CONTROLLED DRUG DELIVERY VIA REMOTELY HEATED CORE-SHELL MAGNETIC MICROCAPSULES

X. Li, K. Iwai†, F. N. Pirmoradi†, Y. Chen, and L. Lin
Berkeley Sensor and Actuator Center, Mechanical Engineering Department
University of California, Berkeley, USA
†These authors contributed equally to this work.

ABSTRACT

We report the development of magnetically-driven, 300 μm in typical diameter, core-shell microcapsules for the on-demand and local delivery of encapsulated drug agents. These microcapsules are fabricated through a multi-stage microfluidic/optofluidic flow-focusing device with oil-based core and thermoresponsive polymer shell. In the prototype capsules, the shell structure is constructed by UV-curable polyethylene glycol diacylate (PEGDA) with embedded 20% w/w poly N-isopropylacrylamide (PNIPAm) nanogels and 0.5% w/w magnetic iron oxide nanoparticles (10 nm in diameter). Experimentally, the releases of the oil fluorescent dye from the core of the capsules have been successfully demonstrated by remotely triggering the capsules with induction heating. As such, this drug delivery scheme could be useful for remotely-triggered, site-specific applications.

KEYWORDS

Core-shell droplets, drug delivery, magnetic particles, microfluidics, optofluidic device

INTRODUCTION

Controlled delivery of therapeutic agents with remote triggering functions could have broad clinical applications [1]. Previously, several of the microfluidic and optofluidic flow-focusing devices have been utilized to fabricate microdrug carriers with double emulsions to encapsulate oil- and water-based agents [2,3]. While the physical “transportation” of these carriers to desirable locations have been established, the function of remote control for “on demand” drug release has been difficult to achieve.

In this work, poly N-isopropylacrylamide (PNIPAm) [4] has been chosen as the thermal sensitive material. Under a temperature change over 33 °C in deionized water, PNIPAm shrinks exhibits volume changes [4, 5]. This property has been studied and applied previously in controlled drug release applications [6, 7] by using both capsule- and membrane-type devices without the remote trigger function.

On the other hand, magnetic nanoparticles have been used in biological and medical applications [8]. They could be heated up remotely by alternating magnetic fields [9] due to the generation of eddy currents as one possible thermal activation trigger for biomedical applications [10]. For example, PNIPAm membranes with embedded magnetic particles have been shown to change their permeability for drug release by the applied magnetic fields [11].

In contrast to these prior works, we introduce a new class of core-shell capsules by embedding thermosensitive PNIPAm nanogels and magnetic iron oxide nanoparticles as the polymer shells to encapsulate drug agents using a multi-stage microfluidic/optofluidic process. Results show successfully controlled drug release via a remote induction heating process of magnetic particles which results in the shrinkages of PNIPAm in the shell and the release of the drug from the core.

DESIGN

Figure 1 conceptually depicts the structure of the microcapsules and the controlled drug release process. This microcapsule has a core-shell structure, with oil phase therapeutic agent in the core and polymer in the shell with embedded iron oxide nanoparticles. When the iron oxide nanoparticles are heated by the remotely triggered induction heating, they heat up the polymer shell and result in the shrinkage of thermal sensitive PNIPAm and the formation of micro/nano gaps and channels. The release of the oil phase drug in the core is then released. The nanogels can go back to the original state without the induction heating and stop the drug release process.

Figure 2 shows the fabrication process of the core-shell microcapsules via photopolymerization of emulsion droplets using a dual-stage microfluidic flow-focusing process. The mixture of the UV curable PEGDA with thermal sensitive PNIPAm nanogels and iron oxide nanoparticles is injected at the first junction, which forms oil phase droplets after the flow passes through the junction. The double emulsion [12] structure is formed after the second junction. The UV light exposure process cures the shell of the microcapsules.
**FABRICATION**

The shell material shown as the light grey color liquid in Figure 2 contains three major parts: thermal sensitive PNIPAm nanogels; UV curable PEGDA; and iron oxide nanoparticles with N-isopropylacrylamide (NIPAm, 99%), N,N’-Methylenebis (acylamide) (BIS, 99%), Sodium dodecyl sulfate (SDS 99%), ammonium persulfate (APS, 99%), PEGDA (average Mn 250), Dimethylpropionic acid (DMPA 98%), and TWEEN 20 - all from Sigma-Aldrich. The are used without further purification. The iron oxide nanoparticles (EMG 1200, average diameter 10 nm) are acquired from Ferrotec Ferrofluid.

Thermal sensitive nanogels were prepared via free radical polymerization of NIPAm with cross linker BIS, surfactant SDS and initiator APS [4, 5]. The polymerization reaction is conducted at 70 °C, which is higher than the phase transition temperature (33 °C) of PNIPAm. At this temperature, the polymerized PNIPAm chains will be cross linked to each other by BIS and crimple to form shrunken micro/nano hydrogel particles. Surfactant SDS can be used to control the size of the fabricated nanogels [13] and avoid the nanogels from aggregation. Specifically, 2.8 gram of NIPAm with 0.28 gram of BIS and 0.04 gram of SDS are mixed together in 188 ml of DI water in a 400 ml conical flask. This solution is stirred at 200 RPM for 30 min with purged Nitrogen to remove air dissolved in the solution and heated to 70 °C. Afterwards, 0.12 gram of APS and 12 ml of DI water are added to initiate the reaction. The solution is stirred, purged with Nitrogen and water bath at 70 °C for 4 hours. The white water suspension of PNIPAm nanogels are then cooled down to room temperature.

Because it is difficult to uniformly mix PEGDA and water and to keep the mixture stable, the nanogels need to be dehydrated before the mixing process. We have chosen the lyophilization (freeze drying) process to dehydrate the nanogels as it has been widely used in food and biomedical material storage applications. The process starts with freezing the material and reducing the pressure to cause direct sublimation of the frozen water in the material without damaging the structure of the material. In our work, the water suspension of nanogels is frozen by liquid Nitrogen and put into a vacuum flask for 3 to 4 days with temperature of -84 °C and pressure of 0.04 mbar (FreeZone Plus 4.5 Liter, LABCONCO Inc.) to remove water in the nanogels.

The iron oxide nanoparticles (from Ferrotec Ferrofluid) are coated with fatty acid, which makes them easily to be suspended in toluene. They are suspended uniformly in toluene and mixed with (mass percentage) PEGDA (69.5%); PNIPAm (20%); iron oxide nanoparticles (0.5%); TWEEN (20.5%); and DMPA (5%). TWEEN 20 is added to increase the viscosity of the liquid mixture to promote the formation of the double emulsion structure. Toluene is evaporated out of the solution by stirring at room temperature. The mixture is kept at 4 °C and away from light.

The multistage microfluidic flow-focusing technique is shown in Figure 3 in PDMS based structures with the 50µm-wide constriction channel at the center. This dual stage flow-focusing device is fabricated using the standard soft lithography microfabrication processes. The soft polymer material - poly(dimethylsiloxane) (PDMS) is cast onto a silicon wafer mold with microfabricated patterns made of SU-8 photoresist on the silicon wafer. Liquid PDMS mixed with curing agent (10:1 w/w) is carefully poured to cover the silicon wafer mold after being degased to clear the bubbles inside. The PDMS structure is baked at 100 °C for 1 hour for curing. After that, cured PDMS is peeled off the mold and the inlet and outlet ports are made by mechanically punched holes. The surface of PDMS is then treated with oxygen plasma (120W for 10 s) to modify the surface from hydrophobic to hydrophilic to promote bonding. During the process, the first junction is selectively covered with Kapton tape to maintain the hydrophobicity of PDMS. Water is then infused into the second junction to keep its hydrophilic state while bonding the PDMS to the glass substrate by baking at 75°C for 30min.

**Figure 2**: The schematic diagram showing the fabrication of the microcapsules by a multi-stage microfluidic/optofluidic flow focusing process to generate core-shell droplets.

**Figure 3**: An optical microscope showing the fabrication of microcapsules in real time. Left Red Portion: Hydrophobic region. Right Blue Portion: Hydrophilic region.
with surfactant (P105, 2% w/w), respectively. The surfactant in the oil environment is used to avoid the fabricated microcapsules form aggregation and blocking the microchannels. The microcapsules are cured under UV light of 23.4 mW/cm² with wavelength of 365 nm. Figure 4 shows fabricated samples under an optical microscope and SEM.

**Figure 4:** (a) An optical photo and (b) SEM cross-sectional photo of cured microcapsules.

**RELEASE TESTS AND RESULTS**

In order to verify the release principle and to prove the on-demand release capability from the microcapsules, four different tests are conducted.

**Size Transition Temperature**

Figure 5 shows the PNIPAm nanogels’ diameter versus temperature plot by using the technique of dynamic light scattering, which can determine size distribution of small particles in suspension or solution. This method has been widely used to determine the size of PNIPAm nanogels [14]. Experimentally, the nanogels are suspended in water at 0.15 ppm w/w, and heated by water bath from 29 °C to 39 °C. It is observed that the diameter of the nanogels decreased from 348.7 ± 3.4 nm at 29 °C to 275.4 ± 2.7 nm at 39 °C, with a transition temperature at about 32-33 °C.

**Figure 5:** Experimental characterizations of diameter versus temperature for the PNIPAm nanogels, measured by the technique of dynamic light scattering.

It is noted that the normal human body temperature is 37 °C, which is higher than the size transition temperature of PNIPAm nanogels. In order to utilize the size transition property of PNIPAm nanogels, we need to adjust its threshold temperature by the copolymerization of NIPAm with N-isopropylmethacrylamide (NIPMAm) and acry-lamide (AAm). For example, Hoare et al. has successfully adjusted the size transition temperature of nanogels form 32 °C to 46 °C [11].

**Induction Heating**

The induction heating experiments are conducted by using an induction heater (under RF frequency 15MHz, 800W). A membrane with thickness of 125±25 µm made of the same shell composition and cured under UV light (23.4 mW/cm², 365 nm wavelength) is placed between two glass slides and observed by an infrared camera (FLIR A320). The emissivity of the membrane is characterized as 0.98. Figure 6a shows the temperature changes of the membrane during the induction heating process showing controllable temperature with respect to heating time.

**Figure 6:** (a) Measured temperature versus induction heating time for a fabricated 125µm-thick thermoresponsive composite membrane. (b) Measured absorbance intensity versus time in the test chamber. Without heating, there is no drug penetration. Under the treatment of heating at 40°C, the absorbance intensity increases over time in this one-hour characterization test. (c) The testing setup for (b).
Thermal Permeability

In order to verify the thermal permeability of the polymer composite, a membrane is sandwiched by two chambers (Side-by-Side cells, PermeGear, Inc.) [11] as shown in Fig. 6c. An oil dye (absorbance peak: 594 nm) is placed in the control chamber while heater water bath at 40°C is used to heat up the system. The specific absorbance testing results in Fig. 6b shows that under a 1-hour test, the specific absorbance spectrum increases continuously in the test chamber, implying that the oil dye in the control chamber has diffused through the membrane into the test chamber.

Release Test on Microcapsules

Fabricated microcapsules with mineral oil mixed with fluorescent dye (Nile Red) inside are immersed in mineral oil and heated by the induction heater. It is found that without the inductive heating, the light intensity remains strong after 60 minutes. Under the induction heating, the light intensity decreased as the dye concentration reduces over time, implying that the microcapsules were remotely triggered to release drug by the inductive heating.

CONCLUSION

We have developed a new class of microcapsules for remotely triggered drug delivery applications by core-shell droplets via the microfluidic/optofluidic flow focusing technique. The shell material contains UV curable PEGDA with embedded thermal sensitive PNIPAm nanogels and iron oxide nanoparticles which can be heated up remotely by induction heating. The resulting shrinkage of nanogels causes the release of the drug agent from the core. Size property of PNIPAm nanogels has been characterized with a transition temperature at about 32 °C. Induction heating test on a 125 µm-thick membrane of the same shell material has shown that iron oxide nanoparticles can be induction heated to increase the temperature of the membrane over the transition temperature of the PNIPAm nanogels. Thermally triggered release tests have further proved the increased permeability of the shell material. Finally, the decrease of fluorescent concentration in the core of the prototype microcapsules under induction heating has proved the on-demand drug release capability of the microcapsules.

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REFERENCE


CONTACT
X. Li, tel: +86-1352-139-7719; Lixinhao11@gmail.com