Mold-Templated Inorganic-Organic Hybrid Supraparticles for Codelivery of Drugs

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ABSTRACT: This paper reports a facile and robust mold-templated technique for the assembly of mesoporous silica (MS) supraparticles, and demonstrates their potential as co-delivery vehicles for both brain-derived neurotrophic factor (BDNF) and dexamethasone (DEX). The MS supraparticles are assembled using gelatin as a biodegradable adhesive to bind and cross-link the particles. Microfabricated molds made of polydimethylsiloxane are used to control the size and shape of the supraparticles. The obtained mesoporous silica-gelatin hybrid supraparticles (MSG-SPs) are stable in water as well as in organic solvents such as dimethyl sulfoxide, and efficiently co-encapsulate both BDNF and DEX. The MSG-SPs also exhibit sustained release kinetics in simulated physiological conditions (> 30 days), making them potential candidates for long-term delivery of therapeutics to the inner ear.

INTRODUCTION

Inner ear ailments, such as sensorineural hearing loss and Ménière's diseases, are common health issues that affect a large number of people at all ages.¹⁻³ Many of these diseases are difficult to treat, as the inner ear is secluded from systemic blood circulation by a cochlea-blood barrier, limiting the access of systemically administered therapeutics.^{4,5} Macro-, micro- and nanoscale drug delivery systems can provide new and improved ways of treating diseases, including facilitating spatiotemporally controlled codelivery of therapeutics.⁶⁻⁸ To improve treatment efficacy of inner ear drugs, several local drug delivery techniques have been developed. Intratympanic delivery relies on the permeability of the round window membrane (RWM) in the middle ear, where therapeutic agents are deposited using delivery vehicles such as hydrogels, nanoparticles or mini osmotic pumps, to slowly diffuse into the inner ear.⁹⁻¹¹ However, drugs with limited diffusion capacity, such as neurotrophins, are more effective when placed directly into the intracochlear fluid inside the inner ear (intracochlear delivery) through an incision on the RWM or a perforation on the cochlear bony wall.⁴ This

mode of delivery, however, presents new sets of safety challenges.¹²⁻¹⁵ Intracochlear delivery using mini osmotic pumps, for example, shows improved efficacy in animal models, but may be challenging to translate to the clinic, as they can promote bacterial infection in the inner ear.¹² The use of smaller carriers, such as nanoparticles or virus vectors, also risk delivering the medication to unintended sites, such as the brain, as they can be transported through the cochlear aqueduct.¹³⁻¹⁵ Carriers providing longer-term release of therapeutics that are large enough to reduce these safety issues, yet small enough to enable local release, are therefore of considerable interest.

Recently, we reported a new class of mesoporous silica based supraparticles (MS-SPs) as effective vehicles for the sustained delivery of brain-derived neurotrophic factor (BDNF) to the inner ear.¹⁶ The particles were prepared by confining mesoporous silica particles in small droplets followed by drying under airflow and calcination at 823 K for 6 h. Compared to smaller micrometer- or nanometer-sized particles, the ~800 μm -sized resultant supraparticles are less likely to be carried to the brain, where the drug may have unwanted side effects. The particles also had a high loading capacity for BDNF and exhibited long-term release profiles, which resulted in enhanced neural protection upon implantation in the cochlea of a guinea pig thus demonstrating that therapeutically relevant doses of functional BDNF can be delivered using supraparticles. However, this technique is time-consuming, and the manual production process poses challenges in achieving monodisperse MS-SPs. Increasing throughput and reproducibility, as well as facilitating co-encapsulation of diverse biomolecules, are therefore key challenges for advancing this technique. Several new methods, including both “bottom-up” and “top-down” approaches, have recently been developed for the production of micro- and nanoparticles for drug delivery.¹⁷⁻¹⁹ These have proven powerful for controlling the size and shape of drug delivery particles, as well as to enable increased production rates, which could help address these issues.

Herein, we present a robust, well-controlled and efficient technique for the assembly of MS supraparticles using a mold-templated method, and demonstrate their potential as vehicles for the codelivery of BDNF and dexamethasone (DEX). BDNF is a neuron growth factor that promotes survival and regeneration of auditory neurons following sensorineural hearing loss,²⁰ while dexamethasone is an anti-inflammatory agent that reduces negative tissue reactions upon implantation of a biomedical device into the cochlear.²¹ Gelatin is used as a biodegradable adhesive to bind and stabilize the mesoporous silica particles, thus avoiding the need for calcination (Scheme 1). The mold-templated soft lithography-based technique described here enables: (i) manufacturing of hundreds of supraparticles in parallel; (ii) control over size of the supraparticles; and (iii) simplified loading of bioactives and therapeutics. The improved production rate and reproducibility, as well as the longer-term (> 30 days) co-release of two potent drugs, demonstrate its potential for improved cochlear delivery of therapeutics for the treatment of inner ear ailments.

Scheme 1. Submicrometer-sized MS particles can be assembled into supraparticles either through calcination to form mesoporous silica supraparticles (MS-SPs), or by using gelatin to form mesoporous silica–gelatin hybrid supraparticles (MSG-SPs).

EXPERIMENTAL SECTION

Materials. Tetraethyl orthosilicate (TEOS), poly(acrylic acid) (PAA, $M_w \sim 250$ kDa, 35 wt% solution in water), cetyltrimethylammonium bromide (CTAB), ammonium hydroxide solution (28–30%), dexamethasone (DEX), rhodamine B isothiocyanate (RITC), sodium dihydrogen orthophosphate monohydrate ($\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$), disodium hydrogen orthophosphate dehydrate ($\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$), and sodium chloride (NaCl) were purchased from Sigma Aldrich (St. Louis, MO, USA). Gelatin (Type B) and calcium chloride were purchased from ChemSupply (Gillman, South Australia, Australia). Fluorescently labeled DEX was obtained from Life Technologies (Carlsbad, CA, USA), while BDNF was obtained from Merck Millipore (Darmstadt, Germany). Dimethyl sulfoxide (DMSO) was obtained from Fisher Scientific (Waltham, MA, USA). Ultrapure water with a resistivity greater than $18 \text{ M}\Omega\cdot\text{cm}$, from an inline Millipore RiOs/Origin purification system, was used. All chemicals were used without further purification.

Synthesis of MS Particles. Mesoporous silica (MS) particles with an average size of 700 nm were prepared according to a modified literature method.²²⁻²⁴ Briefly, 1 g of CTAB was completely dissolved in 50 mL of water with stirring. Subsequently, 3 g of PAA solution was added with vigorous stirring at room temperature (25 °C) until a clear solution was obtained. Next, 3.5 mL of ammonium hydroxide solution was added to the above solution with vigorous stirring, resulting in a milky suspension. After stirring for 20 min, 4 mL of TEOS was added to the above solution. After further stirring for 15 min, the mixture was transferred into a Teflon-sealed autoclave, which was left at 100 °C for 48 h. The as-synthesized MS particles were washed with water and ethanol three times, and finally dried at 80 °C. The organic templates were removed by calcination at 550 °C for 6 h.

BDNF Labeling. BDNF was labeled following a previously published protocol with slight modifications.²⁵ 100 µg of BDNF was dissolved in 100 µL of PBS at pH 8. 3.6 µL of RITC (1 mg mL⁻¹ in DMSO) was then added under vigorous vortexing. The sample was covered with aluminum foil to shield it from light and then left standing at room temperature for 45 min. After this, the sample was centrifuged at 14 000 g for 20 min using nanosep tubes (Pall Corporation, cut off M_w 3 kDa) to remove unreacted dye. The labeled BDNF was then redispersed in 100 PBS (pH 8) and its concentration was measured using a NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific).

Fabrication of PDMS-Molds for Mold-Templated Assembly. Polydimethylsiloxane (PDMS)-molds were prepared using soft lithography from masters prepared through 3D-printing or standard UV lithography.²⁶ Two different masters were designed using computer-aided design software (AutoCAD 2013; Autodesk, San Rafael, CA, USA). The designs were ten-by-ten arrays of pillars, with the dimensions (diameter × height) of either 500 µm × 500 µm or 200 µm × 200 µm. The larger feature size (500 µm) was manufactured directly in an acrylic-based polymer (FullCure720; Stratasys, Rehovot, Israel)

through 3D-printing (Objet Eden 260V; Stratasys, Rehovot, Israel). A chrome mask was made for the smaller feature size (Melbourne Center for Nanofabrication, Clayton, Victoria, Australia) and transferred onto a silicon wafer through standard UV lithography with a positive photoresist (AZ 40 XT; MicroChemicals, Ulm, Germany) followed by deep reactive ion etching (Plasmalab100 ICP380; Oxford Instruments, Abingdon, UK) with subsequent dissolution of the photoresist. Etch depth was measured using a surface profilometer (Ambios XP200; Ambios Technology, Santa Cruz, CA, USA). The patterns were then transferred into polydimethylsiloxane (PDMS; Sylgard 184, Midland, MI, USA) molds through soft lithography creating wells that could be used for the mold-templated assembly of supraparticles. Each master was used to create several PDMS-molds.

Assembly of MS-SPs, MSG-SPs and Drug Loading. MS-SPs were prepared as described previously.¹⁶ Briefly, the MS nanoparticles were dispersed in ultrapure water with a particle concentration of 10 wt% and briefly sonicated to form a stable colloidal suspension. A 0.5 μL aliquot of the MS nanoparticle dispersion was then applied to a flat surface, which was pre-covered with a paraffin film. The droplets were dried under air flow to drive assembly of the MS nanoparticles into MS-SPs via capillary force action. The mesoporous silica-gelatin hybrid supraparticles (MSG-SPs) were assembled by entrapping the MS particles within a gelatin network, followed by drying on a microfabricated PDMS mold, which determined the size and shape of the resulting supraparticles. To prepare DEX preloaded MSG-SPs, 5 mg of the MS particles were washed once with ultrapure water and then incubated with 40 μL of DEX solution (5 mg mL^{-1}) in DMSO for 6 h. The particles were subsequently centrifuged at 5000 g for 3 min and, after removal of the supernatant, re-dispersed in 10 μL of gelatin solution (10 mg mL^{-1} in ultrapure water) via 30 s sonication and with vigorous vortexing. 10 μL of 0.5 M calcium chloride cross-linker was then added and the mixture vortexed vigorously for 1 min. The particles were then centrifuged at 5000 g for

3 min and the supernatant withdrawn, after which the adsorption and cross-linking of the gelatin were repeated three more times. After the fourth adsorption and cross-linking step, the gelatin entrapped particle droplet was placed on the PDMS template, and spread gently using parafilm tape to fill the molds. For 200 μm -sized supraparticles, the molds were first plasma treated for 3 min to make the surface hydrophilic, and the gelatin entrapped particles diluted to obtain a total silica content of 10 wt%. The filled molds were then transferred into a vacuum desiccator (~ 10 kPa), and the particles were dried for 45 min. The resulting supernatants after each centrifugation step, during the drug loading and particle assembly process, were collected and used to quantify remaining (i.e., not loaded) DEX. Unlabeled DEX was quantified using UV-Vis spectrophotometry, while FITC-DEX was quantified by fluorescence spectroscopy. Simultaneous encapsulation of both the DEX and BDNF was achieved by incubating five DEX preloaded supraparticles with 8 μL of 0.84 mg mL^{-1} BDNF solution in ultrapure water for 3 days at 23 $^{\circ}\text{C}$. The amount of BDNF adsorbed onto the particles was then calculated by subtracting the amount of BDNF remaining in the supernatant after incubation from the initial amount added. The calibration curves used in quantification of each drug are provided in the Supporting Information.

Characterization. Fluorescent images were taken using a Leica TCS SP2 AOBs confocal microscope (Leica, Germany) equipped with an argon laser ($\lambda = 488 \text{ nm}$), using a 10 $\times$ oil immersion objective (Leica, Germany). Scanning electron microscopy (SEM) images were taken using a SEM Philips XL30 (Eindhoven, Netherlands) operated at 10 kV. The SEM samples were prepared by placing supraparticles on silicon wafers followed by gold sputter-coating. The dimensions of six MSG-SPs from the mold with larger wells, four MSG-SPs from the mold with smaller wells and ten MS-SPs were measured using SEM. The primary MS particles were imaged using transmission electron microscopy (TEM; Philips CM120 BioTWIN, operated at 120 kV). The TEM samples were prepared by air drying 1 μL

of diluted samples on Formvar-coated copper grids. Fluorescently labeled BDNF and DEX were quantified using a Fluorog-3 spectrofluorometer (Jobin Yvon Inc., USA) at 488 nm excitation wavelength for FITC-DEX and 546 nm excitation wavelength for RITC-BDNF. A spectrophotometer (absorbance at 241 nm; NanoDrop 1000) was used to quantify unlabeled DEX.

Release Studies. In vitro release studies were conducted by incubating five supraparticles in 85 μ L PBS (pH 7.3) at 37 °C. At various time intervals, 75 μ L of the supernatant was aspirated and the amount of drug released was quantified by fluorescence spectroscopy for the fluorescently labeled drugs, and UV-vis spectrophotometry for unlabeled DEX. The samples were redispersed in 75 μ L of fresh buffer and reincubated for continued release studies.

RESULTS AND DISCUSSION

Submicron MS particles were assembled into supraparticles of different sizes using gelatin as an adhesive, through a mold-templated procedure that uses a microfabricated mold made of polydimethylsiloxane (PDMS) (Scheme 2). Two different potent therapeutics (i.e., DEX and BDNF) could be easily encapsulated, and drug release was monitored for up to 45 days.

Scheme 2. A mixture of MS particles and gelatin is added to the “wells” of a mold manufactured in PDMS. Following drying in vacuum, the mesoporous silica-gelatin hybrid supraparticles (MSG-SPs) are extracted by inverting the mold and gently “tapping” on the back.

Mold-templated assembly. The molds for the assembly of supraparticles were prepared through soft lithography using PDMS-replicas of microfabricated masters (Figure 1). The masters were made of either 3D-printed polymer structures (for supraparticles ~ 650 μm in diameter), or silicon wafers patterned using standard UV lithography and deep reactive ion etching (for supraparticles ~ 200 μm in diameter).

Figure 1. (a) Photograph of 3D-printed master used for soft lithography to make PDMS-molds. (b) Tilted SEM image of a PDMS mold for supraparticle assembly. An incision has been made through one well to show the inside of the well. The inset shows a schematic of the mold where an incision has been made through several of the wells.

The MS particles were first entrapped within a gelatin network by cross-linking gelatin in the presence of the MS particles (Figure 2ab), using calcium ions that bind and bridge the carboxylic groups on the gelatin surface.^{27,28} Gelatin, a polymer “generally recognized as safe” (GRAS) by the U.S. Food and Drug Administration (FDA), was chosen owing to its well-proven high biocompatibility and biodegradability.²⁹⁻³² The gelatin-entrapped MS particles were then transferred to the patterned PDMS-molds and dried in a vacuum desiccator (~10 kPa) for 45 min at room temperature. Upon drying, the particles

adopt the size of the well, and are easily removed by inverting the PDMS-mold and gently tapping (Figure 2cd and Figure S4). The dimensions of the particles were measured to be $190 \pm 7 \mu\text{m}$ (mean $\pm$ standard deviation) and $650 \pm 20 \mu\text{m}$ for the smaller and larger MSG-SPs, respectively, and $700 \pm 70 \mu\text{m}$ for the MS-SPs. The final molds (Figure 2b) for the larger MSG-SPs were slightly larger than the design, which is expected as these features are close to the feature size limit of the 3D printing process used. The mold-templated gelatin-enabled MS supraparticle assembly presented here enables hundreds of supraparticles to be prepared simultaneously in less than two hours, an improvement of two orders of magnitude compared to the approximately one week required to produce an equal number of particles using the previously reported technique for production of MS-SPs.¹⁶ Furthermore, mold-templating enables control over the size and shape of the supraparticles.

Figure 2. (a) TEM of primary MS particles. (b) SEM of gelatin-entrapped MS particles. (c) SEM image of MSG-SPs. (d) Photograph of MSG-SPs in a microcentrifuge tube.

Drug loading. The resulting supraparticles were stable in water as well as organic solvents such as ethanol and dimethyl sulfoxide, without the need for any heat treatment, thus simplifying the loading of therapeutics and biomolecules. This facilitates co-encapsulation of multiple therapeutics, for example DEX and BDNF, in the same matrix. DEX was preloaded by incubation with primary MS particles prior to assembly, while simultaneous encapsulation of both the DEX and BDNF was achieved by incubating the DEX preloaded supraparticles with BDNF solution in water. In both cases, the amount of drug loaded was estimated by monitoring the change in drug concentration in the solutions before and after incubation.

$1.14 \pm 0.29 \mu\text{g}$ (mean $\pm$ std) of DEX was loaded per supraparticle (i.e., $15.4 \mu\text{g mg}^{-1}$) by preloading DEX in primary MS particles prior to MSG-SP assembly. This is $\sim 80\%$ more than the $0.63 \pm 0.05 \mu\text{g}$ (i.e., $6.30 \mu\text{g mg}^{-1}$) obtained when postloading the drug into pristine mesoporous silica supraparticles (MS-SPs). DEX has previously been shown to be effective in suppressing tissue inflammation at a concentration as low as 80 ng mL^{-1} ,²¹ thus indicating therapeutic relevancy for sustained release from the supraparticles (that can load over 1000 ng per particle), as the intracochlear volume is typically $\sim 75 \mu\text{L}$.³³

The DEX pre-loaded MSG-SPs also exhibited a high capacity for loading BDNF, with an encapsulation efficiency of $>99\%$ after a 3 day incubation period, corresponding to $\sim 22.6 \mu\text{g mg}^{-1}$ ($\sim 1.34 \mu\text{g}$ per supraparticle). The efficient loading could be due to favorable electrostatic interactions between the negatively charged silica-gelatin matrix and the positively charged BDNF (isoelectric point = 10).³⁴ Confocal microscopy confirms successful infiltration of BDNF into the particles (Figure 3), and the presence of DEX and gelatin on the surface of the particles does not appear to hinder the infiltration of BDNF. In hydrated form, the gelatin component is expected to be highly porous, thus providing a matrix for BDNF infiltration. Intracochlear BDNF doses as low as $\sim 4\text{--}7 \text{ ng}$ (corresponding to intracochlear concentrations around $50\text{--}100 \text{ ng mL}^{-1}$) have been demonstrated to provide neuroprotective

effect.³⁵⁻³⁷ Single supraparticles can encapsulate around 200-300 times this amount (~1300 ng), highlighting the therapeutic relevance of the MSG-SPs for sustained release.

Figure 3. Confocal microscopy images of MSG-SP loaded with FITC-labeled DEX (green) and RITC-labeled BDNF (red).

Drug release. Release profiles for both BDNF and DEX were investigated by incubating five MSG-SPs in 75 μL of phosphate buffered saline (PBS, pH 7.3) at 37 °C for several weeks. At various time intervals, the supernatant was withdrawn and the amount of drug eluted was quantified by UV-Vis spectrophotometry for unlabeled DEX and by fluorescence spectrofluorometry for the fluorescently labeled BDNF and the fluorescently labeled DEX. As depicted in Figure 4, the release profile for DEX was characterized by two phases: burst release was observed within the first day, followed by sustained release for more than 30 days. The burst release within the first day was about 25 ± 1 % for the MSG-SPs, while the MS-SPs released about 43 ± 1 %. After 30 days the MSG-SPs had released about 72 ± 6 % while the MS-SPs released about $87 \pm 0.7\%$. A possible reason for the relatively lower release rate of the MSG-SPs, especially during the burst release phase, is the presence of gelatin, which may act as a pore blocker,³⁸ thus slowing the diffusion of the drug from the supraparticles.

Figure 4. Sustained release profiles of DEX from MS-SPs and MSG-SPs. Mean $\pm$ standard deviation from three experiments ($n = 3$). Error bars for some data points are too small to be visible as they are within the size of the data points.

Co-release of DEX and BDNF was investigated from MSG-SPs over several weeks (Figure 5). BDNF was released at a slow rate during the first few days, followed by a steady release for more than 40 days. For example only 3% of BDNF was released within the first 4 days. This, however, steadily increased thereafter, releasing up to 57% within 45 days. The lack of burst release within the first day suggests that most of the BDNF was incorporated deep within the matrix rather than on the supraparticle surface. Electrostatic interactions between the silica-gelatin matrix and neurotrophin can also be an explanation for the relatively slow release rate. The observed slower release rate for DEX in the presence of, compared to in the absence of, BDNF (compare Figures 4 and 5), especially after the first burst release, could be caused by an increased diffusion barrier resulting from the presence of BDNF, which may also act as a pore blocker during the postloading.

Figure 5. Co-release of BDNF and DEX from MSG-SPs. Pooled mean value from five supraparticles.

Incorporation of DEX in BDNF delivery vehicles is expected to provide synergistic effect in the treatment of sensorineural hearing loss, by reducing tissue inflammation, when BDNF carriers are implanted into the cochlear. However, to the best of our knowledge, no other report has reported co-delivery of these two important therapeutics, probably due to their different physical and chemical properties making co-encapsulation challenging. BDNF, for example, is a hydrophilic protein with a molecular mass of 14 KDa,³⁹ while DEX is a small hydrophobic molecule with a molecular mass of 392 Da.⁴⁰ The ability of MSG-SPs to co-encapsulate and simultaneously release these drugs, therefore highlights their potential for the treatment of sensorineural hearing loss.

The release of therapeutic molecules from the MSG-SPs is driven by a concentration gradient between the particles and the surrounding media, as well as by the gradual degradation of the hybrid supraparticles. SEM images revealed that the supraparticles underwent a morphological transformation during incubation in PBS, from a well-ordered structure where the primary MS particles are clearly visible, to a more porous and irregular morphology, suggesting gradual dissolution of the particles (Figure 6). In physiological

conditions gelatin is known to undergo hydrolytic degradation through cleavage of the peptide bonds, into constituent amino acids.⁴¹ MS particles, on the other hand, gradually break down into soluble silica species.⁴²⁻⁴⁶ The silicate byproducts can eventually be excreted from the body through urine.⁴⁷ The degradation occurs throughout the supraparticle and there is therefore no large apparent decrease in size during the 45 days investigated.

Figure 6. SEM of MSG-SPs showing their morphology (a) before and (b) after 30 days of incubation in PBS (pH 7.3) at 37 °C.

CONCLUSION

We have demonstrated a rapid mold-templated technique (hundreds of particles in ~2 h) for the well-controlled assembly of robust MS-gelatin hybrid supraparticles, without the need for any heat treatment. The hybrid supraparticles exhibited high loading capacity ($15 \mu\text{g mg}^{-1}$ for DEX and $23 \mu\text{g mg}^{-1}$ for BDNF) and can effectively co-encapsulate BDNF and DEX in the same matrix. *In vitro* release studies demonstrate that the particles exhibit sustained release of both BDNF and DEX over the course of several weeks, while scanning electron microscopy shows dissolution of the particles in simulated physiological conditions. Future work will aim

at investigating the efficacy of these carriers in promoting the survival of auditory neurons in animal models of sensorineural hearing loss.

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Notes

The authors declare no competing financial interest.

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SUPPORTING INFORMATION AVAILABLE

Concentration calibration curves for DEX, DEX-FITC and BDNF-RITC, SEM images of supraparticles. This information is available free of charge via the Internet at <http://pubs.acs.org>.

ABBREVIATIONS

DEX, dexamethasone; BDNF, brain-derived neurotrophic factor; PDMS, polydimethylsiloxane; MS, mesoporous silica; MS-SPs, mesoporous silica supraparticles; MSG-SPs, mesoporous silica-gelatin hybrid supraparticles.

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