Perspective Article: Flow Synthesis of Functional Materials

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Continuous-flow synthesis of specific functional materials is now seen as a reliable synthesis approach that gives consistent product properties. This perspective article aims to survey recent work in some of the relevant areas and to identify new domains where flow synthesis of functional materials can be better than the conventional synthesis methods. It also emphasizes the need for developing high-throughput integrated synthesis and screening systems for almost all functional materials so that laboratory-scale recipes can be transformed into reliable manufacturing processes. New areas relevant to functional materials which have remained unexplored in flow synthesis are also highlighted.

Keywords: Flow synthesis, functional materials, nanoparticles, nanocatalysts, MOFs, energy storage devices

1. Introduction

Advanced functional materials occupy a prominent place in the day-to-day life of a significant portion of the global population. The impact of these materials on the quality of human life is seen either in the direct form (viz., communication devices, energy storage devices, light-emitting devices, reflecting mirrors, currency notes, precious metals and their various forms and compositions, cosmetics, diagnostics, paints and coatings, stain resistant fabric, biomimetic colorants, etc.) or indirectly (viz,. catalysts, display technologies, toughened surfaces of high speed machining components, drag-reducing lubricants, functionalized nanosilica for precise chemical separations, light-weight materials, nanocomposites in conducing inks, etc.) [1]. In general, functional materials can be classified based on their functionality and quality of performance. A variety of these functional materials is used over a very wide range of quantities (from a few mg to few tons) [2].

The functionality of these materials depends on the dimensions of the material, viz., size and shape for particulate matters, pore size and surface area in the case of porous materials, and thickness for films. This implies that attaining the desired dimensions through controlled synthesis is the key to retain the properties that make these materials functional in true sense. A few such examples that highlight the impact of size on the specific property and hence application are given in Figure 1. The only way to achieve such consistency in the properties is through wet chemical synthesis or through biological routes. Among the two, the later approach is precise yet unreliable due to the scarcity and purity of specific biological moieties needed for certain activity and the former option of chemical synthesis becomes a more reliable approach, albeit only if the synthetic recipe allows consistent product quality at all scales of production. Continuous-flow synthesis of the functional materials not only paves the way to achieve consistency in properties but it is also scalable and yet decentralized, giving it a flexibility of on-site-on-demand production [3]. This article aims to provide developing a broader perspective of the utility and relevance of flow synthesis for the manufacture of a variety of functional materials and also gazes in to the crystal ball, developing a map for exploration in as yet new areas, which might rise to prominence in the coming years.

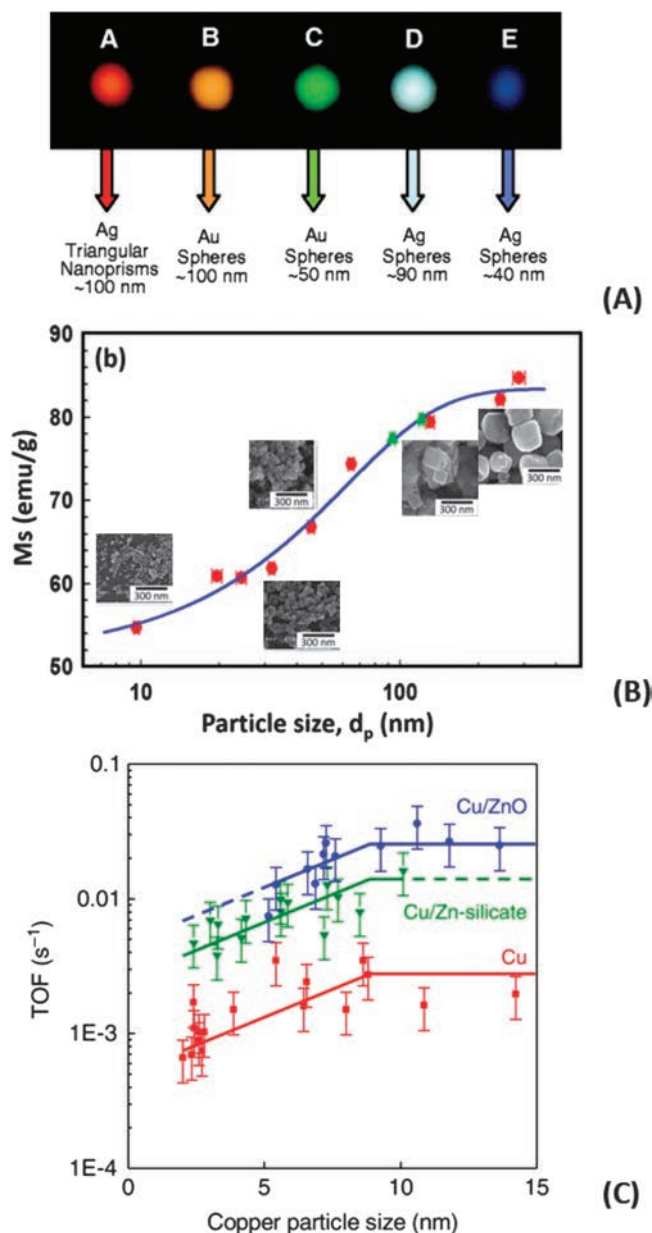## 2. Types of Functional Materials and Scope for Flow Chemistry

As mentioned above, the fabrication of nanomaterials of tailored properties involves the control of size, shape, structure, and composition. Wet-chemical methods have been considered as the most valuable methodology to assure an accurate control at the nanoscale, compromising the productivity and cost of production. A plethora of nanomaterials can be produced using wet-chemical procedures adapted to microfluidic systems (Figure 2) by a careful regulation of crystallization kinetics and thermodynamic parameters in liquid media with the assistance of selected solvents, ligands, and surfactants [7]. Microtechnology and flow chemistry can be considered as the new pillars of wet chemistry because these two disciplines enable an excellent control of syntheses at the nanoscale. The most interesting fact is that microflow production of nanomaterials is not only applicable to well-known wet-chemistry methods (emulsification, sol-gel, solvothermal, hydrothermal, photochemical, electrochemical, sonochemical, etc.) but also allows the exploration of entirely new paradigms such as the use of supercritical fluids [19], multiphase flows [20], or reactive-gas atmospheres [14].

2.1. Metal and Metal Oxide Nanomaterials. During the last decade, there has been considerable activity in the production of metal and metal oxide nanoparticles with the assistance of microfluidics [3, 21]. Numerous demonstrations of the production of pure spherical materials [22], anisotropic nanostructures [20, 23], or hybrid nanomaterials have been reported [24]. Mostly, procedures developed in batch type reactors were translated to microsystems, decreasing the time required due to the fast heat and mass transfer achieved. These types of nanostructures were produced in different types of microsystems [25] from simple capillary tubing microfluidic reactors [23] to sophisticated silicon and glass-based microfluidic reactors [19a].

Though the list of publications devoted to size control has been increasing during the last decade, we believe that research efforts should also be focused in controlling the shape and chemical composition of nanostructures produced in continuous fashion. The fascinating shape-dependent properties and surface-dependent properties of nanomaterials justify the great research efforts that should be applied in the field of shape-controlled synthesis of noble metal nanocrystals. This remark is a challenge because the synthesis conditions required to control the shape and composition of nanoparticles are not usually the same as the ones
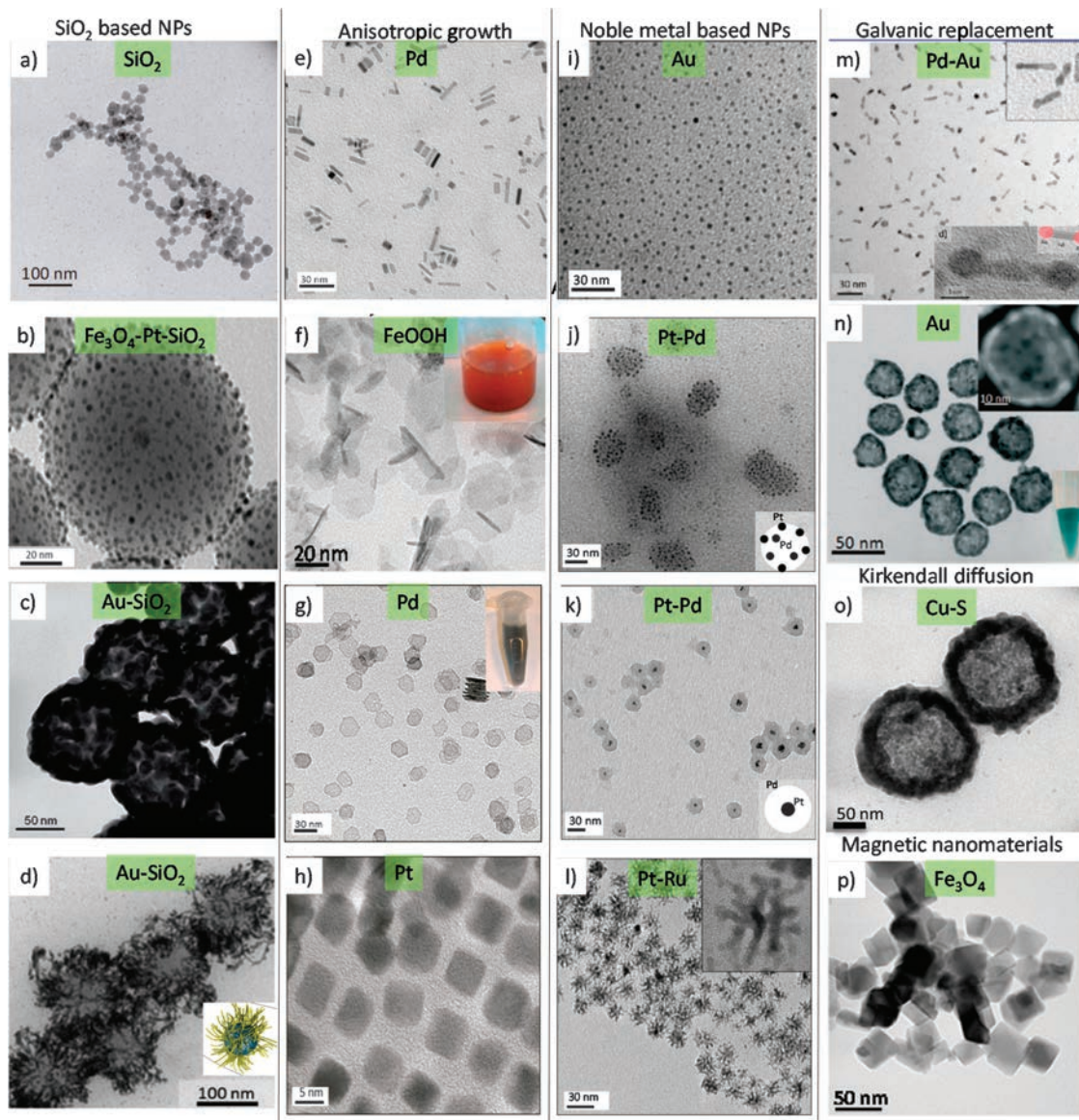
Figure 1. Effect of nanomaterial size on specific properties. (A) Surface plasmon resonance [4], (B) magnetization of Fe3O4 nanoparticles [5], and (C) catalytic activity for methanol synthesis [6] (reproduced with CC license from the respective sources)

reactor wall surface and also reduces the particle size distribution. However, it is also worth noting a limitation of multiphase flow reactors, where some capping agents or stabilizers solubilized in the dispersed phase can be transferred to the continuous phase, decreasing their concentration in the reaction media and then promoting a non-controlled nanocrystallization process. In addition, the phenomenon of interfacial adsorption of nanocrystals can occur in liquid–liquid flow reactors [27], which need a new method of separation that must overcome the interfacial energy barrier. This phenomenon implies the gradual adsorption of nanocrystals at the liquid–liquid interface followed by the limited growth of nanocrystals (only on the facets exposed to the aqueous phase). To overcome this problem, additional surfactants should be added, promoting a possible modification in the nanocrystals growth. Interestingly, the response of the growing nanocrystals to the flat or curved interfaces that are constantly undergoing a motion and their possible penetration through the interface are new fundamental scientific areas that will help to explore the time scales for such nanoscopic events. Eventually, detailed analysis of such phenomena would help design methods that will allow easy separation of fully grown crystals from the interface.

2.2. QDs and Light-Emitting Materials. Light-emitting nanomaterials have been successfully produced using microfluidics systems due to the excellent control achieved during nanocrystallization process. This type of nanocrystals must be quantum size-engineered via ultraprecise colloidal synthesis to provide an accurate control over the particle size and size-dispersion. For instance, the growth of InP nanocrystals was tuned using a continuous three-stage microfluidic reactor to precisely tune reaction conditions in the mixing, aging, and sequential growth regimes [19a]. Microfluidic synthesis of ZnO [28] and GaN [29] quantum dots (QDs) is also reported where nucleation, growth, and functionalization stages can be separated in a hydrodynamically controlled environment in supercritical ethanol and hexane, respectively. The use of a supercritical solvent [30] or slug flow [31] in a microfluidic reactor results in narrower residence time distributions, producing homogeneous reaction conditions ideal for nanocrystal synthesis. Microfluidics are also a versatile tool for fast screening of reaction parameters [32], including even in situ monitoring of light-emitting properties. In addition, microfluidic reactors can unveil the mechanisms of nucleation and growth of semiconductor nanocrystals to gain knowledge and guide the efficient design of nanomaterials. This extraordinary outcome of microfluidics is due to the fact that microreactors can incorporate in situ spectroscopic techniques to get access to information on both short and long time scales without interfering with the reaction under study [33]. For instance, the nucleation and growth of some cesium lead halide perovskite nanocrystals occur on unusually fast time scales (over a millisecond to several seconds time span) [34]. Carbon dots are one of the most relevant nanomaterials due to their excellent luminescent properties and high biocompatibility as well as their low cost synthesis. The synthesis of carbon dots was performed in continuous flow [35] at 190 °C at a flow rate of 10 µL/min. The flow rate was a critical parameter to get the maximum fluorescence. However, new approaches should be included in order to increase the productivity of carbon dots. New materials with upconversion light properties, where a long wavelength radiation is converted to short wavelength emission via a two-photon or multiphoton mechanism, are not produced yet in continuous flow. These types of materials are being used in photochemical or imaging applications because they have high light penetration depth and signal-to-noise ratio, due to near-infrared (NIR) light excitation located in the "optical transmission window" of the biological tissues [36]. However, the synthesis is challenging due to the severe conditions required and the high number of synthesis stages required. These limitations should not

required to control the size. For instance, kinetically controlled reactions are required to form metastable nanostructures with a variety of shapes that are different from their thermodynamically stable counterparts [26]. A single microreactor was recently designed to address the shape/chemical composition control in a continuous fashion by selecting the proper flow pattern and synthesis parameters to switch between thermodynamic and kinetic regimes [15]. This microreactor was able to produce a broad library of metal nanoparticles: nanorods (Figure 2e), nanosheets (Figure 2f and g), nanocubes (Figure 2h), monometallic and bimetallic spherical NPs (Figure 2i), core–shell nanostructures (Figure 2k), nanodendrites (Figure 2l), Janus nanostructures and nanodumbbells (Figure 2m) [15].

Single-phase microreactors have been successfully applied to the production of NPs, but they are prone to suffer from fouling that could limit their potential in production of NPs. On the other hand, two-phase flow (gas–liquid/liquid–liquid) in microreactors overcomes these shortcomings as the reaction domain can be confined into the dispersed phase slugs, inhibiting growth at the

Figure 2. Nanomaterials produced in continuous flow. Silica-based nanomaterials: (a) 20 nm SiO$_2$ NPs, from Ref. [8] with permission of 2017 Elsevier B.V.; (b) Fe$_3$O$_4$–SiO$_2$ core–shell NPs with Pt NPs decorating the surface, from Ref. [9] with permission of 2012 Royal Society of Chemistry; (c) Au–SiO$_2$ nanoshells, from Ref. [10] with permission of 2012 Royal Society of Chemistry; (d) Au–SiO$_2$ nanourchins, from Ref. [11] with permission of 2014 Royal Society of Chemistry. Anisotropic nanostructures: (e) Pd nanorods, from Ref. [12] with permission of 2015 American Institute of Chemical Engineers; (f) FeOOH nanosheets, from Ref. [13] under CC license; (g) Pd nanosheets, from Ref. [14] under CC license, (h) Pt nanocubes, from Ref. [14] under CC license. Noble metal nanostructures, from Ref. [15] under CC license: (i) Au NPs; (j) Pt decorating Pd corers; (k) Pt–Pd core–shell nanostructures; (l) PtRu nanodendrites. Galvanic replacement reaction to produce nanostructures: (m) Au–Pd nanodumbbells, from Ref. [16] under CC license; (n) Au hollow NPs, from Ref. [17] with permission of 2013 Royal Society of Chemistry; (o) CuS NPs produced by Kirkendall diffusion, from Ref. [18] under CC license; (p) magnetite NPs, from Ref. [13] under CC license

be a major inconvenience as microfluidic reactors enable the continuous multistep production of nanomaterials [17]. Finally, metal-air batteries are considered as the most promising candidate for the power source of electric vehicles because of their high specific energy [37]. Several types of nanomaterials have shown very promising catalytic activity and stability [38]: metal oxides, carbonaceous materials, metal oxide–nanocarbon hybrid materials, metal–nitrogen complexes, transition metal nitrides, conductive polymers, and precious metals. However, the practical application of metal-air batteries is still challenging because the production of some of the most active electro-catalysts is still not adapted to a large-scale production and further development in scalable production techniques are required.

2.3. MOFs, COFs, and Zeolites. The synthesis of designer microporous materials is of significance in a very large variety of industrial applications ranging from chemical catalysis to advanced separations, and there has been tremendous activity in

this area on both academic and industrial research fronts. Interest in microporous materials such as zeolites, metal-organic frameworks (MOFs), and covalent organic frameworks (COFs) stems from the inherent tunability of pore sizes in such materials at the nanometer scale, by a choice of the starting materials. Since this area has been the focus of much activity, it is nearly impossible to review synthetic advances in a comprehensive form here; instead, we focus on the general features of the synthesis methods and the application of flow chemistry in enabling the synthesis of such materials. Broadly speaking, microporous materials are synthesized by hydrothermal or solvothermal crystallization, typically in batch reactors. Taking the synthesis of MOFs as an example, an archetypal synthesis would involve mixing metal precursors (say a salt or complex) with an organic linker in a polar solvent, followed by heating in an autoclave, leading to nucleation and growth of MOF crystals over a period of hours to days [39]. Zeolites, which are

aluminosilicates, are likewise synthesized in aqueous solutions under hydrothermal conditions in autoclaves. Nearly all microfluidic methods for the synthesis of such materials can therefore be divided into two related types, which are similar to those discussed above for metals/oxides and semiconductor materials. The most commonly encountered reactor type is the single-phase laminar flow reactor, in which precursors are mixed upstream and travel through a long, heated tubular reactor under backpressure [40]. While such reactors enable fast heat transfer, they suffer from two key drawbacks: fouling on the channel walls and broad residence time distributions due to the laminar velocity profiles. These drawbacks have been overcome with the use of segmented or droplet-based reactors [41], in which the precursors in the appropriate solvents are dispersed as droplets in an immiscible carrier fluid that mitigates contact between the growing crystals and channel walls, allowing robust long-term operation [42] and tunable particle attributes. Encouragingly, recent reports have demonstrated the use of micro- and mesoscale systems for the scaled-up production of MOFs up to several kilograms per day [40a, 43].

3. Challenges in Flow Synthesis of Functional Materials and Possible Solutions

This section will highlight the most important challenges that have arisen during the formation of functional nanomaterials, as well as the possible solutions that would help face those challenges.

3.1. Scalability. Functional nanoparticles can realize their full potential only if produced in large quantities. Continuous-flow synthesis helps to achieve consistency in the product properties and overcomes most of the limitations of a batch or semi-batch synthesis of materials that is conventional. A few excellent examples from the literature and from industry showcase various scale-up approaches used for synthesis of specific functional materials. The earliest known materials that are produced in large quantities yet have sub-micrometer sizes include titanium oxide, activated carbon, mesoporous silica, liquid crystals, and carbon nanotubes. In the last decade, the number of such materials being produced in large quantities has increased almost exponentially. For example, the recent report on continuous-flow high-throughput flash synthesis of catalytic materials, viz., zeolites, binary metallic composites, etc., opens up a new class of materials being synthesized in flow [44]. The flow synthesis of nanoporous cement is one such example from an altogether new application of flow synthesis in an almost untouched segment of construction chemicals [45]. Another class of materials that find application in surface modification is the metal and metal oxide nanocomposites made by fast pyrolysis. For example, the scalability of flow synthesis of functional materials has been demonstrated for zirconia [46] and yttria stabilized zirconia (YSZ) in a flame spray pyrolysis reactor up to 600 g/h production rate [47]. In such systems, the metals in dissolved form (usually in solvents) are fed through a capillary with a piston pump and then dispersed by oxygen that facilitates pyrolysis in presence of combustible gases like methane fed through the surrounding nozzle. Such continuous units need cleaning through periodic gas-pressure shocks.

It is also possible to produce these composites in supercritical conditions. Continuous supercritical water (450 °C and 24.1 MPa) based large-scale production of Zn–Ce oxide nanomaterials is reported using confined jet mixer [48]. In such systems, the apparent solubility of one metal in the other oxide lattices decides the phase consistency. Highly efficient and almost instantaneous mixing in such continuous hydrothermal processes makes it a scalable process. One more approach is the use of diffusion flame aerosol reactors where co-flow burners can be used for local instantaneous mixing of precursors followed by entrance in a highly combustible zone for a very short period results in producing oxide nanoparticles (viz., silica, titania) [49]. Flame reactors are routinely used to manufacture more than 90% in volume and value of nanoscale commodities today. A major breakthrough in the mass production (15 kg/h and purity ~99.9%) of carbon nanotubes (CNTs) was reported over a decade ago where a fluidized bed reactor was used [50]. Very rarely are such case studies of large-scale manufacturing reported in the literature. Recent reports of kilogram-scale continuous-flow synthesis of Ag nanoparticles [51] and Pd nanoparticle [52] suspension are also seen in the literature. These trends clearly show that while flow synthesis of functional materials, viz., nanoparticles, nanowires, MoFs, CoFs, and catalysts, is demonstrated at the laboratory scale, equivalent growth in the literature on their large-scale manufacturing processes is rarely seen. One major reason is the lack of sufficient data generated from the laboratory-scale experiments which can facilitate scale-up. The general methodology of scale-up does not necessarily apply for the case of functional materials, and the approach needs very careful evaluation. This leaves behind a plethora of challenging problems relevant to reaction engineering, fluid mechanics, and process control, all of which would lead to a reliable scale-up.

3.2. Reproducibility. The classic sources like "organic synthesis" on synthesis of organic molecules emphasize that the procedures and protocols given in this source are actually reproduced by the editorial team. In the recent time, a similar aspect over a broad arena of research areas is encouraged by Nature Protocols [53]. Nevertheless, when it comes to materials chemistry and synthesis leading to specific functionality, it is hard to find such efforts useful for the community at large. Continuous-flow synthesis approach actually opens up such an opportunity to develop standard synthesis protocols. However, such an activity may remain restricted largely due to very specific functionality–property–contents relationship which creates niche market space for individual materials. Flow synthesis approach for these materials would showcase a built-in reproducibility provided a detailed analysis of relative rates of various phenomena is performed to quantify their effects on the properties of material.

3.3. Process Design Guidelines. Continuous-flow synthesis of nanoparticles and other functional materials has been explored for long, and many reviews give insights on the type of experimental set-ups that are needed for such syntheses. However, the real applicability of given functional materials can be realized only if the said material is synthesized in adequately large scale (i.e., manufacturing a material). In order to transform a flow synthesis into a process that can be used for manufacturing, a systematic approach is essential, which most of the times indeed needs starting-from-the-scratch. The reason for not being able to translate a laboratory-scale batch synthesis procedure/recipe into a working flow synthesis process is the lack of availability of the sufficient information about a few key data, which includes the following: reaction kinetics, nucleation and growth rates of particles/materials, role of additives/surfactants on the kinetics, role and sensitivity towards pH, effect of specific addition rates on the functionality of the final material (viz., mesoporosity, surface plasmon resonance, shape of particle, composition, etc.), relative rates of simultaneously occurring reactions that can give different composites or types of materials, etc. The approach will remain almost unchanged whether the synthesis is by reduction or condensation or polyol process or by fast pyrolysis. A few guidelines from the literature can be adapted to develop system specific approach [54]. The data required to scale-up any system involve physicochemical properties of all the components and thermodynamic parameters

(which can be obtained from standard data bases, viz., http://www.crct.polymtl.ca/online.html, https://srdata.nist.gov/, http://www.ddbst.com/, etc.). It is also possible to use Group Contribution Methods and also the density functional theory to estimate a few properties which may not be available in the known literature.

The scale-up of a continuous-flow synthesis approach into a practicable process goes through a sequence of systematic steps. Process means a synthesis protocol for large-scale production of the said material using an engineered plant that comprises of storage vessels (for reactants/products/solvents/additives, etc.), dosing instruments (viz., pumps/mass flow meters/screw conveyers for solids, etc.), reactors (for carrying out the reaction and they are designed specifically for a given reaction based on the information of the reaction kinetics, number of phases involved in the reaction, relative rates of different phenomena, viz., heating/cooling/reaction/phase change, etc.), separation or purification units (viz., distillation/extraction/centrifugation/filtration/drying), a process data acquisition, and control unit (that helps to maintain the desired operating conditions in every section of the plant and helps to get the product in a consistent quality). Since scale-up of functional materials is relatively more challenging than conventional organic synthesis, it is advised to have a reproducible laboratory-scale synthesis protocol to be verified using a bench-scale synthesis facility which can have a production rate greater than 10 to 20 times the laboratory scale. Once the consistency in the synthesis approach is verified in a bench-scale facility, depending upon the type of material and the quantity to be produced per day, one can go for numbering-up of bench-scale facility or putting a pilot-scale facility having production capacity greater than 10 to 50 times the bench-scale facility. It is always advised to explore the economic viability of numbering-up option first before scale-up. In certain cases, a minor scale-up by choosing larger reactor dimensions without compromising on mixing, heat transfer, mass transfer, and residence time distribution always help before

going for numbering-up. A typical scale-up approach can be seen in Figure 3.

3.4. In-line Monitoring. Miniaturized analysis and real-time detection systems have enabled to extract valuable information regarding the chemical composition, size, and shape of the nanomaterials produced in microfluidic systems [55]. Spectroscopic methods for analysis of chemical reactions permit the monitoring and thereby help direct control of nanocrystallization media on a millisecond time scale. A variety of different types of spectroscopy systems has been used with microfluidics, including ultraviolet–visible (UV–vis) absorption, Fourier transform infrared spectroscopy, fluorescence spectroscopy, and Raman spectroscopy. Fluorescence spectroscopy has been largely applied in microfluidic systems to determine physical properties of semiconductor nanomaterials [56]. However, not all the analytical techniques integrated in flow chemistry can be directly applied in the field of nanomaterial production. For instance, absorption spectroscopy for real time analysis is rarely used to track the formation of nanocrystals because the inherent limitations of microsystems: small path lengths and low analytical concentrations [55]. Some attempts have been made to overcome aforementioned limitations: (1) increasing microchannel dimension for a selected section [57], (2) coupling monolithically integrated waveguides for absorbance detection in the evanescent wave field and segmented flow operation, and (3) enhancing the inherently weak Raman signal by bringing the target molecules into the proximity of metallic nanostructures. This approach is facilitated by surface-enhanced infrared spectroscopy (SEIRA or SERS) using a combination of microfluidic devices with plasmonic structures (LocSERS) [58]. However, these attempts limit the detection to specific points of the channel and no studies on NPs kinetics can be carried out. As an alternative, a microspectroscopic monitoring system was developed for spatially-resolved UV–vis spectroscopy measurements at any point of interest along the microfluidic reactor [59]. This technique was crucial to reveal that silver nanoprisms were shaped from
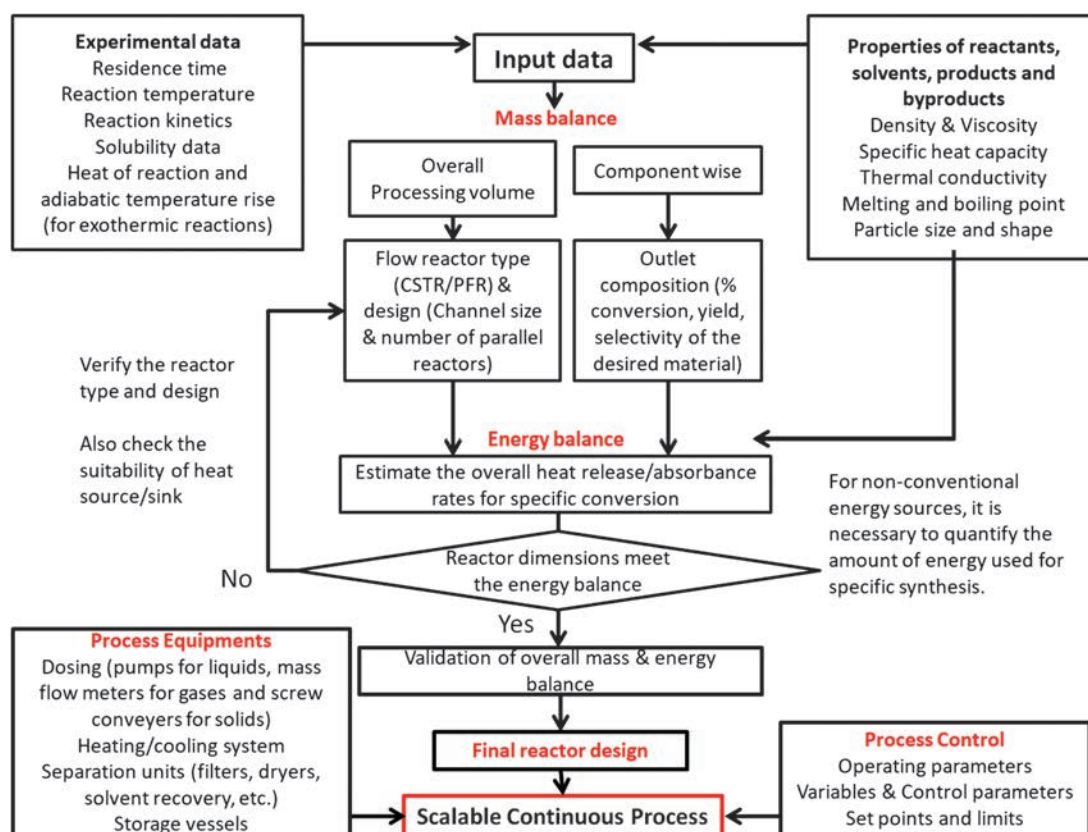
Figure 3. Schematic representation of typical input data needed for design of a continuous scalable process for functional materials

nanospheres to nanoprisms within a microchannel length of 1.5 cm [59]. On the other hand, Raman spectroscopy can provide invaluable non-invasive information on nanoparticles: the type of nanoparticles (chemical fingerprint), the colloid concentration (intensity of Raman peaks), and size of nanoparticle (Raman peak shifts and their widths) [60]. However, unwanted Raman signals can be obtained if there is a fouling process on the microchannel wall. Combination of microreactor technology with spectroscopic detection techniques allows developing a quick and reliable protocol to optimize and characterize the formation of nanomaterials. However, the development of affordable and miniaturized spectroscopic instruments for real-time detection will ease the integration in portable microsystems and fine tune the required properties of nanomaterials.

3.5. Separation, Recovery, and Purification. Microfluidics offers miniaturization of conventional nanoparticle sorting techniques, reducing the minimum sample volume, decreasing the duration, and improving the resolution of separation [61]. Microparticle separation has been widely applied and well established by using microfluidics. However, the translation from micro- to nanoscaled materials is facing difficulties with implementation because the effect of Brownian motion is more prominent as the particle size is decreased [62]. Nanoparticle separation by size is challenging because fabrication of nanosieves may require the growth of nanopores and nanoarrays or the use of specialized and expensive methods of fabrication [63].

The particle separation, recovery, and purification techniques can be classified into active and passive methods [64]. The active separation requires an external field to drive the separation [61] such as field flow fractionation, centrifugal forces, optical manipulation, magnetic field, acoustic forces, and electric fields. For instance, nanoparticles of different sizes can be separated by tuning the magnitude and frequency of the acoustic field (large particles experience a much stronger acoustic force and move more rapidly across the microchannel) [65]. Active separation techniques have a high separation performance, but they are limited by the need of being integrated in a microfluidic system, which could be challenging under a high extension. On the other hand, the passive techniques do not require the presence of an external field but only relie on the hydrodynamic and surface forces. Some types of passive separation techniques include the use of inertial microfluidics [66], filtration [67], and electrostatic sieving [68]. The selection of the proper type of separation techniques is crucial to achieve a high performance, but also nanoparticle size, pH, and selected buffers influence the breakdown of separation in the nanoregime [61].

The separation of nanoparticles using microfluidics is still limited because there are several challenges to face, viz., (1) Brownian motion of nanoparticles reduces the separation efficiency, especially in passive separators, and (2) the reported microfluidic separation techniques can be used for effective separation but it is required to have slow flow conditions that impede processing large volumes of colloids. These facts are critical impediments to translate the microfluidic separators to industrial applications. Although the numbering-up concept is also considered to increase the separation throughput [69], it is still little away from realization.

3.6. Process Control. The synthesis of reproducible nanoparticles is conditioned by important reaction parameters such as temperature, molar relation of reagents, addition of precursors, stirring ratio, and mass transfer. Most of these parameters are difficult to control when the process is performed in batch conditions [70], but they can be overcome when microfluidic systems are applied since most of these parameters can be automatically controlled by means of computer-assisted systems. Process control in microfluidic systems provides

additional advantageous features such as reproducibility and fast screening of synthesis conditions that are mostly related with the exquisite and versatile control of all stages of nanomaterials production, from reproducible injection of reagent solutions, residence time distribution, reaction conditions, and real-time nanomaterial monitoring [71]. To this end, it is necessary to integrate temperature, flow and pressure measurements, and auxiliary components such as valves, pumps, and on-line monitoring. Additionally, optimization algorithms integrate the measurements of all integrated systems to direct the synthesis of nanomaterials to the proper size, shape or chemical composition. Algorithms were successful to obtain the optimal conditions, but several issues need to be addressed to make them more appealing for production of nanomaterials by microfluidics [55]: (1) The translation of product specifications to an objective function via weighting coefficients can lead to the omission of desirable synthesis conditions. (2) The number of experiments required is high and less accurate prediction is generated for unsampled points, and (3) they can be computationally expensive in the absence of sufficient data. Consequently, further development in algorithm designs will boost the progression of microfluidic reactor technology to produce bespoke nanomaterials.

3.7. Distributed Manufacturing. For a few functional materials, the shelf life within the active period is not very long. In such cases, it is essential to develop protocols and systems that allow on-demand distributed manufacturing of these materials. Such systems will be useful for long expeditions (including into space), at critical healthcare facilities (viz., cancer treatment centers, for feeding a fresh formulation to a 3D printer that makes a precise dental implant, etc.). Such an approach is more relevant for the chemical industry that uses noble metal catalysts which need to be recovered and recycled. Also, making monoliths out of composites of ceramic and MoFs/CoFs for specific applications will also need the fabrication to be done on-site.

3.8. Shelf Life and Formulations. Little attention has been paid to the shelf life of nanoparticles, especially during their storage. For instance, colloidal stability is generally needed because physical properties of nanoparticles are size dependent, and they become even more critical in fields such as biomedicine or electronics. Usually, produced nanoparticles are spherical in shape because spheres have the smallest surface area per unit volume of any geometry, and therefore, spherical morphology provides an efficient way to minimize their surface free energy [72]. However, nanoparticles can be nanoengineered with other metastable shapes that endow them with unique physical properties. It was described that the surface plasmon peak of anisotropic gold nanoparticles with a rod shape could evolve after 50 days of storage at room temperature. This phenomenon was due to reshaping of gold nanorods towards a spherical and more stable geometry [72]. In addition, it was also observed that the instability was also occurring if the colloid was stored at low temperatures (4 °C), indicating that it was a thermodynamically driven process which cannot be easily avoided. This fact is a critical issue in the applicability of nanomaterials because a shift of the plasmon resonance peak, even if only a few nanometers, can reduce signal intensities by orders of magnitude [73]. Thiol ligands were considered to provide shape stability for months (thiol-frozen shape evolution) and address the lack of stability of shaped nanoparticles [72, 74]. However, the alternative of thiol-frozen shape evolution could not be appropriate if surface of nanomaterials should be accessible, for instance, to be refunctionalized or to run a chemical reaction (catalyst).

Spherical nanoparticles are also unstable below a size of ~5 nm and, unless thiol capped, will coarsen at room temperature [75]. Additionally, these small nanocrystals are prone to spontaneous alloying when they are dispersed with some metallic nanoparticles [75]. Consequently, stability of nanoparticles and then

shelf life is a critical issue to commercialize nanoparticles. Considering the difficulties in producing engineered nanoparticles by conventional batch-type reactors and the limited shelf life of certain types of nanoparticles, the use of on-demand technology that enables the fast and controlled production of nanomaterials is demanded. Microfluidic systems and their inherent properties for nanomaterial synthesis as well as the portability and reproducibility are envisaged as the more convenient technique to produce nanomaterials on-demand.

4. Path Forward for Flow Chemistry in Functional Materials

As is evident from the very diverse types of materials that have been explored using microfluidic–flow chemistry techniques, this relatively nascent field of exploration, lying at the boundary between chemistry and engineering, can only grow further and faster. Here, we lay out what we think are the frontiers ahead of the field.

4.1. Enabling New Science — Flow Chemistry for High-Throughput Exploration and Mapping of the Materials Synthesis "Phase Space". Most nano- and micro-scale material categories highlighted typically involve wet-chemical preparation techniques that are far from equilibrium; in other words, there is a tremendous variety of possible kinetically stable particle morphologies starting from the same materials and stoichiometries, which may or may not relax to their thermodynamically stable equilibrium morphologies within timescales of interest or application. Since the design "phase space" is inherently multi-dimensional, with coordinate axes described by the various processing parameters (concentration, temperature, mixing order and rates, heat transfer rates, interfaces, pH, additives, etc.), there is a tremendous number of possible path-dependent outcomes as far as particle attributes are concerned. It is shown here that flow chemistry techniques, coupled to appropriate online multi-scale sensing and analysis, can truly enable paradigm shifts in our ability to explore these complex, multi-dimensional parameter spaces, and indeed "discover" material architectures that would be impossible to access using conventional batch chemistry techniques. Such efforts would borrow from robust recent activity in the parallel area of flow chemistry for automated reaction optimization and molecular discovery in organic synthesis [76].

4.2. The Road to Applications — from the Laboratory to the Market. Given the considerable activity and progress in applications of flow chemistry techniques to materials synthesis, we see a very promising road ahead for their eventual commercial translation [1]. We expect the already intense proof-of-concept activities to continue branching out and subsuming new materials in their scope, such as self-energizing materials, multi-functional catalysts, organic memory devices, etc. On the translational front, we anticipate two key developments, which are complementary to each other. First, we foresee progress in the development of flow chemistry-enabled systems for on-demand synthesis and distributed manufacturing of a variety of materials for highly customized point-of-care/point-of-use applications. Potential applications lie in the biomedical and healthcare space, where tabletop systems that synthesize and dispense, on demand, drug products in the appropriate dose forms for consumption may be envisioned [77]. Crucially, such systems would enable both molecular synthesis and formulation into the appropriate delivery vehicle — the latter could be accomplished by online unit operations such as crystallization and encapsulation. A parallel area of application for point-of-use flow chemistry systems would be in the consumer products space, such as in foods and cosmetics. Secondly, scaled-up high volume production of advanced materials using flow chemistry will advance in certain materials classes, particularly for applications that involve large consumer markets with immediate existing demand and favorable economics. Here, we foresee progress in the space of advanced materials for catalysis (metallic, metal oxide nanoparticles), separations (MOFs, COFs), and optically active/responsive materials for solar cells and photonic/plasmonic metamaterials. Progress in scaled-up synthesis of such materials will face two key challenges — fouling prevention in long-term operation and increasing production scales [78].

4.3. On-Demand Synthesis of Nanopigments, Optically Active Materials, etc. In the recent time, going beyond the definition of conventional optically active materials, the new generation chemical entities that can be subjected to various illumination wavelength ranges have found many new applications in variety of forms. Some of these include biomarkers, organic light-emitting diodes (LEDs), optical brighteners, contrast enhancers [79], substances that can absorb/emit radiations from various wavelengths by reducing/enhancing the emission wavelength, conjugated polymers, etc. [80]. Many of materials/alloys and composites in nanoform have got attention due to a wide range of optoelectronic or optomechanical properties they can offer to generate long wavelength laser at room temperatures [81] or coatings or tools for developing highly polished mirrors coated with several layers of SiO_2 and TiO_2-doped Ta_2O_5 for detection of gravitational waves [82]. Reproducibility and high-throughput screening of the material are two key parameters that would ensure meeting the functional requirement of such materials. Another class of functional nanopigments that includes the organic–polymer composites for variety of applications based on their bioavailability. The first of its kind, a continuous-flow synthesis of nanoscale aqueous hydrothermal precipitation of bioavailable carotenoids as natural additives that are used for making colloidal hydrosol formulations to analyze the pigmentation of natural edible materials was reported in 1989 [83]. The approach has remained largely unchanged except that the complexity in chemical synthesis [80] and ability to target oriented formulations using techniques like "drop-on-demand" will help explore other untouched areas like limited dosage of pesticides/herbicides agricultural industry, nano-encapsulated fragrances, drug nanoparticles, etc.

4.4. Multifunctional Catalysts. Catalysts are ubiquitous in the chemical transformations. The ability of certain enzymes to change their functionality and specificity depending upon the situation and severity of conditions brings out an excellent example of multifunctional catalysts [84]. Taming metal, metal oxide, and their composite nanoparticles for such "on-demand" functionality will need high-throughput screening and rapid characterization that would enable formation of vast libraries of variety of composites in the form of nanoalloys or two or more metals, core–shell materials, in-situ grown/impregnated nanoparticles on supports, etc. [85]. Most of the multistep flow synthesis that have appeared in the recent time and for almost every synthetic drug that goes in treatment of cancer, acquired immunodeficiency syndrome (AIDS), and tuberculosis (TB), all involve catalytic reactions with different catalysts including for specific chiral functionalities [86]. This also involves work-up at the end of every reaction step. With the advent of organometallic catalysts and multifunctional catalysts either in free form or in impregnated form, the ability to carry out seamless synthesis is not a distant dream. However, this distant moment cannot be achieved without using high-throughput screening in flow or without using flow synthesis of multifunctional catalytic material to achieve stereoselective syntheses.

4.5. Flexible Organic Electronics and Organic Memory Devices. Memory devices are known to be made out of inorganic rigid semiconductors which employ high-temperature manufacturing methods. These methods are well established but

use heavy metals which upon completion of the life cycle of the said device need to undergo severe conditions for recovery. In such a situation in the recent time, an alternative of exploring the organic molecules that can be potentially alternative to the inorganic semiconductors will soon get momentum. Since functionality towards specific performance is the key to successful use of these molecules, flow synthesis would serve as a better tool to synthesize, screen, and investigate their properties (viz., reversible threshold-voltage shift, tunable conductivity, shelf life, active oxidation and reduction states, effect of electromechanical stress on functionality, etc.). The ongoing efforts of using polymeric materials may just be the beginning of this revolution, but high-throughput screening couples with flow synthesis will reduce the exploration time significantly. The possibility of dissolving the organic molecules in solvents and using them to make thin films would help to use printing technology as a viable option to expensive lithographic techniques. The ability of organic molecules to get integrated with inorganic materials can also be exploited to create a library of function specific molecules that would help make integrated organic device circuits using 2D or 3D or even 4D printing [87]. The molecular level connections through chemical bonds would also make the devices suitable for flexible surfaces [88].

With the advent of innumerable wearable systems that monitor several health related activities and even send signals of vital parameters, viz., electrocardiogram (ECG), heart bits, muscle activity, blood pressure, non-contact glucose monitoring, etc., store data and analyze it to suggest a visit to doctor, personalized medicine would take this intervention/innovation further ahead. A lot would depend on having a truly flexible electronics integrated with suitable display technology. Since the organic electronics is still at its infancy, flow synthesis approach would again pave way to print these devices on demand. Since the signal strengths may vary from infants to adults to aged population, integrating flow synthesis of formulations with 2D/3D printing to make a device of the desired sensitivity and accuracy would make the personalized wellness get actually realized. Integration of functional materials of precise performance, viz., nanowires, nanomembranes, fluorescent biomarkers/stress indicators, stretchable polymeric interfaces, etc. can all be made possible through flow synthesis [89].

4.6. Quality Testing of Functional Materials. The quality of functional materials is something that is experienced based on its performance alone. However, the performance indicators, which are closely associated either noticeable or measurable parameters usually help to check the performance of a material. Since the functional materials are prone to be used in several daily encountered appliances, it is necessary to develop a few on-site testing measures to monitor their quality. For the bulk materials, many such quality tests are available, viz., color, strength, shape/sphericity measurement, surface plasmon resonance (SPR), absorbance or emission wavelengths, performance over a large number of cycles, etc. For the functional materials that go into the consumer goods, a few quality measurement and control tests are known to be developed over the last decade or so; however, with the exponentially growing platform of these materials and the envisaged applications, it is necessary to develop new methods and identify new parameters that can help a high-throughput analysis. The approach can be realized only if the material synthesis is transformed into flow synthesis. For example, the quantum dots that go in making display devices need very precise range of size and composition to ensure that a display shows spatially uniform performance for all colours. Same goes in making electronic inks or cathodes/anodes in flexible batteries where the formulations if made in continuous mode would help achieve the desired homogeneity. The organic nanomedicines with excipients for targeted drug delivery will also need consistent

quality at the smallest length scale. These regulatory areas will evolve rapidly and will rely on the flow synthesis techniques.

4.7. Nanoparticles in Translational Research. A vast body of literature on the use of nanomaterials for therapy, imaging, drug delivery, etc. showcases the promise materials hold in having a better human life, both in terms of healthcare and wellness. Continuous-flow synthesis in these areas is still at its infancy, and considering the advantage of generating absolutely reproducible materials in terms of properties (shape, size, and composition), it is essential to have targeted efforts to synthesize libraries of nanomaterials to study their biocompatibility, suitability, interaction with metabolic system under in vitro in microenvironments that mimic the in vivo conditions, etc. [89a, 90]. The concepts like organ on chip will help to use these continuously synthesized libraries to rapidly understand the usefulness and compatibility of materials. Given the fact that this would bring the concept of serendipity back but high-throughput screening coupled with deep learning based on artificial intelligence and big data analysis techniques will accelerate the translational research. With the abundance of unexplored abilities of a large number of natural products (including marine chemicals) which can be extracted or even synthesized, the biocompatible nanoparticles can be used for targeted drug delivery, maybe beyond the blood–brain barrier that might reduce the span for very long-term treatment.

Before we summarize, we bring out a few more areas relevant to functional materials that are not yet explored using flow synthesis in functional materials. Some of these include functional glasses, flexible display devices, self-energizing and shape memory materials, encapsulating agents for variety of formulations for agrochemicals, health care, cosmetics and water treatment industry, and, finally, the materials for quantitative CO_2 sequestration. Light-weight materials that use carbon nano tubes may not be relevant for every application, and hence, new light-weight high-strength ceramics and metal-free illuminating/lighting systems can be among the next generation materials to be synthesized. This list is rather incomplete and is based on the imagination of the authors.

5. Summary

Despite significant benefits of microfluidic technology to tune and control the production of nanomaterials, this technology has yet to be widely embraced by the nanomaterials community. This is mainly due to the limited awareness of the operational simplicity and unique advantages of microfluidic technology. Microfluidic systems are one of the best examples of process intensification where it is feasible to do more with less.

The area of challenging chemistries in organic synthesis (viz., flash chemistry, picosecond synthesis, synthesis involving in situ highly reactive radicals or toxic gases) could be explored only because of the miniaturized reaction environment in flow synthesis. Analogous domains of hitherto challenging materials chemistries can be explored, where it is very likely that many new surprises lie hidden in terms of the sheer possibilities that flow synthesis opens up.

An important component of any scalable synthesis is the availability of reliable information about the reaction kinetics. For the case of functional materials, the nucleation and growth kinetics are as important as the reaction kinetics. Conventional batch methods may allow the simultaneous measurements of both with certain compromises in terms of sampling protocols, work-up, etc. Flow synthesis would offer a seamless and contactless measurement using variety of miniaturized in-line and on-line measurement techniques. Like bench top nuclear magnetic resonance (NMR), the entire community would be thrilled to use such miniaturized versions of electron microscopes and in-line scattering

measurements. Scale-up of functional materials, viz., MOFs, QDs, co-crystalline materials, catalysts, etc. would need special attention. Many new flow synthesis concepts that can handle suspensions with higher solid percentages will need to be explored. One area that has not yet been explored using flow synthesis is the synthesis of highly viscous gels. Mixing of such viscous fluids, obtaining homogeneity at microlength scales, their discharge, etc. are major challenges in conventional techniques. Flow synthesis can help to overcome these challenges, provided new concepts of scale-up are evolved.

Looking back at the last three decades of flow synthesis, significant progress has been made in terms of basic microfluidics, complex organic syntheses, controlled synthesis of many functional materials, generating formulations for the consumer goods, agrochemicals, etc. Concomitantly, due to the rapid advances in materials science in this period and the discovery of new classes of nanomaterials, the length scales over which controlled flow synthesis is required have become smaller, such that a change in the size or shape of a nanomaterial by only a few nanometers can result in significant deviation from the expected properties, rendering it unfit for the intended application. Making flow synthesis more versatile and truly plug-and-play for such systems showing unique properties would remain a challenge in the next decade and beyond.

In this review, we have deliberately excluded biological soft matter, polymeric materials, and organic nanocrystals. This would open up fresh minds and inspire them to look for new areas and newer challenges.

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