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Flow chemistry and the synthesis of energetic materials

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Foreword

This report has been produced by the European Commission's Joint Research Centre (JRC) in the frame of the JRC's ongoing research to develop safe, high-purity explosives solutions. JRC's products are used for testing threat-detection equipment deployed across the European Union for security applications such as aviation security, law enforcement, and the protection of public spaces.

Abstract

Flow chemistry is seen as a disruptive innovation that expands chemistry's horizon and opens up new market possibilities. In addition to pharmaceutical applications, flow chemistry is expanding into organometallic chemistry, fine chemicals, polymers, peptides, nanomaterials, and energetic materials synthesis.

In Chapter 2 of this report, we review the principles of flow chemistry, and highlight the potential benefits compared to performing reactions in batch mode. For example, flow reactors facilitate the fast dissipation of heat created during highly exothermic reactions, such as mixing of sulfuric-nitric acid, nitration reactions, or possible side reactions such as oxidation of nitro-aromatic compounds. Heat transfer rate in flow reactors can be magnitudes of orders faster than in a batch reactor and this prevents the hot-spot generation that can stimulate side reactions or runaway reactions to occur.

Flow chemistry is also ideally suited for performing optimisation with design of experiments, which is a statistical approach used to optimise chemical processes and which allows a fuller investigation of parameter-space of a reaction, including cross-factor interactions. Reaction parameters such as temperature, pressure, flow rate, and amount of reagents can be controlled in a very precise and automated way via the system software, and it also straightforward to plan a sequence of experiments.

Until now, the industrial production of energetic materials (i.e., explosives, propellants & pyrotechnics) has been dominated by traditional batch processing. Despite improvements in safety practices, accidents still occur during the production and processing of energetic materials for both the civilian and military market. The manufacturing of many high explosives is mainly done by applying nitration, as most are nitro compounds. Nitration is an exothermic chemical process to introduce a nitro group ($-\text{NO}_2$) into an organic compound, and this step poses an elevated safety risk. However, the inherent advantages of flow chemistry are attracting interest in the energetics materials community, because of its potential to improve safety, reproducibility, and efficiency in the production of energetic materials.

In Chapter 3 of this report, we review over 40 publications concerning the application of flow chemistry to synthesise energetic materials. The compounds concerned include nitro compounds, polynitrogen compounds, azides, styphnates, peroxides, peracids and energetic ionic liquids. Around three quarters of the publications were published during the last 10 years.

Looking to the future, we can expect flow chemistry to play a central role in the trend towards increased automation in the selection, optimisation, and synthesis of novel compounds. In the area of energetic materials, a more widespread adoption of flow chemistry could – as part of a broad range of initiatives – contribute to enhanced safety in the production of explosives.

1 Introduction

1.1 Development of flow chemistry

For centuries, chemistry has played an integral role in our civilisation and its importance has only increased over time. Central to any branch of chemistry are chemical reactions. Reactions, be it in the lab or at an industrial scale, have traditionally been done in test tubes, flasks, beakers, tanks and reactors. In chemistry, this approach is typically referred to as batch chemistry, batch reactions or batch processes. At the beginning of 20th century, however, things began to change. The first modern continuous process was probably the Haber–Bosch process for the industrial production of ammonia from hydrogen and nitrogen catalysed by an immobilised iron catalyst [Haber & Le Rossignol, 1913]. The petrochemical industries also began to widely employ continuous processes, due to the radically lower cost of production achieved through economies of scale.

It would take some decades, however, before continuous methods – commonly referred to in the laboratory as flow chemistry – would become an important tool in research laboratories and other industries. The first to adopt flow chemistry at laboratory scale were analytical laboratories, followed by organic synthesis laboratories and later the pharmaceutical industry. In fact, continuous-flow reactors have been reported nearly a decade ago as a tool used in pharmaceutical companies for drug discovery, and flow chemistry is proving an invaluable tool for drug discovery in the pharmaceutical industry [Trojanowicz, 2020]. Flow chemistry helps pharmaceutical companies to (i) increase the number of compounds synthesised, (ii) evaluate biological activity faster, and (iii) produce on an industrial scale [Baraldi & Hessel, 2012].

In healthcare, continuous-flow manufacturing has the potential not only reduce the cost of healthcare but also to facilitate access to life-saving therapeutics in regions of the world where healthcare access is limited. Thus, flow chemistry is considered critically important to the future of healthcare [Extance, 2017]. For example, Novartis funded the Massachusetts Institute of Technology (MIT) with 65 million US dollars for a research programme aiming to develop new way to produce drugs based on flow synthesis [Richards, 2007]. Flow chemistry can be applied for the development and synthesis of drugs [SEQENS, 2020], vaccines [Fuchs et al., 2016] & [Rosa et al., 2021], and test kits [Organ, 2021], including for the recent Covid-19 pandemic.

In addition to pharmaceutical applications [Gerardy et al., 2018] & [Baumann et al., 2020], flow chemistry is expanding into organometallic chemistry [Timothy, 2016], fine chemicals, polymers [Leibfarth et al., 2015], peptides [Simon et al., 2014] and nanomaterials synthesis [Sebastian & Jensen, 2016] & [Marre & Jensen, 2010], including the continuous growth of metal and semiconductor nanoparticles [Jensen, 2017]. In the field of green chemistry, flow chemistry brings the promise faster development and application of greener catalysts and synthetic methodologies [Rogers & Jensen, 2019]. Performing reactions in flow can significantly reduce the environmental impact, both in laboratories and at production scale [Fitzpatrick & Ley, 2018], & [Rogers & Jensen, 2019].

In recent decades, flow chemistry has considerably progressed from basic laboratory techniques to complex, multistep processes. Today, flow chemistry is adopted by an increasing number of sectors, as indicated by the market overview in Figure 1.

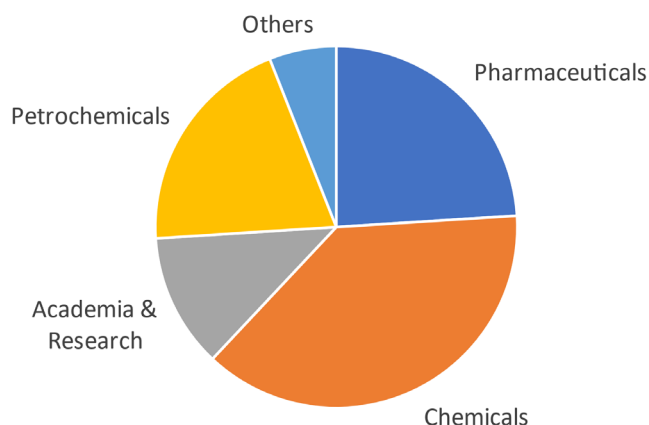


Figure 1. Global flow chemistry market share, by application, 2020 (%). [Source: reproduced from Grand View Research, 2022].

Flow chemistry is seen as a disruptive innovation [Bruno, 2014] that expands chemistry's horizon and opens up new market possibilities. Flow chemistry is drawing chemists and chemical engineers together and is creating new fields of research with broad applications. In the last decade, flow chemistry has established itself as an important field in modern chemistry. This is reflected by the number of reported scientific publications and patents involving the application of flow chemistry, which is steadily increasing year by year. This is illustrated in Figure 2, which shows the SciFinder® search results for the topic "continuous flow chemistry".

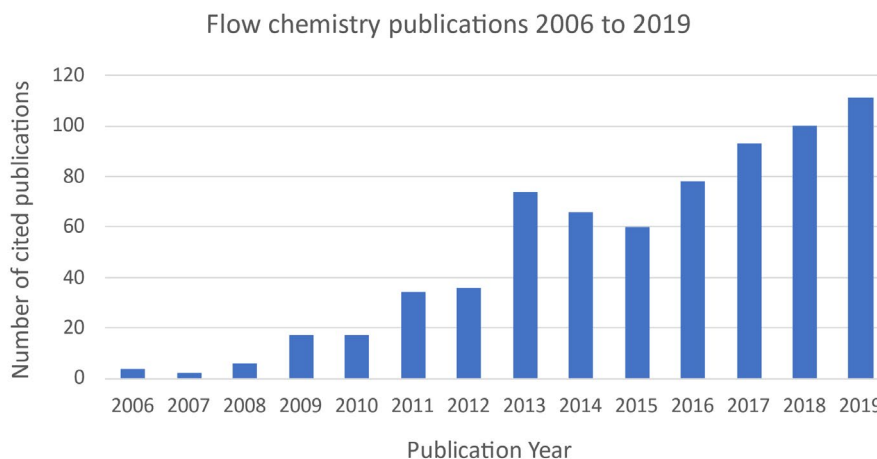


Figure 2. Number of cited publications for continuous flow chemistry. [Source: reproduced from Baumann et al., 2020.]

The huge expansion of flow chemistry applications and research performed is reflected in the market value which estimated at around 1 billion US dollars and is projected to reach 3.2 billion US dollars by 2028 [GlobeNewswire, 2021]. This expansion in market value is driven by future potential applications in synthesis, cascade catalysis and next-generation engineering which includes novel unit operations, in situ characterisation, solids handling, automation and machine intelligence [Hartman, 2020]. The concept of automation in the synthesis process using flow chemistry systems and robots is depicted in Figure 3.

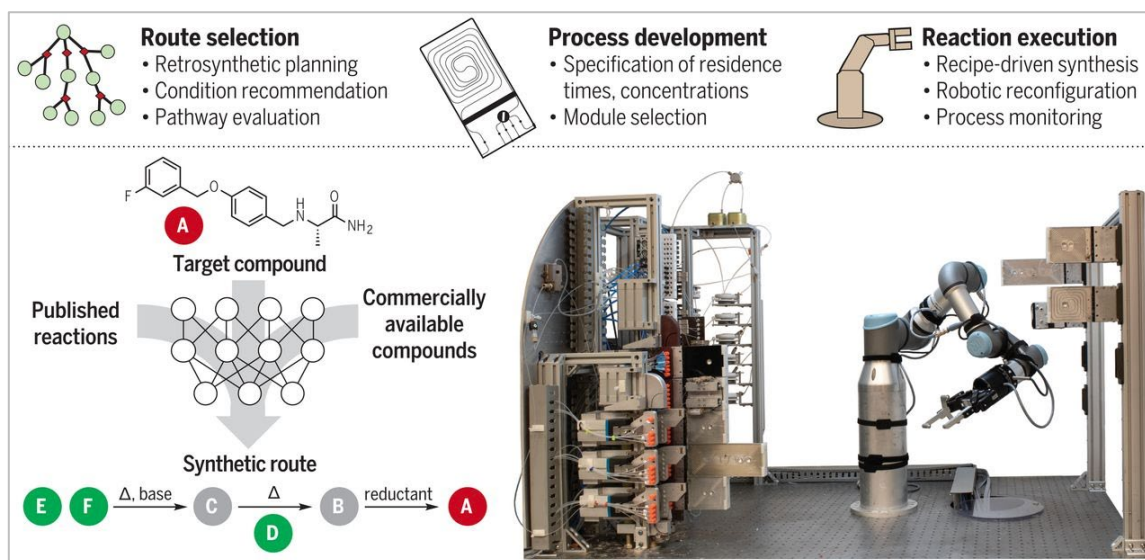


Figure 3. Illustration of future concept of applying flow chemistry in combination with automation technology and artificial intelligence to revolutionise the organic synthesis by using state-of-the-art robotics and reconfigurable reaction platforms. [Source: Coley, 2019, © AAAS]

1.2 Potential benefits of flow chemistry

Performing reactions in continuous flow simply means the reactions are performed in a pipe, tube, capillary, or micro-capillary rather than in traditional batch stirred vessels [Baumann et al., 2020]. Continuous flow chemistry describes the performance of a reaction in a continuous manner within narrow channels exploiting their intrinsic properties resulting in strictly controlled reaction conditions [Plutschack, et al., 2017].

The introduction of flow chemistry is an important step forward because it offers several critical advantages over the more traditional batch approach. The hazardous nature of certain specific chemicals and reactions can limit or exclude their use, especially on a large scale. However, often these chemicals can provide better efficiency if they can be used safely. Finding alternative is often expensive and requires long reaction sequences. Some of these issues relate to reactions that are highly exothermic, extremely fast, and have the tendency to accumulate heat and form hot spots. These reactions normally involve unstable species that are difficult to handle and are potentially toxic or explosive. This presents specific safety problems and can result in runaway reactions, undesirable side products or unplanned explosive damage to the reaction apparatus. Examples of such processes include nitrations, halogenations and organometallic-based reactions, which are widely used in several important industries such as pharmaceutical industries, production of explosives, and production of fine chemicals [Movsisyan et al., 2016].

Continuous flow reactors offer several unique advantages over batch ones and offer a solution to the problems outlined above. Reactors are characterised by narrow and well-defined channels with internal dimensions in the micron to millimetre range, and by internal volumes ranging from a few microliters to millilitres. The true power of continuous flow chemistry lies in managing the flow of chemicals through these narrow channels, exploiting their intrinsic properties to process chemicals under strictly controlled conditions and to operate continuously for long periods without intervention [Monbaliu et al., 2016]. The narrow channels of flow chemistry reactors affect fluid dynamics, heat and mass transfer for streams of chemicals. This results in efficient mixing even with immiscible phases, efficient heat and pressure management, precise control over the residence time and local stoichiometry, inherent safety, potentially seamless scalability and on-demand production [Monbaliu et al., 2016]. As early as 2000, advances in microreactors for chemistry were reported in the literature, including the description of elemental operations such as mixing and heat exchange with micro-channels and their first applications in gas-phase, liquid- and gas-liquid fine-chemical synthesis [Ehrfeld et al., 2000].

Despite the promise of flow chemistry, it is necessary to note that flow chemistry is not a universal solution, nor is it always advantageous for every problem in chemistry. Batch reactors will remain the first choice for the near future for several reasons. They are more robust, versatile, and cost-efficient. Batches are traceable, they are compatible with gas, liquids and solids and one can find them in practically every chemistry lab. In fact, one of the biggest problems flow chemistry scientists need to solve is the compatibility of reactors with solids. Other challenges include the scarcity of know-how, high starting cost, and product traceability.

1.3 Safety of explosives production

The production, storage and transportation of explosives has always been a dangerous occupation. Since the beginning of industrial high explosives, thousands of people have died in the accidents over the years, and the material losses are almost impossible to estimate. Despite improvements in safety practices, incidents and accidents still occur during the production of high explosives for both the civilian and military market. For a historical perspective, a 1985 monograph [Biasutti, 1985] provides an overview of accidents in the explosives industry.

A specialised database called SAFEX is dedicated to accidents in explosives production [SAFEX, 2022]. Access to the database is restricted to manufacturers of explosives or of dedicated raw materials used by the sector. SAFEX collaborates with the UK Health and Safety Executive's (HSE) Explosives Incidents Database Advisory Service (EIDAS). The SAFEX-EIDAS database now contains more than 20,000 incident records dating back to the early 1900's.

In Europe, accidents related to the production, processing and transport of explosives are reported under the Major Accident Reporting System (MARS – later renamed eMARS after going online), as part of the broader reporting of industrial accidents required by the EU's Seveso Directives. The purpose of eMARS – which is maintained by the European Commission's Joint Research Centre (JRC) – is to facilitate the exchange of

lessons learned from accidents and near-misses involving dangerous substances, with a view to preventing chemical accidents and mitigating their potential consequences.

In 2015, the JRC published a bulletin aiming at providing insights into lessons learned from accidents involving explosives reported under eMARS [JRC, 2015]. In preparing that bulletin, 62 accidents were studied. The most common type of accident found in the study was that of production and storage of explosives. The study remarked that accidents involving explosives are still occurring with a regular tendency, with two to four events a year almost every year since 2000. In the five years preceding the study, there were 20 major accidents in Europe involving explosive substances. Many of the events studied also appeared to be repeat accidents, that is, the same accident occurred more than once within the same facility over a number of years. In the years since the 2015 bulletin, a further five accidents related to the production of explosives were published in eMars [JRC, 2022], bringing the total number of accidents involving explosives between 2010-2020 to 29, with a total of 45 fatalities and 28 injuries.

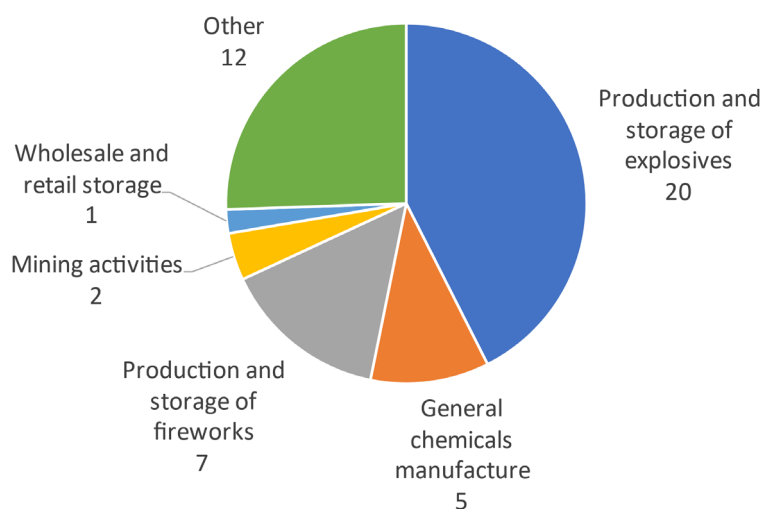


Figure 4. Major accidents involving explosives by industrial activity. [Source: reproduced from JRC, 2015]

Unfortunately, we can expect the number of reported accidents involving the production of explosives to increase, because it takes on average about three years for the reporting process to be completed, following investigation, internal review, and translation process. If there is substantial legal activity around the accident, the delay in publishing a report can be much longer than three years.

In the last few years, media reports have highlighted additional tragic accidents involving the production of explosives. In March 2018, a blast at a munitions disposal plant in Germany caused one fatality [DW, 2018]. In August of the same year, a blast at a UK military factory in the UK caused one death and one serious injury [Guardian, 2018]. In Poland, a blast on the grounds of an explosives plant in southern Poland killed one person and seriously injured another in January 2021 [Associated Press, 2021]. In February 2022, a blast at an explosives factory in Poland resulted in the deaths of two workers [PolskieRadioPL, 2022].

1.4 Scope of this report

In this report, we review the principles of flow chemistry and summarise the state of the art concerning the application of flow chemistry to the synthesis of energetic materials (i.e., explosives, propellants, and pyrotechnics). In Chapter 2, we discuss the components of a flow chemistry system, highlight the potential benefits compared to traditional batch reactions, and discuss the inherent suitability of flow chemistry with design of experiments. In Chapter 3, we summarise literature concerning the use of flow chemistry to synthesise energetic materials, including, nitro compounds, azides, peroxides, and ionic liquids. Finally, in the annex, we present examples of flow chemistry apparatus that are commercially available at the time of writing.

2 Overview of flow chemistry

2.1 Introduction

In a flow chemistry system, reagents or precursors are pumped to a mixing junction and flow into a temperature-controlled reactor. The main advantage of flow chemistry is the large surface area of the reactor. This facilitates vigorous mixing due to high rates of mass transfer and fast dissipation of heat, which allows highly exothermic reactions to take place safely. By using flow chemistry, faster, safer, automated, scalable procedures can be developed, and high-purity products can be obtained [Movsisyan et al., 2016] & [Hartman, 2020].

The first industrial applications of flow chemistry were found mainly in the pharmaceutical sector. Nowadays, transforming processes from batch to flow is an important goal for other industrial applications, including flavour and fragrance. The reason is that several applications involve highly exothermic or hazardous nitration reactions [Baumann et al., 2020]. The application of flow chemistry is important for processes associated with considerable safety risks. Flow chemistry can improve safety with well-controlled pressure, stable temperatures, homogenous mixing, and fast dissipation of heat. Moreover, a smaller amount of hazardous materials is present in the reactor at any time due to the continuous flow of reagents and removal of the synthesis products. Despite the potential advantages of flow chemistry, however, energetic materials have traditionally been prepared in batch reactors.

Transposing batch methods to flow chemistry can be complex, however, due to issues such as precipitation and compatibility of the system with the reagents. Often, as the reagents are modified to be compatible with a flow chemistry process, the method need to be re-optimised. As flow chemistry may not be beneficial for all the reactions, changing an established batch process to continuous flow only makes sense when clear benefits (e.g., improved safety) can be realised.

In this chapter, we outline the main components of a flow chemistry system in sections 2.2 and 2.3. In section 2.4, the potential advantages of flow chemistry synthesis are discussed. More details regarding the challenges of transposing a batch to flow reaction are discussed in section 2.5. Finally, the inherent compatibility of flow chemistry with process optimisation using design of experiments (DoE) is discussed in section 2.6.

2.2 Main components of a flow chemistry system

Components of a flow chemistry system can be classified in two categories: essential and optional. The essential parts of flow chemistry system are the components necessary to run a reaction in flow, namely (i) pumps, (ii) a reactor, (iii) a pressure regulator and (iv) a collection device. A system may also include optional components for enhancing the automation of the process or for monitoring the reaction in real time. The different categories of flow chemistry components are discussed in the sub-sections below. A representative example of a complete flow chemistry system is depicted in Figure 5.

2.2.1 Pumps

Pumps deliver the reagents and solvents to the reactor at controlled flow rates. In flow chemistry, the pumps used are mainly HPLC pumps and syringe pumps. The type of pump used usually depends on the supplier of the flow chemistry system. The basic advantage of both kinds of pumps is their ability to maintain a stable flow rate in a range of back pressures and for different viscosities of solvents/reagents.

The main advantage of the HPLC pump is that flow can be maintained for an unlimited time, compared to syringe pumps which must be refilled when empty. To overcome this problem, the so-called Push-Pull Dual Syringe Pump is developed. To ensure continuous flow, the system comprises two syringes that provide simultaneous infusion and withdrawal with opposing syringes on a single drive [Kurth et al., 2020]. The main drawback of HPLC pumps is linked to the high pulsations at a low flow rate resulting in inaccuracy at very low flow rates. Pumping of low-boiling-point solvents could be problematic when using an HPLC pump. Syringe pumps don't have any flow and pressure pulsations and provide high flexibility in the flow-rate range (from 1.0 $\mu\text{l}/\text{min}$ to 250 ml/min). A broad range of flow rates can be achieved by using interchangeable syringes of

various volumes according to the desired flow rate. The main disadvantage of syringe pumps is the fact that glass syringe pumps cannot operate at high pressure.

Another kind of pump occasionally used in flow chemistry systems is the peristaltic pump. The main advantage of this kind of pump is that the reagent/solvent does not have any direct contact with the pumping system. Furthermore, they can pump well-dispersed slurries and gasses, which is not always possible with syringe or HPLC pumps. The main drawback of peristaltic pumps is the limited pressure at which they can operate (<10 bar) and the low accuracy of the flow rate (particularly at low flow rates).

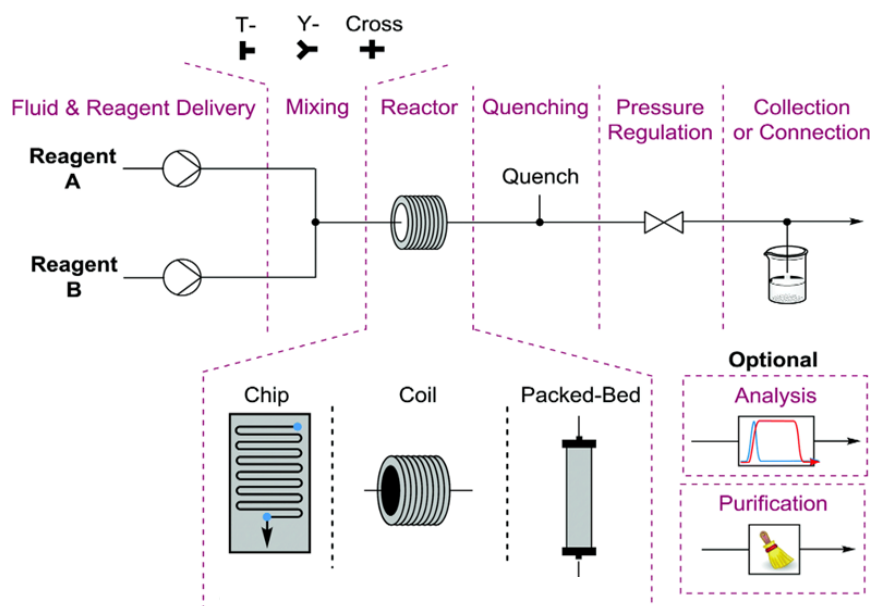


Figure 5. An example of a complete flow-chemistry system [Source: Guidi et al., 2020, licensed under [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)].

2.2.2 Reactors

The reactor is where the mixing of the reagents and the reaction takes place in well-controlled conditions (e.g., reaction temperature, mixing ratio, residence time). The three main types of reactors are described below.

- **Coiled-tube reactors** are tubular reactors that are usually placed in a glass manifold that enables fast mixing and a uniform temperature with no hot spots in the whole reaction volume. They are usually made of inert material like PTFE but also from stainless steel or Hastelloy if higher temperatures (>150 °C) are required.
- **Glass chip microreactors** are microstructure devices which are placed inside a glass manifold which results in excellent visibility and follow-up of the reaction. They are usually at microliters level up to 2 mL range. Those reactors are ideal for performing reactions at micro-scale and they offer also enhanced mixing efficiency. In some cases, external energy is introduced to induce mixing (active micromixers) [Sigma-Aldrich, 2009]
- **Column reactors or fixed bed reactors** consist of a column within a glass manifold. Column reactors are used to perform solid-phase chemistry by using catalysts, solid-supported reagents, or scavengers.

2.2.3 Pressure regulator

The pressure regulator is a very important part of any flow chemistry system as the higher pressure enables the reactions to occur at higher temperatures than the boiling point of the solvents. Moreover, it facilitates higher solubility of gases in the reaction mixture when needed. One option is to have an adjustable pressure regulator, which allows the user to accurately define the desired back pressure in the reaction. A simpler,

lower-cost device is a static back-pressure regulator (BPR), which is a cartridge-type device that creates the desired back pressure as a fluid presses against a spring-loaded plunger.

2.2.4 Collection device

A collection device allows the system to start and stop the collection of the output stream depending on the real-time purity of the product, as defined in the software settings. An automated fraction collector facilitates the automation of the process and the selectivity of the collection. This is typically achieved by using the “dispersion modelling tool” in the flow chemistry software, which models the axial dispersion occurring within the reactors. This is used to predict the steady-state section of the reaction mixture flow stream, thereby ensuring the optimum quality of product is collected. This is particularly beneficial for sample collection when the automated fraction collector is integrated in the flow chemistry system.

2.2.5 Optional components

Additional components may be used for enhancing the automation of the process including the collection of the product with the desired properties or for monitoring the analysis in real time.

- A **purification module** can be a column filled with scavengers or flow separator which enables liquid-liquid extraction based on hydrophobic membrane. This enables the collection of a purified final product by applying fully automated process.
- An **in-line analysis device** is used for monitoring the process of synthesis in real time via analytical flow-through cell in flow path. The analysis is based on spectroscopic techniques like FTIR, NIR, Raman, UV-VIS. Lately NMR is also applied for flow chemistry in-line analysis.

2.3 Reactor configurations

Generally, reactors are chosen to meet all the requirements imposed by the reaction mechanism, reaction rate and production capacity. Other parameters that must be considered when selecting a reactor are reaction heat, heat transfer coefficient and reactor size. Different reactor configurations are described in the sub-sections below.

2.3.1 Batch reactor

A batch reactor operates with all the starting materials placed in the reactor before the start of the reaction, and the products are removed once the reaction is completed. Batch reactors are very versatile and are compatible with all type of chemical reactions, including synthesis of fine chemicals, polymers, peptides, and nanoparticles. The size of a batch reactor varies from hundreds of millilitres in small lab-scale synthesis to 76,000 litres in large industrial plants [Kayode Coker, 2001]. Glass and stainless steel are the most common materials used to make a such a reactor. Examples of different types and sizes of batch reactors are presented in Figure 6. Despite their popularity, the inherent properties of batch reactors limit the chemical space accessible, hence restricting the way chemical strategies are designed. The scale-up of a batch reactor is process-dependent and limited by the mixing efficiency and heat transfer.

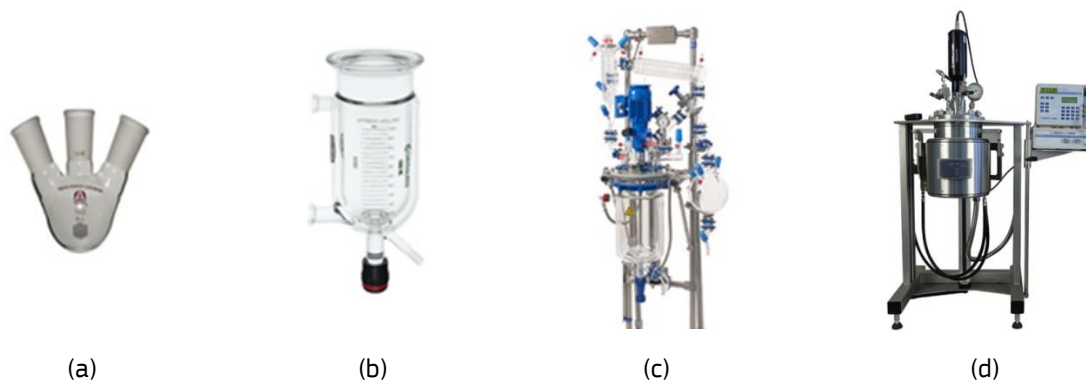


Figure 6. Example of batch reactors: (a) lab-scale, round-bottom glass vessel (100 mL), (b) lab-scale jacketed glass reactor (up to 2 L), (c) Small pilot-scale jacketed glass reactor (up to 15 L), (d) Lab-scale high-pressure stainless steel reactor (up to 5 L). [Sources: (a) Merck, 2022, © 2022 Merck KGaA, (b) Chemglass, 2022, © 2022 Chemglass, (c) Buchiglas, 2022a, (d) Buchiglas, 2022b.]

The **benefits of batch synthesis** include the following:

- robust, well-established process
- very versatile and relatively affordable.
- simple design and relative ease of production
- compatible with all branches of chemistry
- compatible with mass production of chemicals
- established procedures for product traceability based on batch numbers
- widely used in research laboratories and for industrial production

The **limitations of batch synthesis** include the following:

- low surface-to-volume ratio that affects the heat exchange efficiency
- presence of potential hot spots due to poor mixing efficiency and/or poor heat exchange (can trigger side reactions and lower the product purity)
- safety concerns when handling toxic and hazardous materials
- scale up is resource intensive and time consuming
- large footprint, especially for mass production
- production variability
- only conventional reaction conditions can be applied

2.3.2 Semi-batch reactor

A semi-batch reactor combines attributes of the batch and the continuous-stirred tank reactor. It is essentially a batch reactor but has a continuous input stream during operation. In other words, some reactants are charged into the reactor at time zero, while other reactants are fed gradually and continuously as the reaction proceeds. When the reactor is full, it is operated in the batch mode to complete the reaction. No product is removed from the reactor until entire reagents have been added and the reaction is complete. A good temperature control and the capability of minimising unwanted side reactions (e.g., thermal runaway reactions) by maintaining a low concentration of certain reactants are the main advantages of a semi-batch reactor. Semi-batch reactors are commonly used in emulsion polymerisation processes when the polymerisation rate is controlled by monomer addition (feeding) rate.

2.3.3 Continuous stirred-tank reactor

A continuous stirred-tank reactor differs from a batch reactor in that the reactants are continuously fed into the reactor and the reactions products are also continuously withdrawn. A continuous stirred-tank reactor (CSTR) can be used alone or as a part of series of reactors (Figure 7). It is characterised by a good mixing and temperature control. However, a disadvantage is that the conversion of reactant per volume of reactor is low, therefore large reactors in series are needed to achieve high conversion. Applications of CSTR include homogeneous liquid-phase reactions and heterogeneous gas-liquid, liquid-liquid, solid-liquid and gas-solid reactions.

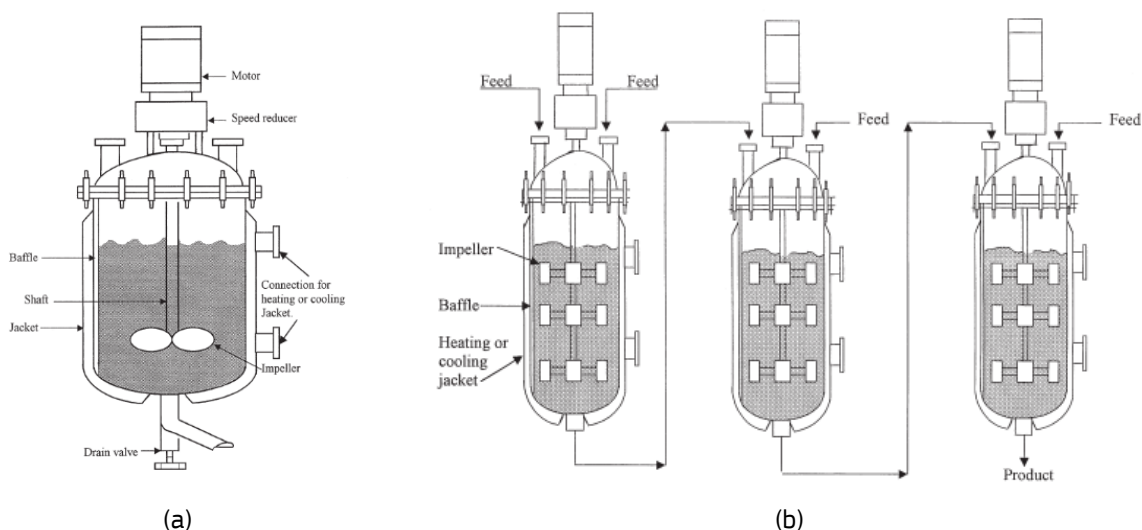


Figure 7. Examples of continuous stirred-tank reactors: (a) single continuous stirred-tank reactor and (b) series of continuous stirred-tank reactors [Source: Kayode Coker, 2001, © 2001 Gulf Publishing Company, Houston, Texas].

2.3.4 Continuous-flow reactor

A continuous-flow reactor differs from a continuous stirred-tank reactor in that the reagents are continuously fed into a tubular reactor rather than a tank reactor. The shape of a continuous-flow reactor can vary from a tube to a helical coil with different internal dimensions (Figure 8). Tubular reactors are commonly used in heterogeneous solid-liquid or solid-gas reactions in the presence of a catalyst. They can be formed from one long tube, or several shorter tubes arranged in a tube bank (Figure 8a, Figure 8b). Other types of continuous-flow reactors are the coiled-tube reactors with an internal volume up to several millilitres (Figure 8c) and continuous flow microreactors which usually have an internal volume of less than a millilitre (Figure 8d). The continuous-flow reactors offer a wide range of advantages for processing chemicals including fast mixing, efficient heat transfer, reduced footprint, safe handling of hazardous or instable materials and of highly exothermic reactions, and homogeneity of the production [Monbaliu et al., 2016].

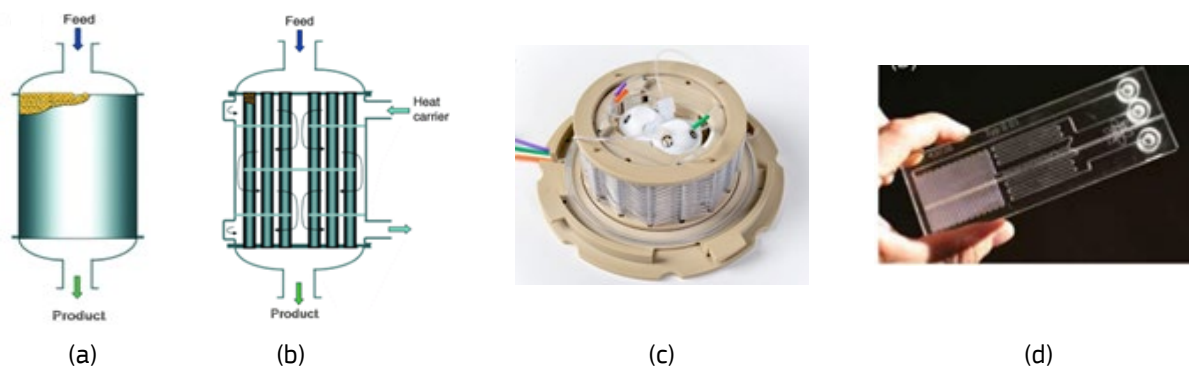


Figure 8. Example of continuous-flow reactors: (a) single-tube reactor, (b) multi-tubular reactor, (c) coiled-tube reactor and (d) continuous-flow microreactor. [Sources: (a) & (b) Eigenberger, 2015, © 2002 Wiley-VCH Verlag GmbH & Co. KGaA, (c) Vapourtec, 2022a, © 2022 Vapourtec Ltd, (d) Sigma-Aldrich, 2009, © 2009 Sigma-Aldrich Co.]

2.4 Advantages of flow synthesis

Compared to traditional batch synthesis, there are many potential advantages of applying flow chemistry in various chemical reactions. The main benefits of using flow chemistry are summarised below.

2.4.1 Faster reactions

Faster reactions can be achieved due to vigorous mixing. This is particularly important when mass transfer limitations prevent the reaction from occurring, or when temperatures above the boiling point of the solvent needed to be applied – a process known as superheating. By pressurising the system – in some cases up to 300 psi – the reaction can be performed 100 to 150 °C above the boiling point of the solvent. This enables reactions to occur significantly faster – even 1,000 times faster. Such rapid reactions under these conditions are not possible in batch. Fast reactions in flow chemistry can produce higher yields and significantly reduce the consumption of reagent and solvents [Chong et al., 2019].

When mass transfer is a limiting factor for the reaction to occur, a rapid mixing reactor containing chemical-resistant static mixers along its entire length can be used to enhance the mixing efficiency. The intense mixing achieved using this kind of reactor is particularly effective for biphasic flow reactions because the phases are prevented from separating. This results in a higher reaction rate and, in many cases, in a higher purity product. [Dumman et al., 2003].

2.4.2 Safer reactions

Due to the continuous feeding of reagents into the reactor and the removal of the final product, the process of flow chemistry means that only a small amount of hazardous product is present during the synthesis process. At any instant in time, the actual reacting volumes are smaller than the accumulative volume of final product. Moreover, the high surface-area-to-volume ratio allows excellent control of exothermal reactions. Therefore, the formation of hotspots, temperature gradient and thermal runaways is greatly minimised.

2.4.3 Excellent purity and reproducibility

Flow chemistry enables excellent reaction selectivity and reproducibility of the process, thanks to rapid diffusion mixing and excellent control over reaction conditions. The rapid diffusion mixing occurs because the high surface-area-to-volume ratio means that heat is dissipated rapidly, which in turn enables precise temperature control due to the fast heating or cooling. This is contrary to a batch reaction, where mixing efficiency is determined by the stirring, viscosity of the reagents and shape of the reactor. The mixing achieved in flow reactors is generally more homogenous and efficient compared to batch reactors.

2.4.4 Rapid reaction optimisation

When using a flow chemistry system on a small scale, the reaction conditions can be quickly and conveniently modified (e.g., different reactor sizes can be used). The main reaction parameters, such as reaction time, temperature, ratio of reagents, concentration and amount of reagents can be varied in a sequence of experiments during method development. One reaction can follow another, separated by using a solvent to clean out the system, and the resulting products can be analysed in-line. The application of design of experiments is a powerful tool to facilitate rapid and efficient optimisation, and this topic is discussed in more detail in section 2.6.

2.4.5 Scalability

In traditional batch processes, the transfer from research to mass production often creates challenges related to the scaling up of the process. In flow chemistry, such issues are eliminated due to the inherent mixing efficiency and heat transfer. In flow synthesis, production can be upscaled from milligram to kilogram levels by using larger reactors in combination with higher flow rates. Alternatively, the synthesis can run for a longer time to obtain more product.

2.4.6 Pros and cons of flow chemistry

In section 2.3.1, we summarised the benefits and limitations of *batch* reactions. A complementary analysis for *continuous flow* synthesis is given below.

The **benefits of continuous flow synthesis** include the following:

- high surface-to-volume ratio and efficient heat exchange
- excellent control over reaction conditions
- efficient mixing which prevents formation of hot spots and thermal runaway
- unconventional reaction conditions possible, e.g., high temperature and pressure (superheating)
- reduced reaction time
- reduced footprint
- reduced material consumption
- potentially higher product quality and reaction yield
- fast transfer from R&D to mass production
- scaling up is generally easy (by increasing reactor volume or using more flow devices)

The **limitations of continuous flow synthesis** include the following:

- relatively new technology with need for highly specialised personnel and know-how
- high cost of flow chemistry systems
- processing high viscosity liquids is challenging
- processing of heterogeneous reactions can be challenging
- clogging or rupture of the system due to the appearance of solid precipitates
- requires the selection of appropriate dosing/ pumping devices and connectors
- lack of established procedures for product traceability
- transposing batch processes to flow requires research effort and revalidation of established methods

2.5 Transposing batch reactions to continuous flow

Flow chemistry offers many potential benefits but transposing a batch reaction to continuous flow can be a complex and challenging process. It is often necessary to modify the methods and reagents used in established batch procedures. Particular attention must be paid to avoid the formation of intermediates or final products in solid form, which can obstruct the outlet flow stream and prohibit the continuity of the flow process [Zhang et al., 2010], [Johansson et al., 2020] & [Kyprianou et al., 2020]. The main reaction parameters, like reaction time (residence time in flow processes), temperature, reagents ratio to the final yield, and the purity of the product often need to be re-evaluated and optimised. This is mainly due to the use of solvents which are needed to dissolve solid reagents, intermediates, or final products, but which can also significantly affect the kinetic and thermodynamics of the reaction.

This first step in transposing a batch reaction to flow is a rigorous investigation of the reaction in batch, including the identification of key parameters that can affect the final product. Identifying intermediate products or other possible by-products of the reaction is of high importance. Such products can be determined using suitable analytical techniques (e.g., IR, Raman spectroscopy) and real-time process monitoring. The relevant concentrations of compounds of interest can also be determined off-line using high-performance liquid chromatography with a diode-array (HPLC-DAD) or mass spectrometry (HPLC-MS), or gas chromatography-mass spectrometry (GC-MS). These analytical methods can be used during the batch reaction as well as during optimisation of the flow reaction.

After a thorough study and characterisation of the reaction in batch, the next step is to transpose the reaction from batch to continuous flow. Suitable solvents should be evaluated based on the solubility of reagents/intermediates/final products, boiling point, chemical compatibility and the potential to facilitate the purification of the final product. Again, the critical parameters and the applicable range to achieve high yield and purity are determined from the study of the batch reaction. Compared to batch processes, temperatures and reaction times might differ significantly in flow synthesis due to vigorous mixing, efficient dissipation of heat and mass transfer which can facilitate faster reactions at lower temperatures [Kyprianou et al., 2020].

The number of experiments needed to design and optimise reactions for flow synthesis can be significantly reduced by applying design of experiments (DoE). The range of possible values of reaction parameters will be limited by the particular flow-chemistry system used. The residence time is limited by the flow rates of the system and the volume of the reactor. The temperature range is limited by the system capacity, the material of the reactor, the boiling point of the solvent and whether pressurised systems can be used to perform the reaction above the boiling point of the solvent. Several papers describe the transposition of batch reaction to flow reaction [Roberto et al., 2014], [Maljuric et al., 2020], [Bleie et al., 2015] & [Kyprianou et al., 2020].

2.6 Design of experiments with flow chemistry

Design of experiments (DoE) is a statistical approach used to optimise chemical processes and which allows a fuller investigation of parameter-space of a reaction. It is often considered a better optimisation approach compared to the traditional approach of varying one factor at a time (OFAT), also referred to as one variable at a time (OVAT) [Leardi, 2009]. Although the OFAT approach is widely used by chemists, it suffers from a few drawbacks, namely (i) it only permits the exploration of a smaller portion of the reaction space, (ii) the outcomes may be affected by the starting conditions, and (iii) the interaction among variables is not accounted for [Weissman & Anderson, 2015] & [Gioiello et al., 2016].

On the contrary, DoE allows one to predict the responses in the whole reaction space, including the interaction among factors, using a mathematical model. The difference between the OFAT approach and DoE is illustrated conceptually in Figure 9. In this figure, an experiment with three factors is optimised using either the traditional OFAT approach (left) or a face-centred design (right), which is a common optimisation design in DoE. The OFAT approach does not require a pre-determined number of experiments and may or may not exceed the number of experiments in a DoE. In the example shown in the figure, the assumption is that a new factor is investigated once the best condition for that particular variable is found. On the other hand, DoE experiments are evenly distributed in the reaction parameter-space, yielding more information (including cross-factor interactions). This information is then used to determine the response surface and identify the optimum set of conditions.

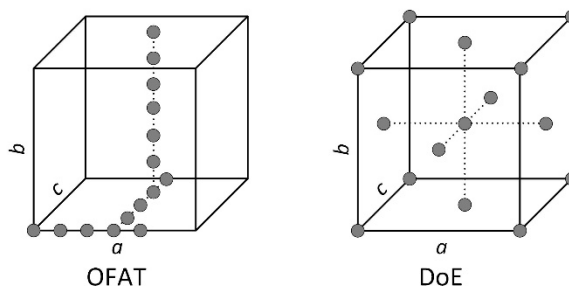


Figure 9. Distribution of experiments in the parameter-space of a chemical reaction using two different approaches: one factor at a time, or OFAT (left), and a face-centred design used in design of experiments, or DoE (right).

Experimental responses are expressed as a function of factors according to a polynomial equation:

$$Y = \beta_0 + \sum_{i=1}^k \beta_i x_i + \sum_{i=1}^{k-1} \sum_{j=i+1}^k \beta_{ij} x_{ij} + \sum_{i=1}^k \beta_{ii} x_{ii}^2 + e \quad (\text{Eqn. 1})$$

In this equation, we note the following: the constant term (β_0), the linear coefficients that measure the linear dependence of the corresponding variables ($\beta_i x_i$), the interactions between variables that describe the variables joint influence ($\beta_{ij} x_{ij}$), the quadratic terms for non-linear influences that also gives the curvature of the response surface ($\beta_{ii} x_{ii}^2$), and the error of the model (e) [Carlson, 1992].

Different DoE models for screening and/or optimisation exist including, full factorial, fractional factorial, and surface response designs [Leardi, 2009], [NIST/SEMATECH, 2021] & [Owen et al., 2001]. Software tools for optimisation processes are commercially available and can be used for planning experiments, selecting the best design, and interpreting the results. [Weissman & Anderson, 2015] & [Gioiello et al., 2016].

Flow chemistry is ideally suited for performing optimisation with DoE. Reaction parameters such as temperature, pressure, flow rate, and amount of reagents can be controlled in a very precise and automated way via the system software, and it is also straightforward to plan a sequence of experiments. Combining DoE with flow chemistry is therefore a winning strategy.

The first published examples of DoE for screening or optimisation of chemical reactions performed in continuous-flow reactors and microreactors date back to the late 2000s [Gioiello et al., 2016], [Ferstl et al., 2007], [Usutani et al., 2007], [Nagaki et al., 2007], [Nagaki et al., 2008] & [Benali et al., 2008]. Since then, several works have been published and most of them are already reported in recent literature reviews or articles [Weissman & Anderson, 2015], [Gioiello et al., 2016], [Bogdan & Dombrowski, 2019], [Wirth et al., 2019]. Most of the research focuses on combining DoE and flow chemistry for the screening and optimisation of synthesis of compounds for pharmaceutical applications.

In the energetic materials field, only a few examples have been reported. One example is the optimisation of the continuous flow synthesis of benzyl azide in a microreactor [Delville et al., 2011]. The optimisation was done using a D-optimal design, a non-standard DoE [Leardi, 2018]. The authors of this JRC report recently described the optimisation of the third nitration step of 2,4,6-trinitrotoluene at the JRC using flow chemistry and DoE, in particular a face-centred design [Kyprianou et al., 2020]. It is also interesting to note that a recent special issue of the Journal of Flow Chemistry – dedicated to teaching activities – highlighted the importance of introducing the concept of combining flow chemistry and DoE to undergraduate and PhD student's curricula [van Summeren et al., 2021], & [Taylor et al., 2021].

Finally, recent advances in machine learning open the door to implementing DoE in closed-loop experimental systems for self-optimisation of chemical processes. Self-optimised DoE gives the opportunity to learn from each experiment and to update the DoE model in a sequential fashion [Houben & Lapkin 2015]. It is considered a very powerful technique, especially when complex syntheses with many factors and multiple (conflicting) objectives are identified [Houben & Lapkin 2015], [Schweidtmann et al., 2018], [Gioiello et al., 2020] & [Fath et al., 2020]. Flow chemistry is perfectly suited for this kind of approach thanks to the full automation of the process and the possibility of having full control of the factors via software that can include a self-optimisation DoE algorithm.

3 Synthesis of energetic materials using flow chemistry

3.1 Introduction

In the previous chapter, we reviewed the principles of flow chemistry systems and highlighted the potential benefits of flow synthesis compared to batch processes. In this chapter, we review the scientific literature concerning the application of flow chemistry specifically for the synthesis of energetic materials, i.e., explosives, propellants, and pyrotechnics. For some synthesis processes, flow chemistry is inherently safer than batch synthesis. For this reason, a more widespread adoption of flow chemistry could – as part of a broad range of initiatives – contribute to enhanced safety in the production of energetic materials.

Energetic materials are a significant class of compounds containing large amounts of stored chemical energy. Energetic materials can liberate heat and exert high pressure under some stimuli, like impact, shock, or heat. There are two major categories of explosives: high explosives (like molecular ones such as TNT or RDX) and low explosives (mostly propellants, such as gunpowder or smokeless powder). High explosives can be further divided into sensitive primary ones (used for initiation or ignition of other energetic materials) and secondary ones (requiring stronger initiating stimuli, e.g., blasting cap). Additionally, within secondary explosives, so-called booster explosives can be distinguished. The last group is tertiary high explosives (the least sensitive ones, requiring an additional charge to be set off).

The manufacturing of many high explosives is mainly done by applying nitration, as most are nitro compounds. Nitration is an exothermic chemical process to introduce a nitro group ($-\text{NO}_2$) into an organic compound, and this step poses an elevated safety risk. The detonation of a small amount of explosive in the piping just after batch nitration has been reported in extreme cases [Held, 2012]. The process of nitration is usually performed in batches, often in large factories, due to the importance of explosives as strategic materials.

There is a growing trend in the field of energetic materials to develop methods that offer increased process safety, yield, selectivity, quality, and reduction of infrastructure costs. Flow chemistry is attracting a lot of interest, particularly (but not only) for its potential to improve safety compared to current batch processes, as outlined in the previous chapter. For example, flow chemistry facilitates the safe use of elevated temperatures. Flow reactors facilitate the fast dissipation of heat (high surface-to-volume ratio) created during highly exothermic reactions, such as mixing of sulfuric-nitric acid, nitration reactions, or possible side reactions such as oxidation of nitro-aromatic compounds [Kyprianou et al., 2020] & [Plutschack et al., 2017]. Heat transfer rate in flow reactors can be magnitudes of orders faster than in a batch reactor and this prevents the hot-spot generation that can stimulate side reactions or runaway reactions to occur.

In fact, most molecular explosives can theoretically be synthesised either in batch or with continuous nitration [Urbanski, 1964], [Agrawal & Hodgson, 2007] & [Meyer et al., 2007]. Compared to batch synthesis, continuous flow systems can produce small amounts of product on demand with little to no excess. Moreover, modules can be used for single-step reactions or in multi-step processes, in which modules are connected to each other in reconfigurable combinations to create the desired final product. Process conditions can be controlled more precisely leading to excellent reproducibility and safety.

In the sections below, we present and discuss the state of the art concerning the synthesis of energetic materials using flow chemistry systems.

3.2 Nitro compounds

Nitration is a very common process in the production of molecular aromatic high explosives, which are known for their long-standing military applications. Highly concentrated (i.e., white fuming) nitric acid, or so-called mixed acids (nitric acid added to sulfuric acid) are the nitrating agents typically used for the nitration process. Sulfuric acid acts as an inhibitor or moderator of the nitration. This is because the nitration of aromatic compounds is acid catalysed. It involves an electrophilic substitution by the nitronium ions (NO_2^+). These ions are formed during the acid catalysed ionisation of nitric acid and they act as the reactive species. However, nitro derivatives of aromatic compounds are used in a variety of other industrial domains, not only explosives (see Figure 10).

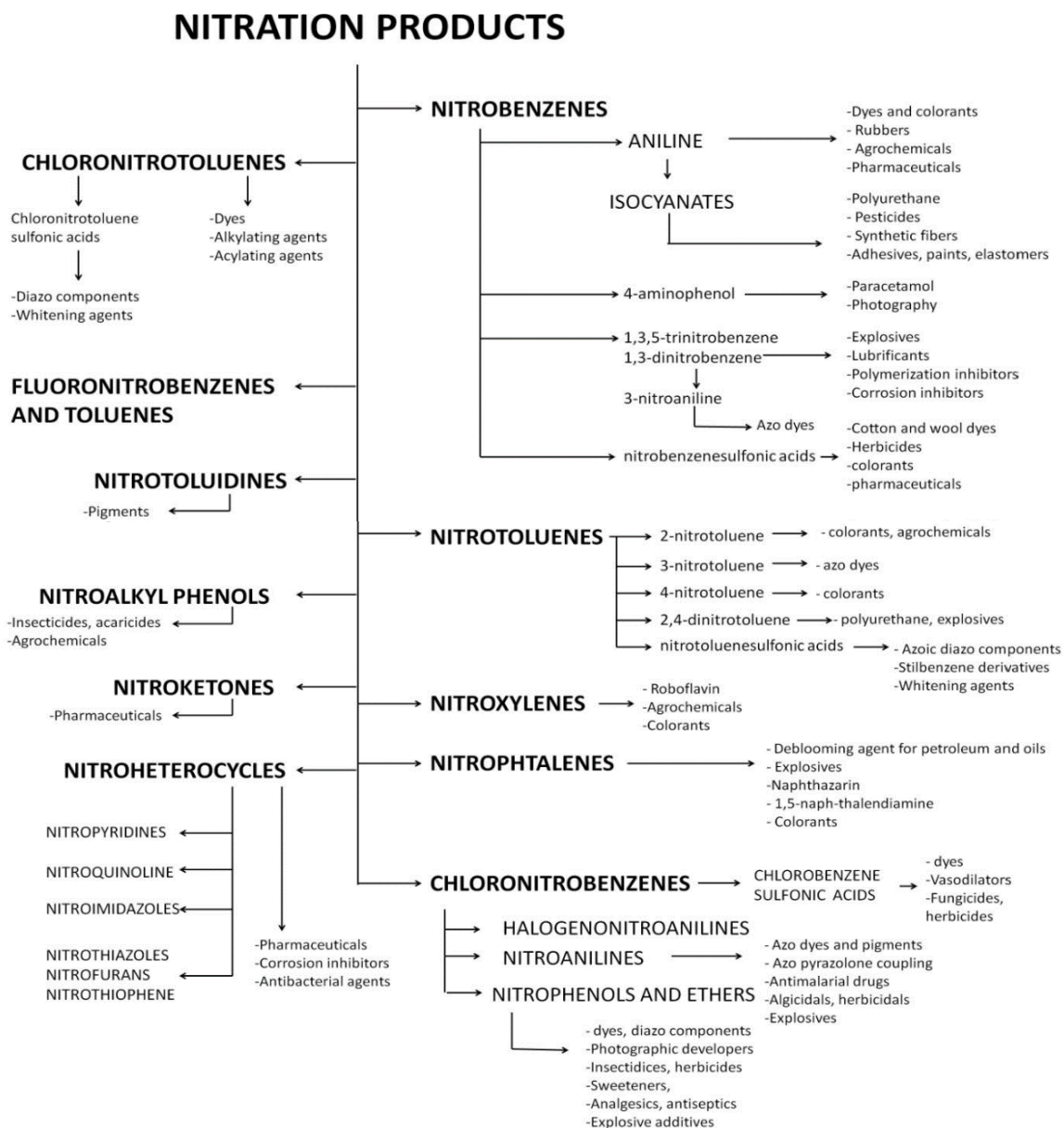


Figure 10. Main industrial nitrated products [Source: Russo, 2017].

Nitro derivatives of aromatic compounds are used, for example, in the production of many fertilisers, pesticides, dyes, perfumes, pharmaceuticals, or active pharmaceutical ingredients (API). Almost 65 % of APIs require at least one nitration step in the whole process. Moreover, conventional aromatic nitration usually follows a batch or a semi-batch approach, where the mixing of reactants and the reaction itself are carried out very slowly [Kulkarni, 2014]. Generally, more acidic nitrating mixtures and higher temperatures are required to carry out poly-nitration reactions, which is the case for production of majority of molecular explosives. For this reason, dangerous side reactions can be triggered, such as exothermic side reactions and the rapid formation of unwanted NO_x gases. The formation of such gaseous products can immediately pressurise the reactor and lead to a so-called thermal explosion. Catastrophic thermal runaway scenarios are caused by conditions in which the heat generation of a chemical reactive system exceeds the heat dissipation capacity of the thermal exchange system. In real nitration process conditions, nitro compounds (including explosives production) are always present as a reaction mixture of different isomers, acids, and impurities, which further increases the risk of explosion (lowering their thermal stability). For these reasons, nitration processes are amongst the most hazardous chemical operations carried out in the chemical industry.

Understandably, the quest for a safer way to produce poly-nitrated compounds (e.g., explosives) is a very active field of research, and flow chemistry seems to be particularly promising. This is particularly so for small-scale reactions where the limited amounts of products, high costs, and complexity of their manufacturing, are not an issue. For example, recently in China, the Nanjing Refinery Co. Ltd. reported the use of advanced-flow reactors (AFRs) type G4 (manufactured by Corning) for an industrial nitration process, which reduces the production footprint and enhances safety [Corning, 2022].

The application of continuous flow microreaction technology to perform nitration reactions was reported as early as the 1950s [Kappe et al., 2020]. Nitration reactions in continuous flow have received significant attention since that time, mostly due to improved safety. Small operational volumes, extensive heat transfer and a variety of materials for production can be adapted to extreme nitration reaction conditions (e.g., high pressure and temperature, risk of explosive reaction).

The nitration of aromatic hydrocarbons is an important process, as these are precursors of the most known secondary molecular explosives. In fact, some of these processes have already been investigated in microreactors [Burns, 2002], [Antes et al. 2003], [Panke, 2003] & [Halder et al., 2007]. The use of microreactors makes it possible to safely carry out toluene nitrations in inherently unsafe acetic anhydride mixtures. A corrosion resistant microreactor made of PTFE and tantalum was developed in 2005 for different nitration reactions [Henke & Winterbauer, 2005]. That microreactor could be easily adapted to conditions that can be encountered in an industrial plant due to the modular type of construction. In most cases, the results could be directly scaled up and pilot-scale plants were not required. Also, the nitration of naphthalene was successfully carried out in microreactors – at much higher temperatures and reaction rates than in batch modes [Kulkarni, 2014]. Another interesting investigation on the nitration of benzyl alcohol and benzaldehyde to nitrobenzaldehydes in microreactors was performed at University of Naples [Russo, 2017]. The results showed that using a continuous-flow microreactor it was possible to carry out the reactions in a safe way, in both homogeneous and heterogeneous conditions with relatively low residence times. The authors of this JRC report also investigated the nitration of 2,4-dinitrotoluene (DNT) into 2,4,6-trinitrotoluene (TNT) at gram-scale with the use of a fully automated flow chemistry system [Kyprianou et al., 2020].

The synthesis of a modern, secondary high explosive, 2,6-diamino-3,5-dinitropyrazine-1-oxide (LLM-105), via nitration process in flow, has been reported in the literature [Zuckerman et al., 2015]. The LLM-105 is a relatively new, insensitive heterocyclic energetic compound that is an important secondary military explosive with excellent thermal stability. It was synthesised for the very first time in the USA by oxidation of 2,6-diamino-3,5-dinitropyrazine (ANPZ) using trifluoroacetic acid (TFA) at room temperature [Pagoria, 1998]. However, in practice it is quite difficult to synthesise the precursor of this explosive (ANPZ) through a classical synthesis route. Therefore, the authors of the report used so-called DAPO process in which LLM-105 is synthesised via nitration of DAPO (2,6-diaminopyrazine-1-oxide) using 90 % nitric acid and pumped through a commercial microreactor system. The final product exhibited high purity and the process was extremely reproducible. Furthermore, the overall synthesis time was reduced compared to the batch mode and without the need for hazardous 100 % nitric acid or nitrate salts in 10 % oleum. Moreover, the microreactor eliminated the possibility of exothermic runaway reactions, rendering the whole process much safer.

Another noteworthy study was performed by the team from the Centre for Continuous Flow Synthesis and Processing (CCFLOW) in Graz [Kappe et al., 2020]. In this study, highly concentrated nitric (fuming, 99 %) and fuming (oleum) sulfuric acids (in some cases together with acetic acid or acetic anhydride) were used as the nitrating agents. This approach allowed the authors to develop a scalable continuous flow method for the acetylation and nitration of 4-fluoro-2-methoxyaniline (a key API used for production of drugs for non-small cell lung carcinomas treatment). The process was successfully transferred from laboratory to pilot-scale by using a larger flow reactor. The reactions carried out during this investigation were often extremely fast and highly exothermic. Besides, some of the mixtures used for the nitration (especially $\text{HNO}_3/\text{H}_2\text{SO}_4$ with acetic anhydride) could form highly explosive acetyl nitrate ($\text{CH}_3\text{C}(\text{O})\text{ONO}_2$).

A recent report described the synthesis of the explosive TATB (1,3,5-triamino-2,4,6-trinitrobenzene) using a micro-channel method, that is, a microreactor made of borosilicate glass [Weifei et al., 2020]. TATB is a heat-resistant explosive with a very low detonation sensitivity and high thermal stability. The apparatus was divided into three modules which were mutually isolated to avoid the coupling of dangerous sources and to decrease process risk. The synthesis consisted of several crucial and hazardous steps (like nitration) and involved the use of hazardous reagents (like concentrated nitric acid) but finally proved to be an attractive alternative for traditional batch method.

There are also a few patents regarding the synthesis of other liquid nitro explosives (or other liquid nitrate esters and their derivatives) of commercial interest using microreactors. One of the earliest is from Germany

(applied by Dynamit Nobel GmbH company). The patent has been published worldwide and concerns a method for producing liquid nitrate esters (e.g., nitroglycerine), where a polyalcohol is esterified by means of nitrating acid and the reaction takes place in one or several microreactors [Türcke, 2012]. Another example is the US patent concerning an efficient process for the mononitration of alkanediols. The process is claimed to be easily controllable and safe for operators [Francescutti, 2008].

An interesting report regarding the manufacture of nitroglycerine was published by researchers from the Fraunhofer Institute for Chemical Technology (ICT) in Pfinztal, Germany. They have further developed a method for safer production of nitroglycerine (the patent mentioned above was elaborated by the same team) as well as other liquid nitrate ester explosives (e.g., ethylene glycol dinitrate, EGDN) in tailored microreactor processes [Türcke, 2012]. These microreactors work continuously; the base materials flow through tiny channels into the reaction chamber in assembly line. Here they react with one another for several seconds before flowing through other channels into a second microreactor for purification. Researchers at ICT have built reactors for many other chemical processes – not only for manufacture of explosives. One example is a microreactor that produces polymers for organic light-emitting diodes (OLEDs), which are commonly found in displays and monitors.

Fraunhofer ICT has experience going back two decades producing other energetic compounds via nitration process in microreactors. The nitration of N,N'-dialkyl substituted urea in microreactors is one example of such work [Antes et al., 2001]. This process is the key step in producing DNDA aliphatic nitamines (dinitrodiazaalkanes), which can be used as components for energetic binders (in the form of eutectic mixtures of 2,4-dinitrodiazapentane, 2,4-dinitrodiazahexane, and 3,5-dinitrodiazaheptaneunder, known as DNDA57) [Antes et al., 2012]. The substance, DNDA57, is already being produced commercially by the German company, DynITEC GmbH.

A similar approach with the use of an advanced flow chemistry system was recently applied at FOI (Swedish Defence Research Agency) to produce TEGDN (triethylene glycol dinitrate), which is a useful energetic plasticiser in explosives and propellant formulations [Ek, 2021]. In another report, TEGDN was synthesised with high yield in a chip based microreactor a decade earlier by Chinese researchers at the Beijing Institute of Technology [Han et al., 2010]. They were using a mixture of nitric and sulfuric acid and found the optimal mole ratio of nitric acid/alcohol for diethylene glycol as 5, and for triethylene glycol as 4, and achieved a yield of over 86 % of triethylene glycol dinitrate.

Finally, a microfluidic oscillator coupled with a microreactor was recently successfully used for recrystallisation, crystal growth and for preparation of HNS (2,2',4,4',6,6'-hexanitrostilbene) and HMX composite explosives [Zhao et al., 2018].

3.3 Polynitrogen compounds

Tetrazoles, and in particular 5-substituted tetrazoles (a type of five-membered aza- compounds), are an important class of nitrogen containing heterocycles which are widely used for synthesis of high-density energy materials, such as propellants and explosives. Current methods to synthesise these compounds are very often tedious, dangerous, and result in impurities. For example, sodium 5-nitrotetrazolate dihydrate (NaNT) is a useful precursor compound for the synthesis of lead-free primary explosives [Klapötke, 2017]. Other tetrazole derivatives (e.g., ammonium 5-nitrotetrazolate) are perceived as new generation of nitrogen-rich energetic materials which often are characterised by low sensitivities and favourable energetic properties (such as high detonation velocities and pressures). Additionally, they are relatively easier to synthesise, especially compared to e.g., pentazoles (which additionally are extremely sensitive). Many of tetrazole derivatives (e.g., bistetrazoles) are therefore interesting candidates to find applications as environmentally friendly secondary high explosives. Unlike conventional energetic substances they do not derive their energy through the oxidation of a molecule carbon backbone but through their high (positive) heat of formation [Klapötke, 2017]. This is because triple bonds between nitrogen atoms (N₂) are much more energetic than N-N single bonds or double bonds in other compounds.

The most efficient method of synthesis of NaNT from 5-aminotetrazole involves the formation of a potentially hazardous tetrazole-diazonium intermediate. However, many diazonium salts are thermally unstable and sensitive to friction and shock (this is a reason why commercial production is still not really scaled up). One of the first approaches towards synthesising sodium 5-nitrotetrazolate by using a relatively safer method, such as a continuous microreactor technique, was achieved at MIT in 2005 [Kralj et al., 2005]. The method was then patented by Pacific Scientific Energetic Materials Corporation [Renz et al., 2007]. In their

process, sodium nitrotetrazolate was prepared by reacting aminotetrazole, nitric acid, and sodium nitrite to form a first reaction product, and then reacting this intermediate product with a base to form sodium nitrotetrazole. This approach avoided the formation of extremely unstable diazotetrazole compounds. The whole process was carried out in a continuous flow system at ambient temperature. The process was further improved (and patented) by Pacific Scientific Energetic Materials with an even less hazardous procedure, enabling more efficient, large-scale manufacturing processes [Bragg et al., 2016].

A safe, efficient, and scalable synthesis of 5-substituted tetrazoles in flow is reported by another research team from MIT [Palde & Jamison, 2011]. The authors prove that the hazards associated with hydrazoic acid (HN_3) are essentially eliminated, shock-sensitive metal azides such as $\text{Zn}(\text{N}_3)_2$ are avoided, and residual NaN_3 is quenched in-line with NaNO_2 . This approach appears to be a safer alternative for synthesising tetrazoles without prior generation of highly hazardous HN_3 and its subsequent reaction with nitriles ($\text{R}-\text{C}\equiv\text{N}$). The authors highlight that their new in-flow process advantages (such as high yield, minimal HN_3 generation, and short reaction time) are possible only because the reactions were conducted at elevated temperature (190°C). This critical reaction factor was in turn feasible only because the whole process was in flow in NMP (N-Methyl-2-pyrrolidone) and water mixture, and there was no headspace in which HN_3 could accumulate to an explosive level. The authors also claim that, since the process is performed in flow, the method can be scaled up for manufacturing larger quantities of 5-substituted tetrazoles.

A more recent report describes an efficient continuous flow process for the synthesis of 5-substituted 1H-tetrazoles carried out at Nantes University [Le Grogneq et al., 2020]. In this novel approach, the authors carried out the reaction in-flow, between a polymer-supported organotin azide (generated in situ and then immobilised in a packed bed reactor) and organic nitriles to obtain valsartan in the final step. Moreover, according to the authors, the method is rather simple and relatively fast (as it takes up to 15 minutes) and guarantees a low concentration of tin residues in the products (<5 ppm). Valsartan is a medicine used to treat high blood pressure; however, the process can be also adopted for the manufacture of other tetrazole derivatives, including high explosives.

3.4 Azides and styphnates

Since their discovery at the end of the 19th century, azides have been exploited for their high reactivity and usefulness as intermediates in organic synthesis. Various chemical production processes depend on the use of organic and inorganic azides, including production of pharmaceuticals, novel rocket propellants, and agricultural chemical components. Some organic and inorganic azides have strong explosive properties, because the azido group is highly energetic (due to the $\text{N}\equiv\text{N}$ bond). Trace amounts of acid or certain metal salts may catalyse their explosive decomposition due to the formation of molecular nitrogen. Additionally, many of azides (especially inorganic ones) show high sensitivity to heat and shock stimuli.

A 2011 paper describes how small volumes and highly controlled reaction conditions render continuous flow microreactors ideal systems for the synthesis of potentially explosive compounds such as organic azides [Delville et al., 2011]. The authors used a small scale (semi-automated) continuous flow setup to produce benzyl azide from benzylamine using imidazole-1-sulfonyl azide hydrochloride as diazotransfer reagent. Additionally, the optimisation of the reaction was also performed (using design of experiments) as well as scale-up experiments to the level of grams.

Oseltamivir, sold under the brand name of Tamiflu, is an anti-influenza drug currently manufactured by Hoffmann-La Roche. Most synthesis routes for Tamiflu involve the potentially explosive azide chemistry. Therefore, the development of alternative, safe processes for Tamiflu synthesis that can be adopted at large scale is of great interest. A relatively recent paper describes the use of potentially hazardous azide intermediates in a flow chemistry system for the synthesis of Tamiflu [Sagandira & Watts, 2019]. The safety concerns associated with the use of azide intermediates (as azidating agents) can be addressed when a suitable microreactor system is used. The authors used a two-step approach, using various azidating agents in a thermally controlled flow microreactor. The azide intermediates were safely synthesised in full conversions and isolated yields greater than 89 %. Furthermore, some of the reactions appeared to be relatively easy to scale-up, making microreactor technology a viable tool in the synthesis of Tamiflu.

Another study about the chemistry of azides in flow was reported by the Dutch company, InnoSyn [InnoSyn, 2021]. Their approach facilitates the safe use of sodium azide for the manufacture of other potentially hazardous (explosive) components such as triazoles and tetrazoles. These molecular functional moieties (especially azoles) are often encountered in new APIs or used as an attractive heterocyclic backbone with

energetic functional groups nitro ($-\text{NO}_2$), nitrate ($-\text{ONO}_2$), nitrimino ($-\text{NNO}_2$), and nitramino ($-\text{NH}-\text{NO}_2$) to replace the traditionally used high performing explosives. However, their production and the use of sodium azide alone in batch processes can pose significant safety issues. This is because sodium azide is highly toxic, can form easily the even more lethal HN_3 , and many metal azides are shock sensitive and explosive. Since there is no accumulation of hazardous mixtures, flow chemistry seems to be particularly good approach for many syntheses involving the use of this hazardous reagent.

Another study [Gutmann et al., 2012] describes the in situ generation of HN_3 , either from an aqueous feed of sodium azide upon mixing with acetic acid, or from neat trimethylsilyl azide upon mixing with methanol in a continuous-flow reactor. The authors claim that, despite the explosive properties of HN_3 , the process can be performed safely at remarkably high temperatures with a relatively high yield.

Heavy metal azides are well-known primary, powerful explosives. Lead azide ($\text{Pb}(\text{N}_3)_2$) has a long history of use in various blasting caps and detonators and is probably the most widely used primary explosive, both by the military and commercial sectors. Even more sensitive is silver azide (AgN_3) which is not used as much in practical applications due to its high cost and photosensitive nature. A recent study demonstrates the feasibility of a safe and efficient method for fast preparation of silver azide with improved physical properties by using a microreactor like structure. The authors prepared “supermixed composite explosives” by utilising a microfluidic platform [Chen et al., 2020].

Another recent report also from the Eindhoven University of Technology describes the use of a flow chemistry system involving a two-step synthesis of hazardous diazonium salts which is a sensitive explosive compound [Kuijpers et al., 2020]. This hazardous intermediate compound can be subsequently reacted away to yield a diazo dye. The research is an example of multi-step reaction done in flow and shows convincingly how to handle hazardous intermediates. The sensitive diazonium salts are generated in the first step and immediately reacted away in an electrophilic substitution reaction. Moreover, the investigation involved the use of cheap and easy-to-operate capillary microreactors and only a single syringe pump in each experiment.

Styphnic acid and especially some of its metallic salts are explosive materials too. Styphnates can be extremely sensitive to shock and friction, especially when dry. This is why some of them have been used as typical primary explosives (e.g., used as primers). Lead styphnate is particularly efficient, as only small amounts of this primary explosive are needed to induce deflagration-to-detonation transition and therefore has a long history of use. The team from Nanjing University of Science and Technology in China has been optimising the synthesis of barium and lead styphnate (barium and lead trinitroresorcinatate) through a segmented flow synthesis method for a few years now [Zhou et al., 2016], [Zhou et al., 2020] & [Zhao et al., 2017]. Their approach with microreactor systems demonstrates the potential for continuous, safe, and efficient synthesis of these hazardous ionic materials.

3.5 Peroxides and peracids

There are various studies on the use of flow chemistry equipment to produce certain organic peroxides of industrial significance. However, the synthesis and handling of organic peroxides is accompanied by various challenges and safety issues that need to be addressed.

The synthesis of tert-butyl peroxyvalate (TBPP) and tert-butyl peroxy-2-ethylhexanoate (TBPEH) using a simple capillary microreactor equipped with orifice-type inserts is described by a joint research effort of Fraunhofer ICT-IMM and the Federal Institute for Materials Research and Testing (BAM) [Illg et al., 2016]. These substances are catalysts for polymerisation processes (e.g., ethylene and styrene polymerisation). The latter peroxide is particularly sensitive and must be generally stored or transported with inert solids to mitigate the explosion hazard.

Some organic hydroperoxides are liquid explosives, such as methyl ethyl ketone peroxide (2,2-dihydroperoxybutane), also known as MEKP. This compound is an efficient catalyst used quite intensively by the polymer industry. However, in pure form this transparent liquid is quite sensitive to heat, friction, shock, flame, or other sources of ignition, posing risks in production, storage, and transportation. This is one of the reasons why commercial methyl ethyl ketone peroxide is a mixture of compounds and is usually supplied blended into dimethyl phthalate in a mixture containing about 60 % peroxide. It has been demonstrated at East China University Science and Technology that MEKP can be synthesised at high throughput with moderately concentrated hydrogen peroxide in a microreactor for on-site and on-demand production [Zhang et al., 2010]. The authors also investigated the influence of acid concentration, residence time, feeding rate and ratio, and reaction temperature on the yield. They showed that, under optimised conditions, the reaction

can be completed in a few seconds, and the product contains less than 2 % residual methyl ethyl ketone (MEK) in weight and has a mass active oxygen fraction higher than 22 % in weight, which is in accordance with the standard for industrial applications.

There are also other studies with the use of microreactor systems and hydrogen peroxide as reactant for synthesis of other unstable compounds. A recent report from the National Institute of Technology of India describes the experimental approach towards the synthesis of performic acid (PFA) using Corning advanced-flow reactors (AFRs) [Gaikwad et al., 2017]. PFA is a non-toxic chemical frequently used in the chemical, medical and food industries. It is also a very unstable and explosive chemical, since even 50 % solution is highly reactive which makes its use within 12 hours mandatory. Processing and transportation of PFA is risky (due to auto-acceleration and uncontrolled reactions) and therefore its production using microreactors might be advantageous. The authors studied the effect of different parameters such as temperature, flow rate (residence time), catalyst and reactant concentration. Advanced-flow reactors are small and provide the full benefits of intensified microscale continuous processes, but with the capability to meet industrial-scale production. The research demonstrated the feasibility of getting maximum conversion rate with optimal reaction conditions at low temperatures compared to batch reactors. Methods for the production of organic peroxides by means of a microreaction techniques are also the subject of patents by the European Patent Office [Azzawi et al., 2006].

Finally, catalytic microreactors were found to exhibit exceptional activity for the direct synthesis of hydrogen peroxide from hydrogen and oxygen [Ranganathan & Sieber, 2018]. Hydrogen peroxide is an important chemical, and an energetic material itself in a concentrated (or pure) form. It is industrially produced by the anthraquinone oxidation process, which is quite energy intensive and thus not environmentally friendly. Therefore, a lot of research is carried out on the direct synthesis of peroxide from its elemental constituents. However, one of the difficulties of using a microreactor for the direct synthesis of peroxide is the incorporation of the metal catalyst within the tubing of such a reactor. A solution could be the incorporation of an Au-Pd alloy onto the walls of a silica coated capillary microreactor. The innovation in the design lies in the fact that the catalytic particles were formed in situ on the walls of the microreactor by a layer-by-layer self-assembly creating a multi-layer catalyst. By using this approach, the researchers were able to produce 210 mol of $H_2O_2/(kg_{cat}\cdot h)$ with a H_2 conversion of 40 % and selectivity of 70 %.

3.6 Energetic ionic liquids

Ionic liquids are a class of non-molecular ionic compounds that have a melting point below 100 °C. These compounds are liquid salts, so they do not require any other solvent (in fact, they can be an environmentally friendly alternative to some volatile organic solvents). This category of compound also includes energetic ionic liquids, which are relatively novel kind of explosives and rocket propellants. Energetic ionic liquids typically consist of imidazole or 1,2,4-triazole salts as well as tetrazole derivatives, with positive heat of formation [Klapötke, 2017]. Such compounds are of great interest as new generation of stable high-energy materials and monopropellants, especially as hypergolic, rocket ones.

There is a growing number of studies describing the successful implementation of microreactor technology for ionic liquid synthesis. Continuously operating microreactor systems can be used for synthesising ionic liquids on a large scale, which is sometimes problematic for batch processes. The alkylation step, for example, is sometimes prone to thermal runaway reactions and thus can be a limiting step [Waterkamp et al., 2007].

The use of a continuously operating microreactor system has been reported [Waterkamp et al., 2007] for a more intensive synthesis of 1-butyl-3-methylimidazolium bromide ([BMIM]Br). With this microreactor system, the authors were able to thermally control the strong exothermic alkylation process even at elevated temperatures (up to 85 °C) obtaining high reaction rates in a solvent-free environment. The product purity achieved was above 99 %. The results achieved represent a more than twentyfold increase of the space-time-yield compared to a conventional batch process.

The US Department of Defense planned to manufacture energetic ionic liquids using off-the-shelf microreactor equipment that could then be transitioned to the chemical industry [US Department of Defense, 2017]. The objective was to develop a safe, low-cost, and continuous production of energetic ionic liquids and synthesising the raw materials that, when blended, would produce AF-M315E (advanced rocket hypergolic liquid monopropellant).

3.7 Explosive volatile compounds

A semi-permeable polydimethylsiloxane (PDMS) membrane, when adequately applied to a microreactor system can separate two adjacent channels, typically one containing a liquid phase and the other a gas phase. Recently, this approach enabled the generation of many explosive gases, toxic gases, or volatile compounds in situ and on demand.

Diazomethane, for example, is an extremely sensitive explosive and toxic gas. Yet, it is also a valuable and versatile medium in organic chemistry. It is used for the preparation of methyl esters from carboxylic acids, homologation of ketones or carboxylic acids (Arndt–Eistert reaction) and cyclopropanation reactions.

The liberation of diazomethane from the commercially available precursor Diazald has been reported in the literature [Struempel et al., 2008]. Diazald (N-methyl-N-nitroso-p-toluenesulfonamide) is used as a relatively safe and easy-to-handle precursor to diazomethane. A commercially available microreactor (Little Things Factory GmbH, type ST-MI018, 0.12 mL internal volume) was used in this research. The solution enabled in situ conversion of diazomethane to the desired product and avoided handling and storage of explosive diazomethane solutions, thus making this medium accessible for the fine chemical sector.

Trifluoromethyl diazomethane is an explosive, toxic, and highly volatile compound that is a valuable reagent for organic synthesis (for the introduction of the trifluoromethyl group). It has been shown that it can be prepared from the corresponding amine and aqueous sodium nitrite within a tube-in-tube reactor [Kappe & Pieber, 2016]. The authors postulated that an analogous approach can be applied for hydrogen cyanide (HCN) preparation – with the use of aqueous solutions of sodium cyanide (NaCN) and sulfuric acid. Moreover, it is believed that this concept can be expanded in a relatively simple manner for the in situ generation of other gases for organic synthesis.

The on-demand generation, separation, and reaction of a number of gases with the use of membrane microreactors is discussed in a recent publication [Hone & Kappe, 2020]. Their work includes dangerous gases like carbon monoxide, diazomethane, trifluoromethyl diazomethane, hydrogen cyanide, ammonia, and formaldehyde. Single-channel microreactors are mostly used for gas–liquid reactions. A semi-permeable membrane with an exceptionally large surface area allowed the separation of gases and low molecular weight compounds. The membrane was necessary to ensure the gas generation and that the consumption occurred in two separate channels. The authors claim that the concept would be especially useful for “difficult-to-handle” gases for organic synthesis in the future.

Microreactor technology undoubtedly offers the advantage of handling other hazardous compounds, such as very volatile and toxic ones. Syntheses previously considered very risky for safety reasons, such as those involving hydrazine, phosgene or cyanides, could potentially be performed with relatively low risk using flow chemistry technology. One example is the synthesis of diimide (diazene) from hydrazine and molecular oxygen [Fanelli et al., 2017].

4 Summary

Flow chemistry is seen as a disruptive innovation that expands chemistry's horizon and opens up new market possibilities. In addition to pharmaceutical applications, flow chemistry is expanding into organometallic chemistry, fine chemicals, polymers, peptides, nanomaterials and energetic materials synthesis.

Compared to traditional batch synthesis, flow chemistry offers many potential benefits. For example, flow reactors facilitate the fast dissipation of heat (high surface-to-volume ratio) created during highly exothermic reactions, such as mixing of sulfuric-nitric acid, nitration reactions, or possible side reactions such as oxidation of nitro-aromatic compounds. Heat transfer rate in flow reactors can be magnitudes of orders faster than in a batch reactor and this prevents the hot-spot generation that can stimulate side reactions or runaway reactions to occur.

Flow chemistry is also ideally suited for performing optimisation with design of experiments, which is a statistical approach used to optimise chemical processes and which allows a fuller investigation of parameter-space of a reaction, including cross-factor interactions. Reaction parameters such as temperature, pressure, flow rate, and amount of reagents can be controlled in a very precise and automated way via the system software, and it also straightforward to plan a sequence of experiments.

Until now, the field of explosives production has been dominated by traditional batch processing. However, the inherent advantages of flow chemistry are attracting interest due to the potential to improve safety, reproducibility, and efficiency in the production of energetic materials. In Chapter 3, we review over 40 publications concerning the application of flow chemistry to synthesise energetic materials (i.e., explosives, propellants & pyrotechnics). The compounds concerned include nitro compounds, polynitrogen compounds, azides, styphnates, peroxides, peracids and energetic ionic liquids, and around three quarters of the publications date from the last 10 years.

Looking to the future, we can expect flow chemistry processes to play a central role in the trend towards increased automation in the selection, optimisation, and synthesis of novel compounds. We expect that flow chemistry will also be taken up at larger scale for the industrial production of certain energetic materials, thereby contributing to an improved safety profile of the process.

Annex: Examples of commercially available flow chemistry apparatus

Disclaimer: This section is intended to give readers an impression of the kinds of flow chemistry apparatus that is commercially available. This is not an exhaustive list, and the inclusion of commercial products in this report does not constitute an endorsement by the European Commission.

The majority of manufactures of flow chemistry apparatus are based in Europe and the United States. Table 1 indicates some producers of complete flow chemistry systems and the main product characteristics.

Table 1. Flow chemistry suppliers and selected product characteristics.

Manufacturer	Type of pump	Type of reactor	Reaction temperature	Additional features
Syrris (Cambridge, UK) https://www.syrris.com/	<ul style="list-style-type: none"> - syringe pumps (maximum pressure 20 bar) - possible to pump volatile (DCM, Diethylether); viscous(glycerol); very corrosive liquids (fuming Nitric acid; oleum) - flow rate: 1 μL - 10 mL/min 	<ul style="list-style-type: none"> - glass-chip microreactors - coiled-tube reactor with Asia Cryo Controller - column reactors 	<ul style="list-style-type: none"> -15 °C to 250 °C -70 °C to 250 °C 	<ul style="list-style-type: none"> - FLLEX in-line liquid-liquid extraction module. - Asia Sampler and Dilutor enables on-line reaction analysis (automated sample extraction, dilution and transfer to analytical device).
Vapourtec (Suffolk, UK) https://www.vapourtec.com	<ul style="list-style-type: none"> - HPLC pump (maximum pressure 200 bar) - flow rate: 0.05 - 10 mL/min - the R2C and R2S pump series exhibit strong acid resistance 	<ul style="list-style-type: none"> - coiled-tube reactors - glass-chip microreactors - column reactors 	<ul style="list-style-type: none"> -70 °C to 250 °C -40 °C to 150 °C 	<ul style="list-style-type: none"> - four independent heated reactor zones. -possibility for automated reagent addition - high variety of different tube/chip reactors available. - possibility to add to the system the SF-10 peristaltic pump

Manufacturer	Type of pump	Type of reactor	Reaction temperature	Additional features
Uniqsis (Cambridgeshire, UK) https://www.uniqsis.com/	<ul style="list-style-type: none"> - HPLC pump (maximum pressure 100 bar) - flow rate: 0.1 to 100 mL/min - option to choose a flow path with various materials (PEEK & PTFE; all PTFE; PTFE & stainless steel; PTFE & Hastelloy) 	<ul style="list-style-type: none"> - coiled-tube reactors - microreactors 	-40 °C to 300 °C -88 °C if FlowSyn Polar Bear™ is applied. -30 °C to 150 °C or 260 °C when hot chip is used	<ul style="list-style-type: none"> - wide range of reaction temperatures possible & pumps can withstand high pressure. - possibility to add in-line UV-Vis spectrometer; gas addition module.
ThalesNano (Budapest, Hungary) https://thalesnano.com/	<ul style="list-style-type: none"> - HPLC pump (maximum pressure 200 bar) - maximum flow rate: 0.1 to 10 or 50 mL/min according to the selected pump. 	<ul style="list-style-type: none"> - PHOENIX Flow Reactor - Microreactors not available 	10 °C to 450 °C	<ul style="list-style-type: none"> - specialised in particular applications like: Flash Pyrolysis Platform, H-series for hydrogenation reactions.
Chemtrix (Echt, the Netherlands) https://www.chemtrix.com/	<ul style="list-style-type: none"> - labscale: syringe pump for Labtrix Start and Labtrix S1 - flow rate: 0.1 – 100 µl/min - Pmax = 20 bar - wetted materials: glass, PTFE, PCTFE & FFKM 	1 – 19.5 µl glass microchip reactor	-50 °C to 195 °C	<ul style="list-style-type: none"> - the company offers a unique silicon carbide reactor with the systems Protrix, Plantrix Mr-260, Plantrix Mr-555, which can be advantageous in certain applications.
	<ul style="list-style-type: none"> - labscale: HPLC pump for Gramflow - flow rate: 0.2-10 mL/min - Pmax = 20 bar - wetted materials: glass, PTFE, FFKM 	1 mL glass chip reactor	-20 °C to 150 °C	

Manufacturer	Type of pump	Type of reactor	Reaction temperature	Additional features
	<ul style="list-style-type: none"> - pilot scale: Kiloflow: HPLC pump - flow rate: 0.2-20 mL/min - Pmax = 20 bar - wetted materials: glass, PTFE, FFKM 	0.8 - 18 mL reactor volume-glass reactor	-20 °C to 150 °C	
	<ul style="list-style-type: none"> - pilot scale: Protrix®: HPLC pump - flow rate: 0.2-20 mL/min - Pmax = 25 bar - wetted materials: SiC, PTFE, FFKM 	1 - 13.5 mL ceramic silicon carbide reactor.	-30 °C to 200 °C	
	<ul style="list-style-type: none"> - production scale: Plantrix MR260-HPLC pump - flow rate: 17-600 mL/min - Pmax = 25 bar - wetted materials: SiC, PTFE, FFKM 	2.9 - 170 mL ceramic silicon carbide reactor.	-30 °C to 200 °C	
	<ul style="list-style-type: none"> - production scale: Plantrix MR555-HPLC pump - flow rate: 80-6667 mL/min - Pmax = 25 bar - wetted materials: SiC, PTFE, FFKM 	100 - 4000 mL ceramic silicon carbide reactor.	-30 °C to 200 °C	
FutureChemistry Holding (Wageningen, the Netherlands) https://futurechemistry.com/	<ul style="list-style-type: none"> - syringe pump (maximum pressure 6.5 bar). - flow rate range not specified. - no further information regarding compatibility with strong acids and other corrosive chemicals. 	<ul style="list-style-type: none"> - basic quench microreactor - short quench microreactor - custom designed microreactor possible 	-10 °C to 200 °C (if high temperature modules is added)	<ul style="list-style-type: none"> - back pressure regulator up to 5 bar. - compatibility with GMP requirements. - option to add Flow-IR in-line analysis, and gas & photochemistry modules.

Manufacturer	Type of pump	Type of reactor	Reaction temperature	Additional features
Cetoni GmbH (Korbussen, Germany) https://cetoni.de/	<ul style="list-style-type: none"> - syringe pumps (glass, stainless steel) with various chemical compatibility. - pressure range 10 – 890 bar. - option for heated syringe. 	<ul style="list-style-type: none"> - microchip reactors - coiled-tube reactors - column reactors 	up to 200 °C (Qmix Q+ heating module) -10 °C to 100 °C (Qmix Q- heating module)	<ul style="list-style-type: none"> - high availability and choice of syringe pumps with various characteristics. - possibility of full automation and use of robotics for sample preparation and analysis. - integration of DoE in the software.

Some companies are focused only on the reactor development rather than complete flow chemistry systems, including:

- Corning (<https://www.corning.com>)
- Ehrfeld Mikrotechnik BTS (<https://ehrfeld.com/en/products/lonza-flowplater.html>)
- LittleThingsFactory (<https://www.ltf-gmbh.com>)
- Shaoxing East Lake High-Tech Company Limited (<http://www.el-ht.com/wzsy>)

Furthermore, certain companies offer 3-D printing devices to print microfluidic devices on demand, including:

- Dolomite (<https://www.dolomite-microfluidics.com/3d-printing-microfluidics>)
- Covestro Additive Manufacturing (including former DSM Additive Manufacturing) (<https://am.covestro.com>)

Examples of commercially available flow chemistry systems and apparatus are illustrated overleaf in Figure 11.



(a) Syrris: Asia



(b) Vapourtec: R-Series



(c) Uniqsis: FlowSyn™



(d) ThalesNano: Phoenix Flow Reactor™



(e) Chemtrix: Labtrix® S1



(f) Cetoni: Nemesys

Figure 11. Examples of commercially available flow chemistry apparatus. [Sources: (a) Syrris 2022b, (b) Vapourtec 2022, © 2022 Vapourtec Ltd (c) Uniqsis 2022, © 2022 Uniqsis, (d) ThalesNano 2022, © 2004-2021 ThalesNano Inc. (e) Chemtrix 2022, © Chemtrix 2022 (f) Cetoni 2022, © 2022 Cetoni GmbH]

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List of abbreviations and definitions

AFR	advanced-flow reactors
ANPZ	-3,5-dinitro pyrazine
API	active pharmaceutical ingredients
BAM	Bundesanstalt für Materialforschung und -prüfung (Federal Institute for Materials Research and Testing)
BPR	back pressure regulator
CCFLOW	Centre for Continuous Flow Synthesis and Processing
CSTR	continuous stirred-tank reactor
DAD	diode-array detection
DAPO	2,6-diaminopyrazine-1-oxide
DNDA	dinitro-diaza-alkanes
DNT	2,4-dinitrotoluene
DoE	design of experiments
EGDN	ethylene glycol dinitrate
EIDAS	Explosives Incidents Database Advisory Service
eMARS	Major Accident Reporting System
FFKM	perfluoro-elastomers
FOI	Totalförsvarets forskningsinstitut (Swedish Defence Research Agency)
FTIR	Fourier-transform infrared spectroscopy
GC-MS	gas chromatography-mass spectrometry
HMX	1,3,5,7-Tetranitro-1,3,5,7-tetrazocane
HNS	2,2',4,4',6,6'-hexanitrostilbene
HSE	Health and Safety Executive
HPLC	high-performance liquid chromatography
ICT	Institut für Chemische Technologie (Institute for Chemical Technology)
JRC	Joint Research Centre
LLM-105	2,6-diamino-3,5-dinitropyrazine-1-oxide
MEK	methyl ethyl ketone
MEKP	methyl ethyl ketone peroxide
MIT	Massachusetts Institute of Technology
MS	mass spectrometry
NaN ₃	sodium 5-nitrotetrazolate dihydrate
NIR	near-infrared spectroscopy
NMR	nuclear magnetic resonance
NTREM	New Trends in Research of Energetic Materials
OFAT	one factor at a time

OLED	organic light-emitting diode
OVAT	one variable at a time
PDMS	polydimethylsiloxane
PFA	perfluoroacetic acid
PTFE	polytetrafluoroethylene
RDX	1,3,5-Trinitro-1,3,5-triazinane
TATB	2,4,6-Trinitrobenzene-1,3,5-triamine
TBPEH	tert-butylperoxy-2-ethylhexanoate
TBPP	tert-butyl peroxyvalerate
TEGDN	triethylene glycol dinitrate
TFA	trifluoroacetic acid
TNT	2,4,6-Trinitrotoluene
UV-Vis	ultraviolet-visible spectroscopy

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