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Continuous Flow Processing of Slurries: Evaluation of an Agitated Cell Reactor

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ABSTRACT: A general method for the continuous processing of suspensions and particulates is reported. A commercially available agitating cell reactor which uses a transverse mixing motion to maintain solids in suspension has been successfully applied to a salt-forming reaction. The flow device delivered 208 g of *N*-iodomorpholinium hydroiodide salt over a 9-h period (equating to 3.88 kg/week) under optimized conditions. The reactor is suitable for the medium-scale (5 kg) processing of solid-forming reactions and appears to offer the potential for a variety of more complex applications.

INTRODUCTION

The application of continuous flow processing and enabling technologies has gained in popularity over recent years in both academic and industrial laboratories.[1] The uptake of these methods can be considered an endorsement that flow chemistry truly offers benefits for many reactions over traditional batch transformations.[2] A fully optimized flow process can be used to continually synthesize complex products in a single telescoped process from inexpensive and simple starting materials, a task unparalleled by batch chemistry methods.[3] Further to this, the residency time within a flow reactor for such a process is often significantly shorter than the total time for the individual batch reactions due to improved heat/mass transfers and a reduced number of workups and downstream processing events. The use of in-line scavengers and catch and release techniques allows for products to be isolated in high purity and facilitates multistep sequences of integrated reactions.[4] Additionally, continuous flow processing can offer significant safety benefits; for example, hazardous or sensitive intermediates can be generated and immediately consumed in a subsequent synthesis step.[5] However, as with any emerging technique, there are still significant issues and limitations associated with flow synthesis that require innovative solutions. For instance, during segmented flow, dispersion is one such problem, especially when one wishes to introduce a third stream of a precious reagent. Nevertheless, solutions to this particular problem are beginning to emerge.[6] Examples of other restrictive hurdles which inhibit the adoption of flow chemistry include the need for continuous in-line solvent switching,[7] rapid workup and extraction processes,[8] access to low temperature conditions,[9] and the perennial problem of dealing with the formation and processing of solids or suspensions that clog and foul up flow devices. While headway has been made in solving all of these issues, there is scope for improvement.

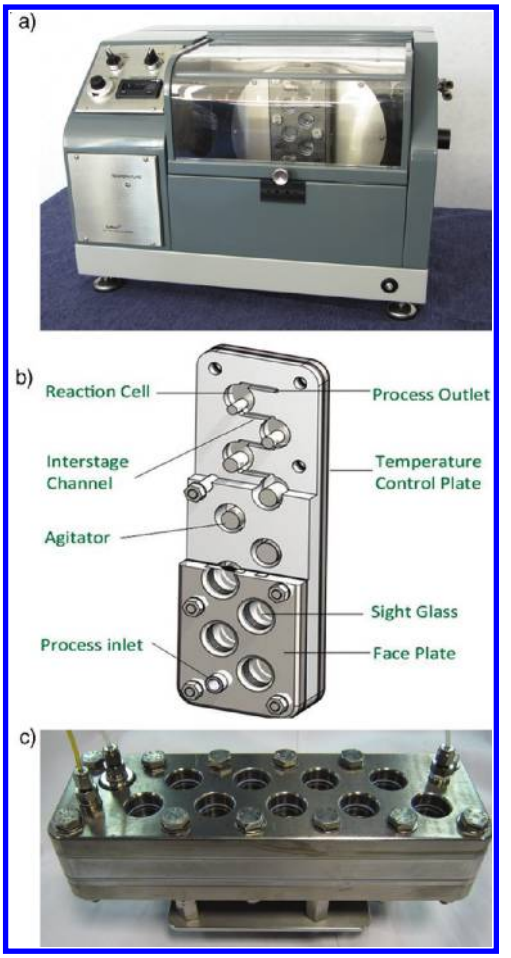

Figure 1. (a) The Coflore ACR. (b) Reactor block, agitated cell reactor. (c) Profile of the reactor block.

Probably the most problematic issue for standard continuous flow reactors is fouling due to solid build up occurring at back pressure regulators and small gauge tubing connectors or at sharp turns in the reactors channeling. Critical obstruction of such fittings have been prevented by the brief introduction of an auxiliary solubilizing solvent introduced immediately prior to the problematic site.[10] Alternatively, the use of ultrasonication or pulsed agitation can prevent the build up of particulates in certain cases.[11] There are also a number of targeted methods using

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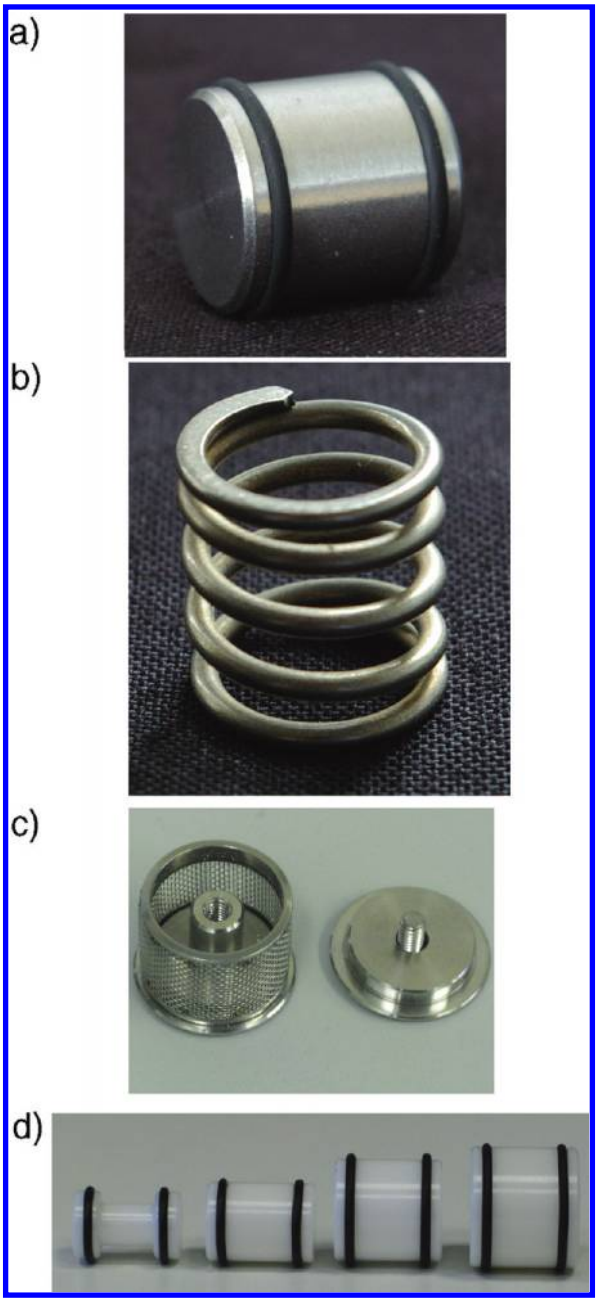
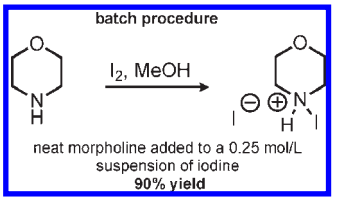


Figure 2. (a) Hastelloy agitator. (b) High shear agitator. (c) Catalyst basket agitator. (d) Variable volume agitators in PTFE.

specifically engineered reactors which have been designed to facilitate the transport of slurries.[12] However, these solutions are typically geared towards a specific synthesis problem and as such none of these can be considered to be particularly general. Herein, we describe our initial results using a commercially available agitating flow reactor to alleviate the problem of flow processing slurries.

The Coflore agitating cell reactor (ACR) is a recently developed flow device broadly based on the continuously stirred tank reactor (CSTR) principle[13] (Figure 1). It features a reaction block which is mounted on an laterally shaking motor. Like other CSTRs, it relies on mechanical stirrers for mixing, although, where traditional mechanical mixers employ rotating stirrers, the Coflore reactor utilizes freely moving agitators within the reactor

Scheme 1. Batch mode conditions for the preparation of *N*-iodomorpholinium·HI



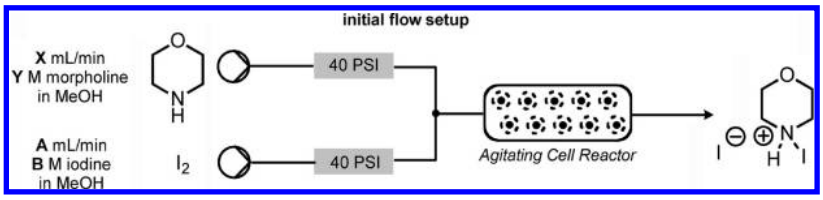
block. The reactor block is constructed from a series of layers. A back plate which can be heated or cooled (−40 to 140 °C with the addition of a heater/chiller unit). A central flow plate containing the cells, interconnecting channels and the agitators, and a front plate which features a series of precision cut circular holes. The holes can be covered with either borosilicate windows or metal plates, the latter are best used for work at elevated temperatures and pressures. Alternatively, the disk covers can be replaced with injection ports, which allow reagents to be introduced directly into the interior of the cells, thus providing additional input sites. The reaction chambers are made up of a series of individual cells each with an internal volume of approximately 9.8 mL, these are joined by wide bore, square cut, interconnecting channels; 30 mm in length and 4 mm in width. The volume of the cells is reduced depending on the type of agitator used. Several agitator types have been designed for the reactor block: variable volume, high shear and catalyst basket agitators (Figure 2). The agitators move transversely across the cells when the body of the reactor is shaken by the agitator motor. The oscillation frequency (agitation rate) can be varied accordingly in order to achieve optimal flow conditions depending upon the precipitate or slurry density (0.1−10 Hz operating frequency). The whole system is sealed with a series of PTFE gaskets. The total internal volume of the hastelloy reactor block reported here is around 100 mL (not accounting for the high shear agitators used) and has a safe working pressure of 10 bar in its current configuration.

The agitators move in rapidly reversing transverse movements and consequently generate efficient mixing without the need for mixing baffles. By employing this transverse mixing method as opposed to conventional rotational mixing, the problems of centrifugal separation are avoided when materials of different density are present. The agitators do not use drive shafts for motive power which negates the requirement for further mechanical seals or magnetic couplings and avoids the problems associated with seal leaks, buffer fluids and stabilizing bushes. With specific regard to the continuous processing of slurries, the ACR is very simple in design with no dead volumes to trap or cause solid build up (Figure 1). This particular agitative mode of mixing is ideal for keeping suspensions uniformly dispersed and preventing solids from settling out.

RESULTS AND DISCUSSION

In order to test the reactor's ability to process a slurry we opted for a reaction which quickly produces a suspension upon mixing of two input streams (note: standard piston pumps commonly used in flow equipment are not designed to pump slurries through the head piece) and where the starting materials were relatively inexpensive. The formation of the hydroiodide salt of *N*-iodomorpholine by reaction of morpholine with iodine met these criteria.[14] This salt has been used as a source of electrophilic

Table 1. Initial flow setup and results



entry	X	Y	A	B	combined conc	comment
1	1.5	0.1	1.5	0.1	0.050	suspension slow to form
2	0.3	1.0	3.0	0.1	0.091	suspension quicker to form, less solvent waste
3	0.6	1.0	6.0	0.1	0.091	slurry processed for 7.5 h, 65.5 g, 71%

iodine and has recently found utility for the synthesis of iodoalkynes.[15] Furthermore, a new flow process could be benchmarked against the traditional method of making this useful iodinating reagent. Typically the batch mode reaction is run by the addition of an equimolar amount of neat morpholine to a stirring solution of elemental iodine in methanol (Scheme 1. The reaction mixture is then matured for one hour before filtration and drying of the resulting orange solid, the whole process usually generates around 90% yield of product.

Initial efforts to translate this reaction into a flow process highlighted that the batch reaction was not homogeneous with respect to iodine. It was observed that the maximum solubility of iodine in methanol was only 0.1 M, higher concentrations were always associated with solid iodine being present. Initially therefore, a 0.1 M solution of iodine was mixed with an equimolar solution of morpholine in methanol. However, at these concentrations (0.05 M after mixing of the two streams), it was found that the formation of a product suspension was expectedly slow (Table 1, entry 1). In order to produce a mixed stream with a concentration greater than 0.05 M the concentration of morpholine was increased to 1 M and the pump flow rates used to ensure a 1:1 stoichiometry was still present at the T-piece, thus providing a 0.091 M mixed solution (Table 1, entry 2). We were delighted to find that under these conditions the desired salt was produced quickly and that indeed the ACR facilitated the continuous processing of a slurry by ensuring a uniformly dispersed suspension was present at all times (initially this was tested for one hour, Table 1, entry 2, see Figure 3). Moreover, we found that the process remained effective at increased flow rates (Table 1, entry 3). The reactor configuration for this process consisted of two Knauer K120 pumps feeding the two reagents into a T-piece, the output of which was fed into the reactor by a 20 mm long (1/16" i.d.) tube, the distance between the T-piece and the agitating cell reactor was kept short so that any formed solids would also be agitated by the oscillation of the reactor. The output of the reactor was fixed to a large sinter funnel on top of a buchner flask attached to a low vacuum. With regards to waste disposal, the buchner collection flask was periodically switched such that waste solvent could be disposed of in a safe and orderly fashion. Overall, this protocol allowed us to continuously process a slurry for 7.5 h which delivered 65.5 g of isolated solid product (71% yield) which is the equivalent of 1.47 kg/week of continuous processing time.

However, given the difference in yields between the batch method and the current flow process (approximately 20% in favor of the batch), it was suspected that the product was partially soluble in methanol as the only real difference between the two methods was the concentration of the formed product suspension. Indeed this was verified upon repeating the batch reaction under concentrations matching those used in flow when we obtained a near identical yield of 73%. Moreover, concentration

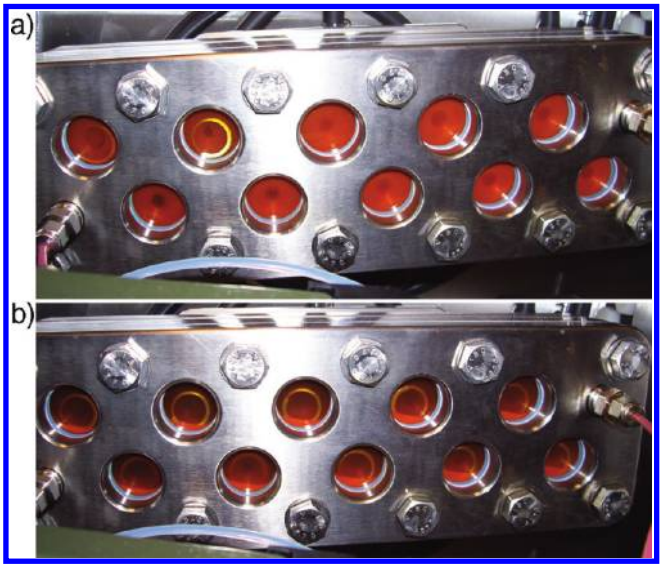


Figure 3. (a) Rector block, agitation on, uniformly dispersed suspension. (b) Reactor block, agitation off, settled out solid.

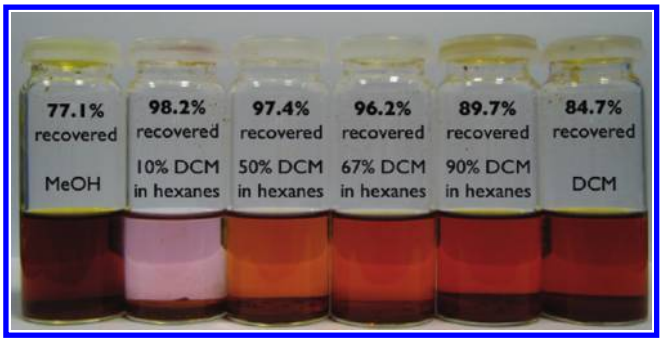


Figure 4. Solubility tests of *N*-iodomorpholine·HI in a variety of solvents. Percentage recoveries represent the quantity of solid reisolated after filtration.

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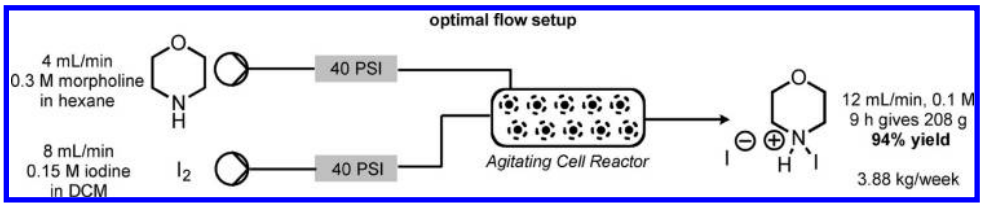
Scheme 2. Optimized flow conditions



of the methanol liquor resulted in the precipitation of additional product. To improve the isolated yield of the flow process an alternative solvent system was sought which would ideally enable near quantitative precipitation of the HI salt whilst also providing >0.1 M homogeneous solutions of the starting reagents. We began by carrying out solubility tests, measuring 1 mmol (341 mg) of the *N*-iodomorpholinium salt into a series of vials and stirring them in 10 mL of the solvent system to be assessed (Figure 4). For these investigations dichloromethane was chosen as the polar component and hexane as the nonpolar solvent; these were mixed in a number of ratios. It was found that with applied ultrasonication a 0.15 M solution of iodine in dichloromethane could be readily prepared.

In order to quantitatively determine the solubility of the salt in the six solutions the remaining solids were filtered (using their own liquor to wash any remaining particulates from the vials) and dried to constant mass. The percentage recoveries are overlaid in Figure 4, showing methanol to be the best solute. It should be noted that the disparity in recoveries for the methanol batch reaction compared to this control test is likely due to the differences in concentration (0.091 M for the batch mimic of flow and 0.100 M for the latter test). With regards to the 10%, 50%, and 67% solvent mixtures we considered the potential flow characteristics prior to conducting the full flow experiment. A 10% DCM in hexane ratio would arise from the merging of a 0.15 M iodine in DCM solution with a 0.017 M morpholine in hexane stream flowing at 9 times the rate which would provide a 0.015 M product concentration. In the case of the 50% mixture, both reactant streams could be run at the same flow rates and concentrations which would lead to a 0.075 M concentration of the mixed streams, whereas a 67% mixture would be created by mixing two parts of the iodine solution to one part of a 0.3 M morpholine solution, leading to a 0.1 M concentration at the streams' unison. Therefore, we opted for the latter conditions as this would provide a suitable challenge to the agitated cell reactor; not only would the concentration of the product stream be higher than the methanol process but the slurry should contain ~20% more solid material. Having selected a set of conditions the specified mixtures were pumped through the ACR reactor continuously for a period of time. Under this regime, constant processing was easily maintained for a period of 2 h, after which some blocking at the input T-piece was observed. The reactor block setup was therefore reconfigured, replacing the first borosilicate window with an injection nozzle, thus the initial mixing and suspension formation occurred within the agitated reactor block. In this improved configuration the heavier slurry was successfully processed for 9 h giving 208 g of solid product in a 94% yield (Scheme 2), with very little manual handling (restocking of the reagent bottles and removal of solvent waste). This initial trial of the agitating cell reactor equipment adequately demonstrates its suitability for medium-scale processing as up to 3.88 kg of material could be obtained if the process was run for one week.

CONCLUSIONS

In conclusion, advantages of the ACR are accrued through easy containment of corrosive reagents and the ability to continually process material on-demand. This work therefore constitutes a proof of principle of the new agitating cell reactor and opens up new opportunities for the processing of slurries and solid precipitates. The concept is highly adaptable to include solid phase reagents and scavenging protocols and is readily scaled by appropriate engineering of the system. We are in no doubt that agitating cell reactors offer an exceptional improvement to the flow chemist's repertoire and provide a viable alternative to batch processing for medium scale synthesis. Salt forming reactions are a common process for the preparation of many API's, the present study demonstrates the potential for such processes to be carried out in continuous flow with minimal manual handling.

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