Screening of nanoparticle properties in microfluidic syntheses

Abstract: The possible diversity of nanoparticles is extremely high. This variability corresponds to a huge potential of possible functions in future materials and nanotechnical devices. Apart from rational designs, there is an urgent need for screening strategies for specific nanoparticle properties. Miniaturized screening techniques are challenged for efficient screening procedures. The review gives an overview on the possibilities of tuning and screening of nanoparticle properties and focuses on the application of microfluidic techniques for nanoparticle synthesis. Furthermore, the variation of parameters during the generation of nanoparticles and its connection with the resulting nanoparticle properties are highlighted as well. Among other microfluidic techniques, microsegmented flow is particularly promising for the synthesis of different types of homogeneous nanoparticles and offers interesting approaches for the screening of process parameters and nanoparticle properties. The tuning of reactant concentrations in the micro-flow-through synthesis of nonspherical silver particles and gold/silver core/shell particles and their effects on the shape, size, and optical parameters of the formed nanoparticles are given as examples for the application of microsegmented flow in the screening of nanoparticle properties.

Keywords: micro-flow-through synthesis; nanomaterials; nanoparticles; nanoparticle screening; process parameter tuning.

1 Introduction

The development of microtechnologies and nanotechnologies follows two main long-term principles of technical evolution: (i) stable solid-state devices made by an established set of standard materials and functions have been developed, miniaturized, integrated, and parallelized; (ii) millions of new compounds have been synthesized to expand the basis of chemical compounds as functional materials. Both ways were labeled by the terms “top-down” and “bottom-up” strategies. However, the suggestion of two revolutionary and complementary approaches must not be taken as a fundamentally new thinking in technical development. In reality, both these strategies correspond to the absolute conservative concept of far-equilibrium creation and stable connection of fixed units of traditional manufacturing and to the stochastic ongoing of chemical processes with large numbers of equal molecular objects. The collaboration of recent engineering with recent chemical synthesis still appears to be a joint project between frozen giants and chaotic dwarves.

This traditional thinking of engineers and chemists is in strong contrast to the example of living nature. Cells and complex organisms can organize complex dynamic processes based on movable and highly flexible hardware with dynamic functional units at the nanoscale. At the same time, they tolerate molecular stochastic systems and use them to realize a well-determined, but not absolutely strict, organized system. The living nature tells us that it is possible to overcome the dilemma of determinism and chaos at the nanoscale by overcoming the barrier between hardware and software and between device and material.

Cells teach us how molecular units can be converted from stochastic objects to responsible and unique functional tools. It demonstrates how the trivial spontaneous dynamics of atoms and molecules in the near neighborhood of quantum fluctuations is converted to a directed activity of a self-organizing system by keeping a well-adapted distance to thermodynamic equilibrium.

Despite a large number of developments in microfabrication and nanofabrication, in chemical and...
super-molecular syntheses, and in material development, we are still far from giving our materials such a specific functionality. However, we have already recognized some basic principles for the further development of materials and devices in the above-mentioned direction. Further developments in these fields lead to a number of theses:

i. The number of possible materials is very high. The desire to realize all thinkable materials would lead to unlimited possibilities. Therefore, material development should always be a selective process.

ii. An efficient search process for new materials demands a stepwise approach, which combines rational concepts and systematic screenings with stochastic elements.

iii. Material development has to promote from arbitrary and occasional synthesis of new shapes and compositions into a concept-driven tuning of material properties.

iv. There is an urgent need for integrated synthesis and screening of new materials and the development of feedback loops for the evaluation and modification of materials.

v. The nature of understanding materials has to become converted from solid-state interpretation to recognizing modular, hierarchically constructed, changeable, and self-modifying nanoscale objects.

vi. The essential functional material components have to be transferred from dead crystals, grains, and particles into nano-operators with self-moderating entropy export function. Therefore, the stability of the components should no longer be realized by a kinetic stabilization, which is based on sufficiently high activation barriers for any kind of change, but by maintaining the dynamics through the exchange of matter, energy, and signals with the environment.

vii. Concept-based material development must be accompanied by tuning of constitutional and functional properties and by screening and evaluation in multidimensional parameter spaces. The economy and ecology of material development demand fast-working and strictly miniaturized synthesis and screening procedures.

The search for improved and new properties of particles can be divided into two main issues: the first is the tuning of properties, which is always related to quantitative parameters. It involves aspects such as geometric dimensions of the nanoparticles (e.g., size, diameter, aspect ratio). In addition, the quantitative composition such the concentration of certain atoms and their local distribution within the nanoparticle volume and the presence of other components such as ligands are important. In case of plasmonic nanoparticles, the optical behavior (specifically, the spectral position of the plasmon resonance wavelength, the photonic interaction probability, which determines the absorbance, and the enhancement of the fluorescence quantum yield in case of, e.g., dye-coupled nanoparticle systems) is strongly connected to physical characteristics such as size and shape. Other important aspects that significantly specify the characteristics of a nanoparticle ensemble are connected to its chemical behavior, for example, the catalytic activity or even the photocatalytic activity, which can be regarded as the chemical quantum yield. A careful analysis should also be given to the distribution of particle properties inside a particle population because this is the measure of the homogeneity of the ensemble.

The screening of such properties can be simply realized by a stepwise variation of the respective parameters. The high number of required single tests results from the quantitative variation of parameters or parameter sets.

The second issue is the testing of individual combinations of components, which is always related to a combinatorial problem. Therefore, the type and number of involved components and the type of connections has to be screened. This screening problem has a qualitative nature. It demands for the operation of different entities. The high number of required single tests results from the high number of possible combinations.

The aim of this review is to give an overview of the enterprises that were conducted in fields of parameter screenings during the syntheses of different types of nanoparticles and microparticles. Sections 2 and 3 will show that there are numerous publications that focus mainly on the synthesis of nanomaterials, while other publications describe the possibility of changing the physical properties of nanoparticles – which more or less means a screening of the response on parameter changes without an optimization of the synthesis. Next to the metallic nanoparticle systems, composite, inorganic, organic – in the narrower sense polymeric – nanoparticles, and microparticles were also prepared by different synthesis methods, and the response of the particle systems on parameter changes were investigated by different laboratories, and the results of which are given in Table 1. In Section 3, microfluidic synthesis methods and screening experiments on various materials for various physical characteristics are discussed, and tables are presented to provide the reader a thorough overview of publications that deal with the targeted modification of the physical properties (size, shape, plasmonic resonance, photoluminescence), the variation of process parameters (pressure, temperature), and reaction conditions (reactant compositions, concentration ratios). In Section 3, it should become clear
that microfluidic synthesis is a method that is exceptionally well suited to tune and screen nanoparticle properties. Finally, Section 4 shows that the microsegmented flow technique is particularly suited for the tuning of the nanoparticle properties in two-dimensional parameter spaces with a simultaneous optimization of the synthesis regarding yield and size distribution of the obtained particles.

2 Search for new nanomaterials and tuning of nanoparticle properties

2.1 Challenges in screening multidimensional parameter spaces

The wide spectrum of aspects of nanoparticle formation poses a huge challenge in parameter screening. The important aspects of nucleation kinetics, particle growth, and nanoparticle conversion must be reconsidered aside from aspects of composition and initially obtained morphology [12]. Each single step in the multistep chain of particle formation is affected by the concentrations of all involved chemical species as well as the solvent, temperature, and other factors. The complexity of the involved kinetic parameters and temporal control of process steps is still enhanced in composed nanoparticles. A strict control of parameters allows the synthesis of hybrid nanocrystal structures with high homogeneity, for example [13, 14].

The deposition of molecular layers on nanoparticles is frequently used for particle stabilization [15], coupling of particles [16], and adaptation of solubility [17]. Molecular functionalization leads to an high number of variations of nanoparticle properties.

The selection of nanoparticle properties is mainly driven by their prospective applications. Nanoparticles are used in a high number of applications, and a still higher number of promising new fields for nanoparticle use are under discussions. An important field for screening of nanoparticle properties such as size and surface charge [18] is the search for efficient catalysts [19, 20]. Aside from the well-known catalytic activities of different transition metals such as palladium [21], gold nanoparticles became very attractive due to their catalytic potential for partial oxidation of organic compounds [22–25]. Their size, shape, and specific surface are very important for catalytic activities. Instead of separated nanoparticles, nanostructured materials such as sponges and sieves are also of interest for catalytic applications [26].

Functionalized core/shell particles are of interest due to their tunability of binding properties, and such particles are required for applications such as drug carrier systems [27]. They are also very promising for biosensing in the fields of biomedicine and analytics [28]. Silver and gold nanoparticles are very efficient components in miniaturized analytical systems for Raman spectroscopy due to their strong surface-enhanced Raman effect (SERS) [29–32]. The general concept of the use of nanoparticles in sensing applications is based on the combination of a universal signal transduction principle with

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Table 1 Tuning of properties of selected metal nanoparticles.

<table>
<thead>
<tr>
<th>Material</th>
<th>Tuned parameter</th>
<th>Tuning parameter/tuning method</th>
<th>Preparation method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag prisms</td>
<td>Shape of disks</td>
<td></td>
<td>Photochemical preparation</td>
<td>[1]</td>
</tr>
<tr>
<td>Ag</td>
<td>Shape type</td>
<td>pH, applied ligands</td>
<td>Batch</td>
<td>[2]</td>
</tr>
<tr>
<td>Triangular silver nanoprisms</td>
<td>Thickness: 8–26 nm Plasmon peak: 630–730 nm</td>
<td>Silver salt concentration, radiation parameters</td>
<td>Photochemical preparation</td>
<td>[3]</td>
</tr>
<tr>
<td>Triangular Ag prisms</td>
<td>In-plane resonance</td>
<td>Seed/silver flow rate ratio</td>
<td>Segmented flow synthesis</td>
<td>[4]</td>
</tr>
<tr>
<td>Au nanostars</td>
<td>Shape; aspect ratio</td>
<td>Reactant ratio</td>
<td>Batch synthesis</td>
<td>[6]</td>
</tr>
<tr>
<td>Au nanorods</td>
<td>Aspect ratio: 9–26</td>
<td>Seed mediation</td>
<td>Batch</td>
<td>[7]</td>
</tr>
<tr>
<td>AuAg</td>
<td>Plasmon resonance</td>
<td>Reactant ratio</td>
<td>Batch, reflux</td>
<td>[8]</td>
</tr>
<tr>
<td>AuAg</td>
<td>Plasmon resonance</td>
<td></td>
<td>Batch</td>
<td>[9]</td>
</tr>
<tr>
<td>AuPt</td>
<td>Size: 1–2 and 6–11 nm</td>
<td>Emulsion structure</td>
<td>Batch: microemulsion</td>
<td>[10]</td>
</tr>
<tr>
<td>Au-Ag-Hg nanorods</td>
<td>Size: 34–58 nm Plasmon peak: 480–800 nm</td>
<td>pH, reaction time</td>
<td>Batch</td>
<td>[9]</td>
</tr>
<tr>
<td>Pairs of spherical PNIPAM/gold nanoparticles</td>
<td>Plasmon spectrum (frequency)</td>
<td>Particle distance/temperature</td>
<td>Batch synthesis</td>
<td>[11]</td>
</tr>
</tbody>
</table>
specific molecular recognition. The optical properties of the nanoparticles are mainly responsible for signal transduction, whereas surface modification is used for specific interaction with analytic molecules. The common tuning of transduction properties and the tuning of recognition properties generate a combinatorial problem that demands efficient screening strategies.

### 2.2 Organic and, in a narrower sense, polymeric nanoparticles

Emulsion polymerization is a very convenient approach for the formation of polymer nanoparticles. The particle size and size distribution can be tuned by the concentration of the reaction components, in particular, surfactants and initiators [33].

Instead of emulsion polymerization, the polymerization of monomers in small droplets can be applied for the formation of polymer particles. Polymerization can be initiated thermally by UV radiation or γ irradiation [34]. The initiation of polymerization by radiation is of particular interest for applications in micro-continuous-flow processes.

The self-organization of amphiphilic molecules can be used for generating nanoparticles of well-defined size. Their characteristics correspond more to a super-molecular assembly than to a rigid nanoparticle. Stable lipid nanoparticles have been obtained by a phase transformation process [35]. Different types of micellar or vesicle structures can be realized by choosing different amphiphilic molecules. Block copolymers are particularly suited for this purpose [36].

Variations in the composition of the reactant mixture and in the reaction temperature result in different particle properties. Thus, the density and size of self-cross-linked N-isopropylacrylamide microgel particles were tuned by temperature, monomer, and initiator concentration [37]. The tuning of the optical properties can also be achieved in case of polymer particles [38] and by controlling the size and structure of nanoparticles of luminescent low-molecular-weight organic substances. This strategy was used for the generation of nanocrystals of organic dyes [39–41].

### 2.3 Inorganic nanoparticles of compound semiconductors, oxides, and salts

Quantum dots are well known for remarkably changing electronic and optical properties with modifications in their size, shape, and composition. Thus, their properties are tunable by addressing these features during nanoparticle synthesis [42–45]. The optical properties of quantum dots have many applications in cell biology and medicine, e.g., for labeling and sensing purposes [46]. Particle properties are successfully tuned in quantum dots using surface modification by copolymers [47].

A large parameter space for tuning of properties can also be found in the field of nanoscale salt crystals and metal oxides. The control of reactant concentrations and reaction conditions leads to the nucleation and growth and aggregation of the primarily formed nanoparticles, for example, in the case of copper oxalate [48, 49] or lithium-iron phosphate [50]. Variation of geometric features over a wide range was successful in case of TiO$_2$ nanorods with lengths between 30 and 200 nm using a surface-assisted synthesis strategy [51] as well as for the formation of special nanocrystal shapes such as tetrapods in the case of iron oxide particles [52, 53]. Figure 1 shows an example of a successful size variation in a wide dimensional range in the synthesis of TiO$_2$ nanorods. The size of aluminum spinels was chosen by the variation of the droplet size in a microemulsion synthesis [54].

### 2.4 Optical properties of metal nanoparticles

The optical properties of metallic nanoparticles are strongly related to their composition, morphology, and internal structure [55]. The optical spectra can be tuned in a wide range by variation of particle shape and size [56–59] and by the construction of bimetallic multishell particles of gold and silver [60, 61]. The structure of metal-organic frameworks can be varied in a wide range by ligands. Such a variation was demonstrated, for example, for the effect of organic acids on Zr-based nanocrystals [62]. Kinetic effects play a crucial role for the formation and properties of plasmonic nanoparticles [63, 64]. This needs strategies for tuning the concentration and reaction parameters for nucleation as well as for the growth of silver and gold nanoparticles. Figures 2 and 3 illustrate the significant influence of pH and comparatively small changes in the reactant concentration ratios on the shape of ligand-controlled synthesized shape anisotropic silver nanoparticles.

The type and application of suited ligands are important for the type and homogeneity of the formed particles and for particle-particle interactions [65]. Polar organic molecules, surfactants, hydrophilic and amphiphilic polymers as well as chelate ligands and heterocycles are
2.5  Composite particles and templating

The combination of different materials is particularly suited for the tuning of properties through the variation of composition. There are different strategies in using the high number of possibilities in the construction of com-posed nanoparticles, among them chemical coupling, grafted synthesis, and colloidal assembling [68]. Thus, inorganic nanoparticles such as PbS and Au were used to tune the refractive indices of the nanocomposites [69].

The spectrum of possible features is enhanced by a combination of different nonspherical shapes, by templating, and by the generation of composite particles [70]. The ratios of sizes and numbers as well as the position of embedded particles [71, 72] can be used for the variation of the particle properties. In Figure 4, an example of metal-polymer hybrid particles is shown. The combination of inorganic nanoparticles and polymers can also be used for the tuning of functional physical properties, for example, in the case of magnetic composite particles [73] and for the generation of special geometries by templating. Both organic/organic and
organic/inorganic composite particles are very important for functional nanomaterials [74, 75]. Polymer/polymer core/shell particles are a special case of composed polymer materials [76]. A specific application is the use of porous polymer beads for the generation of nanoporous inorganic nanoparticles by templating [77] and hollow spheres [78].

For the optimization of the particle properties, a tuning of porosity, the pore size distribution, and the specific surface are of interest and require a tuning of particle composition and conditions of particle formation. Aside from rigid polymer particles, dendrimer molecules [79] or micellar structures can also be used for the stabilization of nanoparticles [80, 81] and for templating during the synthesis of inorganic nanoparticles. ZnSe nanostructures have been generated by lyotropic liquid crystals formed by an amphiphilic block copolymer [82].

Nanosilver is largely applied for different antibacterial purposes. Instead of pure silver nanoparticles, silver/polymer composites are of interest for this application [83]. Gold and silver nanoparticles have great potential for applications in bioanalytics and sensing [84–87]. Sensitivity and selectivity can be enhanced by nanoparticle/molecule assemblies [87]. Functionalized polymer particles and composite particles are promising probes for reading chemical signals from microfluidic systems and for the direct report of physiological states from the cytoplasm [88].

3 Microfluidic synthesis as basic principle for tuning of nanoparticle properties

3.1 Advantages and challenges of microfluidic approaches in nanoparticle synthesis

At first sight, the formation of particles appears to be critical if performed in small channels because particle formation always is accompanied by the risk of blocking. In fact, an uncontrolled particle formation is dangerous in case of the application of microfluidics. However, in the controlled synthesis of nanoparticles, the diameters of single particles are far below the internal diameter of microchannels in microreactors. There are 5 orders of magnitude between the length scale of the particle and the reactor, in case of a typical nanoparticle size of 5 nm and a channel diameter of 500 μm, and even in the case of submicron particles (for example, 500 nm diameter) and very small reactor channels (for example, 50 μm), there is still a difference of 2 orders of magnitude in the length scale. Thus, blocking must only be expected if undesired large particles are formed or in case of formation of large aggregates. However, in the application of microreactors in nanoparticle synthesis, the aims are strict control of...
reaction, realization of high process homogeneity, and narrow distribution of the particle sizes. Thus, the blocking of minichannels or microchannels by aggregation of nanoparticles should normally be excluded. A more important risk comes from the tendency for wall-induced nucleation, sedimentation, and adsorption of nanoparticles at the channel walls. These effects can cause serious problems, in particular if the deposited particles act as nuclei for further material deposition. This can lead to the formation of large particles if the continuous-flow process is running over a longer time. In result, a significant chemical reactor fouling takes place, which can cause an increase in fluid resistance or even the blocking of the channel [89].

In contrast, microreaction technology offers an important set of advantages for microparticle synthesis [90–93], which are used in the different developments of nanoparticle syntheses [94]. They are based on the high rates of mass and heat transfer [92], which allow a fast initiation of nucleation and ensure homogeneous conditions for particle growth. These aspects are important in microreaction technology and are particularly interesting for nanoparticle formation because the initiation of nucleation by mixing or temperature changes is a highly time-critical process [95, 96].

Despite these general aspects, a continuous flow process provides the additional advantage of continuously induced convection. Thus, a permanent homogenization of the reaction mixture can be realized, and sedimentation or formation of particle concentration gradients due to density effects can be avoided.

A third aspect is the possibility of online monitoring. The transition from the batch to the continuous-flow principle involves the projection from the time axis of the reaction progress into the space. The progress of reaction can be monitored at different positions. A comparatively high
time resolution can be achieved if higher flow rates are applied. The application of a segmented flow allows operating with very narrow residence time distributions resulting in a very precise temporal control and reproducibility. The monitoring allows the investigation of reaction kinetics and realization of feedback loops for reaction control.

In addition, a micro-continuous-flow synthesis is well suited for the continuous production of small volumes of special materials with constant product quality. Thus, this appears to be important for future production of special nanomaterials in a wide spectrum of material properties and applications.

Finally, a micro-continuous-flow process allows a fast change of reaction conditions. This can be used for the optimization of the reactions and for the tuning of reaction parameters [97–100]. In particular, the regular segmentation and transport of small volume elements in the microsegmented flow [101–104] is perfectly suited for a systematic variation of reactant composition and reaction conditions and allows an efficient screening of these parameters. These aspects will be further discussed next.

### 3.2 Micro-continuous-flow synthesis of nanoparticles and tuning of process and product parameters

Microreaction technology and micro-continuous-flow processes have been applied to nearly the whole spectrum of nanoparticle syntheses. Microfluidic techniques have been investigated for the generation of salt-like particles by precipitation [105–109] and the synthesis of oxide nanoparticles [110–113], particles of compound semiconductors [114–117], and metal nanoparticles [118–126]. Aside from inorganic materials, particles of organic substances, especially polymer nanoparticles [127–131], have been synthesized by micro-continuous-flow processes. Additionally, microfluidic techniques are of great interest for the synthesis of functional composite particles. They allow the production of composed nanoparticles with high homogeneity. This was used, for example, for the synthesis of silica/silver microspheres for application in SERS [132]. Figure 5 shows the micro-flow-through setup used for the synthesis of gold-seeded silica and SiO₂/Au core/shell particles.

Although many articles describe special microreactors, experimental arrangements, and synthesis procedures for the generation of nanoparticles without giving details on the effects of a variation of the process parameters, there are separate reports dealing mainly with the tuning of reactant compositions, reaction conditions, and the consequences of the variation for the product parameters [134]. Furthermore, the size of oxidic and semiconductor nanoparticles was tuned, as summarized in Table 2 [135, 133, 140–142]. The size variation of nanoparticles of rare earth materials [136] and compound nanoparticles [137–139] resulted in a shift of their optical properties.

Several materials show very strong changes in both the size and the shape of formed nanoparticles in dependence of the reaction conditions. Interesting examples of microfluidically synthesized dielectric/gold hybrid particle systems are given in Figure 6. Another widely used and typical material for this large variation of particle properties is zinc oxide (Table 3). The tuning of reactant ratios by variation of flow rate ratios in the micro-continuous flow syntheses allowed a variation of particle types [147, 148], with tuning of aspect ratios resulting in star- or flower-like submicron and microparticles [141] and a size tuning resulting to large particles [144, 145]. The variation in the shapes and sizes of these particles also changes their absorption spectra and photoluminescence [144, 146].

The tuning of the optical properties is also of interest in the micro-continuous-flow synthesis of noble metal nanoparticles (Table 4). In particular, silver and gold nanoparticles show distinct plasmon resonances in the visible range of the electromagnetic spectrum that can be...
Table 2  Parameter tuning of compound semiconductors, magnetic, and oxidic materials, mainly prepared by micro-continuous flow synthesis.

<table>
<thead>
<tr>
<th>Material</th>
<th>Tuned parameter</th>
<th>Tuning method</th>
<th>Preparation method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BaSO₄</td>
<td>Particle size: ∼70–200 nm</td>
<td>Microflow synthesis</td>
<td>[135]</td>
<td></td>
</tr>
<tr>
<td>Au/SiO₂ core/shell Nps</td>
<td>Shell thickness: 14–40 nm</td>
<td>Segmented-flow synthesis</td>
<td>[133]</td>
<td></td>
</tr>
<tr>
<td>Eu/Y₂O₃ nanoparticles</td>
<td>Photoluminescence</td>
<td>Y/Eu ratio</td>
<td>Flow synthesis</td>
<td>[136]</td>
</tr>
<tr>
<td>CdSe nanoparticles</td>
<td>Particle size: 2.4–2.7 nm</td>
<td>Flow synthesis</td>
<td>[137]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Photoluminescence: 525–545 nm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CdSe nanoparticles</td>
<td>Particle size: 2.8–4.2 nm</td>
<td>Reaction rate</td>
<td>Flow synthesis</td>
<td>[138]</td>
</tr>
<tr>
<td></td>
<td>Photoluminescence: 530–620 nm</td>
<td>(Flow rate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CdSe nanoparticles</td>
<td>Photoluminescence: 530–620 nm</td>
<td>Reaction temperature</td>
<td>Flow synthesis</td>
<td>[139]</td>
</tr>
<tr>
<td>CoPt₃</td>
<td>Size: 4–10 nm (4–16 nm)</td>
<td>Reaction temperature</td>
<td>Organometallic synthesis (-)</td>
<td>[140]</td>
</tr>
<tr>
<td></td>
<td>Reactant concentration</td>
<td></td>
<td>(Batch)</td>
<td></td>
</tr>
<tr>
<td>TiO₂</td>
<td>Size: 2–7 nm</td>
<td>Reactant ratio, flow rate</td>
<td>Flow synthesis in vortex reactor</td>
<td>[141]</td>
</tr>
<tr>
<td>Cobalt oxalate</td>
<td>Aspect ratio: 0.2–4</td>
<td>Effector (PMMA) concentration</td>
<td>Precipitation (batch) (-)</td>
<td>[142]</td>
</tr>
</tbody>
</table>

(-): Batch process.

shifted by a variation in the particle shape and size. The particle properties can be tuned by shifting the reactant ratios, which in turn can easily be controlled by flow rate variation in microfluidic experiments [4, 150, 149, 151, 143].

In case of polymer particles, there is a larger set of different preparation methods and strategies for the size variation (Table 5) [131, 153, 152, 154–160]. They include thermal and photochemical polymerization, precipitation, and solvent evaporation techniques. The addressed particle size covers the whole range between the sub-millimeter and the mid-nanometer regions. Several microfluidic methods are among the reported preparation techniques. Aside from nanoparticle synthesis, microfluidics, in particular, droplet-based methods, are a highly attractive option for the generation of polymer microparticles of high homogeneity [152, 153, 161–163].

Figure 6  TEM images of gold-seeded SiO₂ core particles.
The density of the surface coverage depends on the ionic gold concentration and the volume fraction of gold-seeded silica particles (A) within the growth solution. The corresponding values are as follows: (B) 0.29 mM, 1.2×10⁻⁵%, (C) 0.39 mM and 3.8×10⁻⁶%, and (D) 0.4 mM and 3.4×10⁻⁶%. The UV-Vis extinction spectra in (E) display a red shift of the spectral position of the plasmon resonance wavelength with an increasing surface coverage in connection with a half-width widening due to an anisotropic growth of gold islands with different size. (F, G) Corresponding SEM images of the TEM recordings above. All scale bars correspond to 100 nm except for (F) (1 μm). Reprinted with permission [133]. Copyright © 2010, American Chemical Society.
Table 3  Parameter tuning of ZnO microparticles and nanoparticles.

<table>
<thead>
<tr>
<th>Particle type</th>
<th>Tuned parameter</th>
<th>Tuning method</th>
<th>Preparation method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branched crystals</td>
<td>Length of branches: 0.2–1.4 mm</td>
<td>Reactant ratio (flow rates)</td>
<td>Microsegmented flow synthesis</td>
<td>[143]</td>
</tr>
<tr>
<td></td>
<td>Aspect ratio: 1–6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compact particles</td>
<td>Size: 20 nm–0.4 μm</td>
<td>Water content in ethanol</td>
<td>Microsegmented flow synthesis</td>
<td>[144]</td>
</tr>
<tr>
<td></td>
<td>Absorption peak: 316–370 nm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compact nanoparticles</td>
<td>Particle size: ~30–45 nm</td>
<td>Reactant concentrations and reaction time</td>
<td>Cold precipitation (batch)</td>
<td>[145]</td>
</tr>
<tr>
<td>Spherical nanoparticles</td>
<td>Photoluminescence: 430–580 nm</td>
<td>pH variation</td>
<td>Ethanol-based precipitation</td>
<td>[146]</td>
</tr>
<tr>
<td>Different types</td>
<td>Particle size: ~30–45 nm</td>
<td>pH variation</td>
<td>Hydrothermal batch synthesis</td>
<td>[147]</td>
</tr>
</tbody>
</table>

Table 4  Size tuning of plasmonic nanoparticles in microfluidic preparations.

<table>
<thead>
<tr>
<th>Material</th>
<th>Size range (nm)</th>
<th>Tuning parameter/tuning method</th>
<th>Preparation method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spherical gold nanoparticles</td>
<td>3.5–5.2</td>
<td>Reactant concentration</td>
<td>Micro-continuous-flow synthesis</td>
<td>[149]</td>
</tr>
<tr>
<td>Spherical gold nanoparticles</td>
<td>10–40</td>
<td>Reactant flow rate ratio</td>
<td>Micro-continuous-flow synthesis</td>
<td>[148]</td>
</tr>
<tr>
<td>Compact gold nanoparticles</td>
<td>19–58</td>
<td>Volume ratio of reactants</td>
<td>Micro-mixing on chip</td>
<td>[150]</td>
</tr>
<tr>
<td>Spherical silver nanoparticles</td>
<td>10–20</td>
<td>Reactant flow ratio</td>
<td>Micro-continuous-flow synthesis</td>
<td>[151]</td>
</tr>
</tbody>
</table>

Table 5  Tuning of the size of polymer microparticles and nanoparticles (examples).

<table>
<thead>
<tr>
<th>Material</th>
<th>Size range</th>
<th>Tuning parameter/tuning method</th>
<th>Preparation method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-linked polystyrene microrods</td>
<td>Length: 1–5 mm</td>
<td>Slug length in segmented flow tube diameter in segmented flow</td>
<td>Thermal polymerization of microfluid segments</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Diameter: 0.25–1 mm</td>
<td>Flow rates</td>
<td>Photochemical polymerization of microdroplets</td>
<td>+</td>
</tr>
<tr>
<td>Tril(propylene glycol) diacrylate/acrylamide core/shell particles</td>
<td>Different; between 0.1 and 1.4 mm</td>
<td>flow rates ratio</td>
<td>Photochemical polymerization of microdroplets</td>
<td>+</td>
</tr>
<tr>
<td>PMMA, cross-linked</td>
<td>0.27–0.45 mm</td>
<td>Capillary number/flow rates</td>
<td>Photochemical polymerization of microdroplets</td>
<td>+</td>
</tr>
<tr>
<td>Polyacrylates</td>
<td>Different; between 0.1 and 0.2 mm</td>
<td>Flow rates</td>
<td>Photochemical polymerization of microdroplets</td>
<td>+</td>
</tr>
<tr>
<td>Nonspherical polyacrylate microparticles</td>
<td>Different; between 25 and 140 μm</td>
<td>Flow rates</td>
<td>Photochemical polymerization of microdroplets</td>
<td>+</td>
</tr>
<tr>
<td>UV-curable polymer NOA 60</td>
<td>60–100 μm</td>
<td>Slug length in segmented flow</td>
<td>Photochemical polymerization of microfluid segments</td>
<td>+</td>
</tr>
<tr>
<td>Methacrylic acid copolymer</td>
<td>0.1–0.7 μm</td>
<td>Content of polyvinyl alcohol</td>
<td>Nanoprecipitation/batch</td>
<td>[158]</td>
</tr>
<tr>
<td>Poly(lactide-co-glycolide)</td>
<td>0.1–0.4 μm</td>
<td>Polymer concentration</td>
<td>Solvent evaporation technique</td>
<td>[159]</td>
</tr>
<tr>
<td>Cross-linked PMMA</td>
<td>60–500 nm</td>
<td>Surfactant concentration</td>
<td>Microfluidic emulsion polymerization</td>
<td>+</td>
</tr>
<tr>
<td>Polycaprolactone</td>
<td>70–230 nm</td>
<td>Temperature, solvent composition</td>
<td>Nanoprecipitation/batch</td>
<td>[160]</td>
</tr>
</tbody>
</table>

The + represents the microfluidic preparation method.
4 Microfluid segment technique as a promising tool for the evaluation of nanoparticle properties in multidimensional parameter spaces

4.1 Potential of microsegmented flow in nanoparticle synthesis and screening

The segmented flow technique is one of the important microfluidic techniques in nanoparticle synthesis. This technique meets some essential requirements that arise from the demand of a continuous production of homogeneous nanoparticles. Of major importance is the compartmentation in fluid segments of equal size, distance, and reactant composition. Thus, an extremely high homogeneity for all partial volumes is ensured [164, 165]. The transport of the reactant mixtures and the formation or the already formed product particles within fluid segments are an ideal plug flow. These flow characteristics cause an extremely well-defined narrow residence time distribution. For small regular microfluid segments, the distribution of the residence times can be neglected. The reaction mixture is separated from the inner surface of the reactors or tube walls by the hydrophobic carrier liquid. Hence, the embedding of the reaction mixture inside the fluid segments leads to a decoupling of the particle nucleation and growth of the otherwise non-negligible wall interactions. By preventing wall contact between reactant mixture and channel walls, wall-induced particle nucleation as well as particle adsorption are efficiently suppressed. The transport of the fluid segments in microflow-through channels causes a segment-internal circular convection, which is driven by friction at the fluid-fluid interface between the individual aqueous segments and the surrounding carrier liquid. This segment internal convection promotes a fast mixing of reactants, a fast heat transfer, and further ensures a permanent convective homogenization of the reaction mixture. In addition, particle sedimentation or partial separations due to density differences in the dispersion medium are suppressed. The conditions of the local convection are very reproducible from segment to segment because the circulation pattern is constant in case of equal segment sizes, intermediate segment distances, and viscosities of the used liquids [166, 167].

For high-throughput screening purposes, it is very important to have a simple method for realizing larger parameter fields, for online processes, and for product monitoring. The automated flow rate control during the mixing procedures offers a unique possibility for an accurate variation of the composition of small liquid volumes. A continuous shift in flow rates leads to a stepwise variation of concentrations in the formed droplets [168]. A very high resolution of a concentration can be achieved in case of slowly shifted flow rates. Faster-shifted flow rates allow the combination of concentration variations of two or three components. Thus, a complete screening in two- or three-dimensional concentration spaces becomes possible [104, 169].

Several optical methods are available for the noncontact monitoring of processes in microfluid segments. They can be used for the monitoring of the fluidic processes and the quality of segments as well as for monitoring chemical reactions inside the segments. Micro-flow-through photometry and fiber-based optical spectroscopy [170] are well established. Similarly, fluorescence detection can possibly enhance the sensitivity or specificity of segment or microdroplet measurements [171, 172]. The use of Raman spectroscopy can provide more specific molecular information [173]. In particular, SERS is a very promising method for the monitoring of processes in microfluid segments [30, 174]. Microfluidics in combination with advanced optical characterization methods will become a key toolbox for the search of new functional materials [104].

In the following, two examples of the application of the microsegmented flow technique for the tuning of reactant composition and thus the physical properties of the nanoparticles are presented. The two chosen examples from the area of plasmonic nanoparticles are of particular interest because of the high sensitivity of the optical response on the nanoparticles shape, size, and composition.

4.2 Microfluidic synthesis and parameter screening of plasmonic Au/Ag core/shell nanoparticles

Both spherical gold and silver nanoparticles show characteristic plasmon resonance absorptions, which depend on the polarizability of the core electrons of the respective materials. Thus, the spectral position of the typical plasmon mode of spherical silver nanoparticles is dependent on the diameter of the spheres between 395 and 430 nm. The plasmon mode of spherical gold nanoparticles is due to the much harder polarizable core electrons between 510 and 550 nm. Absorption peaks between these both values are found in case of mixed compositions of
both metals in the state of an alloy. However, the shape of the spectra deviates significantly in case of core/shell particles. The diameter of the core and the thickness of the shell affect the resulting optical spectra. The absorption of the obtained colloidal solution of the Au core/Ag shell particles should be dependent on the concentration of particles, which is expected to be identical with the concentration of applied gold core nanoparticles, and on the ratio between the silver salt concentration and the gold core nanoparticle concentration. Recently, microfluidic experiments are shown to be capable of fast and simple tuning of the silver shell thickness with a low consumption of chemicals [175, 176].

For the experimental implementation of a combinatorial synthesis screening, e.g., the adjustment of the thickness of a silver shell around gold core particles through a targeted control of the core nanoparticle density as well as the silver salt concentration, different concepts for the experimental setup are suitable. Microfluid segments with volumes in the nanoliter range and clearly predetermined reactant composition can be generated through various microfluidic construction elements. Chip reactors with a sufficient number of inlets and an appropriate architecture for the experiment are well suited as fluoropolymer-based reactor tubes, which are joined by standard fluid-connecting material of PEEK or PTFE. A microfluidic arrangement for a synthesis experiment with a combinatorial variation of the reactant flow rates is shown in Figure 7.

A PTFE tubing material with an inner diameter of 0.5 mm is suitable for the tube reactor, with clear and transparent FEP tubing used to attach the flow-through units for optical analysis.

The quality of the compartmentation is determined using a four-channel photometric unit and measuring the segment length and intermediate segment distances. The optical response of the colloidal solution within each fluid segment on changes in the reactant composition is read in situ by a fiber-coupled UV-Vis spectrophotometer.

The flow rates of each pump of the multichannel syringe pump system are separately controlled from each other by a computer program. The fluid segments are formed in the desired composition with the help of a PEEK multi-nozzle unit or two connected PEEK cross-junctions. Therefore, the reactant solutions are dosed into the presented organic carrier stream in such a way that a seed-containing mixture and its appropriate diluent initially form the fluid segments, in which silver nitrate and water are added by two opposite inlets that follow downstream after a very short residence section. The total flow rate is kept constant over the whole experimental run to ensure constant microfluidic conditions.

The reaction and the deposition of metallic silver on the gold core start immediately after mixing the educts. The segments were conducted through a residence loop with a length of 150 cm. The residence time in this loop is ~70.7 s in case of an applied total flow rate of 249 μl/min. After this period, the reduction of the silver salt and the formation of silver shells are completed.

A typical flow rate program is shown in Figure 8A. In this case, a nonlinear variation of silver nitrate flow

![Figure 7](image-url)
rate was chosen to realize a strong variation in the silver shell thickness. The initial seed nanoparticle density is set as 100% and is linearly decreased during the combinatorial run in steps of 20%. Both concentrations were varied in six steps. Each of the concentration pairings is represented in the experiment by ∼200 segments. Thus, each single experiment is performed with a high redundancy and reproducibility of the single measurements. The individual flow rates of the reactant solutions can be directly taken from Figure 8. Both superimposed changing flow rates cover a complete two-dimensional parameter space. The whole experimental run consists of ∼36×200 segments, corresponding to a total volume of consumed reactant solutions of ∼0.5 ml each. The strategy of the combinatorial synthesis screening of nanoparticle properties in microfluid segment sequences is a new approach that is well suited for an optimization of existing synthesis protocols or for a fundamental study of the feasibility of producing new nanoparticle systems.

The absorption spectrum of each generated fluid segment containing a colloidal solution that is altered by optical properties according to the reactant composition, which, in turn, is adjusted by the programmed flow rate changes, was measured by in situ spectrophotometry. The
comparison of absorption spectra of the same combinatorial step demonstrates a high reproducibility of nanoparticle formation. There are only slight deviations from segment to segment within one combinatorial step of \(\sim 4\%\) in the peak absorbance.

In Figure 8B, the optical spectra for core/shell particles were obtained at the same maximum gold core particle density, but different concentrations of silver nitrate are shown. It can be seen that the plasmon resonance is blue shifted with decreasing silver nitrate concentration. This indicates a decreased average thickness of the silver shell. In the optical spectrum, the plasmonic contribution of the gold core increases with decreasing silver shell thickness. In case of a very low silver nitrate concentration, thin silver shells with an average thickness of \(1.4\) nm result, and thus, next to the expected silver plasmon resonance peak at \(\sim 400\) nm, the optical spectrum is visibly influenced by the typical gold plasmon absorption band at \(520\) nm. The corresponding size distribution spectra in Figure 8C reflect the expected shift in the particle diameter with increasing ratio of silver nitrate flow rate to gold seed flow rate. In addition, the DCS spectra prove for all concentration ratios a monomodal size distribution and very narrow full widths at half maximum. This indicates very homogeneous conditions for the formation of silver shells under microfluidic conditions [176].

4.3 Microfluidic screening of the synthesis parameters during the preparation of flat, triangular silver nanoprisms with tunable aspect ratio

Nonspherical plasmonic particles are particularly interesting due to the symmetry breaking in the optical resonance. As a result, two or more plasmon resonance peaks can be observed. The longest axis of the particle is related to the lowest energy for electronic excitation. Thus, the longest absorption peak wavelength is determined by the extension of the particle in the direction of this longest axis.

Here, the formation of triangular silver nanoprisms was studied in a microfluidic experiment with an automated tuning of the ratio between the silver seed nanoparticle concentration and the concentration of silver nitrate [177].

Figure 9 shows that the flow-through synthesis of triangular silver nanoprisms is advantageous compared with conventional synthesis methods regarding size distribution and yield of the desired shape. Furthermore, it was known that different lateral extensions of the triangular silver nanoparticles depend on the ratio of silver seed nanoparticles to the amount of silver nitrate during the prism growth [4, 178]. Thus, a linear/linear variation of the reactant ratios is suitable for the two-dimensional combinatorial parameter screening during the micro-flow-through synthesis of silver nanoprisms. Using a slowly...
changing pair of flow rates, the seed particle density was varied by appropriate dilution between 100% and 0% in steps of 20%. The slowly changing flow rates were overlain by two fast alternating flow rates to vary the concentration of silver nitrate over the whole parameter space between 100% (which is equal to a silver nitrate concentration of $1\text{ mm}$) and 0%, again in discrete steps of 20% (Figure 10A).

Again, during the combinatorial synthesis run, the UV-Vis spectrum of each generated segment was taken in situ – this way, the optical properties of the nanoprisms that were formed under the conditions of each possible reactant ratio were recorded. In Figure 10B, an example of the optical response in case of constant maximum silver nitrate concentration but stepwise decreasing silver seed nanoparticle density is given. The examined conditions show that a lower amount of dosed silver seed nanoparticles leads to the formation of nanoprisms with larger edge lengths, which corresponds to a significant red shift of the long-wavelength plasmon absorption peak. The corresponding DCS size distribution spectra are shown in Figure 10C. This chart summarizes the measured Stokes equivalent sedimentation diameters of the different prism ensembles, which were obtained under conditions of constant maximum silver nitrate addition but decreasing silver seed concentration. An identical behavior was also observed for conditions with lower silver nitrate concentrations. In case of nanoparticle samples with high aspect ratios, only the sphere-like sedimentation diameter

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**Figure 10**  (A) Linear-linear flow rate run for the combinatorial synthesis of triangular silver nanoprisms. (B) UV-Vis spectra for conditions of constant maximum addition of silver salt ($c(\text{AgNO}_3=1\text{ mm})$) and in steps of 20% decreasing silver seed nanoparticle density. A red shift of the main dipole resonance wavelength occurs with decreasing seed particle concentration due to an increasing lateral expansion. (C) The corresponding DCS size distribution spectra clearly demonstrate an increasing particle size.
can be obtained by measurement methods such as centrifugal sedimentation spectroscopy. The actual lateral extension can only be determined by SEM imaging. Nevertheless, DCS measurements are useful for an evaluation of the particle quality. Narrow, regular DCS size distribution peaks and the absence of side populations indicate monodispersed particle samples even in the case of shape anisotropic nanoparticles.

5 Conclusions

We have shown in this work that there are diverse applications for nanoparticles of various materials, compositions, and shapes in the fields of scientific research and technology. Nanomaterials are currently an indispensable part of catalysis or sensor applications.

It is noticeable that most of the relevant publications either deal with the synthesis of nanoparticles or microparticles, such as syntheses of organic and polymer particles, oxidic and salt-like materials, composite particles of different materials, and of noble metal nanoparticles, or with the screening of large parameter spaces such as screenings for the particles catalytic potential or the possibility to alter the optical properties. Only a few publications treat both: the synthesis of nanoparticles and the screening of the physical properties (see Table 1).

It should be noted that the microfluidic synthesis of nanomaterials can be considered as a basic principle for the tuning of the particle properties. Based on the high rates of mass and heat transfer, rapid nucleation processes can be initiated and in connection with the fast response of the microfluidic system on parameter changes, which is virtually predestinated for screening applications (see Table 2).

The micro-flow-through approach is well suited for a wide spectrum of materials. Thus, the synthesis and tuning of the particle properties were successfully transferred to microfluidic systems for oxidic materials such as zinc oxide (Table 3) and noble metal nanoparticles, preferably of gold or silver (Table 4). In addition, in the synthesis of polymer particles, an increasing number of microreaction strategies are currently among the most reported preparation techniques (Table 5).

The possibilities that arise around the structure, the composition, and the surface functionalization of the nanoparticles are so vast that intelligent, reproducible, and facile synthesis methods are required. This means that a detailed synthesis strategy that satisfies several conditions is needed. First, high mixing rates are necessary to achieve a shorter nucleation phase, a more regular deposition of further material, and thus considerably more homogeneous particle samples. Second, for an application-oriented generation of novel nanomaterials, the process parameters must be varied in situ and screened specifically. Both requirements are met by the nanoparticle synthesis in microfluid segment sequences. In general, microfluidic synthesis of nanoparticles leads to more homogeneous nanoparticles, with higher yields of the desired shape or structure compared with conventional synthesis methods. The nanoparticle synthesis in microfluid segment sequences opens the possibility of online multiparameter screenings. Reactant ratios can be adjusted in situ in combination with an immediate response of the system. The combinatorial reactant ratio screening was successful for both binary spherical core/shell nanoparticles and shape anisotropic particles with high aspect ratios. With the combinatorial deposition of a silver shell around a gold core nanoparticle, the silver shell thickness was precisely adjustable between 1.4 and 20 nm. By altering the seed particle/metal salt ratio in case of the combinatorial synthesis of triangular silver nanoprisms, the main plasmon resonance wavelength can be tuned exactly between 550 and 900 nm. These results are promising in terms of the possibility of optimizing syntheses conditions and are a good starting point for the creation of new materials that exhibit the intended properties.

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