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Microscale reactors: nanoscale products

John and Andrew deMello review recent applications of microfluidic technology in the synthesis of compound semiconductor nanoparticles

Nanoscale science

Nanoscale science (or nanotechnology) is the exploration and exploitation of the physical, chemical, and biological properties of systems in which phenomena length scales are comparable to the dimensions of the structure. Nanotechnology has been widely recognized as one of the key research topics of the 21st century, and one that will only realise its full potential by the development of new tools for manipulating matter at the atomic/molecular scale. Over the past decade the discovery of novel phenomena, properties and processes at the "nanoscale" has opened revolutionary opportunities for the creation of novel materials and devices with superior chemical, physical, optical, electronic and/or biological properties. Nanocrystalline semiconductors are of particular interest in this regard owing to their tuneable optical and electronic properties.[1] They are seen as tailored precursors in creating functional materials for use in a variety of applications including biological sensing, optoelectronics, electroluminescent displays, fibre optic communications and lasers.

The physical characteristics of nanocrystallites are determined by quantum confinement effects with properties such as the optical band gap often differing considerably from the bulk semiconductor. As these properties are ultimately determined by the physical dimensions of the crystallites, there is considerable interest in processing routes that yield nanoparticles of well defined size and shape.[2] There are two main routes to nanoparticle formation: top-down and bottom-up approaches.[2–4] In 'top-down' routes nanometre-sized structures are engineered from bulk materials using a combination of lithography, micromachining and etching. The creation of sub-100 nm structures requires lithographic techniques beyond the optical domain, such as electron beam and X-ray lithography, which are technically challenging and do not lend themselves readily to reproducibility. Alternative 'bottom-up' approaches involve the chemical growth of particles on an atom-by-atom or molecule-by-molecule basis until the desired size is achieved. This growth process occurs spontaneously in super-saturated solutions, and has been successfully used to create spherical, cubic, tubular and tetrahedral crystallites of well defined size and shape.[4] The bottom-up approach – which may be carried out at the lab bench using standard techniques in synthetic chemistry – has attracted considerable interest owing to its versatility and ease of use, and is by far the dominant route to nanoparticle production. In practice, for many applications, deviations about the mean particle diameter must be lower than one percent to achieve the desired selectivity in physical properties. This is beyond the tolerance of most standard syntheses (which rarely yield size distributions better than ±5 %), and in general it is necessary to employ some form of post-treatment to extract the desired particle size; typical treatments include electrophoresis, chromatography, sedimentation precipitation, and photo-corrosion. In this manner, it is possible to obtain nanoparticles with extremely narrow size distributions (better than ±5 %) but, since the starting point is a polydisperse sample from which the desired particle size must be subsequently isolated, yields are generally low. Clearly, it would be preferable to use direct techniques, requiring no post-treatment, to prepare such crystals.

In the past two years we and other research groups have shown that microfluidic systems offer a promising strategy for obtaining high-quality nanoparticles which in principle could deliver highly monodisperse particles in a direct single-shot process that requires no subsequent size selection. The aim of this mini review is to summarise the advantages and limitations of the microfluidic approach, highlight progress to date, and identify possible directions for future research.

How do nanoparticles form?

We start by briefly describing the process of particle formation. In common with other colloids, nano-particles are formed by an initial nucleation stage in which tiny seed particles precipitate spontaneously from solution and a subsequent growth phase in which the newly formed seeds capture dissolved atoms or molecules. In most cases, nucleation and growth occur concurrently throughout particle formation, and the final particles therefore exhibit a broad (and undesirable) size distribution. To obtain monodisperse particles, it is necessary to arrange the reaction such that all nucleation takes place in a short period of time and additional material is supplied so slowly that it can find its way to the nuclei without the solute concentration reaching a level at which further nucleation can take place.

LaMer and Dinegar expressed this situation in a simple diagram[5] of the kind shown in Fig. 1 which shows the variation in solute concentration with time. The solute, which in effect is the dissolved feed-stuff for the particles, is formed by a chemical reaction (*e.g.* hydrolysis of metal alkoxides, hydration of metal ions, decomposition of organic compounds *etc.*). As the reaction proceeds, the solute concentration increases and rises above the supersaturation concentration, eventually reaching a critical concentration at which nucleation occurs and many nuclei form in a short burst. This nucleation process – and the subsequent growth of these nuclei – lowers the solute concentration to a value which is below the critical nucleation concentration (thereby halting further nucleation and freezing the number of nuclei) but which is still sufficient to allow particle growth to occur. The formed particles then grow at a rate that just consumes all further solutes that are generated by the chemical reaction. The process of particle growth lowers the overall free energy of the system (particles plus solutes) so, in the absence of any competing process, growth will continue until all of the solute has been consumed; moreover aggregation of individual particles also lowers the free energy of the system so the particles will tend over time to coagulate and precipitate out of solution. Nanoparticles will therefore only be obtained if (i) growth stops, *e.g.* due to reagent depletion, when the particles are still in the nanometre size range and (ii) there is no subsequent tendency for particle aggregation. In general, particles of a given size may be stabilised by one of two

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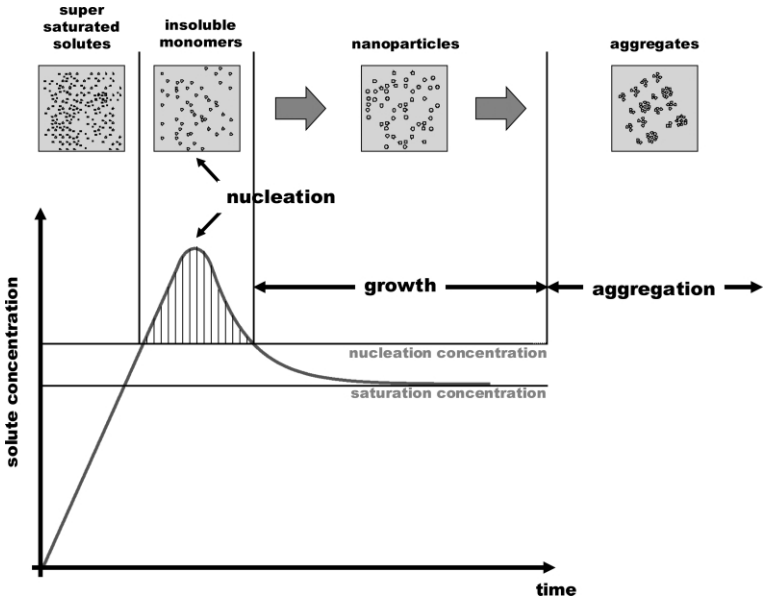

Fig. 1 Cartoon illustration of nucleation and growth during the preparation of monodisperse nanoparticles.

effects: electrostatic- or steric-repulsion. In the first case, particles with a net surface charge (arising for example from the differential solution of anions and cations from the crystal surface) tend to repel one another and are prevented from aggregating. In the second case, a surfactant is used to sheath the particles and hence prevent them from capturing further solutes or aggregating with other particles. The use of electrostatic repulsion is generally limited to aqueous media and is very sensitive to the addition of electrolytes. The use of surfactants is somewhat more versatile and is the preferred means of stabilising nanoparticles. The size and shape of the particles may be carefully controlled by varying the type, concentration, and time-of-addition of the surfactants.[6] In many cases the surfactant may be the solvent medium itself, a common choice being for example the organic ligand trioctylphosphine oxide used in the preparation of CdSe nanoparticles.

In the nucleation phase, nucleation and growth occur concurrently meaning that the earlier the nuclei form, the larger they ultimately grow. To obtain monodisperse nanoparticles, it is therefore important to ensure that nucleation occurs on a time-scale short compared with the characteristic growth time. It is also important that all nuclei should form and grow in an identical chemical environment with state functions (notably pressure, temperature and concentration) assuming well-defined intensive values throughout the reaction vessel. If there are significant variations in physical conditions across the reaction chamber, the size of critical nuclei and the particle growth rate will vary according to location, and a broad distribution of particle sizes will be obtained. This is typically the case for conventional syntheses in bulk reactors where rigorous (turbulent) stirring is used to ensure rapid mixing of reagents. In many respects, microfluidic systems – which allow for rapid thermal and mass transfer – are an ideal medium for nanoparticle production. The benefits of microreactors are varied and depend on the specific application one has in mind. However, in the specific context of nanoparticle synthesis, it is possible to point to the following key advantages:

• the ability to control the temperature or temperature gradient along the flow profile and to rapidly heat or cool the reagent mixture;

• the ability to efficiently mix reagents on a rapid time-scale in order to ensure a homogenous reaction environment;

• the ability to operate within continuous-flow regimes and to thereby allow additional reagents to be added downstream as required;

• the ability to continuously vary the composition of the reaction mixture by varying the differential injection rates of the inlet channels.

Does miniaturisation help us?

The first report of using microfluidic reaction systems to synthesise compound semiconductor nanoparticles was made by our group at *Imperial College London* in 2002.[7] Studies focussed on the use of a continuous flow microfluidic mixer for the controlled production of cadmium sulfide nanoparticles in aqueous solution. The rationale for this work was to transfer an established synthetic protocol for CdS nanoparticle synthesis[8] from a macroscale batch format to a microfluidic continuous flow format. The reaction involved the precipitation of CdS particles following the mixing of $CdNO_3$ and Na_2S in aqueous solution (in the presence of a sodium polyphosphate stabiliser). In conventional macroscale reactors, "mixing" and "reaction" occur simultaneously rather than consecutively, and reactions of this nature may therefore be "throttled" by insufficient mixing. To effect rapid mixing of the reagent streams a microfabricated mixer (based on the principle of distributive mixing and flow lamination) was used to initiate nucleation and subsequent growth of CdS nanoparticles. Detection and size analysis of the generated nanoparticles was achieved by measuring UV-VIS absorption spectra in the flowing effluent stream. Spectral analysis of the produced nanoparticles demonstrated the existence of a broad range of crystallite sizes (approximately between 3 and 12 nm). Interestingly, under all experimental conditions the simple process of reaction vessel downsizing was sufficient to lower the polydispersity of the crystallites. Furthermore, an increase in volumetric flow rate (and thus a reduction in reaction residence times) resulted in further improvements in crystallite monodispersity. This behaviour combined with the existence of an isosbestic point in absorption spectra indicated that a variation in volumetric flow rate provides a direct means of improving monodispersity (*i.e.* reducing the second moment of the size distribution) without affecting the modal energy gap or the symmetry of the size distribution.

Subsequently, Hideaki Maeda and colleagues at the *National Institute of Advanced Industrial Science and Technology* in Japan and *Kyushu University* applied a similar approach to the preparation of titania (TiO_2) nanoparticles within microchannel environments.[9] In this study the authors used the interface between two immiscible flowing streams to provide a small volume reaction vessel, in the belief that particle growth mechanisms within such a regime may be different to those within bulk phases. Specifically, a 9 cm microchannel (200 μm deep and 360 μm wide) was carved within a ceramic substrate and enclosed with a glass coverplate. By using two different immiscible liquid systems the authors were able to successfully demonstrate the generation of titania nanoparticles *via* the rapid hydrolysis of titanium alkoxide. Although, the authors did not report on-line detection of nanoparticles, TEM and electron diffraction measurements of colloidal effluent indicated the presence of titania particles with diameters less than 10 nm and the anatase polymorph (Fig. 2).

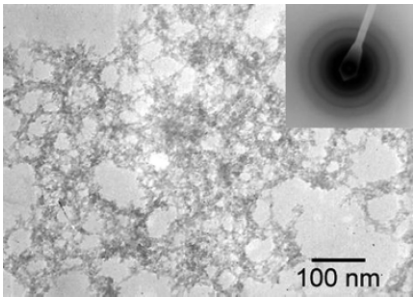

Fig. 2 TEM image and electron diffraction pattern of TiO_2 nanoparticles prepared from a cyclohexane–water system within a 9 cm long microchannel (200 μm wide by 360 μm deep). Adapted from ref. 9.

Importantly, the approach was shown to compare favourably with macroscale synthesis methods with respect to experimental simplicity.

Soon after these initial studies the same group applied the ideas of continuous flow synthesis to the preparation of CdSe nanoparticles in conventional capillaries.[10,11] CdSe nanoparticles are of considerable current interest as optical tags in chemical and biological analyses. This is primarily due to high photoluminescence quantum efficiencies, relatively low photodegradation rate coefficients and the extensive characterisation of optoelectronic properties in the literature.

As already noted, the widespread adoption of compound semiconductors in sensing applications will be determined by the ability to generate large quantities of high-quality stable crystallites with narrow size distributions. Conventional approaches to CdSe nanoparticles synthesis have been moderately successful in achieving these aims. For example, CdSe nanoparticles can be synthesised *via* precursor routes involving the direct reaction of selenium and cadmium acetate dissolved in a mixture of TOP (trioctylphosphine) and TOPO (trioctylphosphine oxide) at high temperature.[12] Unfortunately, preparation of CdSe nanoparticles *via* batch reactions is limited to relatively small volumes (approximately 5–50 mL), due to difficulties associated with reaction control as reactor size is increased. Although the instantaneous volumes associated with continuous-flow microfluidic reactors are most usually measured in hundreds of nanoliters, operation of multiple devices for extended periods of time can very easily simulate large-scale reactor flows. Microfluidic reactors therefore offer a highly effective means of producing large quantities of product whilst retaining precise control of reaction conditions (such as temperature and reagent concentrations).

In the initial experiments described by Nakamura *et al.* an established direct protocol for CdSe synthesis was performed within a fused silica capillary (200–500 μm id) immersed in a oil bath[12]. Reaction temperatures could be varied between 230 and 300 °C and reaction residence times were determined by volumetric flow rates and capillary dimensions. Off-line analysis of product solutions *via* both absorption and fluorescence spectroscopy indicated a systematic dependency of particle size as a function of reaction variables. For example, for a fixed reaction residence time, higher temperatures yield larger nanoparticles. Similarly, at a fixed reaction temperature, increased reaction residence times yield larger particles. Perhaps the most interesting outcome of these studies is the demonstration of segmented flow operation. Since, hydrodynamic pumping of fluids through microchannels is characterised by a velocity distribution orthogonal to the flow direction, a residence time distribution (RTD) will naturally occur. To counteract this effect the authors simply introduced 500 nL nitrogen bubbles at defined intervals.

A more detailed assessment of size-controlled growth of CdSe nanoparticles within microfluidic environments has been reported by Emory Chan, Richard Mathies and Paul Alivisatos at the *University of California, Berkeley*.[13] In these studies the authors synthesise CdSe nanoparticles directly by reacting dimethyl cadmium with selenium dissolved in boiling TOPO and octadecene within a glass microchannel reactor. Photoluminescence measurements provide a powerful approach to particle analysis, since the peak emission wavelength and the full width at half maximum intensity increase monotonically with particle diameter and size distribution respectively.[14] The microfluidic reactor is configured so as to allow for dilution pre- and post-reaction (Fig. 3). Fluorescence probing of the nanocrystal product is then performed downstream in a capillary flow cell. The authors elegantly demonstrate that CdSe nanocrystal size may be tuned by precise variation of experimental parameters, including temperature, volumetric flow rate and precursor concentration. For example, increasing the system temperature in 10 °C increments from 180 to 210 °C yields four different sizes of nanoparticles (with average diameters of 2.44, 2.54, 2.64 and 2.69 nm). Furthermore, increasing system temperature is shown to narrow the size distribution of the resulting nanoparticles. Although variation of overall volumetric flow rate is used to vary reaction residence times, the authors also show that precursor concentration can be controlled through

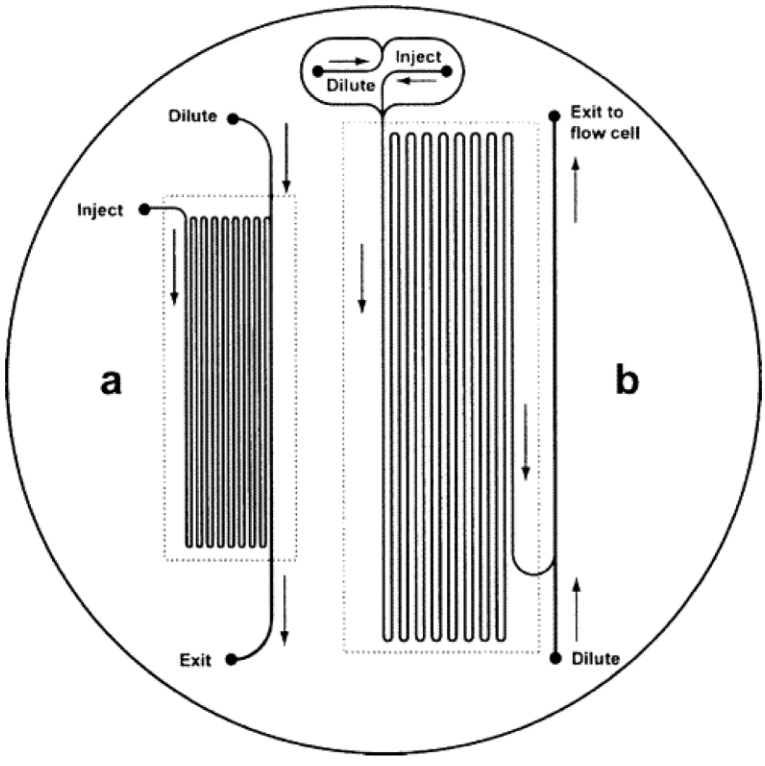

Fig. 3 Schematic of a microfluidic reactor for CdSe nanoparticle synthesis. Dotted lines indicate boundaries of heated reactor regions. Precursor enters through inject vias and can (a) react directly in a serpentine 65 cm-long, 150 μm-wide, 47 μm-deep, 4.7-μL channel, or (b) be diluted before reacting in a 105 cm-long, 200 μm-wide, 57 μm-deep, 12.5-μL channel. The nanocrystal product is diluted and quenched before exiting to a capillary flow cell. Adapted with permission from ref. 13.

variation of relative flow rates of precursor and octadecene, indicating concentration-dependent kinetics.

A similar continuous-flow approach to size-selective synthesis of CdSe nanocrystals has been recently described by Moungi Bawendi and associates at *Massachusetts Institute of Technology*.[15] One of the primary drivers for using a microfluidic device in this study is the ability to rapidly and continuously optimise reaction parameters whilst using minimal amounts of reagents. Importantly, the authors address common difficulties associated with performing reactions in microfluidic systems and accordingly utilise a modified precursor route involving TOP-Se and cadmium oleate. This approach avoids potential problems with gas evolution and handling of high-melting point solvents. Specifically, the reactor consists of a convective mixer interfaced to a heated glass capillary (that can be maintained at temperatures between 180 and 320 °C). The authors present a detailed assessment of how variation of reaction parameters can be used to control average particle size, particle size distributions and nucleation rates. Of particular interest is the observation that the ratio of the size distribution to average particle radius becomes unacceptable high when at low temperatures or high volumetric flow rates. This results in a relatively narrow range of monodisperse particle sizes. To overcome this problem, Bawendi and co-workers use variations in precursor concentration to access a wider range of acceptable products. For example, Fig. 4 illustrates absorption and photoluminescence spectra of samples prepared at four different flow rates and at temperatures between 180 and 320 °C. High photoluminescence quantum efficiencies and narrow emission peak widths demonstrate the production of high quality samples. In conclusion, the authors note that residence time distributions and intrinsic nucleation/growth processes define the range of acceptable nanoparticle sizes that can be generated at a specific precursor concentration.

In recent work we have also explored the influence of residence time distributions on population dispersity using direct on-chip monitoring of CdSe nanoparticle fluorescence.[16] These studies confirmed the role of the residence time distribution in determining size dispersity and revealed a dramatic broadening of size distributions at low flow rates. It is clear that the successful direct synthesis of near monodisperse nanoparticles in microreactors will depend intimately on the ability to create novel channel architectures which minimise variations in fluid velocity across the channel (plug flow) and hence the spread of residence times.

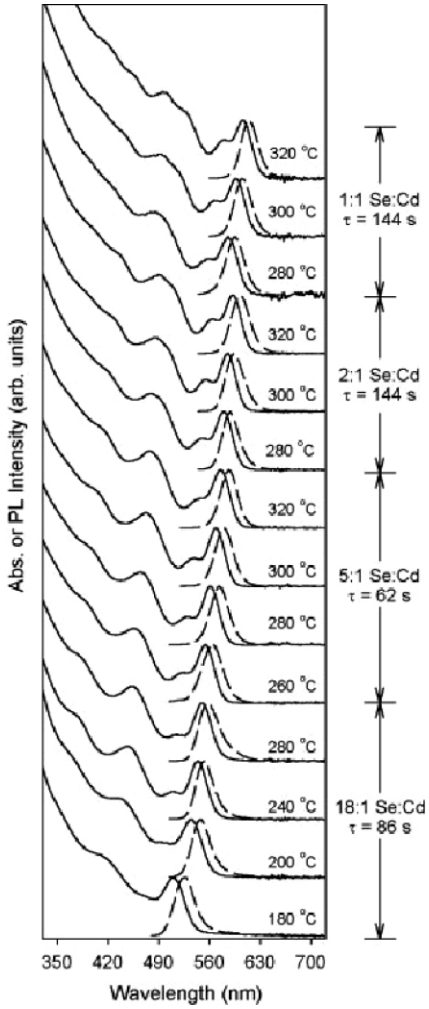

Fig. 4 Absorption and photoluminescence spectra from CdSe samples prepared using four TOP-Se concentrations. For each TOP-Se concentration, the average partcle size was controlled by varying the temperature at a fixed flow rate. Adapted with permission from ref. 15. © 2003 Wiley-VCH.

Perspective

While there have only been a handful of studies describing microfluidic approaches to the synthesis of nanoparticles it is already evident that such methodologies should play an important role in manufacturing nanoscale materials for a variety of applications. As has been demonstrated, microfluidic systems allow experimental variables such as temperature, flow rate and reagent concentration to be varied and controlled in a rapid, reproducible and precise manner. This directly leads to products whose size and optical properties can be tuned to a particular application.

The difficulties associated with synthesising appreciable amounts of high quality nanoparticle samples are evidenced by the scarcity of commercial sources for such materials. Accordingly, there is a real need for alternative synthesis strategies which can generate appreciable amounts of products without sacrificing crystallite quality and monodispersity. The notion of performing nanomaterial synthesis using microfluidic devices may appear nonsensical on first assessment, since instantaneous reaction volumes are typically in the nanolitre to low-microlitre range. However, this ignores the possibilities of parallel synthesis and the ability to run individual reactors for extended periods of time. For example, a microreactor generating product at a concentration of 2.8% at a flow rate of 20 ml per hour will yield 0.56 ml of product in 1 h. One hundred reactors operating in parallel will therefore produce 56 ml per hour, a rate comparable to many fine chemical processes. In addition, the stability, optical properties and chemical functionality of nanocrystalline materials have been shown to be greatly improved by capping or passivating the nanoparticle surface. Microfluidic systems are ideally suited to performing such processes in a sequential fashion. A nice example of such an approach has recently been reported by Wong *et al.*[17] where ZnS-coated CdSe composite nanoparticles were synthesised in a capillary/mixer based microflow system. The multistep synthesis involved three distinct processes (CdSe synthesis, mixing of CdSe with ZnS raw materials and coating of CdSe nanoparticles with ZnS) performed sequentially and in continuous flow. Using this method, the authors were able to demonstrate the formation of ZnS coatings whose thickness could be controlled through variation of reaction residence times.

Although, the primary aim of the studies outlined in this mini review has been to assess direct (microfluidic) routes for nanoparticle synthesis, it should not be forgotten that one of the most valuable capabilities of working within planar chip formats is the facile integration of additional processing components. This means that size-selection of nanoparticles post-synthesis to yield size distributions better than ±5 % should be easily achievable within monolithic systems.

It is fair to say that over the last decade we have witnessed a tremendous evolution of synthetic methods for producing quantum dots. These improvements are now beginning to generate materials which can realistically be used in optoelectronic applications. The authors anticipate that the continued development of microfluidic systems will create invaluable tools for improving the properties and yields of this important class of materials.

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