinations, and controlled release via tuning linkages within the frameworks (i.e. cleavage of coordination bond in acidic media), to name a few. Thus, it is surprising that, compared to oral and injectable routes of administration, there is a lack of consideration of MOFs for aerosol delivery of therapeutics. This may, however, correlate to a similar lack of research in the biological fate of inhaled metals.

While pulmonary administration of drugs is not suitable for every treatment approach, there are advantages in targeting the lungs. The intent of this focused review is to first provide a cursory introduction to inhalation technology for drug delivery followed by a brief MOF background and review of current MOF applications in the biomedical field. The sparse activity with respect to MOFs for aerosolized delivery to the lungs will be apparent and should motivate future research in this area.

### 2. Aerosols for pulmonary therapy

In ~1500 B.C., the first use of inhaled drugs was recorded by the Egyptians. Individuals struggling to breathe were instructed to inhale vapours from hot black henbane (*Hyoscyamus niger*) (Breasted J.H., 1930). The Greeks also used Cu to treat pulmonary diseases (400 B.C.) (Borkow G. and Gabbay J., 2005). While inhaled therapies continued to evolve over the centuries, a breakthrough came in the 1950s with the invention of a portable metered dose inhaler (MDI) that reliably delivered medication to the lungs and ushered in modern pulmonary delivery (Stein S.W. and Thiel C.G., 2017). Inhaled therapies have progressed over recent decades and are now predominantly used to deliver therapies to the lungs to treat chronic ailments such as asthma (Alangari A.A., 2014), CF (Agent P. and Parrott H., 2015), and COPD (Patton J.S. and Byron P.R., 2007; Sims M.W., 2011). Research into inhaled drugs for other applications including antivirals (Jefferson T. et al., 2006; Zhou Q. et al., 2015), anticancer (Lee W.-H. et al., 2015; Zarogoulidis P. et al., 2012), gene therapy (Laube B.L., 2015; Davies L.A. et al., 2014), peptide and protein delivery (Okamoto H. et al., 2002), and antibacterials (Banachewski B. and Hofmann T., 2019; Muttitt P. et al., 2009) is ongoing. This is especially apparent in the latter area as emergence of drug resistant bacterial strains necessitates novel treatment regimens (Van Duin D. and Paterson D.L., 2016; Ventola C.L., 2015). The general reasoning is straightforward: deliver the cure to the site of infection rather than ingesting or injecting the drug (Fig. 1).

Pulmonary administration of therapeutics allows for direct drug delivery to the target organ. First pass metabolism is avoided thus limiting possible systemic side effects at a presumably much lower dose compared to other routes of administration (Borghardt J.M. et al., 2018; Lipworth B.J., 1996; Stein S.W. and Thiel C.G., 2017). Conversely there has also been an interest in using inhalation to rapidly deliver drugs, such as insulin, systemically to other parts of the body (Henry R.R. et al., 2003; Hickey A.J. and Da Rocha S.R., 2019; Laube B.L., 2005; Mortensen N.P. and Hickey A.J., 2014). In either case, designing a molecule for inhalation is no trivial task. There are challenges associated with formulating an active pharmaceutical ingredient (API) into a respirable aerosol capable of producing the desired therapy. These include broad considerations such as excipient inclusion, pharmacokinetic/pharmacodynamics (PK/PD) of the inhaled formulation, drug product manufacturing, physicochemical properties, and stability which are recounted more thoroughly elsewhere (Hickey A.J. and Da Rocha S.R., 2019; Huazhzi Z. and Yuantao N., 2001; Maa Y.F. and Prestrelski S.J., 2000; Mortensen N.P. et al., 2014). Though arguably, the first hurdle to be overcome when considering pulmonary delivery is producing an aerodynamic diameter suitable for respiration and delivery.
The lungs contain a vast network of internal branches that confer an enormous canvas for particle deposition. Fig. 2 shows a diagram of adult lungs and corresponding cross-sectional areas of the 24 bifurcating airway generations, increasing from 2.54 cm² to 10⁴ cm². However, it is generally accepted that only particles with an aerodynamic diameter of roughly 1–5 μm will be respirable. The aerodynamic diameter of a particle, which equates the particle to a sphere of unit density with the same settling velocity regardless of its actual shape and density, is defined, in simplified form from Stokes’ law, as

\[ d_{ae} = \sqrt[3]{\frac{d_v \rho_p}{\chi}} \]  

(1)

where \( d_{ae} \) is the aerodynamic diameter, \( d_v \) is the equivalent volume diameter equal to the non-spherical volume diameter of the particles in question (can be determined experimentally (DeCarlo P.F. et al., 2004)), \( \rho_p \) is the density of the particles and \( \chi \) is the dynamic shape factor. Full derivations and considerations can be found in the literature (Crowder T.M. et al., 2002; DeCarlo P.F. et al., 2004; Hickey A.J. and Edwards D.A., 2018). One generally cannot rely on the geometric mean size of particles (found via optical techniques) and their bulk/tapped density to predict aerodynamic diameter and size distributions without detailed knowledge of the particle’s density and considerations for any internal cavities and shape factors. Indeed, particle diameter and density do not need to both be explicitly specified (Edwards D.A. et al., 1997; Hickey A.J. and Edwards D.A., 2018). Rather, an experimentally determined descriptor of an aerosol’s aerodynamic particle size distributions (APSD) can be measured via inertial impaction. This mass based characterization will generate an APSD from which mass median aerodynamic diameter (MMAD or the median particle size at which 50 % of the aerosol mass lies below and above calculated from a lognormal cumulative distribution), geometric standard deviation (GSD), and fine particle fraction (FPF) can be determined. These are several basic standard quantifiable attributes for aerosol drug characterization prior to in vivo experiments that give the researcher a detailed idea of particle behaviour under the influence of an airstream. The theory and practice of inertial impaction can be found in the literature (Marple V.A. et al., 2003; Mitchell J.P. and Nagel M.W., 2003). The United States Pharmacopeia (USP), among other compendiums such as European Pharmacopoeia (Ph. Eur.), contain several useful chapters detailing proper characterization of pharmaceutical aerosols to better anticipate performance prior to in vivo studies (see for example chapters <601> and <1601> in the USP). Finally, research regarding predicting in vitro – in vivo correlations and airway modelling is also available (Byron P.R. et al., 2010; Hofmann W., 2011; Olsson B. et al., 2013).

Many factors contribute to inhaled aerosol deposition including airway geometry, temperature and humidity, particle solubility and crystallinity, and the breathing patterns of the individual. However, there are three primary outcomes dictated by aerodynamic particle size which are summarized in Fig. 3 (Finlay W.H., 2019; Labiris N.R. and Dolovich M.B., 2003). Particles with MMAD larger than ~5 μm typically a) impact the back of the throat and

![Fig. 2 (a) Breakdown of lung branching generations (b) and corresponding surface area. Compiled Figure: (a) Adapted with permission from (Klein-streuer C. et al., 2008), Copyright 2008 by Annual Reviews; (b) reprinted from xPharm: The Comprehensive Pharmacology Reference, Robert M. Lust, The Pulmonary System, Pages 1-6, Copyright (2007), with permission from Elsevier (Lust R.M., 2007).](image-url)
conducting airway above the 10th lung generation, b) are swallowed and never reach the lungs, or c) are removed in the upper airways via mucociliary clearing. Particles with MMAD ~1–5 μm deposit via impaction and gravitational sedimentation. Lastly, particles <1 μm generally arrive through diffusion or Brownian motion; there is a chance they are exhaled due to slow settling in the airways. There are other considerations involved in the inhalation of particles at lower primary size in the nano range (Muralidharan P. et al., 2015; Paranjpe M. and Müller-Goymann C.C., 2014; Yang W. et al., 2008; Zhang J. et al., 2011). Thus particles with mass median aerodynamic diameter between 1–5 μm have the best chance of reaching the lower airways. (Labiris N.R. and Dolovich M.B., 2003; Patton J.S. and Byron P.R., 2007). Additionally, alveolar macrophages have evolved to phagocytose particles in this size range (especially 2–3 μm). This spurs the design of aerosolized treatments for bacteria that reside in the macrophage, such as *Mycobacterium tuberculosis* (*Mtb*), the causative organism of TB (Biggs D.L. et al., 2003; Champion J.A. et al., 2008; Edwards D.A. et al., 1997; Gharse S. and Fiegel J., 2016; González-Juarrero M. and O’Sullivan M.P., 2011; Skozen S.L. et al., 2011). Other factors to consider for particle size engineering are: controlled release strategies (Adi H. et al., 2010; Cook R.O. et al., 2005; Smyth H.D. and Hickey A.J., 2011), specific lung disease target and API (which could help determine necessary size and release kinetics of the aerosol particles) (Patton J.S. and Byron P.R., 2007), and inspiratory flow of the individual patient (Kleinstreuer C. et al., 2008; Labiris N.R. and Dolovich M.B., 2003).

It is worthwhile to note again that it is the aerodynamic diameter that is important for respirable particles. For example, it has been shown that engineered porous particles with seemingly irrespirable (>5 μm) mean geometric sizes were actually more suitable for respiration compared to solid particles at a similar size (Edwards D.A. et al., 1997). For more detailed pharmaceutical aerosol formulation troubleshooting, design considerations, and synthetic strategies, the reader is directed to the literature for reviews (Finlay W.H., 2019; Hickey A.J. and Da Rocha S.R., 2019; Pilcer G. and Amighi K., 2010; Vehring R., 2008).

Respirable therapeutic aerosols can be delivered from several devices (Hickey A.J. and Da Rocha S.R., 2019; Ibrahim M. et al., 2015; Sims M.W., 2011). Pressurized metered dose inhalers (pMDIs) and nebulizers deliver an API from solution or suspension. Both devices offer a classical view of an aerosol mist or cloud that delivers the drug directly from a liquid formulation that is atomized to form aerosol droplets. In both devices, careful consideration is needed when selecting surfactants, cosolvents, and, in the case of the pMDI, propellants that do not a) degrade the API or b) impact resulting APSD. Nebulizers offer a more predictable delivery simply depending on the tidal breathing pattern of the individual while the device is continuously generating and aerosol. On the other hand, pMDIs require more coordination between device and patient. Dry powder inhalers (DPI) contain a solid dosage form of the API and are gaining increasing attention for pulmonary delivery (De Boer A.H. et al., 2017; Frijlink H.W. and De Boer A.H., 2004; Timsina M.P. et al., 1994). While there is still some coordination necessary for delivering drug to the patient, the devices can be made cheaply, do not rely on a power supply or compressed air (as with nebulizers), and only depend on the inspiratory flow of the individual to disperse the powder. There are unique physical mechanisms to consider when dispersing dry powders in the micrometer size range including electrostatics, Van der Waals,
and capillary forces (Dunber C.A. et al., 1998; Hickey A.J., 2018). However, a solid dosage form offers better chemical stability compared to those in solution. And while pMDIs and nebulizers are more or less dependent on the device to dictate APSD, dry powders can be manufactured to well controlled particle sizes as via milling, physical mixing, supercritical fluid, or spray drying (Telko M.J. and Hickey A.J., 2005; Vehring R., 2008).

Given the rise in impactful research in the fields of medicinal metals and inhalational therapies from the mid-1900s, there is very little overlapping study. Fe-chelates delivered via nebulization have been suggested as an option for CF treatment (Musk Jr. D.J. and Hergenrother P.J., 2008). However, there are not many groups suggesting delivering metals therapeutically to the lungs. This may be due to a lack of specific research into metals as a pulmonary therapy as well as a concern over inflammation and toxicity (Bierkandt F.S. et al., 2018; Born P.J.A. et al., 2006; Donaldson K. et al., 2002; Jamuna B.A. and Ravishankar R.V., 2014; Nel A. et al., 2006; 2013). However, there is evidence that a variety of transition metals can be advantageous in the treatment of pulmonary bacterial ailments. Ag, Cu, Fe, Pd, and Zn have been suggested for tuberculosis (TB) (Chao A. et al., 2019; Ellis T. et al., 2018; Palazzo F. et al., 2013; Pieters J., 2008; Poole K., 2017), Ag and Pt for lung cancer (with some evidence of dose-dependent toxicity) (Foldbjerg R. et al., 2011; Ndagi U. et al., 2017), and Ag, Cu, and Zn for viruses, including coronavirus (Bright K.R. et al., 2008; Raha S. et al., 2020; Ranford J.D. et al., 1993; Shittu M.O. and Afolami O.I., 2020; Skalny A.V. et al., 2020). Indeed, with the emergence of drug resistance, novel therapeutics and unique drug delivery strategies are needed to overcome said resistance to traditional regimens. Utilizing metals may be an intriguing option provided toxicity concerns are addressed (Allahverdiyev A.M. et al., 2011; Chen C.-W. et al., 2014; Ong Y.C. et al., 2019; Sloan D.J. et al., 2013; Turner R.J., 2017; Van Duin D. and Paterson D.L., 2016). MOFs and coordination polymers are an emerging class of materials that may be suitable as a drug delivery vehicle to the lungs.

3. Biomedical applications of MOFs

MOFs are highly crystalline and porous coordination polymers that are assembled by the formation of multiple coordination bonds between inorganic metal nodes (either metal ions or metal oxide clusters) and multitentative organic ligands. MOFs offer structural designability at the molecular level together with tunable porosity and chemical functionalization. Due to their tailored features, especially elevated surface area and hybrid organic-inorganic compositions, MOFs have been studied for a myriad of applications such as gas storage and separations (Sumida K. et al., 2012), nonlinear optics (Yu J. et al., 2012), catalysis (Corma A. et al., 2010; He X. and Wang W.-N., 2019; Luz I. et al., 2010), sensing (Kreno L.E. et al., 2012), or molecular-based magnetisms (Coronado E. et al., 2013). During the last decade, MOFs have also been considered for medical applications ranging from precisely-controlled release of drugs to imaging (Chen W. and Wu C., 2018; Della Rocca J. et al., 2011; He C. et al., 2015a; McKinlay A.C. et al., 2010).

Nano and micro sized MOF particles are required to exploit certain biologically relevant mechanisms (Novio F. and Ruiz-Molina D., 2017). For instance, particle sizes ~500 nm influence the circulating time in the blood stream and facilitate their introduction into cells by endocytosis. Particles smaller than 250 nm are most suitable for crossing the vascular endothelium (Jiménez-Marqués M. et al., 2016). Fortunately, MOFs of many size ranges can be easily prepared by conventional methods (i.e., solvothermal/hydrothermal synthesis, microwave-assisted, sonochemical) (Stock N. and Biswas S., 2012) or alternative methodologies ranging from microemulsion and templating (Luz I. et al., 2017; 2019) to spray-drying (Carne-Sanchez A. et al., 2013) and continuous-flow techniques (Friščić T., 2011). MOFs also exhibit a high external surface-area-to-volume ratio which aids in colloidal stability, biocompatibility, recognition capabilities, and biodistribution (Oh M. and Mirkin C.A., 2005). Showcasing their potential for stability in biological pH, MOFs can be made to withstand pH as low as 1.2 (as in the gastrointestinal tract) (Ding M. et al., 2019; Rojas S. et al., 2018) and there have even been reports of manufacturing MOFs with local “buffer” environments that were appropriate for pH 1.5–12.5 (He H. et al., 2018).

The surface of MOF nano- and micrometric crystals can be functionalized to address specific biological and medical needs via two attachment techniques: covalent (i.e. condensation, click chemistry, and conjugation reactions) or non-covalent (i.e. electrostatic interactions, dispersion forces, and hydrogen bonding) (Sapsford K.E. et al., 2013). On one hand, organic or inorganic nanomaterials have been considered to address the challenges related to the use of conventional treatments, diagnosis, monitoring, and control of biological systems (i.e., drug resistance, systemic toxicity, poor treatment efficacy, and safety) (Patra J.K. et al., 2018). But MOFs are hybrid organic-inorganic materials that offer potential advantages compared to these purely organic or inorganic carriers for biomedical applications. These advantages are: size control over nano and micrascale and the ability to compose MOF superstructures of individual MOF sub-components; tailored structures (physicochemical properties including metal-ligand compositions, crystallinity, particle size, and morphology) allowing for the incorporation of multiple functionalities that can demonstrate multi-stimuli-responsive controlled
Biodegradability and stability of MOFs are arguably the most important concerns that need to be addressed prior to potential therapy. The decomposition of MOFs at a desired region is recommended to avoid endogenous accumulation. As illustrated by Fig. 4, three main approaches have been developed to incorporate drugs or biologically active components in MOFs and are classified by the type of interaction (bond strength) between them. They include 1) encapsulation of the drug within the MOF pore system (weak interaction) (Horcajada P. et al., 2008), 2) the drug is the organic linker in the MOF via coordination bond (medium interaction) (Rojas S. et al., 2017), and 3) the drug is bonded via post-synthetic modification to the MOF framework via covalent bond (strong interaction) (Taylor-Pashow K.M.L. et al., 2009). This variety of possibilities enables the pinpoint triggered release of therapy at the target by different biologically induced stimuli, such as pH, temperature, magnetic field, ionic species, pressure, or even light radiation. For bio-applications, the precise chemical stability of MOFs is also crucial to enable targeted drug release and avoid the excessive early decomposition and/or accumulation of the MOF individual chemical constituents. The most widely investigated approach is pH-responsive MOF carriers, especially for cancer therapy (Wu M.-X. and Yang Y.-W., 2017), because the acidic tumor microenvironment can disassemble the MOF scaffold via cleavage of the coordination bonds (which are sensitive to external acidic pH), thus releasing the hybrid components. Therapies targeting endo-lysosomal release of MOF cargo in macrophages may benefit from this strategy as well since the pH value in a macrophage lysosome is between 4–5 while the phagosome remains neutral (Chen T.-T. et al., 2018; Russell D.G. et al., 2009).

The first examples considering MOFs as potential drug delivery systems via drug encapsulation (Fig. 4a) within the MOF pores were reported by Horcajada et al. (Horcajada P. et al., 2006; 2008). These MOFs (intended for general administration) were built from low-toxic iron and multi-carboxylate ligands (MIL-100, MIL-101, and MIL-53) and were suggested for the delivery of the drug ibuprofen, exhibiting high drug-storage capacity and a complete drug-controlled release under physiological conditions. The large “breathing” effect of the flexible framework of MIL-53 was demonstrated to be an interesting feature for potential applications in drug delivery. The same group also reported the first biodegradable therapeutic MOF with pellagra-curative, vasodilating, and antilipemic properties (BioMIL-1) (Horcajada P. et al., 2008). This MOF was built up from a non-toxic Fe species and a therapeutically active linker nicotinic acid (Fig. 4b). The release of the drug, a constituent of the framework, was achieved via degradation of the hybrid crystalline phase simulated physiological conditions (Miller S.R. et al., 2010).

The ability to combine metals and organic molecules in a single element in the MOF hybrid structure (Fig. 4b), opens up the possibility of pursuing synergetic effects between metal and drug upon delivery via framework degradation (Rojas S. et al., 2017). For example, in the work by Tamames-Tabor et al., azelaic acid was combined as a linker with an endogenous transition metal cation, in this case Zn^{2+} (Tamames-Tabar C. et al., 2015). The authors asserted that since both linker and metal exhibited interesting antibacterial and dermatological properties for the treatment of skin conditions, both components should be combined into a biocompatible and bioactive MOF (BioMIL-5), which they found to be stable in water and in bacterial culture medium. The progressive slow release of both active constituents allowed growth suppression of Staphylococcus epidermidis over 7 days, suggesting that this MOF can be a good candidate for future bio-applications in skin care and cosmetics.

Taylor-Pashow and coworkers demonstrated that both an optical contrast agent (BODIPY dye) and an anticancer prodrug (ethoxysuccinato-cisplatin) could be covalently bonded to the free amine functionalization of (Fe)MIL-

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**Fig. 4** Strategies for drug inclusion within MOFs: a) encapsulation of the guest drug within the MOF host pore system (weak interaction); b) the guest drug acts as organic linker within the MOF host bonded by coordination bonds (medium interaction); c) the guest drug is bonded via post-synthetic modification to the MOF host framework via covalent bond (strong interaction).
nanoMOFs. These nanocrystals were then released upon disassembly of the MOF framework under acidic conditions present in a tumor environment. In addition, the rate of cargo release was further controlled by coating the MOF sub-constituents with an inert silica shell. The potential utility of this multicomponent MOF drug system for optical imaging and anticancer therapy was demonstrated in vitro using HT-29 human colon adenocarcinoma cells (Taylor-Pashow K.M.L. et al., 2009).

Research concerning the toxicity of MOFs and overall regimen implications (Sajid M., 2016) continues to be conducted. It is thought that MOF constituents will progressively break down in the body; however, since the field maturing, there is still work that needs to be done to elucidate MOF toxicity and pharmacokinetics further (regardless of administration route), both at the super-structure level and for the fate of each sub-constituent (He C. et al., 2015b; Horcajada P. et al., 2012; Novio F. and Ruiz-Molina D., 2017; Sun C.-Y. et al., 2013). On the other hand, the desirable triggered release and biocompatibility properties, along with their large surface areas and high porosities, have positioned MOFs as promising materials for drug delivery and other therapeutic applications (Beg S. et al., 2017; Giménez-Marquès M. et al., 2016; Horcajada P. et al., 2012; Liang Z. et al., 2018; Wu M.-X. and Yang Y.-W., 2017; Rojas S. et al., 2018). MOF lung delivery via a systemic route (Simon-Yarza M. et al., 2017) has been considered but the manufacture and delivery of MOFs as an aerosol has not until recently been explored.

4. Facile generation of MOF aerosols via spray drying

The wide applicability of MOFs has generated wide appeal across scientific research fields as summarized above. MOFs are especially gaining traction in the medical field for enhancing drug delivery via oral (Abuçafy M.P. et al., 2018; Chen Y. et al., 2018) and intravenous (Bian R. et al., 2015; Zhao H.-X. et al., 2016) routes. One area that has thus far remained largely unexplored is the use of MOFs as inhalation therapies for pulmonary disorders. This is despite the existence of a relatively facile manufacturing method commonly used to generate respirable microparticles: spray drying.

Spray drying is used as a controllable, continuous process to generate solid nano and microparticles from solution for various applications from food additives to fuel cells to ceramics to pharmaceuticals (Eldridge J.A. et al., 2014; Ramavath P. et al., 2014; Santana L.P. et al., 2008; Ziaee A. et al., 2017). Its main pharmaceutical application is manufacturing amorphous particles from an otherwise water insoluble API for use in solid dosage forms, i.e. tablets. Among other things, this strategy increases drug product bioavailability (Baghel S. et al., 2016). As mentioned above, however, dry powders suitable for therapeutic inhalation delivery can also be produced with a spray dryer. Recently, spray drying has been demonstrated by Carne-Sanchez et al. (Carne-Sanchez A. et al., 2013; Garzón-Tovar L. et al., 2016) as a versatile continuous flow method to assemble nanoMOFs into micrometric hollow spherical superstructures (Fig. 5). This strategy conceptually mimics the standard emulsions used to confine the synthesis of MOF materials but does not require secondary immiscible solvents or surfactants, which can reduce production time and cost. In the work by Carne et al. in 2013, the generality of this continuous flow strategy was proven for a broad range of MOFs (i.e. HKUST-1, Cu-BDC, NOTT-100, MIL-88A, MIL-88B, MOF-74, UiO-66, and ZIF-8, among others). Members of this research group have also demonstrated the synthesis of UiO-66 in aqueous solution (Avci-Camur C. et al., 2018), addressing one of the challenges currently precluding the industrial exploitation of nanoMOFs: the lack of water-based, efficient methods for their synthesis. This unique MOF morphology obtained by spray drying (the arrangement of MOF nanocrystal sub-components into hollow spherical microparticulate superstructures) can seemingly address three attributes of aerosolized drugs: 1) generation of hollow, low density spherical particles suitable for respiration, 2) potential for MOF microparticle disassembly into MOF nanocrystals suitable for a wider range of endocytosis, and 3) controlled pH-triggered coordination bonds to be cleaved under acidic macrophage or tumor environment releasing the active drug(s). A review of MOF spray drying can be found in the literature (Troyano J. et al., 2020).

The synthesis of MOFs via spray drying starts with atomization of a precursor solution into microdroplets using a two- or three-fluid nozzle (Fig. 5). This step is accomplished by simultaneously injecting the solution at high speed and compressed air or nitrogen. Each precursor droplet (and is suspended by) a gas stream heated to a certain temperature. The solvent then begins to evaporate causing the precursors to diffuse radially to the droplet surface (Fig. 5b). It is important to note that spray drying can be utilized under completely aqueous conditions and the inclusion of organic solvents is not necessary, but can aid in the formulation process (dissolving solutes, impacting precipitation rate of the solid particles, etc.). As the evaporating droplet shrinks, precursor concentrations at the droplet surface increase until supersaturation is reached at which point MOF nanocrystals begin forming and arranging into a well-packed shell at the drop surface. Spray drying is a mature technology that can be transferred from bench to pilot to manufacturing scale in many industries, including pharmaceutical (Dobry D.E. et al., 2009; Kemp I. et al., 2016; Poozesh S. and Bilgili E., 2019). Theoretical
and experimental considerations for particle engineering via spray drying can be found elsewhere (Vehring R., 2008; Vehring R. et al., 2007).

The discovery that this robust technique could be used to manufacture hollow hybrid microparticles incorporating metal species, i.e. MOFs, had the potential to initiate more research toward their aerosol characterization specifically for pharmaceuticals. But there have been very few accounts suggesting the use of MOFs for pulmonary delivery and even less using this widely available and scalable manufacturing technique.

5. Aerosolized MOFs for pulmonary therapy: Pioneer works and future prospects

The specific potential for aerosol delivery of MOFs for pulmonary therapies has recently begun to appear in the literature. Hu et al. showed that budesonide (an anti-asthma drug) can be loaded into γ-cyclodextrin (CD) MOFs that exhibit acceptable respirable particle sizes (MMAD just under 5 μm), good cell viability and biocompatibility in A549 human lung alveolar cells, similar budesonide distribution and PK as the commercial control, and were well tolerated in rats when administered via insufflation (DP-4R Penn-Century insufflator) (Hu X. et al., 2019). However, this version of MOF does not contain transition metals. Iron based MOFs (MIL-88A(Fe) and MIL-100A(Fe)) were shown to be endocyted by alveolar macrophages in vitro subsequently accumulating in acidic regions where airway-based pathogens, such as Mtb, are known to reside (Guo A. et al., 2019). Wyszogrodzka et al. (Wyszogrodzka G. et al., 2018) reported that Fe-MIL-101-NH₂, a widely studied biocompatible Fe-MOF carrier for drug delivery, can be an effective carrier for isoniazid (INH), a first-line anti-TB drug. This group demonstrated that MOF particles accumulate in the cell cytoplasm. They reported sustained drug release inside cells in contrast to fast dissolution of crystalline INH powder. Additionally, these MOFs had low cytotoxicity and can serve as MRI contrast agents; i.e. a theranostic system combining diagnostics and delivery. Their work was extended to theophylline, an anti-asthma and COPD drug, loaded into Fe-MIL-100 microparticles (via traditional MOF synthetic routes). As in the previous case, the drug was found to have sustained release in vitro and was nontoxic against human epithelial cells and murine macrophages after uptake. There were minor increases in reactive oxygen species which subsequently returned to baseline after 72 h. (Strzempek W. et al., 2019). These studies showcased promise for biocompatibility of MOFs for lung delivery, but aerosol characterization was lacking.

Even with the discovery that MOFs could be spray dried into hollow spheres in size ranges suitable for respiration in 2013 (Fig. 5), there are very few accounts utilizing this
proven aerosol generation technique as a possible drug product manufacturing mechanism. Anti-TB MOF delivery to the lungs would be a reasonable therapy target considering that MOFs and MOF composites have been suggested for use as antimicrobial applications previously (Shen M. et al., 2020; Wyszogrodzka G. et al., 2016). To reach this end, designing MOFs to efficiently deposit in the lungs via dry powder aerosol to locally attack TB can be realized by spray drying. To the best of our knowledge, there are only three reports that characterize aerosolized spray dried MOFs for potential pulmonary delivery – all motivated by anti-TB potential. This strategy is understandable as DPIs have shown promise as an alternative treatment for TB with benefits over standard oral and intravenous regimens such as lower systemic toxicity, local access to the lung granulomas containing Mtb, and avoiding painful injections. Activity in this research area is well documented (Braunstein M. et al., 2019; Dharmadhikari A.S. et al., 2013; Hickey A. et al., 2016a, b; Mehta P. et al., 2018). In a more recent work using the same MOF-based delivery system as above, Wyszogrodzka et al. produced MOFs where INH was encapsulated in Fe-MIL-101-NH₂. Afterwards, it was combined with poly(lactide-co-glycolide) and leucine via spray-drying leading to a microparticle composite (Fig. 6a) (Wyszogrodzka-Gawel G. et al., 2019). This MOF exhibited good aerodynamic properties, controlled release of INH, uptake by macrophages in vitro, low cytotoxicity, and extended their theranostic application. Importantly this was the first reported use of MOFs as a dry powder for inhalation. Similarly, Fernandez-Paz et al. recently produced nanoparticle aerosols from (Fe) MIL-100 MOFs and various biocompatible carbohydrates (i.e. mannitol) via spray drying (Fernández-Paz C. et al., 2020). Notably, these MOF composite particles did not result in an inflammatory response when delivered to rats intratracheally and the release of the intact MOF constituent nanoMOFs embedded within the superstructure carrier was determined to be uniform along the lungs, reaching the bronchioles and alveoli. Therefore, state-of-the-art MOFs can be spray dried, subsequently filled with drugs, and utilized as aerosolized microparticles using soluble glue-like excipient components. However, despite the existence of the initial work of Carne-Sanchez et al. (Carne-Sanchez A. et al., 2013) demonstrating the continuous-flow preparation of several MOF compounds via spray drying, the utilization of “pure” MOF hollow spheres, i.e. where all metal and organic MOF components are considered active (bioMOFs), as aerosolized drug carriers was not considered in these first publications (Horcajada P. et al., 2012; Rojas S. et al., 2017).

Our group has experience with the preparation of inhalable anti-TB drugs via spay drying and the characterization of dry powder aerosols (Durham P.G. et al., 2016; Durham P.G. et al., 2015; Hickey A.J. et al., 2020; Mortensen N.P. et al., 2014; Pitner R.A. et al., 2019; Stewart I.E. et al., 2019). Given the rise in multi drug resistant (MDR) and extensively drug resistant (XDR) TB (Sloan D.J. et al., 2013; Van Duijn D. and Paterson D.L., 2016), novel treatments are necessary including via a) inhalation, b) new drugs, and/or c) inclusion of metals. Therefore, we recently developed a spray drying procedure for preparing Cu-POA (pyrazinoic acid) hollow spherical microparticles (Fig. 6b). Our choice of Cu was based on evidence of its anti-TB potential (Festa R.A. et al., 2014; Neyrolles O. et al., 2015; Speer A. et al., 2013; Wolschendorf F. et al., 2011) as well as demonstrated in vitro synergy with other known anti-TB drugs (Manning T. et al., 2015a; 2015b; 2017; Speer A. et al., 2013). POA has been explored as an anti-TB candidate since it is considered a prodrug of pyrazinamide (PZA), a current first line TB drug experiencing drug resistance from Mtb (Durham P.G. et al., 2015; Via L.E. et al., 2015). Our results show that this potential anti-TB MOF can be spray dried in one step from a mostly aqueous solution, excipient-free, to produce a dry powder with APSD suitable for respiration (Luz I. et al., 2020). The use of pure metal-drug compounds linked by coordination bonds can enable the controlled local release of the organic drug and the metal “codrug” simultaneously, in this case Cu²⁺ and POA (Fig. 6b). This approach avoids the use of unnecessary inactive components, i.e. organic ligands or metal ions typically found in MOF carriers. These do not contribute to the therapeutic treatment and only provide structural roles, thus removing them can reduce possible toxic contributions. As well, since the polar functional groups of POA are coordinated to the Cu, moisture uptake can be avoided. However, that is not to say excipients are unnecessary during spray drying the formulation process in general; indeed excipients are a common formulation strategy to prevent moisture ingress, encapsulate particles, control release, or aid in dispersion (Bosquillon C. et al., 2001; Gordon M.S. et al., 2000;
Rather this is an alternative approach that designs inhalable MOFs or coordination polymers composed of solely therapeutic metal and organic components. In addition to mitigating the risk of possible toxic responses higher doses can be achieved (no excipient).

To facilitate this design, non-essential MOF properties for drug release applications can be obviated depending on the requirements of the delivery system, i.e. porosity or crystallinity. This unleashes a myriad of possibilities for designing multifunctional drugs containing the suitable metal-drug components linked by stimuli-responsive coordination bonds widening the range of pulmonary disease targets. These materials may be considered as MOFs, if porous and crystalline, or simply as coordination polymer particles (CPP) if amorphous or non-porous (Novio F. et al., 2013).

Although TB has been the primary potential target for most of the early work on spray dried therapeutic aerosolized MOFs, it is certainly not the only potential pulmonary target. As mentioned above, lung cancer, other chronic conditions such as asthma, and viruses might benefit from a unique respirable therapy that includes coordination metal-organic components. As well, using the lungs as a strategy to deliver drugs via MOFs systemically can also be considered once more information on toxicity and pharmacology is discovered.

Considering MOFs can be fabricated to remain stable in neutral solution, it may be possible to formulate active species for inclusion in nebulizers and pMDIs as suspensions (Wang G.-Y. et al., 2014). Indeed, metal-phenolic (Fe) capsules have recently been explored as nebulized drug carriers for pulmonary delivery while not specifically defined as MOFs. Accumulation in alveolar macrophages with low inflammation was indicated in vivo which suggests that MOFs could be utilized in similar nebulizer applications (Ju Y. et al., 2020). MOFs can also be spray dried into aerosolized microparticles for use in DPIs. Since MOFs and traditional organic APIs are capable of being spray dried separately as well, this might enable combination therapy of several distinct inhaled (or otherwise administered) drugs; synergistic and additive effects might be possible with the inclusion MOFs. Additionally, several APIs and/or metals could be coordinated to the MOF scaffold. This may aid in controlled release and the well-triggered delivery of several medications at their appropriate time.

6. Conclusion

The goal of this review was to briefly present two promising individual areas of research (MOFs and aerosol drugs) whose potential intersection has not been, to our knowledge, thoroughly investigated. While there is risk associated with utilizing inhaled metals as a therapeutic agent given toxicity concerns, there exists dose-dependent toxicity associated with almost any drug. Moreover, MOF metal and organic synthetic components can be diluted or concentrated to adjust their final concentration levels to reflect a desired therapeutic window. Therefore, expanding the use of metals in medicine to include pulmonary administration should not be discounted as there are inherent tradeoffs with any regimen once a toxicity threshold is established. To facilitate this work we believe MOFs, as an emerging class of drug delivery vehicles, offer a unique approach toward inhaled therapy. They are capable of being formulated into highly porous, hollow microparticles or manufactured as low-density dry powders with appropriate aerodynamic diameters thus hurdling the first barrier for use as a pharmaceutical aerosol. However, there is a need for further contributions toward characterizing the aerodynamic performance of MOFs to ensure suitability for pulmonary delivery and assessing or connecting their activity and efficacy toward specific lung targets in vitro and in vivo. We believe considering this area of research offers great potential for collaboration and advancement over several disciplines including materials science, aerosol physics, biology, pharmacology, and medicine.

Nomenclature

| Acronym | Definition                      |
|---------|---------------------------------|
| API     | active pharmaceutical ingredient|
| APSD    | aerodynamic particle size distribution|
| BDC     | benzene-1,4-dicarboxylate       |
| BODIPY  | boron-dipyromethene             |
| CF      | cystic fibrosis                 |
| COPD    | chronic obstructive pulmonary disorder|
| CP      | coordination polymers           |
| CPP     | coordination polymer particle    |
| CD      | cyclodextrin                    |
| DPI     | dry powder inhaler              |
| EPR     | enhanced permeability and retention effect|
| FPF     | fine particle fraction          |
| GSD     | geometric standard deviation     |
| HKUST   | Hong Kong University of Science and Technology |
| INH     | isoniazid                       |
| MMAD    | mass median aerodynamic diameter|
| MDI     | metered dose inhaler            |
| MOF     | metal organic framework         |
| MIL     | materials of Institute Lavoisier|
| MRI     | magnetic resonance imaging      |
| NP      | nanoparticle                    |

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