The 2013 World Congress on
Advances in Structural Engineering and Mechanics (ASEM13)
Jeju, Korea, September 8-12, 2013

Smart microcapsule membranes for stimuli-responsive controlled-release

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ABSTRACT

The target of a controlled drug delivery system is for an improved drug treatment (outcome) through rate-/time-programmed and/or site-specific drug delivery. Environmental stimuli-responsive controlled-release systems have been developed specifically for this purpose. These environmental stimuli-responsive release systems can release specified chemicals or drugs at a particular site where an environmental condition, such as temperature, pH or other information, is different from that at other sites. In developing environmental stimuli-responsive controlled-release systems, one of the important parameters is to reduce the response time of the release rate to stimuli. As the release rate from microcapsules is generally controlled by the thin microcapsule membrane, an increase in the release rate in response to stimuli may be expected when compared to gels and microspheres. Therefore, microcapsules with a thin membrane are suitable for stimuli-responsive controlled-release systems. Recently, the authors' group has developed efficient approaches to fabricate monodisperse microcapsules with stimuli-responsive membranes. For different application purposes, smart microcapsules with thermo-responsive, pH-responsive, ion-recognizable membranes are designed and successfully fabricated with either oil-in-water-in-oil double emulsions or water-in-oil-in-water-in-oil triple emulsions that generated via microfluidic approached as synthesis templates. In this presentation, the design, fabrication and performance of monodisperse smart microcapsules with stimuli-responsive membranes will be introduced and discussed.

1. Introduction

The target of a controlled drug delivery system is for an improved drug treatment (outcome) through rate- and time-programmed and site-specific drug delivery. Environmental stimuli-responsive controlled-release systems have been developed

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specifically for this purpose. These environmental stimuli-responsive release systems can release specified chemicals or drugs at a particular site where an environmental condition, such as temperature, pH or other information, is different from that at other sites. In developing environmental stimuli-responsive controlled-release systems, one of the important parameters is to reduce the response time of the release rate to stimuli. As the release rate from microcapsules is generally controlled by the thin microcapsule membrane, an increase in the release rate in response to stimuli may be expected when compared to gels and microspheres. Therefore, microcapsules with a thin membrane are suitable for stimuli-responsive controlled-release systems.

Recently, the authors' group has developed an efficient microfluidic approach to fabricate monodisperse microcapsules with stimuli-responsive membranes. For different application purposes, smart microcapsules with thermo-responsive (Chu 2007; Liu 2010; Wang 2009), pH-responsive (Liu 2011a; Wei 2011), ion-recognizable (Liu 2011b; Pi 2010) membranes are designed and successfully fabricated with either oil-in-water-in-oil (O/W/O) double emulsions or water-in-oil-in-water-in-oil (W/O/W/O) triple emulsions that generated via microfluidic approached as synthesis templates. In this presentation, the design, microfluidic fabrication and performance of monodisperse smart microcapsules with stimuli-responsive membranes will be introduced and discussed systematically.

2. Monodisperse Thermo-Responsive Microcapsule Membranes Prepared with W/O Single Emulsions as Templates

In biomedical fields, microcapsules are widely investigated as effective drug delivery carriers for the treatment of deadly diseases such as cancer. Because most anticancer drugs have harmful side effects on normal tissues, the most ideal delivery carriers should be able to transport and release the anticancer drugs specifically to the targeted tumor site without drug leakage during the transport process. Up to now, numerous studies have been conducted on using an external magnetic field for targeted drug delivery by incorporating magnetic nanoparticles into drug delivery carriers. Some stimuli-responsive carriers, such as core/shell microparticles and microcapsules functionalized with magnetic nanoparticles, have been designed for magnetic-guided drug delivery and subsequent controlled drug release by an external trigger such as temperature, pH, ultrasonic and high frequency magnetic field. Most of the carriers mentioned above were designed for hydrophilic drugs. However, it is worth noting that currently available anticancer drugs such as paclitaxel and carmustine are usually lipophilic molecules. Therefore, design of carriers for lipophilic drugs is of great importance and necessity. Recently, the author's group developed on a novel type of monodisperse stimuli-triggered self-bursting microcapsule with oil core for encapsulating lipophilic substances.

Fig.1 schematically illustrates the concept of the as-proposed thermo-induced self-bursting microcapsule with magnetic-targeting property and its fabrication procedure. The proposed microcapsules are monodisperse and each of them has a core/shell structure comprising an oil core and a thermo-responsive membrane composed of crosslinked PNIPAM hydrogel and homogeneously embedded superparamagnetic Fe_3O_4 nanoparticles (**Fig.1a**). The expected oil-core/polymer- shell structure and monodispersity can be achieved by using a microfluidic fabrication technique. The oil

core can be used to encapsulate lipophilic drug molecules. In the PNIPAM hydrogel membrane, the embedded Fe_3O_4 nanoparticles contribute a magnetic-response property to the microcapsule and the PNIPAM network makes the shell thermo-responsive. As a result, the Fe_3O_4/PNIPAM shell enables the microcapsule to undergo magnetic-guided targeting delivery, have no unintended drug leakage during microcapsule transport, and exhibit thermo- triggered drug release.

Because the microcapsules are fabricated at temperatures below the LCST, the as-prepared microcapsules are initially in a swollen and hydrophilic state. Because the encapsulated oil phase and loaded lipophilic chemicals inside the microcapsule are immiscible with, or insoluble in, aqueous solutions, there is no way for them to pass through the hydrophilic PNIPAM membrane via solution/diffusion when the temperature is below the LCST, although the concentration gradient exists between inside and outside of the microcapsule. Therefore, when the microcapsules are stored, transported, or delivered at temperatures below the LCST, there is no leakage of encapsulated lipophilic substances from the microcapsules. After the microcapsules reach the desired site via magnetic guide, a burst release of their encapsulated lipophilic substances can be triggered by an external thermal stimulus, *e.g.*, local heating. When the environmental temperature is increased from one below the LCST to another one above the LCST, the PNIPAM membrane shrinks rapidly. During the membrane shrinkage process, internal pressure in the oil core gradually increases because the oil phase is incompressible. When the internal pressure reaches a certain critical value, the PNIPAM membrane ruptures due to its limited mechanical strength. Such dramatic shrinkage and final rupture of the PNIPAM membrane squeeze the oil core out from the microcapsule with a strong boost to the environment. In such a release process, the loaded lipophilic drug molecules are released, together with the ejecting burst of the encapsulated oil phase from the microcapsule, which leads to not only rapid release but also complete release (**Fig.1**).

The fabrication procedure of the microcapsules consists of three major steps as follows. Briefly, the first step is to prepare superparamagnetic Fe_3O_4 nanoparticles and modify them with a silane-coupling reagent to introduce polymerizable groups (**Fig.1b**), the second step is to prepare monodisperse oil-in-water-in-oil (O/W/O) double emulsions as templates for subsequent core/shell microcapsule preparation (**Figs.1c** and **1d**), and the third step is to synthesize the PNIPAM microcapsule membrane via photo-initiated polymerization. Since the aqueous solution containing NIPAM monomer and well-dispersed Fe_3O_4 nanoparticles with polymerizable groups was used as the middle aqueous phase, a superparamagnetic and thermo-responsive PNIPAM hydrogel membrane can be obtained after polymerization of the middle aqueous phase initiated by UV irradiation (**Fig.1e**).

The polymerized microcapsules are featured with oil-core/PNIPAM-membrane structure (**Fig.2a**). Sudan III, an oil soluble industrial dye, is used as a model chemical to demonstrate the ability of these microcapsules to load lipophilic chemicals or drugs. In microcapsules loaded with Sudan III, the inner oil cores exhibit a red color (**Fig.2b**), which is different from the color of the pure oil cores shown in **Fig.2a**. The lipophilic Sudan III molecules dissolved in the inner oil core are protected by the membrane and could not permeate through the PNIPAM membrane of the microcapsule at temperatures below the LCST because no solution/diffusion of lipophilic substance in

the hydrophilic membrane is available. Since the PNIPAM membrane could protect the inner oil core against various instability processes, such as aggregation and coalescence, the oil-core-containing microcapsules is a better microcarrier than emulsions, which are usually employed as delivery systems for lipophilic drugs but are intrinsically thermodynamically unstable.

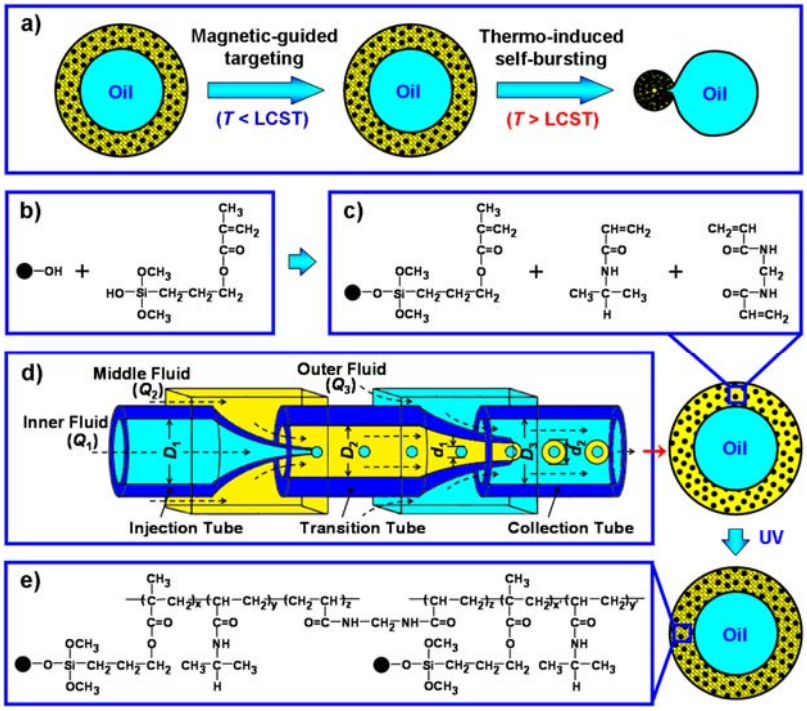

Fig.1. Schematic illustration of the concept of the proposed thermo-induced self-bursting microcapsule with magnetic-targeting property (a) and its fabrication procedure (Wang 2009). (b) The Fe3O4 nanoparticles with hydroxyl groups and silane-coupling reagent. (c) Aqueous phase containing MPTMS-modified Fe3O4 nanoparticles, NIPAM monomer and MBA crosslinker for fabricating microcapsule shell. (d) Capillary microfluidic device used to prepare monodisperse O/W/O double emulsions. (e) The chemical structure of the microcapsule shell after UV-initiated polymerization.

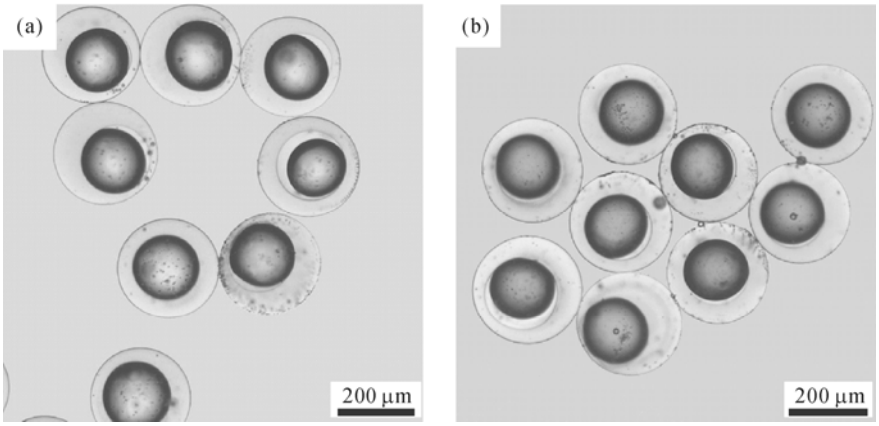

Fig.2. Optical micrographs of monodisperse microcapsules with pure oil core (a) and with Sudan III-loaded oil core (b) in water at 20 °C (Wang 2009).

Owing to the shrinkage of the thermo-responsive PNIPAM microcapsule membrane upon heating, a thermo-induced self-bursting release performance can be achieved by increasing the environmental temperature across the LCST. **Fig.3a** illustrates the burst release of the inner oil core from the microcapsule when temperature is increased from 20 °C to 60 °C. With an increase in the temperature, the thermo-responsive PNIPAM membrane of the microcapsule shrinks dramatically. Since the inner oil core is incompressible but the internal pressure in the oil core keeps increasing, due to the membrane shrinkage, the PNIPAM membrane finally ruptures because of the limited mechanical strength, which results in a burst release of the inner oil core **(Figs.3a3** to **3a4**). With the shrinkage and rupture of the PNIPAM membrane, the inner oil phase is squeezed out of the microcapsule within a very short time, and spreads fast into the surrounding environment. As a result, the release from such a microcapsule is complete, leaving just a hollow cavity without any leftovers inside the microcapsule (**Fig.3b**). Such a rapid and complete burst release of the encapsulated oil phase and lipophilic chemicals means that a high local drug concentration can be rapidly achieved. To determine the release rate of the inner oil core, we investigated the burst release behavior during the first 3.2 s after the PNIPAM membrane ruptures (**Fig.3c**). The optical microscope snapshots show that the encapsulated oil phase shoots out very quickly due to the strong boost resulting from shrinkage and the squeeze function of the microcapsule membrane. In addition, the radius of the circular edge of the released oil phase increases by ~250 μm within 3.2 s. This spread speed is much faster than that in diffusion-driven release systems. Such a quick release and spread rate may make our microcapsules be of specific interest and significance, especially in certain cases where released substances need to cross some media with high viscosity or low permeability.

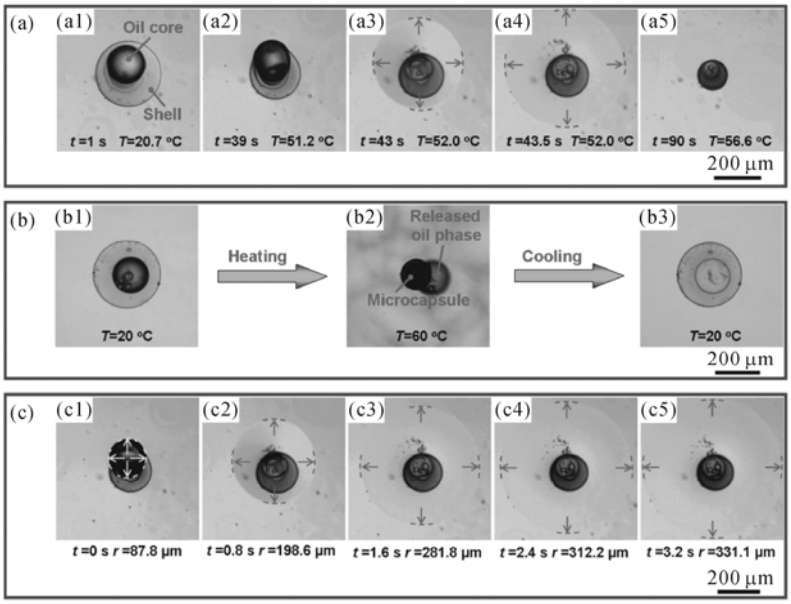

Fig.3. Optical microscope snapshots of the thermo-induced self-bursting behavior (a) and complete release performance (b) of the as-prepared microcapsules. (c) Thermo-induced burst-release process of inner oil core from the microcapsule (shown in (a)) during the first 3.2 s of release, in which time-dependent increase of the radius (*r*) of the circle edge of released oil phase is used to valuate the release rate (Wang 2009).

3. Monodisperse Thermo-Responsive PNIPAM Hollow Microcapsules Prepared with W/O/W/O Triple Emulsions as Templates

3.1 Thermo-Responsive Squirting Microcapsules for Nanoparticle Delivery

Nowadays, nanoparticles are becoming more and more prevalent in the fields of disease diagnosis and therapy. However, several challenges still remain for their practical applications, such as how to protect nanoparticles from premature degradation or unwanted interaction with biological molecules before reaching the targeted site, how to selectively deliver nanoparticles only to diseased tissue, and how to achieve a wide distribution of nanoparticles at the targeted site. Some promising nanoparticle candidates for drug delivery systems, such as protein nanoparticles, liposomes, micelles, usually exhibit low physical and chemical stability. Besides, micelles disassemble if they are diluted below the critical micelle concentration. Thus, nanoparticle delivery carriers are wanted to protect the stability of encapsulated nanoparticles and prevent them from degrading prematurely before delivery, and to deliver them only at the targeted site. For stimuli-triggered site-targeting delivery, the delivery triggered by physical contact may not be practicable in the human body, and delivery triggered remotely is more preferable. Furthermore, some biological tissues present diffusion obstacles for nanoparticles and/or their surrounding media are quite viscous, in which situations a higher initial momentum for the nanoparticle delivery is very important.

Some interesting delivery behaviour can be found in some plants in the natural environment when they eject seeds from fruits for the widest possible distribution. For example, the ripe fruit of *ecballium elaterium* (**Fig.4a**), also called squirting cucumber or exploding cucumber, is highly turgid. When it is ripe or is disturbed by sniffing animals or whatsoever, the ripe fruit squirts a stream of mucilaginous liquid containing its seeds into the air over a considerable distance by a sudden contraction of the wall of the fruit (**Fig.4b**). Inspired by the squirting cucumber, the author's group recently developed a novel thermo-triggered squirting capsule for nanoparticle delivery. The proposed microcapsule is composed of a crosslinked PNIPAM hydrogel membrane and encapsulates water-based nanoparticles by dispersing the aqueous phase that contains nanoparticles into its oil phase core (**Fig.4c**). Because the encapsulated nanoparticles exist in the water phase of the W/O emulsion core inside the microcapsule, the swollen and hydrophilic PNIPAM hydrogel membrane of the microcapsule can protect the encapsulated nanoparticles when the temperature is below the LCST (**Fig.4c**). To eject the encapsulated nanoparticles, what we need to do is just apply a heat stimulus to increase the local environmental temperature above the LCST. Upon heating, the PNIPAM hydrogel membrane shrinks rapidly, which results in a sudden increase in the liquid pressure inside the microcapsule, because both the continuous oil phase and the dispersed water phase in the capsule are incompressible. When the internal pressure increases to a critical value, the PNIPAM hydrogel membrane ruptures suddenly due to its limited mechanical strength. At the same time, the encapsulated nanoparticles are squirted out from the microcapsule together with the oil phase stream into the environment with great momentum (**Fig.4d**), just like the seed-ejection of a ripe squirting cucumber.

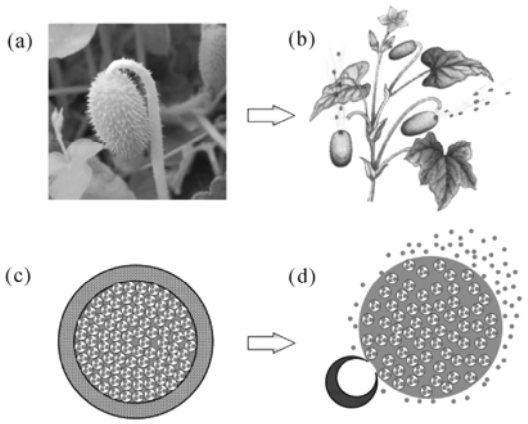

Fig.4. (a) A picture of squirting cucumber; (b) Schematic illustration of squirting cucumbers ejecting seeds together with a stream of mucilaginous liquid; (c) A microcapsule with crosslinked PNIPAM hydrogel membrane containing nanoparticles in the inner water phase of W/O emulsion core at temperature below the LCST; (d) Nanoparticles being squirted out from the microcapsule together with the oil phase stream due to the dramatic shrinkage and sudden rupture of PNIPAM hydrogel membrane triggered by an increase of temperature above the LCST (Liu 2010).

3.1.1 Primary W/O Emulsions Containing Nanoparticles

3 ml of water containing 0.2% yellow-green fluorescent (505/515) carboxylate-modified FluoSphere® polystyrene beads (200 nm, Invitrogen F8811) was employed as the water phase, and 7 ml of soybean oil containing 0.56 g polyglycerol polyricinoleate (PGPR 90, Danisco) as surfactant was employed as the oil phase. The two phases were mixed by magnetic agitation for 10 min and then homogenized (16,000 r/min, 1 min) by a BRT homogenizer (B25 10 mm head).

3.1.2 Microfluidic Preparation of (W/O)/W/O Emulsions

The microfluidic device for fabrication of (W/O)/W/O emulsions is illustrated in **Fig.5**. The prepared W/O primary emulsion containing nanoparticles was employed as inner fluid. The middle fluid was monomer aqueous solution containing surfactant Pluronic F127 (1% (w/v), Sigma-Aldrich), monomer NIPAM (1 mol·L^{-1}, Kohjin), crosslinker *N*,*N*'-methylenebisacrylamide (MBA) (0.02 mol·L^{-1}) and initiator 2,2'-azobis(2-amidinopropane) dihydrochloride) (0.005 mol·L^{-1}). Soybean oil containing 8% (w/v) PGPR was employed as the outer fluid. The inner, middle and outer fluids were separately pumped into the injection, transition and collection tubes of the microfluidic device. (W/O)/W/O emulsions generated in a collection tube were collected in soybean oil containing 2% (w/v) 2,2-dimethoxy- 2-phenylacetophenone (BDK) as photo initiator.

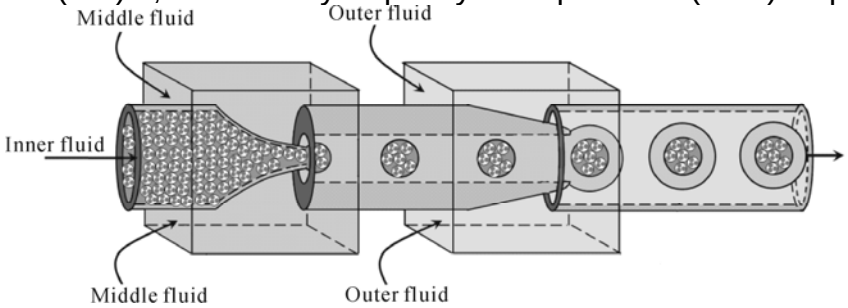

Fig.5. Schematic illustration of the microfluidic device (Liu 2010).

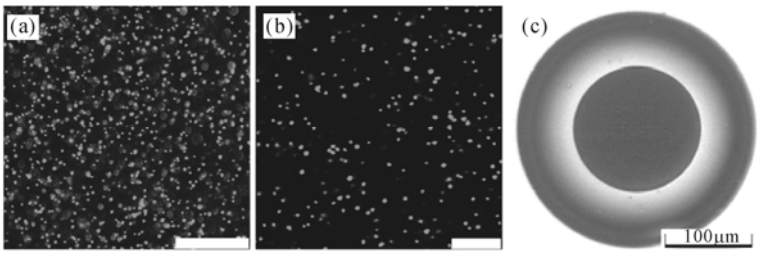

Fig.6. (a, b) CLSM images of primary W/O emulsion containing nanoparticles in the inner water phase at different magnification. Scale bars: (a) 25 μm; (b) 10 μm. To see the emulsion droplets more clearly, the emulsion shown here is diluted with soybean oil to one third of the original concentration before CLSM observation. (c) Optical microscope image of prepared (W/O)/W/O emulsions containing nanoparticles in the innermost water phase. Scale bar is 100 μm (Liu 2010).

The CLSM images of the primary emulsion show that the nanoparticle aqueous suspension forms droplets with a size ranging from 570 nm to 920 nm and disperse well in the emulsion without coalescence (**Figs.6a** and **6b**). The optical micrograph of a typical (W/O)/W/O emulsion droplet is shown in **Fig.6c**.

3.1.3 UV-initiated Polymerization of PNIPAM Microcapsule Membrane

The collected (W/O)/W/O emulsions were converted into microcapsules by polymerization with UV irradiation for 10 min in an ice-water bath. Under UV light, the activated photo-initiator BDK diffused to the interface between the outer oil phase and middle aqueous phase, where it initiated the polymerization of the NIPAM monomer and MBA crosslinker in the middle aqueous phase to build the hydrogel membrane of the microcapsules. A 250-W UV lamp with an illuminance spectrum of 250 ~ 450 nm was employed to produce UV light. An ice-water bath was introduced to ensure the polymerization was carried out at a temperature below the LCST of PNIPAM. The microcapsules were separated from oil by adding deionized water into the container. When the oil phase and water phase had separated completely, the capsules settled into the bottom water layer and the upper oil layer was removed. The microcapsules were washed with deionized water several times and then dispersed in water.

In a bright field under a microscope at room temperature (below the LCST), the PNIPAM hydrogel membrane is transparent while the inner primary emulsion is dark (**Fig.7a**). Actually, the thickness of the hydrogel membrane of the prepared microcapsule is not perfectly uniform along the circumference, as seen in **Fig.7a** This membrane thickness difference results from the density difference between the encapsulated W/O emulsion and the NIPAM monomer solution in the (W/O)/W/O emulsion. Although the density of both the inner W/O phase and the middle aqueous monomer phase has been adjusted carefully, a slight density difference does still exist, so the encapsulated W/O emulsion is not in the exact center of the (W/O)/W/O emulsion droplet. Consequently, the thickness of the polymerized hydrogel membrane is a little thicker on one side, but a little thinner on the other side, of the microcapsule. The CLSM fluorescent images illustrate that no leakage of nanoparticles from the prepared hydrogel capsule is observed (**Figs.7b and 7c**). This result is also assured by

the fluorescence intensity profile (**Fig.7d**). Inside the microcapsule the intensity is quite high (from 50 to 260), whereas the intensity outside is nearly zero. The innermost nanoparticle suspension is separated from the hydrogel membrane by the continuous oil phase of W/O emulsion inside the capsule, and the oil phase cannot permeate through the PNIPAM hydrogel membrane and then prevent the encapsulated nanoparticles from leaking.

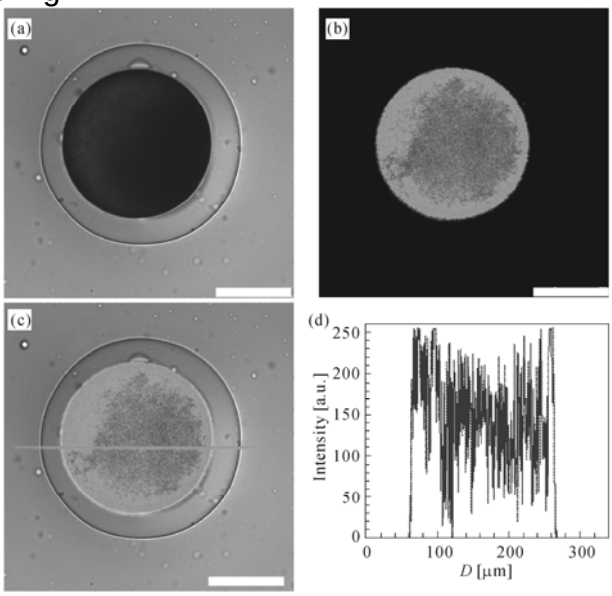

Fig.7. CLSM images of the prepared microcapsule at room temperature, in which (a) shows transmission channel image, (b) shows green channel image and (c) shows the overlay of green channel and transmission channel images. Scale bars are 100 μm. (d) Fluorescence intensity profile corresponding to (c) (Liu 2010).

3.1.4 Thermo-Responsive Burst Squirting for Nanoparticle Delivery

To observe the squirting of nanoparticles from the prepared microcapsules upon heating, a glass slide with a drop of microcapsule suspension is placed on a thermostatic stage under a microscope. When the temperature increases from 20 °C to 50 °C, the hydrogel membrane of the microcapsule shrinks rapidly. The inner oil phase cannot permeate through the shrinking hydrogel membrane, leading to deformation of the capsule. During the deformation in the thermo-triggered squirting process, the encapsulated W/O phase tends to breach the thinner side of the hydrogel membrane which is stretched by the incompressible inner oil phase. When the shrinkage reaches a high degree, the hydrogel membrane turns into an “8” shape, of which one head (the side with the thinner membrane) is full of the encapsulated W/O primary emulsion and the hydrogel membrane becomes extremely thin. When the inner pressure reaches a critical value, the hydrogel membrane ruptures and the contained oil phase, together with the encapsulated nanoparticles, are squirted out into the surrounding water (**Fig.8**).

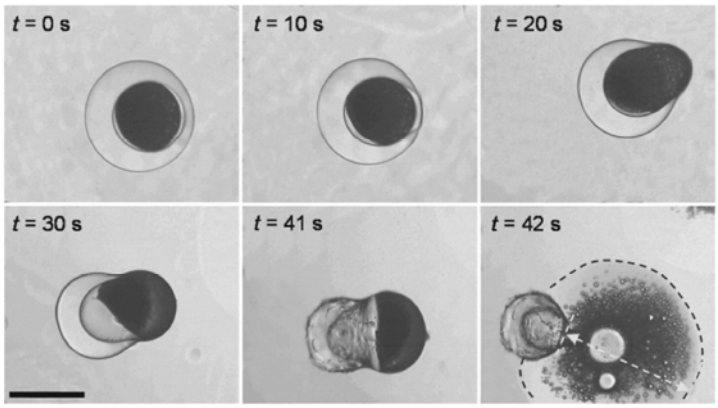

Fig.8. Microscope snapshots of thermo-triggered squirting of nanoparticles from microcapsules by increasing environmental temperature from 20 to 50 °C. The blue dashed line indicates the propagating front of the squirted liquid containing nanoparticles, and the yellow arrow shows the propagating distance of the squirted liquid containing nanoparticles (Liu 2010).

3.2 Thermo-Responsive Trojan-Horse-Like Microcapsules

Recently, the author developed a novel scalable and controllable microfluidic technique, which can be used to fabricate highly monodisperse multiple emulsions with independent control of both the size and the number of inner droplets (Chu 2007). This technique is easily scalable to a higher order multiple emulsions, *e.g*., monodisperse and controllable triple emulsions. The utility of the tight control afforded by this technique makes it an effective way to fabricate novel thermo-responsive Trojan- horse-like microcapsules with a crosslinked PNIPAM hydrogel membrane.

Fig.9 illustrates the schematic diagram of the capillary microfluidic device for generating controllable monodisperse triple emulsions. Both the diameter and number of the individual drops, at every level, are precisely controllable, as illustrated by the series of drops, with the innermost varying in number from one to seven and the middle ones varying in number from one to three. To prepare the Trojan-horse-like microcapsules with a PNIPAM hydrogel membrane containing controllable aqueous droplets inside, W/O/W/O emulsion droplets are used as synthesis templates. The outermost fluid is an oil phase containing surfactant, while the outer middle fluid (II) is an aqueous solution of the monomer NIPAM, crosslinker and initiator. The inner middle fluid (I) is an oil phase containing the reaction accelerator while the innermost fluid is another aqueous solution containing to-be-released chemicals. Once the triple emulsions are formed, the accelerator in the middle fluid (I) diffuses into the outer aqueous phase containing the monomer NIPAM and the initiator and catalyzes polymerization of NIPAM. **Fig.10** shows the optical micrograph of a typical Trojan-horse-like microcapsule consisting of a membrane of thermo-responsive PNIPAM hydrogel which encapsulates an oil drop containing several water droplets.

Fig.11 shows the optical micrograph time-series with the forced expulsion of the oil and water droplets contained within the PNIPAM microcapsule when the temperature is rapidly increased from 25 to 50 °C. Upon heating from 25 to 50 °C, the thermo-responsive hydrogel rapidly shrinks by expelling water; however, because of the incompressibility of the inner oil, the hydrogel membrane breaks, providing

spontaneous, pulsed release of the innermost water droplets into the continuous oil phase, as shown in **Figs.11b** ~ **11e**. This structure has Trojan- horse-like behavior, protecting the innermost water droplets in the hydrogel membrane until their temperature-induced release. This demonstrates the utility of this microfluidic technique to generate highly controlled capsules with multiple internal volumes that remain separate from each other; it also highlights the potential of this device to create highly engineered structures for controlled release of actives. Further refinements could adjust the thickness of the layers and the number of droplets, enabling fine control over diffusion of actives contained within the innermost droplets. This would facilitate highly controlled release of the actives.

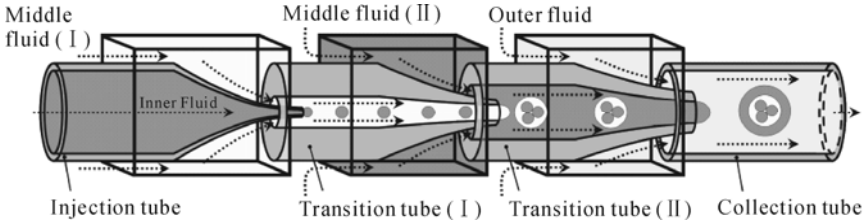

Fig.9. Schematic diagram of the capillary microfluidic device for generating triple emulsions (Chu 2007).

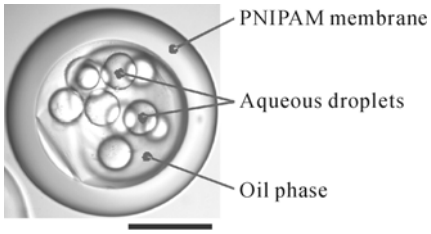

Fig.10. Optical micrograph of a typical Trojan-horse-like microcapsule consisting of a membrane of thermo-responsive PNIPAM hydrogel which encapsulates an oil drop containing several water droplets. The scale bar is 200 μm

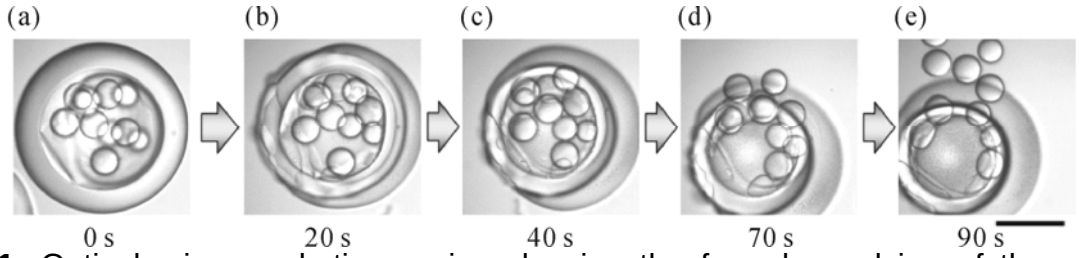

Fig.11. Optical micrograph time-series showing the forced expulsion of the oil and water droplets contained within the PNIPAM microcapsule when the temperature is rapidly increased from 25 °C to 50 °C. The scale bar is 200 μm (Chu 2007).

4. Summary

Smart microcapsules with thermo-responsive hydrogel membranes can be fabricated with either O/W/O double emulsions, or W/O/W/O triple emulsions as synthesis templates (Chu 2007; Liu 2010; Wang 2009), and have numerous potential applications in various fields. Such smart microcapsules with a PNIPAM hydrogel membrane can be easily converted into other stimuli-induced self-bursting ones by simply changing the thermo-responsive membranes into other stimuli-responsive ones,

such as pH-induced (Liu 2011a; Wei 2011), molecular-recognition-induced (Liu 2011b; Pi 2010), and so on. Besides the application in the field of targeted delivery and controlled release of drugs, such microcapsules can find myriad applications in various fields. For example, these microcapsules can be applied to site-specific and/or route-specific transport and release functional substances such as corrosion inhibitors, self-healing agents and lubricants and other chemicals to certain sites, even to some hand-unreachable micro-spaces.

Acknowledgements
The authors gratefully acknowledge support from the NSFC (21136006), the 973 Program of China (2009CB623407) and the Program for Changjiang Scholars and Innovative Research Team in University (IRT1163).

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