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4 **Well-Designed Microcapsules Fabricated Using Droplet-Based Microfluidic Technique**
5 **for Controlled Drug Release**

6
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24 **Abstract**

25 Microfluidics is an emerging technology for synthesis of drug-loaded micro- and nano
26 capsules for targeted delivery and controlled release, which has extensive applications in
27 tumor therapy and pharmacological study in healthcare. A number of polydimethylsiloxane
28 (PDMS) microfluidic devices have been developed and widely used, while PDMS based
29 microstructure device does not support long-term stability and repeated use, moreover it
30 requires special facilities for fabrication and plasma bonding. Therefore in our study, a non-
31 PDMS tube-in-tube glass-capillary micro-device was fabricated and successfully used for
32 generation of drug-loaded microcapsules with different structures and sizes. Compared with
33 the PDMS and other conventional microfluidic devices, the glass-capillary microfluidic
34 device has many advantages, including simplicity of fabrication, low cost, high throughput,
35 reliability of generating droplets with uniform size and morphology, as well as ease of
36 profound cleaning by rinsing with acid solution, and as a result, the availability for reuse.

Furthermore, the size distribution and morphology dependent drug release mechanism for drug-loaded microcapsules was also studied in our work, providing significant guidelines for producing suitable microcapsules for the specific applications. By understanding the release kinetics, it can be possible to design and fabricate drug delivery micelles for the target applications, and regulate the release of drugs to satisfy the applications with required drug release profile.

1. Introduction

Currently, advanced techniques are being directed towards evolution of innovative pharmaceutical products and many focuses are paid on tackling the limits related to conventional drug delivery. Low bioavailability, poor stability, and uncontrollable drug release are the most common obstacles encountered. Therefore, desired encapsulation and drug release pattern are very important for overcoming the aforementioned obstacles.(1, 2)

There are many systems designed for the encapsulation of drugs to achieve protection and controlled drug release. (3-5) Among all encapsulation systems, polymer microcapsules have the utmost potential to deliver the drugs in a controllable way. Recently, some studies reported the use of polymer in the encapsulation of drugs and they are majorly focused on the influence of the microcapsule size on drug release kinetics.(6-9) However, the effect of microcapsule morphology on the drug release kinetics from the final microcapsules as drug carriers has rarely been studied. By rapid stirring of immiscible liquids consisting of emulsifier and organic solvent with dissolved drug in the droplets, microcapsules can be obtained. But the resultant microcapsules are polydispersed both in size and morphology, which equally lead to the difficulty of quantitative investigation of the effects of size and morphology.

Microfluidic system has been widely used for encapsulation, particularly for the controlled capsule producing for drug delivery applications. Microfluidic methods not only enhance the

encapsulation efficiency compared to the traditional production techniques, but also ensure the drug carrier particles with uniform size and controlled chemical components. Polydimethylsiloxane (PDMS) is the commonly used material for microfluidic devices; however the fabrication of PDMS microfluidic devices and the hydrophilic surface treatment are relatively complicated.(10-15)

In this work, two different droplet generation devices based on glass-capillary and flow-focusing technique were developed to obtain microcapsules with different size distribution and morphology. The polymeric microcapsules were generated by dissolving the drug and polymer in the organic solvent for the dispersed phase, followed by mixing it with the continuous phase (aqueous phase) to form the emulsion. During the process, emulsions with different structures and sizes were generated by the microfluidic devices with different attribute. After thorough emulsion the droplets were solidified by solvent evaporation process.(16, 17) Biodegradable polymers can be degraded into nontoxic organic and inorganic components and this property makes them the suitable material for the preparation of emulsion. Different polymers have been studied for encapsulation of various active ingredients, such as PLA (Poly *lactic* acid), PLGA (Poly lactic-co-glycolic acid), and PCL (Polycaprolactone).(18, 19) PLGA was chosen since it can degrade slowly into biocompatible substance and thus release the encapsulated drugs gradually for long period of time.(8, 9, 20) Moreover, it is essential to form a stable emulsion system that maintains the physicochemical state of the dispersion and prevents the phase separation. Therefore the biocompatible polymer, polyvinyl alcohol (PVA), was selected as the stabilizer due to its favorable properties of good mechanical strength, durable stability ot temperature and pH variations.(21, 22) Monodisperse emulsion droplet templates were generated using a homemade microcapillary microfluidic device to explore the influence of the size and morphology of the microcapsules on drug release.

2. Materials and methods

2.1. Design and fabrication of the microfluidic devices.

To fabricate single and core-shell emulsion systems, two kinds of glass-capillary microfluidic devices were developed and two experiment systems were fabricated as shown in **Figure 1**. For the single emulsion device, three cylindrical capillaries were used with a dimension as follow: the inner injection capillary with body diameter of 0.5 mm and tip diameter of 35 μm , the outer injection capillary with body diameter of 0.8 mm, and the collection capillary with body diameter of 0.5 mm and tip diameter of 120 μm . They were tapered by directional heat stretching and the tips of the capillaries were polished to desired diameter using sand paper. Subsequently, the inner injection and collection capillaries were inserted into the outer injection capillary coaxially (**Figure 2A**). For the core-shell emulsion technique, similarly, a glass-capillary microfluidic device with four cylindrical capillaries were developed with dimension as follow: inner injection capillary with body diameter of 0.2 mm and tip diameter of 40 μm , middle injection capillary with body diameter of 0.4 mm and tip diameter of 90 μm , collection capillary with body diameter of 0.4 mm and tip diameter of 120 μm . And finally these capillaries were inserted into the outer injection capillary with diameter of 0.8 mm for coaxially fluid flow (**Figure 3A**). The tips of the capillaries were also polished to desired diameter using sand paper. The middle injection capillary was rinsed by the hydrophobic solution (Trimethoxy(octadecyl)silane), which favored the contact of the organic phase with the capillary wall, whereas the collection capillary was hydrophilic accordingly to prevent the saturating of the organic shell of the core-shell double emulsion with the wall of the collection capillary.(23-25)

2.2. Microcapsule generation.

For the preparation of emulsion droplets, dichloromethane (DCM) with 7% (w/v) PLGA (75:25) and 0.7% (w/v) rifampicin were used as the organic dispersed phase. DCM is a

115 routinely used organic solvent for PLGA and various other drugs and easily evaporates at
116 room temperature. Rifampicin is a drug for the treatment of tuberculosis, while in this
117 study we used it as a model drug to investigate the encapsulation and controlled release of
118 active ingredients from the microcapsules. Deionized water with 2% (w/v) PVA formed
119 the aqueous phase (continuous phase). PVA was added as emulsifying agent and
120 surfactant to prevent droplets from aggregation. For the single emulsion droplet, the
121 organic phase was pumped through the inner injection capillary as the inner phase and the
122 aqueous phase flowed in the outer injection capillary as the outer phase. The flow rates of
123 both the aqueous phase and organic dispersed phase were adjusted by syringe pump
124 (Legato110, KD Scientific, USA) to fabricate droplets with different sizes. For the core-
125 shell emulsion droplet, PVA solution (2%, w/v) was used in both the inner phase (through
126 the inner injection capillary) and the outer phase (through the outer injection capillary),
127 whereas DCM loaded with PLGA and rifampicin was present in the middle phase
128 (through the middle injection capillary). The core-shell double emulsion droplets were
129 generated when the three phases entered in the collection tube (**Figure 3A and Figure**
130 **3B**). After collection, the solvent DCM was evaporated at room temperature for 24 hours
131 and the droplets were solidified to form PLGA polymer matrix with encapsulated
132 rifampicin.

133 2.3. Microcapsule characterization.

134 To study the influence of the size and morphology of the microcapsules on the drug
135 release process, we prepared different sizes of single emulsion and core-shell emulsion
136 droplets in our studies. The sizes of single and core-shell emulsion droplets were
137 characterized by microscopic image analysis using Image J (version 1.48, National
138 Institutes of Health, USA) and the morphology of the PLGA microcapsules were observed
139 using an optical microscope (Nikon ECLIPSE Ti-U). For analyzing the *in vitro* release
140 kinetics of the drug inside the microcapsules, the fabricated microcapsules loaded with a

certain amount of rifampicin were dispersed in 40mL phosphate buffered saline (PBS) solution (pH 7.4) in a beaker and shaken (ZWY-2102C, China) at 90 rpm at room temperature. At each pre-determined time interval, the dispersions were centrifuged at 80 ×g for 5 min at room temperature, and then 2 mL of supernatants were collected and filtered through the filter paper with pore size of 30 μm, and assayed for rifampicin by UV-visible spectrophotometer at 473 nm. After assessment of rifampicin, the PBS solution was substituted by fresh PBS solution.

Position of Figure 1

3. Results and discussion

For the drug-loaded single emulsion system as shown in **Figure 2A and B**, the size of the droplets was controlled by changing the flow rates of both the organic dispersed phase and the aqueous phase. By decreasing the aqueous phase flow rate and increasing the organic dispersed phase flow rate, the size of the droplets was increased.(26, 27) Using three pair-sets of different flow rates on organic disperse and aqueous phases, we obtained monodisperse emulsion droplets with diameters of $50 \pm 8 \mu\text{m}$, $100 \pm 13 \mu\text{m}$, and $180 \pm 12 \mu\text{m}$, respectively, with confidence level of 90%, as shown in **Figure 2C, 2D and 2E**. The encapsulation efficiency was calculated according to the following formula:

$$\eta = A/B \times 100\% \quad (1)$$

where A is the amount of rifampicin encapsulated in microcapsules (μg), and B is the actual amount of loaded rifampicin in the experiment (μg). Thus the drug encapsulation efficiencies were $85.2\% \pm 1.1\%$, $82.1\% \pm 0.9\%$, and $79.2\% \pm 1.2\%$ based on the results of three independent experiments for microcapsules with diameters of 50 μm, 100μm, and 180μm, respectively, and accordingly the amounts of rifampicin loaded per particle were about $4.69 \times 10^{-5} \mu\text{g}$, $3.64 \times 10^{-4} \mu\text{g}$, and $2.11 \times 10^{-3} \mu\text{g}$, respectively. By using microfluidic emulsification technique, the resultant emulsion droplets possessed fine size distribution and consistent

morphology, as shown in **Figure 2**. The size and size distribution of the microspheres can remarkably influence the drug release kinetics.

we produced monodispersed droplets with different sizes using solution with certain viscosity, namely the organic dispersed phase (containing DCM and certain concentration of rifampicin and PLGA) and the aqueous phase with PVA. The fabricated droplet size and the break-up frequency were dependent on the flow rates of the organic dispersed phase and the aqueous phase only. Three pair-sets of different flow rates on the organic disperse and aqueous phases in the single emulsion droplet experiments were (15 $\mu\text{L}/\text{min}$, 80 $\mu\text{L}/\text{min}$), (25 $\mu\text{L}/\text{min}$, 80 $\mu\text{L}/\text{min}$), and (40 $\mu\text{L}/\text{min}$, 85 $\mu\text{L}/\text{min}$), respectively. The radii of the injection syringe of the organic solution and aqueous solution were 4.5 mm and 5.5 mm, respectively. In the series of experiments, it was observed that the resultant single emulsion droplets were not only highly uniform in size distribution but also consistent in shape. The final products remained spherical and barely observed fragmented.

Position of Figure 2

To investigate the effect of morphology of the microcapsules on the drug release kinetics, we also fabricated core-shell emulsion droplets as shown in **Figure 3A and Figure 3B**. Polymer microcapsules were obtained from the water-in-oil-in-water (W/O/W) core-shell emulsion droplets. By independently controlling the flow rates of each phase, we obtained highly monodisperse core-shell emulsions with high encapsulation efficiency. From the viewpoint of thermodynamics, the water-in-oil emulsion system can only maintain relative stability due to various factors, such as interfacial tension, interfacial properties of the film, and the viscosity of the medium. With the added surfactant, we can significantly reduce the oil/water interfacial tension and the adsorption on the interface towards the film, which can ensure the stability of the emulsion system to some extent.

In our core-shell emulsion (W/O/W) fabricating process, the surfactant span 80 (5%, v/v) was added in the middle organic phase for further preventing droplets from coalescence and

making inner core sturdy. The flow rates of the inner phase, middle phase, and outer phase were 5 $\mu\text{L}/\text{min}$, 30 $\mu\text{L}/\text{min}$, and 120 $\mu\text{L}/\text{min}$, respectively. The radii of the corresponding syringes were 4.5 mm, 5.5 mm, and 10 mm, respectively. The stable annular polymer microcapsules were generated after the DCM solvent evaporation process. The monodispersed core-shell emulsion droplets with outer diameters of about 180 μm are shown in **Figure 3C**. The drug encapsulation efficiency was $78.5\pm 1.1\%$, and 1.28×10^{-3} μg drug was loaded per particle. The inner core of each core-shell emulsion droplet has homogeneous size with diameter of about 60 μm . The size uniformity of the droplet templates and the inner cores represents the maximum consistency that the resultant microcapsules can retain.

Position of Figure 3

For drug encapsulation, the release kinetics has a prodigious importance for controlled drug delivery, whereas, drug release kinetics is related to the size and morphology of microcapsule. Similarly, the influence of the production conditions on the characteristics of the microcapsules is profoundly important for drug release kinetics. The drug molecules were uniformly dispersed and physically detained in the PLGA polymer matrix. The polymer matrix can prolong the release time and provide a relatively long-range therapeutic effect, (28, 29) therefore, it has a prodigious importance in the treatment of chronic diseases which require long-term drug therapy. The use of drug-loaded microcapsules can significantly reduce the frequency of administration, consequently relieve the suffering of patients. Correspondingly, our research findings should be applicable to other drugs which possess analogous encapsulation mechanisms, although for simplicity as well as for generality rifampicin was selected as a model drug in our studies.

Generally, the release of drug from PLGA matrix can be divided into three stages. The encapsulated drugs inside the PLGA matrix are firstly released from the surface of the microsphere and the drugs absorbed on the outer surface are detached from the surface, which

thus generally results in an initial high release rate. After that, in the second stage, drugs diffuse homogeneously from the interior of the PLGA microcapsules to the outer ambient continuously, therefore a consecutively release at a relatively low release rate can be obtained. In the last phase, the PLGA polymer starts to degrade, which results in a burst release. Our results showed that the release from microcapsule suspensions all followed the triphasic release pattern as shown in **Figure 4A** and **B**. For quantitative analysis, the drug release rate was defined as the percentage of the released amount of rifampicin from the total amount in the microcapsule. Their initial release rate and the overall average release rate were different from each other although they all had similar specific release profiles. Microcapsule suspensions with bigger diameters required longer time period to complete the release profiles than microcapsules with smaller diameters. Moreover, monodispersed microcapsules with smaller size had a very high initial release rate, which led to the release of a large quantity of the encapsulated drugs. As the size of the microcapsules increased, the initial release of drugs was decreased and most of the loaded drugs were released during the later phase. Furthermore, in our outcomes there was a homogeneous and stable drug release period for all microcapsules with different sizes and it could be represented by the zeroth-order model equation:

$$Q_t = Q_{t_0} + Kt \quad , \quad (2)$$

where Q_t is the amount of drug released from time t_0 to time t , Q_{t_0} is the amount of drug released from the initial time to time t_0 , and K is the release constant expressed in unit of amount/time.(30) From our experiment results, we can see that the zeroth-order model could be used to describe the drug release from day 3 to day 8 for microcapsules with diameter of 50 μm and the constant K was 7.12. For microcapsules with diameter of 100 μm , the zeroth-order model could be applied from day 3 to day 10 and the value of K was 5.53. For microcapsules with diameter of 180 μm , there was a longer and slow releasing period and the

zeroth-order model could be used from day 2 to day 12, and the value of K was 3.56. With increase in the size of the microcapsules, there would be a longer stable release process and the value of K was decreased. The release of drug was through the diffusion of the pharmaceutical molecules from the surface of the microcapsules and the later degradation of the PLGA polymer. Smaller microcapsules owned higher surface area-to-volume ratio which resulted in a more significant initial drug release. After that the drugs remaining in the capsules continued diffusing from inside to the surroundings at a relatively homogeneous rate, therefore entered the period with relatively stable release. Meanwhile, when the microcapsules were in an aqueous medium, the hydrophobic PLGA polymer matrix remained undissolved while water permeated into the microcapsules. The established gradient of osmotic pressure further forced the degradation of the PLGA.(31, 32). As the PLGA polymer degraded, the drug release entered the subsequent stage because the diffusion of the drugs through the degraded microcapsules was sped up. With increasing microcapsule size, the PLGA degradation products had longer diffusion pathway and larger diffusion resistance, then the release of these compounds from the inner part of microcapsules could be hindered in a certain extent. Therefore, burst release of microcapsules with larger size appeared later than microcapsules with smaller size..These behaviors indicated that the size of the resultant PLGA microcapsules affected the release kinetics significantly.

As for the microcapsule structure, the fabricated core-shell microcapsules had different structure and morphology from the monodispersed single layer microcapsules. The release process of the core-shell microcapsules also followed the three-stage release pattern as shown in **Figure 4B**. However, it differed apparently from the single layer microcapsules in the initial burst release rate and the average release rate during the whole release procedure as well. Core-shell structure microcapsules with core diameter of 180 μm had a higher initial release rate than the single layer particles with diameters of 180 μm . When the PLGA

polymers started to degrade, the core-shell microcapsules also had a higher release rate in the second stage than the single layer microcapsules. For core-shell microcapsules with size of 180 μm , the zeroth-order model could also be applied from day 3 to day 11 and the value of K was 5.31. The different behaviors may be attributed by the fact that the core-shell microcapsules had a larger surface area-to-volume ratio, and consequently, the rate of the drug diffusion out of the particles would be higher.

Position of Figure 4

4. Conclusion

We demonstrated that the shape and size of the drug-loaded PLGA particles strongly affected the drug release kinetics. For microcapsules with smaller average size, their initial release rate was higher, which suggested that the larger superficial area resulted in higher initial release. The subsequent release rate and release time were also highly related to the size and morphology of the microspheres. Our investigation provides guidelines on how to fabricate microcapsules with appropriate size and morphology with the target drug release kinetics for different applications. However, the throughput of medicine production of our device can be further improved in our future work. We could enhance the rate of medicine production by increasing the injection rate of both the organic phase and the PVA aqueous phase, using glass capillary array in the microfluidic device, and operating a few microfluidic devices in parallel.

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Figure 1. (A) Schematic illustration of the system used to develop single emulsion droplets;
(B) Schematic illustration of the system used to develop core-shell double emulsion droplets.

Figure 2. (A) Schematic illustration of the microfluidic device used to fabricate single emulsion droplets; (B) optical microscope images of a typical production at flow rates of the inner and outer phases of 25 $\mu\text{L}/\text{min}$ and 80 $\mu\text{L}/\text{min}$, respectively. Optical microscope images of microcapsules with diameters of (C) 50 μm , (D) 100 μm , and (E) 180 μm . Size distribution of the microcapsules with diameters of (F) 50 ± 8 μm , (G) 100 ± 13 μm , and (H) 180 ± 12 μm (confidence level: 90%).

Figure 3. (A) Schematic illustration of the microfluidic device used to fabricate core-shell double emulsion droplets. (B) Optical microscope image of a typical production at certain flow rates of the inner, middle and outer phases which were 5 $\mu\text{L}/\text{min}$, 30 $\mu\text{L}/\text{min}$, and 120 $\mu\text{L}/\text{min}$, respectively. (C) Optical microscope image of core-shell double emulsion microcapsules. (D) Size distribution of the inner core: $60 \pm 15 \mu\text{m}$ (confidence level: 90%); (E) Size distribution of the outer shell: $180 \pm 15 \mu\text{m}$ (confidence level: 90%).

Figure 4. (A) Release rate of rifampicin from microcapsules with different diameters. (B) Release rate of rifampicin from microcapsules with different morphology.

Table of contents (TOC)

A Non-polydimethylsiloxane (Non-PDMS) tube-in-tube glass-capillary microdevice is successfully fabricated and used for generation of drug-loaded microcapsules with different structures and sizes. The microcapsules can be used to design and fabricate drug delivery vehicles for the target applications, and regulate the release of drugs to satisfy the applications with required drug release profile.

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