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Continuous Flow Reactor Technology for Nanomaterial Synthesis

Watts P[*]

InnoVenton: NMMU Institute for Chemical Technology, Nelson Mandela Metropolitan University, Port Elizabeth, South Africa

[*]**Corresponding author:** Watts P, InnoVenton: NMMU Institute for Chemical Technology, Nelson Mandela Metropolitan University, Port Elizabeth, South Africa, Tel: +27-41-504-3694; Fax: +27-41-504-9281; E-mail: Paul.Watts@nmmu.ac.za

Introduction

A significant number of precisely made nanomaterials have been developed for a wide variety of applications. For example, inorganic nanomaterials, such as quantum dots, are of interest because of their highly defined optical and electrical properties; where it is well established that their properties can be very finely tuned by carefully controlling their size and shape. Of more interest, nanomaterials have also been developed for diagnostic and therapeutic applications. For example, the specificity and sensitivity of magnetic resonance imaging can be greatly improved by using nanoparticles as contrast agents. As therapeutic agents, they allow targeted delivery and sustained release of drug molecules. Regardless of application, one current problem is to be able to prepare nanomaterials with reproducible properties on a large scale; this article introduces how new chemical technology may offer one solution to this challenge.

Continuous manufacture [1] has been gaining interest in the organic chemistry arena for the last decade. Although the majority of synthetic chemistry in academia and industry is performed using batch techniques that have been in place for decades, a major problem observed with conventional reactor technology is the failure to reproducibly scale-up successful laboratory reactions; this is particularly relevant for exothermic processes. The application of micro reaction technology and continuous flow chemistry is now widely accepted as a way of overcoming this problem, with large volume production demonstrated through the replication of unit processes [2]. A key advantage of flow reactor technology is the ability to very accurately control reaction parameters [1]. For instance, the regulation of temperature and concentration profile is crucial in maintaining control over a reaction, not only to ensure selective product formation, but also from a safety perspective. Due to the excellent heat and mass transfer, and predictable flow properties exhibited by micro reactor systems a high degree of reaction control is attainable. For example, in traditional large-scale reactor vessels, fluctuations in temperature are difficult to correct, as any alterations made take time to have an effect on the system as a whole; in comparison changes are observed almost immediately within flow reactors. Along with increasing the rate of mixing, decreasing the channel diameter results in an inherently high surface to volume ratio, allowing rapid dissipation of any heat generated over the course of a reaction.

Over the past decade, a wide variety of different chemical processes have been performed within such systems [3-5]. Critically it has now been demonstrated that the scale of manufacture can be very easily modified by simply increasing the volume of the flow reactor system [6]. Several chemical companies now manufacture at the 100-tonne scale using this approach [7]. In addition to the synthesis of small organic molecules, continuous flow synthesis is emerging as a tool for the preparation of highly defined materials; a selection of examples being detailed within this article.

Synthesis of Nanomaterials via Polymerization Reactions

When performing polymerizations in batch, the removal of heat from the reaction can be difficult, with the consequence that large molecular weight distributions are often obtained. Consequently, by performing such reactions in microfluidic continuous flow systems, where the high surface to volume ratio ensures rapid dissipation of heat, polymers with a narrow molecular weight distribution should be attainable.

Yoshida and co-workers [8] reported the controlled polymerization of butyl acrylate in a stainless steel capillary reactor (dimensions = 500 μm (diameter) x 1.0 m (length) consisting of a micro mixer followed by a heated channel (80-100°C) and a cooled (0°C) section. Using pressure-driven flow, the authors introduced a solution of AIBN (azobisisobutyronitrile) (0.03 to 0.05 M) in toluene from one inlet and neat butyl acrylate from the other inlet. Employing a reagent residence time of 3 minutes afforded yields of 87%. Critically the product had a Polydispersity Index (PDI) of 3.14 whereas when performing a comparable reaction in a batch reactor not only was the yield lower (50 %) but the product had a PDI of 212. It was therefore concluded that the reduction in PDI obtained when employing a micro reaction system was simply due to efficient heat removal. With respect to production, the authors importantly demonstrated the ability to operate the reactor, on a laboratory scale, for hours with no sign of fouling or pressure build-up. Other examples of polymer synthesis in such systems are reviewed by Park [9].

Along with the ability to prepare polymers of narrow molecular weight distribution, the preparation of polymeric beads has been demonstrated within microfluidic systems. Zourob and co-workers [10] used a micro reactor consisting of a polymeric reaction channel (dimensions = 200 μm (wide) x 200 μm (deep) x 2.0 cm (length)), for the preparation of molecularly imprinted polymers (MIP). To prepare an MIP, an argon purged solution of (R,S)-propranolol (1.0 mmol), methacrylic acid (10.0 mmol), trimethylolpropane trimethylacrylate (3.0 mmol) and 2,2-dimethoxy-2-phenylacetophenone (1.5×10^{-2} g) in MeCN (3.0 ml) was introduced into a mineral oil carrier stream and polymerization initiated using UV-light (60-80 mW cm^{-2}). The (R,S)-propranolol template was subsequently removed from the polymeric beads by washing with MeOH and MeCN. The aforementioned polymerisation methodology was subsequently repeated using a perfluoro-(1,3-dimethylcyclohexane) carrier stream, and the resulting beads washed with chloroform and acetone. Using this approach, near-monodisperse polymeric beads were obtained in all cases, affording a coefficient of variation (CV) of < 2%, compared to analogous batch

reactions whereby a CV of 67% was attained for beads prepared using mineral oil and 17% for those prepared in perfluoro solvent. Importantly, although the technique provides a simple means of preparing monodisperse polymeric beads, the technique did not affect the internal morphology of the beads, affording pore sizes and specific surface areas comparable to those obtained by conventional polymerization techniques. In addition, by altering the flow rate of the mixture the authors found the particle size ranged from 10 to 120 μm, again affording near-monodisperse beads.

Synthesis of Nanoparticles

As observed for polymerizations, controlled and reproducible techniques are required for the fabrication of nanoparticles, as any changes in the temperature or concentration across a reactor vessel can lead to variations in particles prepared. In addition, to ensure that a narrow size distribution of particles is achieved, it is essential that the reagents mix thoroughly on a time scale that is shorter than the reaction itself. To this end, reaction miniaturization provides the desired reaction control, coupled with the ability to achieve production scale quantities via process intensification and scale-up as discussed earlier.

In 2002, de Mello [11] reported the first example of nanoparticle production in microfluidic devices, describing the synthesis of cadmium sulfide nanoparticles. Under pressure-driven flow (10 and 300 μl min^{-1}), an aqueous solution of cadmium nitrate and sodium polyphosphate (4×10^{-4} M) was mixed with an aqueous solution of disodium sulfite (4×10^{-4} M) in a micro mixer (internal volume of 600 nl). To monitor the physical properties of the nanoparticles produced, the outlet of the micro mixer was coupled to a quartz cell (10 mm path length) through which UV-Vis spectra were obtained. Using this approach, the authors reported controlled initiation of nucleation followed by growth, affording CdS nanoparticles with a size distribution unparalleled by macro-scale investigations. In addition, a direct link between residence time and particle size was reported, confirming that crystallite monodispersity could be increased by reducing residence time and hence reducing the risk of coalescence.

Following this initial example, Maeda and co-workers [12] demonstrated the preparation of composite nanoparticles comprising of a Cadmium Selenide (CdSe) core and a Zinc Sulfide (ZnS) shell. To prepare the composite nanoparticles within a micro fluidic system, three steps were required, firstly CdSe synthesis (300°C), followed by the introduction of the ZnS and finally the ZnS coating step (220°C). To enable a series of steps to be performed at different reaction temperatures, the microfluidic system comprised of a 10 cm length of micro capillary (200 μm i.d.), connected to a ceramic micro mixer (85 cm) followed by 20 cm of micro capillary. Using this approach, the first portion of micro capillary could be maintained at 300°C, and the second at 220°C employing a flow rate of 100 μl min^{-1} enabled a residence time of 2 sec to be achieved for the CdSe synthesis, 8 sec for mixing with ZnS followed by 2 sec for ZnS coating.

Further to the fabrication of inorganic nanoparticles, Wagner and co-workers [13] reported the preparation of metallic nanoparticles, using a seed-mediated approach, in a Pyrex/silicon micro reactor (volume = 25.0 μl). The 12 nm gold seed particles were prepared off-chip and filtered through 0.2 μm filter, in order to remove any aggregates. Prior to investigating the preparation of larger Au nanoparticles within the micro reactor, the 12 nm Au seeds were passed through the reactor at a flow rate of 50 μl min^{-1} and analysed by UV-Vis spectroscopy. Using this approach, the authors reported no change in both the concentration and electronic properties of the 12 nm Au seeds, confirming that the particles remain unaffected by the micro reactor surface. The fabrication of larger Au nanoparticles was subsequently investigated in a micro reactor, using the following methodology; aqueous solutions of 12 nm Au seeds (3×10^{-4} M) chloroauric acid (2.5×10^{-5} to 1.0×10^{-3} M) and ascorbic acid (2.4×10^{-3} to 6.0×10^{-2} M) were introduced into the micro reactor from three separate inlets and the resulting nanoparticles analysed by UV-Vis spectroscopy. Comparison of the spectra obtained with those from the 12 nm seed particles enabled the authors to investigate the effect of flow rate and the seed/Au^{3+} ratio on the particle size of the resulting nanoparticles. Employing a seed/Au^{3+} ratio of 1:3, the authors observed an increase in particle size, from 15.4 to 18.7 nm, as a function of decreased flow rate (50 to 10 μl min^{-1}) whereas reducing the proportion of Au^{3+} (1:1.25) was found to increase nanoparticle size to 23.7 nm.

Employing droplet based flow, Lee and co-workers [14] were able to fuse droplets of $Cd(NO_3)^2$ and Na_2S within a silicone oil continuous phase to obtain a super-saturated solution of CdS, from which nanoparticles were precipitated. Compared to batch techniques, a blue-shift was observed which indicates the formation of smaller particles. Owing to the excellent control over molecular weight distribution obtained for polymers and semiconductors prepared under continuous flow conditions, a large proportion of work has been undertaken into the continuous flow preparation of metal oxide nanoparticles. In an early example, Jensen and co-workers [15] evaluated the effect of reactor design, flow velocity, reaction time and flow type on the formation of SiO_2 particles using the Stober process. Comparing segmented flow with laminar flow, the authors were able to conclude that segmented flow offered a facile means of obtaining narrow particle size distributions when compared with laminar flow; whereby axial dispersion led to a large size variation. The flow synthesis of TiO_2 nanoparticles was also studied by Wang and co-workers [16] via the hydrolysis and condensation of titanium tetraisoproxide. By varying the flow rate of two reactant solutions, the authors were able to generate a stable laminar interface at which particle growth occurred. Collecting the nanoparticles offline and subjecting them to analysis by UV-Vis and TEM, the authors were able to generate TiO_2 as the anatase polymorph.

In an alternative approach to new technology, Raston [17] used a spinning disk reactor to demonstrate the ability to rapidly mix reagents, tuning particle size as a function of rotating speed (500 to 2500 rpm). Investigating the preparation of superparamagnetic Fe_3O_4 nanoparticles, the authors were able to obtain 5-10 nm particles with a narrow particle size distribution and a high saturation magnetisation. Employing a microwave flow reactor, Bondioli and co-workers [18] developed techniques for the preparation of monodisperse, spherical nanoparticles of zirconia via the hydrolysis and condensation of tetra-n-propylzirconate. Maggini [19] have reported the use of a Coflore agitated reactor (AM Technology UK) to functionalise nanotubes, where reaction time could be reduced from 15 hours to 30 min.

Conclusion

In summary the use of continuous flow chemistry, as well as other new technology such as spinning disk and microwave reactors, has become reasonably well established in the field of conventional organic synthesis, where manufacturing can adopt the research methodology used by research scientists. Early research shows that nanomaterials

can also be prepared in flow reactors with the key benefit being the ability to prepare particles more reproducibly with more defined sizes. There is no reason why this methodology cannot be scaled to full production volume in the same way as small molecule synthesis.

References

1. Wiles C, Watts P (2011) Recent advances in micro reaction technology. Chem Commun (Camb) 47: 6512-6535.

2. Wiles C, Watts P (2011) Micro reaction technology in organic synthesis. CRC Press, USA.

3. Glasnov TN, Kappe CO (2011) The microwave-to-flow paradigm: translating high-temperature batch microwave chemistry to scalable continuous-flow processes. Chemistry 17: 11956-11968.

4. Baumann M, Baxendale IR, Ley SV (2011) The flow synthesis of heterocycles for natural product and medicinal chemistry applications. Mol Divers 15: 613-630.

5. Wiles C, Watts P (2012) Continuous flow reactors: A green chemistry perspective. Green Chem 14: 38-54.

6. Wiles C, Watts P (2010) The scale-up of organic synthesis using micro reactors. Chemistry Today 28: 3-5.

7. Braune S, Pochlauer P, Reintjens R, Steinhofer S, Winter M, et al. (2009) Selective nitration in a microreactor for pharmaceutical production under cGMP conditions. Chemistry Today 27: 26-29.

8. Iwasaki T, Yoshida J (2005) Free radical polymerization in microreactors. Significant improvement in molecular weight distribution control. Macromolecules 38: 1159-1163.

9. Park JI, Saffari A, Kumar S, Gunther A, Kumacheva E (2010) Microfluidic Synthesis of Polymer and Inorganic Particulate Materials. Annu Rev Mater Res 40: 415-443.

10. Zourob M, Mohr S, Mayes AG, Macaskill A, Pérez-Moral N, et al. (2006) A micro-reactor for preparing uniform molecularly imprinted polymer beads. Lab Chip 6: 296-301.

11. Edel JB, Fortt R, deMello JC, deMello AJ (2002) Microfluidic routes to the controlled production of nanoparticles. Chem Commun (Camb) 1136-1137.

12. Wang H, Li X, Uehara M, Yamaguchi Y, Nakamura H, et al. (2004) Continuous synthesis of CdSe-ZnS composite nanoparticles in a microfluidic reactor. Chem Commun (Camb) : 48-49.

13. Wagner J, Kirner T, Mayer G, Albert J, Kohler JM (2004) Generation of metal nanoparticles in a microchannel reactor. Chem Eng J 101: 251-260.

14. Hung LH, Choi KM, Tseng WY, Tan YC, Shea KJ, et al. (2006) Alternating droplet generation and controlled dynamic droplet fusion in microfluidic device for CdS nanoparticle synthesis. Lab Chip 6: 174-178.

15. Khan SA, Günther A, Schmidt MA, Jensen KF (2004) Microfluidic synthesis of colloidal silica. Langmuir 20: 8604-8611.

16. Wang H1, Nakamura H, Uehara M, Miyazaki M, Maeda H (2002) Preparation of titania particles utilizing the insoluble phase interface in a microchannel reactor. Chem Commun (Camb) : 1462-1463.

17. Chin SF, Iyer KS, Raston CL. Saunders M (2008) Size Selective Synthesis of Superparamagnetic Nanoparticles in Thin Fluids under Continuous Flow Conditions. Adv Funct Mater 18: 922-927.

18. Bondioli F, Corradi AB, Ferrari AM, Leonelli C (2008) Microwave-hydrothermal synthesis of nanocrystalline zirconia powders. J Am Ceram Soc 84: 2728-2730.

19. Salice P, Feraroli D, de Filippo CC, Menna E, Gasparini G, et al. (2012) Efficient functionalization of carbon nanotubes: an opportunity enabled by flow chemistry. Chemistry Today 30: 37-39.