



SILICA PARTICLES AS MATERIAL FOR ENCAPSULATION AND CONTROLLED RELEASE OF DRUGS AND BIOLOGICALS

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ABSTRACT

Bioactive molecules can be easily encapsulated within silica particles by combining sol-gel polymerization with either spray-drying or chemistry. Spray-drying faces challenges, including low yield, surface segregation, and size limitations. In contrast, sol-gel emulsions enable the production of nanoparticles with homogeneous drug distribution, and permit ambient temperature processing. Necessary for handling biologicals. 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.

KEYWORDS

Sol-gel synthesis, polymerisation, ceramic matrix, spherical ceramic particles

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 patented¹. 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 mm, 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^{1,2,4-7}.

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

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inorganic polymerisation reaction, using metal alkoxides as oxide precursors:

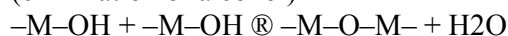
1 hydrolysis



2 condensations



(elimination of alcohol)



(Elimination of water)

(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, 7-9}. By changing the solvent/surfactant combination, the particle size can be varied from 10 nm to 50 nm. 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 micro emulsion 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 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%. Micro particles may be produced in 50–100 g batches using a 5 L stirred tank reactor^{3, 10}. 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.

Figure 1.
TEM of 60 nm particles synthesised Using a NP-9/cyclohexane/water micro emulsion.

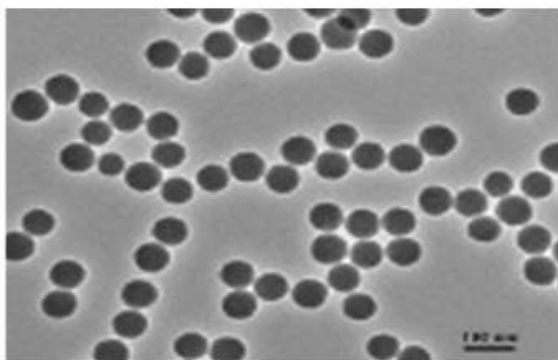
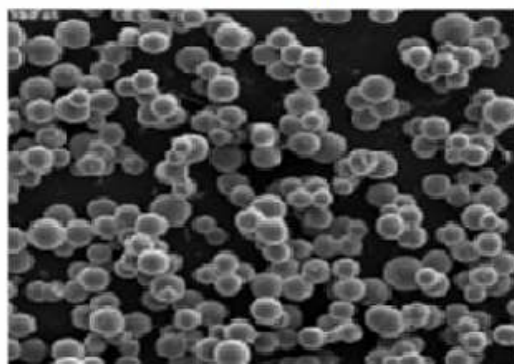


Figure 2.
SEM of micro particles synthesised using a sorbitan monooleate/ Kerosene/water emulsion.



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 micro porous (pores < 2 nm)

matrix, whereas base catalysed synthesis gives rise to a material with larger pores. Moreover, parameters such as water-to-lakeside ratio, addition of catalysts, use of alkyl-substituted alkoxy silanes,



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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 supernatant 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 micro particles. Figure 3 illustrates the influence of the drying time at 100°C on the release of orange II dye from 20 nm micro particles 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, 11, 12, 13}. Figure illustrates the effect on the release rates of orange II dye from 40 nm 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 proteins⁵. Importantly, elimination of alcohol and use of more moderate pH conditions (pH = 5–7) render the synthetic process more suitable for the encapsulation of bio molecules. The particles are typically in the size range 1–10 nm.¹⁴⁻¹⁸

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 nonaggregated, 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, 19, 20}. 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



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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 bloodstream²¹⁻²³.

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 products²⁴⁻²⁸ (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 sensors²⁹⁻³¹. 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 micro particles could be exploited with inclusion in toothpastes³²⁻³⁶.

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.

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