Flow chemistry

The aims of green chemistry and industry support one another when a process is considered for upscaling; it needs to be safe, generate minimal waste and be energy efficient. A fundamental approach to green chemistry for industrial application is to address such issues at the outset of the project, ideally at the reaction discovery stage. Flow chemistry is an enabling technology that fits well at the interface between reaction discovery and scale up; such reactors offer substantial improvements in the management of heat and mixing as well as scalability, energy efficiency, waste generation, operational safety, offer a wide range of reaction conditions and unique opportunities for catalyst supports, telescoping reactions among others.[1][2][3]

The advantages in efficiency and sustainability that continuous flow offers are that it allows for efficient use of energy and time. Both aspects being directly related to reaction rate as a slow reaction would require more time for completion. The standard approach for speeding up a reaction is to increase its temperature, however batch reactors are limited to the boiling point of the reaction solvent/reagents. By comparison flow reactors lend themselves well to safe temperature and pressure manipulation beyond that of standard atmospheric conditions. Thus reactions carried out in flow are often faster than the corresponding batch reactions and offer improved energy, time and even space efficiency, as faster reactions will require smaller reactors.[4] Many green solvents such as acetone or methanol have low boiling points making them inapplicable for use in certain reactions; performing reactions at high pressure in a flow reactor allows for their safe use at high temperatures.[4] Supercritical fluids add an extra facet, as they are inaccessible in the absence of high temperature conditions, thus their applicability in flow reactors offers further advantages over batch reactors.[4]

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1. C. Wiles and P. Watts, Continuous flow reactors: a perspective, *Green Chem.*, 2012, **14**, 38-54.
2. S. V. Ley, On Being Green: Can Flow Chemistry Help?, *Chem. Rec.*, 2012, **12**, 378-390.
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4. S. G. Newman and K. F. Jensen, The role of flow in green chemistry and engineering, *Green Chem.*, 2013, **15**, 1456-1472.

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Flask, Pipe, CSTR

The flask is an integral piece of equipment to the synthetic organic or medicinal chemist at lab scale however, on large scale the flask is uneconomical. The bulk chemical, petrochemical and polymer industries all opt for the use of pipes as the reaction vessels of choice, allowing them continuous operation and enhanced control over reaction conditions. The pharmaceutical and fine chemical industries on the other hand, frequently use continuous stirred tank reactors (CSTRs) to perform their reactions. The reason for the disparity of approach between these industries is that in the pharmaceutical industry, process development occurs incrementally over a number of years beginning with milligram scale and increasing successively by several orders of magnitude up to a scale of tons, as required.[1] As such scale up in the pharmaceutical industry is carried out by gradual increase in the size of the reactor rather than performing a costly and time-inefficient redesign of a process.[1]

1. S. G. Newman and K. F. Jensen, The role of flow in green chemistry and engineering, *Green Chem.*, 2013, **15**, 1456-1472.

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Catalysis

Catalysis is an important aspect of green chemistry and there have been many efforts to develop supported catalysts for use on large scale. In small scale batch reactions, the catalyst, reagents, reactants and solvent are mixed together and stirred until reaction completion, after which the bulk liquid is separated by filtration, and the catalyst is collected for re-use or disposal.[1] In continuous systems, the catalyst can be fixed in space over which the reaction mixture is allowed to flow, allowing the reaction and the separation steps to be combined into a single stage.[1] The catalyst remains in the reactor, allowing for ease of recycling; this system also allows the catalyst a longer lifetime as a result of the reduced exposure to the external environment.[2] As a result, reaction rates and catalyst turnover numbers are augmented through use of high catalyst concentrations and continuous recycling.

An area of chemistry that has been difficult to implement on large scale pharmaceutical production is photochemistry; light has long been considered a valuable tool for performing synthetic reactions, it acts as a traceless agent facilitating the reaction without the production of further waste or the need for removal from the reaction mixture.[1][3][4]Though photochemistry has found application on industrial scale, its use is still uncommon in the pharmaceutical and fine chemicals industry; largely due to the use of batch reactors and the challenges associated with using photochemistry on a large scale, where the sheer volume of the reactor does not allow for complete light penetration.[5][6] Flow chemistry allows better access to photochemistry as a tool at a range of scales using inexpensive equipment: the reaction mixture is pumped through a transparent tubing or transparent chip microreactor which is irradiated with a light source, the small diameter of the tubes allows for satisfactory light penetration, permitting all reaction molecules to be exposed to the same amount of heat and light. This comprehensive light exposure generally means that photochemical reactions run in flow tend to be orders of magnitude faster than their corresponding batch reactors.[1]

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technology, *Green Chem.*, 2010, 12, 1687-1703.

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Challenges

One of the major challenges to the efficiency and sustainability of fine chemical and pharmaceutical industrial scale production is that the final product usually involves a multiple step synthesis with numerous work-up and purification steps required at each stage, which impact negatively on the material efficiency of the industry. Thus, approaches that circumvent or simplify these steps can have an enormous environmental impact on multi-step chemical syntheses; even here continuous flow reactors offer a great advantage as they are well suited for telescoping reactions and many methods have been developed to enable this.[1][2]

Reaction scale-up usually requires costly re-optimisation reactions due to the change in mixing and heating properties, thus reactions that may have worked well on bench-scale batch reactions may require increased times, super-cooling, or may be impossible to carry out on large scale. Good reactions should be easily scaled without requiring re-optimisation, since a green reaction should be scalable by default. Again flow methods offer an advantage: the basic way to modify the total amount of product prepared in a continuous system is to change the length of time the reaction is run. *Ergo*, continuous flow processes allow facile alteration of the amount of product output without the need to modify the whole process or by running multiple batches, therefore meeting the green chemical engineering principle of running to meet needs.[1]

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Case studies

This case study was provided by Dr Katherine Jolley during her time at the University of Leeds.

Amines, amides and nitrogen heterocycles are an important class of compounds being one of the most common structures present within pharmaceutical and biologically active compounds and are present in most of the top selling drugs e.g. Aripiprazole for the treatment of depression, Imatinib for the treatment of cancers and Telaprevir for the treatment of Hepatitis C.

The use of *N*-chloramines as reagents offers a convenient and atom efficient route to formation of key nitrogen functionalities including amines, amides and imines, however due to the hazards associated with the formation and reaction of chloramines[1][2] they are an underutilised class of reagents.

N-Chloramines are prepared by reaction of the amine precursor with an electrophilic chlorine source such as chlorine, *N*-chlorosuccinimide (NCS) or hypochlorite salts. Due to the exothermicity of *N*-chloramine formation and the instability of the products formed the reactions often require cooling or controlled addition of reagents.[2] Despite its atom efficiency, use of chlorine gas is undesirable due to its toxicity, strong oxidising properties and it being difficult to handle and use. In addition, hydrochloric acid is produced as a byproduct of the reaction meaning additional processing is required for its neutralisation and removal after chloramine formation. NCS is frequently used for chloramine formation,[2][3][4] however the reaction is atom inefficient and removal of the succinimide by-product is required. Use of hypochlorites as chlorinating reagents is also common, although *t*BuOCl is an expensive and hazardous reagent and is thus less widely used. Recent reports of its formation *in-situ* to avoid the hazards associated with its use are inefficient with high levels of waste generated.[5] NaOCl is a more desirable reagent, being an inexpensive by-product of chlorine manufacture, however in some reports use of NaOCl in chloramine formation has given low yields and can require long reaction times.[2][6][7]

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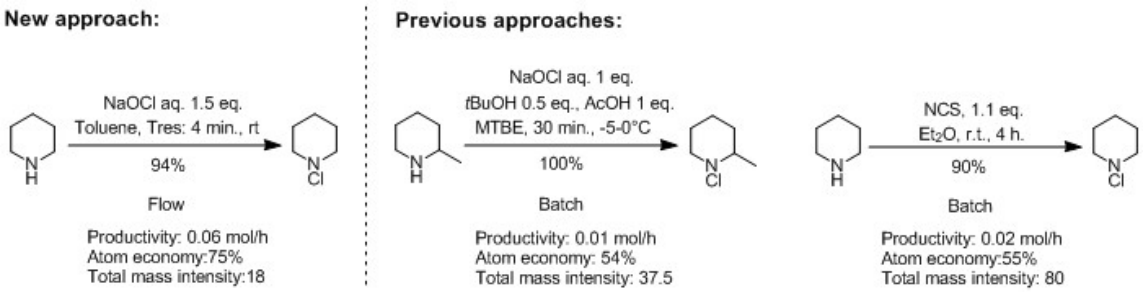
Given the importance of amines and amides, the development of alternative, safer or more sustainable routes to their synthesis is a key field of research. Within the CHEM21 project, researchers have developed a continuous, biphasic process for formation of *N*-chloro-*N*,*N*-dialkylamines by reaction of amines with aqueous NaOCl with enhanced mixing by use of in-line static mixers.[8] Use of continuous flow methodology is beneficial to the reaction allowing:

- Precise control of reaction parameters e.g. reaction time/temperature;
- Improved heat transfer properties removing the need for external cooling of the reaction/reactor;
- Limited volume of reagents reacting at any one time;
- Increased productivity and consistency of product formation.

Use of NaOCl as the chlorinating agent is both economical and convenient and allows for a more atom efficient reaction than use of NCS or *in-situ* formation of *t*BuOCl. Use of biphasic reaction conditions also allows for facile separation of the product within the organic solvent from the water soluble NaOH by-product. Continuous phase separation by way of membrane separators is well known in the literature.[9]



Scheme 1: ***Comparison of CHEM21 continuous synthesis of chloramines[8] with previously published procedures.[5][10]***

The methodology described allows safe and convenient formation of a range of *N*-chloro-*N,N*-dialkylamines without the need for purification or isolation of potentially hazardous or unstable products giving safe and efficient access to an underutilised class of reagents. The reactors used for the process are comprised of widely available generic

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equipment making the methodology accessible to all. Continuous separation of clean product solution from the reaction mixture also means that the process can easily be coupled to further processes for direct use of the chloramine products formed in subsequent reactions. The continuous reaction of chloramines to form more complex amine or amide products has also been investigated within the scope of this project and will be reported in due course.

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Summary and further reading

In summary, flow chemistry offers a viable and in certain cases superior alternative to batch processes; offering increased safety, efficiency and scalability. The application of continuous flow methods on process scale has seen rapid take up in recent years, and the research communities have been developing these approaches further to expand their scope of application.

Recommended reading:

J. A. Blacker, J. R. Breen, R. A. Bourne and C. A. Hone, The Growing Impact of Continuous Flow Methods on the Twelve Principles of Green Chemistry, in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, The Royal Society of Chemistry, 2016, ch. 12, pp. 140-155.

Reviews on the developments in flow chemistry and more detailed information on their advantages over batch reactors can be found in the following papers:

S. G. Newman and K. F. Jensen, The role of flow in green chemistry and engineering, *Green Chem.*, 2013, **15**, 1456-1472.

C. Wiles and P. Watts, Continuous flow reactors: a perspective, *Green Chem.*, 2012, **14**, 38-54.

S. V. Ley, On Being Green: Can Flow Chemistry Help?, *Chem. Rec.*, 2012, **12**, 378-390.

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