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Review paper

Activated pharmaceutical ingredients produced by microreactors *versus* batch processes: A review

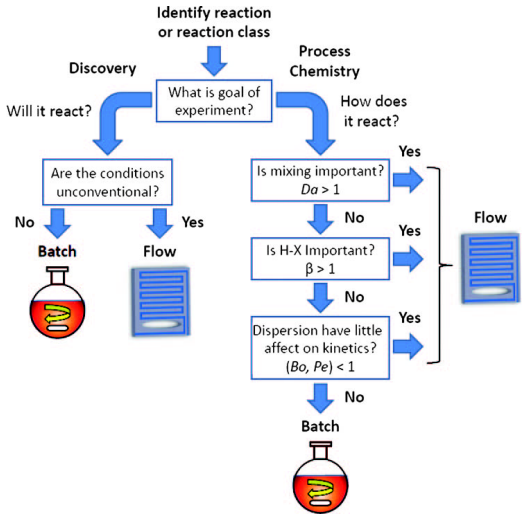
Farzad Bastan, Mohammad Kazemeini*

Department of Chemical and Petroleum Engineering, Sharif University of Technology, Tehran, Iran

HIGHLIGHTS

- The importance of the new technology 'microfluidic and microreactor' in pharmaceutical industry is addressed.
- The properties of micro reactor and its benefits toward batch reactor (yield, conversion, mass transfer and heat transfer) are discussed.
- Syntheses of active pharmaceutical ingredients, intermediates and lead compounds are reported employing microreactors and continuous flow technology.

GRAPHICAL ABSTRACT



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ABSTRACT

In the pharmaceutical industry, drug synthesis is usually carried out by batch method. However, in recent years, continuous methods, specifically microfluidics and microreactors, have attracted a great deal of attention due to advantages such as better mass and heat transfer, safety, selectivity, yield, and surface-to-volume ratio. Thus, in this review, different microreactor properties such as flow regime pattern, operating pressure, selectivity, safety, reaction phase, operating and control, materials, and cost are addressed and discussed. In addition, microreactor applications in the synthesis of chemicals and drugs, polymerization, nanoparticle synthesis, photochemical, biodiesel production, and catalytic microreactors are presented in detail. Furthermore, a comparison of the flow process of a pharmaceutical industry's microreactor and a batch reactor used for different APIs, intermediates, and lead compounds is presented. The results revealed that 50% of such reactions would show more promising results when carried out in a microreactor system, while only 44% of examined cases preferred such systems. Ultimately, these authors believe that the current review is very suitable for newcomers in pharmaceutical industry material production research who might be attracted to this new technology due to the elementary and basic microfluidics concepts discussed in the present manuscript.

* *Corresponding author: Tel.: +9821-66165425 ; Fax: +9821-66165425 ; E-mail address: kazemini@sharif.ir*
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1. Introduction

The usual methods of synthesis performed in most laboratories are the discontinuous type. In the batch mode method, the reactions occur in a closed vessel where reactants are mixed at a specific pressure and temperature for a specified time. Then, the mixture is removed from the vessel and purified to separate the main product. On the other hand, the lesser-used continuous flow method is less discussed [1]. One such method, flow chemistry, is defined as a set of chemical processes that are carried out in continuous flows performed in continuous reactors. This type of chemistry is obtained using cutting-edge microreactor technology [2-5]. In the batch method, the concentration of products and reactants changes over time. However, in the continuous method, the concentration of products and reactants does not change with time but changes in different reactor locations [6]. Furthermore, after a certain amount of time, the desired product's concentration increases, and the reactants' concentration decreases. Moreover, in the continuous method and related reactors, different shapes and sizes are fed to the reactor, and the product mixture leaves at the end of the reactor at the same rate. As the mixture of reactants and products moves from the beginning of the reactor to the outlet, the amount of the raw material decreases. However, the amount of product usually increases from the reaction's beginning to the reactor's outlet [1,7]. In the continuous mode and related rectors, the reaction occurs from the injection point, and the reaction continues through the reaction vessel and finally stops at the outlet point. In other words, the time the material spent passing through the reactor is considered the reaction time [6,7]. The decision roadmap for the features of a chemical reaction to ensure the success in flow operations is based on the relevant reaction times scales (Fig. 1).

Flow chemistry enables the use of small amounts of reagents as well as the safe and secure use of dangerous and toxic raw materials [8,9]. In addition, continuous synthesis eliminates the need to separate toxic or dangerous intermediates. Reducing reaction time and improving efficiency due to improved heat transfer and mixing are also among the advantages that can be mentioned [10-12]. In the traditional synthesis method, the production rate of a chemical reaction increases with the increase in device size, and due to mass and heat transfer limitations, scaling up in batch systems is often difficult. On the other hand, in continuous method synthesis, increasing the reactors numbers results in increasing production. Number scaling techniques are superior to size scaling because the physical characteristics of the synthesis device or equipment remain unchanged [2]. Continuous systems usually require less equipment volume and human intervention than batch systems [13-15]. One of the disadvantages of the discontinuous system is the large amounts of reactant waste produced in the start-up, overhaul, and cleaning of discontinuous systems. On the other hand, the amount of waste reactants in a continuous system is extremely less than in a batch system and ultimately improves economic efficiency [16]. A comparison between batch and continuous processes is presented in Table 1.

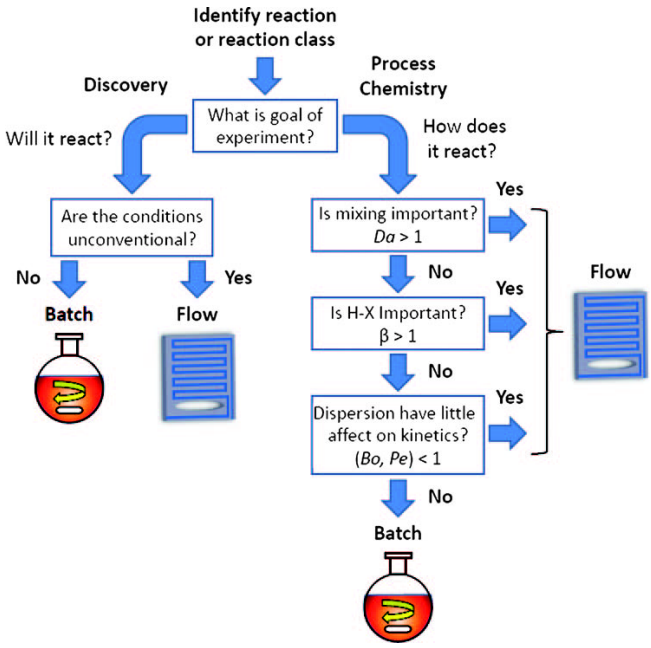

Fig. 1. Choosing a proper approach for a reaction (Da = Damköhler numbers, H-X = Heat exchange, Pe = Péclet Number) [17,18].

Four main types of continuous reactors have been addressed in the literature (Fig. 2). Type I, all reactants pass through the reactor vessel, and the product is obtained at the exit point. Type II, one reactant is placed in an enclosed reactor while the other reactant passes through the reactor; in a competition of the reactions, the desired product is achieved in the outlet mixture. Type III, homogeneous catalysts are used. The catalyst is injected into the reactors in conjunction with the reactants, and the catalyst is recovered and separated from the products. Lastly, in Type IV, heterogeneous catalysts are used. In other words, a solid catalyst is placed in the reactor, and passing the reactants through

Table 1. Comparison between batch and continuous processes.

Factor	Contiuous	Batch
Type of materials	Easier for use with flowing materials (today, almost any material can be produced with a continuous process; investment cost is the decisive factor).	Can be used with all types of materials (with non-flow materials, it is easier to use the batch process).
Installation size	Relatively small installation. Significant savings in land and installations.	Relatively large installation. Massive investment in land and installations.
Reactor	At all locations, conditions are constant over time (durable condition).	Changes occur in the concentrations of materials over time.
Feeding raw materials	Constant feeding of raw materials during the entire reaction process.	Raw materials are fed before the start of the reaction.
Control of the set of actions in the system	• Complex control • Automatic control must be used • Control of reactor conditions is more difficult than a batch process.	• Simple control • It is an easier-to-control reaction. • Manual control can be done.
Shut down time	Often	Rare
Workforce	Many people needed	Few people needed

the reactor and over the surface of the heterogeneous catalyst, the reaction takes place. It is worth noting that, at the end of the reaction and reactor, there is no need for catalyst recovery and separation [19].

Depending on the production scale, the diameter of the channel (pipe) in a continuous system may differ (from 0.1 to 10 mm). Based on the production scale, continuous reactors can be categorized into three main groups: (a) micro-scale (Fig. 3), (b) milli-scale, and (c) macro-scale reactors. The amount of product produced from microreactors is not greater than kg/year scale, making them perfect for expensive materials, such as pharmaceuticals. With milli-reactors, hundreds of kg per year could be achieved, making them suitable for synthesizing certain chemicals. In contrast, macro-scale reactors, which can be a large number of parallel or attached channels, can produce tons of desired products per year [7].

By controlling the reaction parameters, the researchers could conduct any reaction and survey different aspects of a specific issue. Finally, with the emergence of microfluidic technology, the aforementioned desired outcome was achieved perfectly [21-24]. Microfluidics is the science and technology of processing fluids in microchannels with at least one dimension less than 1 mm (for example, channel depth, width, or diameter). A

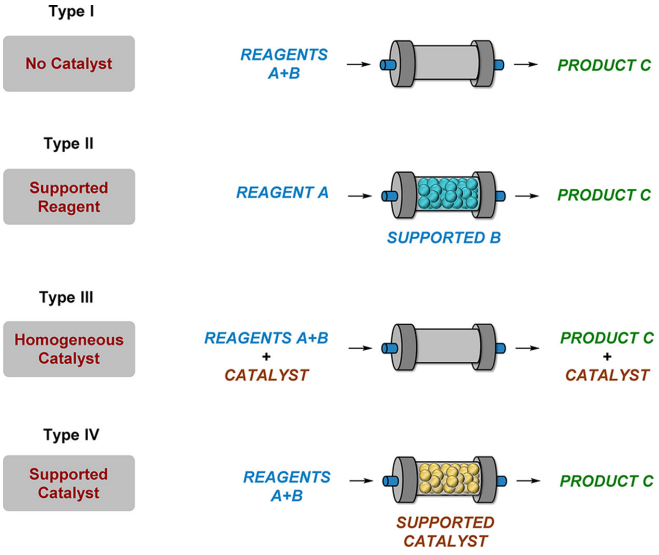

Fig. 2. Four main types of continuous reactors [20].

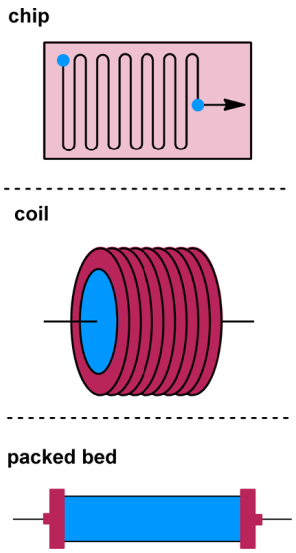

Fig. 3. Examples of different manufactured microreactors [19].

microreactor is a device in which chemical reactions are carried out in a chamber with lateral dimensions of less than 1 mm. The most common form of such a container is microchannels. Due to their small dimensions, microreactors minimized the consumption of reactants and energy loss (Fig. 4).

To illustrate the importance and position of the new technology (microfluidics and microreactors), the authors have focused on the elementary and basic concepts of microfluidics in the presented review to provide a guide for new researchers attracted and trying to find their way in this well-known technology.

2. Microreactors properties

2.1. Flow regime pattern

Calculating the Reynolds number in the microreactor (usually 10 to 500) revealed that the flow regime is laminar. Therefore, the mixing mechanism will be diffusion [26-29]. Laminar flow has some advantages, like inhibiting the presence of gradients in thermodynamic parameters [30]. In addition, a microreactor's surface-to-volume ratio is very high. Thus, microreactors allow a swift heat transfer, enabling precise temperature control. Furthermore, working with microreactors is very safe due to the high-efficiency heat exchange (Table 2). On the other hand, the release and accumulation of intense heat can cause a lot of danger if manipulated incorrectly in batch systems [31].

The major flow regimes of reactions that contain liquid and gas at the same time and are carried out in a microreactor system are flocculent (Taylor) and annular. For a given liquid velocity (e.g., much less than 1 m/s), liquid-gas flocculent flow predominates at relatively low gas-to-liquid flow ratios, where gas bubbles are divided. The results of the formation of circular currents mixing and mass transfer will also

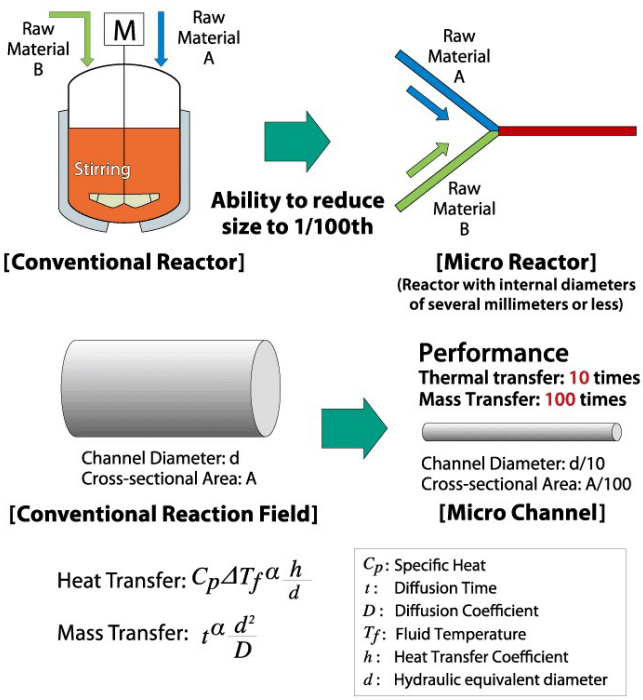

Fig. 4. A comparison of conventional reactors and microreactors [25].

increase. On the other hand, annular flow occurs in very high gas-to-liquid flow ratios [33].

Since the synthesis of some products consists of multiple steps and purification will be mandatory in every step, batch methods can be very time-consuming, difficult, and expensive. In addition, mechanical and human errors will increase dramatically through each step, affecting the process's safety. On the other hand, a multi-step reaction could be carried out in a single reaction using microreactors (Fig. 5), reducing the manual and purification steps and leading to a more economical process [34].

2.2. Operating pressure

Since the dimensions of a microreactor are very small and by increasing the pressure, the amount of force that

Table 2. Heat exchanging in micro and macro systems [32].

Parameter	Shell and tube heat exchanger	Compact heat exchanger	Microchannel heat exchanger
Surface-to-volume ratio [$m^2.m^{-3}$]	50-100	850-1500	>1500
Heat transfer coefficient (liquid) [$W.m^{-2}.K^{-1}$]	~5000 (tube side)	3000-7000	>7000
Heat transfer coefficient (gas) [$W.m^{-2}.K^{-1}$]	20-100	5-300	400-2000
Approach temperature [°C]	~20	~10	<10
Flow regime	Turbulent	Turbulent	Laminar

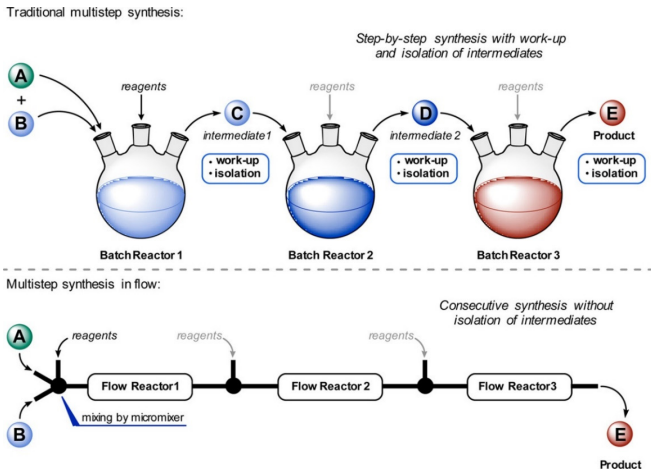

Fig. 5. Multi-step reaction in traditional batch and continuous systems [15].

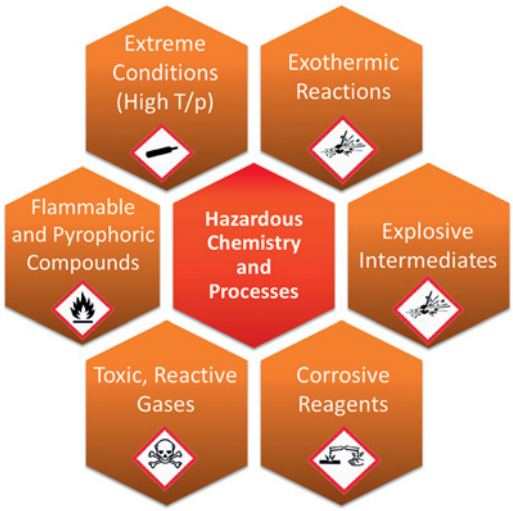

Fig. 6. Different sources of danger in the reaction process [32].

is produced is low, even in high pressure (up to 400 bar), the operation of the microreactor would be simpler due to the small force produced. However, operating larger reactors with such pressures (up to 400 bar) would be a bigger problem that requires unique protections and procedures [30].

2.3. Selectivity

One of the most important aspects of any reaction is selectivity. It is well known that microreactors provide a better approach to selectivity due to its unique properties, such as mass and heat transfer improvements related to a high surface-to-volume ratio [34-40]. Viviano *et al.* showed that small-scale discontinuous microwave processing is a useful tool for optimizing reaction conditions to achieve high product yield and selectivity in the shortest possible reaction times. The resulting temperature histories were easily transferred to high-temperature continuous flow reactors (stainless steel coils with a diameter of 1000 μm). Due to the high surface-to-volume ratio in this type of microreactor, rapid heat transfer to the reaction mixture can be achieved (heat exchange). Using suitable static mixers in conjunction with a mesofluidic tubular reactor, the conditions obtained from laboratory scale instruments can be directly scaled by a factor of 10 without re-optimizing the conditions [41-44].

2.4. Safety

Fig. 6 represents the sources of danger in a chemical reaction. Since the dimension of a microreactor is small and it can not hold much reaction solution, the impact will be negligible in an emergency or failure and could be taken care of with minimum dangerous effect. In addition, using toxic and hazardous reactants and products will be much safer in the case of leakage or malfunction of equipment [16,45].

2.5. Reaction phase

The multiphase reaction is one of the most common reactions in which obtaining the desired product can sometimes be difficult [46]. The key element to a good multiphase reaction with desired rate and product selectivity is the size of the interfacial area [47]. In other words, improvements in mass and heat transfer related to a high surface-to-volume ratio or larger interfacial area could be obtained by a microreactor [34].

2.6. Operating and control

In a continuous system, specifically in the microreactor process, measurement of related process parameters such as flow, pressure, and temperature is much easier, making reaction control more effective. Furthermore, the integrity of the control system affecingt related equipment, such as valves, pumps, compressors, heaters, etc., will be performed proficiently [31]. As a result, microreactors allow for easier synthesis by easily changing these conditions, including (a) temperature control using heating elements such as baths, (b) controlling the flow rate with different type of injection pumps, and (c) controlling the flow path by changing the geometry of microreactors [48].

2.7. Microreactor material

In microreactor systems, reactions occur on the inner side of the reactors. Table 3 shows the performance of materials used for microreactor fabrication. Choosing the type and material of the reactor depends on the nature of the reactants, products, and the reaction itself (Fig. 7) [49-51]. Stainless steel, glass, silicon, and ceramic are usually used to fabricate chip-based reactors because they provide more efficient heat and mass transfer [52]. Stainless steel and fluoropolymer with different outer and inner diameters are utilized to assemble coil reactors [53]. Finally, glass, polymer, and stainless steel would be the best choice to carry out a heterogenous reaction in a packed column [19,54].

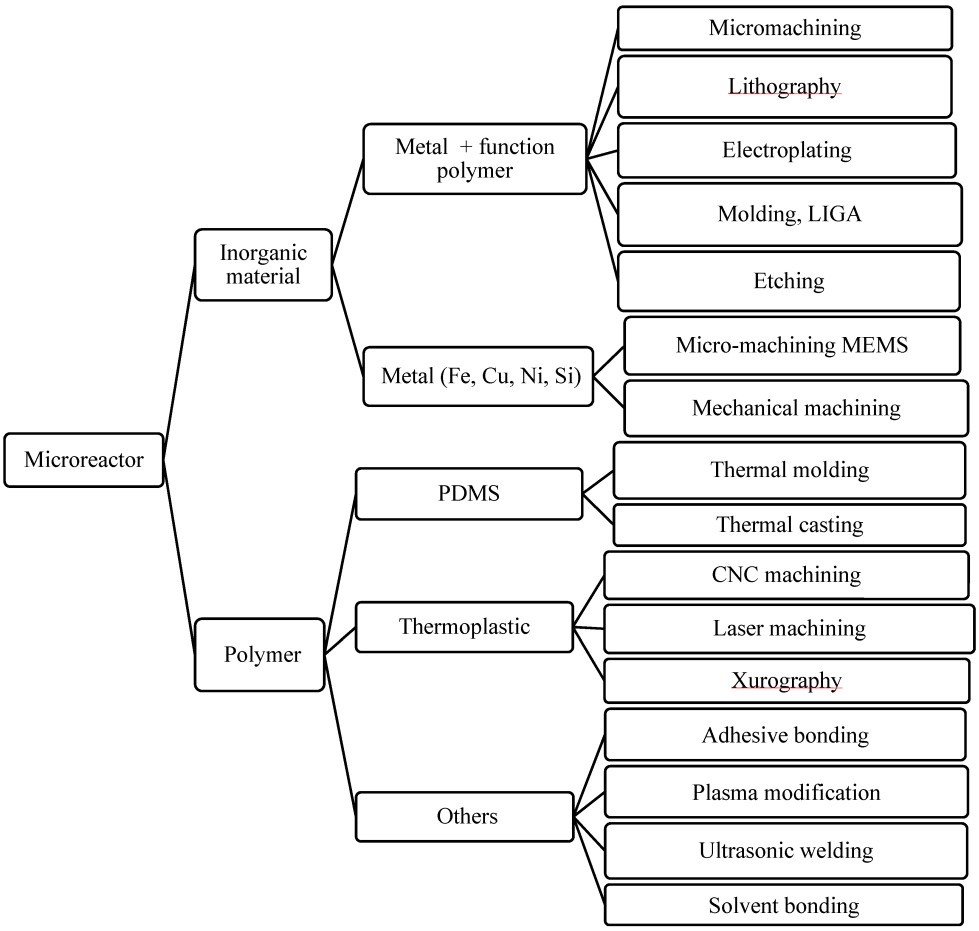

Fig. 7. Materials and fabrication of microreactors [55].

Table 3. Advantages and disadvantages of materials used for microreactor fabrication [56].

Material	Advantages	Disadvantages
Silicon	• Cheaper • Well-characterized material • High-precision fabrication	• Expensive fabrication techniques • Clean-room required
Glass	• Visual of reaction and flow • Electroosmotic flow (EOF) possible • Withstands high operating pressures	Difficulty in creating high aspect ratio structures.
Polymer	• Low cost • Various fabrication techniques • Tunable properties • Disposable microreactors possible	• Chemical compatibility • Thermal stability
Metal	• No clean-room required • Durable materials • Well-established fabrication techniques	• Replacement with noble metals possible • Issues with variable pressure drop

2.8. Cost

Another advantage of a microreactor is that they can be used together in parallel to increase the product scale. This advantage is related to the important fact that the optimized and fabricated reactor in a laboratory is the same reactor that will be used in the process. [16]. Due to the reduction of construction and operation costs, work steps, raw materials, solvents, and waste, these reactors are economical [30].

2.9. Microreactor application

Since microreactors provide more advantages like safety, stability, small size, selectivity, affordability, and low costs, their applications have expanded in recent years (Fig. 8).

2.9.1. Synthesis of chemicals and drugs

A batch system is frequently used to synthesize drugs and related compounds. However, by expanding the function and advantage of microreactors, the desire to move toward continuous and specifically microreactors to produce drugs and chemicals is rising [58]. The general application of microreactors is industrial production due to the high manufacturing rate, which makes large-scale production more accessible [55]. Furthermore, as mentioned earlier, microreactors could be more effective for reactions with toxicity reactants, high temperature, high pressure, multi-phase, and heterogeneous reactions. In addition, most drugs and the aforementioned properties that make microreactors more suitable to synthesize such materials [56].

2.9.2. Nanoparticle synthesis

Nanoparticles have been noted for more than 20 years. The introduction of microreactor technology has provided different methods to produce nanoparticles in small-scale reactors. Nanoparticles can be synthesized by continuous flow mechanisms, gas-liquid metameric flow systems, and droplet-based small-scale reactors. Different nanoparticles can be obtained by microfluidic chemical synthesis methods. A continuous flow reactor at atmospheric pressure is used to synthesize nanoparticles. Various stable forms can be produced due to the ability of microreactors to control growth parameters such as growth rate and surface energy by simply controlling material input flow rate and temperature [56].

2.9.3. Photochemical applications

Since microreactors can overcome issues related to batch photochemistry, they have been utilized in the photochemical industry to produce different kinds of products in recent years. For instance, microreactors can provide uniform irradiation to the reactants due to their small channel. As a result, the time to reach a specific conversion in a photochemical reaction for a specific amount of catalyst loading will decrease dramatically. Additionally, the formation of side products will occasionally decrease [52].

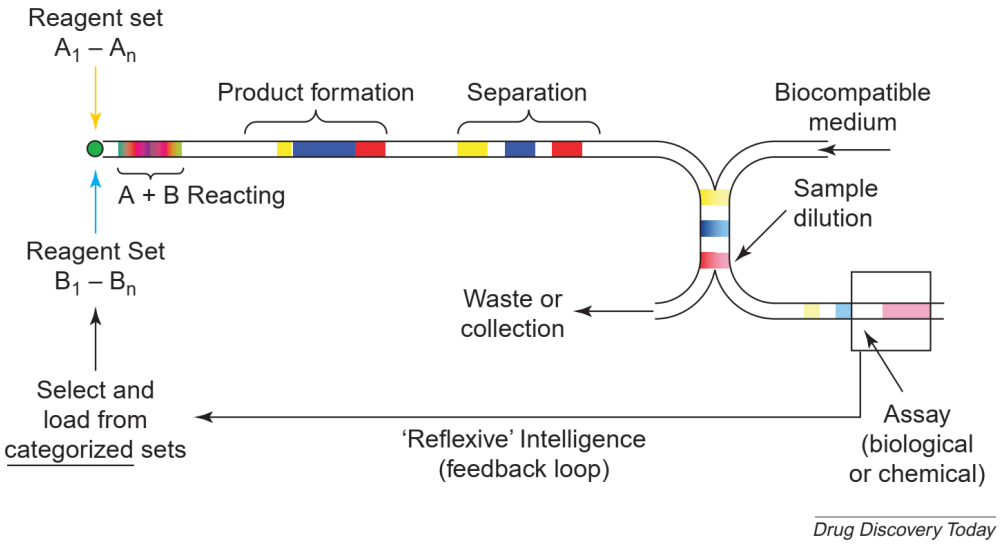

Fig. 8. Different ways of utilizing a microreactor [57].

2.9.4. Miscellaneous application

It is worth noting that microreactors have found their way into the polymerization process in recent years. By controlling the intermediate steps of polymerization, microreactors have shown promising results due to obtaining narrow particle sizes [56]. Thus, polymers can be easily produced using continuous-flow microreactors that operate at high temperatures. Microreactors with different geometries can be used to synthesize polymers for drug delivery [55]. In addition, because microreactors are capable of decreasing reaction time and can be fabricated in different shapes, which results in efficient mixing of reactants and reaction mixture, they have been investigated and compared to batch and conventional continuous reactors for biodiesel production in recent years [59].

2.10. Catalytic microreactor

The catalyst plays an important role in producing reactions in industrial processes, and heterogeneous catalysts are at the center of this attention due to its advantages. Heterogenous catalysts' most beneficial characteristic is their very high surface area (surface-to-volume). This unique feature assists the heterogeneous catalyst in acting efficiently by creating a much bigger interfacial area. As mentioned earlier, due to the microreactor's small size (10-1000 μm), heat and mass transfer would be much more efficient. The concept of combining microreactors and heterogeneous catalysts can lead to the creation of a strategy that provides a cleaner, safer, and more stable method to perform various types of catalytic reactions [60]. Heterogeneous catalytic reactors can be classified into two groups: 1) packed-bed and 2) wall-coated [61].

2.10.1. Packed bed

Solid catalysts can be filled directly in coil (capillary) or chip microreactors in the form of powder particles. This simple and convenient method of using the catalyst makes it possible to directly use commercial catalysts in the laboratory and therefore expands the field of application of microreactors in multiphase catalytic reactions [33]. In addition, the use of these types of reactors has advantages over traditional batch reactors. The amount of catalyst loading in a packed usually high, significantly affecting the reaction kinetics and reducing the reaction time. Since the catalyst is fixed inside the reactor, there is no need to separate or recover the catalyst after the reaction (the reaction mixture passes through the reactor). On the other hand, the limitations of this type of microreactor are higher pressure drop and poor heat transfer [60].

2.10.2. Wall coated

One way to install heterogeneous catalysts in microreactors is to place a film layer of catalyst on the channel where the reaction solution flows. By performing catalyst coating, the mass transfer will be improved due to direct contact between the solution and catalysts. Moreover, as the catalysts are not in the way of the solution, the pressure drop will be much less than in packed bed reactors. In addition, the amount of catalyst that can be loaded in a wall-coated reactor is lower than in a packed bed reactor [60].

2.11. Micromixer

A high surface-to-volume ratio in microreactors makes them perfect to utilize in the medical and biomedical field; however, the laminar flow regime, which is related to the small size of the channel, causes poor mixing and, ultimately, a slow process. As a result, improving the mixing mechanism, microreactor efficiency will dramatically improve in the biomedical and medical areas [62]. A micromixer is a micro device that improves reaction efficiency by making turbulence in the flow regime, leading to efficient diffusion and reducing reaction time. Thus, researchers have been investigating different kinds of micromixers to obtain desired outcomes for microfluidic processes in biomedical fields in recent years [63].

In general, micromixers are divided into active and passive categories. Active micromixers require external energy to increase mixing [64]. This energy can be provided by ultrasonic waves, pressure fields, thermal, magnetic, electric, etc. Passive micromixers use the special geometry of these devices, including elbows and curved channels, to manipulate the virtual layer between the mixing fluids and increase the mixing rate [65]. In active micromixers, the length, complete mixing time, and occupied space are less than in passive micromixers. Besides, the geometry of these types of

micromixers is simpler [66]. On the other hand, the construction of this type of micromixer is done with complex processes and is more expensive. In addition, their control is difficult and expensive, and coordinating with other microfluidic devices is not easy. Some of the external energies used in these micromixers, such as ultrasonic waves and high-temperature gradients, cause damage to biological fluids, so these micromixers cannot be used in any biological process. External energy is not used in passive micromixers; the mixing length and the volume occupied by these micromixers are greater, and their geometry is more complicated than active micromixers. However, these micromixers are made with simpler methods, their cost is lower, their processes are safer, and they coordinate well with other microfluidic devices [67].

The disorder enhancement mixer and separation and association (SAR) mixer are the most famous types of passive micromixers to date. Despite the simple, functional principles and ease of production, the micromixers of disorder need a long mixing path (at least 4 mm) to achieve complete mixing. SAR micromixers use the separation and recombination of fluid streams to perform the mixing process. This micromixer can mix in a shorter distance than the disorder-increasing mixer [68].

3. Using microreactors in pharmaceutical industry

In recent years, a large number of studies focusing on developing efficient production and operation have been conducted regarding the application of microreactors not only in basic laboratory research but also in the field of medical and biomedical. The main idea is that the pharmaceutical and chemical industries can benefit from the advancement of this technology, especially since it is necessary to develop new technologies that make the synthesis operation, process investigation, high-speed production, and metabolic studies of new chemical entities effective, as well as the reduce the extremely high related development costs. From a medical and biomedical perspective, clinical diagnostic devices are increasingly leaning towards the use of continuous systems and complex multiple biochemical processing all in one platform and in real time. Shrinking the dimensions of biomedical systems equipment can also reduce the cost of treatment and medical care.

The use of micro equipment for tissue engineering has also attracted much attention. Using micro equipment with laboratory tissue and modified organs has provided completely new conditions and possibilities for transplantation. In this context, the use of micro equipment has significantly improved the transplantation, reproduction, and modification of the cell structure by creating controlled conditions. The general framework of the tissue provides the basic cell support necessary for the density and proper use of cells in tissue engineering. Carrying out cell frame transfer operations in a microreactor can be accompanied by cell proliferation and disintegration to achieve appropriate tissue displacement. Also, essential nutrients can be provided by removing cellular wastes through the microfluidic network. Neurodevelopmental microengineering incorporates all the advantages of microfluids to create better interactions among the related cells. Researchers believe this research will provide a deeper understanding of the nervous system and will be effective in the formation of neurogenesis and neuronal migration to axonal routing [69].

Researchers have shown a lot of interest in using microfluidic systems for drug discovery. Compared to conventional synthesis, the product purity increases in a microreactor, and the reaction time reduces dramatically. It is worth noting again that performing a reaction in a microreactor system improves the reactivity, product yield, and selectivity compared to the batch system [70,71]. Roberg et al. claimed that by using a microreactor in pharmaceutical processes, 50% of their reactions would show more promising results, and 44% of the pharmaceutical industry would prefer to carry out the reaction in a microsystem [72]. Also, one of the most important goals of miniaturization is system continuity. This leads to better process control and compaction [73]. Therefore, an optimized microreactor could be easily applied to the industry.

Furthermore, since predicting pharmacokinetic function in the human body is the most challenging issue in drug discovery, simulating interactions in normal and diseased cells and reproducing cell-cell interactions that exist in living organisms could be done using cell-based microfluidic devices. Testing the synergistic effects of combination drugs would be another application. Combination drugs have produced promising results for treating different diseases; however, the high cost of the number of combinations needed to produce an effective treatment make it very expensive [71,74].

application of microdevices is to ensure the stability of hepatocytes in isolated human liver cells used for drug screening; the microdevices are used to test nutrients, oxygen, metabolic wastes, and novel drug concentration gradients [74].

Table 4 compares the flow process with the batch process for pharmaceutical and chemical compounds that have attracted more attention in recent years.

4. Conclusions

In recent years, researchers have shown a great interest in the application of microfluidics in pharmaceutical ingredient synthesis, resulting in a large number of publications. It was revealed that the most important advantage of a microreactor (continuous) over the batch method is the reduction in reaction time and increased yield due to improved mass and heat transfer caused by a larger surface-to-volume ratio. In addition, by comparing batch and continuous methods, it was concluded that other microreactor advantages, including a larger range of operating pressure, higher selectivity, more safety, better operating and control, a variety of materials, and lower cost, pave the way of applying of this new and novel technology in other areas. Moreover, a review of the pharmaceutical industry and a comparison of flow and batch processes for different compounds show that 50% of such reactions showed more promising results when using a microreactor. In fact, in 44% of examined cases, when the reaction was carried out in a microreactor system, the operation was indeed preferred over the batch systems.

In addition, our review found that different types of tangibles, real-case applications of microreactors and flow processes in pharmaceutical and fine-chemical productions have been understudied. Our compilation of microreactors grouped by the API type actually synthesized is the first in the microreactor literature.

Table 4. Comparison of the flow process with the batch process for some pharmaceuticals and chemicals.

Compound	Microreactor		Batch reactor		Ref.
	Yield (%)	Reaction time (min)	Yield (%)	Reaction time (min)	
1 (Aminonaphthalenes derivative)	52	34	83	180	[75,76]
4 (Tert-butyl ester)	50	34	81	1200	[75,76]
5 (Fig. 9)	70	24	57	2160	[75,76]
6 (Fig. 9)	82	5	80	960	[75,76]
7 (Fig. 9)	100	47	86-96	180	[75,76]
8 (Fig. 9)	87	23.5	98	60	[75,76]
9 (Fig. 9)	72	31	70	120	[75,76]
10 (Fig. 9)	100	48	100	210	[75,76]
13 (Artemisinin, Fig. 10)	46	-	-	-	[77]
18 (Quinolone derivative)	18	-	7	-	[78]
24 (2,2-Dimethylchromenes)	92	4	-	-	[79]
28 (4-(4-methoxyphenyl)-3-buten-2-one, Fig. 11)	67	10	40	20	[80]
28 (4-(4-methoxyphenyl)-3-buten-2-one, Fig. 11)	97	10	95	10	[80]
28 (4-(4-methoxyphenyl)-3-buten-2-one, Fig. 11)	90	1	94	1	[80]
28 (4-(4-methoxyphenyl)-3-buten-2-one, Fig. 11)	73	10	40	20	[80]
32 (7-Ethyltryptopho)	73-75	4	-	-	[81]
36a (Azetidin-2-ones, Fig. 12)	61	210	64	420	[82]
36b (Fig. 12)	20	210	26	420	[82]

Therefore, this paper is beneficial for newcomers to the pharmaceutical and fine-chemical industries and decision-makers to obtain ideas about the possibilities, challenges, and impact of the new flow technology. The most crucial advantage of microsystems is their fast and readily achievable scale-outs (as opposed to scale-ups) as it is possible to avoid problems with temperature control, mixing, formation of impurities as well as safety issues commonly encountered when upsizing batch technology. Ultimately, there should be no need to scale up microreactors; instead, scaling out in terms of parallel reactors is needed to perform a process on an industrial scale.

Disclosure statement

No potential conflict of interest was reported by the authors.

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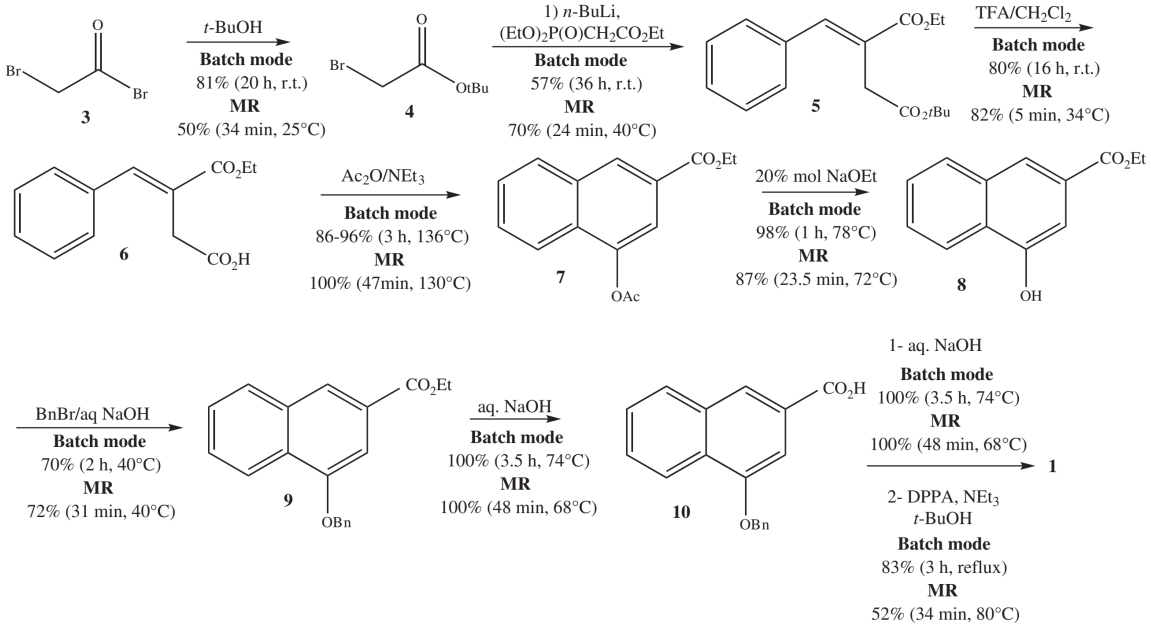

Fig. 9. Synthesis comparison for batch mode and microreactor of 1 (MR = residence time) [83].

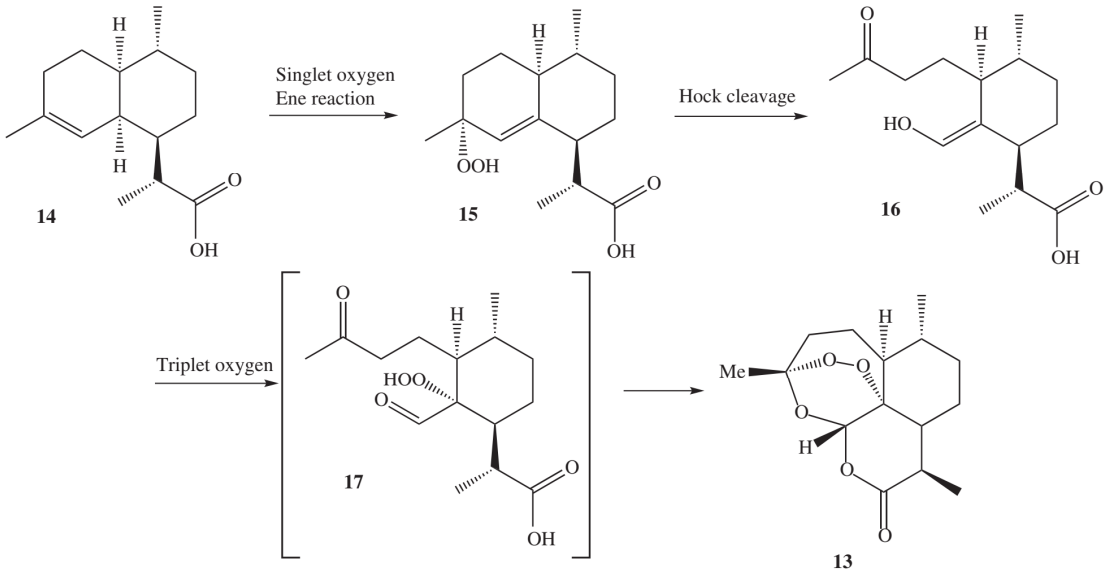

Fig. 10. Artemisinin synthesis [77].

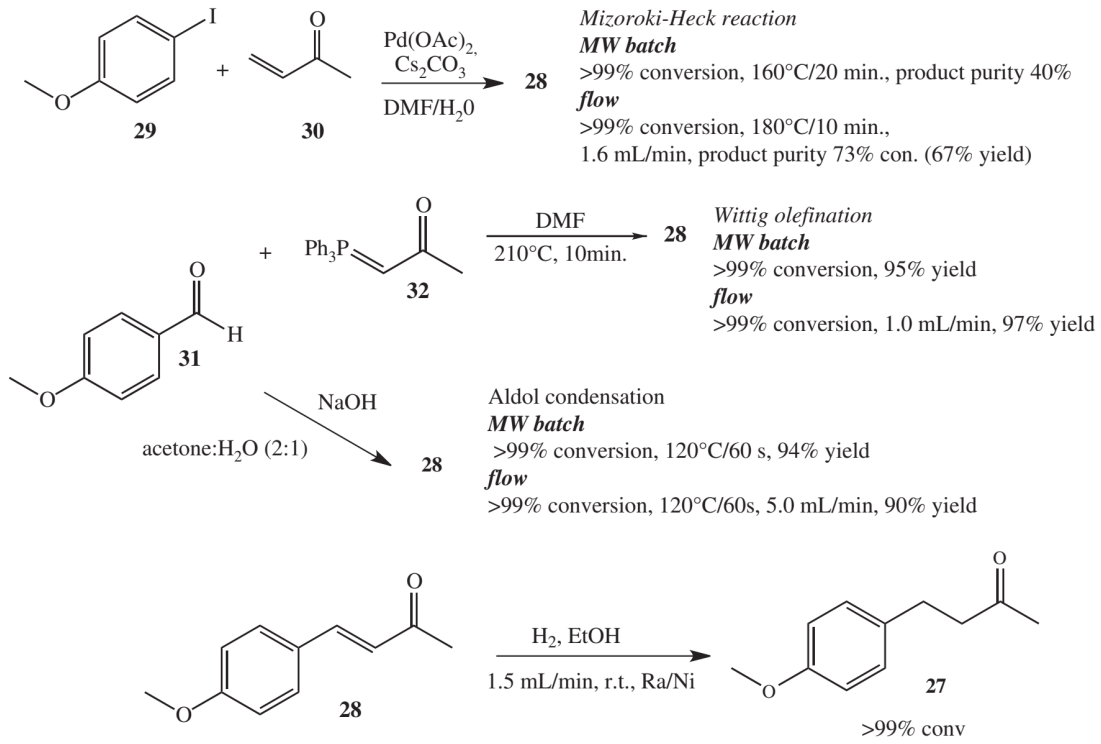

Fig. 11. Different approach to synthesize 4-(4-methoxyphenyl)-3-buten-2-one [80].

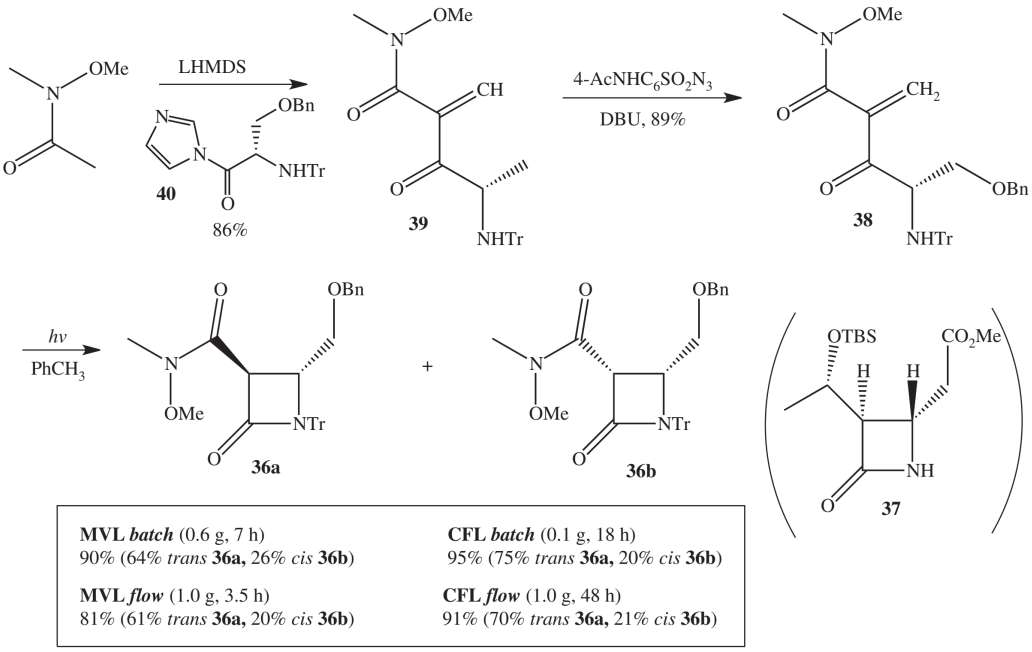

Fig. 12. Azetidin-2-ones synthesis [82].

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