

# Continuous flow production of metal-organic frameworks

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While thousands of metal-organic frameworks (MOFs) are known to exist, only a handful are produced commercially. The myriad of potential applications imply that many different MOFs will be required at large scale and versatile production methods could enable this expansion. Continuous flow chemistry is a versatile technique that is compatible with a broad range of laboratory syntheses, with many innovative heating and workup processes, and also with well-established scaled processing methods. With a general synthetic method defined, the state of the art sees a wide and expanding range of MOF materials becoming market-ready in the near future. Key challenges currently lie in increasing processing efficiency, particularly in product work-up.

## Addresses

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Current Opinion in Chemical Engineering 2015, 8:55–59

This review comes from a themed issue on **Nanotechnology**

Edited by **Hong Yang** and **Hua Chun Zeng**

For a complete overview see the [Issue](#) and the [Editorial](#)

Available online 13th March 2015

<http://dx.doi.org/10.1016/j.coche.2015.02.001>

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## Introduction

Metal-organic frameworks (MOFs) are porous, crystalline materials derived from organic linkers bound periodically by metal coordination centres. MOFs have unprecedented internal surface areas and uniform pores (see [Figure 1](#)). Pore size and shape can be tuned by varying the organic linkers, leading to a vast range of possibilities for designing materials with desired functionalities for a raft of potential industrial applications [1–5]. Two decades of research into MOFs has uncovered a large number of high performing materials in gas storage [6–8], automotive components [6,9–11], carbon capture [12], gas separation [13], drug delivery [14], sensing [15], photoelectronics [16] and catalysis [17\*].

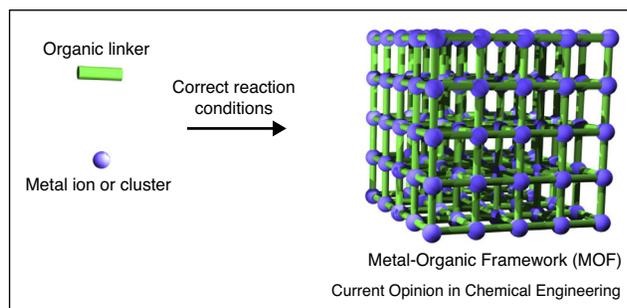
A crucial pre-requisite for accessing the potential applications of MOFs is the ability to routinely synthesise these materials in large quantities (kg scale or higher) with high efficiency. High volume production of MOFs has been slow to develop and whilst more than 4700 MOFs have been reported, only 7 are commercially available [18]. As a consequence, the cost of these materials has remained prohibitively high, and their enormous potential has yet to make a significant impact on prospective markets. Scaled-up production using traditional laboratory routes such as the classical solvothermal synthesis remains challenging due to extended long reaction times and the production of low quality materials. Furthermore, the wide variety of methods for preparing MOFs and the singular nature of some of the preparations provides an inherent risk of inflexibility for any prospective production process. Specifically, switching a bespoke production system to a different MOF material is likely to require significant re-tooling, or indeed a completely new production train.

## MOF synthesis chemistry

The classical synthesis of MOFs involves mixing solutions of the metal salt and organic linker, placing the mixed solution in a sealed reaction vessel and heating it to promote the growth of insoluble frameworks that precipitate as fine crystals [19]. This synthesis method is known as *solvothermal synthesis*, the reaction takes place over days or hours. Earlier slow solvent evaporation methods take place over days or weeks, but may still be employed to produce very large single crystals. The sealed solvothermal synthesis systems may be heated to temperatures and pressures above the solvent's boiling point. In this aspect the chemistry resembles hydrothermal Zeolite synthesis. The solvothermal method also includes heating to reflux at ambient pressure [20]. Extensions of solvothermal synthesis employ more efficient heating methods such as microwave or ultrasonic radiation producing a reduction in reaction time — hours to minutes [21].

One of the barriers to scaled MOF synthesis relates to the nucleation of the MOFs at a reaction surface and therefore the size of the reaction vessel becomes a significant parameter. Consequently, reactions that proceed well in small vessels do not readily scale into larger vessels using identical reaction conditions. This factor limits the scaling of MOF chemistry to a small number of MOFs that are

Figure 1



Schematic representation of metal-organic frameworks.

robust in their preparation, each requiring bespoke equipment [8,22–25,26<sup>••</sup>,27<sup>••</sup>,28,29<sup>••</sup>,30,31].

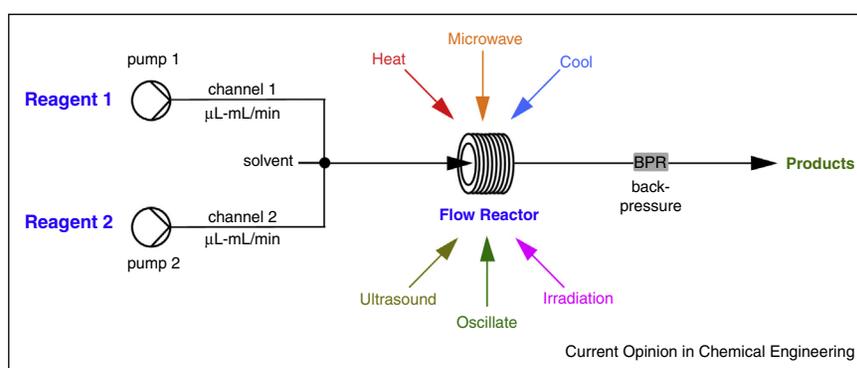
The limitations of the solvothermal method have been overcome by alternative techniques, which have led to successful production of MOFs in commercially useful quantities. Handling large volumes of solvent is not required when MOFs are synthesised mechanochemically, by milling the metal and linker precursors [32]. This results in very efficient production and very high STY (space-time yield — kilograms of product per cubic metre of reaction mixture per day) [8] but results in low surface areas, as the synthesis conditions are not conducive to the formation of the crystalline structures that constitute good quality MOFs. Another commercially viable method produces MOFs by dissolving a metal anode into an electrolytic solution containing the organic linker molecule [8]. Electrochemical systems have a much lower demand for solvent handling and recycling than solvothermal methods and, importantly, can be operated continuously. The main disadvantage of this method is that it can only be used to produce a small number of MOFs and product quality is slightly lower than achieved with solvothermal syntheses [29<sup>••</sup>,30,33,34]. Another promising alternative that has yet to reach commercial implementation involves

injecting metal and organic spacer solutions, similar to those used in solvothermal synthesis, into a spray-drying system [35]. This strategy is continuous and has been demonstrated to work for a number of MOFs. However the technique does use large amounts of complex solvent mixtures, and it is unclear if the process will perform well on a large scale.

Therefore, a method to conveniently expand the scale of a broad number of MOF syntheses whilst minimising the size and cost of the reactor is extremely attractive to those seeking a versatile route to commercial MOF production. Recently continuous flow chemistry has shown great promise for the scalable synthesis of advanced functional materials [36]. Continuous flow technology has been recognised as an attractive alternative to conventional batch processing and this approach may ameliorate the aforementioned challenges associated with the scaled synthesis of MOFs [37–44]. In its simplest form, a continuous flow reactor comprises the continuous pumping of reagents into a tubular reactor and the isolation of products which exit from the reactor (Figure 2).

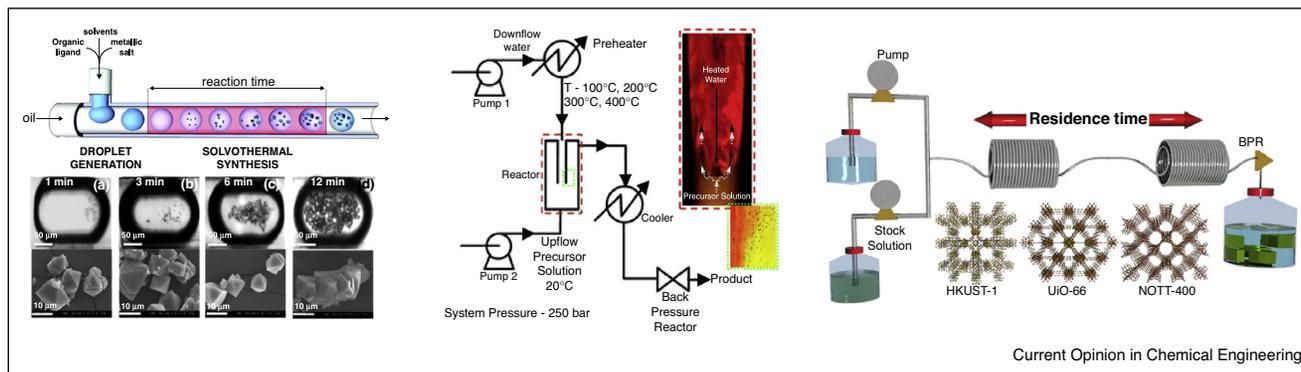
The advantages of using flow chemistry are derived from the greatly increased surface to volume ratio of the reaction, giving inherent improvements to heat and mass transfer, and leading to rapid syntheses, new synthetic pathways, and greater efficiency [45<sup>•</sup>]. The technique is also coherent with established large-scale chemical processing techniques, allowing laboratory research and development to dovetail smoothly with process development. Small amounts of MOFs can be made within oil droplets using microfluidic reactors (Figure 3 — Left, Table 1) [25,45<sup>•</sup>,46<sup>••</sup>]. While it allows excellent control of the MOF's morphology, microfluidic processing is hampered by low quality of the final products and a low STY. Proof of concept meso- and macroscale flow production has also been reported [26<sup>••</sup>,27<sup>••</sup>,29<sup>••</sup>,47<sup>••</sup>], and pumped metering of a spacer ligand solution into a stirrer-tank reactor has been described [23,48,49]. Gimeno-Fabra *et al.* showed

Figure 2



A general schematic representation of continuous flow synthesis methodology.

Figure 3



Left: Schematic representation of a continuous flow microfluidic device for producing MOF crystals (top). Optical and SEM micrographs of HKUST-1 crystals obtained *via* the microfluidic approach after (a) 1, (b) 3, (c) 6, and (d) 12 min of synthesis. Reproduced from Faustini *et al.* [46\*\*]. Centre: Schematic representation of the continuous synthesis system used for the instant production of HKUST-1 MOF. Reprinted with permission from the work of Gimeno-Fabra *et al.* [26\*\*]. Right: Schematic representation showing the general flow reactor for the production of MOFs. Reprinted with permission from the work of Rubio-Martinez *et al.* [29\*\*].

that counter-current mixing of precursor solutions with water at the high temperature of 300 °C (Figure 3 — Centre, Table 1) can lead to MOFs under hydrothermal conditions [26\*\*]. The high temperatures were used in order to increase the rate of crystal growth, with a limitation in that heating beyond 300 °C can lead to Cu<sub>2</sub>O forming as a waste-product. The material produced is of high quality and with an excellent STY and good particle size control; however high-temperatures and pressures limit the practicality of the technique. The evolution of continuous flow systems can be conceptualised as the combination of metered dosing of ligand into a stirred tank of metal

precursor [48,49] with a more subtle version of the rapid heating afforded by high temperature water systems [26\*\*]. It is significant to these developments that the stirred tank systems established that good quality materials could be produced under mild conditions and with a good STY.

Nucleation in MOF synthesis is usually rapid and crystal growth is generally the step that needs to be promoted by heating [26\*\*]. Bayliss *et al.* [47\*\*] developed the system described by Gimeno-Fabra *et al.* [26\*\*] by introducing the metered addition of both ligand and metal solutions whilst retaining the use of high temperature water for

Table 1

The recent evolution of the continuous production of MOF materials. In the case of the familiar MOF HKUST-1, continuous flow techniques have seen a more than order of magnitude increase in space-time yield (STY) from that of the best established commercial process.

MOF	Synthesis	Time	Temperature (°C)	SA BET	g h <sup>-1</sup>	STY kg m <sup>-3</sup> d <sup>-1</sup>
HKUST-1 (Basolite C300) <sup>a</sup>	Electrochemical	150 min	n/a	1820	n/a	225
HKUST-1 <sup>b</sup>	Flow chemistry (mesoscale)	10 min	140	2046	1.48	592
HKUST-1 <sup>c</sup>	Flow chemistry (mesoscale)	5 min	60	1673	2.04	n/a
HKUST-1 <sup>d</sup>	Microfluidics	1 min	90	1105	0.004	5.8
HKUST-1 <sup>e</sup>	Flow chemistry (macroscale)	5.1 min	200	1554	2.1	730
HKUST-1 <sup>f</sup>	Hydrothermal flow chemistry	n/a	300	1950	132	1760
HKUST-1 <sup>b</sup>	Flow chemistry (macroscale)	1.2 min	140	1805	61.2	4533
MIL-53 <sup>e</sup>	Flow chemistry (macroscale)	5 min	250	919	n/a	1300
UiO-66 <sup>b</sup>	Flow chemistry (mesoscale)	10 min	130	1186	1.68	672
UiO-66 <sup>g</sup>	Hydrothermal	24 h	130	1147	n/a	n/a
NOTT-400 <sup>b</sup>	Flow chemistry (mesoscale)	15 min	85	1078	2.78	741
NOTT-400 <sup>h</sup>	Hydrothermal	72 h	85	1350	n/a	n/a

<sup>a</sup> Mueller *et al.* [30].

<sup>b</sup> Rubio-Martinez *et al.* [29\*\*].

<sup>c</sup> Kim *et al.* [27\*\*].

<sup>d</sup> Faustini *et al.* [46\*\*].

<sup>e</sup> Bayliss *et al.* [47\*\*].

<sup>f</sup> Gimeno-Fabra *et al.* [26\*\*].

<sup>g</sup> Cavka *et al.* [51].

<sup>h</sup> Ibarra *et al.* [52].

heating. In order for any production technique to be viable, pure MOFs must be readily attainable without a loss in product quality, so controlled crystal growth is desirable. Given the wide array of MOFs known, and the likelihood of a large range of applications each requiring different MOFs in the future, a versatile fabrication technique is crucial. The ability to avoid harsh processing conditions such as high temperature and pressure, both increases the versatility of the system as well as potentially leading to reduced capital and operating costs. When these factors are considered it becomes clear that an ideal system should involve perfect mixing of the MOF precursor solutions followed by controlled heating of the nucleated reaction mixture in a continuous reaction system. To this end, Kim *et al.* [27\*\*] employed simple electrical resistance heating giving a system performing both efficient mixing/nucleation of the precursor solution along with a milder crystal growth process. We recently described an optimised continuous flow chemistry system for the production of a diverse range of MOFs, each with different reaction requirements, but all using mild conditions (Figure 3 — Right, Table 1). It was demonstrated that the results can be extended 30-fold in scale, allowing greater than a kilogram per day production from a bench-top reactor. This was achieved without a loss in yield or product quality. Through systematic identification and optimisation of the key factors influencing the synthesis of MOFs *via* continuous flow methods, it has been demonstrated that fast synthesis can be achieved without a loss in product quality, and moreover with the ability to control the product's particle size [29\*\*].

Over the past 2 years continuous flow chemistry has been developed as a viable means of synthesising a diverse set of MOFs in a commercially-viable manner (see Table 1). Indeed there has been extensive activity aimed at developing other continuous systems. For example a recent paper describes the use of screw extruders for continuous mechanochemical MOF synthesis with exceptionally high STYs [53]. At this point in time a key benefit to the continuous flow approach is that it emulates the conditions present inside the small vials commonly used in laboratory syntheses. As an extension of the conventional solvothermal synthesis it is a versatile approach to a number of MOFs, removing the need for customised equipment for each class of material. Furthermore, by emulating the more common laboratory method it has the potential to be parsimoniously adapted to producing new MOF materials as they are identified. Nevertheless MOF processing is still at an early stage and it is possible that new, improved, synthetic techniques may come to the fore. It is likely that the application of high efficiency heating, such as microwave or ultrasonic heating [50] may lead to further improvements to MOF production using flow chemistry strategies.

## The remaining challenge

Flow chemistry and continuous flow manufacturing are poised to impact the future synthesis of metal organic frameworks. The reproducibility of reaction conditions and therefore product quality have proven to exceed those obtained by batch processing and importantly, flow has enabled, for the first time, access to a broader range of MOFs at commercially viable quantities *via* a unified synthesis platform. Remaining challenges in the field relate to the downstream processing of crude reaction mixtures for the isolation of pure products and recycling of solvents and unreacted reagents. Specifically, techniques for continuous in-line analysis, particle size control, material recycling and MOF isolation/activation need to be developed to a point where whole-system automation is viable. It is clear that the existing continuous flow and semi-batch technologies, such as continuous flow centrifugation and drying, could readily be applied to address this challenge and work in our laboratories is presently investigating these options.

Moving beyond the simple reactor and pump configuration, we envisage in-line monitoring of product quality and real-time adjustment of reaction conditions to enable the synthesis of high quality products. Borrowing from established flow chemistry methods in organic synthesis, we also foresee opportunities for complex multi-step synthesis to enable the productions of MOF materials with enhanced functionality (for example, multilayer systems and polymer hybrids). Overall, continuous flow methods will enable access to high quality MOFs which are simultaneously complex and scalable, and this will permit their application to address future technological challenges.

## Acknowledgements

MRH acknowledges FT 130100345 for funding. All authors acknowledge the CSIRO for funding support.

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