Flow reactor design and construction for organic synthesis

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ABSTRACT: In the new field of drug synthesis known as flow chemistry in organic synthesis, numerous reagents and solvents are utilized by additions and distillations and mixed in a continuous reactor, such as a glass micro reactor or continuous-stirred stainless steel reactor (CSSR).
Key Words: Reactor, Flow, temperature,cssr

In flow chemistry, a chemical reaction is carried out in a stream of fluid that is continuously flowing through a system of interconnected channels. Where the channels converge, the fluids come into contact, and the reaction occurs. The following basic elements are typically found in flow reactors: one or more fluid control devices, which load the solutions of various reactants into the reactor section, the reactor, which can typically be heated or cooled, allowing reactions to take place under precise temperature and pressure control, and suitable reservoirs to collect the resulting mixture (Figure 1).
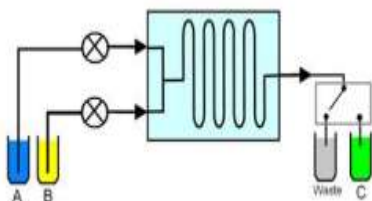

Figure 1 shows the general layout of a flow reactor.

On the basis of channel size and volume, laboratory sized flow reactors may generally be split into two major classes: micro- and meso-flow reactors. Micro-flow reactors have channels with a diameter of 10 to 1000 m, whereas meso-flow reactors have bigger channels with a diameter of up to 1000 m, however this distinction is not always clear-cut.The fundamental distinction between these two types of machinery has to do with the reactors' shapes and production methods. In particular, photolithography and micro-patterning techniques from the semiconductor microelectronics industry are used to design and manufacture micro-flow reactors, which are typically planar objects the size of a small plate, or "chips." A number of different micro reactors have been created recently, and some of them are being sold commercially. A micro reactor's applicability is determined by its size, the chemical and physical characteristics of the material used to build it, and the method employed to introduce reagents and solvents into the system. Figure 2 presents a few different micro reactors to show the variety of miniaturized reaction devices that have been documented thus far. There have been a variety of materials employed, including glass, silicon, stainless steel, metals, and polymers.
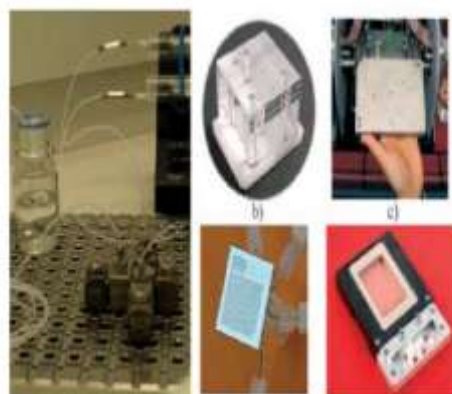

Figure 2 shows silicon-based micro reactors, glass micro reactors, and stainless steel micro reactors in order of appearance.

Instead, meso-flow reactors are made of plastic tubing with T or Y-shaped connections (which is typically the same material used for HPLC instruments) (Figure 3).
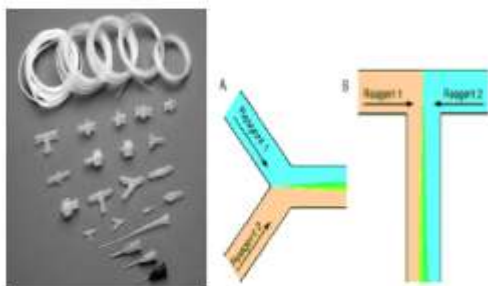
Figure 3: T- or Y-shaped connectors in meso-flow reactors made of PTFE.

As all the properties listed apply to both categories of micro- and meso-flow reactors, the name "micro reactor" (MR) will be used to refer to both types of reactors. In micro reactors, the fluid behavior is primarily non-convective, with "laminar flow" and mixing determined only by diffusion. All flow reactors require precise fluid control, which is accomplished using one of two major methods: hydrodynamic flow or electro kinetic the former, also known as pressure-driven flow, is frequently related to peristaltic or syringe pumps that impart a positive pressure to the system's input. These devices' extensive compatibility with any solvent and any building material is their key benefit. Hydrodynamic flow has a parabolic shape, which can cause non-homogeneous residence times since the flow is quicker in the channel's centre and slower towards the sides (Figure 4).
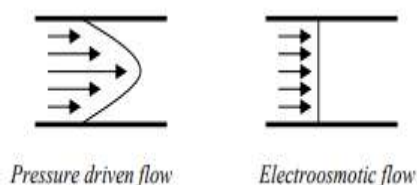

Figure 6 shows the velocity profiles for electro osmotic and pressure-driven flow.

The application of a potential difference at the system's ends is related to the alternate electro kinetic flow. The immediate migration of ions in solution towards the electrode with the opposite charge is the initial effect of this. Electro osmotic flow, the second element of electro kinetic flow, results from the electrical double layer that develops on channels with charged surfaces. Glass and silica surfaces have a negative charge at neutral to basic pH due to the partial ionization of surface hydroxyl groups. Positive species in the solution create a second layer close to the channel's surface in reaction to the negative surface charge. Viscous friction between the moving ions and the remaining solution generates net flow of the fluid towards the negative electrode when an electric potential is provided between the channel ends, causing the mobile positive ions to migrate towards the negative electrode (Figure 5). Precision in fluid handling is made possible by the linear relationship between the velocity of electro osmotic flow and the applied voltage. When compared to hydrodynamic flow, the velocity profile in this example is essentially flat across the channel, considerably reducing reagent dispersion. Unfortunately, only polar solvents like water, methanol, acetonitrile, dimethylformamide, and tetrahydrofuran and device materials like silicon, glass, and treated PDMS (Polydimethylsiloxane) may be used with electroosmotic flow.
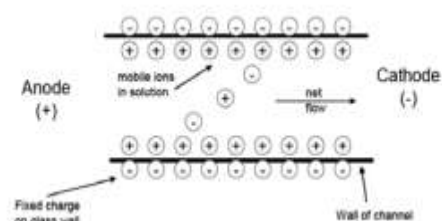

Figure 5 Electro osmotic flow

A sizable number of laboratory scale gadgets were commercialized in recent years. Although the majority of the fundamental characteristics listed in this paragraph are present in all instances, producers added additional features to give the end user the widest possible range of applications. These additional features include the ability to use solid catalyst or polymer-supported reagents, gaseous reagents (for example, for hydrogenations and carbonylations), and more reactors in parallel or in series. The use of more complicated devices, combining two or more distinct approaches to take use of their unique advantages, was described in certain examples in the literature. Examples of microwave flow reactors and photochemical flow reactors stand out in this regard.

Principles and key parameters
As opposed to flow processes, where it depends on both the ratio of reactant concentration and flow rate, batch processes define reaction stoichiometry as the ratio between the moles of

reactants. Due to the ability to independently change concentrations and flow rates to achieve the ideal conditions, the flow system is much more adaptable. The Residence Time (RT), which is used to describe reaction time in flow processes, is determined by the relationship between the reactor volume and the total flow rate.

RT (min) = Reactor Volume (mL) / Total Flow Rate (mL/min)

The amount of synthesized product produced each hour, or output, is determined by a relationship between the flow rate, concentration, molecular weight of the product, and the reaction yield rather than by the traditional concept of batch scale.

OUTPUT (g/h) = Flow Rate (mL/min) x Conc (mmol/mL) x MW (g/mol) x Yield (%) x 0.0006

Advantages of the flow technique

There are two primary categories in which the benefits of flow processes carried out in micro reactors can be divided. The first is connected to the channels' tiny size and involves the ability to precisely control reaction conditions, efficiently transmit mass and heat, and operate in superheated environments. The second factor relates to the continuous character of the process and involves the ease of reaction scale-up, the ability to carry out successive synthetic steps with independent control of reaction parameters, and the potential introduction of in-line reaction monitoring. Using assisted scavengers or sorbents to purify the water and the option of connecting the reactor to in-line analysis equipment to allow for real-time monitoring.The purpose of the following paragraphs is to highlight these various qualities through the examination of literary examples.

Benefits associated with the narrow channel dimensions

Mechanical stirring is typically used in traditional batch reactors, like round-bottom flasks, to manage the distribution of mass and heat. However, in the majority of cases, inhomogeneous temperatures and mixing are not achieved due to the formation of concentration gradients and hot spots in relation to reactor geometry, which can result in low yields and reaction selectivity. On the other hand, micro reactors provide a quick and effective reagent mixing due to the constant and controlled addition of small quantities of reagents, lowering the time needed to create a homogeneous solution to as little as milliseconds and preventing the formation of hot spots.

The simulation of the neutralization reaction (HCl/NaOH) carried out in batch and in a flow reactor (Figure 8) provides an illustration of this benefit. The concentration distribution in an MR is depicted in the figure, which also highlights the MR's effective mixing capabilities. Hot spots can emerge because the chemical distribution in a batch system is less homogeneous than in an MR.

Batch synthesis:
Concentration equivalent: 0.8 (blue)-
1.0 (green)-1.2 (red). Formation of
hot spots

Flow synthesis:
Reagent A injected in a flow stream
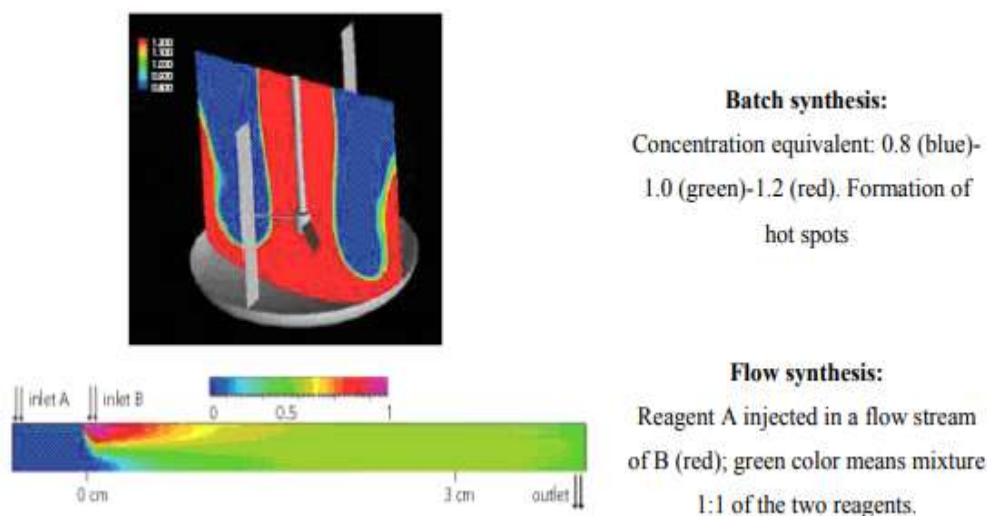of B (red); green color means mixture
1:1 of the two reagents.

Figure 6 illustrates how HCl and NaOH neutralize one another.

Another crucial factor for getting optimal results from a reaction is temperature. The channels' tiny dimensions allow for an effective transfer of heat in this instance as well.
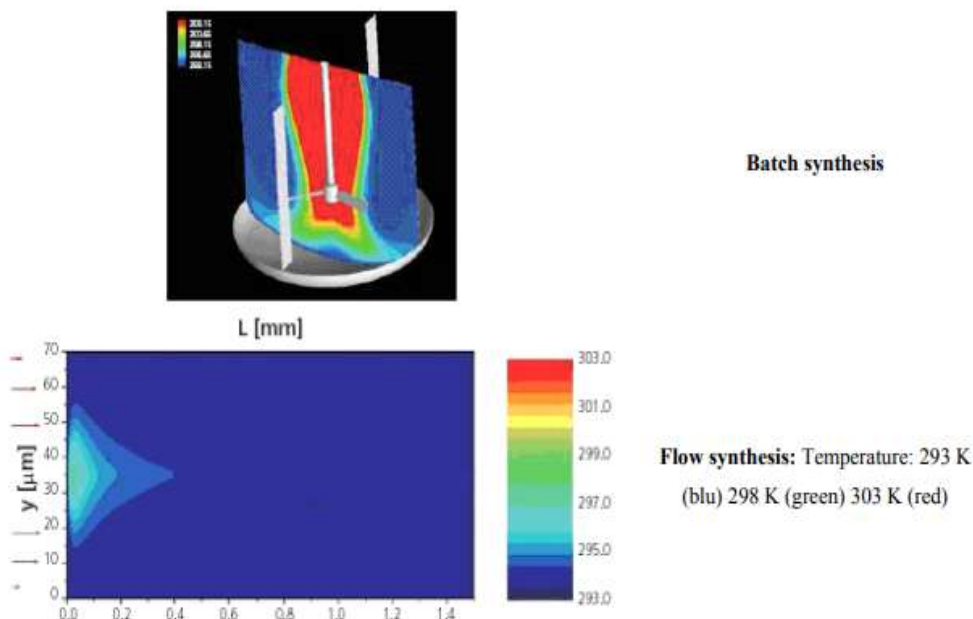
Figure 7. The reaction between HCl and NaOH to neutralize it

This point is highlighted in Figure 7, which simulates the temperature distributions for an HCl and NaOH neutralization reaction in a batch vessel and in a channel. In MR, the typical distances between the flow of reagents and the walls of the micro reactors that exchange heat are short. A steep temperature gradient also drives heat exchange. Concentration and temperature gradients are constant along the whole flow channel. When compared to traditional synthesis, these steady gradients offer superior control over the reaction conditions. In reality, a multi-m3 batch vessel's temperature transfer is more challenging than it is in an MR, which causes the vessel's temperature to vary greatly. The high surface-to-volume ratio, also known as specific surface area, is the second property of micro reactors. Fast heating and cooling are made possible by the large specific surface area, which is directly related to a high heat-exchanging efficiency. Figure 10a displays a qualitative distribution of the inner temperature of a typical reaction in both a micro reactor and a traditional batch reactor.
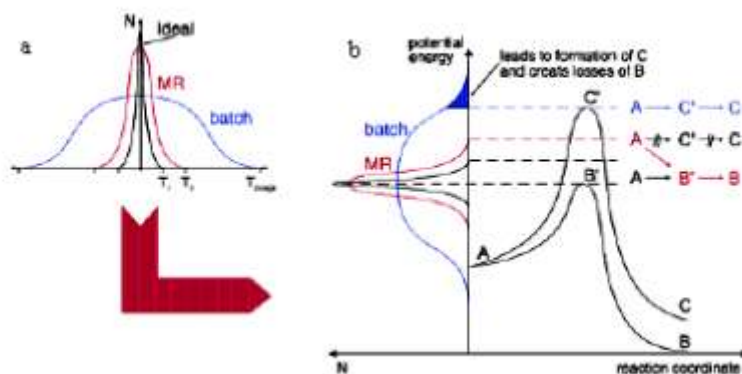

Figure 10 shows the association between the temperature distribution (a) and the synthesis pathway (b).

The micro reactor's greater capacity for heat transfer makes it possible to prevent temperature fluctuations during the process. Contrarily, a classical reactor has a wider

temperature range around the specified setting, mostly due to the smaller specific surface area and mixing problem. This variable distribution may affect how the synthetic process is carried out. The relationship between reaction temperature and the synthetic pathway is schematically depicted in Figure 10b. The potential energy profile is related to the reaction temperature both along the reaction coordinate and when traversing transition states.

The production of B is encouraged if the activation energy provided by the reaction is limited, displaying a maximum in accordance with the set temperature (transition state B'). The reaction is demonstrated to proceed from the conversion of starting material A to product B. A side reaction profile is also feasible; it offers the by-product C and calls for a greater activation energy (transition state C'). The narrow temperature distribution in the MR confines the reaction to the target product B, whereas the batch reactor's wide temperature range permits the formation of the undesirable by-product C.

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