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# Continuous Flow Reactors: A Precise Review

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Review Article

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## ABSTRACT

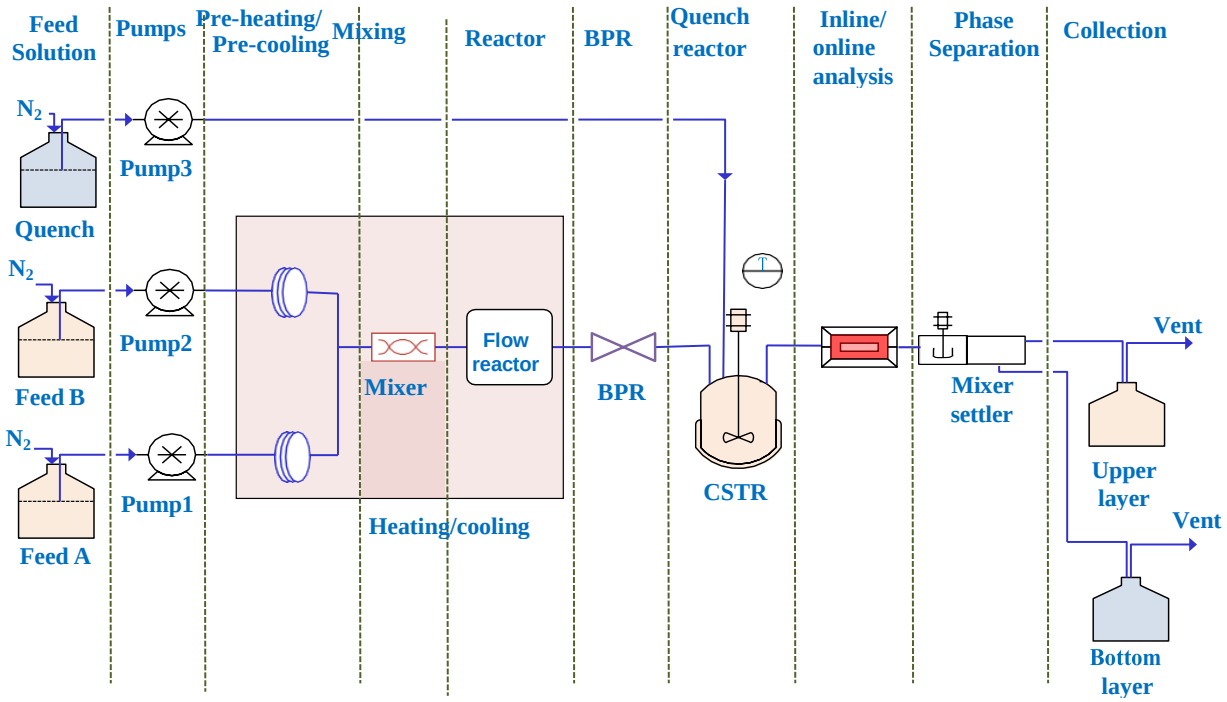
Flow chemistry has being used in petrochemicals and bulk chemicals production from several decades however it has seen only significant interest in pharmaceutical industry and fine chemicals from about a decade. Nowadays, there are many kinds of flow chemistry equipment in the market for process research and development as well as for continuous manufacturing. However, there is still considerable gap between the increasing interest in this technology and the available information especially about the diverse flow equipment. In flow technology the most important part is to choose the proper flow reactor to meet the need of a specific reaction. Typically, physical state of the feed solution as well as reaction mixture is the crucial element to be considered in choosing flow reactor. Choice of flow reactor is also dependent on the specific window of process parameters and the required efficiency of mass and heat transfer. In this review we would discuss regarding prime flow reactors those are in use in chemical and pharmaceutical industry, allowing the correct reactor to be chosen to suit the required chemistry. Moreover, the other unit operations, including inline quench, inline and online monitoring of reactions and industrial applications of flow mode would be discussed as well.

## INTRODUCTION

From last decade, flow chemistry has been emerging as a torrent for chemical and pharmaceutical industries due to its advantages over the conventional batch processing. These advantages include improved safety profile, better quality control, cost reduction and better greenness from sustainability perspective [1-3]. Using fully optimized flow process, many of the complex products are being produced from simple and inexpensive starting materials. Moreover, many of the process conditions those are off limit in batch mode could be readily realized under flow mode. Precisely controlled residence time, small hold-up volume, high heat/mass transfer efficiency and reduced post-processing makes flow chemistry highly adoptable [4]. Furthermore, inline quench becomes significant for the reactions involving highly unstable intermediates and products. Also inline quench leads to the intrinsically safe process for handling hazardous reagents [5].

Inline and online analysis makes flow chemistry more robust and in good alignment with the regulatory requirement of Quality-By-Design (QBD) during the manufacturing of pharmaceuticals [6]. Figure 1 represents a set of flow mode equipment consisting pumps, reactors, back pressure regulator, inline or online analytical tools and post processing equipment etc. In this review we would discuss mainly regarding principal flow reactors being used in the chemical and pharmaceutical industry for process development.

**Figure 1.** Complete Process Flow Diagram (PFD) in flow mode.




## DISCUSSION

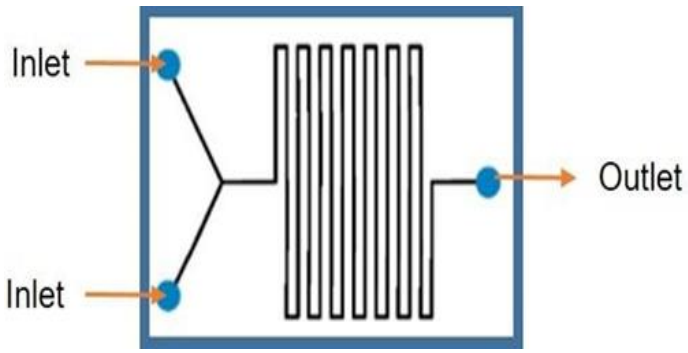
### Types of flow reactors and suitable reactions

Till date, a variety of flow reactors have been evolved to conduct different types of chemical reactions by providing suitable conditions required for the specific reaction. For example, Plug Flow Reactor (PFR) for homogeneous reactions, Continuous Stirred Tank Reactor (CSTR) for solid-liquid or liquid-liquid two phase reactions, Packed Bed Reactor (PBR) for solid-liquid or gas-solid-liquid reactions, Bubble Column Reactor (BCR) for gas-liquid reactions [5]. Also micro-reactor and spinning disc reactor are actively in use for tackling the specific challenges in continuous synthesis. In order to introduce the new energy input (example: light, electricity) to drive the reaction, various photo-flow reactors and electro-flow reactors have been developed as well. There are also continuous reactor units integrated with several kinds of reactors and the switching among different type of reactors is possible based on the specific need of the reactions. All these kind of flow reactors are discussed in details in the following sections of this article.

**Microfluidic reactor/micro reactor:** Microfluidic reactor is one of the widespread reactor type in continuous flow technology and those are generally made from polymers, glass, silicon etc [7,8]. These kind of reactors possess a

narrow channel (ID<1 mm) and the module has designed to increase number of collisions of the fluid. Large surface area and low reactor volume contributes to the efficiency of the reactor. Microfluidic reactor is characterized by laminar flows with a low reynolds number, it helps to eliminate any back-mixing in the system that may cause by fluid turbulence [7]. Figure 2 shows the surface view of microfluidic reactor. The true strength of microfluidic reactor lies in its scaling up. These kinds of reactors can be scaled up simply by increasing number of reactors instead of increasing reactor size. So we may use same reactor for research and manufacturing, which is beneficial for mitigating the scaling up challenges. High surface area to volume ratio has great potential advantages for multiphase reactions however complications by clogging of solid has been a concern. A variety of reactions could be conducted in this reactor, for example, the highly hazardous reactions like nitration reactions are being conducted using microfluidic reactor safely [9,10].

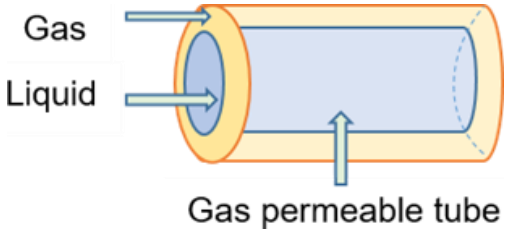
**Figure 2**. Surface view of a microfluidic reactor.




**Tubular reactor/Plug Flow Reactor**: Ideal Plug Flow Reactor (PFR) Figure 3.1 has no mixing in the direction of flow and has complete mixing in the perpendicular direction of flow [11]. The concentration of reactants doesn't vary in the radial direction however it varies along the length of the reactor. The PFR types are divided into adiabatic and polytropic PFRs, either with or without heat exchange through the tube wall. The most common non-adiabatic or polytropic PFRs are the types with coolant surrounding the tube wall and heat transfer through the tube wall surface area. It can be achieved with a jacketed PFR or by placing PFR in oil or in water bath. Homogeneous reactions are preferred using PFR because tube connectors and back pressure regulators are easy to get clogged by building up of solid, if the reaction is heterogeneous [5]. PFR along with static or magnetic mixers reduces reaction time by increasing mixing efficiency. For PFR, a variety of Materials of Construction (MoC) is readily available and is not so costly. Fast reactions are ideal for scaling up in PFR to achieve high throughput, however scaling up of long residence time reactions, using PFR may not be feasible due to the limited throughput and the associated high pressure inside the long tube. Homogenous reactions, including nitration, organometallic reactions and photo-chemistry are being conducted in flow mode using PFR [1,2]. Moreover, tube in tube reactor generally consists of gas permeable inside tube and non-permeable outside tube. Inside permeable tube is made up of Teflon AF-2400 [12], which is an amorphous fluoropolymer, highly permeable to gas however non-permeable to liquid. This reactor is useful for gas-liquid reactions however these kind of tubes are highly costlier. Figure 3.1 represents PFR and Figure 3.2 represents inside view of tube in tube reactor.

**Figure 3.1**. Plug Flow Reactor (PFR).

**Figure 3.2**. Inside view of tube in tube reactor.



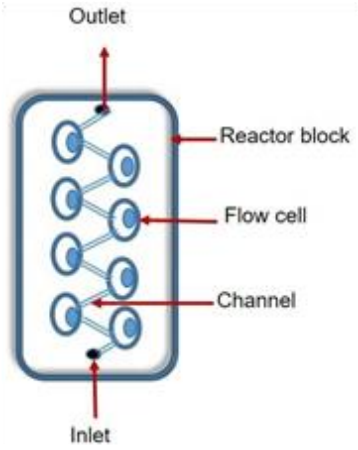

**Continuous Stirred Tank Reactor and agitation reactor:** The biggest hurdle of most of the flow reactors is clogging induced by the build-up of solid in the flow path. To mitigate the clogging issue some special types of reactors are being used like Continuous Stirred Tank Reactor (CSTR) and agitation reactor [5,13]. CSTR is also an inexpensive type of flow reactor and it resembles batch reactor however with inlets and outlets attached to it. This kind of reactor is convenient to operate and also one can add or remove reactors to make a required series. CSTRs are able to handle slurry with moderate particle size, which makes it significant especially for the reactions possessing slurry [13]. Also this reactor is ideal where the intermediates or products get precipitated. Biphasic reactions having organic and aqueous phase could also be conducted using this reactor. Moreover, CSTR would be the great choice for quench reactor in case of precipitation while quenching the reaction. Many kinds of slurry reactions could be conducted in CSTRs including oxidation-reduction reactions and hydrolysis reactions. Even though scaling up of CSTR is challenging, we may find a number of case studies, which has scaled up using CSTRs [5,14]. Figure 4.1 shows series of CSTRs.

**Figure 4.1**. Series of CSTRs. (Photo credit: WuXi STA)

Agitation reactors are based on the principle of continuous stirred tank reactors. It features a reaction block which is mounted on the agitator [15]. The agitation reactor utilizes freely moving agitator within the reactor block. The

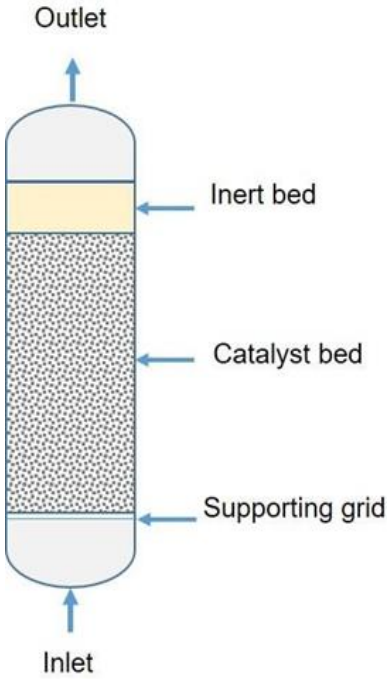
reactor block is constructed from a series of layers containing cells and the cells can be heated or cooled to get desired temperature. Also volume of these cells can be reduced depending on the type of agitator used. Several agitator types have been available for the reactor block, depending on the need of the reaction. The oscillation frequency can be varied accordingly, in order to achieve optimal results, depending on the density of slurry. This specific agitating mode of mixing is ideal for keeping suspension uniformly dispersed and preventing solid from settling out. This reactor type is ideal for solid-liquid reactions containing hazardous reagents [15]. Scaling up of this reactor becomes challenging and also dependent on the reaction type. Figure 4.2 represents inside view of agitation reactor.

**Figure 4.2**. Inside view of agitation reactor.



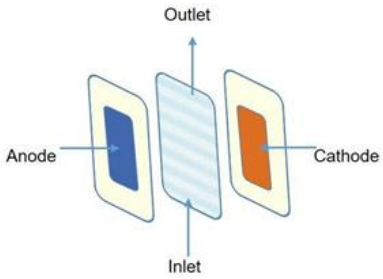

**Packed Bed Reactor/trickled bed reactor:** Catalytic Packed Bed Reactor (PBR) is one of the most important, non-costlier and simplest form of flow reactor for process development as well as for continuous manufacturing [16]. In this kind of reactor, reaction takes place in the form of a heterogeneously catalyzed reaction on the surface of catalysts. Moreover, in this reactor a number of immobilized catalysts including immobilized enzymes could be used for catalysis. For synthesis of expensive intermediates or products, packed bed reactors have been increasingly used in the recent years [5]. Figure 5 represents inside view of packed bed reactor. These kinds of reactors are generally operated in a stationary mode for prolonged production time. However, the non-stationary dynamic operating mode is also of great importance. In pharmaceutical industry, the primary driver of using PBR is to achieve process intensification and cost reduction in the use of highly expensive metal catalysts or enzymes. In PBR, the amount of catalyst that is in contact with substrate is more than the batch mode [16]. So that reaction rate gets considerably accelerated. Besides, it is possible to feed the substrates continuously into PBR until the catalyst loses its activity, thus performance of the catalyst maximizes efficiently. PBR is specific for solid-liquid and solid-liquid-gas type reactions. However high viscosities and low thermal conductivities of feed solution, also irregular shape of immobilized catalyst when being placed inside the reactor may lead to the complications. For continuous hydrogenation there are assembled reactors in which pumps, fixed bed reactor, hydrogen generator, temperature controller, BPR and gas-liquid separator are all integrated in a single unit [17]. These continuous hydrogenation reactors are useful tools for the quick feasibility evaluation and process optimization.

**Figure 5.** Inside view of packed bed reactor.




**Continuous electrochemical reactor:** We have been witnessing a remarkable elevation of work in the field of continuous electrochemistry in the recent years. By the use of electrochemistry, hazardous or waste generating oxidants or reductants could be replaced by electricity as well as by simple electron acceptors or donors [18,19]. Electrochemical reactions in flow cells could be carried out with recirculation of the electrolyte solution. This type of operation benefits by the enhanced cell conductivity, improved mass transfer and high electrode surface area to feed solution ratio. However this semi batch type of operation is not a complete continuous process. Continuous process can be achieved by getting high conversion to the desired product in a single pass through the flow cell [20,21]. Single pass operation enables the potential integration of the electrochemical reaction with synthetic or post processing steps in a continuous manner. Thus, development of single pass continuous flow electrochemical process and flow reactors suitable for this type of operation have attracted considerable interest in chemical and pharmaceutical industry [20,21]. Moreover, multi-dimensional electrodes or extended reactor channel length have been developed as well to increase electrode surface area. Using this type of reactor, variety of organic reactions could be conducted at small and large scale, in which greenness of electrochemistry has been well demonstrated. Number of types of reactions are being conducted by using flow electrochemistry efficiently to contribute to the green chemistry [19-21]. Figure 6 represents inside view of continuous electrochemical reactor.

**Figure 6.** Inside view of continuous electrochemical reactor.



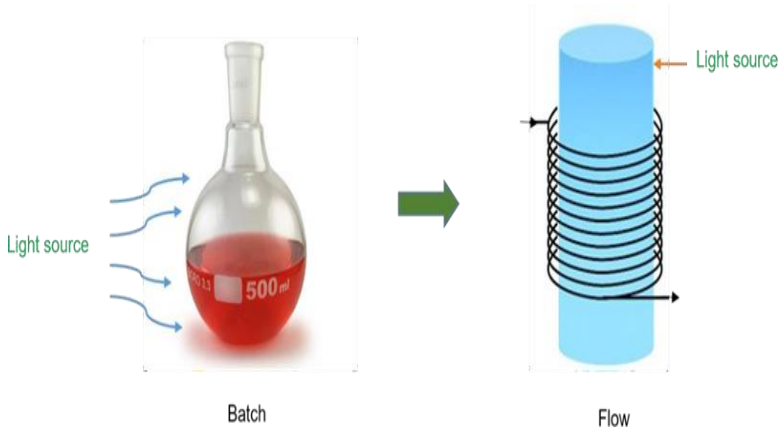
**Bubble column reactor:** Bubble column reactors are extensively used in research and manufacturing of gas-liquid and gas-liquid-solid type of reactions [22]. In a bubble column, gas in the form of bubbles comes in contact with the liquid. The purpose is simply to increase the contact area between the two phases and thus to promote the mass transfer [22]. In bubble column reactor, gas need to feed at the bottom and rises in the liquid and finally escapes from the upper surface. The gas gets consumed to a greater or lesser extent depending on the intensity of mass transfer and the rate of chemical reaction. The advantages of bubble column reactor are excellent heat and mass transfer, as well as the flexibility of gas-liquid ratio. Additionally, this type of reactor also presents a high value of effective interfacial area, low maintenance cost due to simple construction, relatively low cost for construction and it's convenient to operate. One of the most important reaction, ozonolysis could be safely manufactured in large scale using continuous bubble column reactor [23]. Because of potential hazards of ozonide intermediate, almost no one prefers to scale it up in batch mode, even though the products of ozonolysis are valuable compounds. However bubble column reactor is ideal for continuous ozonolysis manufacturing, regarding process control and process safety [23]. Figure 7 shows surface view of bubble column reactor.

**Figure 7**. Surface view of bubble column reactor.

**Continuous photochemical reactor:** For photochemistry in flow mode, tube reactors, CSTRs and micro-reactors are mostly being used by choosing appropriate light source. Photochemistry is currently one of the important research field in the scientific community. The recent exploitation of flow methods for photo chemistry has provided a new opportunity for large scale manufacturing [1]. According to the Beer-Lambert law, light transmittance decreases exponentially with the distance from the light source [24]. For a standard batch reactor, light intensity decreases considerably from the flask wall to the center of the reaction mixture. It results in slow reactions and non-homogeneous irradiation. Performing photochemical reactions in micro-channels (ID<1 mm) or using Fluorinated Ethylene Propylene (FEP) tubes allows higher and more homogeneous photon flux [25]. It results in shorter residence time and consequently less side product formation due to even irradiation. Another advantage of photo flow chemistry correlated with the large surface volume ratio, improved heat and mass transfer. Photo-halogenation and photo-redox reactions specially have been conducting in flow mode because of expensive products, less side-

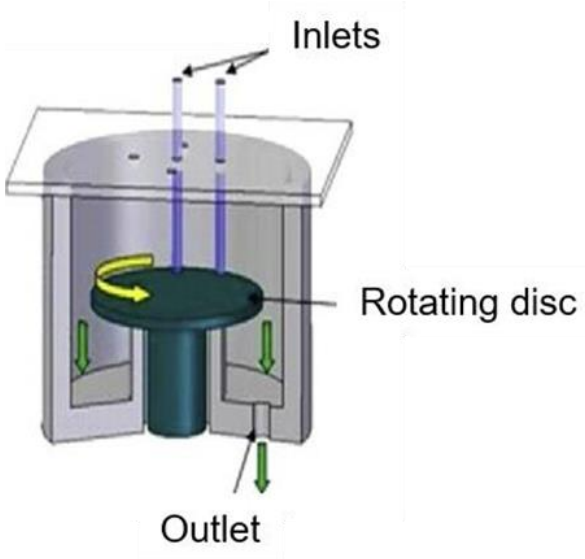
products formation, excellent control of parameters and high yields [5,25,26]. Figure 8 represents photochemical batch reactor and flow reactor.

**Figure 8**. Photochemical batch reactor and flow reactor.




**Spinning disc reactor:** In spinning disc reactor, a rotating disc is enclosed in a narrow cylindrical encasing. Generally, the distance between the rotor and the stator is in mm level. This leads to significant larger shear rates in the gasses and liquids, it provides larger interfacial area available for mass transfer and a higher degree of turbulence [27]. Moreover, volume of the reactor is completely filled with liquid so the residence time in the reactor can thus be controlled independently from the disc speed. It allows a powerful combination of introducing high shear without losing residence time. Finally the incorporation of cooling and heating layers parallel to and in close proximity of the disc allows excellent heat transfer. Process optimization and then scaling up of the reactor could be easily achievable to get optimum results. Fast reactions of Liquid-liquid, gas-liquid and solid-liquid type with small particle size could be conducted in this reactor. Figure 9 represents inside view of spinning disc reactor.

**Figure 9**. Inside view of spinning disc reactor.



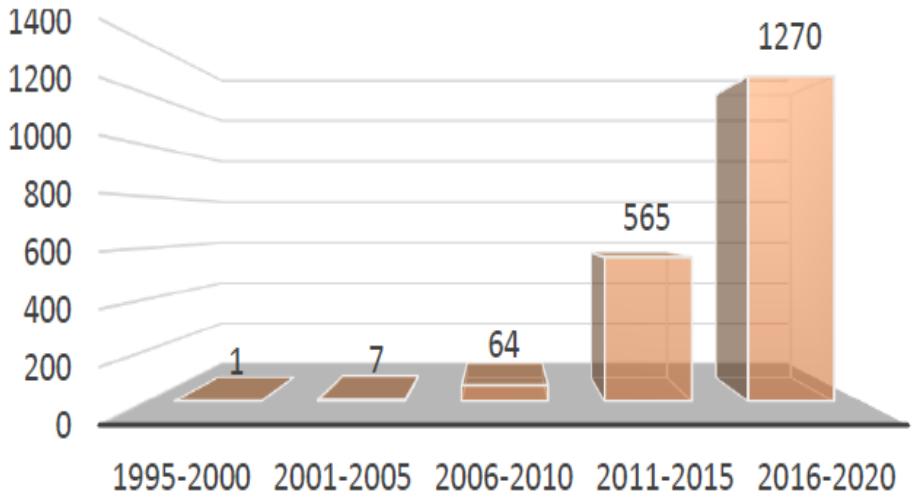
## Inline quench and inline/online analysis

Inline quench has great advantage in flow chemistry and became troubleshooting phenomenon in case of unstable intermediates and products. Many of the difficult chemistries in batch mode especially for large scale production, made easier by inline quench in flow mode. Inline quench provides quick quenching of reactions or hazardous materials resulting in preventing side products formation and reducing hazards [5]. Moreover several inline/online analytical tools are being used for analysis in continuous mode, continuous FTIR, NMR and HPLC are the most suitable tools till date [28,29]. These tools have great importance in the analysis of highly sensitive reactions. Quick analysis using these tools provides an option to perform the feedback or feed forward controls of process parameters to get desired result.

## Industrial applications

For industrial applications of continuous flow technology, the most important drivers are improving process safety, reducing impurity formation and achieving cost reduction [1]. In flow mode, process parameters could be controlled in a better way than batch mode and a high level of automation could be achieved as well. This is the reason flow chemistry has attracted considerable interest in pharmaceutical industry [1,30]. Currently, pharmaceutical companies are mainly using flow chemistry as an addition to the existing batch approach to tackle the associated technical challenges. One of the key driver is to mitigate the issues of reactions those are typically considered off-limits under batch mode, including highly hazardous reactions, involving extremely toxic or explosive reagents/intermediates [31]. Pharmaceutical and chemical companies are also applying continuous manufacturing to achieve the new process windows to intensify the processes [32,33], for example performing reactions at high temperature/pressure by using low-boiling point solvents (Figure 10).

**Figure 10**. Publications using “flow chemistry and green chemistry” both key words.



## CONCLUSION

In this review prime flow reactors those are in use in chemical and pharmaceutical industry are discussed and reactions types suitable for each flow reactor has explained as well. It allows the correct reactor to be chosen to suit the required chemistry. Furthermore, advantages and disadvantages of each flow reactor has also mentioned. Moreover, the other unit operations *viz*. inline quench, inline and online monitoring of reactions are discussed to mitigate specific issues relating to scale up. Industrial applications of flow mode has explored too and has precisely noted importance of flow processing in pharmaceutical and chemical industry.

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