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Generation of Uniform Polymer Eccentric and Core-centered Hollow Microcapsules for Ultrasound-regulated Drug Release

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Abstract:

In this paper, a strategy was developed for fabricating uniform polydimethylsiloxane (PDMS) microcapsules with eccentric and core-centered internal hollow structures, which can be employed as a novel controlled-release system for site-specific drug delivery under ultrasound regulation. This strategy involved the use of a microfluidic device, through which three phases (*i.e.*, an inner water phase containing drug molecules, a middle oil phase of PDMS solution, and an outer water phase) were delivered at independently adjustable flow rates, allowing the formation of water-in-oil-in-water (W/O/W) emulsion droplets in a microfluidic device. By baking the as-prepared microcapsules afterwards, microcapsules with different inner hollow cores were obtained. The sizes of the inner hollow structures could be tuned, leading to a series of microcapsules with different densities. The densities of these microcapsules were all lower than that of water, which showed a long gastric residence time. Most interestingly, eccentric hollow microcapsules with well-controlled sizes and shapes were also prepared using this method. The eccentric and core-centered hollow microcapsules demonstrated triggered and controlled release of encapsulation under ultrasound, of which the release profiles were consistent with the theoretical simulation. The results showed that the microcapsules had all properties of a floating drug delivery system and a controlled release system, and demonstrated great potential to be used for controlled release, in particular, for the delivery of drugs that are absorbed primarily in the upper segments of gastrointestinal tract.

Keywords: hollow microcapsules; eccentric; microfluidic; ultrasound; drug release

1. Introduction

Site-specific and controlled release of drugs through the use of microcarrier systems are attracting increasing attention in the field of drug delivery, as they can improve the efficacy of the drugs while reducing systemic side effects comparing to conventional administration techniques (*i.e.*, free drugs) [1-4]. Among different carriers, polymeric microcapsules with well-defined structures are promising candidates for site-specific controlled release, showing widespread applications in many fields [5-10]. Taking oral drug delivery as an example, polymer microcapsules are often utilized to deliver drugs to stomach, small intestine, and colon for localized treatment [11-13]. Unfortunately, after oral administration most microcapsules exhibit sharp increases in drug release to potentially toxic levels, followed by a relatively short therapeutic period with proper drug concentration, which eventually drops off until re-administration [14-16]. To this end, it is necessary to introduce a microcapsule system that can release drugs in a sustained and well-controlled manner. Besides, to overcome physiological adversities such as short gastric residence time and unpredictable gastric emptying, a floating drug delivery system is highly preferred for the delivery of stomach medicine [17-20]. A floating drug delivery system not only shows site-specific drug delivery, but more importantly, can retain at the site for longer periods due to their special "floating" capability, which is ideally for the delivery of drugs that are absorbed primarily in the upper segments of gastrointestinal tract, *i.e.*, the stomach, duodenum, and jejunum [11-13, 17-20]. To date, various types of floating drug delivery systems have been developed, such as granules, powders, capsules, tablets, laminated films and hollow microcapsules for controlled release purpose [23-30]. However the hollow microcapsule may be much preferred one that offers a simple and practical approach to achieve gastric retention. [11, 18, 20-24].

On the other hand, most of polymer microcapsules for oral administration cannot achieve sustained stimuli-responsiveness. Encapsulated drugs are usually released through the destruction of microcapsules (by natural degradation or external stimulus), which is difficult to control [4, 25-28]. For example, when a biodegradable system that was used under ultrasound stimulation, can release the inclusion in a short period by

destroying the microcapsules, but sustained release still remains difficult to achieve [27-30]. To the best of our knowledge, there are very few examples of floating drug delivery microcapsules which also possess the capabilities of both sustained release and controlled release of encapsulated drugs under certain stimuli. Therefore, it is highly necessary to develop a novel drug delivery system combining sustained release with a floating capability, for efficient delivery of drugs into the gastrointestinal tracts.

Herein, we demonstrates a simple strategy for generating uniform polymeric microcapsules with eccentric and core-centered internal hollow structures using a microfluidic device [31-36], which realize a potential controlled-release system for site-specific drug delivery under ultrasound regulation. Polydimethylsiloxane (PDMS) was used as the polymeric matrix. During the fabrication, three phases include an inner water phase, a middle oil phase, and an outer water phase were continuously introduced into the microfluidic device by three syringe pumps at independently adjustable flow rates to form water-in-oil-in-water (W/O/W) emulsion droplets (Figure S1, Step 1). Interestingly, we could obtain two types of uniform microcapsules, one with eccentric inner cavity and one with core-centered inner cavity, after the solidification process performed under static condition and dynamic stirring, respectively (Figure S1, Step 2). The as-prepared microcapsules became hollow after further baking at an elevated temperature, which could potentially float on top of the gastric fluid, resulting in extended gastric residence time, increased treatment efficiency, and reduced dosing frequency [17-20]. Specifically, we chose red ink and rhodamine 6G as model molecules to highlight the inner structures of the microcapsules because of their easy visualization (bright color and fluorescence), as well as to demonstrate the concept of controlled release under ultrasonic regulation. Furthermore, domperidone maleate (a propulsid) was encapsulated into the hollow microcapsules and its release profiles were investigated.

2. Experimental section

2.1 Chemicals and materials

Polydimethylsiloxane (PDMS, Dow Corning, component A and B mixture) and

dichloromethane (DCM, Damao Reagent) were used as the main component for microcapsules (PDMS: DCM = 3:1). Polyvinyl alcohol (PVA, Sigma) at a concentration of 2 wt% was served as the inner and outer water phases. Rhodamine 6G (Aladdin) and domperidone maleate (NICPBP) were used as examples of drugs. The two different glass capillary tubes (with inner/outer diameters of 0.70/1.23 and 0.45/0.65 mm respectively) were obtained from Ace Glass. Sodium chloride (NaCl, Guangzhou Chemical Reagent Factory) and hydrochloric acid (HCl, SCRC) were used to prepare the simulated gastric fluid without pepsin. Deionized (DI) water used in all experiments was obtained by filtering through a set of Millipore cartridges (Epure, Dubuque, IA).

2.2 Preparation and characterization of PDMS microcapsules

The fluidic device was fabricated according to Xia's published work with minor modification [31]. Briefly, the fluidic device consisted of two PVC tubes (0.60/1.50 and 1.45/2.30 mm in inner/outer diameters respectively), two glass capillary tubes and a 30G needle. The device was assembled by inserting the needle and glass capillary tubes into PVC tubes (see Figure S1), which was fixed with epoxy adhesive. The inner, middle and outer phases were introduced using three syringe pumps (KD100, KD Scientific) at independently adjustable flow rates. In a typical demonstration, the flow rates for the inner, middle and outer phases were kept at 0.004, 0.03 and 1.5 mL/min respectively for fabricating the eccentric microcapsules. The inner water droplets formed at the tip of the needle and flowed along the PVC tube into the small glass capillary tube, and then the water-in-oil droplets formed at the exit of the small glass capillary tube and finally flowed along the big glass capillary tube into a 100 mL beaker containing the outer water phase. The PVA solution (2 wt%) containing red ink (or rhodamine 6G, or domperidone maleate) was served as the inner water phase. PDMS and DCM at a mass ratio of about 3:1 was the middle oil phase. We used pure PVA solution (2 wt%) as the outer water phase and collection solution. The microcapsules suspension were kept at 60 °C for 30 min to get rid of DCM, and then at 90 °C for 30 min to solidify the microcapsules. With or without stirring throughout

the solidification process, we prepared two kinds of microcapsules with different internal structures. Because the microcapsules we fabricated are water-in-oil-in-water (W/O/W) emulsion droplets. The density of the inner water phase is higher than the density of PDMS in the outer phase. Without stirring, microcapsules are static and inner water phase will sink to the bottom due to the density contrast and gravity (but the inner droplet cannot penetrate through PDMS and escape, due to the low surface energy of PDMS [37]), and form eccentric microcapsules with a PDMS thin-wall. By stirring, all microcapsules are rotating and the inner droplet will stay near the center as far as possible, and then form core-centered microcapsules after solidification. The hollow microcapsules were obtained by further heating the microcapsules at 90 °C in a drying oven (ZL-1, Boxun). We collected the solidified microcapsules containing water inner core from the beaker, transfer them to a glass petri dish, and then put the dish into an oven at 90 °C for the evaporation of the inner cores. An optical microscope (Inverted fluorescence microscopy, NIKON) with a CCD camera (Digital Sight DS-Fi2, NIKON), a stereoscope (SZ760-DM601, OPTEC) and scanning electron microscopy (SEM, JSM-6010LA, JEOL) were used to investigate the morphology and structures of the microcapsules. The average diameter and standard deviation were calculated by measuring the diameters of over 50 microcapsules randomly selected from the optical micrographs of each sample. The floating properties of microcapsules were evaluated using a beaker filled with 150 ml of simulated gastric fluid without pepsin (pH 2.0, T = 37 °C ± 0.5), and a magnetic stirrer (RCT Synthese, IKA) was applied to simulate the peristalsis of the stomach (rate of stirring: 120 rpm) [17, 38-40].

2.3 UV-vis spectra measurement

A spectrophotometer (UD730, Beckman) was used to measure the release profile of the drug molecules from the microcapsules. The drug molecules were loaded into the microcapsules by directly adding them (at a final concentration of 20 μg/mL for rhodamine, and 340 μg/mL for domperidone maleate respectively) into the PVA solution as inner water phase. After preparation, the four kinds of microcapsules (0.5

g for each sample) were dispersed in vials containing 3 mL redistilled water (or simulated gastric fluid). We applied an ultrasonic cleaner (DL-360B, ZHI SUN INSTRUMENT) to regulate the drug release process (40k Hz, 360 W, 37 °C). For every 15 min, we measured the UV-vis spectra of the solutions. The absorption maximum was recorded as a function of ultrasound time.

3. Results and discussions

3.1 Sizes and inner structures of eccentric and core-centered microcapsules

The as-prepared microcapsules are shown in Figure 1. There are two types of microcapsules with different internal structures, namely eccentric and core-centered, as shown in Figure 1A and C (the core-centered microcapsules are not absolutely core-centered). We chose PDMS as the material to prepare microcapsules because of its low-cost, biocompatibility, and wide-used as oral pharmaceutical excipients [33, 41]. It is clear that, by using microfluidic device, we were able to generate uniform core-shell PDMS microcapsules [42-48], as shown in Figure 1B and D.

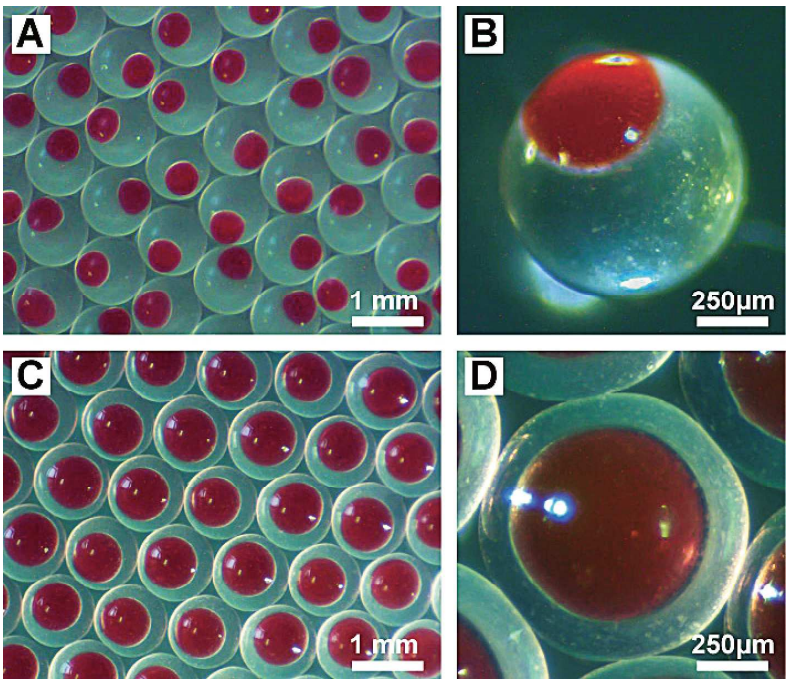

Figure 1. Optical images of two types of microcapsules with different internal structures. (A) and (B) Eccentric microcapsules. (C) and (D) Core-centered microcapsules. The inner water phase was stained with red ink for better visualization.

We examined the morphology and inner microstructures of the PDMS microcapsules using scanning electron microscopy (SEM) after cutting the samples from the middle planes (Figure 2). The eccentric microcapsules in Figure 2A were obtained at flow rates of 0.004, 0.03, and 1.5 mL/min for the inner water phase, middle oil phase, and outer water phase, respectively. The core-centered microcapsules in Figure 2B were obtained at flow rates of 0.007, 0.025, and 0.8 mL/min for the inner water phase, middle oil phase and outer water phase, respectively. The SEM images also demonstrated the uniformity of PDMS microcapsules, and the average diameter of the microcapsules was 808.8 ± 3.5 μm for both eccentric and core-centered microcapsules. The average diameter of internal spherical cores was 482.2 ± 2.0 μm for eccentric microcapsule, and 551.1 ± 2.7 μm for core-centered microcapsule. The insets show the cross-sectional images of the microcapsules at higher magnifications. We could clearly observe two types of internal structures with different wall thicknesses for each microcapsule. To the best of our knowledge, the eccentric hollow microcapsules with controllable structure are first reported in our work, and these microcapsules are ideal for ultrasound-regulated drug release applications [29, 49-55].

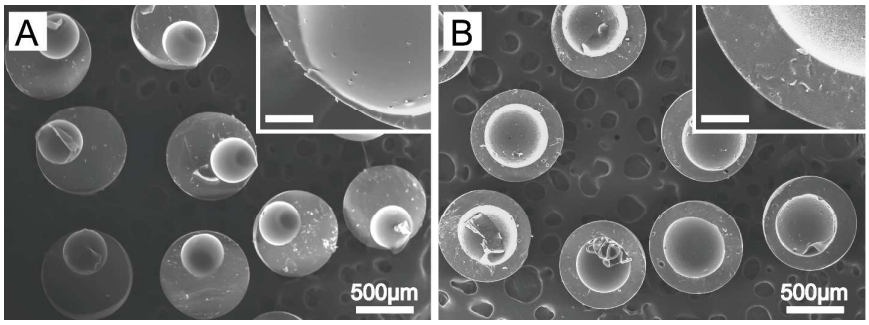

Figure 2. Scanning electron microscope images of hollow microcapsules. (A) Eccentric microcapsules. (B) Core-centered microcapsules. The insets are higher magnification images showing the different wall thicknesses of each microcapsule, and the scale bars are 100 μm.

Besides, we can roughly control (difficult to accurately control) the eccentricity by adjusting the viscosity of PDMS, the speed of stirring and solidification time. Here, we demonstrate the control ability by fabricating one type of the microcapsules

that have a smaller eccentricity than the other eccentric microcapsules. The results are shown in Figure S2. Figure S2 shows three microcapsules with different eccentricities, indicating that we can roughly control the eccentricity of microcapsules. The results are reproducible.

3.2 Densities and floatability of eccentric microcapsules

We can change the sizes of inner water drops by fixing the flow rate of the continuous phase and adjusting the flow rate of the discontinuous phase, as well as the sizes of the inner cores after baking, leading to production of a series of microcapsules with different densities lower than that of water [31-35, 45-48]. As aforementioned, there are three different phases in our microfluidic setup. The inner water phase is the discontinuous phase, and the middle oil phase is the continuous phase at the first emulsion. After the first emulsion, the middle oil phase with water droplets become the discontinuous phase and the outer water phase is the continuous phase. In order to generate eccentric microcapsules with different inner core sizes, we kept the flow rate for the middle oil phase and the outer water phase at 0.03 and 1.5 mL/min, respectively, and then changed the flow rate for the inner water phase, which increased from 0.001 to 0.004, 0.007, and 0.011 mL/min. As a result, the average diameter of the inner cores increased from 401.0 ± 2.1 to 482.2 ± 2.0, 590.9 ± 2.1, and 667.4 ± 2.5 μm. The diameters of the internal cores as a function of the flow rates for the inner water phase were shown in Figure 3. By controlling the flow rates of the inner water phase, we could easily control the size of the internal cores of microcapsules, similar to the observations by others [31-35, 45-48].

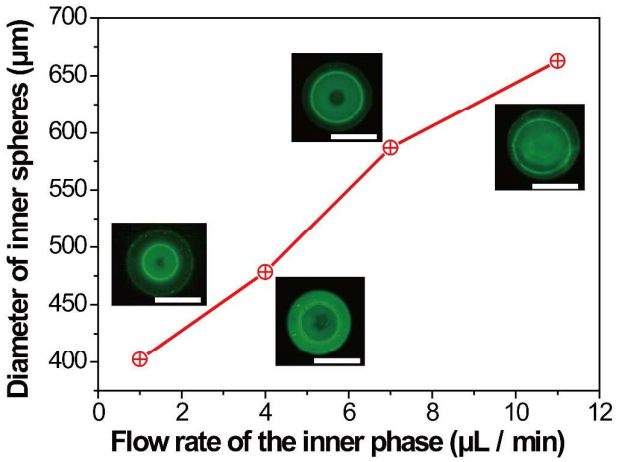

Figure 3. Diameters of the internal spheres as a function of the flow rates for the inner water phase. The flow rate for middle oil phase was 30 μL/min, and the flow rate for outer water phase was 1.5 mL/min.

As shown in Figure 4A, the microcapsules (the internal phase contained rhodamine 6G) before baking settled at the bottom of a vial, indicating a larger density of microcapsules than that of water. After baking, the water in the inner cores of the microcapsules evaporated, and at the same time being exchanged with air due to the gas permeability of PDMS. The air-filled microcapsule could then float on the surface of water, indicating a lower density of microcapsules than that of water. Since the diameter of the inner cores could be controlled by adjusting the flow rate of the inner water phase, it is possible to finely tune the density of microcapsules indirectly. Indeed, Figure 4B shows the densities of the air-filled microcapsules as a function of the diameters of the inner cores. As the size of the inner cores increased, the density of the microcapsules decreased due to the growing volume occupied by low-density air. Additionally, all the air-filled microcapsules we produced had densities lower than water (1.00 g/cm^3) (Figure 4B). The hollow microcapsules had a good floatability, and the time it took for them to emerge onto the surface of water (*i.e.*, floating lag time) was about 5 seconds. After that, they would stay on the surface for more than 12 hours under magnetic stirring. After 12 hours, about 18% of eccentric microcapsules and about 20% of core-centered microcapsules sank to the bottom of the beaker, showing a great floatability of the hollow microcapsules under agitation (Figure S3).

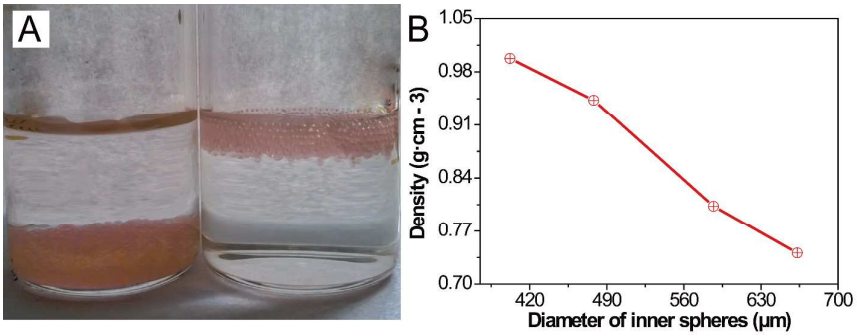

Figure 4. Densities of microcapsules with different sizes of inner cores. (A) The comparison of microcapsules before and after baking. The unbaked microcapsules sank at the bottom of the bottle, whereas baked ones could easily float on the surface of water. (B) The densities of the microcapsules as a function of the diameters of inner cores.

3.3 Release profile of inclusion from the microcapsules under ultrasound regulation

To demonstrate the capability of the microcapsules with different structures to regulate the release of drugs *in vitro*, we used rhodamine 6G as a model drug and applied ultrasound to manipulate the drug release process. The release profiles of rhodamine 6G from four types of microcapsules (*i.e.* eccentric microcapsules before and after baking, and core-centered microcapsules before and after baking) are shown in Figure 5. In all cases, the encapsulation efficiency of rhodamine 6G into the inner water phase approached 100%, suggesting that all drug molecules were encapsulated in the final microcapsules. In order to find out if rhodamine 6G leaked into the middle oil phase, we sliced the as-prepared hollow microcapsules (after baking) and examined them under fluorescence microscope. As shown in Figure S4, the fluorescence images of the cross-sections of hollow microcapsules indicated that the rhodamine 6G was mainly distributed on the surface of the inner cores, and only slightly permeated into the PDMS wall. Figure 5A shows the drug release profiles without ultrasound stimulation. In this situation, rhodamine 6G was barely released, showing a fine sealability of the microcapsules. However, after exposing the microcapsules to ultrasound, drug release from microcapsules started immediately and constantly. The amount of rhodamine 6G molecules released to the external environment increased with the prolonged ultrasonic stimulation time, as shown in

Figure 5B. The eccentric hollow microcapsules prepared after baking showed the highest release rate among all four types of microcapsules, while the core-centered microcapsules prepared without baking had very limited release even when ultrasound was applied. After 2 hours, the accumulated release amount of drug from eccentric hollow microcapsules is close to 70%. Comparing with other three types of microcapsules, microcapsules with eccentric hollow structures were more possible to achieve controlled release with higher release rate, because they are more sensitive to ultrasonic stimulation than other three types of microcapsules.

The eccentric microcapsules not only showed the highest release rate, but also displayed better control of ON/OFF release of drug compared to core-centered ones under ultrasound stimuli. Based on eccentric and core-centered hollow microcapsule, we can realize ON/OFF release of rhodamine 6G (as a model drug) from the capsules by applying ultrasound or not, and the results are shown in Figure S5. As Figure S5 shows, curve a) is the release profiles of rhodamine 6G from core-centered microcapsules and curve b) is the release profiles of rhodamine 6G from eccentric microcapsules. The figure indicates that eccentric microcapsules show a more regular pattern with repeated ultrasonic stimulation, and the amount released in each step was higher than that of core-centered microcapsules. The higher release rate of eccentric microcapsules than core-centered ones, is probably due to the fact that eccentric ones have uneven shell thickness, at places where the shell is thin, the release rate is high. In contrast, core-centered microcapsules have even shell thickness without any places where the shell is particularly thin. The molecules are easier to diffuse through the thin shell of eccentric microcapsules, resulting in higher release rate.

The results in Figure 5 also demonstrated that ultrasound could regulate the release profiles of drugs from these four types of microcapsules. We assume that the major mechanisms of such stimuli-responsive release of drugs from hollow PDMS microcapsules were, ultrasound might change the porosity of PDMS in a nondestructive manner [4, 29], or destroy the wall of the microcapsules (thus eccentric microcapsules with thinner walls showed faster release than core-centered microcapsules with thicker walls).

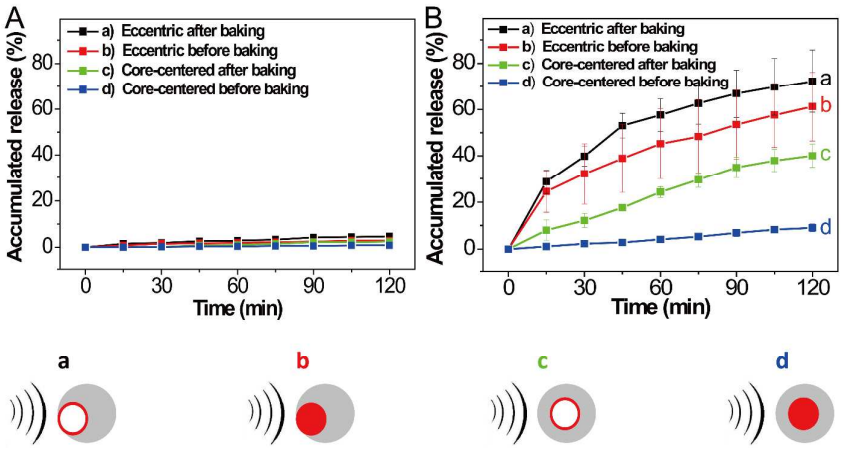

Figure 5. The release profiles of rhodamine 6G (a model drug) from four types of microcapsules. (A) The drug release profiles without ultrasound. (B) The drug release profiles under ultrasound.

Besides, we did an experiment to demonstrate if water could reenter the inner hollow of microcapsules (prepared with baking) under ultrasound. Figure S6A and B show photographs of hollow microcapsules before and after exposure to ultrasound. Due to their great floatability, the eccentric hollow microcapsules could initially float on the surface of water before ultrasonication. After ultrasound exposure, a number of microcapsules sank to the bottom of the vial. This result shows that ultrasound treatment could accelerate the sinking of microcapsules with over 65% of microcapsules settled to the bottom after exposing to ultrasound for 1.5 h (Figure S6 B). Figure S6C shows the weight change of microcapsules as a function of ultrasonication time. The weight increased with time, which indicates that water could have reentered into the inner cores of the microcapsules, resulting in an increase in their weight.

3.4 Simulation of release profiles from the microcapsules

In order to further explain the release profile, a theoretical simulation was performed. We simulated the release profiles of four types of microcapsules by using a model based on Fick's law of diffusion [56]. The average diameters of the microcapsules were 808.8 ± 3.5 μm for both eccentric and core-centered microcapsules; the thickness of the spherical shell of core-centered microcapsules was

128.9 ± 2.0 μm, and the thinnest part of the spherical shell of eccentric microcapsules was 8.1 ± 0.3 μm; the diffusion coefficient of rhodamine 6G in water is 2.8×10^{-10} m^2/s. The release profiles and simulation results are shown in Figure 6, where the simulative release profiles coincided well with the experiment data. In this case, we found that the permeability of microcapsules increased by at least 8 times under ultrasound, and the drug could be released from microcapsules slowly under control. Besides, due to the thin spherical shells, eccentric microcapsules can easily reach a higher release rate of drugs compared to core-centered microcapsules.

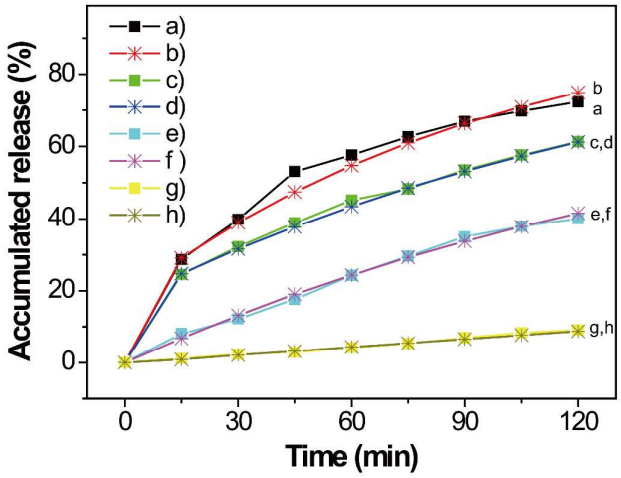

Figure 6. The release profiles of rhodamine 6G from four types of microcapsules and their simulative release situations. -■- Practically release. -※- Simulatively release. a) and b) Eccentric microcapsules after baking. c) and d) Eccentric microcapsules before baking. e) and f) Core-centered microcapsules after baking. g) and h) Core-centered microcapsules before baking.

3.5 Controlled release of domperidone from the microcapsules

We also used the microcapsule as vehicles to deliver domperidone maleate, a type of propulsid. Under acidic environment, domperidone maleate has a higher solubility than usual, and is easy released from encapsulating vehicles [57, 58]. We used simulated gastric fluid as the release medium to study the drug release from the microcapsules under ultrasound. Figure 7 shows the release profiles of domperidone maleate from four types of microcapsules. The release profiles are similar to those of rhodamine 6G, but domperidone maleate showed a higher release rate than rhodamine

6G due to the acid environment. The eccentric hollow microcapsules (after baking) still showed the highest release rate in all the four types of microcapsules, followed by eccentric microcapsules (before baking), core-centered hollow microcapsules (after baking), and core-centered microcapsules (before baking).

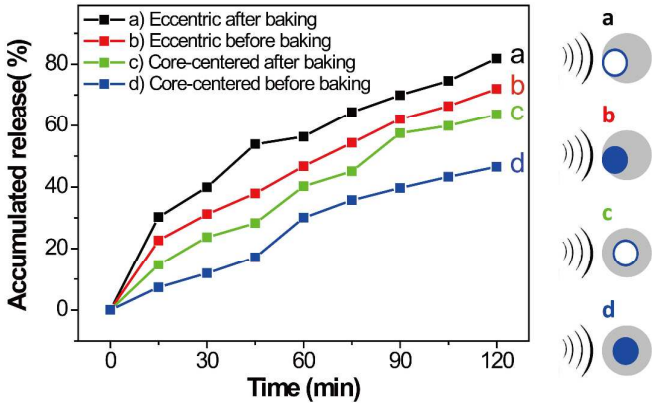

Figure 7. Ultrasound-regulated release of domperidone maleate from four types of microcapsules in simulated gastric fluid.

Furthermore, we tested the in vitro cytotoxicity of the hollow microcapsules based on the viability of HeLa cells. In this case, cells were co-cultured with microcapsules at different mass concentrations. Cell survival percentage was measured by spectrophotometry at 570 nm using ELISA reader in terms of optical density value. The results are shown in Figure S7. As shown in Figure S7, even under the concentration of 9 mg/mL for 5 days, there is no significant difference in cell viability between the cells co-cultured with or without microcapsules in the medium. This result indicates that the hollow microcapsules had no cytotoxicity towards HeLa cells.

4. Conclusions

In summary, we demonstrated a new class of microcapsules prepared using a microfluidic device followed by stirring and baking. Both the eccentric and core-centered hollow microcapsules produced can be promising candidates for ultrasound-regulated drug release. Comparing with the microcapsules reported in literature, our new hollow drug delivery systems offer a range of advantages: i) the

drug molecules can be directly loaded inside the microcapsules during their fabrication process; ii) the microcapsules may demonstrate long gastric residence time due to their low density and great floatability provided by the hollow structure; iii) by controlling the flow rate of the inner phase, it was possible to control the diameter of the inner cores, meaning that we can tune both the drug loading capacity and the density of microcapsules; and iv) the as-prepared hollow microcapsules show well-controlled drug release under ultrasound. We believe that this novel type of microcapsules holds great application potential for controlled drug release, and as contrast agent for ultrasonic imaging, bioreactors, and heat insulating materials.

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Supplementary data

Supplementary data associated with this article is available online.

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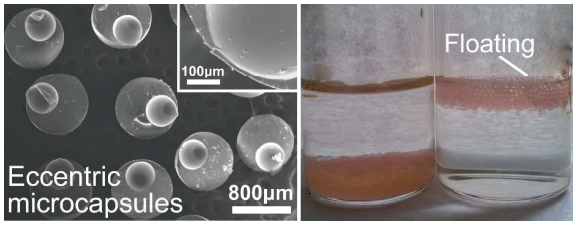
Table of contents entry for

Generation of Uniform Polymer Eccentric and Core-centered Hollow Microcapsules for Ultrasound-regulated Drug Release



Uniform polydimethylsiloxane microcapsules with eccentric and core-centered internal hollow structures show controlled-release behavior for site-specific drug delivery under ultrasound regulation.