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Single-step fabrication of drug-encapsulated inorganic microspheres with complex form by sonication-induced nanoparticle assembly

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Sonication of nanoparticle suspensions confined within aqueous droplets of drug molecules in toluene produces drug-loaded silica or titania porous microspheres with complex morphology and storage/release properties.

The fabrication of inorganic nano- and microspheres for storage and release of ameliorative substances has recently been achieved using surfactant-based processes involving emulsion templating,[1,2] solvent evaporation,[3–5] or spray drying.[6,7] As many surfactants are deleterious to human health,[8,9] these approaches require stringent conditions for removal of the organic templates prior to drug encapsulation. In this paper, we describe a new approach to the one-step formation of drug-loaded silica or titania complex microspheres, in which dispersions of inorganic nanoparticles and drug molecules trapped within micrometre-sized water droplets suspended in toluene are solidified in the absence of surfactants by sonication-induced dissolution of the aqueous phase. This method has recently been used to prepare microspheres with closely packed gold, silica or gold/silica nanoparticles,[10] or zeolite microcrystals.[11] Significantly, spheroids with complex porous microarchitectures can be produced either by multiple collisions and higher-order aggregation,[10] or using non-interacting surfactant molecules.[11] Here we show that the presence of drug molecules not only results in direct encapsulation during nanoparticle assembly but also influences the porosity and morphology of the microspheres.

Sonication of microlitre volumes of aqueous drug solutions (acetylsalicylic acid, ibuprofen, phenylephrine hydrochloride, nortriptyline hydrochloride or chlorpheniramine maleate) that contained silica or titania (anatase) nanoparticles in toluene produced intact microspheres with polydisperse size distribution, 1 to 10 μm in diameter.† In each case, XRD and EDX analysis confirmed the presence of inorganic nanoparticles. In addition, thermogravimetric analysis (TGA) indicated that the microspheres usually contained between 50 and 80% of the original loading level of 10 wt%, except for mixtures such as titania/ibuprofen that showed lower encapsulation values of 20% due to reduced water solubility of the drug at low pH. In general, TGA profiles showed that thermal degradation of the entrapped drugs was prolonged over a wide temperature range, suggesting that the organic molecules were strongly associated with the inorganic nanoparticles throughout the microspheres.

SEM studies indicated that the charge and amphiphilic nature of the drug molecules had a marked influence on microsphere morphology. As a general rule, when the charge on the drug molecule was the same as that of the inorganic nanoparticles, for example for negatively silica/ibuprofen or positively charged titania/phenylephrine hydrochloride combinations, the microspheres exhibited smooth outer surfaces perforated with circular apertures usually less than a micrometre in diameter (Fig. 1a). When fractured, these microspheres displayed an elaborate foam-like interior of spherical pores with interconnecting mineralized walls, 50–100 nm in thickness (Fig. 1b). We attribute these results to the presence of closely packed sub-micron-sized oil droplets within the dispersed water drops, and the solidification of the inorganic nanoparticles within the interstitial spaces during dissolution of the aqueous phase in toluene. The surfactant-like properties of the drug molecules are well documented,[12,13] and surface activity at the oil/water interface and concomitant foam formation are likely to be facilitated by weak adsorption of the drug on nanoparticle surfaces of matching charge.

In contrast, strong interactions between the drug molecules and nanoparticles take place for silica/phenylephrine hydrochloride or titania/ibuprofen combinations with the consequence that formation of the oil-in-water-in-oil micelles was inhibited, and intact non-perforated microspheres with compact roughened surfaces and solid interiors were produced (Fig. 2a). High magnification SEM images showed a highly creased surface texture (Fig. 2b), suggesting that a thin coherent film enclosed the microspheres. One possibility is that electrostatic interactions between drug molecules segregated at the surface of the water droplets and dispersed nanoparticles gives rise to a mineralized film at the oil/water interface during the initial stages of solidification. Combinations of acetylsalicylic acid, nortriptyline hydrochloride or chlorphenir-

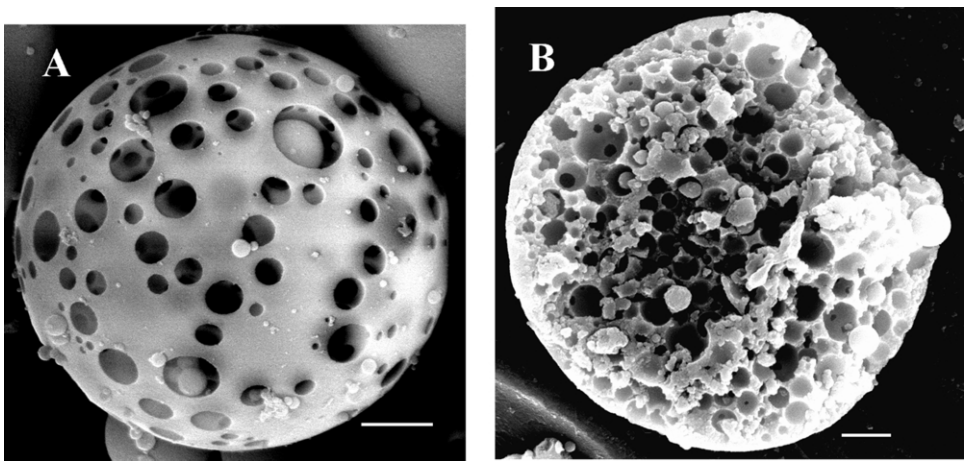

Fig. 1 SEM images of microspheres prepared using charge-matched drug/nanoparticle combinations, (A) intact silica/ibuprofen microsphere with surface perforations, (B) broken perforated titania/phenylephrine microsphere showing foam-like interior. Scale bars = 1 μm.

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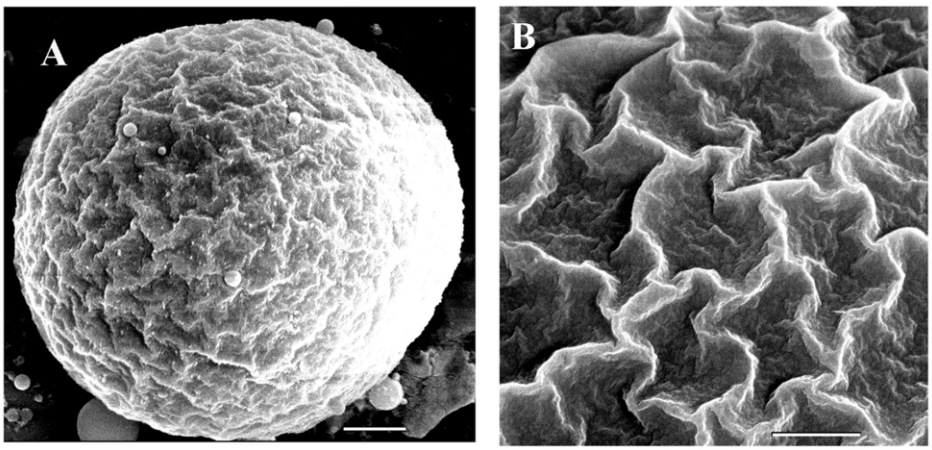

Fig. 2 SEM images of microspheres prepared using charge-mismatched drug/nanoparticle combinations; (A) intact non-perforated silica/phenylephrine microsphere with surface roughening surface texture, scale bar = 1 μm. (B) image of titania/ibuprofen microsphere surface showing creased surface film, scale bar = 1 μm

amine maleate with silica or titania nanoparticles were also investigated, and in each case the microsphere morphologies conformed to the above charge matching/mismatching model.

The above results indicate that drug molecules can be incorporated during the assembly of nanoparticle-containing microspheres and that significant changes in morphology can be induced by judicious choice of appropriately charged drug/nanoparticle combinations. In addition, intercalation of the drug molecules within the microspheres offers the possibility of controlled release without additional processing, such as the removal of surfactant templates. To verify this, the ibuprofen- or phenylephrine-loaded silica microspheres were filtered and dried and immersed in simulated body fluid (SBF) and the amount of drug released into solution monitored by UV-VIS spectroscopy.‡ In both cases, release of the drugs occurred within 30 min, after which steady state conditions corresponding to further release of residual drug molecules were observed up to 3 h after immersion (Fig. 3).

In conclusion, we have demonstrated a facile single-step method for the coassembly of inorganic nanoparticles and drug molecules into microspheres with complex form and slow release properties. The protocol has the distinct advantage that the drug to be delivered can act under certain circumstances as the progenitor of its own morphologically complex delivery scaffold, alleviating the need for auxiliary surfactant templates. Many different combinations of ameliorative substances and inorganic carriers could be used for a wide range of potential applications in drug delivery, environmental protection, smart coatings/barrier technology and tissue engineering.

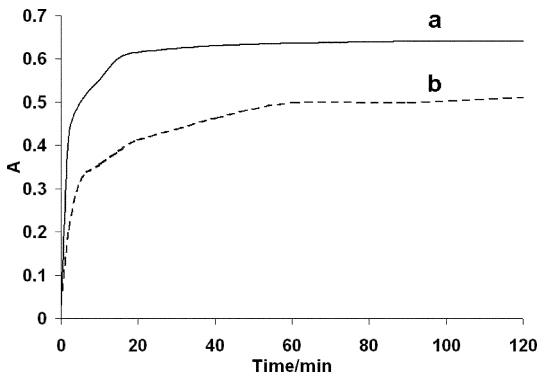

Fig. 3 Plot of increase in absorbance (A) with time at (a) 264 nm (ibuprofen) or (b) 278 nm (phenylephrine) associated with release of drug molecules from silica microspheres.

Notes and references

† Microspheres were prepared according to previously published procedures.[10,11] Briefly, a 25 mg aqueous suspension of silica (Snowtex C, Nisson Chemical Industry, 20 wt%, pH 9–10.5, particle size 12–14 nm) or titania (TKS-201, Tayca Corporation, 32.9 wt%, pH 1, anatase, particle size 6 nm) nanoparticles and drug molecules (10% of particle weight; ibuprofen, phenylephrine hydrochloride, nortriptyline hydrochloride and chlorphenirамine maleate (Aldrich)) were added to a plastic bottle (150 mL capacity), followed by the addition of toluene (100 mL). The mixture was immediately sonicated for 15 minutes at 3–5 °C using an ultrasonic bath (100 W, 50–100 kHz, Clifton, Nickel-Electro Ltd.). The bottle was removed from the ultrasonic bath and allowed to warm to room temperature (0.5 h). Microspheres were collected by filtration through polycarbonate membranes filter (0.2 μm pores). Samples were prepared for SEM or TEM studies by air drying droplets of the suspension onto aluminium stubs or copper grid. Samples were also studied by UV–VIS spectroscopy (Perkin Elmer Lambda II), and thermogravimetric analysis (Netzsch TG409EP) using a heating rate of 5 °C min^{-1} to a final temperature of 1010 °C.

‡ For drug release studies, 0.02 g of ibuprofen- or phenylephrine-loaded silica microspheres were immersed in simulated body fluid (SBF; $[Na^+]$ 0.142 M, $[K^+]$ 0.005 M, $[Ca^{2+}]$ 0.0025 M, $[Mg^{2+}]$ 0.0015 M, $[Cl^-]$ 0.148, $[HCO_3^-]$ 0.0042 M, $[HPO_4^{2-}]$ 0.001 M, $[SO_4^{2-}]$ 0.0005 M, pH 7.25 or 7.40).[14] Drug loadings prior to immersion were determined by TGA and were equal to 9 wt% (ibuprofen) and 5 wt% (phenylephrine). Aliquots of the solution were taken at regular intervals and the amount of released drug determined by UV-VIS spectroscopy by monitoring changes in absorbance at 264 nm (ibuprofen) or 278 nm (phenylephrine).

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