

Encapsulation and controlled release from silica particles

Spherical silica particles are produced using combined sol-gel synthesis and emulsion polymerisation chemistry. Controlled release is achieved by restricting diffusion of encapsulated molecules out of the particles, by tailoring the internal pore structure of the spheres.

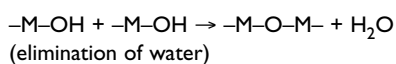
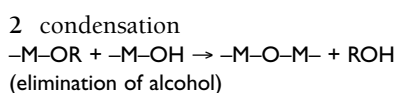
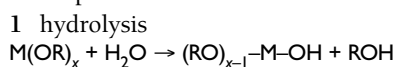
Introduction

As part of an ongoing research program at ANSTO, a technology for encapsulating and releasing a wide range of active molecules from spherical ceramic particles has been developed and patented.¹ The release of the active payload takes place by diffusion of the encapsulated molecules through the porous ceramic matrix. The key to control the release is the ability, using sol-gel chemistry, to produce particles with precisely controlled microstructure. The particles can be synthesised over an extensive size range of 10 nm – 50 µm, thus enabling design of release systems suitable for a wide range of uses. In addition, silica has a number of accompanying attractive properties, including biocompatibility, chemical inertness and optical transparency. With potential applications in the food, chemical, biocide, pesticide, cosmetic and pharmaceutical markets, to name a few, we are actively seeking potential R&D partners for field-of-use applications under options/license agreements.

Particle synthesis

Sol-gel chemistry has revolutionised ceramic production by enabling ambient temperature, solution-based synthesis of metal oxides with tailorable porosity. There are two steps in this process, which is essentially an inorganic polymerisation

reaction, using metal alkoxides as oxide precursors:



(M = Si, Ti, Al..., R = alkyl)

By combining sol-gel with emulsion chemistry, it is possible to produce monodisperse, spherical particles with a designed microstructure based on a judicious choice of solvent/surfactant and sol-gel reaction parameters.² By changing the solvent/surfactant combination, the particle size can be varied from 10 nm to 50 µm. The size of the particles is controlled by the size of the emulsion droplets which act as micro- or nanoreactors for the sol-gel reaction. Adding silicon alkoxide to a water-in-oil microemulsion leads to production of nanoparticles as the alkoxide diffuses into the water droplets where it is hydrolysed; further condensation reactions occur to form silica. Figure 1 shows a TEM micrograph demonstrating the monodisperse nature of 60 nm particles synthesised using a NP-9/cyclohexane/water microemulsion (NP-9 = polyoxyethylene (9) nonylphenylether).

Conversely, addition of an aqueous sol-gel solution containing prehydrolysed silicon alkoxide to a nonpolar solvent/surfactant solution results in production of micron-sized spheres (Fig. 2). When an active

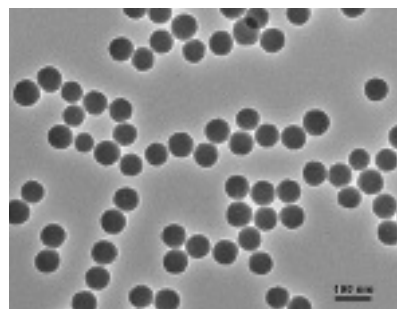


Figure 1. TEM of 60 nm particles synthesised using a NP-9/cyclohexane/water microemulsion.

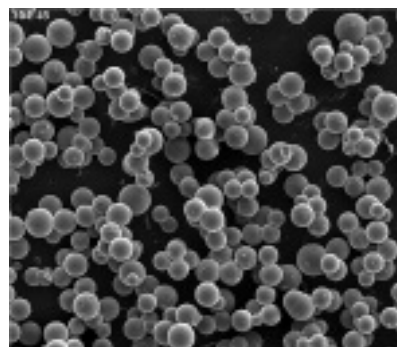


Figure 2. SEM of microparticles synthesised using a sorbitan monooleate/kerosene/water emulsion.

molecule is included in the aqueous phase in either system, encapsulation results as oligomeric silicon oxyhydroxide species polymerise to build an oxide cage around the active species. Encapsulation efficiencies for hydrophilic molecules are typically > 85%, with doping levels typically in the range 5–10 wt%. Microparticles may be produced in 50–100 g batches using a 5 L stirred tank reactor.³ Routine characterisation of the particles includes SEM-TEM, light scattering, and surface area and porosity measurements, with occasional use of FTIR and small angle scattering measurements.

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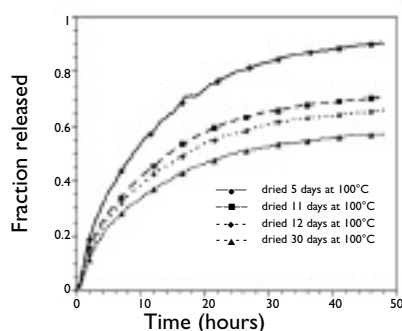


Figure 3. Influence of the drying time on the release of orange II.

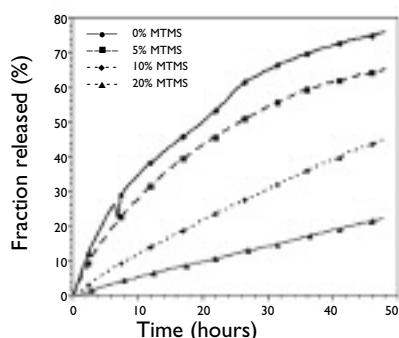


Figure 4. Influence of the MTMS content on the release of orange II.

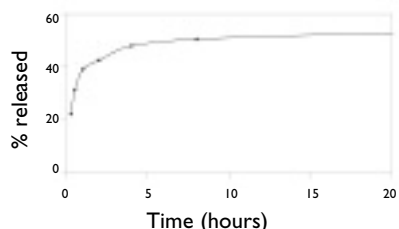


Figure 5. Release of α -chymotrypsin from silica particles.

Release rate control

The particle microstructure is dependent on the nature of the sol-gel solution. Typically, acid-catalysed hydrolysis and condensation result in a microporous (pores < 2 nm) matrix, whereas base-catalysed synthesis gives rise to a material with larger pores. Moreover, parameters such as water-to-alkoxide ratio, addition of catalysts, use of alkyl-substituted alkoxy silanes, drying time and temperature can be adjusted to modify the release kinetics. A convenient means of measuring release rates is to encapsulate a dye inside the particles and monitor the absorbance of a super-

natant solution using a dissolution tester (VanKel/Varian). A comprehensive suite of experiments has been conducted to determine the effect of these parameters on the release rate of various dyes from silica microparticles. Figure 3 illustrates the influence of the drying time at 100°C on the release of orange II dye from 20 μm microparticles into 100 mL of phosphate-buffered saline at pH 7.4. The decrease in the release rate with increasing drying time is related to a gradual collapse of the pores with drying, which restricts the diffusion of the dye out of the ceramic particles.

An alternative means of adjusting the release rate is to modify the chemical composition of the ceramic matrix. Use of an alkoxide mixture consisting of varying ratios of methyltrimethoxysilane (MTMS) and tetramethoxysilane (TMOS) modifies the internal pore structure of the particles. Increasing MTMS content incorporates methyl groups in the structure that provide flexibility to the Si-O-Si network, which further collapses upon drying, leading to gels with smaller pores than the one synthesised from pure TMOS.⁴ Figure 4 illustrates the effect on the release rates of orange II dye from 40 μm particles, which trend downwards with increasing methyl content.

More recently, a procedure has been developed that gives particles with pore sizes suitable for the release of much larger molecules such as proteins.⁵ Importantly, elimination of alcohol and use of more moderate pH conditions (pH = 5–7) render the synthetic process more suitable for the encapsulation of biomolecules. The particles are typically in the size range 1–10 μm . Figure 5 demonstrates the release characteristics of a sample loaded with α -chymotrypsin, a relatively small (~30 kDa) digestive enzyme.

Nanoparticles for drug delivery

One potentially interesting application of this technology is the controlled release of drugs. Drug

delivery systems can improve drug efficacy by maintaining a desired concentration profile in the blood. In order to achieve stability in the bloodstream, particles are ideally in the size range 50–300 nm. Smaller particles can diffuse through blood capillary walls, leading to non-specific distribution in the body, whereas larger particles become trapped in the lungs and the liver. Clearly, it is important that the nanoparticles remain non-aggregated, which presents a challenge. Surface-adsorbed surfactant, which could otherwise usefully act to prevent particle-particle aggregation, must be removed to leave a clean, hydrophilic surface. This is crucial because hydrophobic particles absorb protein markers (opsonins) which result in rapid clearance by the immune system, drastically reducing circulation time in the bloodstream. Ideally, particles should not be dried, but in order to increase product shelf-life, this can be done by introduction of a salt or sugar as matrix before freeze-drying of the aqueous phase, ensuring that the nanoparticles are encapsulated in a gangue which can be redispersed.

Preliminary biodistribution studies conducted using ⁶⁴Cu-labelled 50 and 250 nm particles in Wistar rats indicated a relatively low proportion (compared with alternative delivery vehicles) of nanoparticles in the liver, lungs and spleen, suggesting a low immune response.⁶ However, more comprehensive biodistribution studies conducted using ⁶⁷Ga-labelled particles have recently been completed, which call into question the earlier findings. This study represented a total of 16 experiments with four different particle sizes (20, 50, 100 and 200 nm) in two animal models (Wistar rats and brown mice) with two different tumour models (C6 glioblastoma and B16F10 lung melanoma, respectively). For the larger particles (≥ 50 nm), the majority of the particles were filtered out very rapidly by the reticuloendothelial system (RES), with > 90%

of the particles located in the liver and spleen. In contrast, a significant portion of the 20 nm particles remained in circulation in the blood (liver–blood ratio ~1:1) and tended to distribute throughout various organs. A slight accumulation with time of the 20 nm particles in both tumours was also observed.

Rapid detection of the silica nanoparticles by the RES is interesting, because it suggests that a hydrophilic surface alone is not a sufficient condition for avoiding opsonisation. Methods for surface modification are well established in our laboratory and we are currently investigating options for improving the stability of silica particles in the bloodstream.

Industrial applications of controlled release

While the pharmaceutical market is a potentially lucrative one, others present more immediate commercial opportunities. Many applications are conceivable in the area of home products (e.g. laundry powders, air fresheners, surface cleaners), agriculture, coatings, food and personal care, amongst others, and investigations into a number of these applications are currently underway in collaboration with commercial

partners. Of particular interest are applications that exploit properties of the matrix in addition to the controlled release aspect. For example, the transparency of silica suggests applications in optical sensors.

Pigment-sized dyed ceramic particles added to paint could also be used to release anti-fouling agents over a long time period. In addition to delivering active agents such as enzymes associated with oral hygiene, the abrasive nature and mechanical robustness of ceramic microparticles could be exploited with inclusion in toothpastes.

Conclusion

The unique combination of sol–gel processing with emulsion chemistry has enabled the production of monodisperse, spherical ceramic particles containing encapsulated molecules. The sol–gel reaction conditions and possible post-production treatments result in a defined microstructure which enables controlled release of the active molecules. Controlled release has been demonstrated for species ranging in size from small drug molecules to large proteins. A host of industrial applications exist, some of which may also exploit other properties of

the ceramic matrix in addition to controlled release properties.

Interested parties are invited to direct enquiries to Dr Christophe Barbé, ph. (02) 9717 3824, email cab@ansto.gov.au.

References

- 1 Barbé C.J.A., Bartlett J. Patent WO 01/62232, 2001.
- 2 Osseo-Asare K. Microemulsion-mediated synthesis of nanosize oxide materials. In Kumar P, Mittal K.L. (eds) *Handbook of Microemulsion Science and Technology*. Marcel Dekker, New York, 1999, 549–603.
- 3 Barbé C., Calleja, S., Kong L., Drabarek E., Bush A., Sizgek E., Finnie K. *Proceedings of the Materials Research Society Symposium on Organic/Inorganic Hybrid Materials*, 2004 Fall Meeting, Boston, 29 November – 3 December (in press).
- 4 Scherer G.W., Brinker C.J. *Sol–Gel Science*. Academic Press, New York, 1990.
- 5 Finnie K., Barbé C., Jacques D. Production of ceramic particles for controlled release of biological entities. Provisional patent AU2004907219, 20 December 2004.
- 6 Barbé C., Bartlett J., Kong L. *et al.* Silica particles: a novel drug delivery system. *Advanced Materials* 2004, 16, 1959.

RACI Board elections 2005

In accordance with the rules of the RACI, elections are held each year for positions on the Board of Management of the Institute from which members will be retiring and each second year for the position of President-elect. The positions on the Board that will become vacant at the November 2005 Annual General Meeting are North Eastern Representative, South Eastern Representative and Honorary General Secretary.

Nominations are called for the above-named positions. Nominations will need to be made on the appropriate form (available from the National Office), which must be signed by the candidate accepting nomination and either endorsed by the Nominations Committee, a Branch or Divisional Committee or five Corporate members of the Institute. Nomination forms should be sent to the Chair of the Nominations Committee, 21 Vale Street, North Melbourne, Vic. 3051 by the due date.

North Eastern Representative (Steven Bottle), South Eastern Representative (Dave Winkler) and Honorary General Secretary (Jane Weder), having completed one 2-year term, are eligible for election to this or another position in 2005.

Newly elected members of the Board will hold office from the end of the Annual General Meeting held in November 2005 for a period of two years until the conclusion of the Annual General Meeting to be held in 2007.

Brief election statements including experience and proposed initiatives provided by any candidate will be published in *Chemistry in Australia* or such other publications of the Institute as may be appropriate prior to the election or sent with the ballot papers as the Board may decide.

Nominations close **Friday 29 April 2005**.

Jane Weder, Honorary General Secretary
By Order of the Board