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Managing Solids in Microreactors for the Upstream Continuous Processing of Fine Chemicals

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ABSTRACT: The management of solid compounds is a major challenge facing the upstream, continuous processing of pharmaceuticals and fine chemicals. Many reactions relevant to fine chemical production either react with or form insoluble materials, which become problematic in continuous flow microreactors. The deposition, growth, or bridging of compounds can limit fluid flow from the micro- to the mesoscale, and thereby render continuous reactors inoperable. A comprehensive approach for managing solids consists of solids identification, the development of the root failure mechanism(s), and the application of active and passive techniques for the prevention and remediation. This review examines the basic principles of microreactor design for reactions that involve solids, toward the goal of performing the continuous flow processing of fine chemicals.

1. INTRODUCTION

Synthetic organic chemistry has progressed considerably through the discovery of novel routes to compounds for fine chemicals, pharmaceuticals, and natural products. A common theme in synthesis, the use or the generation of solids, has for decades been managed with traditional batch-wise techniques in the laboratory, intermediary, and the production scales. A new paradigm, however, is emerging in the upstream manufacturing of fine chemicals and pharmaceuticals—continuous processing that requires the management of particulate matter in laminar flow. Microreactors are rapidly becoming an attractive choice for the continuous processing of specialty chemicals.[1−14] The enhanced heat and mass transport characteristics inherent to small-scale laminar flow, offering competitive advantages in terms of the yield and selectivity of fast reactions, have been reported extensively.[15−55] Additional benefits of performing flow chemistry include safer synthesis of hazardous compounds, green chemistry, and the isolation of compounds sensitive to air and moisture. Often, these advantages cannot be realized due to the presence of solids.

Many transformations that find utility in specialty chemical production take advantage of solid starting materials, form insoluble byproduct, or generate products near saturation. Solids are virtually unavoidable in synthesis, from the Nobel-Prize-winning family of Suzuki cross-coupling reactions[56] to the highly versatile palladium-catalyzed amination[57,58] and many other important reactions[59−66] to name a few. Halide salts are particularly troublesome due to their low solubility in the most effective organic reaction solvents. Catalyst precursors and crystalline starting materials warrant the need for dissolution steps. Whichever the case, the approach to carrying out reactions with solids in batch is fundamentally different than in flow.

Understanding the correct strategy for dealing with solids requires a multifaceted approach. The identification of the materials chemistry combined with a thermodynamic analysis is an effective first step toward mitigating the impact. For example, early engineering decisions can be made by evaluating the nucleation and precipitation time scales relative to the residence time. Judging the impact on continuous flow reactor operation, however, must be accompanied by understanding the hydrodynamic failure mechanisms. The presence of solids can result in the flow-induced deposition, bridging, or random detachment of deposits constraining the production. Predictive models applicable to fine chemical manufacturing are in their infancy, yet have tremendous potential to keep the field flowing. Comprehensive understanding will ultimately yield engineering solutions, both active and passive, that enable the continuous synthesis involving solids.

The need to manage particulate matter remains a central problem in upstream continuous fine chemical manufacturing. In response, we highlight a few examples of reaction classes that have gained attention in the synthetic and process chemistry literature and also warrant fundamentally different engineering approaches to ensure that a continuous process remains operational. Rather than attempt to survey all the diverse reactions relevant to fine chemical manufacturing, our goals are two-fold: (i) present first principles related to solids handling in upstream continuous manufacturing, and (ii) guide the reader to possible engineering strategies from a reactor-design perspective. We conclude by discussing some industrial perspectives and the outlook including the challenges that have yet to be addressed.

2. MICROREACTOR DESIGN

There are numerous considerations that must be made when designing a continuous flow reactor system for fine chemical manufacturing. The desired production scale, the materials chemical compatibility, safety, the operating limits, the role of heat and mass transfer limitations, the resulting separation scheme, and the nature of solids involved should all be evaluated to ensure the most appropriate reactor design has been selected. A brief discussion follows before we analyze the challenges and the possible solutions to managing solids.

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2.1. Production Scale, Materials of Construction, and the Operating Conditions. Microreactors are available in a variety forms, each with different internal volumes, length scales, and materials of construction. The term “microreactor” or “microreactor technology” (MRT) is used broadly in the literature referring to continuous reactors of microliter-to-milliliter volumes and micrometers-to-millimeters in the length scales. A less common definition, a “mesoscale reactor”, is the more accurate notation for continuous reactors that exhibit characteristic length scales of millimeters and internal volumes on the order of milliliters. For consistency, we presume the same notation and thereby use the term “microreactor” interchangeably.

Choosing the appropriate reactor materials and the scale depends on the chemical reactions to be performed, the operating conditions required achieving the target selectivity and yield, and the availability of fabrication techniques. Figure 1 outlines a few different microreactors based on both the scale and the materials of construction. Metal devices (Figure 1a,b)[3,67] are able to withstand high temperatures and pressures, which are desirable because synthetic organic transformations require temperatures from cryogenic to superheated[68] and pressures in excess of 200 bar.[31,47,69] Metal tubing can also serve as a microreactor available in a number of stainless steel and Ni-alloy grades. Corrosion takes place, however, when most metals (even Hastelloy) are in contact with strong acids for long periods of time. Alternatively, ceramic microstructures (see Figure 1c) are chemically inert and stable at very high temperatures.[70] The use of fluoropolymer tubing, another alternative to overcome the surface chemistry challenge, presents the opportunity to scale up by simply increasing the tubing diameter and/or the length. Depending on the manufacturing and/or research goals, it is possible to engineer reactors with internal volumes ranging from 100 μL to 100 mL, giving production rates on the order of mg/h to g/h (i.e., residence times from 1 to 10 min).

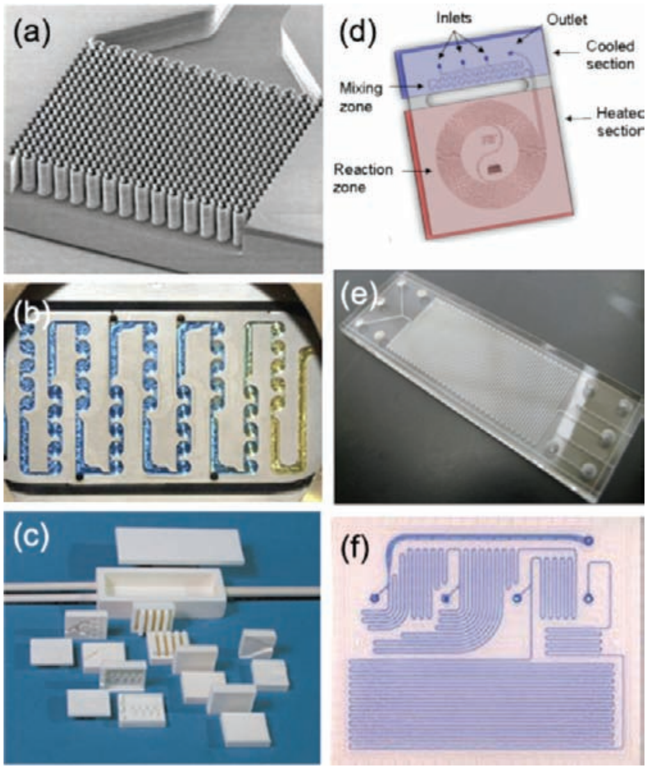


Figure 1. Microreactors are available in a variety of geometries and materials of construction. (a,b) Metal devices are fabricated from stainless steel and special alloys. (Reprinted from refs 3 and 75, copyright 2010/2011, with permission from Elsevier). (c) Ceramic devices are chemically inert and capable of withstanding high temperatures (with kind permission from Springer Science+Business Media: ref 70). (d) Devices made from silicon have high heat transfer coefficients, which simplifies the thermal management of highly endothermic and exothermic reactions. (Reprinted with permission from ref 76, copyright 2010 American Chemical Society.) (e,f) Microreactors also can be fabricated from glass (ref 67, copyright Wiley-VCH Verlag GmbH & Co. KGaA, reproduced with permission).

Silicon- and glass-based microreactors, as shown in Figure 1d−f, have the advantages of high bond strengths of the materials and transparency, which offer opportunities for the online analysis of reaction progress at high-pressure conditions. Additionally, the high heat transfer coefficient of silicon enables precise control over the reaction temperature, which may be necessary to control runaway reactions. Glass and silicon micoreactors are fabricated in volumes of microliters (Figure 1d,e)[35,71,72] to milliliters (Figure 1f).[1,8−10,49,67,73,74] Etching of the reactor surfaces by strong bases, however, is a limitation that also must be considered for either silicon- or glass-based microreactors.

The materials surface chemistry and roughness, an important consideration when there exists the potential for the accumulation of material on reactor surfaces, is amplified in continuous flow micro- and mesoscale reactors. The majority of nucleation processes are heterogeneous, and thus the high surface-to-volume ratios encountered in micro- and mesoscale reactors (2 orders of magnitude larger than that of batch reactors) lower the energy barriers and the induction times for nucleation. It is readily known that fluoropolymer surfaces exhibit nonstick properties, which could minimize the mass of the material accumulated.[29,77] In the presence of strong acids or bases, metal and glass (and silicon) reactor surfaces can undergo nanoscale etching, generating surface imperfections or local sites for deposition (or growth) and propagation. Therefore, continuous reactor fabrication techniques that generate rough-surface devices (i.e., increasing the nucleation sites) are more likely to cause accumulation problems. Particle-to-particle and particle-to-wall attraction on any surface, a phenomenon that depends on the ionic strength of the fluid media (i.e., chemistry dependent) and the relative particle and wall surface charges, creates scenarios whereby free-flowing particles are prone to deposit. Manipulation of the surface chemistry and the morphology has been shown to be effective in the engineering of surfaces that minimize accumulation; for example, superhydrophobic and superoleophobic surfaces[78−80] exposed to laminar flow limit the retention of material such as proteins.[81] Overall, the main goal to address surface accumulation problems ought to be the engineering of materials that, in the worst case, result in adhesive failure mechanisms.[82]

2.2. Reactor Integration. Engineering a stable fluidic interface between a microreactor and the upstream and downstream unit operations, and capable of tolerating high pressures and temperatures, introduces additional materials engineering challenges. Commercially available fittings and tubing (e.g., Swaglok, IDEX Corporation, etc.) made up of metal or polymers are commonly used to interconnect fluid delivery systems, and many can tolerate the high pressures (up to 1400 bar) and temperatures (to 180 °C) routinely encountered within the upstream petroleum and natural gas industry. There exist within the petroleum, natural gas, and petrochemicals industry a considerable infrastructure and knowledge base on continuous flow chemistry.

Figure 2 illustrates schematically an effective approach to the interconnecting of micro- and mesoreactor technology: compression packaging. As shown in Figure 2a,b, devices can be sandwiched between compression parts made from metal.[75,76] The rapid addition, removal, or replacement of devices from a process is a major advantage of compression-type packaging, especially when dealing with solids. Furthermore, compression parts can be designed as heat exchangers to control the reaction temperature, as can be seen in Figure 2b. The integration of multiple reactors and thermal elements in series enables the creation of continuous reactor platforms capable of performing complex synthetic pathways and rapid scale-up (see Figure 2c,d).[3,67]

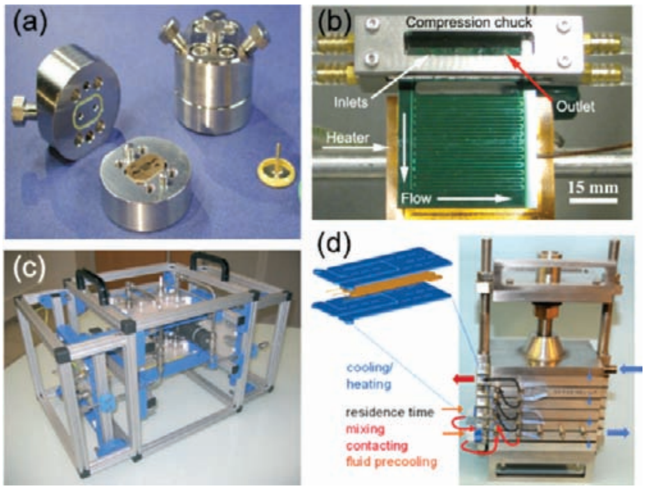


Figure 2. (a) Example of packaging a micromixer by compression. (Reprinted from ref 75, copyright 2010 with permission from Elsevier.) (b) Compression parts also can serve as heat exchangers for silicon devices (reprinted with permission from ref 76, copyright 2010, American Chemical Society). The integration of more than one reactor in series enables a continuous reactor platform; for example, (c) glass microreactors (copyright Wiley-VCH Verlag GmbH & Co. KGaA, reproduced with permission),67 and (d) metal microreactors (reprinted from ref 3, copyright 2011 with permission from Elsevier) with integrated heat exchange capabilities.

3. EXAMPLES OF REACTIONS THAT INVOLVE SOLIDS

In practice, a variety of reaction classes must be considered, each with their own unique strategies for addressing potential solids handling issues. We begin, however, by revisiting a survey of 86 different reactions (2005) performed at Lonza,[6] as shown in Figure 3. The reactions were classified by the order of magnitude of their half-lives, with Type A being the shortest (~1 s) and Type C the longest (>10 min).[6] The analysis concluded that 50% of the reactions (shaded regions of Figure 3) would have cost benefits (i.e., net positive incremental cash flow) by switching to a continuous process from batch.[6] Of the three categories, 63% involved the use of solids, and thus Roberge et al.,[6] concluded the use of microreactors to be limited primarily to homogeneous reactions with gas–liquid and liquid–liquid reactions to some extent. Although the state of microreactor technology in 2005 was insufficient for solids handling reactions, it is quite possible that unpublished attempts were made, whether successful or not, to perform the reactions in continuous flow. The analysis of Figure 3 underscores the societal need to develop solids management strategies in fine chemical manufacturing.

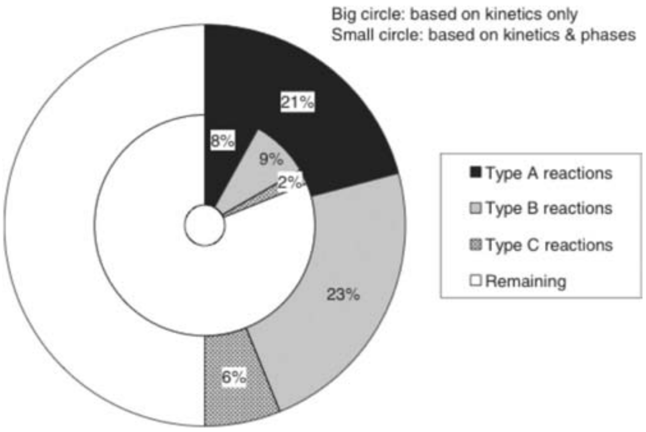


Figure 3. Summary of 86 different reactions surveyed in 2005 and performed at Lonza. The analysis concluded that 50% of the reactions (shaded regions) would benefit from a cost analysis by switching to a continuous process from batch. The reactions were categorized as Types A, B, and C according to the kinetics. Of these three categories, 63% involved the use of solids (copyright Wiley-VCH Verlag GmbH & Co. KGaA, reproduced with permission).[6]

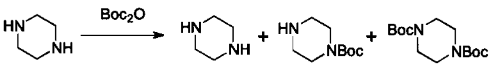
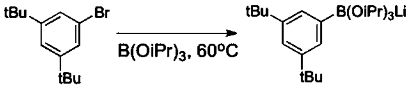
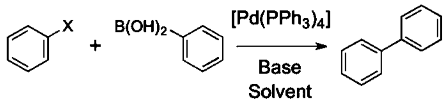
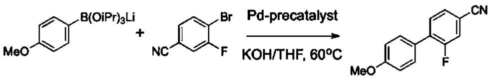
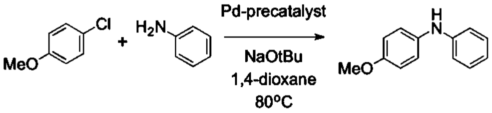
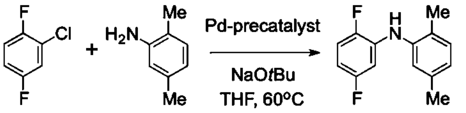
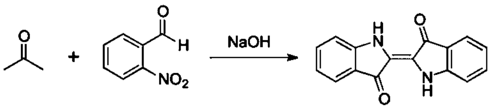
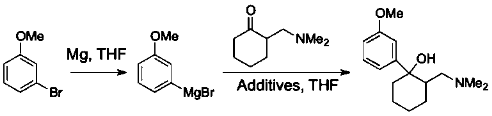
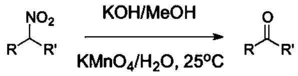
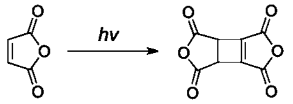
Although the nature of solids may differ from reaction to reaction, the insoluble materials typically fit into one of three categories: (1) starting materials, (2) reaction byproduct, or (3) reaction products. Table 1 outlines selected examples of synthetic organic reactions that involve the use or generation of insoluble compounds. Many of the reactions in Table 1 overlap with more than one category, demanding a more sophisticated engineering solution with a higher degree of complexity (i.e., the risk of process failure increases).

3.1. Starting Materials.

Reactants and ligands can often take the form of a solid in organic synthetic chemistry. Small-molecule aromatics (e.g., organic substrates) may be available in solution form, while higher-molecular weight compounds are available as crystalline materials. Many of the useful ligands in palladium-catalyzed reactions[36,57,61−63,83−96] are also prepared and stored as crystalline compounds. The logistical availability alone can dictate whether the materials will arrive in the form of solids or wet chemistry. In the laboratory, milligram-to-gram quantities are generally available in either form, and the addition of a solid substrate to a batch flask is trivial when the chemistry is not adversely affected by moisture or air. Otherwise, the addition can be challenging, which is especially true on intermediary and production scales. One must therefore consider the engineering of the unit operations that feed solids (e.g., extruders), both as crystalline and amorphous materials, directly to a continuous reactor or pretreatment step (e.g., dissolution) when the upstream reaction steps require such compounds.

An important consideration in any such case is the dissolution time (and/or the mixing time) relative to the reaction time scale. The rate of dissolution of a solid material in a solvent is controlled by the surface area per unit mass.[97,98] Several classes of reactions are highlighted in Table 1 that may

Table 1. Selected examples of synthetic organic reactions that involve the use or the generation of insoluble compounds

Reaction Type	Example	Possible solids	Impact on a continuous flow process[(a-g)]	Ref
Boc-protection (*e.g., the selective Boc-protection of diamines*)		Insoluble reaction products when carried out in a solvent other than MeOH.	(a-f)	50
Borylation		Lithium borate product	(a-f)	86
C-C bond formation (*e.g., Suzuki, Suzuki-Miyaura couplings*)		Halide salt by-product, starting materials (e.g., ligand), and catalyst (e.g., Pd-black)	(a, c-e)	56
		Starting materials (e.g., lithium borate and ligand), and catalyst (e.g., Pd-black)	(a, c, d, and g)	86
C-N bond formation (*e.g., Pd-catalyzed amination, adol condensation*)		Halide salt by-product, starting materials (e.g., base [NaO*t*Bu] and ligand), catalyst (e.g., Pd-black)	(a-g)	76
		Halide salt by-product, starting materials (e.g., base [NaO*t*Bu] and ligand), catalyst (e.g., Pd-black)	(a-g)	107
		Indigo reaction product	(a-f)	123
Organometallic (*e.g., Grignard reactions*)		Starting materials (e.g., Mg shavings) and metal salt by-products	(a, b, d-f)	14
Oxidation (*e.g., Nef oxidation*)		Manganese dioxide by-product	(a, d-f)	66
Polymerizations (*e.g., photo-dimerization*)		Polymer product	(a, b, d-f)	124

[a]Deposition or growth on process equipment surfaces. [b]Loss of valuable product due to accumulation. [c]Loss of valuable Pd-catalyst via the precipitation of Pd-black. [d]Fouling that influences the performance of online analytics. [e]Pressure losses that result in a reduction in pumping efficiency or, worse, plugging. [f]Considerable deposition or growth that reduces the heat transfer coefficient—a reduction in heat exchanger/reactor temperature control efficiency. [g]May require extra pretreatment steps to introduce solids into the process.

require the dissolution or the handling of solid starting compounds in continuous manufacturing. Palladium-catalyzed C−C and C−N bond-forming reactions are widely used to prepare pharmaceuticals and fine chemicals. The Heck reaction,[61−63,87,89,91,99] Pd-catalyzed amination,[57,58,65,100−111] Sonogashira,[36,60,92,95,112−114] Suzuki,[56,95,115−118] and Suzuki−Miyaura[56,60,85,86] couplings all routinely use bases and ligands that are available as crystalline starting materials. Grignard-type reactions,[14,59,119,120] an important family of synthetic transformations (see Table 1), require the use of a solid magnesium source. Adjusting the particle size distribution, the shape factor, or the surface roughness of such starting materials and before the addition to a pretreatment step (or a reactor itself) can influence the outcome of the reaction when mass transport limitations exist.[97,98] Mixing, another critical aspect when dealing with solids, must also be considered and depends on the type of the reactor or conditioning vessel that will be used. For example, mixing is fundamentally different from a batch vessel to a continuous-stirred tank and a tubular reactor. We have recently outlined a discussion on the importance of mixing time scales relative to the reaction time scale for laboratory-scale reactors.[23]

As a general rule, the larger the number of aromatic rings within an organic compound, the more likely it will either arrive as a solid material or undergo recrystallization during the upstream reaction steps. That is, the engineering goal should be to operate at the highest concentration possible to reduce the equipment capital costs while maximizing the production rate, but the trade-off is the potential for recrystallization on localized surfaces.

3.2. Reaction Byproduct. Insoluble reaction byproduct can undergo nucleation or deposition on pump surfaces, transfer tubing, analytics, reactor walls, heat exchanger surfaces, and within the separation steps of a continuous fine chemical process. Any surface exposed to wet chemistry that forms insoluble reaction byproduct has the risk of fouling. For example, the generation of halide salts are routine in reactions such as the Grignard reaction, Pd-catalyzed amination, and Suzuki−Miyaura and Suzuki couplings (see Table 1). Sonogashira coupling and the Heck reaction generate salt byproduct as well. Salt byproduct exhibit low solubility in the organic solvents routinely used to carry out the above-mentioned reactions. Other examples include the Si-based byproduct of the Hiyama reaction[121] and MnO_2 formed in the Nef oxidation[66] of Table 1. The precipitation of Si-based products is particularly challenging in the petroleum and natural gas industry because it severely limits the production.[122] Similarly, we anticipate the precipitation of inorganic compounds in the continuous processing of specialty chemicals to demand considerable attention. Assessing the risk of and management strategies for byproduct precipitation will aid in the successful engineering of a continuous flow reactor or process.

Many of the reactions of Table 1 take advantage of palladium precatalyst (e.g., using biaryl phosphane ligands) or another form such as palladium acetate. Upon completion of the catalytic cycle, palladium can undergo oxidation and precipitation to form palladium black. The formation of palladium black can be viewed as a byproduct that also creates the need to manage colloidal materials in continuous flow.

3.3. Reaction Products. Reaction products themselves undergo crystallization when the chemistry is performed near supersaturation and thus create the potential for downstream solids handling problems. For example, the selective Boc-protection of diamines (see Table 1) was carried out in a continuous microreactor.[50] Using any solvent other than MeOH or performing the reaction at reduced temperatures resulted in the precipitation of the product.[50] Similarly, the lithium borate product generated during the borylation of an aryl halide was insoluble in the reaction solvent.[86] The synthesis of indigo[123] and the photodimerization of maleic anhydride,[124] two other transformations relevant to fine chemicals, also generated insoluble reaction products.

An important challenge is the choice of the reaction solvent for synthetic organic transformations. In many cases, the fastest reaction rates, requiring the shortest residence times and the least capital cost, are performed in nonpolar or polar aprotic solvents and under concentrations that approach saturation. Simply choosing a different solvent (e.g., a polar protic solvent) is not always an option because it can adversely affect the complex and elegant, yet efficient, catalysis involved in a number of synthetic reactions.

4. COMBINED REACTION AND TRANSPORT CONSIDERATIONS

4.1. Influence of Solids on the Mass Balance. Understanding how to manage solids during continuous fine chemical synthesis starts by considering the influence on the mass balance. If Reynolds number (Re) < 2100, then the flow is laminar in a cylindrical pipe, an approximation that generally holds for continuous flow reactors of micrometer-to-millimeter cross-sectional diameters (and residence times of 1−10 min) for both single- and multiphase flow. Let us also consider as an example a palladium-catalyzed reaction that generates 1 M of product (e.g., 1 M of insoluble salt byproduct),[84] which gives less than 3 vol % solids generated in flow. The deposition, growth, or plugging of a continuous flow reactor by the generated solids implies that the normal operation is unsteady state, and thus there exists a nonzero and time-dependent accumulation term in the overall mass balance. Understanding the accurate time dependence of such a term requires the formulation of constriction and bridging models,[125−134] which have yet to be extensively developed in fine chemical manufacturing. Simplified constriction models can be formulated on the basis of assumptions that the decrease in the cross-sectional radius is localized to regions of high reactant or particle concentrations, and it takes place at a constant rate;[76] both are accurate assumptions when the reactant concentrations and the surface-to-volume ratio are large (i.e., microscale reactors). Monitoring the accumulation is therefore possible through the direct measurement of the pressure losses.[76] The most accurate approach upon scaling up, however, is the development of models from first principles that take into consideration the axial and radial concentration gradients, whereby the cross-sectional radius changes with time and the axial position. Related models have been developed for the deposition of waxy paraffin in subsea petroleum and natural gas pipelines; a flow assurance problem.[125,135]

Pressure losses may also arise when the volume fraction of suspended particles is sufficiently high (e.g. > 10 vol%), resulting in frequent particle-to-particle and particle-to-wall collisions. The overall influence is an increase in the effective viscosity, which in turn influences the convective flux terms of the mass balance equation (i.e., the superficial velocity is influenced). Both Newtonian and non-Newtonian fluid flow behavior are possible, depending on the solids fraction, and thus one might consider the experimental development of correlations that describe the effective viscosity when convective pressure losses are observed.

Nonideal flow reactors generally involve dispersion that introduces mixing limitations. However, particle-to-particle and particle-to-wall interactions that depend on Stokes number, as we will later see, have the potential to enhance the mixing. Thus, the diffusive flux terms of the mass balance can be influenced by the flow of particle suspensions. When the mixing time scale of a homogeneous reactor is on the order of the reaction time scale (i.e. a mixing limited reaction),[23] the addition of particles could actually reduce the mixing time, a potential advantage in continuous processing. A similar result has been observed when immiscible liquid−liquid or gas−liquid flow is established.[136,137]

4.2. Influence of Solids on the Energy Balance.

The flow or accumulation of solids can also impact the heat transport of continuous flow reactors and process equipment. Similar to our mass balance analogy, unsteady-state operation brought about by material accumulation can influence the reactor temperature as a function of time. Furthermore, heat transport in and out of a continuous flow reactor can occur via conduction or convection. Material deposits change the effective thermal conductivity of the reactor walls and therefore directly influence the conductive flux terms in the overall energy balance; hence, the heat added or removed could be compromised.

Our discussion of the generalized transport equations has been primarily independent of the scale because the mass and energy balances are fundamentally independent of the scale. That is, the scale influences which terms (e.g., convective, diffusive, or conductive) control the heat and mass transport contributions. Conduction generally dominates over convective heat transfer in microscale flows, whereas convective heat transfer becomes critically important upon scaling up to mesoscale reactors and beyond. Moreover, diffusive fluxes influence the mass balance equation in microscale flow. Solving the mass and energy balances in production scenarios, a system of partial differential equations, requires a numerical approach, as many industrial reactors are nonideal.

Another important consideration, liquid−liquid or gas−liquid multiphase flow, raises additional design considerations. If the immiscible phases move through the reactor at the same flow rate, then separate mass and energy balances can be performed independently of one another to fully describe the axial and radial temperature and concentration gradients. For example, stable liquid−liquid or gas−liquid segmented flows fall into this category.[38,136,138] When the reaction products or byproduct partition into one phase from the other, then it is necessary to apply a dispersion model that accounts for the corresponding boundary conditions.[138,139] The need for extensive modeling can be minimized through the creation of droplets in which solids remain dispersed within a continuous phase.[51,123,140−145] Scaling up from the micro- to the mesoscale introduces challenges towards this end, as unstable multiphase flow profiles periodically expose reactor and equipment surfaces that experience infinite residence times to a dispersed phase. Overall, there remains tremendous opportunities to develop first principle accumulation models for continuous fine chemical manufacturing that influence the mass and energy balances of reactors, separation schemes, and other unit operations. A more extensive discussion of how to predict reactor performance by developing combined transport and reaction models can be found in a number of textbooks[146−148] and recent articles.[3,4,10,23]

5. INORGANIC SCALE NUCLEATION PRINCIPLES

As we have discussed, synthetic transformations that find utility in fine chemical production commonly involve the formation of byproduct. Inorganic salt byproduct are of special interest for two important reasons: (1) the palladium-catalyzed C−C and C−N bond-forming reactions that are widely used in synthetic routes involve the formation of halide salt byproduct, and (2) halide salts are often insoluble in the organic solvents routinely used to carry out the intermediary reaction steps. We anticipate the precipitation of halide salts to be fast in most organic solvents, which fosters a need to understand the crystal growth rates in relationship to the complex catalytic cycles of the C−C and C−N bond-forming reactions. As an alternative, the chemistry may be carried out in the presence of an aqueous phase.[60,92,94,102,106,149] Thus, we examine the equilibrium of a salt of the form M_mX_x in water, a fundamental example of thermodynamic saturation, to demonstrate a general understanding of salt precipitation mechanisms and its role on the continuous manufacturing of fine chemicals. The equilibrium reaction of M_mX_x in water is expressed by

$$M_mX_x(s) \leftrightarrow mM^{z+}(aq) + xX^{z-}(aq) \tag{1}$$

where dissociated M^{z+} and X^{z-} ions are in equilibrium with the crystalline form, m is the number of the cations, x the number of the anions, z^+ the charge on the cation, and $z-$ the charge on the anion. When there are an adequate number of M^{z+} and X^{z-} ions to exceed the solubility limit, generally the case in a reaction performed in organic solvent, the reverse reaction is favored. These ion pairs could be generated, for example, as a byproduct of palladium-catalyzed C−N bond-forming reactions, which are routinely performed in nonpolar and polar aprotic solvents (e.g., toluene, tetrahydrofuran, dimethylformamide, etc.). In an ideal solution, the equilibrium exists under dilute conditions and the solubility product, K_{sp}, is defined as

$$K_{sp} = [M^{z+}]^m[X^{z-}]^x \tag{2}$$

where $[M^{z+}]$ is the cation concentration and $[X^{z-}]$ the anion concentration. A state of supersaturation is possible when activity above the solubility product exists for a period of time in the bulk fluid or at a heterogeneous surface. The supersaturation ratio, SR, or the activity exceeding the solubility product, is written as[150]

$$SR = \bar{\gamma}\sqrt{\frac{[M^{z+}]^m[X^{z-}]^x}{K_{sp}}} \tag{3}$$

When supersaturation exists (i.e., $SR > 1$), precipitation can be expected, and the rate of precipitation is a function of the induction time, t_{ind}: the time after achieving a supersaturated condition and before the appearance of the first detectable nucleus. For reaction solvents in which the salt solubility is moderate-to-high (e.g., polar protic solvents) or under dilute reaction conditions, the time necessary to form the first nucleus, J, is much greater than the time for the same nucleus to continue growing to a detectable size. The induction time in this scenario yields the following relationship for the primary nucleation rate,[151]

$$J = \frac{1}{t_{ind}} = A\exp\left[-\phi\beta\frac{\gamma^3\nu^2}{(k_BT)^3(\ln(SR))^2}\right] \tag{4}$$

where A is the frequency factor, ϕ is the energy barrier factor ($\phi = 1$ for homogeneous nucleation and $\phi < 1$ for heterogeneous nucleation), β is the shape factor, γ is the crystal surface energy, ν is the molecular volume of the crystalline phase, k_B is the Boltzmann constant, and T is the absolute temperature. As shown schematically in Figure 4, homogeneous and heterogeneous nucleation are two fundamentally different mechanisms. In homogeneous nucleation, supersaturated molecules are in equilibrium with ion pairs that form atom clusters, or small seed crystals that serve as nuclei. The subsequent growth of nuclei give rise to crystal formation and even further growth, which takes place at imperfections on the crystal's surface. In heterogeneous nucleation, supersaturated molecules again are in equilibrium with ion pairs.

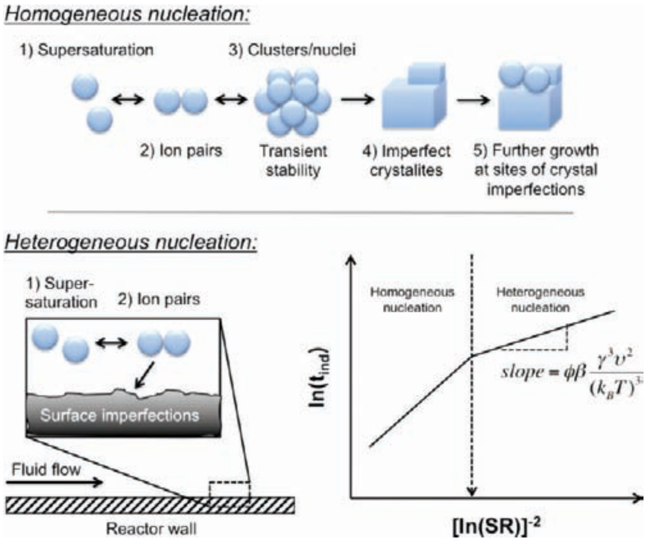


Figure 4. Overview of homogeneous and heterogeneous nucleation theory. The cartoon illustrates the formation of nuclei from supersaturated ion pairs that eventually yield crystal growth. Similarly, heterogeneous nucleation takes place at surface imperfections, which are likely throughout a continuous fine chemical process. Homogeneous and heterogeneous can be differentiated by plotting the $\ln(t_{ind})$ as a function of the $[\ln(SR)]^{-2}$. A change in the slope implies the transition from homogeneous to heterogeneous.[151]

Surface defects on a reactor wall or catalyst surface, for example, lower the surface free energy and promote the attachment followed by the growth of crystals, and hence one must consider the surface chemistry as a mitigation strategy. Equation 4 can be applied to correlate the induction time relative to the supersaturation ratio, and graphically elucidate whether or not nucleation is homogeneous or heterogeneous (see Figure 4).[151,152] It should be noted that the dominant nucleation mechanism in industrial continuous flow reactors is typically heterogeneous. A deeper understanding of the classical nucleation theory[153] and additional models derived from it have been reported previously for inorganic and organic crystallization.[152,154−159]

In continuous fine chemical manufacturing, a quantity of fundamental importance is the ratio of the induction time relative to the time necessary for a crystal nucleus to flow from the entrance to the exit of a reactor (i.e., the residence time τ), α, which can be expressed as

$$\alpha = \frac{t_{\text{ind}}}{\tau} \tag{5}$$

One must consider the potential for salt byproduct to be problematic when $\alpha < 1$ as crystals are expected to form within the bulk flow. When $\alpha > 1$, bulk crystal formation is not expected, but it does not necessarily imply that salt byproduct formation will be mitigated. For example, the equipment walls themselves would be exposed to infinite residence time, and thus the potential for the deposition (or nucleation) of crystals followed by growth is possible. Strategies must be developed in this case to periodically remove the buildup.

Another possible scenario is a highly concentrated reaction system (e.g., 1 M in substrate), desirable in fine chemical manufacturing, or the use of nonpolar and polar aprotic solvents exhibiting low inorganic salt solubility. Here, the induction time could again be small relative to the residence time, and thus $\alpha < 1$. Defining the crystal growth rate, r_g, becomes useful under this operating regime, which can be expressed in a general form for surface reaction controlled and mass transfer controlled (i.e., diffusion limited) growth,[98,150]

$$r_{\text{g}} = \frac{\text{d}D}{\text{d}t} = \frac{2k}{\rho_{\text{c}}}\sqrt{K_{\text{sp}}}\,(SR - 1)D^{\delta} \tag{6}$$

where D is the particle size, t is the time, and ρ_c the molar density of the crystalline phase. Here, k and δ are parameters that depend on whether the growth rate is controlled by the surface crystallization rate or a mass transfer rate. When crystal growth is surface-rate limited, k is equivalent to the specific reaction rate, k_g, and $\delta = 0$.[98] When diffusion controls the crystal growth, $k = ShD$ where Sh is the Sherwood number, D the diffusivity, and $\delta = -1$.[98] A population of discrete particle sizes would grow in reality, and therefore a population balance model (a nonlinear partial differential equation) coupled to eq 7 represents a more accurate prediction of the growth phenomena.[98,150] Evaluations, as we will soon learn, should be based on the largest particle sizes. Estimation of the crystal growth rate of the largest particle sizes using, for example, eq 7 is a critical step in understanding the crystal growth time scale relative to the residence time (i.e., the ratio of the growth rate to the particle convective transport rate through the reactor and in the axial direction), expressed as

$$\eta = \frac{r_{\text{g}}\tau}{L} \tag{7}$$

where L is the reactor length. When $\eta > 1$, there exists the potential for blockages that plug continuous flow reactor systems. The risk is mitigated when $\eta < 1$ as large crystals are either removed from the reactor (or process) before they have time to aggregate or undergo hydrodynamic bridging (in laminar flow). The challenge is not eliminated altogether when $\eta < 1$ because downstream transfer tubing and other unit operations will likely intercept the insoluble material.

The impact of solids on a fine chemical process can be severe, including shutdown time. A complete thermodynamic model for each reaction component and solvent mixture is therefore needed to accurately predict the phase behavior of the complex chemistry used in fine chemical manufacturing. Such predictions are made possible using thermodynamic simulators with known molecular interaction parameters and activity coefficients. If the interaction parameters are unknown, quite possible for the discovery of novel synthetic methodologies, then it is necessary to experimentally evaluate the equilibrium conditions. Multiphase microreactors represent excellent tools for accomplishing this goal because the phase equilibrium can be rapidly screened for a variety of thermodynamic conditions.[24,38,138,160−168]

6. HYDRODYNAMIC FAILURE MECHANISMS

The issue of solids handling in continuous reactor systems has gained considerable attention in recent years as the evolution from traditional batch processing to continuous flow continues to impact the fine chemicals industry. There are certain classes of reactions, susceptible to generating solids that one must consider when designing a continuous flow process. The reactions and products themselves, however, are only part of a much bigger challenge that should be overcome to successfully engineer the continuous production of fine chemicals. Three hydrodynamic mechanisms can lead to plugging in laminar flow: (1) constriction,[126−129,131−134] (2) bridging,[76,130,134,169,170] and (3) the random detachment of deposits.[82] Herein, we discuss each of the three mechanisms from the perspective of flow and reaction within a continuous flow microreactor, while keeping in mind that laminar flow through a packed bed also presents the analogous set of challenges.

6.1. Deposition, Constriction, and Internal Plugging.

Insoluble byproduct may nucleate (1) on equipment surfaces, (2) in the bulk fluid and undergo deposition,[126−129,131−134] or (3) a combination of both leading to the constriction of flow paths within a continuous process. For example, the NaCl formed during the Pd-catalyzed amination of Table 1 was found to reduce the cross-sectional diameter, even in a fluoropolymer capillary (see Figure 5a).[76,107,150] For scenarios (2) and (3), internal plugging is possible when the flow-induced deposition of particles onto a process' surfaces occurs. As an example, we consider the deposition of stable colloidal particles near a flow constriction, as shown in Figure 5b,c.[130] The inertial impaction of a stable particle onto a surface can lead to deposition. The Stokes number, *St*, a quantity useful in characterizing the risk of internal plugging via inertial impaction, is the ratio of the viscous to the inertial forces acting on a flowing particle. In other words, Stokes number is the characteristic time spent by a particle near the wall to the time required for the particle to be transported to the wall's surface, which yields the following

$$St = \frac{2}{9}\left(\frac{W}{D}\right)^2 \frac{\rho_p}{\rho_s} Re \qquad (8)$$

where ρ_p and ρ_s are the particle and the solvent densities, respectively. For $St < 1$, the convective forces acting on a stable particle (i.e., no attraction) in a microreactor are likely to prevent the particle itself from undergoing inertial impaction. For $St > 1$, inertial impaction is simply a matter of time. We point out, however, that attraction and repulsion can influence a particle's velocity near a microreactor's wall. Thus, the accurate prediction of a discrete particle's trajectory, and in the presence of a system of particles, must include the analysis of the interaction energies. For colloidal particles, both van der Waals attraction and electrostatic repulsion models have previously been developed.[129]

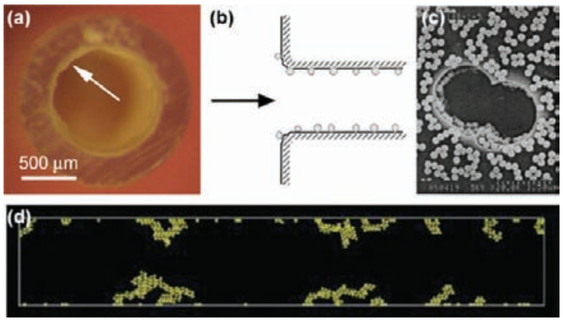


Figure 5. Examples of particle deposition and growth on surfaces exposed to laminar flow. (a) The generation of NaCl byproduct formed during palladium-catalyzed amination can lead to constriction (Reprinted with permission from ref 76, copyright 2010, American Chemical Society). (b,c) The flow-induced deposition of stable, colloidal particles near a constriction (copyright 1999, Cambridge University Press. Reprinted with the permission of Cambridge University Press).[130] (d) Dendrite formation or the retention of flowing particles on previously deposited particles, simulated for asphaltene deposition on microchannel walls (reprinted with permission from ref 171, copyright 2008, American Chemical Society).

Multilayer layer deposition eventually constricts the flow path via dendrite formation. Dendrite formation, or the retention of flowing particles on previously deposited particles, is illustrated in Figure 5d for asphaltene deposition on microchannel surfaces.[171] The plugging by a gradual constriction of the flow path is possible in any of the aforementioned scenarios, especially during the continuous manufacturing of fine chemicals. Identifying a potential constriction problem in a continuous reactor is made possible through the monitoring of the pressure losses (e.g., the pressure drop from the inlet to the outlet of a reactor, ΔP). When the pressure drop changes with respect to the residence time (i.e., $d\Delta P/d\tau \neq$ constant), there exists the potential for the process shutdown and the remediation of accumulated material. Overall, there remain numerous opportunities for the development of such models as synthetic methodologies often utilize different reaction components with varying thermodynamic and kinetic parameters.

6.2. Hydrodynamic Bridging.

Particles traveling along streamlines in laminar flow have the potential to contact one another when (1) the flow path cross-section is reduced or (2) particle growth occurs. The potential is a serious consideration that must be made when designing reduced length scale flow reactors or the flow and reaction through a packed bed. The bridging of particles across the flow path (i.e., hydrodynamic bridging)[76,130,134,170,172] takes place by the simultaneous arrival of stable particles whose sizes are smaller than the cross-section, as illustrated in Figure 6a,b for stable colloidal particles (0.25 µm latex spheres) entering a pore throat.[130] At a sufficiently high flow velocity, hydrodynamic forces can overcome particle-to-particle and particle-to-surface repulsion, resulting in the

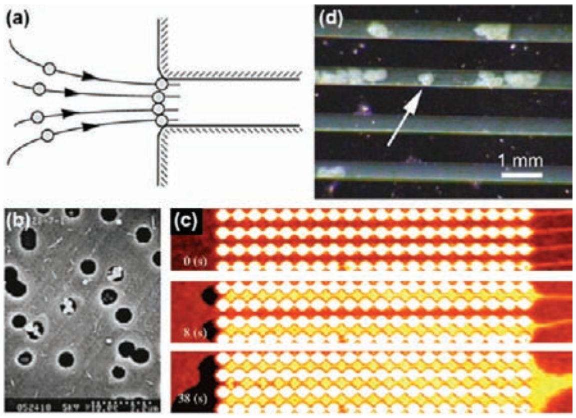


Figure 6. Mechanisms that result in the blockage of laminar flow paths. (a,b) Type I hydrodynamic bridging—the bridging of stable colloids by the simultaneous arrival of particles at a constriction point (copyright 1999, Cambridge University Press. Reprinted with the permission of Cambridge University Press).[130] (c) The rapid (e.g., 38 s) hydrodynamic bridging of latex microspheres (shaded red) within parallel microfluidic channels, constraining fluid flow as shown by the absence of any microspheres (shaded yellow) (Figure 6c reprinted with permission from ref 173 as follows: Wyss et al. *Mechanism for Microchannel Clogging*, 2006; Vol. 74, pp 061402−2, copyright 2006 by The American Physical Society). (d) Type II hydrodynamic bridging—the reactive bridging of NaCl crystals generated from palladium-catalyzed transformations (reprinted with permission from ref 76, copyright 2010, American Chemical Society).

formation of a stable bridge across the flow path entrance.[130] The flow is thus constrained, and pressure losses occur. For example, fluid flow through a microfluidic device has been characterized by the design of constriction and expansion microchannels (see Figure 6c).[173] Here, latex microspheres (shaded red) bridge during the flow through parallel channels and within seconds (e.g., 38 s), constraining fluid flow and shown by the absence of any microspheres (shaded yellow). Type I bridging in laminar flow reactors can be expected at unions, reducers, or virtually any other change in the cross-sectional geometry. Type II bridging has been shown to occur during the formation of NaCl in microchannels, generated from palladium-catalyzed aminations, as seen in Figure 6d.[76,150] In either Type I or II, blockages are expected for aspect ratios (i.e., the ratio of the flow path length scale to the particle size, W/D) of less than 3−4, or 33% of the flow path cross-sectional dimension.[130] The general rule, however, only considers particle-to-particle or particle-to-wall repulsion. In practice, aspect ratios that do not result in hydrodynamic bridging are greater than 10 because attraction is common in fine chemical mixtures.[76] Hydrodynamic bridging can cause severe, unexpected plugging of continuous flow paths. Consequently, estimation of the aspect ratio for a laminar flow reactor is critically necessary to avoid a possible shutdown scenario.

The velocity of fluid flow (in the axial direction) is an important consideration when the aspect ratio is favorable for hydrodynamic bridging. For microreactor internal volumes from 100 μL to 100 mL and τ = 1 to 10 min, the average velocity (U_{avg}) can range from $0 < U_{\text{avg}} < 10$ cm/s. Ramachandran, et al.[130] showed that increasing the velocity from 0.012 to 0.6 cm/s results in an increase in the normalized pressure drop across the porous membrane of Figure 6b.[130] The observation implies that a critical velocity, U_{Crtl}, exists to overcome interparticle repulsion, and thus induce the retention of stable particles by hydrodynamic bridging.[130] It is also true that at higher particle concentrations, a greater number of particles arrive simultaneously at a constriction, which increases the probability of a bridging event by particle arrangement in the required spatial locations. A force balance in this regime also gives relationships, from first principles, that describe bridging when interparticle and particle-to-wall attraction and repulsion exists.[130] When the velocity is on the order of 1 cm/s, above the critical velocity in this example, bridging is a statistical phenomenon as illustrated in Figure 7 for the device shown in Figure 6c.[173] The average number of particles that pass through a constriction point before clogging, N^*, increases by a W^3/D^4 dependence for W/D values from 2 to 10 (see Figure 7), and expressed as

$$N^* \cong \frac{1}{2}\sum_{n=0}^{N}\frac{(WH - nD^2)^2}{\theta^2 D^2 H^2} \cong \frac{W^3 H}{6\theta^2 D^4} \tag{9}$$

where $\theta = \varepsilon/D$ is the ratio of the particle sticking distance from the wall (ε) to the particle diameter, n the number of sticking events, and H the microchannel height.[173] Plotting $N^*D^4/(W^3H)$ as a function of the ratio of W/D confirmed the statistical relationship, shown by the dashed line in Figure 7.[173] The ionic strength, also an important parameter in the prediction of bridging, influences the critical velocity and the average number of particles by influencing attraction and repulsion forces as well as the particle sticking distance. The aspect ratio, the particle concentration, ionic strength, and interparticle attraction and repulsion must all be considered to accurately predict hydrodynamic bridging. A more detailed explanation of these influences, including predictive models, can be found in previous literature.[130,134,169,170,172] As we have seen, hydrodynamic blockages can arise from the contact of particles, but the formation of an unstable film by way of deposition (or growth) introduces the potential for detachment within a continuous reactor.

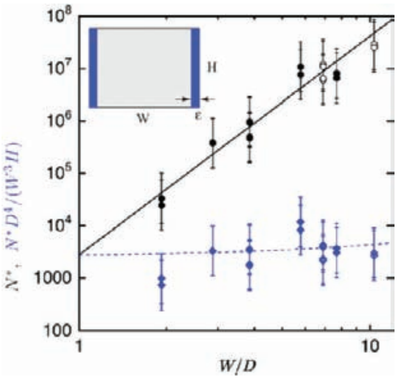


Figure 7. At high enough velocities (e.g., $U_{\text{avg}} \approx 1$ cm/s), the average number of particles that pass through a fabricated microchannel pore before clogging, N^*, increases by a W^3/D^4 dependence for W/D values from 2 to 10. Plotting $N^*D^4/(W^3H)$ as a function of the ratio of W/D validates the statistical relationship of eq 9. (Figure 7 reprinted with permission from ref 173 as follows: Wyss et al. *Mechanism for Microchannel Clogging*, 2006; Vol. 74, pp 061402−4033. Copyright 2006 by The American Physical Society).

6.3. Random Detachment by Adhesive or Cohesive Failure. The formation of compounds on microreactor surfaces creates the potential for the random detachment, or breaking, of the material in the presence of shear stress. If the material becomes mobile, then there exists the opportunity for it to undergo bridging downstream within a reactor, transfer tubing, or other unit operations. The inherent random nature of such breaking makes it virtually impossible to forecast with a predictive model. Instead, understanding the detachment mechanism can yield insight on how to manage it. A wall deposit, either amorphous or crystalline, can fail under shear stress by i) adhesive, or ii) cohesive failure.[82,174] Adhesive failure is defined as the detachment of the material at the deposit-wall interface. Surface chemistry modification, manipulation of the roughness, and externally applied forces (e.g., acoustics) are strategies that limit the formation of any deposits that in turn undergo adhesive failure. Cohesive failure, however, is the breakage of the deposit within its own amorphous or crystalline network. Correlating the deposit thickness to a cohesive failure event is an important step in understanding how to manage it. Laboratory experiments that examine cohesive and adhesive failure are made possible using a parallel plate apparatus, which has been demonstrated for paraffin deposition on metal surfaces.[82,174] In fine chemical synthesis, salt byproduct present the opportunity for deposition and/or growth. One must therefore consider the potential for nucleation and growth in addition to the deposition of particles from the bulk fluid.

7. ACTIVE AND PASSIVE TECHNIQUES FOR SOLIDS MANAGEMENT

Strategies for managing solids in continuous fine chemical manufacturing fit into two categories: (1) active and (2) passive approaches. Active techniques are those requiring the

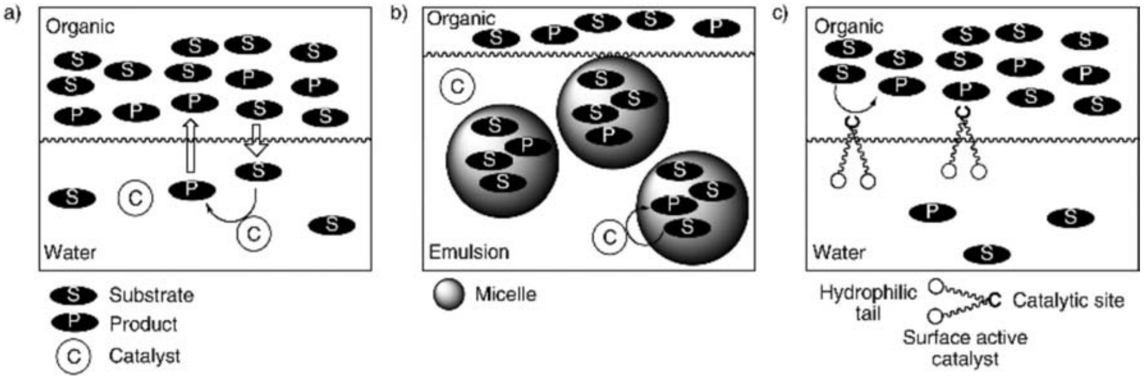


Figure 8. Aqueous-based transition metal-catalyzed reactions can take place (a) in the bulk water, (b) in a surfactant supported micelle, or (c) at the interface of the immiscible aqueous−organic phases (reprinted with permission from ref 149, copyright 2009, American Chemical Society).

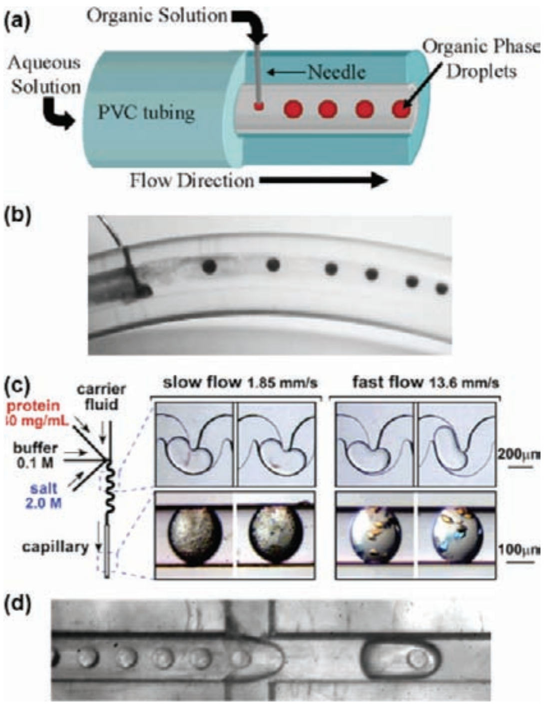


Figure 9. One approach to prevent clogging in microreactors is to perform the chemistry within dispersed droplets.[141,143,179] (a,b) Clogging can be eliminated for polymerization reactions by dispersing an organic reaction mixture within an aqueous phase.[145] The same strategy was applied to make possible the indigo synthesis of Table 1 (reprinted with permission from ref 145, copyright 2005c American Chemical Society). (c) Other studies have examined, for example, protein crystallization using stable multiphase flows (reprinted with permission from ref 140, copyright 2005c American Chemical Society). (d) A similar approach can be adopted for the dispersion of polymer products (copyright Wiley-VCH Verlag GmbH & Co. KGaA, reproduced with permission).[142]

application of external forces. Passive approaches involve the flow without mechanical agitation or any external forces being applied beyond pumping.

7.1. Multiphase Flow and Hydrophilic Ligands. The use of water as a cosolvent is an attractive media to manage halide salt byproduct.[106,149] Recent advancements in organic synthetic chemistry have expanded the scope of palladium-catalyzed cross-coupling reactions with the design of hydrophilic and water-soluble ligands.[60,92,94,102,149,175] Aqueous-based reactions, shown conceptually in Figure 8, can take place in the bulk water (Figure 8a), in a surfactant-supported micelle (Figure 8b), or at the interface of the immiscible aqueous−organic phases (Figure 8c).[149] The design of catalytic ligands for each of the three scenarios represent passive approaches to managing halide salt byproduct.

A trade-off exists, however, as the turnover numbers can be reduced in aqueous-based systems due to mass transport limitations,[175] which presents the opportunity for new science and engineering. Thus, the engineering of liquid−liquid microflows are needed and have received considerable attention for other chemistry problems[28,38,51,136−139,144,175−178]—a few examples are illustrated in Figure 9.[140,145] Microreactor clogging can be eliminated for polymerization reactions by dispersing an organic reaction mixture within an aqueous phase (Figure 9a,b).[145] The same strategy was applied to make possible the indigo synthesis of Table 1.[123] Protein crystallization, an important problem in biologics and medicinal chemistry, has been carried out in droplets dispersed in a carrier fluid (see Figure 9c).[140] Polymer products can be dispersed, and hence contact with the microreactor walls eliminated using the same technique (see Figure 9d).[142]

The creation of the stable liquid−liquid or gas−liquid segmented flows that make the phase behavior of Figure 9 possible is a topic that has been examined extensively. We point out, however, the importance of the length scales in establishing such flow behavior. The Bond number is defined as the ratio of the gravitational forces relative to the interfacial forces. In large-scale systems, the body forces dominate over surface forces, and thus the Bond number,

$$Bo = \frac{\Delta\rho g W^2}{\sigma} > 1 \tag{10}$$

Here, $\Delta\rho$ is density difference between the two immiscible phases, g the acceleration due to gravity, and σ the surface tension. In microscale flows, however, surface forces dominate over body forces such as gravity (i.e., $Bo \ll 1$). Consequently, one must consider the reactor length scales to realize the formation of stable of immiscible liquid−liquid or gas−liquid flows. A detailed review outlines the conditions necessary to achieve stable segmented flow and the overall influence of a gas phase, surface tension reducers, and the temperature.[38]

7.2. Fluid Velocity and Residence Time. As was shown for hydrodynamic bridging, there exists a critical velocity above which the flow-induced bridging of particles is possible at constriction points.[130] The Stokes number also elucidates when the deposition of particles are expected, and in turn induce

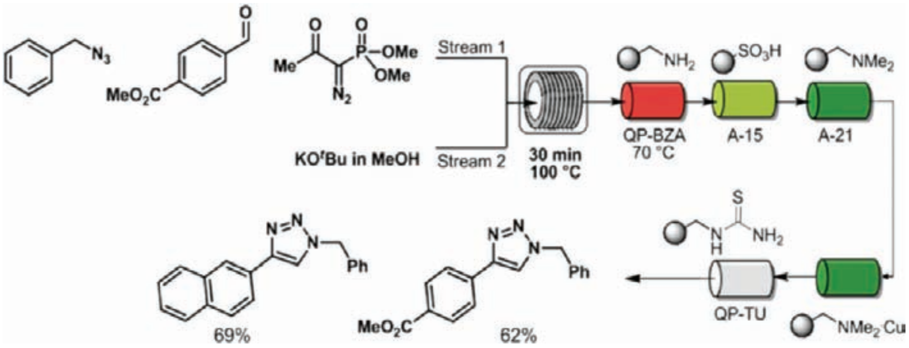


Figure 10. Multistep formation of triazoles in flow made possible using solid-supported scavengers to remove the byproduct (With kind permission from Springer Science+Business Media: ref 186, copyright Springer-Verlag, 2001).

dendrite formation that has the potential for internal plugging. Shear stress at the fluid-wall interface is a critical parameter when the random detachment of deposits occurs, owing to sloughing. Towards this end, the mechanical abrasion of inert particles (or the precipitated material itself) with a reactor's walls has the potential to constrain wall-buildups. Monitoring the growth of particles in the bulk flow can also yield insights on whether enough time has been spent within a reactor to achieve critical aspect ratios. A passive approach to the elimination of particle deposition, constriction, and hydrodynamic bridging is therefore the manipulation of the flow rate, which can be estimated in advance using the guidelines prescribed above combined with laboratory experiments that support predictive models.

7.3. Reactor Design. Thus far, we have discussed the problem of solids handling in the context of continuous flow micro- and mesoscale reactors. Continuous stirred-tank reactors (CSTRs) are excellent vessels of choice for solids forming reactions due to their mechanical agitation capabilities.[180] Furthermore, extruders offering utility in the downstream formulation of pharmaceuticals may also substitute upstream reactors when high solids concentrations are necessary. The replacement of laminar flow microreactors with CSTRs or extruders is not without challenges. For example, transfer tubing, peripheral equipment, and downstream unit operations still require a management plan for dealing with the solids formed in such upstream reactors. Moreover, convective heat transfer becomes more important, yet less efficient, than the conductive heat transfer that typically controls microreactors.

7.4. Immobilization. Many important reactions in fine chemical and natural product syntheses can be carried out using solid-supported reagents, catalysts, or byproduct scavengers.[16,181−186] The immobilization of compounds on a polymer support, a useful strategy to eliminate the need for continuous recycling, creates the challenge of the flow and reaction in porous media. The advantage of the reduced-length scales in terms of the mixing and the mass transport are worth the effort to prepare and regenerate a packed bed. It should be noted, however, that reproducible flow profiles through packed-bed microreactors are challenging at low velocities due to hydrodynamic anomalies.[187] The work of others undergirds the importance of the packing technique[188] and operation at higher flow rates[187] to ensure uniform flow. As evident in Figure 10, solid-supported scavengers can take on the form of a packed bed that, when combined inline with a sequence of reaction steps, make possible the multistep synthesis of triazoles among other important compounds (e.g., azides, aromatic alkynes, fluorinated aromatics, imidazoles—a variety of diverse aromatic and nonaromatic heterocycles).[186] The use of solid-supported compounds in packed beds promises to continue expanding the scope and the utility of many reactions central to medicinal chemistry and natural products.

7.5. Acoustic, Electrophoretic, Magnetic, and Mechanical Forces. There are a number of active techniques that have demonstrated utility when passive strategies do not adequately control the flow-induced accumulation of solids. Differences in the density and the compressibility between a particle and the solvent in which transport occurs generate a driving force for acoustic forces to displace particulate matter.[189−201] Thus, the presence of an acoustic standing wave forces particles to position themselves at pressure nodes in laminar flow, which has been demonstrated for the separation of red blood cells from lipids under frequencies of MHz.[196−198,202] The working principle relies on two criterion in order to trap flowing particles: (1) the diameters of the particles must be less than half the wavelength of an acoustic standing wave, and (2) a net force acts upon the particles when a phase difference parameter (ϕ), given by

$$\phi = \frac{5\rho_p - 2\rho_s}{2\rho_p + \rho_s} - \frac{\beta_p}{\beta_s} \tag{11}$$

is nonzero.[196−198,202] Here, β_p and β_s are the particle and the solvent compressibility, respectively. For $\phi > 0$ or $\phi < 0$, an acoustic force acting on a particle or a system of particles can be expected, and there exists the potential for the acoustic streaming of particles in laminar flow.[196−198,202] Alternatively, imposing acoustic waveforms with frequencies of kHz can generate cavitations.[195] For example, ultrasonic baths operating in the kilohertz regime have been applied to manage the formation of solids in flow chemistry, as can be seen in Figure 11. Performing Pd-catalyzed C−N bond-forming reactions in an ultrasonic bath prevents the clogging of fluoropolymer capillaries by NaCl formation (Figure 11a).[76,84,107] The working principle has recently been applied to engineer fluoropolymer microreactors sandwiched between a piezoceramic actuator, which delivers on-chip ultrasound to manage the NaCl formation.[77] Polymer reaction products, the photodimerization of maleic anhydride for example of Figure 11b, also constrain fluid flow in microreactors.[124] In this case, the clogging was mitigated by injecting the reactants into a capillary, coiled around a light source and positioned within an ultrasonic bath.[124] The byproduct MnO_2 formed during the Nef oxidation can also result in flow-induced clogging, which can be prevented using sonication (see Figure 11c).[66] The use

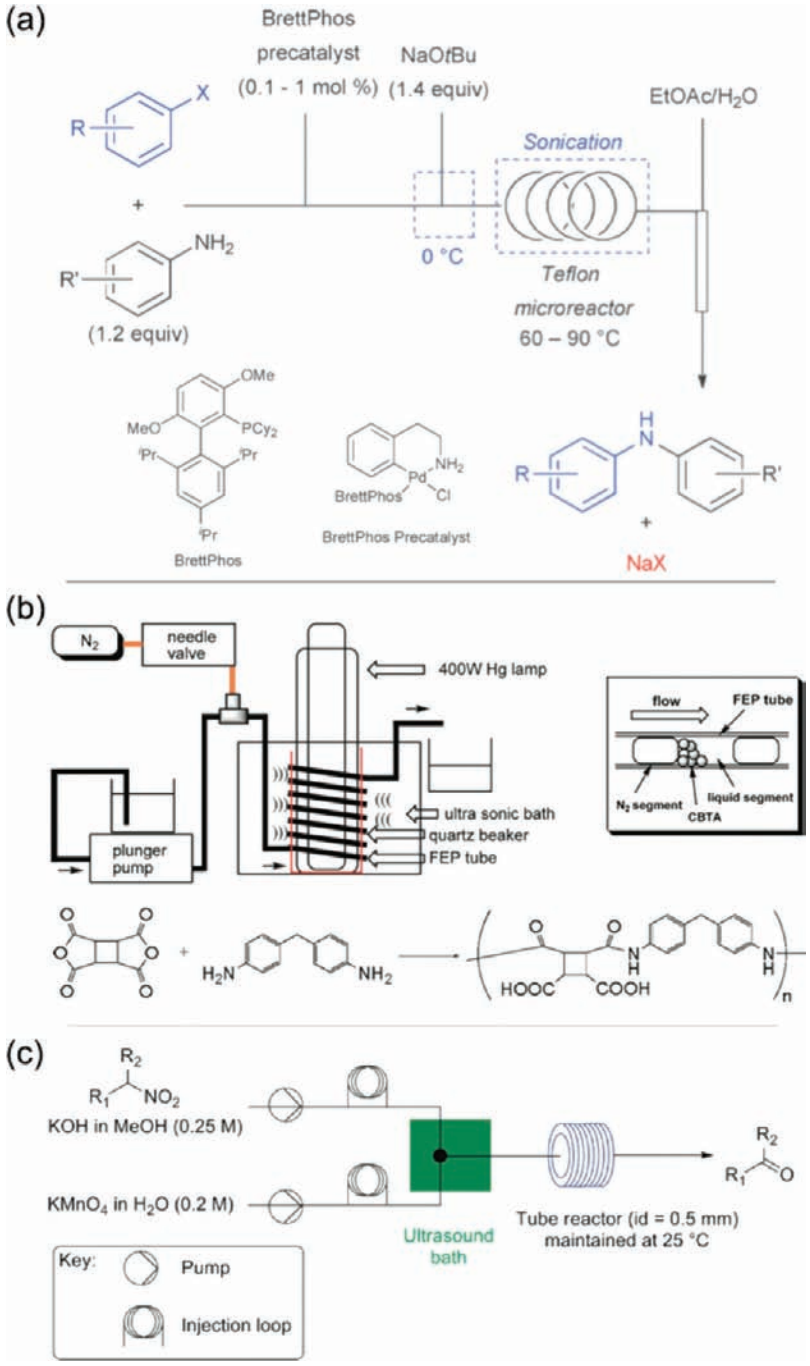


Figure 11. Sonication has been applied to prevent clogging during synthetic transformations. For example, (a) performing Pd-catalyzed C−N bond-forming reactions in an ultrasonic bath prevents the clogging of Teflon capillaries by NaCl formation (reproduced from ref 84 with permission from The Royal Society of Chemistry). (b) Polymer reaction products, the photodimerization of maleic anhydride for example, also constrain fluid flow in laboratory-scale reactors. Here, the clogging was mitigated by injecting the reactants into a capillary coiled around a light source in an ultrasonic bath (reprinted with permission from ref 124, copyright 2010, the American Chemical Society). (c) Finally, performing the Nef oxidation leads to clogging from MnO_2 formation, which can be prevented using sonication (reprinted with permission from ref 66, copyright 2010, the American Chemical Society).

of acoustic forces to manage solids has tremendous potential, as industrial scale ultrasonic baths are available in addition to the engineering of integrated reactor systems.

Mechanical agitation, another active technique, can also ensure the continuous flow of solids. One observes in Figure 12 a flow reactor cell (The Coflore ACR) with integrated unbound agitators.[203] The mechanical vibration of the flow cell enabled the production of *N*-iodomorpholinium hydroiodide salt without blockage.[203] In principle, the reservoirs shown in Figure 12 emulate a cascade of milliliter-scale CSTRs.

In addition to agitation, electrophoretic[204,205] and magnetic[206−211] particle manipulation, although primarily used in nonreactive microfluidic systems, have the potential for solid control. A challenge towards this end is the application of such techniques to concentrated suspensions where interparticle and wall interactions are frequent. One must also consider the

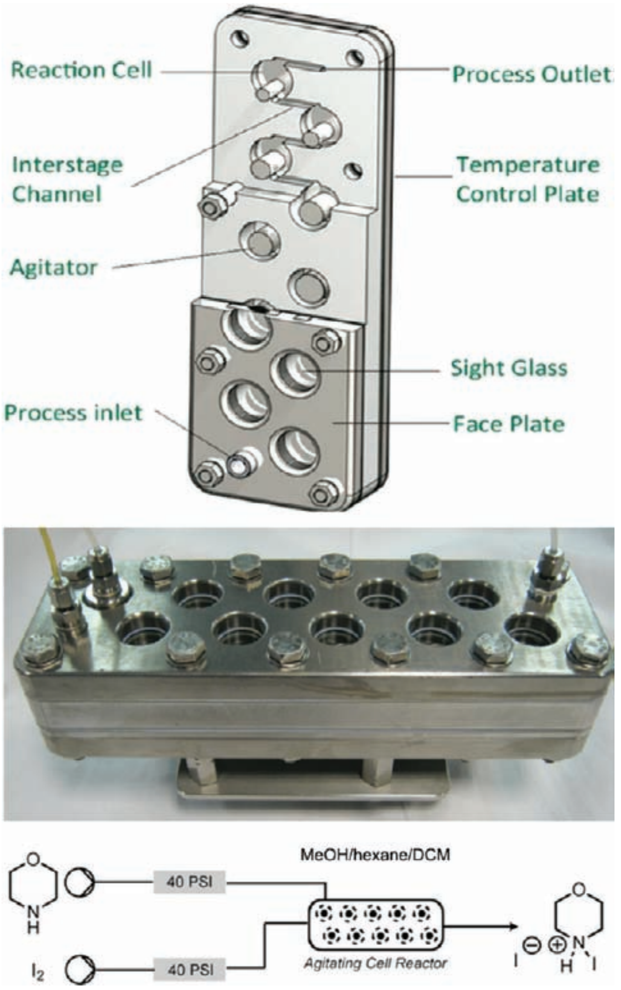


Figure 12. Agitated cell reactor used to produce *N*-iodomorpholinium hydroiodide salt without blockage (reprinted with permission from ref 203, copyright 2011, American Chemical Society).

magnitude of such forces, similar to acoustics, relative to the viscous and the inertial forces (i.e., *St* number). The delivery of adequate forces to the flow path may in turn diminish upon scaling up. Scaling out or the innovation of novel, unexplored reactor designs promise to overcome such challenges.

8. EVALUATING THE RISKS OF SOLIDS HANDLING

Perhaps the most important step in managing solids during the continuous processing of fine chemicals is the analysis of the potential impact, both from manufacturing cost and capital investment point-of-views. There are numerous and more sophisticated approaches to analyzing risk in chemical processing, but a simple and very effective approach is applied herein.[212] Figure 13 accompanies the discussion by relating risk to the technical considerations that have been previously described. One must ask early in the conceptualization of a continuous fine chemical process based on microreactor technology: "what is the probability that insoluble material will be generated or used within the process?" Given the information of Figure 3 and the reactions of Table 1,[6,14,50,56,66,76,86,107,123,124] the probability is quit high for a broad range of transformations and the useful synthetic pathways that utilize them. Consequently, special attention should be given to assess the potential losses associated with either constriction or blockage-type mechanisms.

Identifying the probability for either constriction or plugging is critically necessary and accomplished by considering the first principles. For reaction classes that are known to generate insoluble materials, thermodynamic and nucleation predictions are essential tools in evaluating the certainty of solids generation and the supersaturation conditions leading to either mechanism. For constriction, $St > 1$ is a necessary condition that leads to multilayer deposition. Likewise, the change in the pressure drop with time is an indication that constriction could result. For these conditions it is highly probable (e.g., 5 in the risk matrix of Figure 13) that, as an example problem, constriction will occur during the generation of 1 M halide salts in palladium-catalyzed C−N bond-forming reactions carried out in mesoscale tubular flow reactors. The economic consequences related to the manufacturing and the capital costs are somewhat ambiguous without data that directly relates each to our example. Regardless, the risk matrix of Figure 13 is further applied to yield qualitative information that could ultimately guide an investment decision. If the heterogeneous mixture is pumpable for 100 reactor volumes before any constrictions occur, then an appreciable quantity of product will be manufactured and the economic impact on the operations is intermediary (e.g., assigned probability of 3). The scenario gives an intolerable operating regime of 15 denoted by the red highlight of Figure 13. It is likely however that intolerable could be shifted to negligible, highlighted in blue, by practicing steps that reduce both the impact and the probability of constriction that result in manufacturing-related cash flow losses. The best practices based on our discussion throughout this article are listed in Figure 13 highlighted in blue. A similar analogy can be made to assess the impact of constriction on the capital investment. Since the capital investment of a continuous chemical process is commonly greater than incremental manufacturing costs, an impact of 4−5 could be expected; a scenario that gives a nonoperable regime of 20 is highlighted in black. It is anticipated that the nonoperable risk could potentially be reduced to undesirable (5 < square < 9, highlighted in yellow) through technological innovations, and a few are presented in Figure 13 based on the discussion throughout this article. New technological innovations frequently enter markets at higher cost, which was the basis for setting the lower yellow boundary condition of 5.

Evaluating whether or not blockages will form and thus impact the manufacturing costs and/or the capital investment depends on the reactions, the existence of supersaturation, and additionally the time scale needed to form nuclei within a reactor (i.e., $\alpha < 1$) among others. There exists the potential for particles to grow large enough to form blockages when $\eta > 1$ and W/D values are in the range of 10. In this example, however, we presume the reactor cross-section to be sufficiently large to minimize bridging events (e.g., micrometer-sized particles flowing normal to millimeter-sized cross sections); therefore, the probability is low and assigned a value of 2 (see Figure 13). The impact on the manufacturing, however, could be considerable if blockages form such as the complete shutdown of a process to remediate. This information combined with the higher capital costs relative to incremental manufacturing costs yields values of 4 and 5 for the manufacturing and capital investment impacts, respectively. The overall risk of blockages impacting the manufacturing is undesirable (8 and highlighted in yellow), yet many of the steps taken to reduce the probability of constriction could also be applied to reduce the risk to negligible (highlighted in blue). As

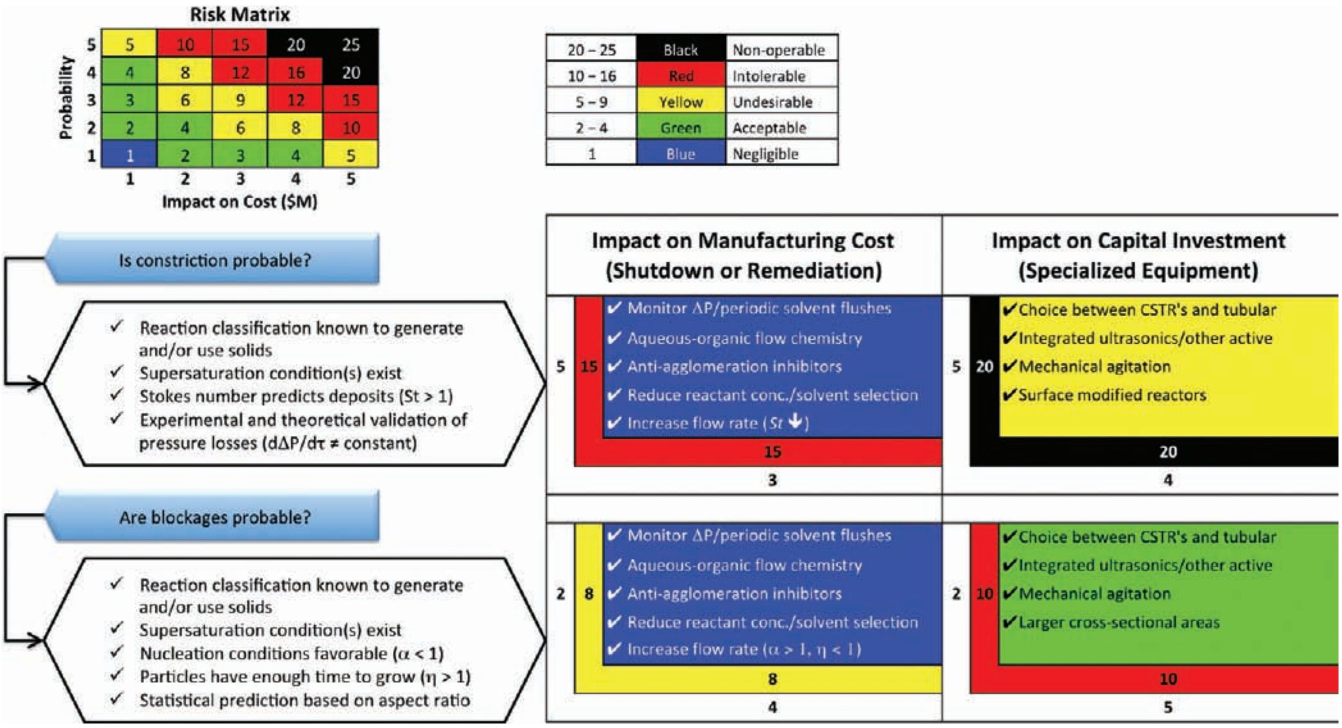


Figure 13. Evaluation of the probability and the impact of constriction and plugging risks on the manufacturing and the capital costs. (Modified from ref 212, copyright 2006, Society of Petroleum Engineers.) As an example problem, the risk of generating 1 M halide salts during palladium-catalyzed C−N bond-forming reactions carried out in mesoscale tubular flow reactors is assessed.

can be seen, the potential risk on the capital investment is intolerable (10 and highlighted in red), but it could be reduced to acceptable (2 < square < 4, highlighted in green) adopting the most appropriate strategies.

The analysis of risk associated with constriction and blockage formation, in this example, is a simplified case that undergirds the importance of technological innovations and the development of operational strategies, when possible, to avoid capital investment. One readily observes in Figure 13 that constriction could most significantly impact capital costs, while there exist operational solutions that could make the risk negligible. In our chemistry example, the use of aqueous−organic immiscible systems stands out as a leading technological choice, yet there remains considerable room for scientific and engineering advancements therein and within the other innovative approaches discussed. The overall impact on the capital investments could indeed be reduced with continued innovations.

9. CONCLUDING REMARKS AND OUTLOOK

A new paradigm is emerging in upstream fine chemical and pharmaceutical manufacturing; understanding how to manage heterogeneous flow and reaction is needed. Flow and reaction in porous media and flow assurance problems in the petroleum and natural gas industries, accustomed to dealing with the flow and reaction of particulate matter in micro- and mesoscale laminar flow, are interrelated to continuous specialty chemical processing. Meeting the challenge of solids handling in continuous fine chemical processing could benefit from knowledge transfer between these existing industries.

Overall, the issue of solids handling in the upstream continuous processing of fine chemicals, a new and exciting field of challenging problems, remains unsolved. It should therefore be no surprise that technology to manage solids in continuous flow micro- and mesoscale reactors is limited. Tremendous opportunity remains to advance the continuous processing of specialty chemicals through the innovation of new solids handling approaches, the engineering of novel reaction systems, and the development of predictive models that make continuous flow chemistry possible. Each scenario is different, and the prediction or development of process handling strategies must be accompanied by an understanding of the plugging mechanisms correlated to the chemistry.

Although there exists new opportunities for flow chemistry that were previously difficult or not attainable, moving forward is not without challenges. A lack of strategies for the separation of insoluble material has the potential to limit continuous processing. As we have seen, the deposition and growth on surfaces (e.g., peripheral equipment, reactors, instruments, supported catalyst, and transfer tubing surfaces) are also important considerations that need to be addressed when salts suspended in organic solvents undergo laminar flow. Strategies to remove such deposits will find utility from micro- to mesoscale reactors, including mechanical and chemical treatments that target the deposit chemistry. The cost, however, of removing wall deposits consisting of organic or inorganic scale is the startup and shutdown time as well as the wasted materials needed to achieve steady-state operation. Consequently, engineering active and passive techniques that prevent the deposits in the first place are ideal.

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Notes

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NOMENCLATURE

α=Ratio of the induction time to the residence time, dimensionless
β=Shape factor, dimensionless
β_p=Particle compressibility, dimensionless
β_s=Solvent compressibility, dimensionless
ε=Particle sticking distance from the microchannel wall, μm
$\bar{\gamma}$=Mean activity coefficient, dimensionless
γ=Crystal surface energy, J/m^2
δ=Surface-reaction to mass-transfer limited parameter, dimensionless
ΔP=Pressure drop across a continuous reactor or process, psig
$\Delta\rho$=Density difference between immiscible phases, g/μm^3
ϕ=Energy barrier factor, dimensionless
η=Ratio of the growth rate to the convective transport rate in the axial direction, dimensionless
ν=Molecular volume of the crystalline phase, m^3/molecule
σ=Surface tension, g/s^2
ρ_c=Molar density of the crystalline phase, M
ρ_p=Particle density, g/cm^3
ρ_s=Solvent density, g/cm^3
τ=Residence time, min
θ=Ratio of the particle sticking distance from the wall to the particle diameter, dimensionless
A=Frequency factor, nuclei/min
Bo=Bond number, dimensionless
D=Particle diameter, μm
D=Molecular diffusivity, μm^2/min
g=Acceleration due to gravity, μm/s^2
H=Microchannel height, μm
J=Nucleation rate, nuclei/min
K_{sp}=Solubility product, M$^{(m+x)}$
k_B=Boltzmann's constant, J/molecule/K
k_g=Specific reaction rate, μm/min
L=Reactor length, μm
$[M^{z+}]$ ==Cation concentration, M
m=Number of cations, dimensionless
N^*=Average number of particles that pass through the microchannel before clogging, particles
n=Number of particle sticking events, dimensionless
Re=Reynolds number, dimensionless
r_g ==Particle growth rate, μm/min
T=Absolute temperature, K
t=Growth or reaction time, min
t_{ind}=Induction time, min
SR=Supersaturation ratio, dimensionless
St=Stokes Number, dimensionless
U_{avg}=Average velocity in the axial direction, cm/s
U_{crtl}=Critical velocity in the axial direction, cm/s
W=Microchannel width or characteristic cross-sectional dimension, μm
$[X^{z-}]$=Anion concentration, M
x=Number of anions, dimensionless
z^+=Cation charge, dimensionless
z^-=Anion charge, dimensionless

REFERENCES

(1) Calabrese, G. S; Pissavini, S. *AIChE J.* **2011**, *57*, 828.
(2) Ducry, L.; Roberge, D. M. *Org. Process Res. Dev.* **2008**, *12*, 163.
(3) Kockmann, N.; Gottsponer, M.; Roberge, D. M. *Chem. Eng. J.* **2011**, *167*, 718.
(4) Kockmann, N.; Gottsponer, M.; Zimmermann, B.; Roberge, D. M. *Chem.—Eur. J.* **2008**, *14*, 7470.
(5) Roberge, D. M.; Bieler, N.; Mathier, M.; Eyholzer, M.; Zimmermann, B.; Barthe, P.; Guermeur, C.; Lobet, O.; Moreno, M.; Woehl, P. *Chem. Eng. Technol.* **2008**, *31*, 1155.
(6) Roberge, D. M.; Ducry, L.; Bieler, N.; Cretton, P.; Zimmermann, B. *Chem. Eng. Technol.* **2005**, *28*, 318.
(7) Roberge, D. M.; Zimmermann, B.; Rainone, F.; Gottsponer, M.; Eyholzer, M.; Kockmann, N. *Org. Process Res. Dev.* **2008**, *12*, 905.
(8) Buisson, B.; Donegan, S.; Wray, D.; Parracho, A.; Gamble, J.; Caze, P.; Jorda, J.; Guermeur, C. *Chim. Oggi-Chem. Today* **2009**, *27*, 12.
(9) Chevalier, B.; Schmidt, F. *Chim. Oggi-Chem. Today* **2008**, *26*, 6.
(10) Lavric, E. D.; Woehl, P. *Chim. Oggi-Chem. Today* **2009**, *27*, 45.
(11) Seeberger, P. H., Blume, T., Eds. *New Avenues to Efficient Chemical Synthesis: Emerging Technologies*; Springer: New York, 2007.
(12) Caygill, G.; Zanfir, M.; Gavriilidis, A. *Org. Process Res. Dev.* **2006**, *10*, 539.
(13) Hessel, V. *Chem. Eng. Technol.* **2009**, *32*, 1655.
(14) Zhang, X. N.; Stefanick, S.; Villani, F. J. *Org. Proc. Res. Dev* **2004**, *8*, 455.
(15) Antes, J.; Boskovic, D.; Krause, H.; Loebbecke, S.; Lutz, N.; Tuercke, T.; Schweikert, W. *Chem. Eng. Res. Des.* **2003**, *81*, 760.
(16) Baumann, M.; Baxendale, I. R.; Martin, L. J.; Ley, S. V. *Tetrahedron* **2009**, *65*, 6611.
(17) Bogdan, A. R.; Poe, S. L.; Kubis, D. C.; Broadwater, S. J.; McQuade, D. T. *Angew. Chem., Int. Ed.* **2009**, *48*, 8547.
(18) Chambers, R. D.; Holling, D.; Rees, A. J.; Sandford, G. *J. Fluor. Chem.* **2003**, *119*, 81.
(19) Chambers, R. D.; Spink, R. C. H. *Chem. Commun.* **1999**, 883.
(20) de Mas, N.; Gunther, A.; Schmidt, M. A.; Jensen, K. F. *Ind. Eng. Chem. Res.* **2009**, *48*, 1428.
(21) Dessimoz, A. L.; Cavin, L.; Renken, A.; Kiwi-Minsker, L. *Chem. Eng. Sci.* **2008**, *63*, 4035.
(22) Geyer, K.; Codee, J. D. C.; Seeberger, P. H. *Chem.—Eur. J.* **2006**, *12*, 8434.
(23) Hartman, R. L.; McMullen, J. P.; Jensen, K. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 7502.
(24) Hartman, R. L.; Naber, J. R.; Buchwald, S. L.; Jensen, K. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 899.
(25) Haswell, S. J.; Watts, P. *Green Chem.* **2003**, *5*, 240.
(26) Hessel, V.; Lowe, H. *Chem. Eng. Technol.* **2005**, *28*, 267.
(27) Iwasaki, T.; Yoshida, J. *Macromolecules* **2005**, *38*, 1159.
(28) Kobayashi, J.; Mori, Y.; Okamoto, K.; Akiyama, R.; Ueno, M.; Kitamori, T.; Kobayashi, S. *Science* **2004**, *304*, 1305.
(29) Kuhn, S.; Hartman, R. L.; Sultana, M.; Nagy, K. D.; Marre, S.; Jensen, K. F. *Langmuir* **2011**, *27*, 6519.
(30) Losey, M. W.; Schmidt, M. A.; Jensen, K. F. *Ind. Eng. Chem. Res.* **2001**, *40*, 2555.
(31) Murphy, E. R.; Martinelli, J. R.; Zaborenko, N.; Buchwald, S. L.; Jensen, K. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1734.
(32) Odedra, A.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2699.
(33) Wada, Y.; Schmidt, M. A.; Jensen, K. F. *Ind. Eng. Chem. Res.* **2006**, *45*, 8036.
(34) Zhang, X. L.; Wiles, C.; Painter, S. L.; Watts, P.; Haswell, S. J. *Chim. Oggi-Chem. Today* **2006**, *24*, 43.
(35) Fletcher, P. D. I.; Haswell, S. J.; Pombo-Villar, E.; Warrington, B. H.; Watts, P.; Wong, S. Y. F.; Zhang, X. L. *Tetrahedron* **2002**, *58*, 4735.
(36) Fukuyama, T.; Rahman, T.; Sato, M.; Ryu, I. *Synlett* **2008**, 151.
(37) Goodell, J. R.; McMullen, J. P.; Zaborenko, N.; Maloney, J. R.; Ho, C. X.; Jensen, K. F.; Porco, J. A.; Beeler, A. B. *J. Org. Chem.* **2009**, *74*, 6169.
(38) Gunther, A.; Jensen, K. F. *Lab Chip* **2006**, *6*, 1487.
(39) Hartman, R. L.; Jensen, K. F. *Lab Chip* **2009**, *9*, 2495.
(40) Haswell, S. J.; Middleton, R. J.; O'Sullivan, B.; Skelton, V.; Watts, P.; Styring, P. *Chem. Commun.* **2001**, 391.

(41) Hessel, V.; S., H.; Lowe, H. *Chemical Micro Process Engineering: Fundamentals, Modeling and Reactions*; Wiley-VCH: Weinheim, Germany, 2004.
(42) Jahnisch, K.; Hessel, V.; Lowe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 406.
(43) Jensen, K. *Nature* **1998**, *393*, 735.
(44) Jensen, K. F. *Chem. Eng. Sci.* **2001**, *56*, 293.
(45) Jensen, K. F. *MRS Bull.* **2006**, *31*, 101.
(46) Kockmann, N.; Kiefer, T.; Engler, M.; Woias, P. *Sens. Actuators, B* **2006**, *117*, 495.
(47) Marre, S.; Jensen, K. F. *Chem. Soc. Rev.* **2010**, *39*, 1183.
(48) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300.
(49) McMullen, J. P.; Jensen, K. F. *Org. Process Res. Dev.* **2011**, *15*, 398.
(50) Muller, G.; Gaupp, T.; Wahl, F.; Wille, G. *Proc. Chem.* **2006**, *60*, 618.
(51) Song, H.; Chen, D. L.; Ismagilov, R. F. *Angew. Chem., Int. Ed.* **2006**, *45*, 7336.
(52) Watts, P.; Wiles, C. *Chem. Commun.* **2007**, 443.
(53) Watts, P.; Wiles, C. *Chem. Eng. Technol.* **2007**, *30*, 329.
(54) Whitesides, G. M. *Nature* **2006**, *442*, 368.
(55) Wilms, D.; Klos, J.; Kilbinger, A. F. M.; Lowe, H.; Frey, H. *Org. Process Res. Dev.* **2009**, *13*, 961.
(56) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6722.
(57) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.
(58) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534.
(59) Wakami, H.; Yoshida, J. *Org. Process Res. Dev.* **2005**, *9*, 787.
(60) Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173.
(61) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.
(62) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.
(63) de Vries, J. G. *Can. J. Chem.-Rev. Can. Chim.* **2001**, *79*, 1086.
(64) Hansen, A. L.; Skrydstrup, T. *J. Org. Chem.* **2005**, *70*, 5997.
(65) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.
(66) Sedelmeier, J.; Ley, S. V.; Baxendale, I. R.; Baumann, M. *Org. Lett.* **2010**, *12*, 3618.
(67) Barthe, P.; Guermeur, C.; Lobet, O.; Moreno, M.; Woehl, P.; Roberge, D. M.; Bieler, N.; Zimmermann, B. *Chem. Eng. Technol.* **2008**, *31*, 1146.
(68) Bedore, M. W.; Zaborenko, N.; Jensen, K. F.; Jamison, T. F. *Org. Process Res. Dev.* **2010**, *14*, 432.
(69) Marre, S.; Park, J.; Rempel, J.; Guan, J.; Bawendi, M. G.; Jensen, K. F. *Adv. Mater.* **2008**, *20*, 4830.
(70) Knitter, R.; Gohring, D.; Risthaus, P.; Hausselt, J. *Microsyst. Technol.* **2001**, *7*, 85.
(71) Kikutani, Y.; Hibara, A.; Uchiyama, K.; Hisamoto, H.; Tokeshi, M.; Kitamori, T. *Lab Chip* **2002**, *2*, 193.
(72) Kikutani, Y.; Horiuchi, T.; Uchiyama, K.; Hisamoto, H.; Tokeshi, M.; Kitamori, T. *Lab Chip* **2003**, *3*, 51.
(73) Braune, S.; Pochlauer, P.; Reintjens, R.; Steinhofer, S.; Winter, M.; Lobet, O.; Guidat, R.; Woehl, P.; Guermeur, C. *Chim. Oggi-Chem. Today* **2009**, *27*, 26.
(74) Monbaliu, J. C. M.; Winter, M.; Chevalier, B.; Schmidt, F.; Jiang, Y.; Hoogendoorn, R.; Kousemaker, M. A.; Stevens, C. V. *Bioresour. Technol.* **2011**, *102*, 9304.
(75) Hu, S. Z.; Wang, A. J.; Lowe, H.; Li, X. A.; Wang, Y.; Li, C. H.; Yang, D. *Chem. Eng. J.* **2010**, *162*, 350.
(76) Hartman, R. L.; Naber, J. R.; Zaborenko, N.; Buchwald, S. L.; Jensen, K. F. *Org. Process Res. Dev.* **2010**, *14*, 1347.
(77) Kuhn, S.; Noel, T.; Gu, L.; Heider, P. L.; Jensen, K. F. *Lab Chip* **2011**, *11*, 2488.
(78) Tuteja, A.; Choi, W.; Ma, M. L.; Mabry, J. M.; Mazzella, S. A.; Rutledge, G. C.; McKinley, G. H.; Cohen, R. E. *Science* **2007**, *318*, 1618.
(79) Tuteja, A.; Choi, W. J.; McKinley, G. H.; Cohen, R. E.; Rubner, M. F. *MRS Bull.* **2008**, *33*, 752.
(80) Li, X. M.; Reinhoudt, D.; Crego-Calama, M. *Chem. Soc. Rev.* **2007**, *36*, 1350.
(81) Koc, Y.; de Mello, A. J.; McHale, G.; Newton, M. I.; Roach, P.; Shirtcliffe, N. J. *Lab Chip* **2008**, *8*, 582.
(82) Lee, H. S.; Singh, P.; Thomason, W. H.; Fogler, H. S. *Energy Fuels* **2008**, *22*, 480.
(83) Li, P. F.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 6396.
(84) Noel, T.; Buchwald, S. L. *Chem. Soc. Rev.* **2011**, *40*, 5010.
(85) Noël, T.; Kuhn, S.; Musacchio, A. J.; Jensen, K. F.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 5943.
(86) Shu, W.; Pellegatti, L.; Oberli, M. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 10665.
(87) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771.
(88) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1992**, *57*, 3558.
(89) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.
(90) Mahavir, P. *Topics in Organometallic Chemistry*; Springer-Verlag: Berlin, Heidelberg: 2004; *Vol. 6*, p 181.
(91) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440.
(92) Moore, L. R.; Western, E. C.; Craciun, R.; Spruell, J. M.; Dixon, D. A.; O'Halloran, K. P.; Shaughnessy, K. H. *Organometallics* **2008**, *27*, 576.
(93) Olofsson, K.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 7235.
(94) Shaughnessy, K. H.; DeVasher, R. B. *Curr. Org. Chem.* **2005**, *9*, 585.
(95) Singh, B. K.; Kaval, N.; Tomar, S.; Eycken, E. V. d.; Parmar, V. S. *Org. Process Res. Dev.* **2008**, *12*, 468.
(96) Singh, U. K.; Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14104.
(97) Leblanc, S. E.; Fogler, H. S. *AIChE J.* **1989**, *35*, 865.
(98) Leblanc, S. E.; Fogler, H. S. *AIChE J.* **1987**, *33*, 54.
(99) Gilbertson, S. R.; Fu, Z. *Org. Lett.* **2001**, *3*, 161.
(100) Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560.
(101) Altman, R. A.; Fors, B. P.; Buchwald, S. L. *Nat. Protoc.* **2007**, *2*, 2881.
(102) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505.
(103) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2047.
(104) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.
(105) Mauger, C.; Buisine, O.; Caravieilhes, S.; Mignani, G. *J. Organomet. Chem.* **2005**, *690*, 3627.
(106) Naber, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 9469.
(107) Noel, T.; Naber, J. R.; Hartman, R. L.; McMullen, J. P.; Jensen, K. F.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 287.
(108) Popa, D.; Marcos, R.; Sayalero, S.; Vidal-Ferran, A.; Pericàs, M. A. *Adv. Synth. Catal.* **2009**, *351*, 1539.
(109) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264.
(110) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J. J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.
(111) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.
(112) Brown, W. S.; Boykin, D. D.; Sonnier, M. Q., Jr.; Clark, W. D.; Brown, F. V.; Shaughnessy, K. H. *Synthesis* **2008**, 1965.
(113) DeVasher, R. B.; Moore, L. R.; Shaughnessy, K. H. *J. Org. Chem.* **2004**, *69*, 7919.
(114) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691.
(115) Basheer, C.; Shahitha, F.; Hussain, J.; Lee, H. K.; Valiyaveettil, S. *Tetrahedron Lett.* **2004**, *45*, 7297.
(116) Huang, R.; Shaughnessy, K. H. *Organometallics* **2006**, *25*, 4105.
(117) Mennecke, K.; Solodenko, W.; Kirschning, A. *Synthesis* **2008**, 1589.
(118) Moore, L. R.; Shaughnessy, K. H. *Org. Lett.* **2004**, *6*, 225.
(119) am Ende, D. J.; Clifford, P. J.; DeAntonis, D. M.; SantaMaria, C.; Brenek, S. J. *Org. Process Res. Dev* **1999**, *3*, 319.

(120) Riva, E.; Gagliardi, S.; Martinelli, M.; Passarella, D.; Vigo, D.; Rencurosi, A. *Tetrahedron*, *66*, 3242.

(121) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58.

(122) Gorrepati, E. A.; Wongthahan, P.; Raha, S.; Fogler, H. S. *Langmuir* **2010**, *26*, 10467.

(123) Poe, S. L.; Cummings, M. A.; Haaf, M. R.; McQuade, D. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1544.

(124) Horie, T.; Sumino, M.; Tanaka, T.; Matsushita, Y.; Ichimura, T.; Yoshida, J. *Org. Process Res. Dev.* **2010**, *14*, 405.

(125) Huang, Z. Y.; Lee, H. S.; Senra, M.; Fogler, H. S. *AIChE J.* **2011**, *57*, 2955.

(126) Elimelech, M.; Gregory, J.; Jia, X.; Williams, R. *Particle Deposition and Aggregation. Measurement, Modeling, and Simulation*; Butterworth-Hienemann: Woburn, MA, 1995.

(127) Marshall, J. K.; Kitchener, J. A. *J. Colloid Interface Sci.* **1966**, *22*, 342.

(128) Privman, V.; Frisch, H. L.; Ryde, N.; Matijevic, E. *J. Chem. Soc., Faraday Trans.* **1991**, *87*, 1371.

(129) Ramachandran, V.; Fogler, H. S. *Langmuir* **1998**, *14*, 4435.

(130) Ramachandran, V.; Fogler, H. S. *J. Fluid Mech.* **1999**, *385*, 129.

(131) Ryde, N.; Kallay, N.; Matijevic, E. *J. Chem. Soc., Faraday. Trans* **1991**, *87*, 1377.

(132) Song, L. F.; Elimelech, M. *J. Colloid Interface Sci.* **1994**, *167*, 301.

(133) Vaidyanathan, R.; Tien, C. *Chem. Eng. Sci.* **1991**, *46*, 967.

(134) Vitthal, S.; Sharma, M. M. *J. Colloid Interface Sci.* **1992**, *153*, 314.

(135) Creek, J. L.; Lund, H. J.; Brill, J. P.; Volk, M. *Fluid Phase Equilib.* **1999**, *158*, 801.

(136) Gunther, A.; Jhunjhunwala, M.; Thalmann, M.; Schmidt, M. A.; Jensen, K. F. *Langmuir* **2005**, *21*, 1547.

(137) Song, H.; Bringer, M. R.; Tice, J. D.; Gerdts, C. J.; Ismagilov, R. F. *Appl. Phys. Lett.* **2003**, *83*, 4664.

(138) Gunther, A.; Khan, S. A.; Thalmann, M.; Trachsel, F.; Jensen, K. F. *Lab Chip* **2004**, *4*, 278.

(139) Trachsel, F.; Gunther, A.; Khan, S.; Jensen, K. F. *Chem. Eng. Sci.* **2005**, *60*, 5729.

(140) Chen, D. L.; Gerdts, C. J.; Ismagilov, R. F. *J. Am. Chem. Soc.* **2005**, *127*, 9672.

(141) Li, W.; Pharn, H. H.; Nie, Z.; MacDonald, B.; Guenther, A.; Kumacheva, E. *J. Am. Chem. Soc.* **2008**, *130*, 9935.

(142) Marcati, A.; Serra, C.; Bouquey, M.; Prat, L. *Chem. Eng. Technol.* **2010**, *33*, 1779.

(143) Seo, M.; Nie, Z. H.; Xu, S. Q.; Mok, M.; Lewis, P. C.; Graham, R.; Kumacheva, E. *Langmuir* **2005**, *21*, 11614.

(144) Shestopalov, I.; Tice, J. D.; Ismagilov, R. F. *Lab Chip* **2004**, *4*, 316.

(145) Quevedo, E.; Steinbacher, J.; McQuade, D. T. *J. Am. Chem. Soc.* **2005**, *127*, 10498.

(146) Levenspiel, O. *Chemical Reaction Engineering*, 3rd ed.; John Wiley & Sons: New York, NY, 1999.

(147) Fogler, H. S. *Elements of Chemical Reaction Engineering*, 4th ed.; Prentice Hall: Upper Saddle River, NJ, 2005.

(148) Bird, B. R.; Stewart, W. E.; Lightfoot, E. N. *Transport Phenomena*, 2nd ed.; John Wiley & Sons: New York, NY, 2002.

(149) Shaughnessy, K. H. *Chem. Rev.* **2009**, *109*, 643.

(150) Kockmann, N.; Kastner, J.; Woias, P. *Chem. Eng. J.* **2008**, *135*, S110.

(151) Tantayakom, V.; Fogler, H. S.; Charoensirithavorn, P.; Chavadej, S. *Cryst. Growth Des.* **2005**, *5*, 329.

(152) Wolfe, N.; Hartman, R. L., Eds. *Formation, Removal, and Inhibition of Inorganic Scale in the Oilfield Environment*; Society of Petroleum Engineers: Richardson, TX, 2008.

(153) Mullin, J. W. *Crystallization*, 3rd ed.; Oxford: Butterworth Heinemann, 1997.

(154) Tomson, M. B.; Kan, A. T.; Fu, G. *SPE J.* **2004**, *11*, 283.

(155) Burton, K.; Cabrera, N.; Frank, F. *Philos. Trans. R. Soc. London. Ser. A* **1951**, 243.

(156) Slaughter, D. W.; Doherty, M. F. *Chem. Eng. Sci.* **1995**, *50*, 1679.

(157) Zhang, Y. C.; Sizemore, J. P.; Doherty, M. F. *AIChE J.* **2006**, *52*, 1906.

(158) Winn, D.; Doherty, M. F. *AIChE J.* **2000**, *46*, 1348.

(159) Frenier, W.; Ziauddin, M.; Venkatesan, R. *Organic Deposits in Oil and Gas Production*; Society of Petroleum Engineers: Richardson, TX, 2010.

(160) Boyd, D. A.; Adleman, J. R.; Goodwin, D. G.; Psagtis, D. *Anal. Chem.* **2008**, *80*, 2452.

(161) Hartman, R. L.; Sahoo, H. R.; Yen, B. C.; Jensen, K. F. *Lab Chip* **2009**, *9*, 1843.

(162) Hibara, A.; Toshin, K.; Tsukahara, T.; Mawatari, K.; Kitamori, T. *Chem. Lett.* **2008**, *37*, 1064.

(163) Tonkovich, A. L.; Jarosch, K.; Arora, R.; Silva, L.; Perry, S.; McDaniel, J.; Daly, F.; Litt, B. *Chem. Eng. J.* **2008**, *135*, S2.

(164) Wootton, R. C. R.; deMello, A. J. *Chem. Commun.* **2004**, 266.

(165) Zhang, Y.; Kato, S.; Anazawa, T. *Chem. Commun.* **2009**, 2750.

(166) Kralj, J. G.; Sahoo, H. R.; Jensen, K. F. *Lab Chip* **2007**, *7*, 256.

(167) Tokeshi, M.; Minagawa, T.; Kitamori, T. *J. Chromatogr., A* **2000**, *894*, 19.

(168) Aota, A.; Nonaka, M.; Hibara, A.; Kitamori, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 878.

(169) Valdes, J. R.; Santamarina, J. C. *Can. Geotech. J.* **2008**, *45*, 177.

(170) Vaidya, R. N.; Fogler, H. S. *Colloids Surf.* **1990**, *50*, 215.

(171) Boek, E. S.; Ladva, H. K.; Crawshaw, J. P.; Padding, J. T. *Energy Fuels* **2008**, *22*, 805.

(172) Georgieva, K.; Dijkstra, D. J.; Fricke, H.; Willenbacher, N. *J. Colloid Interface Sci.* **2010**, *352*, 265.

(173) Wyss, H. M.; Blair, D. L.; Morris, J. F.; Stone, H. A.; Weitz, D. A. *Phys. Rev. E: Stat., Nonlinear Soft Matter Phys.* **2006**, *74*, 061402.

(174) Venkatesan, R.; Nagarajan, N. R.; Paso, K.; Yi, Y. B.; Sastry, A. M.; Fogler, H. S. *Chem. Eng. Sci.* **2005**, *60*, 3587.

(175) Naber, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 9469.

(176) Yen, B. K. H.; Gunther, A.; Schmidt, M. A.; Jensen, K. F.; Bawendi, M. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 5447.

(177) Kreutzer, M. T.; Gunther, A.; Jensen, K. F. *Anal. Chem.* **2008**, *80*, 1558.

(178) Khan, S. A.; Gunther, A.; Schmidt, M. A.; Jensen, K. F. *Langmuir* **2004**, *20*, 8604.

(179) Xu, S. Q.; Nie, Z. H.; Seo, M.; Lewis, P.; Kumacheva, E.; Stone, H. A.; Garstecki, P.; Weibel, D. B.; Gitlin, I.; Whitesides, G. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 724.

(180) Braden, T. M.; Gonzalez, M. A.; Jines, A. R.; Johnson, M. D.; Sun, W. (Eli Lilly and Co.). U.S. Patent Appl. 2008/072461, 2009.

(181) Baxendale, I. R.; Ley, S. V. In *New Avenues to Effcient Chemical Synthesis: Emerging Technologies*; Seeberger, P. H., Blume, T., Eds.; Springer: New York, 2007, p 151.

(182) Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. K. *Synlett* **2006**, 427.

(183) Baxendale, I. R.; Deeley, J.; Griffiths-Jones, C. M.; Ley, S. V.; Saaby, S.; Tranmer, G. K. *Chem. Commun.* **2006**, 2566.

(184) Qian, Z. Z.; Baxendale, I. R.; Ley, S. V. *Synlett* **2010**, 505.

(185) Ley, S. V.; Baxendale, I. R. *Natl. Rev. Drug Discovery* **2002**, *1*, 573.

(186) Baumann, M.; Baxendale, I. R.; Ley, S. V. *Mol. Divers.* **2011**, *15*, 613.

(187) Hickman, D. A.; Weidenbach, M.; Friedhoff, D. P. *Chem. Eng. Sci.* **2004**, *59*, 5425.

(188) van Herk, D.; Castano, P.; Makkee, M.; Moulijn, J. A.; Kreutzer, M. T. *Appl. Catal., A* **2009**, *365*, 199.

(189) Bengtsson, M.; Laurell, T. *Anal. Bioanal. Chem.* **2004**, *378*, 1716.

(190) Challis, R. E.; Povey, M. J. W.; Mather, M. L.; Holmes, A. K. *Rep. Prog. Phys.* **2005**, *68*, 1541.

(191) Hawkes, J. J.; Barber, R. W.; Emerson, D. R.; Coakley, W. T. *Lab Chip* **2004**, *4*, 446.

(192) Hawkes, J. J.; Coakley, W. T. *Sens. Actuators, B* **2001**, *75*, 213.

(193) Laurell, T.; Petersson, F.; Nilsson, A. *Chem. Soc. Rev.* **2007**, *36*, 492.
(194) Lilliehorn, T.; Simu, U.; Nilsson, M.; Almqvist, M.; Stepinski, T.; Laurell, T.; Nilsson, J.; Johansson, S. *Ultrasonics* **2005**, *43*, 293.
(195) Mason, W. P. *Physical Acoustics*; Academic Press, 1982.
(196) Nilsson, A.; Petersson, F.; Jonsson, H.; Laurell, T. *Lab Chip* **2004**, *4*, 131.
(197) Petersson, F.; Aberg, L.; Sward-Nilsson, A. M.; Laurell, T. *Anal. Chem.* **2007**, *79*, 5117.
(198) Petersson, F.; Nilsson, A.; Holm, C.; Jonsson, H.; Laurell, T. *Lab Chip* **2005**, *5*, 20.
(199) Petersson, F.; Nilsson, A.; Jonsson, H.; Laurell, T. *Anal. Chem.* **2005**, *77*, 1216.
(200) Poesio, P.; Ooms, G. *J. Pet. Sci. Eng.* **2004**, *45*, 159.
(201) Spengler, J.; Jekel, M. *Ultrasonics* **2000**, *38*, 624.
(202) Laurell, T.; Petersson, F.; Nilsson, A. *Chem. Soc. Rev.* **2007**, *36*, 492.
(203) Browne, D. L.; Deadman, B. J.; Ashe, R.; Baxendale, I. R.; Ley, S. V. *Org. Process Res. Dev.* **2011**, *15*, 693.
(204) Durr, M.; Kentsch, J.; Muller, T.; Schnelle, T.; Stelzle, M. *Electrophoresis* **2003**, *24*, 722.
(205) Kralj, J. G.; Lis, M. T. W.; Schmidt, M. A.; Jensen, K. F. *Anal. Chem.* **2006**, *78*, 5019.
(206) Gijs, M. A. M. *Microfluid. Nanofluid.* **2004**, *1*, 22.
(207) Pamme, N. *Lab Chip* **2006**, *6*, 24.
(208) Pamme, N. *Lab Chip* **2007**, *7*, 1644.
(209) Pamme, N.; Manz, A. *Anal. Chem.* **2004**, *76*, 7250.
(210) Pamme, N.; Wilhelm, C. *Lab Chip* **2006**, *6*, 974.
(211) Rodriguez-Villarreal, A. I.; Tarn, M. D.; Madden, L. A.; Lutz, J. B.; Greenman, J.; Samitier, J.; Pamme, N. *Lab Chip* **2011**, DOI: 10.1039/C0LC00464B.
(212) Inyang, E.; Oyinlola, S. In *The Eighth SPE International Conference on Health, Safety, and Environment*; Society of Petroleum Engineers: Richardson, TX, 2006; SPE 98406, p 1.

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