

Analysis of the Current Uses and Future Possibilities of Flow Chemistry in Organic synthesis

He Wang

Dulwich College Beijing, Beijing, 100103, China

Jo3y.w123@gmail.com

Abstract. Flow chemistry is when a chemical reaction is run in a stream by combining various reactants continuously to create chemical reactions. These reactions utilize devices such as pumps to move reactants into reactors where they contact each other. The adoption of flow chemistry into the creation of complex organic compounds and Active Pharmaceutical Ingredients (hereafter as APIs) have allowed tedious and often hazardous batch reactions to become significantly more efficient. This innovative technology also provides chemists with precise control of reaction parameters such as temperature, time, mixing and volume added. These factors allow for better impurity control and product yield. This research paper will provide a detailed analysis of the currently available continuous flow technologies and provide an overview of enabling technologies in this field of research, such as the integration of photochemistry, electrochemistry and artificial intelligence in flow chemistry reactions.

Keywords: Flow Chemistry; Organic Compounds; Pharmaceuticals.

1. Introduction

Flow chemistry has its roots in continuous flow production, where each step in manufacturing a product is conducted right after the other in an assembly line. Flow chemistry utilizes the same principles as continuous flow production, with reactions occurring in a continuous stream and reactants are introduced one after the other in a single operation. Reactions have been conducted in flow for more than 100 years [1], mostly for the synthesis of bulk chemicals. Other early examples of flow chemistry would be in Simulated Moving Bed Chromatography (SMB) in the 1950s [2], where fluids are continuously flowed through various stations to separate different mixtures (as seen in Fig.1). Flow chemistry offers chemists the ability to run reactions with minimal management, high yield, and high efficiency.

Despite these benefits, the synthesis of organic compounds had only recently been able to operate in flow conditions. In the past, continuous flow manufacturing of chemicals were only reasonable for large scale productions, since economies of scale covered the high operation costs. Moreover, the synthesis of organic compounds was often highly sophisticated and often had various processes which flow operations could not manage. Thus, chemists resorted to batch production where they would have better control over the production. Nonetheless, technological advancements have allowed flow chemistry operations to be scaled down, perform complex reactions, and have a high degree of reproducibility. Companies such as Syrris, Vapourtech and Hel group [3] have created flow chemistry products which can easily fit into a laboratory environment for small scaled and precise organic synthesis productions (see Fig.2 for examples).

Currently, the organic chemicals industry (Pharmaceuticals, personal care & Cosmetics, Agrochemicals etc.) is growing at a rapid pace and is estimated to reach a market size of 21.25 billion USD by 2030 [4]. This rapid growth paired with the increasing demand for organic chemicals generates a need for sustainable chemical manufacturing technologies. The chemical manufacturing industry consumes more than 10% of global fossil fuel production and emits an estimated 3.3 gigatons of greenhouse gases per year [5]. Chemists have begun developing and improving continuous flow technologies to resolve these two dire issues in the organic chemicals industry and have already made impressive progress. A sector in the organic chemicals industry which chemists have focused heavily on is pharmaceuticals. As economies around the world become more developed, people begin

investing more into healthcare products and provisions. For example, Myanmar (a newly developed country) currently has one of the fastest growing pharmaceutical markets and is forecasted to become a 1 billion USD industry [6]. As a result, chemists have begun implementing flow synthesis into the production of important pharmaceutical products, with notable examples in the past five years being imatinib, cinnarizine, cyclizine, celecoxib and many others [1]. This research paper will explore how flow synthesis operates when synthesizing organic compounds predominantly for pharmaceutical uses. It will also discuss a comparison between flow and batch processes to understand areas of improvement for flow chemistry. Lastly, it will present enabling technologies and innovations within the field of flow chemistry, such as the integration of photochemistry, electrochemistry and artificial intelligence in flow synthesis. This paper aims to create a comprehensive analysis of flow chemistry's current position in the organic chemicals industry and its potential areas of development for the future.

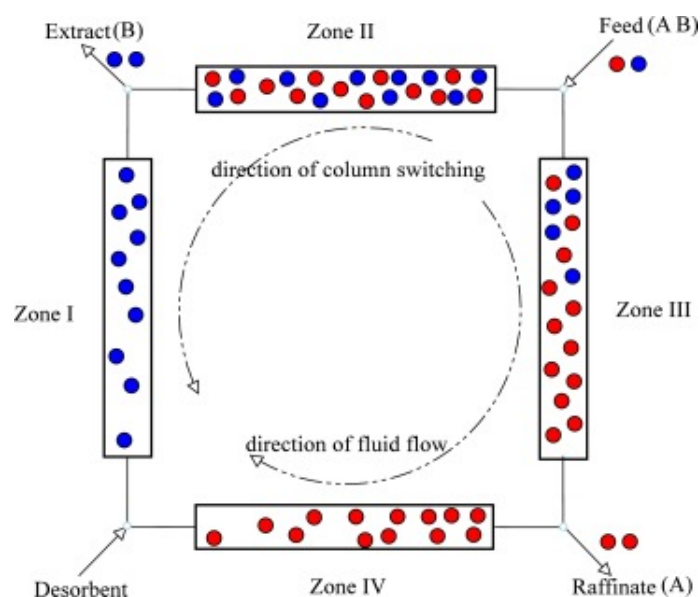


Figure 1. Simplified visual representation of a Simulated Moving Bed Chromatography system [7]



Figure 2. A small-scaled flow reaction system created by Syrris intended for laboratory use [8]

2. Deconstructing a Flow Chemistry Reaction

A typical continuous flow synthesis system consists of fluid and reagent delivery, mixing, reactor, quenching, pressure regulation, collection, and optional sections of analysis and purification [9] (see Fig.3 for a visual representation of the process). These 8 sections are called flow zones which are linked through flow zone connections. These connections typically consist of non-wetted parts and tubing to transfer reagents between zones and ferrules and nuts to secure the connections. A strength of flow chemistry is the standardized connections of components, allowing for exchangeable parts

and easy addition and switching of zones. Moreover, most of the components required to connect different modules are the same as the ones used in High Performance Liquid Chromatography (hereafter as HPLC), making them easily accessible. When considering which type of tubing and connections to utilize, the specification of the reaction needs to be analyzed. Physical characteristics such as pressure and temperature and chemical characteristics of the reagents all play a role in informing which connecting components to utilize. For pressures under 30 bar, components made from polymers such as polytetrafluoroethylene (PTFE), perfluoro alkoxy (PFA), polyetheretherketone (PEEK), and fluorinated ethylene propylene (FPA) are sufficient for use [9]. For high pressure applications or for reactions with temperatures above the boiling point of reagent solvents, materials such as stainless steel and other alloys are utilized.

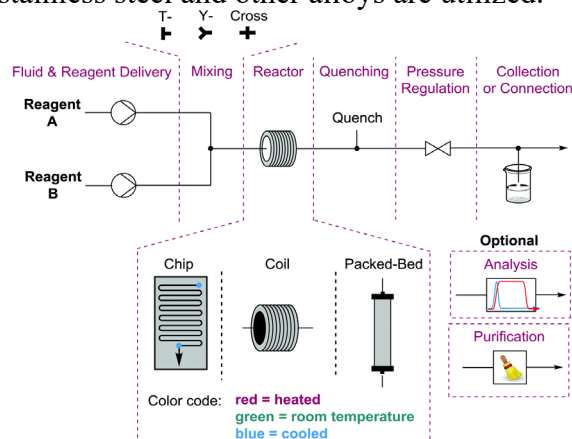


Figure 3. A visual representation of a typical flow chemistry system [10]

2.1 Reagent Delivery

At the beginning of every flow reaction is a reagent delivery system to deliver the respective reagents into the flow stream. Reagents are delivered through pressure-driven processes with pumps (e.g., hydrodynamic pumping) to create a pressure difference between the inlet and outlet of the reactor. Thus, the reagent delivery system must be able to reach pressures higher than that of the reaction system. It is also essential that pumps have precise control over the movement of the reagents to ensure that they deliver reproducible quantities [11]. Reagent delivery can be divided into three sections of liquid, gas and solid delivery, with their commonality of use in that order.

In liquid delivery, three types of pumps can be utilized depending on the nature of the reagent and reaction. These include: HPLC pumps, syringe pumps and peristaltic pumps. HPLC pumps are utilized in reactions of low and high pressures with flow rates of above 0.1 ml per minute. HPLC pumps can come in single piston reciprocating pumps, binary piston pumps and quaternary piston pumps (see Fig.4 for a visual representation). Single piston reciprocating pumps are compact, low cost and provide continuous delivery [12], but a downside is that they create pulsated flows due to the piston recharge cycle. Thus, single piston pumps should be avoided in flow reactions which require biphasic flow.

Syringe pumps deliver a predetermined amount of liquid in a dose and are used in reactions with low flow rates (see Fig.5 for a visual representation). This technique limits the scale and time of the process and cannot operate at high pressures. Developed syringe pumps adopt a dual delivery system, where one syringe delivers the dose of liquid and the other recharges. Their roles then reverse, creating a continuous delivery operation. In both syringe pump and HPLC pump deliveries, the pump is in contact with the liquid in flow, which can cause issues such as contamination, reagents backflowing and pumps being blocked from precipitates. Peristaltic pumps rotate around tubing to periodically compress the tube and block the flow of liquids, creating a vacuum which draws liquids through the tube [13] (see Fig.6 for a visual representation). Since the pump is only in contact with the tubing, there is no risk of reagents affecting the pumps operations such as in HPLC and syringe pumps.

Gas delivery benefits greatly from flow chemistry since it can handle gases that are toxic and too hazardous for batch applications. Gas can be delivered into a flow system by attaching a gas bottle to the reactor through a pressure regulator. For more precise applications, a Thermal Mass Controller (hereafter as TMC) is utilized to regulate the gas flow.

Lastly, solid delivery can be implemented in a flow system, but it is highly uncommon. Nonetheless, strategies such as magnetically pumping slurries have been reported to be successful [9].

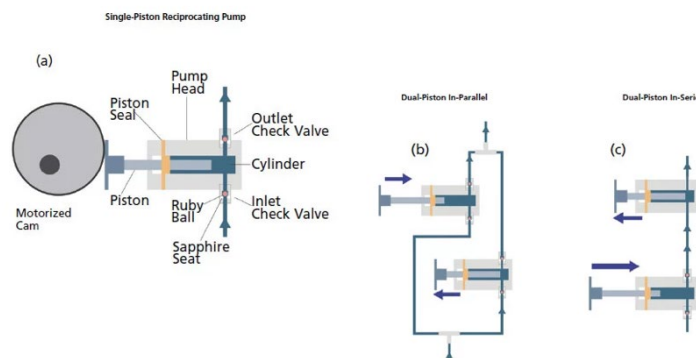


Figure 4. Diagram of single and dual piston pumps [14]

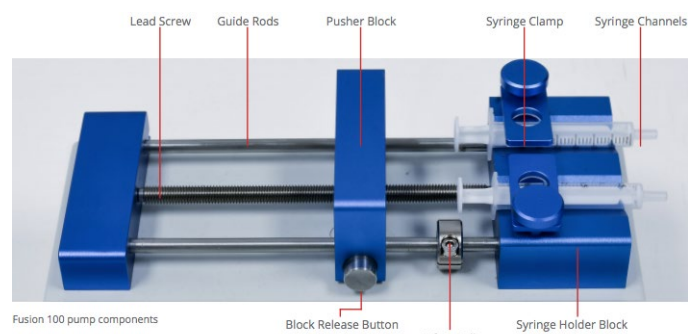


Figure 5. Diagram of a syringe pump (dual syringe) [15]

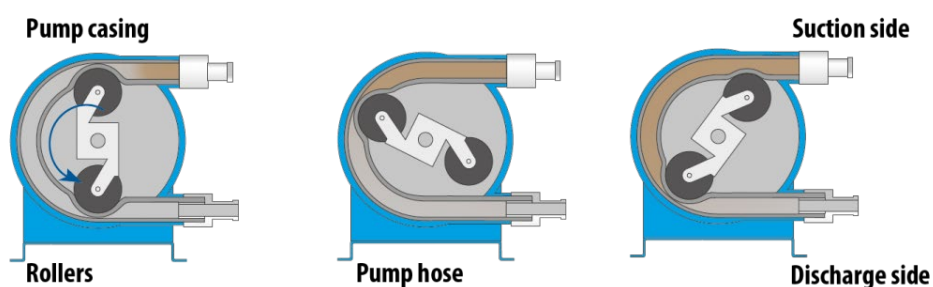


Figure 6. Diagram of a peristaltic pump [16]

2.2 Reagent Mixing

After the reagents have been successfully delivered into the continuous flow system, they need to be combined and mixed. In flow chemistry, this process can be divided into single phase (homogenous) and multi-phase (heterogenous) reactions.

In single phase reactions, the simplest case to mix reagents is to utilize T-shaped or Y-shaped units. These components are used to join two or more reagents together in the flow stream. If the flow rate of the reaction needs to be increased, micro mixing strategies can be utilized to reduce the mixing time. This can be done by adopting T-shaped units with very small diameters and high flow rates or implementing specialized microstructures into the flow system. An example of this is multi-lamination mixing, a device which comprises of multiple small inlets which splits the large stream into multiple small segments. These small segments then recombine, allowing reagents to have

greater surface area contact with each other and thus increasing reaction rates (see Fig.7 for a visual representation of a multi-lamination mixing device).

In multi-phase reactions, the same T-shaped or Y-shaped units and micromixers can be utilized. For gas and liquid mixing, devices such as gas permeable membrane reactors can be utilized. This device uses a “tube in tube” concept, with a gas permeable tube Teflon tube inside a non-permeable outer tube. Liquids are fed into the inner tube and gases are fed into the outer tube. The gas then diffuses into the inner tube to react with the liquid (see Fig. 8 for a visual representation of the device).

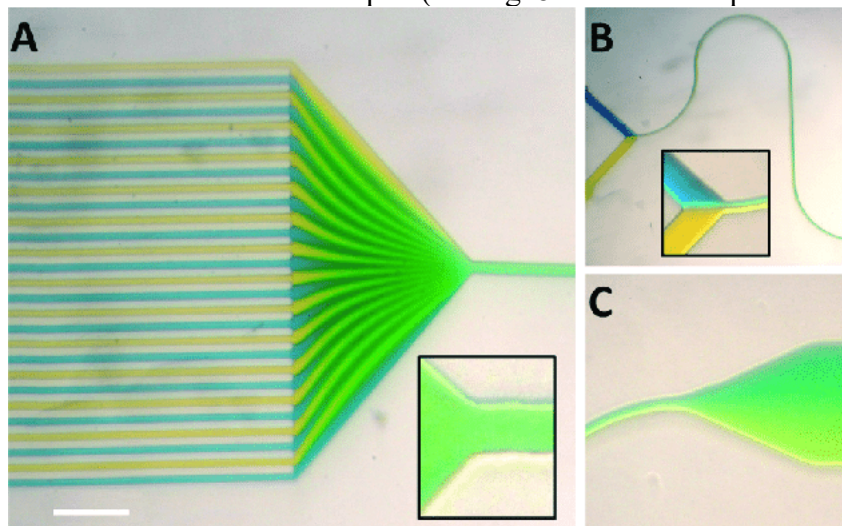


Figure 7. Visual representation of a multi-lamination mixing [17]

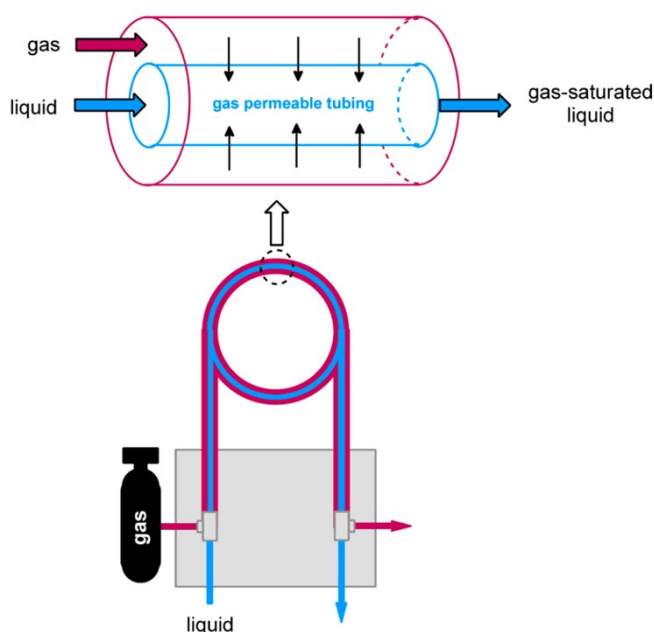


Figure 8. Diagram of “tube in tube” gas permeable membrane mixing [9]

2.3 Reagent Reactors

Once the reagents have been effectively mixed, the reagent stream then enters the reactor where it undergoes various physical and chemical processes. Flow reactors can be split into chip, coil and packed bed reactors [9] (see Fig.9 for a diagram of the three types of reactors). The design of each type of reactor is dependent on the type of transformation the reagents undergo (whether it is exothermic, endothermic, photochemical, electrochemical etc.). Innovative technologies in the flow chemistry realm such as the integration of photochemical and electrochemical processes will be discussed later in the enabling technologies section.

Chip reactors are comprised of a thin pane of glass or silicon with a winding channel in between the pane which allows reagents to travel through [18]. While the reagent travels through the channel, the chip is exposed to external factors such as UV radiation. Chip reactors offer high surface area to volume ratios, making it the most efficient in heat transfer out of the three reactors. Nonetheless, it faces issues such as small production output due to its size and high clogging probability. Chip reactors are also costly due to the complexity of manufacturing and expensive materials.

Coil reactors have reagents pass through tubing arranged in a spiral shape. Coil reactors can be made from plastics and stainless steel, making them significantly more affordable than chip reactors. The diameter and material choice of tubing is dependent on the nature of the reaction. For example, in applications of high pressure and temperature (over 150 °C, 20 bar), stainless steel is the appropriate material choice. In applications requiring UV light, materials such as FEP would be chosen over steel. A table informing which material to choose in which scenario is summarized in Table.1.

Table 1. Summary of which material to use under specific conditions in coil reactors. “Dependent” means the applicability varies case by case [9]

Reaction conditions:	PTFE	PFA	FEP	Stainless Steel
< 50 °C, < 5 bar	Yes	Yes	Yes	Yes
< 150 °C, < 20 bar	Dependent	Dependent	Dependent	Yes
> 150 °C, > 20 bar	No	No	No	Yes
UV radiation	Dependent	Dependent	Yes	No
Corrosive reagents	Yes	Yes	Yes	Dependent

Packed bed reactors are utilized for reactions with heterogenous reagents and catalysts. They are tubular containers filled with solids that are specifically arranged. The reactant solution then passes through the solids and reacts with it. Once it has passed through all the solids it is collected and filtered at the end. Packed bed reactors are typically made from glass, plastics or stainless steel. The size of the solid material is an influential factor in the reaction rate of packed bed reactors. A larger particle size results in lower surface area to volume ratio so the reactor needs to be longer, so the liquid reactant passes through more solids and makes more contacts. Conversely, a small particle size may clog the filter units at the end or reduce the flow rate.

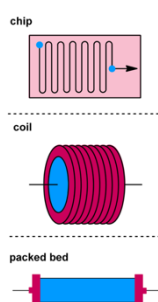


Figure 9. Simple diagram of chip, coil and packed bed reactors [9]

2.4 Quenching

Quenching is the stoppage of a reaction to ensure that the reaction no longer proceeds [19]. Having an effective quenching unit in a flow reaction ensures that the reaction does not drag on in the collection phase, creating results that are reliable and have high reproducibility. The quenching strategy is determined on a case-by-case basis. For single phase reactions, the quenching unit applies thermal or chemical quenching. For thermal quenching, the reaction is stopped through rapid cooling. For chemical quenching, a quenching reagent is applied to the reaction and are once again determined on a case-by-case basis. For packed bed reactors, the reaction stops as soon as it leaves the reaction unit since it is no longer in contact with the solids.

2.5 Pressure Regulation

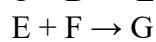
Back pressure regulators (hereafter as BPR) are installed after quenching to maintain a constant pressure for the flow system. They allow reactions to be performed at temperatures above the boiling points of reactants by working at high pressures. In gas/liquid reactions, they also create higher gas solubility which leads to better reaction rates. In a continuous flow system, two types of BPR are utilized: Preset BPR and Adjustable BPR. A preset BPR operates at a predetermined pressure and maintains it throughout the system. This reduces the need for a pressure sensor to be incorporated into the system. An adjustable BPR can adjust the pressure of the system whilst the reaction is occurring. Both modules can operate up to 70 bar and can be used for gas/liquid or liquid/liquid reactions [9].

2.6 Collection

After the reaction is completed, the products are transported into a collection unit or flask. This mixture can then go to analysis or purification.

3. Comparison between Batch and Flow Reactions

To synthesize an organic compound using the traditional batch process, the approach is to gradually reach the final product by first adding one reactant, then waiting for the reaction to finish to add the next reactant. For example, to synthesize G from A, a typical batch process would be as summarized as follows:



This process allows for the reaction to be monitored closely, since after each step the reaction mixture can be analyzed and purified to ensure it is of sufficient quality. This process also ensures that each step is independent of each other, so chemists can surveillance them carefully and conduct complex long-step syntheses. Nonetheless, the batch process is also time consuming and equipment heavy since every step of the reaction needs to be conducted after the other, and a new set of equipment needs to be set up to conduct the next reaction. Conversely, instead of utilizing the step-by-step process in batch production, continuous flow has a multi-step process. An integrated synthetic system is utilized to introduce reactants in succession and the intermediaries after each reaction do not need to be handled (intermediaries of the example being C, E and G). This process significantly reduces the production time of organic compounds and requires less manpower. See Fig.3 for a visual comparison between batch and flow reactions. Aside from the differences in reaction mechanisms, batch and flow chemistry also have differences in the physical processes of their respective reactions. These can include factors such as mixing, temperature and pressure.

3.1 Mixing

Mixing is the way two or more phases come together and become intertwined [9] and is a highly influential factor in the conversion of reactants to products. Batch and flow reactions display different characteristics in terms of mixing which substantially affect reaction rates. To predict the flow patterns within fluids when mixed, The Reynolds Number (Re) is utilized. Variations in the values of Re allocate mixing into three sections of laminar flow, transitional flow and turbulent flow. Low values of Re show characteristics of laminar flow, intermediary values of Re show transitional flow and higher values of Re show turbulent flow. The formula for Re is:

$$Re = \frac{\rho VD}{\mu}$$

ρ represents the density of the fluid, V represents the velocity of the fluid, D represents the characteristic linear dimension (in flow synthesis this would be the inside diameter of the pipe, in batch this would be the diameter of the impeller), and μ represents the viscosity of the fluid. Since values of Re are affected by the shape of the container they are mixed by (characteristic linear dimension), classifying a Re value as “low”, “medium” or “high” is determined on a case-by-case basis. In general, if $Re < 1100$ the flow is laminar, $1100 < Re < 2200$ the flow is transitional, and $Re > 2200$ the flow is turbulent [20]. A visual representation of each type of flow is presented in Fig.4. In terms of mixing, there is no overall advantage of flow over batch or vice versa. Since the Re value is affected by the shape of the mixing container and the characteristics of the reactants (e.g., density, viscosity), chemists must choose the right type of reaction which achieves the optimal Re value for their reaction.

3.2 Temperature

Temperature also plays a prominent role in the effectiveness of a reaction through its influence on the rate of heat transfer in a reaction system. It is vital for heat transfer systems in chemical processes to operate at high efficiency since ineffective heat transfer systems can decrease the rate of reaction and increase energy costs. The formula for the rate of heat transfer is:

$$Q = UA\Delta T$$

Q represents the rate of heat transfer, U represents the heat transfer coefficient, A represents the heat transfer area and ΔT represents the change in temperature. This equation shows that the rate of heat transfer is directly proportional to the area of heat transfer, therefore a larger area results in a better heat transfer rate. In continuous flow, the small channels and tubing have high heat transfer rates due to the large area to volume ratio. In batch reactors, heat transfer is significantly less efficient due to the larger containers which reactants are housed in, creating a lower surface area to volume ratio. Moreover, heat transfer in a batch reactor is also affected by the impeller, which can often cause temperature gradients between reactants around the impeller and at the sides of the container. Though temperature gradients are also present in flow reactors, they are much smaller due to the heat transfer coefficient, U . The formula for U is:

$$\frac{1}{U} = \frac{1}{h_1} + \frac{L}{\lambda} + \frac{1}{h_2}$$

h_1 is the convective heat transfer coefficient before the medium (e.g., the outside of the metal container of a batch reactor), L is the thickness of the medium, λ is the thermal conductivity of the medium, and h_2 is the convective heat transfer coefficient after the medium (see Fig.5 for a visual representation). Flow reactors typically have tubes with low thicknesses and efficient heat transfer due its high surface area to volume ratio, resulting in greater U values and higher Q (rate of heat transfer). Thus, in both high and low temperature reactions, flow systems outperform batch systems in terms of heat transfer [9].

3.3 Pressure

Controlling the pressure of a reaction is vital in the efficiency of a reaction since it affects the reaction speed, position of equilibrium and phases of the reactants. Oftentimes when one of the reactants is a gas, increasing the reactor pressure allows the gas to occupy a smaller volume, leaving more room for liquids and thus increasing the solubility of the gas. In reversible chemical reactions, efficient pressure control is needed to create a favorable equilibrium.

In high temperature batch reactions, solvents with high boiling-points are needed for the reaction to operate efficiently. This downside significantly limits solvent options and complicates the purification process of products. However, utilizing sealed batch vessels and microwave irradiation

allows low boiling point solvents to be used. Though useful in increasing solvent options, microwave batch chemistry is typically limited to 30 ml reaction volumes [9]. Moreover, the vaporization of reactants in a batch microwave reactor decreases the concentration of the reaction solution. Pressurized flow reactors eliminate this headspace and allow for volumes of higher than 30 ml to operate at high pressure and temperature. Thus, it can maintain a uniform concentration of solution throughout the reactor allowing reactions to take place more efficiently.

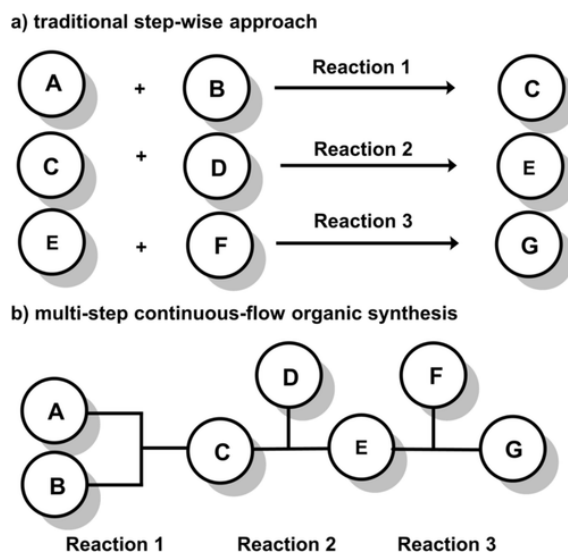


Figure 10. Flow chart of a batch synthesis process (a) and flow synthesis process (b) [21]

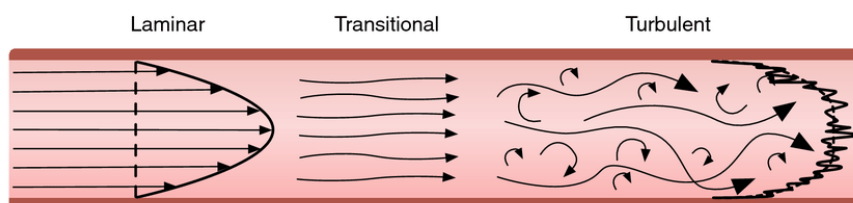


Figure 11. Visual representation of Laminar, Transitional and Turbulent flow [22]

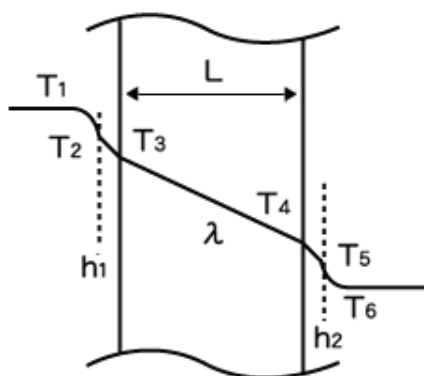


Figure 12. Diagram of heat transfer through a solid medium [23]

4. Utilization of Flow Chemistry in Organic Synthesis

With the growing demand for healthcare products and recent COVID-19 pandemic is an increasing need for efficient medicine manufacturing infrastructure. Additionally, the increase of food demand and decrease of soil fertility has created an urgent need for effective agrochemical solutions. Flow chemistry offers an innovative approach to the manufacturing of organic compounds and has already played an influential factor in the organic chemicals industry, evident through the increasing number

of patents in the past few years [24]. This section will explore the diverse applications of flow chemistry in organic synthesis and analyzing its use in industries such as pharmaceuticals and agrochemicals

4.1 Flow Chemistry in the Pharmaceutical Industry

The manufacturing of complex organic compounds, such as drugs and APIs, require multi-step syntheses. A major disadvantage of batch processes is its inefficient multi-step synthesis. As mentioned in section 2, batch processes often lead to low yield due to the need to handle all the intermediaries in a reaction, leading to numerous human errors. Moreover, multi-step organic synthesis is unsustainable in batch mode since it is highly dependent on human labor and requires a large amount of equipment. In contrast, flow processes reduce the need to handle intermediaries and can integrate in line intermediary purifications. This allows drugs and APIs to be manufactured in a single flow sequence, significantly reducing the manufacturing time and increasing efficiency. This section will explore several examples of API synthesis under flow conditions and provide an example for each type of reactor mentioned in section 1 (coil, chip and packed bed reactor).

A notable example of API production under flow conditions using coil reactors is the synthesis of rufinamide (an anti-seizure drug). This reaction uses PFA tubing, PEEK nuts and three copper coil reactors to synthesize the drug [25] (see Fig.13 for a diagram of the flow process). The synthesis of the API was reduced to 11 minutes under flow conditions, with a production rate of 217 mg/h in 98% yield [26].

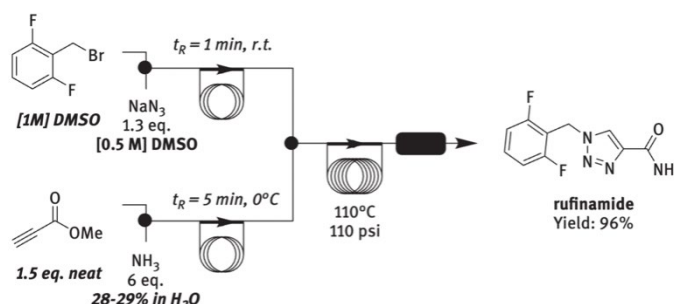


Figure 13. Diagram of the flow synthesis of Rufinamide [26]

An example of API production using chip reactors is the synthesis of efavirenz, a medicine used for HIV treatment. Flow synthesis has allowed the production route to be reduced from five steps to three steps. The process also has in-line purification units to improve reduce the need for external purification methods and thus reduce the production time. Under flow conditions, the production of efavirenz has a residence time of under 2 hours and a yield of 45% [26]. See Fig.14 for a diagram of the process.

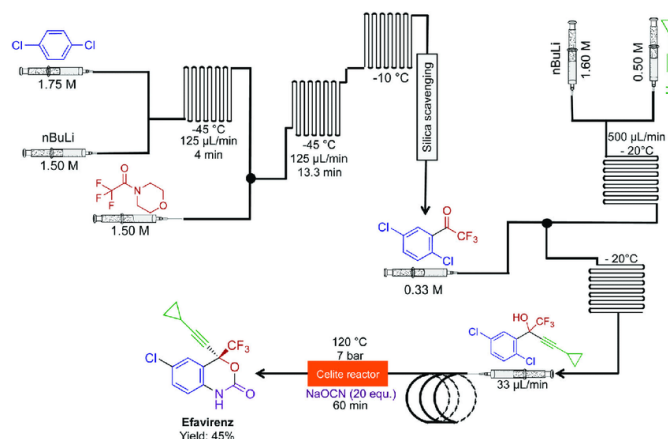


Figure 14. Diagram of the flow synthesis of Efavirenz [27]

Though not commonly used for the manufacturing of APIs, packed bed reactors are vital in treating the waste products of pharmaceutical production. An example would be the use of iron-modified diatomite catalysts in packed bed reactors. Pharmaceutical waste is pumped using peristaltic pumps into the reactors and removed through oxidation. Up to 32.6 % efficiency is reached using this process (see Fig.15 for a diagram of the process) [28].

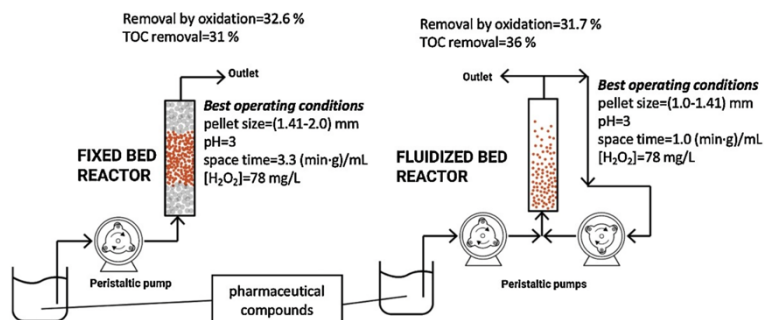


Figure 15. Diagram of the removal of pharmaceutical waste using packed bed reactors [28]

4.2 Flow Chemistry in the Agrochemical Industry

Agrochemicals involves substances such as fertilizers, pesticides and fungicides. With the global agrochemical market at an immense size of 224.9 billion USD in 2021 [29], numerous manufacturers have developed heavy interest in flow chemistry to cover the growing demand. An example of the application of flow synthesis in agrochemistry is the production of hymexazol, a fungicide (see Fig.16 for a diagram of the process). Hymexazol is used for soil disinfection and to control soil-borne diseases caused by fungi such as Fusarium, Aphanomyces and Pythium. Under flow conditions, the production time of hymexazol has been reduced, side-reactions have been inhibited and a product yield of 86% is reached [30].

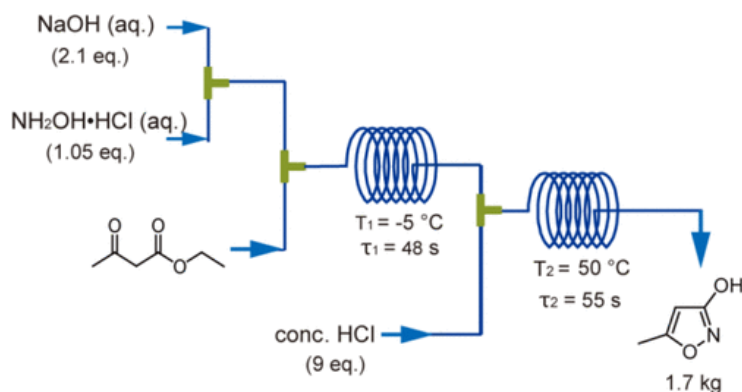


Figure 16. Diagram of the flow synthesis of hymexazol [30]

Another example of flow synthesis in agrochemicals is the production of Boscalid, a fungicide which works on a range of crops including fruits and vegetables [31]. The synthesis is a three-step process, with the first being a Suzuki-Miyaura cross coupling reaction, second a hydrogenation reaction and lastly a in line scavenging with palladium. An overall yield of 42% is reached (see Fig. 17 for a diagram of the flow process) [32].

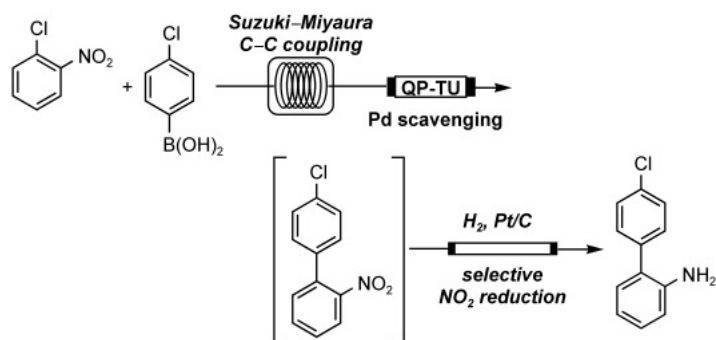


Figure 17. Diagram of the flow synthesis of Boscalid [33]

5. Enabling Technologies in Flow Chemistry

The integration of photochemistry, electrochemistry and artificial intelligence in flow synthesis have emerged as innovative areas of development. Photochemistry and electrochemistry provide traceless reagents (in the form of photons or electrons) and benefit from the flow synthesis conditions. The smaller dimensions and high surface-area to volume ratios offered by flow synthesis are all beneficial for photochemical and electrochemical reactions. These technologies working in combination with flow conditions allows chemical reactions to proceed with higher efficiency and facilitate reactions that are too hazardous to conduct in batch. This section will explore these enabling technologies and provide examples of application.

5.1 Photochemistry in Flow Synthesis

Photochemistry involve chemical which occur when reactants are exposed to light radiation, providing enough energy to cause a reaction. Photochemical reactions are heavily affected by light attenuation (the loss of light intensity as it travels further away from its source) and reactants, products, catalysts etc. can all act as filters that reduce light intensity. For a catalyst concentration of 2.5 millimoles, less than 0.1% of light is transmitted over 0.1 cm from the point of incidence [10]. A ten times reduction of the catalyst (0.25 millimoles) still only allows less than 1% of light to be transmitted to the center of the reactor. This is a limiting factor in batch reactors since lowering the catalyst concentration also lowers the rate of reaction, causing issues in batch scale up operations. In contrast, the small dimensions of flow reactors allow for higher efficiency in light penetration compared to batch reactors. The small diameter of tubing which reagents flow through allow for an even and effective expose to light. Examples of the use of photochemistry in flow would be in light-induced palladium-catalyzed Negishi reactions (see Fig.18 for a diagram of the reaction). Several pharmaceuticals such as ibuprofen, naproxen and flurbiprofen all use this strategy of production and can achieve up to 98% yields.

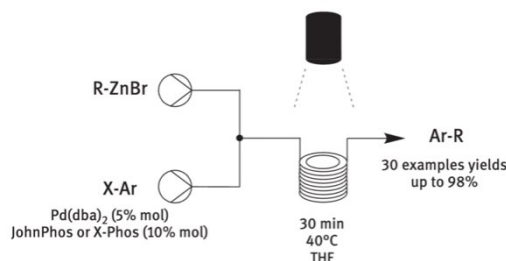


Figure 18. Diagram of light induced Negishi reaction with palladium catalyst under flow conditions [26]

5.2 Electrochemistry in Flow Synthesis

Electrochemistry involves chemical reactions that occur due to electrical currents causing electron movements [34]. Electrochemistry is a more sustainable method of conducting oxidation or reduction

reactions since it reduces the need for often hazardous oxidizing and reducing agents [35]. Scaling up electrochemical processes in batch has been difficult due to the need for cathodes to have large surface area to volume ratios and low energy efficiency due to loss of energy from joule heating. Nonetheless, these issues can be overcome by utilizing flow synthesis with electrochemistry principles. The high surface area to volume ratios offered by microreactors provide efficient temperature control. The lower distance between electrodes also reduces the resistance of the system. Thus, the implementation of electrochemistry in flow conditions allows for more energy efficient, safe and scalable applications. An example of electrochemical flow synthesis is the production of finerenone, a medicine used to reduce the risk of chronic kidney diseases [36].

5.3 Artificial Intelligence in Flow Synthesis

The main goal in organic synthesis is to discover the most efficient routes in producing organic compounds. Currently the process of identifying synthetic routes is a manual and experimental heavy process, making it highly time consuming. However, the integration of automation and artificial intelligence has allowed the development of synthetic routes to be automated. Coley et al. have developed an artificial intelligence which analyzes millions of previously published reactions to produce synthetic routes [37]. This route is then sent to a robotic flow chemistry system which then executes the reaction. The robot is able to automate pumps, connect reagent lines, and clean the flow reaction system once the reaction is completed (see Fig. 19 for a visual representation of the process). This automated system allows chemists to spend less time on setting up reactions and focus more on synthesizing new organic compounds.

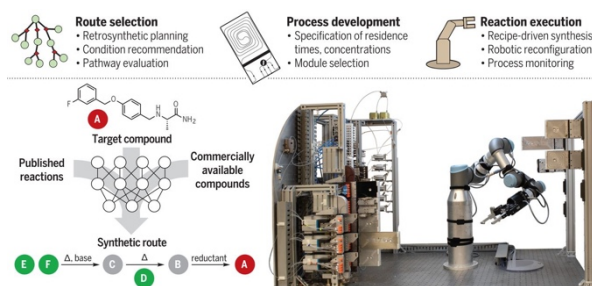


Figure 19. Visual representation of the automated flow synthesis process [37]

6. Conclusion

Flow chemistry has already made significant improvements in the realm of organic synthesis. It has provided an alternative to the traditional batch synthesis method which is often time and resource consuming. Flow synthesis allows reactions to take place with high time and energy efficiency and conducts multi-step syntheses with greater effectiveness than batch, leading to better yield and reproducibility rates.

With the increasing demand in organic chemical industries such as pharmaceuticals and agrochemistry, there is a dire demand for efficient organic synthesis methods. Flow chemistry is the solution to the demand for efficiency and has already benefitted the production speeds of APIs, drugs, pesticides and herbicides to name a few. Implementation of technologies such as photochemistry and electrochemistry have allowed organic synthesis processes which were too dangerous to conduct in batch to operate with safety and ease. Moreover, the addition of artificial intelligence technologies into flow synthesis have allowed the manufacturing of organic compounds to be further optimized.

Flow chemistry serves as an energy efficient, environmentally friendly and scalable solution to organic synthesis. With the increase of patents in flow chemistry over the past few years, there is sure to be greater improvements to flow chemistry and organic synthesis.

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