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Back Pressure Regulation of Slurry-Forming Reactions in Continuous Flow

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The handling of solid components in flow chemical processes is still a significant challenge. Current devices for regulating back pressure in laboratory-scale flow chemistry experiments are vulnerable to blockage by solid particulates. A simple device is presented herein for generating back pressure in continuous flow processes that produce chemical slurries. The prototype was constructed from commercially available components and accommodated the use of superheated reaction conditions generated in an agitating cell reactor used to produce a suspended precipitate product.

Keywords: Back pressure regulation, Plug-flow reactor, Pressure systems, Slurry-forming reactions

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1 Introduction

The use of enabling technologies [1–10] is becoming an increasingly popular tactic in modern synthetic chemistry [11–17]. Machines can assist in almost every aspect of the synthesis process from reagent addition to workup and purification, and even beyond to identification and biological screening [1–10, 18–20]. This popularity is due to the now well documented benefits of improved heat and mass transfer, reaction control, safety, scalability and potential for automation which are characteristic of continuous chemical processes [1–10].

A 2005 survey of 86 different reactions commonly employed in the fine chemical and pharmaceutical industries revealed that 50 % of reactions could benefit from being turned into a continuous flow process, either through improved yields and scalability or for safety considerations [21]. However, 63 % of those reactions contained solid components which were considered incompatible with the microfluidic reactors of the time. Particulates represent one of the most troublesome materials to handle by flow chemists, due to their tendency to cause blockages in tubular flow reactors [22]. This is a significant limitation of flow chemistry which is deserving of more attention.

General techniques for handling particulates in flow reactors fall into two broad categories [22]. The first and most obvious involves the manipulation of the chemical conditions to prevent precipitation. This can be through selection of appropriate solvents, the use of multiphasic systems [23–29], adjustment of reagent concentrations and other transformational sequences [30–32], or by immobilisation of troublesome components

onto a porous support material [33]. The second general approach is to design reactors which are resistant to accumulation of precipitated material. This can be achieved through the use of “non-stick” materials [34], larger-bore passages [35], or the application of external forces such as ultrasound [36–39] or mechanical agitation [40].

An approach from our own laboratory for handling slurry-forming reactions in continuous flow makes use of an agitating cell reactor (ACR) [41], as in the continuous preparation of iodomorpholine hydroiodide [42]. The reactor consists of a series of ten 10-mL reaction chambers set into a hastelloy reactor block. Freely moving agitators are included in each of the cells and are driven by lateral shaking of the reactor block to provide dynamic mixing. The ACR proved remarkably effective at handling flows of the thick chemical slurry and, consequently, further applications of this technology were investigated. Using the reactor at atmospheric pressure limited its application to simple salt-forming reactions. The ability to operate under high pressure, and thus access superheated conditions, is one of the key benefits of continuous processing but currently available flow reactor back pressure regulator systems do not tolerate solid particulates and are a common blockage point in any reactor. Therefore, it would be highly desirable to have a laboratory-scale back pressure regulator which could tolerate low level particulates or even chemical slurries.

2 Design

Two potential concepts for a blockage-resistant back pressure regulator were identified. The first makes use of a peristaltic pump to form a rolling restriction point which would generate backpressure in the system while continually expelling solid material. Early testing revealed that this peristaltic back pressure regulator suffered from durability issues with the peristaltic tubing rapidly deteriorating under the harsh operating con-

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ditions. Realization of this concept would require peristaltic tubing that is both chemically resistant and tolerant of pressures in excess of 0.69 MPa. This high pressure was considered beyond the safe operating window of current commercially available chemically resistant peristaltic pump tubing.

As a result, a second approach was considered, consisting of a collection vessel which could be pressurised by gas. To permit the free flowing of chemical slurries, the flow paths had to be sufficiently wide-bore and without restrictions to prevent blockages occurring under common flow chemistry conditions (Fig. 1). Pressurised collection vessels have been used successfully in continuous flow reactors utilising gases or high temperature and pressure microwave conditions [43–48].

The pressurised collection vessel (Fig. 1) was constructed using commercially available stainless-steel Swagelok® components in a tube-in-tube design. Previously, such a setup was employed as prototype equipment for gas reactors and spray drying systems [49–51]. The tube-in-tube design allows a single, unrestricted polytetrafluoroethylene (PTFE) polymer tube (Fig. 1 b) to deliver the process stream directly into the collection chamber (1 L capacity, PTFE-lined stainless-steel). Around this tube, a pressurised gas feed maintains the vessel and connected upstream flow reactors at a set pressure which can be controlled via an adjustable diaphragm sensing back pressure regulator on the gas outflow. The device can safely accommodate temperatures up to 140 °C and up to 1 MPa of pressure in the upstream flow reactor. The pressurised gas inlet incorporates a quick connect system to facilitate rapid disconnection of the gas feed and simple relocation of the system which also acts as a convenient safety feature. At the bottom of the pressure chamber, a large-bore, quarter-turn valve allows the contents of the chamber to be expelled whilst maintaining back pressure

inside the flow reactor system. This prevents sudden vaporisation of the reaction solvent when under superheated conditions.

The main body of the device was constructed from 316 and 304 grade stainless steel for strength while all valves and regulators were fitted with perfluoroelastomer (FFKM or polychlorotrifluoroethylene (PCTFE)) seals for compatibility under a wide range of chemical conditions. The stainless-steel collection chamber is PTFE-lined but the fluid path contains smaller components with exposed stainless steel and the acid resistance of the device is therefore limited. Inlet and outlet connections to the device consist of perfluorinated polymer (PTFE) tubing in common $1/8$ and $1/4$ in outer diameter (o.d.) sizes. The exception to this is the pressurised gas inlet which was constructed from 6-mm polyvinyl chloride (PVC) tubing to be compatible with an existing 0.5 MPa piped supply of nitrogen gas.

3 Optimization and Initial Testing

To test the prototype pressure chamber, a simple Claisen condensation reaction was chosen which previously was found to produce thick slurries when conducted in flow mode. The conversion of aryl ketones (1) to α -enol- γ -keto esters (2) occurs quickly under superheated conditions and many substrates produce insoluble products as the reaction progresses. These materials are useful for the preparation of a wide variety of heterocycles [52].

The first prototype was designed around a $1/8$ in o.d. ($1/16$ in inner diameter (i.d.)) process inlet tube but while slurries flowed through the tube there was a tendency for hydro-

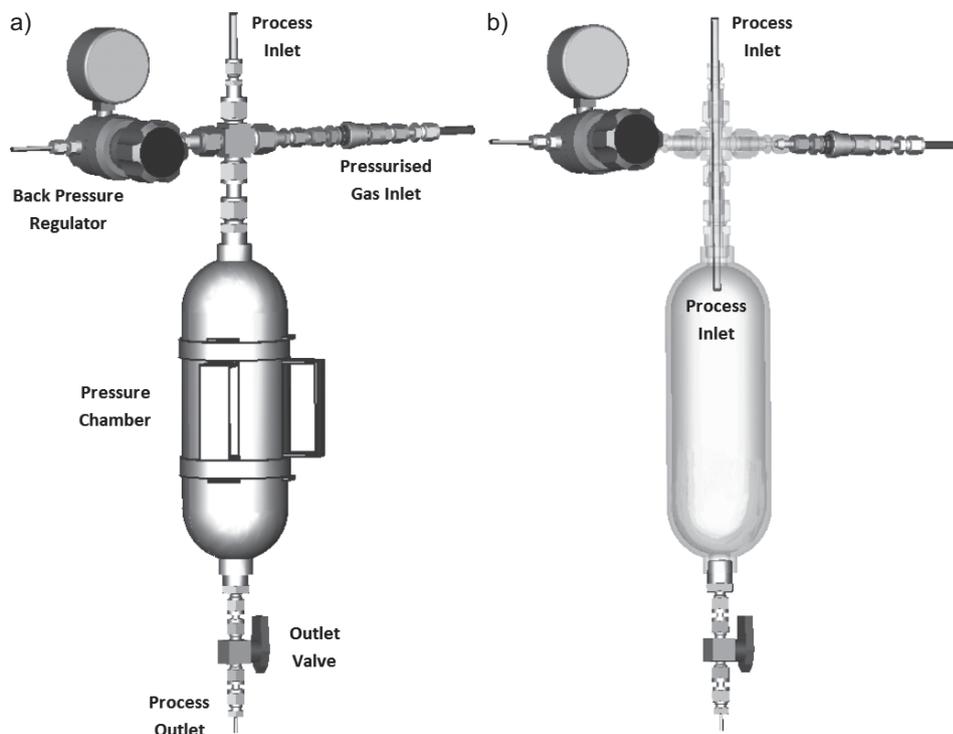


Figure 1. Assembled pressure regulation device (left) and a transect view showing the unrestricted process inlet tube (right).

dynamic blockage [22] to occur at the point of connection to the pressure chamber. It appeared that the crimped Swagelok connection at this point created a minor restriction in the tube diameter and was therefore causing hydrodynamic blockage to occur inside the tube. To obviate this, the device was redesigned around a $\frac{1}{4}$ in o.d. ($\frac{3}{16}$ in i.d.) process inlet tube. Testing confirmed that blockages did not occur at the connection point using this improved configuration. Fig. 2 and Tab. 1 illustrate how the optimized device was assembled from its components.

4 Application

With the newly developed pressure chamber, a series of aryl ketones (**1**) were processed in the agitating cell reactor under conditions where the products precipitated, which aids their isolation by filtration (Fig. 3). A solution of the aryl ketone (**1a–e**) and diethyl oxalate (two equivalents) in methanol was pumped into the ACR via the inlet connection while a second stream containing sodium methoxide (two equivalents) in methanol was pumped into the ACR through a connection to the first reaction chamber. Reaction occurred quickly and often resulted in the formation of a thick slurry. The use of ceramic cylinder agitators inside the reactor cells enabled solid material to remain suspended and travel through the reactor for a residence time of approximately 25 min. A third stream of aqueous

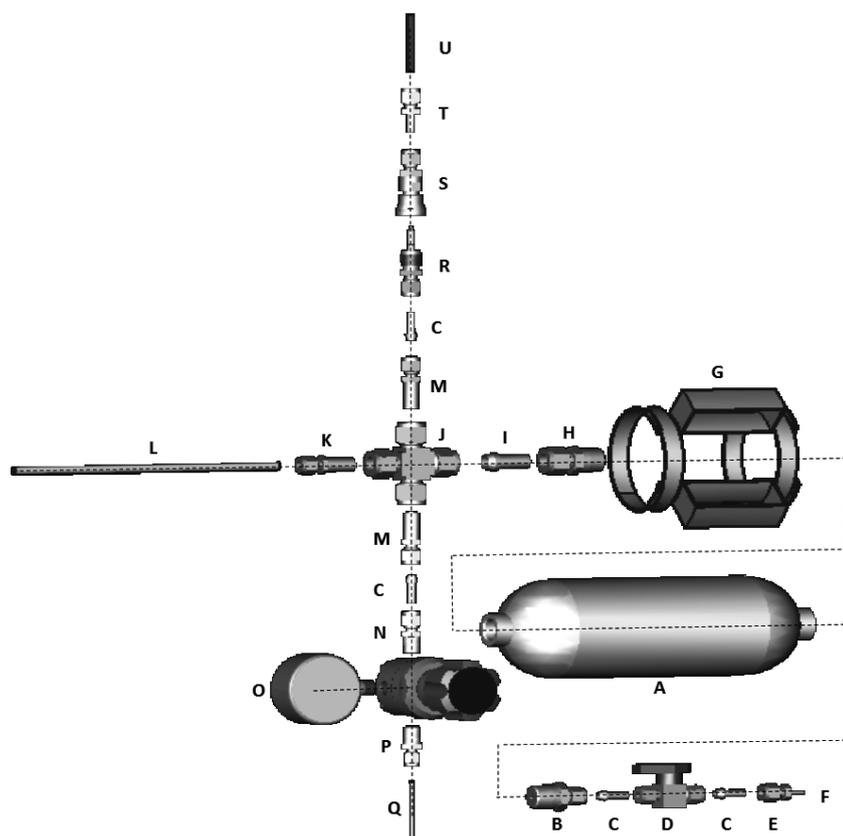
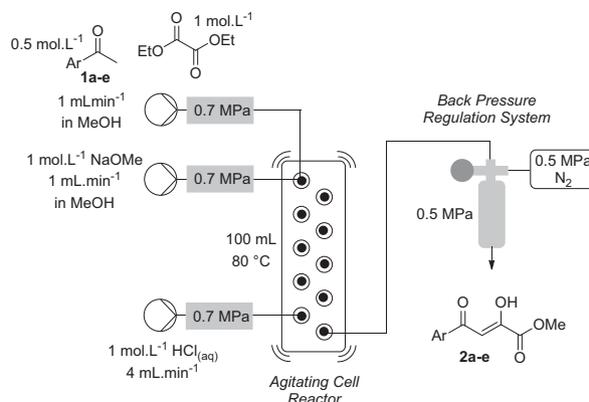


Figure 2. Exploded diagram showing the device components. Refer to Tab. 1 for component descriptions and part numbers.



Entry	Ar	Conversion ^a [%] (Yield [%]) ^b
1 ^c	<i>p</i> -Methylphenyl (2a)	95 (58)
2 ^c	Phenyl (2b)	84 (52)
3	Napthalene-2-yl (2c)	60 (58)
4	<i>p</i> -Methoxyphenyl (2d)	85 (73)
5	<i>p</i> -Bromophenyl (2e)	95 (90)

Figure 3. Preparation of slurries of α -enol- γ -keto esters (**2a–e**) in a continuous agitating cell reactor (ACR) fitted with a blockage-resistant pressure regulation system. ^aAnalysis of the slurry mixture by ¹H NMR spectroscopy. ^bIsolated by vacuum filtration of the output solution. ^cMethanol was removed by rotary evaporation to increase product recovery by filtration.

hydrochloric acid was pumped into the ACR directly into the 9th reaction chamber to quench the reaction and precipitate the product α -enol- γ -keto ester (**2a–e**). The outlet of the ACR was linked to the back pressure regulation system by a 60 cm length of $\frac{1}{4}$ in o.d. PTFE tube to allow smooth passage of the chemical slurry into the pressurised collection vessel.

It was envisaged that the chamber could be periodically emptied by partially opening the outlet valve and allowing the chamber contents to be expelled into a collection vessel at atmospheric pressure. Pleasingly, it was found that this was indeed possible and the chemical slurry was expelled through a 20 cm length of PTFE tubing and delivered into a glass flask without difficulty. Furthermore, the outlet valve could be left partially open to continuously release the chemical slurry. The 0.5 MPa nitrogen gas supply maintained the back pressure in the flow system and no drop in pressure was observed when operating under these continuous conditions.

The crystalline α -enol- γ -keto ester products (**2c–e**) were isolated in good yield by a simple vacuum filtration of the slurry obtained from the reactor (Fig. 3). In the case of α -enol- γ -keto esters **2a** and **2b**, the products were partially soluble in the 1:2

Table 1. Description and part numbers for components used to assemble the back pressure regulation device. ^aPart numbers are provided for specific Swagelok components and refer to the Swagelok catalogue. Where no part number is provided, the component is widely available from multiple commercial sources.

Label	Part No. ^a	Description
A	304L-HDF8-1000T	PTFE-lined, 1000 cc stainless-steel sample cylinder, $\frac{1}{2}$ in NPT _F ports
B	SS-400-1-8	$\frac{1}{4}$ in Swagelok to $\frac{1}{2}$ in NPT _M adapter
C	SS-401-PC	$\frac{1}{4}$ in Swagelok connector
D	SS-4P4T-KZ	$\frac{1}{4}$ in turn plug valve, $\frac{1}{4}$ in Swagelok connections, FFKM seals
E	SS-400-R-2	$\frac{1}{4}$ in to $\frac{1}{8}$ in Swagelok reducer
F		$\frac{1}{8}$ in o.d., $\frac{1}{16}$ in i.d. PTFE outlet tube to collection vessel
G	MS-5K-CY-4 ^o	Stainless-steel carry handles
H	SS-810-1-8	$\frac{1}{2}$ in Swagelok to $\frac{1}{2}$ in NPT _M adapter
I	SS-811-PC	$\frac{1}{2}$ in Swagelok connector
J	SS-810-4	$\frac{1}{2}$ in Swagelok cross union
K	SS-400-R-8	$\frac{1}{2}$ in to $\frac{1}{4}$ in Swagelok bored through reducer
L		$\frac{1}{4}$ in o.d., $\frac{3}{16}$ in i.d. PTFE tubing connected to ACR
M	SS-400-R-8	$\frac{1}{2}$ in to $\frac{1}{4}$ in Swagelok reducer
N	SS-400-1-4	$\frac{1}{4}$ in Swagelok to $\frac{1}{4}$ in NPT _M adapter
O	KBP1G0D4B5A200B0	Diaphragm sensing back pressure regulator, X-750 alloy diaphragm, PCTFE seat, $\frac{1}{4}$ in NPT _F ports, 0–1.7 MPa pressure rating with gauge
P	SS-200-1-4	$\frac{1}{8}$ in Swagelok to $\frac{1}{4}$ in NPT _M adapter
Q		$\frac{1}{8}$ in o.d., $\frac{1}{16}$ in i.d. PTFE tubing for gas exhaust
R	SS-QC4-D-400KZ	$\frac{1}{4}$ in Swagelok quick connect stem, FFKM seals
S	SS-QC4-B-400KZ	$\frac{1}{4}$ in Swagelok quick connect body, FFKM seals
T	SS-6M0-R-4	6 mm to $\frac{1}{4}$ in Swagelok reducer
U		6 mm o.d. PVC tubing to deliver pressurised gas

(v/v) methanol/water solvent and removal of the methanol by rotary evaporation was required in order to recover the solid product in moderate yields of 58 % and 52 %.

The physical characteristics of the chemical slurries were dependent on the substrate and displayed a range of densities, crystallinity, particle sizes, and viscosities. Pleasingly, it was observed that no blockages formed in the back pressure regulation system, even when processing thick chemical slurries such as those formed by the *p*-methoxy and *p*-bromo keto esters (**2d–e**); see Fig. 3, Entry 4 and 5.

In our experience, variation in solubility is a common problem when exploring reaction scope using flow reactors. The inability of standard back pressure regulators to cope with even small quantities of precipitated material has meant that substrates or concentrations have to be selected carefully to minimise the potential for blockages. It is assumed that this blockage-resistant back pressure regulator will be a useful addition to any flow chemist's tool box. The 1-L device presented here

was specifically scaled for use with a high flow ($> 5 \text{ mL min}^{-1}$) 100-mL agitating cell reactor processing chemical slurries. If developing a similar device for use with meso-fluidic reactors, e.g., $< 1 \text{ mL min}^{-1}$ flow rate, then a smaller device should be equally effective at resisting blockage by light precipitates. For example, a 150-mL sample cylinder with $\frac{1}{4}$ in NPT ports could form the pressure chamber of a smaller back pressure regulator connected to a $\frac{1}{8}$ in o.d. process line from a meso-fluidic reactor. Indeed, the early prototype device with $\frac{1}{8}$ in o.d. process inlet tubing was already found to be a useful blockage-resistant back pressure regulator for precipitating reactions performed in a Vapourtec R2/R4 flow reactor [53].

Future modifications to this back pressure regulator could involve the inclusion of a raised outflow tube to enable in-line decanting or even filtration of flow streams producing solid by-products. Such a system could allow the telescoping of processes involving solid materials. The development of these types of devices is currently underway in our laboratories.

5 Conclusions

A simple alternative method of generating back pressure in flow reactor systems was developed. The device is constructed from commercially available components, is adaptable, and most importantly was found to be effective in the flow processing of thick chemical slurries under high-pressure conditions.

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The authors have declared no conflict of interest.

Abbreviations

ACR	agitating cell reactor
FFKM	Kalrez perfluoroelastomer
i.d.	inner diameter
NPT	national pipe thread taper
o.d.	outer diameter
PCTFE	polychlorotrifluoroethene
PTFE	polytetrafluoroethylene
PVC	polyvinyl chloride

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