Encapsulation of Water-Insoluble Drugs in Polymer Capsules Prepared Using Mesoporous Silica Templates for Intracellular Drug Delivery**

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More than 40% of active compounds identified through screening of combinatorial libraries are poorly water-soluble, rendering them unsuitable for further drug development because of difficulties associated with their delivery using conventional formulation techniques.^[1] Nanoparticles can act as drug carriers for water-insoluble cargo and this has become an important emerging area of nanotechnology.^[2] As many potent anticancer agents are hydrophobic molecules, the development of nanomaterials for delivering such drugs has received significant attention.

Mesoporous silica (MS) materials are attractive as potential drug delivery systems due to their high surface areas (up to $\sim 1500 \text{ m}^2 \text{ g}^{-1}$), controllable pore sizes ($\sim 2\text{-}50 \text{ nm}$) and pore structures, and readily tuneable particle sizes ($\sim 60 \text{ nm}\text{--}10 \text{ }\mu\text{m}$) and morphologies.^[3] Recently, several groups have reported the *in vitro* delivery of water-insoluble drugs using MS particles as carriers.^[4-6] However, the MS particles became easily aggregated in aqueous solution after hydrophobic drug loading,^[5] due to the hydrophobic substance is deposited onto the surface of the MS particle as well. Moreover, detailed biocompatibility studies showed that mesoporous silica particles with diameters from 150 nm to $4 \text{ }\mu\text{m}$ have significant toxicity at high concentrations *in vitro*, and cause severe systemic toxicity *in vivo* after intraperitoneal and intravenous injections.^[6] These data suggest that the use of bulk mesoporous silica particles for drug delivery may suffer from these inherent limitations.

Polymer-based materials, such as polymer particles, polymer-based micelles, polymer-drug conjugates, polymer capsules, and polymersomes are alternative materials that have potential for accommodating and delivering poorly water-soluble compounds.^[7] Among the various polymer-based drug delivery vehicles, layer-by-layer (LbL)-assembled polymer capsules are particularly attractive,^[8] as they can accommodate high payloads,^[9] and are compatible with targeting^[10] and controlled release of the therapeutics.^[11] To date, three main approaches have been proposed for incorporating water insoluble compounds within LbL capsules. The first method entails encapsulating the therapeutic through the assembly of

polyelectrolyte multilayers on crystal particles (in instances where the therapeutic forms crystals).^[12] The second technique is to load water-insoluble drugs to the capsule by introducing lipophilic phases inside the capsules, such as back filling of the capsules with an oil-loaded drug.^[13] The third approach is to embed liposomes within polymer capsule multilayers, resulting in hybrid carrier capsosomes.^[14] However, these methods have limitations associated with sample polydispersity,^[12] the necessity for an oil phase,^[13] and capsule size ($>1\ \mu\text{m}$).^[12,14] Thus, developing robust techniques to prepare colloidally stable polymer capsules of submicrometer-size with high payloads of water-insoluble drugs still represents a challenge. This highlights the need for the development of a facile, generic nanocarrier system that combines the advantages of both mesoporous silica materials and polymer capsules to improve the flexibility in their design and application.

Here we demonstrate a facile and versatile approach for encapsulating water-insoluble compounds (e.g., thiocoraline, paclitaxel) in polymer capsules through mesoporous silica particle-mediated drug loading and subsequent generation of a polymer multilayer shell using the LbL technique (Scheme 1). After removal of the silica particles, the water-insoluble small compounds agglomerate into clusters, and are retained in the polymer capsules. This method yields nanocapsules with a high degree of drug loading (similar to MS materials), retained drug activity, and avoids the need for drug stabilization with a lipophilic phase or surfactant, or within smaller carriers.^[13,14] These drug-loaded capsules are as cytotoxic as the free drug (in an organic solvent) to colon cancer cells.

To construct capsules with a high drug loading, we employed a MS-sphere loading and templating approach (Scheme 1). MS spheres were used because of their potential for high loading and adaptability to a range of methodologies.^[15] The monodispersed MS particles were prepared as reported by Yamada and Yano.^[16] Transmission electron microscopy (TEM) revealed that these particles are homogeneous with a diameter of $\text{ca. } 400 \pm 20\ \text{nm}$ (Fig. 1a). At higher magnification, the disordered porous structure becomes apparent (Fig. 1b). Nitrogen

adsorption data indicated that the MS particles have a surface area of $860 \text{ m}^2 \text{ g}^{-1}$ and an average pore size of 2.4 nm with a pore volume of 0.48 mL g^{-1} .

The MS particles were exposed to a solution of the water-insoluble compounds (e.g., thiocoraline, paclitaxel) in chloroform, resulting in loading of drugs into the MS spheres (Scheme 1). Thiocoraline dissolved in chloroform gave a loading of 1.67 wt% into the mesoporous particles. No residual drug remained in the supernatant after loading, as confirmed by UV-vis spectrophotometry (data not shown), which is indicative of quantitative loading. MS particles with higher drug loadings can be obtained through increasing the mass ratio of the drug to particles. For instance, thiocoraline has a higher loading of 19.7 wt% when the mass ratio of the drug to particles was increased to 0.5. After centrifugation and removal of the supernatant, the pellets were dried in vacuum overnight. The dried particles were resuspended in acetate buffer (20 mM, pH 4) at a concentration of 5 mg mL^{-1} . The suspension of the thiocoraline-loaded MS nanoparticles flocculated quickly (less than 5 minutes), probably caused by some hydrophobic drug present on the outer surface of the particles. This tendency for aggregation of the MS particles after hydrophobic drug loading hindered the direct application of the MS nanoparticles as carriers to deliver water-insoluble drugs.

To overcome the aggregation and obtain a stable colloidal dispersion, the drug-loaded MS particles were sonicated and five bilayers of poly(N-vinylpyrrolidone) (PVPON) and thiolated poly(methacrylic acid) (PMA_{SH}) were sequentially deposited via hydrogen bonding onto their surface. The PMA_{SH} chains deposited on the shells were crosslinked via disulfide linkages and PVPON was then released from the shells via disruption of interpolymer hydrogen bonds, which resulted in single-component PMA_{SH} capsules stabilized by disulfide linkages, as reported previously by our group.^[17] The PMA_{SH} multilayers not only impart colloidal stability but also facilitate intracellular release of drugs from the capsules through intracellular cleavage of the disulfide bonds.^[18] Following shell formation, TEM analysis showed a smooth particle surface, suggesting homogeneous deposition of the polymer multilayer on the MS

surface (Fig. 1c). In contrast to naked MS particles (Fig. 1b), no porosity is visible in the polymer multilayer-coated MS particles pre-loaded with thiocoraline, probably due to filling of the pores with the drug (Fig. 1c).

Subsequently, the porous silica template cores were removed by exposure to hydrofluoric acid (HF)/ammonium fluoride (NH₄F) buffer (pH 5). TEM analysis revealed that the individual capsules formed are $\sim 450 \pm 30$ nm in diameter (Fig. 1d), slightly larger than the template particles used. The intact nature and structure of the capsules were further confirmed by high magnification TEM analysis (Fig. 1d, inset). The capsules preserve their structural integrity, and show significantly less folds and creases than those typically found in polymer capsules prepared by the LbL procedure.^[8] This is probably due to the relatively small size of the capsules and the agglomeration of the hydrophobic drugs inside the capsule wall, which may provide extra mechanical strength to the capsules. Fluorescence microscopy (Fig. 1e) revealed that the drug-loaded capsules were well-dispersed in phosphate buffered saline (PBS, pH 7.4) with similar shape and size to the MS template particles. Fluorescence microscopy images of thiocoraline-loaded PMA_{SH} capsules show fluorescence arising from thiocoraline (excitation at 380 nm, emission at 540 nm), which confirms that thiocoraline is retained in the polymer capsules after removal of the MS particles. We note that the thiocoraline-loaded capsules can be dispersed in aqueous solution with a local drug concentration of up to ~ 20 mg mL⁻¹ in the capsules, as opposed to the free thiocoraline, which is largely insoluble in water.

To demonstrate the potential of this system to deliver water-insoluble drugs to cells, we encapsulated the hydrophobic fluorescent probe 1,1'-dioctadecyl-3,3,3',3'-tetramethindocarbocyanine perchlorate (DiI) in PMA_{SH} capsules, and subsequently labeled the capsule wall with Alexa Fluor 488 (AF488) (Fig. 2a-c). DiI has been previously used as a model cargo to follow the intracellular delivery of hydrophobic drugs.^[19] To locate the DiI loaded in the capsules, MS particles with larger diameter (*ca.* 2 μ m) were used as a template to prepare larger capsules, which can be more readily characterized by optical microscopy.

Confocal microscopy images of DiI-loaded AF488-labeled PMA_{SH} capsules clearly showed that the majority of encapsulated DiI was associated with the inside of the capsule shells (Fig. 2d-f), which is in stark difference to the homogeneous distribution of water-soluble substances inside capsules we had observed previously.^[20] The association of the dye with the capsule shell was probably caused by self-agglomeration of the hydrophobic dye molecules (due to the removal of the porous silica supports) to small clusters, which then deposited on the inside of the capsule walls. This hypothesis is further supported by a control experiment in which the particles were examined before silica removal (i.e., the PMA_{SH}-coated DiI-loaded MS particles), in which case the DiI was homogeneously distributed throughout the particles (Supporting Information, Fig. S1). The self-agglomeration property of hydrophobic molecules in aqueous media is believed to play a key role in encapsulating small molecular substances in polymer capsules, which are typically permeable to water-soluble molecules with a molecular weight of up to *ca.* 100 000 Da.^[8c] There was no detectable DiI (*M_w* 934 Da) fluorescence outside of the capsules (i.e., in the solution), suggesting that premature leaking of the small molecular payload from the capsules does not occur.

DiI-loaded AF488-labeled PMA_{SH} capsules (400 nm in diameter) were then added to cell growth media and incubated with LIM1899 colorectal cancer cells^[21] for 24 h. The association of LIM1899 with DiI-loaded AF488-labeled PMA_{SH} capsules was quantified using flow cytometry. The data show that 81.7% of cells exhibited an increase in fluorescence intensity both in FL1 (AF488) and FL2 (DiI) compared with the untreated cells (Supporting Information, Fig. S2), suggesting that the majority of cells have associated with DiI-loaded capsules. Further, the internalization of DiI-loaded AF488-labelled PMA_{SH} capsules was confirmed using confocal microscopy, where the capsules were clearly observed inside the cells (Fig. 2g-j). The majority of the internalized AF488-labeled capsules and their cargo, DiI, appeared to be associated, as demonstrated by overlapping green (AF488) and red fluorescence (DiI).

Following proof-of-concept of cellular uptake of DiI-loaded PMA_{SH} capsules, we evaluated the cytotoxicity of the hydrophobic anticancer drug-loaded PMA_{SH} capsules (400 nm in diameter) in colorectal cancer cells using the MTT cell viability assay (Fig. 3). The PMA_{SH} capsules were loaded with either thiocoraline or paclitaxel to demonstrate the general applicability of this system. Thiocoraline is an antitumor cyclic thiodipeptide isolated from the mycelium of a marine actinomycete, which possesses cytotoxic activity at nanomolar concentrations on a panel of 12 human cancer cell lines.^[22] Paclitaxel is an anti-mitotic anticancer drug in current clinical usage. The drug-loaded capsules were incubated with LIM1899 cells at various capsule to cell ratios (from 25 to 1000:1) for 48 h. As shown in Figure 3a, the unloaded capsules did not affect cell viability, which is consistent with our previous reports.^[14] Moreover, treatment with the supernatant cell media from drug-loaded capsules did not affect cell growth, confirming the successful encapsulation observed using DiI-loaded PMA_{SH} capsules. More importantly, cell viability was reduced in a dose-responsive manner when treated with drug-loaded PMA_{SH} capsules, showing similar efficacy to the free drugs dissolved in DMSO (Fig. 3b). Taken together, these data suggest that the hydrophobic drugs are retained within the disulfide-bonded capsules and released through the intracellular reducing conditions after internalization by the colorectal cancer cells. This is consistent with our previous reports on the intracellular delivery of various therapeutics (including doxorubicin and peptides) using PMA_{SH} capsules.^[13,18]

In conclusion, we have reported the synthesis of water-insoluble drug-loaded capsules that employs MS templating, LbL assembly and disulfide chemistry. The resulting capsules exhibited excellent water dispersity while maintaining potent cytotoxicity to colorectal cancer cells, similar to that of the free drug in organic solvents. Our results demonstrate that this formulation technique can be applied to various low-solubility drugs. Given the tunability of particle sizes and pore sizes of MS particles, as well as the simplicity and versatility of the

LbL technique, this novel approach affords a facile and promising route to translate water-insoluble compounds to relevant clinical applications.

Experimental

Capsule Preparation and Drug Loading: The small molecule, water-insoluble compounds were firstly loaded in the MS particles. Taking the drug thiocoraline as an example, approximately 6 mg of 400 nm diameter MS particles were dispersed in 1 mL of chloroform solution containing 0.1 mg thiocoraline and the mixture was shaken at room temperature for 6 h. After centrifugation at 3000 g for 2 min and removal of the supernatant, the thiocoraline-loaded MS particles were dried in a vacuum desiccator to remove the chloroform. The drug-loaded MS particles were then redispersed in 20 mM acetate buffer (pH 4) with brief sonication. The suspension was then incubated in a 1.0 g L⁻¹ solution of PVPON for 10 min. After being washed three times in acetate buffer (pH 4), the particles were suspended in a 1.0 g L⁻¹ solution of PMA_{SH} for 10 min. PVPON and PMA_{SH} were added sequentially until 10 layers had been deposited, after which time the particles were treated with 2.5 mM chloramine T in 50 mM 2-morpholinoethanesulfonic acid (MES) buffer (pH 6) for 90 s. The particles were washed three times with fresh acetate buffer and dispersed in 50 µL buffer, to which 600 µL of 2 M HF/8 M NH₄F (pH ~5) was added. The resulting capsules were washed three times with acetate buffer (pH 4) and twice with PBS buffer (pH 7.4) by centrifugation (4500 g for 5 min) and finally dispersed in 0.6 mL BPS buffer.

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Scheme 1. Schematic illustration of the encapsulation of water-insoluble therapeutics in PMA_{SH} nanocapsules via mesoporous silica templating. (I) Loading of water-insoluble therapeutics into MS particles; (II) LbL assembly of a multilayer polymer shell on the surface of the drug-loaded MS particles; (III) Removal of the MS particle, leading to polymer capsule encapsulated therapeutics.

Figure 1. TEM images of the MS spheres (400 nm in diameter) at low (a) and high (b) magnifications (the inset in (a) shows the pore distribution of the particles). High magnification TEM image of a MS particle after loading with thiocoraline and PMA_{SH} multilayer assembly on the MS surface (c). TEM images (d) and fluorescence microscopy image (e) of the thiocoraline-loaded PMA_{SH} capsules after removal of the MS spheres.

Figure 2. Confocal laser scanning microscopy images of the DiI-loaded AF488-labeled PMA_{SH} capsules and the uptake by LIM1899 cells. CLSM images of the DiI-loaded AF488-labeled PMA_{SH} capsules (a-c, 400 nm in diameter; d-f, 2 μm in diameter); red fluorescence arising from encapsulated DiI (a, d), green fluorescence corresponding to the capsule wall labeled with AF488 (b, e), and the overlay image (c, f). CLSM images of the uptake of DiI-loaded AF488-labeled PMA_{SH} capsules (400 nm in diameter) by LIM1899 cells (g-j); red fluorescence showing intracellular DiI (g), green fluorescence representing internalized AF488-labeled PMA_{SH} capsules (h), the overlay image with bright-field of cells (i), and magnified image of the framed area in i (white) (j). Cells were incubated with the capsules at a capsule to cell ratio of 100:1 at 37 °C/5% CO₂ for 24 h. Scale bars, 5 μm.

Figure 3. MTT assays of drug-loaded PMA_{SH} capsules on LIM1899 cells. 400 nm PMA_{SH} capsules were used, and cells were treated for 48 h. (a) Column A: Untreated cell; B: Unloaded capsules with a capsule to cell ratio of 1000:1; C: Supernatant solution of drug-loaded capsules in cell media with a capsule to cell ratio of 1000:1; D-I: drug-loaded capsules in cell media with a capsule to cell ratio of 25, 50, 125, 250, 500 and 1000:1, respectively. (b) Cytotoxicity of drug-loaded PMA_{SH} and free drug dissolved in DMSO as a function of drug concentration. The cell viability has been normalized by setting the viability of untreated cell as 100%.

Table of Contents

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Keyword: Bionanotechnology; Polymer capsule; Encapsulation; Drug delivery

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