New All-nanoparticle Microcapsules for Ultrasound and Laser Remote Release

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Abstract

Being extra strong but super easy to break – entities with such properties would be desired for many applications, particularly in drug delivery, where polyelectrolyte multilayer capsules took a prominent place due to applications in catalysis, intracellular delivery, and carriers of biomolecules and enzymes. Assembly of such capsules has been typically performed either by using polymers or a mixture of polymers and nanoparticles, which facilitated improvement of mechanical properties. In this work, we have assembled a new type of microcapsules, where multilayers are constructed solely by using nanoparticles in all layers. X-ray diffraction (XRD) studies confirmed the dissolution of calcium carbonate, while mechanical properties of such capsules probed by atomic force microscopy (AFM) reveal an essential increase in the stiffness and density in the walls. Dual functionality of such new capsules has been achieved by actions of ultrasound and laser. Since ultrasound acts more effectively on denser objects, low intensity (below 1 W/cm^2) of ultrasound has been used to enable release of encapsulated content. Laser has been used to illuminate microcapsules located in cells and effective killing of cells was achieved. Further applications of the assembled microcapsules are expected in conducting catalytic reactions and biomedicine.

Keywords: polymers, microcapsules, nanoparticles, layer-by-layer, cells

1. Introduction

At present, various drug delivery carriers are developed for biomedical applications and theranostics, where both delivery and diagnostics are sought. Incorporation of both functions in a carrier is targeting diagnostics applications. There, a challenge is the development of vehicles which deliver drugs to the target lesion and open a possibility of remote control, monitoring, and the release of biologically active cargos. Designing and developing novel drug delivery carriers with various materials gained increasing attention during the past decade [1,2]. Various stimuli-responsive microcapsules have been prepared so as to control the release of loaded cargos. The stimuli for trigged opening can be logically sort into three categories, including physical, chemical and biological. [3] Most of them are sensitive to single stimulus to achieve individual function. [4,5] At present, multifunctional microcapsules which are sensitive and responsive to multiple exposures have exhibited a great potential at diverse application fields such as cell biology, diagnostics, therapeutics, and nanoanalytics [2,6–8]. These “smart” microcapsules, which are capable of broadening the application of such agriculture is significantly increasing because of their wider and tunable functionalities and now the performance of single-responsive microcapsules is not satisfactory. Such versatile tool involves the incorporation of different types of polymers and nanoparticles used in fabrication of multilayer shell. Among various candidates, the nanoparticles have found special interest in the fabrication of these microcarriers which give the vehicle new properties [9,10]. Novel metal nanoparticles, for example, silver and gold particles entrapped in a polyelectrolyte multilayer can lead to localized temperature rise and the trigger the release of thermal sensitive capsules [11,12]. New generation of micro- and nano- carrier design need to possess strong mechanical properties, high loading capacity of encapsulation and enable versatile methods for releasing of encapsulated cargos.

Mechanical properties of microcapsules are important for assuring successful delivery of encapsulated materials. Initial studies of mechanical properties were conducted by the so-called Atomic force microscope (AFM) colloidal probe approach, where a large bead is mounted on a tipless cantilever [13]. For this characterization, microcapsules were pressed with a colloidal probe AFM coupled with a fluorescence microscope to simultaneously measure forces and track the release of the encapsulated cargo.[14] Eventually, it was shown that weak microcapsules cannot deliver encapsulated cargo inside cells, while stronger capsules facilitated this delivery.[15]

Loading capacity and loading efficiency are important parameters for practical applications of microcapsules. Earlier, it was shown that loading of the produced anisotropic particles is an important aspect for their application as carriers of small and large molecules of biological and biomedical interest.[16] Meanwhile, the release of encapsulated agents is possible by using three main types: chemical, physical or biological stimuli.[3] For example, pH,[17] ionic strength,[18] solvent,[19] ultrasound,[20] temperature,[21] light[22] and an enzymatic degradation[23] have been used to trigger release of encapsulated material from polyelectrolyte multilayer capsules. In this regard, using ultrasound or laser for release is particularly attractive. For ultrasound, one can perform release deeply inside the tissue or conduct catalytic reactions.[24] Since ultrasound is absorbed by optically more dense materials, enhancing the polymeric shell by inorganic particles has been shown in many different reported cases.[25,26] Recently, low intensity ultrasound (LIUS) assisted therapy was proposed as an effective tool to reduce the potential damage to the surrounding normal body by shorting the required exposure duration (REF). Compared with high intensity ultrasound (HIUS), the acoustic intensity of LIUS focused on a target area was usually only 0.125–3 W/cm^2, these effects can facilitate drug delivery and release.[27] Enhancing the walls of microcapsules by silica nanoparticles has been shown to affect and increase efficiency of their activation by ultrasound.[28] There was a recent study that ultrasound was used for delivery through blood-brain-barrier.[29] The latter, using laser, is particularly important in biotechnology due to low absorption of biological materials in that biologically “friendly” window - the near-infrared (NIR) part of the spectrum.[30,31] The polyelectrolyte multilayer capsules functionalized with metal nanoparticles which worked as the absorption area for energy provided by a laser source. These adsorption area can lead to local heating up that destroy the surrounding polymer substrate and let the encapsulated molecules to permeate out of the shell.[11,12,22]

In this work, we have assembled polyelectrolyte multilayer capsules using only nanoparticles (silver and gold) in their layers of shell (utilizing the Layer-by-Layer (LbL) approach). We have investigated the loading efficiency and loading capacity of such capsules as well as probed their mechanical properties using the colloidal probe AFM technique. Subsequently, all-nanoparticle microcapsules were exposed to low intensity ultrasound (LIUS) for triggering release of encapsulated cargo. In addition, remote intracellular activation of microcapsules was triggered upon short laser illumination that would kill cancer cells.

2. Materials and methods

Materials and Reagents

Gold(III) chloride trihydrate ($HAuCl_4$, ⩾99.9%), D-(+)-Glucose ($C_6H_{12}O_6$, 180.16 Da, ⩾ 99.5%), Tetraoctylammonium bromide (TOAB, $[CH_3(CH_2)_7]_4N(Br)$, 98%), Toluene (99.8%), Sodium sulfate anhydrous (Na_2SO_4 ,>99.0%), 4-dimethylaminopyridine (DMAP, $C_7H_{10}N_2$, ⩾ 99%), Sodium carbonate (Na_2CO_3, ⩾ 99.5%), Calcium chloride ($CaCl_2$, ⩾ 93.0%), Ammonium hydroxide solution (28.0-30.0% NH_3 basis), Silver nitrate ($AgNO_3$, ⩾99%), Sodium borohydride ($NaBH_4$, 99%) and TRITC–Dextran (65,000-85,000 Da) were purchased from Sigma-Aldrich. In all experiments, Milli-Q water with resistivity higher than 18.2 MΩ cm was used.

Particles Synthesis

Spherical calcium carbonate microparticle core was produced via a modified previous reported protocol. [32] In briefly: 1 mL of Na_2CO_3 (0.33 M) was injected with agitation into a glass beaker and subsequently an equal volume of $CaCl_2$ (0.33 M) was injected and stirred at 600 rpm for 60 seconds. The mixed solution turned opaque instantly. Then, the slurry was collected and washed with 70% ethanol for three times. At last, the powder was dried in an oven at 70 °C overnight.

Loading of TRITC–Dextran on $CaCO_3$ Particles

The encapsulation of TRITC–Dextran molecules into microparticles was conducted via two different strategies including coprecipitation and adsorption as follows. TRITC–Dextran with final concertation of 0.5 mg/mL was pre-mixed with calcium and carbonate stock solution (0.33 M), respectively, before the synthesis of $CaCO_3$ particles was proceeded by coprecipitation. Then, $CaCO_3$ particles with TRITC–Dextran were synthesized as mentioned above. 1 mL of 0.5 mg/mL TRITC–Dextran was mixed with 10 mg $CaCO_3$ particles and was further stirred at 600 rpm for ~30 minutes. The $CaCO_3$ particle suspension was centrifuged (3000 rpm, 3 min) and washed once with deionized water. The supernatants were collected for the following loading efficiency and capacity estimation.

The synthesis of the microcapsule

The design and synthesis process of composite all-nanoparticle capsules is shown in Figure 1. Hollow all-nanoparticle microcapsules were fabricated as follows. Basically, all-nanoparticle

microcapsules were formed by employing AgNPs and AgNPs alternately or sole AgNPs on the $CaCO_3$ templates and then removing the cores. Subsequently, they were washed with deionized water and used for further work. 10 mg of $CaCO_3$ microparticle powder dissolved in 1 mL of deionized water. A total of 200 µL of fresh $[Ag(NH_3)_2]OH$ reagent was reduced by 200 µL 5% D-glucose on the core to form the first layer after stirring for one hour. After that, AgNPs coated $CaCO_3$ microparticles were washed three times by water. After washing steps, 1 mL prepared gold nanoparticles with a modified method [33] were added and stirred for 15 minutes for the fabrication of the next layer after 3 minutes of the ultrasound treatment. After the incubation process, the sediment was washed and repeated with same gold nanoparticles for second layer until the supernatant shows red color to confirm the formation of nanoparticles. The sacrificial $CaCO_3$ core was dissolved with a concentration of 0.2 M at pH 7 EDTA solution. Further, excessive EDTA salt was removed by washing with deionized water several times. 6 layers silver microcapsules were fabricated by purely employing silver particles as the silver-gold capsules above.

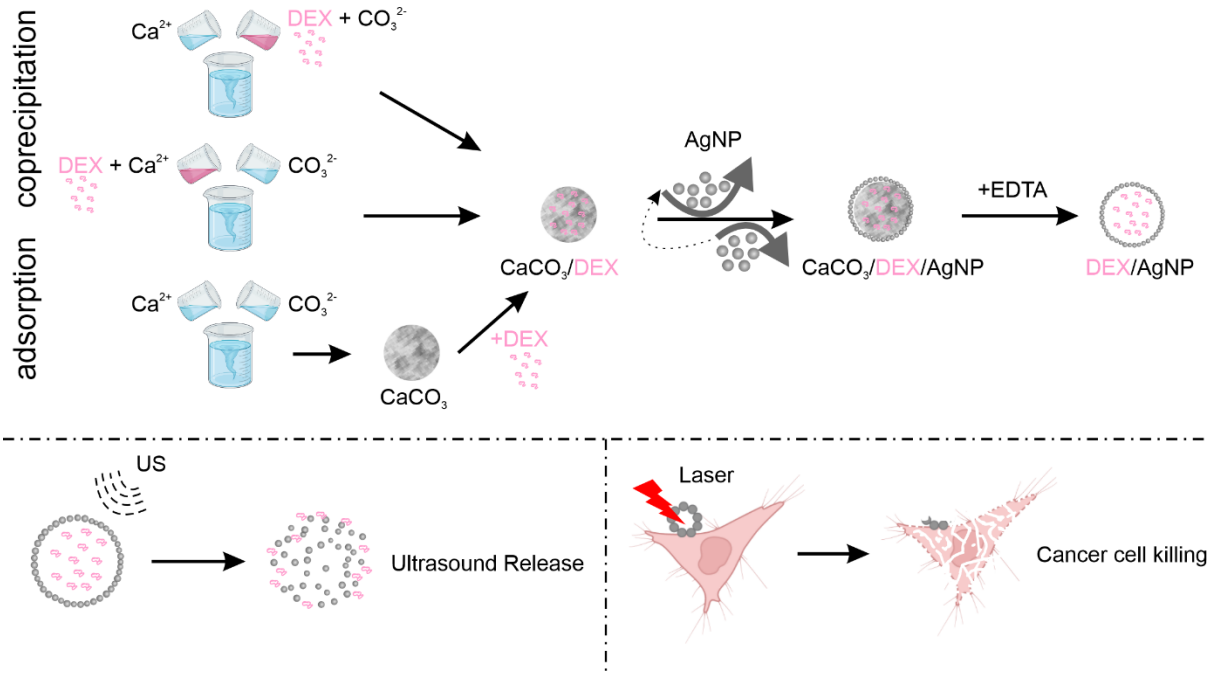

Figure 1. Schematics of the experiment showing major steps employed for the preparation and release process of all-nanoparticle capsules.

Effects of LIUS on all-nanoparticle microcapsules

In our experiments, a ultrasound bath used to destroy the shells, was employed as the stimulus for the microcapsules. In order to study the release process, three equal samples were prepared for each of two classes of all-nanoparticle microcapsules. A total of 1 mL of the microcapsule

suspension was placed into 2 mL Eppendorf microtubes. These Eppendorf tubes were placed in the LIUS bath (frequency 35 kHz and power density 0.64 W/cm^2) and processed up to 3 hours. During the whole process, a hand-made chilled water system was employed to maintain the temperature at 22 °C. Aliquots were successively taken out from the tubes at fixed time intervals (1, 5, 10, 15, 30, 45, 60, 90, 120, and 180 min after treatment). The released molecules were investigated in supernatant solution via UV/vis spectroscopy, and the number of crashed microcapsules was investigated via scanning electron microscopy (SEM).

Investigation of mechanical properties

For all particles, the mechanical strength was analyzed using atomic force microscopy (AFM), (Nanowizard 4, Bruker/JPK BioAFM). For these force measurements an in-home made colloidal probe was used. Hereto, a 30 µm diameter sphere was mounted onto a tip-less cantilever (AIO-TL, BudgetSensors) with a spring constant of 40 N/m. Measurements for all particle types were performed in liquid environment. Repeated force measurements were performed on the different particles to determine their mechanical properties. During these force measurements a setpoint of 500 nN was used. The parameter represents the mechanical properties is the slope. It is a measure for material stiffness and is calculated in the indentation portion of the indentation curve. The unit of this parameter is N/m and it represents how much force is needed to indent the sample over a certain distance. For each sample, the mechanical properties of at least 10 particles were analyzed. Data processing of the collected force curves was performed in the JPK data processing software (version: 6.1.172).

The XRD patterns of the samples were recorded using a powder X-ray diffractometer (Rigaku MiniFlex, Rigaku Ltd., Japan) with Cu-Kα radiation (40 kV, 15 mA, NiCKβ-filter, 1.5406 Å) in the 2Θ angle range from 20 to 80° with a scanning step of 0.01° and a rate of 7°/min. Data were evaluated using the integrated X-ray powder diffraction software SmartLab Studio II and Database pdf4.

Cell cultivation

Hela cells were cultured in Dulbecco's modified eagle medium (DMEM) (Lonza, cat: 12-604F) supplemented with 10% FBS (ThermoFisher, cat: 10500-064) and 1% penicillin/streptomycin (Sigma, cat: P4333). The media were replaced every 3 days, and the cells were maintained in a humidified incubator at 5% CO_2 and 37°C (Innova CO-170, New Brunswick Scientific). Hela cells were seeded into 96-well cell culture plates at a cell density of 10^4 per well in the culture medium and incubated overnight at 37 °C and 5% CO_2. After incubation, both capsules

(Ag/Au) ×4 and (Ag)×6 in concentrations 10, 25, and 50 capsules/cell were added to the wells and incubated for 24 h.

Laser action on cells uptake microcapsules

To analyse the effect of the laser light on the cells internalized microcapsules, the cells were placed on the stage of microscope and were exposed to a near-infrared laser with the wavelength of 785 nm. The incident power of the laser was 90 mW. Target cells with microcapsuels interior were exposed to this laser for a duration of 7 s. 40X (Nikon) objectives were used in these experiments.

3. Results and Discussion

3.1 Ultrasound Release

To study the release of payload activated by LIUS treatment, the suspension of different component of all-nanoparticle microcapsules were placed on the US bath for up to 180 min. The percentage of crashed microcapsules was investigated by SEM images (Figure 2). The microcapsules present completed hollow shell structer before ultrasound stimulu as shown in Figure 2a-c. LIUS can make all microcapsules crash effiently as shown in figure 2d-f. Most of microcapsules with 6 layer of silver nanoparticles or 3 bilayers of silver and gold have been collapsed, but only 76% of (Ag/Au)×4 capsules crashed (Figure 2g) after 180 min,. Short exposure time did lead to a significant amount of crashed microcapsules with 6 layers, especially sole silver nanoparticle microcapsules deformed almost 70% within 15 min (Figure 2g). The percentage of crash microcapsules is found to follow equation $y = k*t^n + b$, whose fitting is shown in Figure 2g with correlation coeficient above 0.96. The (Ag/Au) have a comparable behaviour with diference in how many particles cracked already before treatment which correlate with a positive value of parameter b (0.36 and 0.18 respectively). The samples contained the only silver nanoparticles has a less initial amount of the cracked but look more fragile and has a burst increased of the damaged particles in 10 mintues which realize in higher coefficent (k=0.41) with lower power (n=0.17). SEM images (Figure 2d-f) show that micaocapsule shell with 8 layers appeared to be more firm than these microcapsules composed with 6 layers since it has thicker coating. Due to this fact, microcapsules with shell of 6 layers were choosen for further release investigation.

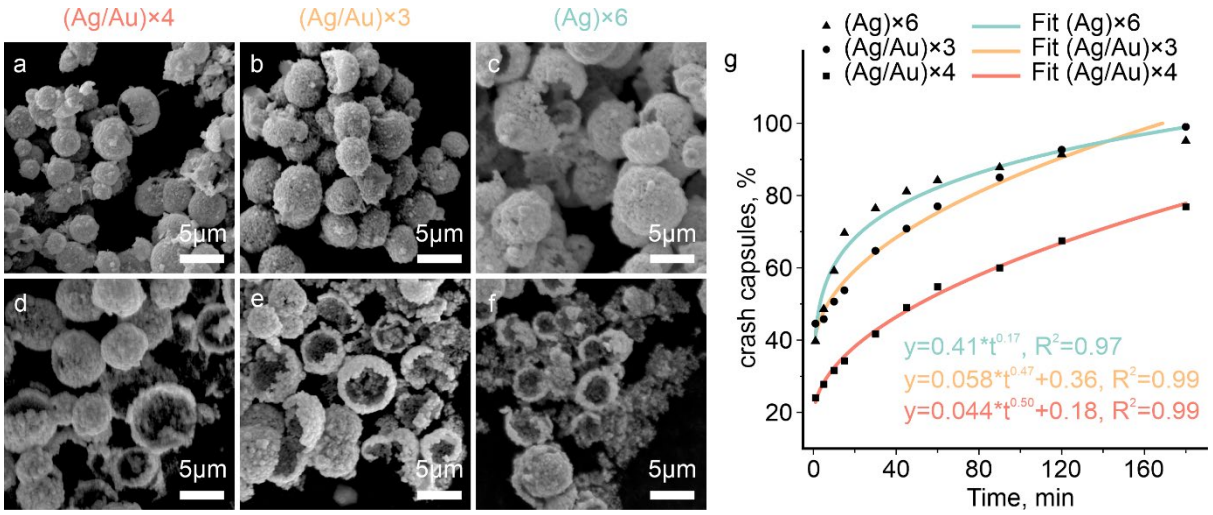

Figure 2. SEM images of the hollow microcapsules fabricated with different layers, before US treatment: (a) (Ag/Au) ×4, (b) (Ag/Au)×3 and (c) (Ag)×6; after the US treatment: (d) (Ag/Au) ×4 (e) (Ag/Au)×3 and (f) (Ag)×6. The duration of US treatment is 60 min. (g) Number of crashed microcapsules dependence on the period of US treatment with fitting curves.

Loading of produced microcapsules is an important property for their application as vehicle of various molecules of biological and medical aspect. Subsequently, the capsules fabricated by 6 layers of silver nanoparticles were chosen to investigate the loading and release behavior. There are various strategies to encapsulate small molecule into microcapsules. We studied the loading capacity (LC) and loading efficiency (LE) of TRITC–Dextran containing particles using two different methods coprecipitation and adsorption to determine the concentration of dextran sulfate, a type of model macromolecule, untreated and treated with LIUS. For particle loading capacity, two different factors size and shape play a important role.[16] As we utilized same $CaCO_3$ particles as the template, Figure 3 shows different strategies did not show significant difference for loading capacity. The loading capacity of all strategies were low, but still over 0.2 μg for 10^9 $CaCO_3$ particles. However, the LE of adsorption present a higher efficiency reaching 55% compared to two coprecipitation methods showing 42% and 49% respectively.

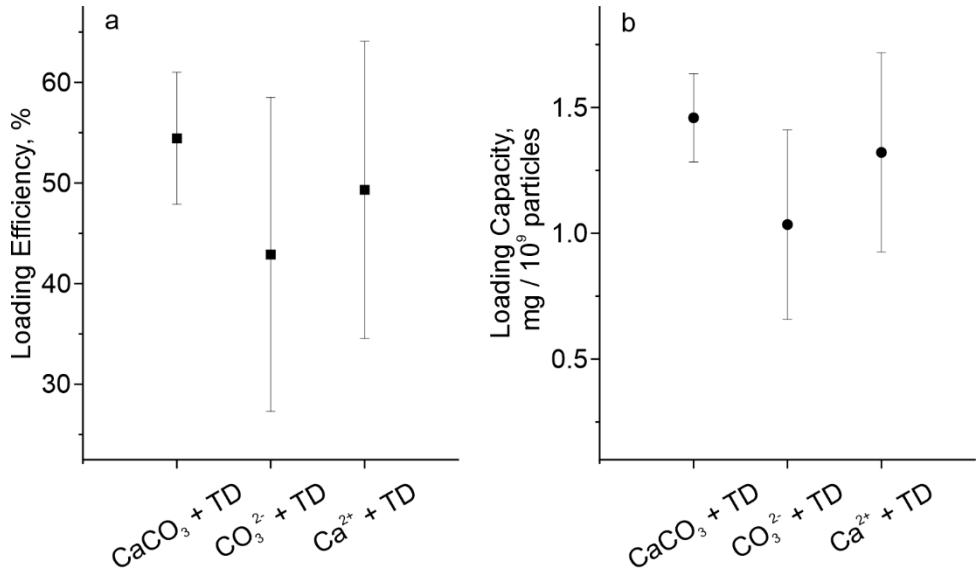

Figure 3. Loading efficiency (a) and capacity (b) of TRITC–Dextran dependence on the encapsulation method: adsorption and coprecipitation.

In addition, fluorescence images (Figure 4) were used to confirm the presence of molecules inside the particles. Silver nanoparticle microcapsules loaded with TRITC–Dextran were treated by US in an aqueous solution under the same condition as earlier described up to 180 min. Aliquots from 180 min interval were collected and characterized using a fluorescence microscope. The capsules displayed spherical shape without US treatment. These capsules were crashed into small fragments and did not keep the original shape. The fluorescence images reveal that TRITC–Dextran was successfully embedded in the structure of silver nanoparticle microcapsules and released from capsules triggered by LIUS (Figure 4).

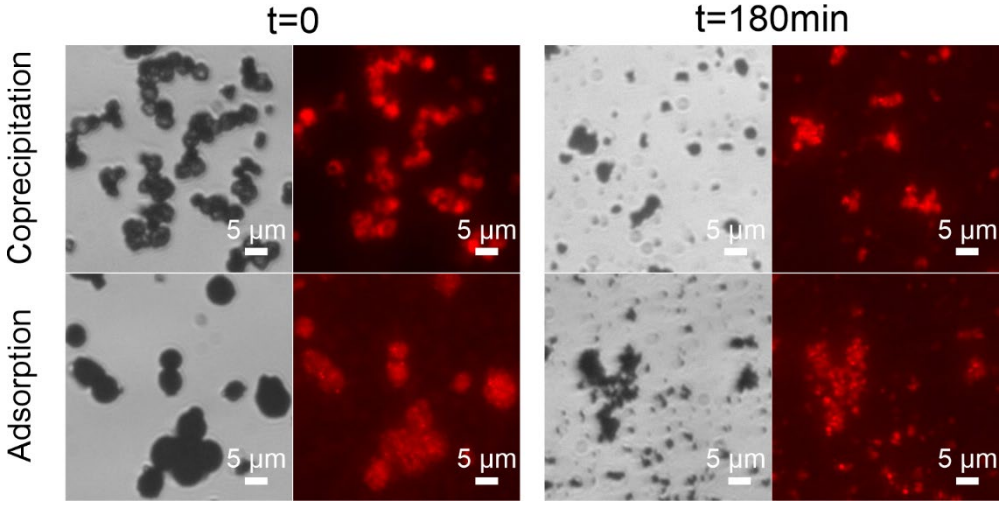

Figure 4. Fluorescence microscopy images of the silver nanoparticle capsules loaded with TRITC–Dextran by two different strategies (coprecipitation and adsorption) treated with US for 0 min and 180 min.

3.2 Mechanical properties of microcapsules

Mechanical properties of microcapsules were investigated by the so-called colloidal probe AFM approach, in which a large bead is mounted on a tipless cantilever. Subsequently, the cantilever is brought in contact with capsules and forces were measured.

The parameter that is represented here is the slope, which is a measure for material stiffness and is calculated in the indentation portion of the indentation curve. The unit of this parameter is N/m and it basically represents how much force is needed to displace the sample over a certain distance. Our colloidal probe AFM studies proved that for the same applied load, all-nanoparticle capsules deform somewhat differently depending on the composite of shell. Deformation increases with increasing the number of layers, while the 8-layer all-nanoparticle capsules are the softest (Figure 5a). This property is essentially different in comparison to microcapsules constructed from polymers, in which the stiffness was increased upon increasing the number of layers.[34] The shell with $CaCO_3$ core inside was found to be stiffer compared to the same hollow shell composite (Figure 5a), while the XRD measurements (Figure 5b,c) revealed that the calcium carbonate core was removed completely. It should be noted that ultrasound can be used to release encapsulated materials,[35] but destruction of capsules can be used to target and kill cells, as it is shown here on an example of remote activation of capsules on cells by laser.

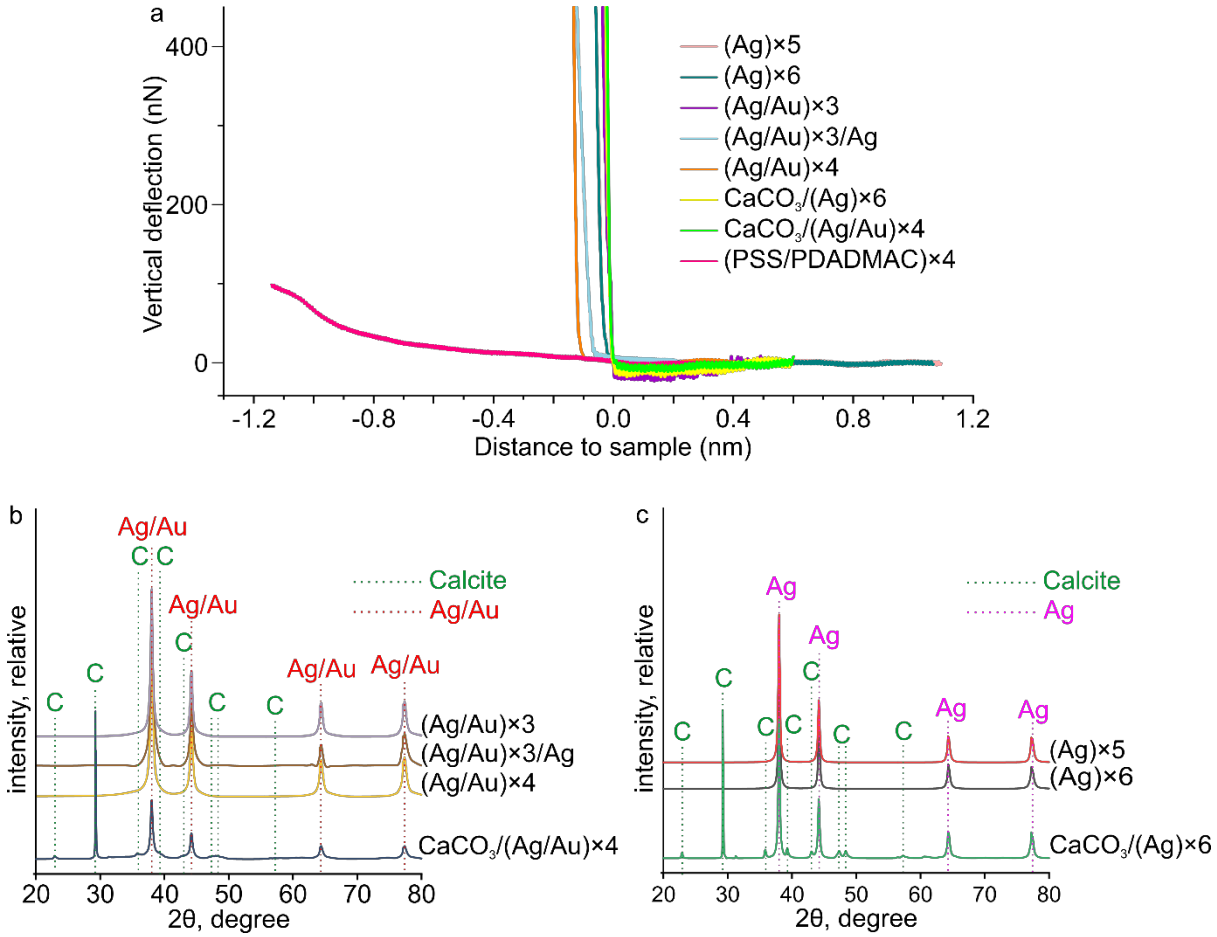

Figure 5. Force-deformation curves (a) for different composite of capsules. XRD diffraction spectra of (b) different composite of Ag/Au capsules and (c) different composite of Ag capsules, where the dash lines indicate silver/gold (red), silver (pink)and calcite (green).

3.3 Effect of near-IR laser light on cells with all-metal microcapsules

During these experiments, a laser with the wavelength of 785 nm which is located on the phototherapeutic window[36] was shined on the cells. In Figure 6 g-i, control cells are presented without any microcapsules inside. Illumination of a near-IR laser (785 nm, 90 mW power) for a duration of 7 s did not show any effects on the cellular morphology, which reveals the fact that these wavelengths do not affect tissue. This is consistent with our previous studies,[22,37] where no harmful effects were found by exposing cells to a near-IR laser. In figure 6c,f a significant morphology change, even a complete destruction, of the target cells can be easily found after a short irradiation of laser (7 s, 90 mW power).

Furthermore, the results of these experiments show interesting and novel approaches for future research and potential phototherapeutic applications, where efficiency still needs to be improved.[38,39] Furthermore, this demonstrated method can be also used for killing cells for fighting diseases and can even be combined with the release of entrapped drugs by remote

opening.[40] Such intracellular release can be used for investigating intracellular processes,[22] killing cancer cells[41] or releasing inside microorganisms[42,43]. Furthermore, one can anticipate to transfer this technology to assembling microcapsules with magnetic nanoparticles[44,45].

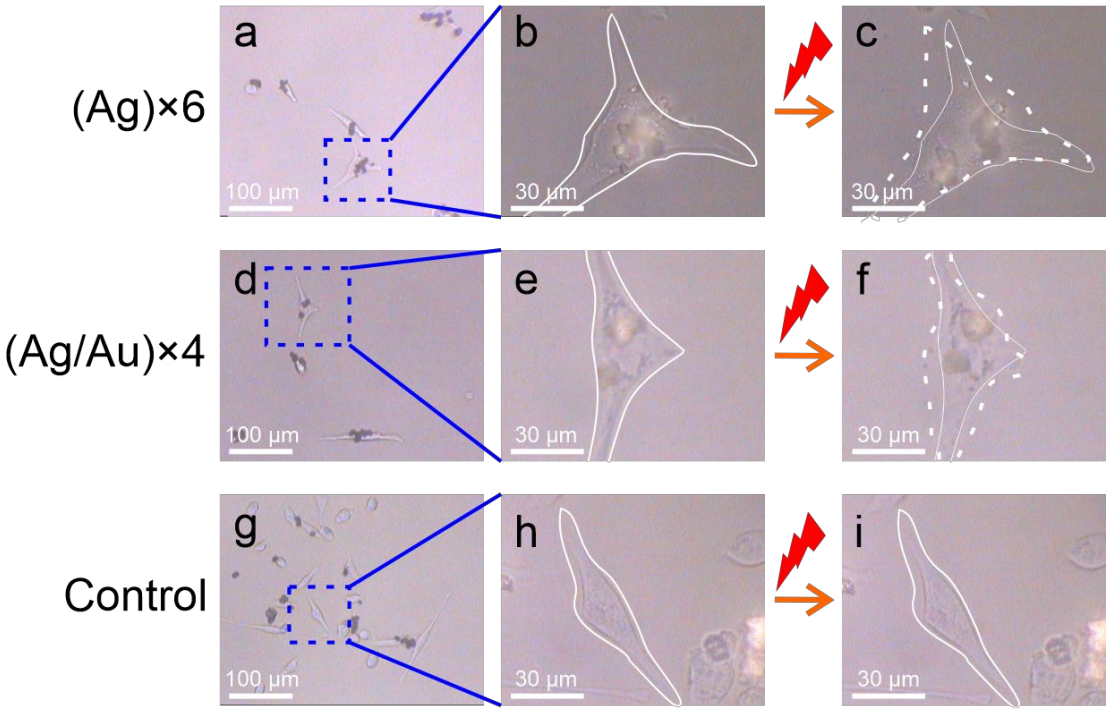

Figure 6. Transmission images demonstrating the destruction of Hela cells internalized microcapsules b, e and h) before, and c, f and i) after the laser beam illuminated the target cell. The red arrows indicate the target cells that were illuminated by laser. The inserted white lines indicate the form of cells before laser exposure (solid) and after (dashed). Control cells did not change the shape, so the cell before and after exposure is highlighted by a solid white line.

4. Conclusion

In conclusion, a new type of microcapsules is fabricated solely based on nanoparticles. The physico-chemical properties and the loading efficiency of these microcapsules were investigated. X-ray diffraction measurements confirmed complete dissolution of the calcium carbonate core. Subsequently, mechanical properties of all-nanoparticle capsules were studied using a colloidal probe AFM technique: it was found that all-nanoparticle capsules are stiffer comparing to the polymeric ones. In the following step, low intensity ultrasound (LIUS) was used for performing release from capsule, two types of all-nanoparticle microcapsules were deformed efficiently by LIUS and encapsulated TRITC–Dextran can be released by the

treatment of LIUS. In addition, the all-nanoparticle microcapsules have been shown to lead to cell death under laser illumination that would open the applications in theragnostic field. The presented all-nanoparticle microcapsules are robust and exhibit good loading capacity characteristics; they are expected to find extensive applications for catalytic reactions as well as carriers of enzymes and other biomolecules.

CRediT authorship contribution statement

Li Jie: Conceptualization, Formal analysis, Writing – original draft. **Van der Meeren Louis**: Formal analysis, Writing – editing & review. **Verduijn Joost**: Formal analysis, Writing – editing & review. **Parakhonskiy Bogdan V.**: Formal analysis, Writing- Reviewing and Editing. **Skirtach Andre G.**: Conceptualization, Methodology, Investigation, Data curation, Supervision, Writing – editing & review, Funding acquisition.

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