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Perspectives of Heterogeneous Process Intensification in Microreactors

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Abstract—Recent developments in microreactor technology basing on different types of heterogeneous reaction systems: phase transfer catalysis, biocatalysis, and synthesis of nanoparticles are reviewed. Special attention is focused on the intensification of processes in microreactors compared with traditional approaches, which makes microtechnique of great interest for industry.

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INTRODUCTION

Over the past decades microstructured reactors (microreactors) have become one of the most studied reaction technique. Therewith special attention has been given to intensification of chemical processes and enhancement of their safety. Owing to the miniature dimensions, microreactors allow material savings in manufacturing and raw material and energy savings in exploitation. Moreover, enhanced heat and mass transfer makes microreactors far superior in performance to commercial classical batch reactors.

Microreactors offer a series of further advantages.

Due to the miniature reaction system, microreactors feature much enhanced driving forces of mass and heat transfer or diffusion flows per unit volume or unit surface [1]. The width of microchannels for material and heat flows usually varies within the range 50–500 μm, and the wall between the reaction and heat transfer channels can be narrowed to 20–50 μm; as a result, the heat transfer coefficient in microreactors increases to 25000 W m^{-2} K^{-1}, which is at least an order of magnitude higher than in standard heat exchangers. Furthermore, the specific surface area of microreactors is higher more than 50 times compared to conventional reactors. The specific interface surface areas in microreactors span the range 5000–30000 m^2/m^3.

The flows in microchannels are mostly laminar, directed, and very symmetric [1]. In multiphase reaction systems, there exists secondary rotational mixing inside fluid droplets due to wall friction of segmented fluid (Taylor or slug flow) [2], which favors intensification of heat- and mass-transfer processes.

The performance is enhanced not by increasing linear dimensions of microreactors but by increasing the number of devices [3, 4], and this provides a good guarantee of preservation of desired operating characteristics at increased total throughput power of the system. In addition, this makes it possible to disconnect or connect microreactor module in a required quantity or modify the system for different-type processes.

With the progress of microreactor technique, it has proved possible to pass from batch to continuous processes, which, too, favored their intensification [5].

The small volume of the reaction system in microreactors much facilitates control of process parameters (temperature, pressure, residence time, etc.). Highly exothermic reactions or reactions with dangerous reagents are safer in microreactors. The application of microreactors under potentially explosive conditions has been reported [6].

As shown in [7–9], microreactor technique is most favorable for intensifying liquid-phase reactions in heterogeneous multiphase systems. The highest interest in microreactor technique is being shown by

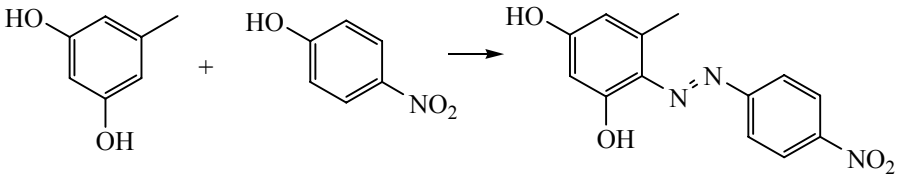
companies involved in small-scale production of pharmaceuticals and laboratories synthesizing special purity substances [10]. In small-scale production industries, 70% falls on homogeneous and heterogeneous liquid/liquid reactions [11].

Since most research effort in the field of microreactor technique is concentrated on further enhancement of intensity and safety of processes in microreactors, which provides economic profits and environmental safety of the production, a great current interest attaches to the use of microreactors for heterogeneous multiphase processes. In the present paper we consider the recent advances in the application of microreactor technique, with special focus on intensification of heterogeneous processes, such as liquid–liquid interface reactions, biocatalytic reactions, and precipitation reactions for nanoparticle synthesis.

Liquid–Liquid Interface Reactions

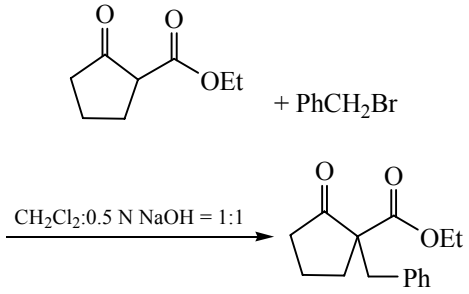
Early in the development of microreactor technique, the main goal of which was to demonstrate its main advantages and feasibility for chemical reactions, research was focused primarily on homogeneous liquid-phase reactions [12, 13]. Later on microreactor technique came to be applied for intensification of liquid-phase reactions either at the interface or with a liquid catalyst present in a different phase than reagents. The problem of efficiency of such processes involving immiscible liquids could be approached in 1951 [14]: The desired effect was reached by adding a little catalytically active quaternary ammonium salt to the reaction system. Since then interface and phase-transfer catalysis has become one of the most efficient methods of synthesis of organic compounds [15, 16], polymers [17], and medicinals [18].

The possibility of this type reactions in microreactors was first explored by Hisamoto et al. [19] on an example of phase-transfer diazotization to form an azo compound (the organic phase contained ethyl acetate and 5-methylresorcinol, and the aqueous phase contained diazo-4-nitrobenzene tetrafluoroborate):



The reaction rate and conversion depend on mixing intensity and interface surface area. It was found that the increase of the interface surface area and fast molecular diffusion, attained in this reaction due to the use of microreactor technique, essentially affect the water–organic phase transfer of the major reaction product, which decreases the probability of by-product formation.

Ueno et al. [20] have studied phase-transfer benzylation of ethyl 2-oxocyclopentanecarboxylate, catalyzed by tetrabutylammonium bromide (5 mol %):



The starting materials were injected, without mixing, into a microreactor (microchannel size 200 μm) . The yield of the target product was 100 %, like in a conventional mixing reactor; the reaction times were the same in both reactors, but this result in the conventional reactor could only be obtained under vigorous stirring (stirrer speed 1350 rpm).

In terms of process intensification, of particular interest are the results of research on microreactors with different microchannel sizes. It was found that as the size is decreased from 200 to 100 μm, the reaction rate increases nearly two times due to increased water−organic interface surface area.

One of the practically important phase transfer-catalyzed alkylation of phenylacetonitrile and its derivatives in the presence of benzyltriethylammonium hydroxide (Fig. 1). This reaction was studied in detail by Makosza and Serafin [22–25]. Mammitzsch [26] was the first to show that this reaction is intensified, when performed in a micromixer/-reactor (Ehrfeld Mikro-technik BTS) (Fig. 2) [27].

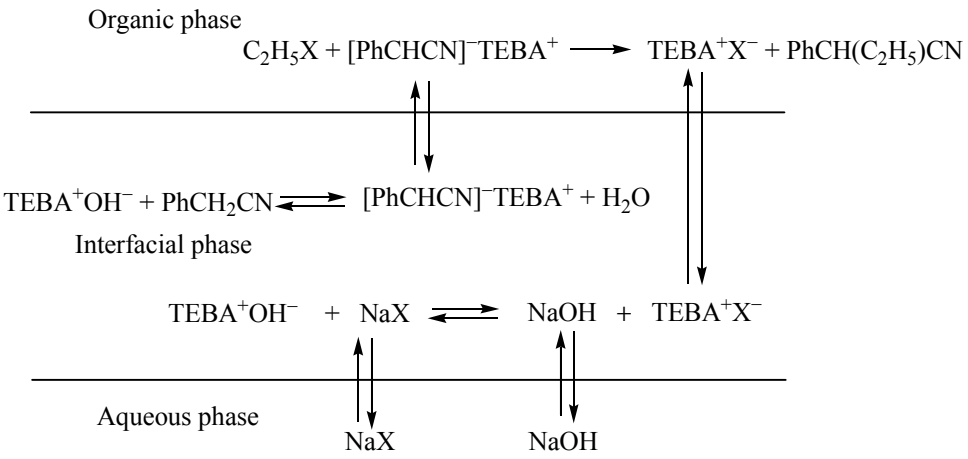


Fig. 1. Scheme of phase transfer-catalyzed alkylation of phenylacetonitrile in the presence of triethylbenzylammonium hydroxide ($TEBA^+OH^-$).

Experiments showed that, owing to the intense micromixing, the reaction in the microreactor features not only a shorter duration, but also increased conversion of phenylacetonitrile and yield of the desired product; at the same time, the reaction selectivity is not worsened. To reach a more than 80 % conversion in the microreactor, as little as 10 min is required, while the minimum time required to reach the same conversion in a mixing reactor is almost three times longer (Fig. 3). Such results are explained by a much larger interface surface area provided by special properties both of the micromixer and the microreactor in itself.

The rate of a phase-transfer catalysis reaction is much affected by the interface surface area which increases, as the aqueous:organic phase volume ratio is increased. The corresponding research was performed on an example of phenylacetonitrile alkylation at the organic-to-water ratio varied over a wide range from 1:3 to 1:10. The conversion of phenylacetonitrile and the yield of the target product increased with increasing volume of the aqueous phase in the microreactor, which was explained in terms of decreasing size of organic droplets and their intense distribution in the interface region, resulting in enhanced performance of the microreactor (see table).

It is important to note that, unlike Cocagne et al. [18] who studied the influence of microchannel size on reaction rate, Mammitzsch [26] undertook an economically more reasonable attempt to optimize the qualitative parameters of the reaction by increasing the

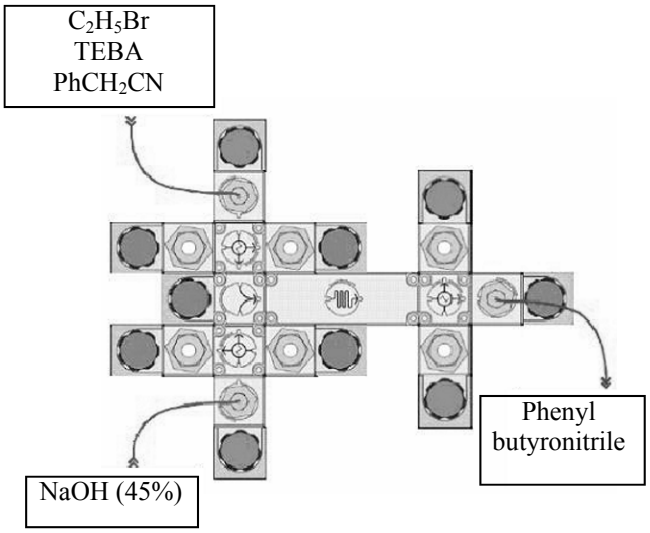


Fig. 2. Scheme of the Ehrfeld microreactor equipment.

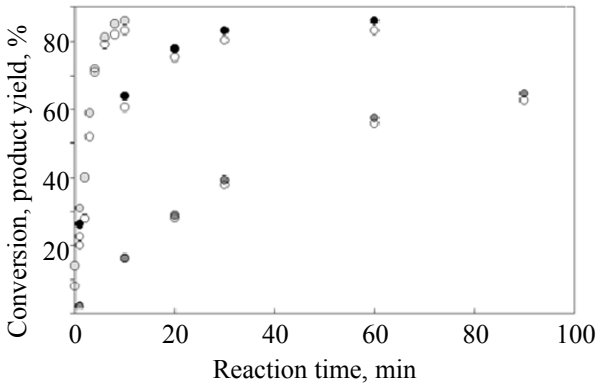


Fig. 3. Comparison of the reaction time, phenylacetonitrile conversion, and target product yield in a mixing reactor and a microreactor. Reaction conditions: 3 mol % catalyst, *T* 305 K, organic-to-aqueous phase ratio 1:10. Reaction results: (○) product yield and (●) conversion.

interface surface area by increasing the volume of the aqueous phase in the system without changing the microchannel size.

Biocatalytic Reactions

Biochemical reactions have some specific features, and their intensification is associated with a number of difficulties. As a rule, biochemical reactions are fairly slow and not always give a high yield of the target product.

For a high performance bioreactors should be very large, but large reactors are more susceptible to bacterial contamination. Moreover, it should be borne in mind that biochemical reactions are mostly exothermic, while the optimal operating temperatures in bioreactors should not be higher than 33 C; as a result, effective heat removal is a prime consideration here [28]. Biochemical reactions, where the role of catalysts is played by poorly water-soluble immobilized enzymes, are classed with heterogeneous processes [29]. Such systems contain the aqueous and organic phases, and the reaction occurs either at the interface or at the enzyme surface, i.e. the process can be diffusion-controlled [30]. All the above-mentioned difficulties can be overcome by means of microreactor technique, which offers a great potential for intensification of heterogeneous bioprocesses. Its application allows one not only to reduce consumption of enzymes, but also to increase considerably the interface surface area for stimulation of heat- and mass-transfer processes. Unfortunately, notwithstanding the fact that microreactor technique offers undeniable advantages, it still very rarely used for biocatalytic reactions. Bioprocess applications of microreactors have been reported primarily for hydrolytic reactions, which are of particular interest in terms of analysis or screening [31, 32] and, quite rarely, for synthesis [33].

Fröhlich and Bertau [34] illustrated the great advantages of microreactor technique over traditional reactors by the example of enzyme-catalyzed siloxane functionalization. The enzyme lipase CA was dissolved in water and activated with hydrophobic substances [35] to facilitate access of the siloxanes to be converted to the catalytic center of the enzyme. Even though the residence time in the microreactor was fairly short, the siloxane conversion could be increased due to accelerated diffusion and rapid removal from the reaction zone of methanol (formate) which is formed by the reaction and tends to rediffuse at the interface and slow down mass transfer, thereby shifting the reaction equilibrium toward the product side. Jaeger et al. [35] concluded that the existing approaches to intensification of biochemical processes, such as addition of auxiliary selective solvents or surface activators, as well as enhancement of mixing of the reaction system in a mixing reactor, have only minor positive effect on conversions and even inhibit the enzyme's activity in some cases. The conversion of siloxanes could be much increased and the reaction time could be much decreased compared with the process in a mixing reactor only by using a multilaminar diffusion micromixer.

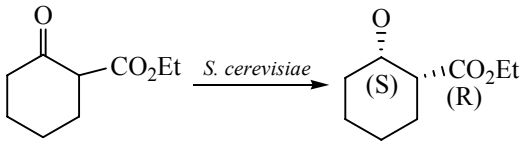
Parameters of phenylacetonitrile alkylation in a microreactor, as a function of the organic-to-aqueous phase ratio[a]

Phase ratio	1:3	1:5	1:8	1:10
Conversion, %	38.5	54.0	62.9	73.8
Yield, %	31.5	51.3	57.6	70.5
Selectivity, %	81.9	95.1	91.6	95.3

[a] Reaction conditions: 1 mol % catalyst, T 305 K, reaction time 4 min.

The interest in biocatalytic processes in microreactors has been sparked by the information that they can be realized with whole cells instead of enzymes as biocatalysts and thus allow to avoid such a labor-consuming operation as enzyme isolation [36]. The use of whole cells [37] makes it possible to extend of the range of bioprocesses feasible in microreactors.

Kliche et al. [38] have studied the biocatalytic reduction of ethyl 2-oxocyclohexanecarboxylate in the presence of *Saccharomyces cerevisiae* into ethyl (1*R*,2*S*)-*cis*-2-hydroxycyclohexanecarboxylate (the reaction by-products were the (1*S*, 2*S*)-*trans* and (1*S*, 2*R*)-*cis* isomers):



The reaction was performed in a Syntics continuous-flow microreactor [38]. Before experiment all components were treated under an inert gas to create anaerobic conditions. An additional pump was installed at the outlet of the microreactor to provide a uniform flow of the reaction mixture along the microchannel and exclude the deterioration of flow uniformity, induced by active release of carbon dioxide during the reaction (Fig. 4).

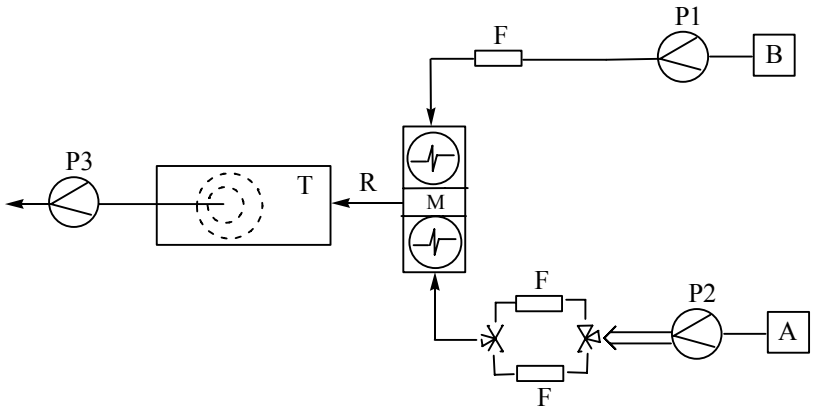


Fig. 4. Device for reactions with whole cells: (A) cell suspension; (B) reagent solution; (P1, P2, P3) pumps; (F) filter; (M) micromixer; (R) reaction mixture; and (T) thermostated microreactor.

The yield of the target *cis* product in the microreactor, like in a mixing reactor, was about 25%, which is much lower than in other works [39, 40]. Obviously, when the reaction is performed in anaerobic conditions, *Saccharomyces cerevisiae* cells suffer a deficit of nutrients and start to generate biotensides which are adsorbed on cell membranes and prevent formation of the target product [41–43].

The reaction in the presence of *Saccharomyces cerevisiae* in a microreactor showed an improved selectivity with respect to the *cis* product (Fig. 5). The higher selectivity was explained by the optimal mixing of the reaction system in the micromixer, which prevented concentration gradient and chemical cellular stress. Note that at a long reaction time the reaction stereoselectivity, having reached a certain point, remains almost unchanged. This effect was explained by increasing concentration of carbon dioxide in the microchannel and the resulting pressure rise, which adversely affected not only the yield of the *cis* isomer, but also stereoselectivity.

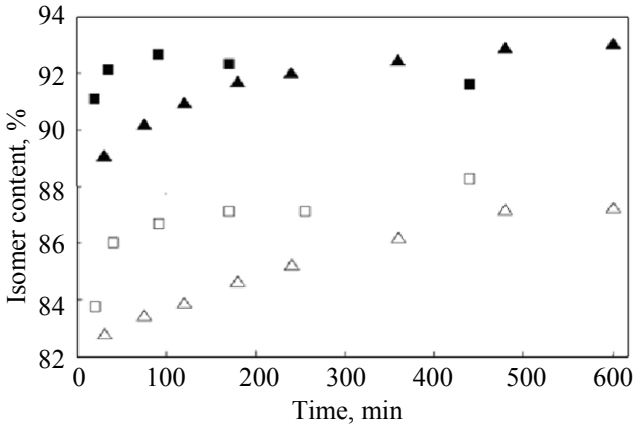


Fig. 5. Change in the contents of (light symbols) enantiomers and (dark symbols) diastereomers in the course of reduction of ethyl 2-oxocyclohexanecarboxylate in (triangles) mixing reactor and (squares) microreactor [38].

The problems associated with flow non-uniformity in the microchannel and the "refuse" of cells to work in anaerobic conditions, as well as the low yield of the *cis* product suggests that the reaction in study is impossible to intensify to a full measure in the microreactor. However, the fact that the reaction could be implemented in a continuous-flow regime and showed enhanced enentioselectivity still counts in favor of microreactor technique. Of no little importance is that biochemical reactions in microreactors require less costly enzymes. Moreover, they involve a lower chemical cellular stress and offer the possibility of optimizing the process with a precise control of system parameters.

Synthesis of Nanoparticles

Nanotechnology is a vigorously developing field of chemical technology [44–46].

Nanoparticles are most commonly synthesized by precipitation from supersaturated solutions. The potential of this method has been repeatedly illustrated by the precipitation of barium sulfate. The quality of thus synthesized nanoparticles is strongly dependent on the rates of particle nucleation and growth [47]. More uniform nanoparticles can be synthesized by performing the reaction without stabilizing additives [48], but, however, to ensure stability of precipitated nanoparticles [49], one should use dispersing agents, such as polyacrylic acid [50] or MelPers 0030 (aqueous solution of polyether carboxylate) [51]. A possible way to approach this problem is to precipitate

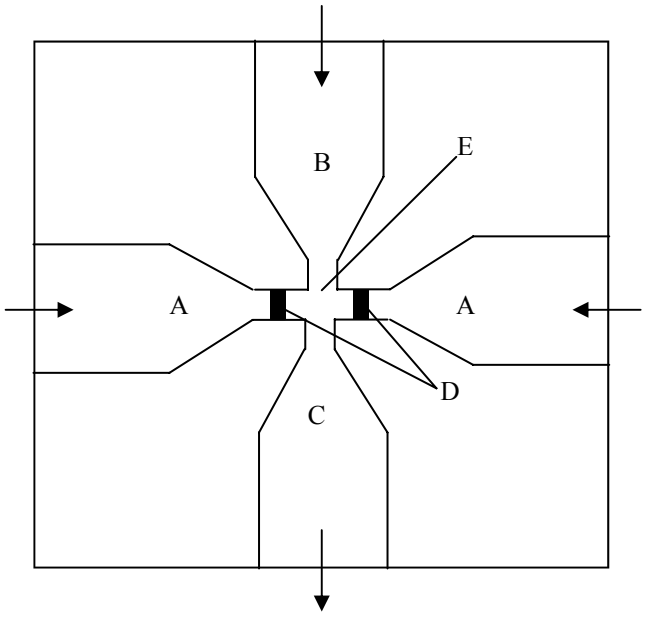


Fig. 6. Schematic design of the MicroJet reactor: (A) reagent inlet zone, (B) gas inlet zone, (C) reactor outlet, (D) nozzles, and (E) reaction zone.

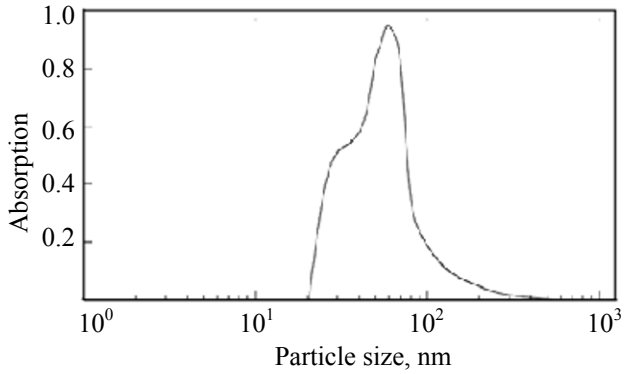


Fig. 7. Bimodal size distribution of the barium sulfate nanoparticles synthesized in the MicroJet reactor [54].

$BaSO_4$ in a continuous-flow reactor, therewith controlling the size and dispersity of the resulting particles. Of key importance here is to provide rapid and intense mixing of the starting materials for a maximum particle nucleation rate. Actually, as shown by Schwarzer and Peukert [52], barium sulfate particles less than 100 nm in size can be obtained using an effective micromixer and electrostatic stabilization of the particles by surface adsorption of excess barium ions. Further improvement of the micromixer was realized in the so-called MicroJet reactor (Synthesechemie), where the starting materials are fed through nozzles (50−350 μm) to form two jets which move under pressure and impinge frontally (Fig. 6). The reaction mixture is transported to the reactor outlet with an inert gas or air influx. This mixer is advantageous in that it is scarcely contaminated, unlike what takes place in microstructured channels [53].

Rüfer et al. [54] performed a systematic research of the precipitation of barium sulfate in a continuous-flow MicroJet reactor. Of particular interest in terms of the reproducibility of nanoparticle synthesis is the stabilization stage aimed at preventing nanoparticles from agglomeration. To trace the effect of process parameters on nanoparticle size, a special experiment

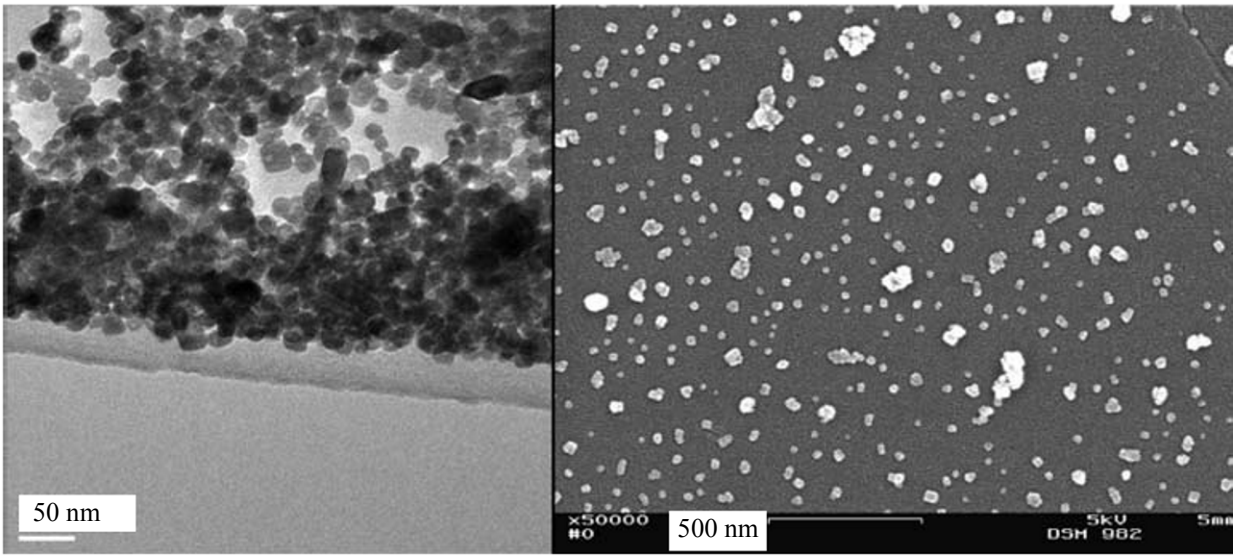


Fig. 8. Micrographs of the barium sulfate nanoparticles obtained by precipitation in a microreactor under optimal process parameters [54]. Registration method: (left) transmission electron microscopy and (right) scanning electron microscopy.

was designed, where the size of crystals formed by the precipitation reaction was optimized by varying, over the widest possible range, the following parameters: concentration, volume flow rate, and stabilizer-to-product weight fraction ratio. Using the MicroJet reactor, Rüfer et al. [54] could synthesize barium sulfate nanoparticles with a bimodal particle size distribution peaking at 25 and 65 nm, as measured by dynamic light scattering (Fig. 7). The electron micrographs (Fig. 8) reveal a uniform distribution of barium sulfate nanoparticles with a size fitting the average nanoparticle size measured by dynamic light scattering.

The experiments in the MicroJet reactor were performed in parallel with the experiments in a conventional mixing reactor to synthesize barium sulfate nanoparticles 300±30 nm in size, which was an order of magnitude larger than the size of particles formed in the microreactor.

Obviously, the intense reagent mixing in a microreactor favors nucleation and formation of nanoparticles with a smaller average size. Unfortunately, no ideal approach to complete prevention of nanoparticle agglomeration has yet been found. Thus, if the stabilizer quantity is increased by 10%, the average nanoparticle size increases 2–3 times. For the process performed in a continuous-flow microreactor, an optimal set of operating parameters, ensuring formation of stable nanoparticles 60−150 nm in size, could be found.

Thus, the considered example of barium sulfate precipitation in a MicroJet reactor provides evidence showing that microreactor technique can be efficiently applied in nanoparticle synthesis. Due to the intense reagent mixing, in microreactors there are almost no concentration gradients, and, as a consequence, fast nucleation at a high supersaturation occurs.

CONCLUSIONS

At present microreactor technique is an area of active research and ever expanding commercialization. The intensity of these works is first of all explained by the fact that microreactor technique meets the resource-saving requirements. Just the environmental and economic advantages of microreactor technique over classical reactors open up wide possibilities for their practical application in chemical industry.

Owing to their unique properties, microreactors make it possible not only to intensify processes at the molecular level, but also to pass from the batch to continuous regime. Thus, the promise microreactor technique holds in chemical technology is associated with the possibility for substantially intensifying chemical processes.

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