

Formation of Uniform Microspheres Using a Perforated Silicon Membrane: A Preliminary Study

K.-Y. Song

University of Saskatchewan,
Saskatoon, SK S7N 5A9, Canada

M. Chiao

B. Stoeber

U. Häfeli

University of British Columbia,
Vancouver, BC V6T 1Z4, Canada

M. M. Gupta

W. J. Zhang¹

e-mail: chris.zhang@usask.ca

University of Saskatchewan,
Saskatoon, SK S7N 5A9, Canada

This paper presents a new method to generate uniform microspheres with biodegradable poly(lactic-co-glycolic acid) (PLGA) material using microelectromechanical system technology. The general idea with this method is such that a liquid phase containing the dissolved microsphere matrix material reaches a continuous phase after a silicon membrane with micron-sized perforations, where microdroplets are formed. After the droplet is detached from the membrane, the solvent diffuses out of the droplets into a continuous phase leading to the formation of solid microspheres. The experiment was performed to verify this method with some promising result. It has been shown that with this method, about 90% of the microspheres are in the range from 1 to 2 μm , which seems to be better than the result obtained with other methods using glass or ceramic membranes. The microsphere with such a size range is useful for intravascular applications and pharmaceutical drug delivery with a slow release of the drug at narrowly defined rates. [DOI: 10.1115/1.3212556]

Keywords: microsphere, uniformity, drug delivery, silicon membrane perforation, PLGA

1 Introduction

As biotechnology grows, protein and peptide drugs are considered as important therapeutic agents in recent medical treatments. When the drugs are injected to the artery, the agents are easily degraded in vivo. Recently, in order to improve the robustness in the drug delivery process, the polymer encapsulation of proteins was proposed to form microspheres [1,2]. For this purpose, poly(lactic-co-glycolic acid) (PLGA) has been examined as one of the potential encapsulating polymers due to its excellent biodegradable and biocompatible characteristics. The biodegradable encapsulated microspheres can deliver a therapeutic at a constant

rate for a longer period of time with very minimal toxicity [3–8]. There are generally three approaches to prepare for microspheres: solvent extraction/evaporation, phase separation, and spray drying [9]. One difficult problem in all these approaches is the uniformity of the microspheres. Uniformity is very important to have a consistent quality for drug delivery and therapeutic treatment, and other medical relevant areas such as chromatographic packing materials and dry and liquid tones for electrophotography.

This paper introduces a new method, based on microelectromechanical system (MEMS) technology, to produce uniform microspheres. The method is essentially based on the idea of the perforated silicon membrane. The size of droplets mainly depends on the pore size on the membrane and the speed of the cross flow. By applying a perforated membrane system, emulsion is involved under low pressure, different from the conventional techniques [10,11]. Additionally, the membrane is conducive to a low energy driver for narrower size distribution by varying and optimizing the operating parameters such as velocity of cross flow, concentration of the emulsifier, and dispersed phase flux [12–16].

2 Materials and Methods

2.1 Materials and Preparation. Poly(lactic-co-glycolic acid) (PLGA) with 0.61 of internal viscosity and 85:15 of a polyanhydride-lactide ratio was purchased from Durect Corp. (USA). The 5% of the PLGA solution as a dispersed phase was prepared after being dissolved in methylene chloride. Poly(vinyl alcohol) (PVA) with 13,000–23,000 of molecular weight and 87–89% of hydrolyzed degree was purchased from Sigma (USA). 1% of the PVA solution, dissolved in distilled water as a continuous phase, was prepared as emulsifier and stabilizer.

2.2 Microspheres. PLGA microspheres were generated using a perforated silicon membrane. The perforation size in square shape on the membrane was $0.5 \times 0.5 \mu\text{m}^2$, and the thickness of the silicon membrane was 2 μm . Figure 1 shows scanning electron microscope (SEM) images of the silicon membrane.

A silicon on insulator (SOI) substrate with 1 μm of silicon dioxide (SiO_2) layer was used. The SOI substrate underwent processes of photolithography, wet etching, and patterning. A focused ion beam (FIB) was used to pattern squares on the exposed SiO_2 layer after the wet etching process. Perforations were then achieved by another wet etching process through the left Si layer. The fabrication process of the perforated silicon membrane is illustrated in Fig. 2. The fabricated membrane was glued to a plastic luer of syringe needle, and the PLGA solution was pumped into the PVA solution, as shown in Fig. 3.

The pumped PLGA flux formed a droplet on the silicon membrane under four major forces caused by the action of the fluid, a drag force produced by a continuous phase flow, a force caused by the interfacial tension, a buoyant force, and an inertial force caused by a dispersed phase flow. The buoyant force and the inertial force are relatively very small, and can be neglected. The major forces on the droplet are described in Fig. 4. Thus, the droplet size can simply be estimated from a torque balance equation before detachment as follows:

$$F_1 = 10.2\pi\mu VR \quad (1)$$

$$F_2 = 2\sigma\pi R_p \quad (2)$$

$$F_1 R = F_2 R_p \quad (3)$$

where R is the radius of the droplet, which eventually becomes a microsphere, and R_p is the radius of a perforation. Thus, an equation for the radius of a microsphere can be derived as

¹Corresponding author.

Manuscript received July 24, 2008; final manuscript received June 2, 2009; published online September 1, 2009. Review conducted by Gary L. Bowlin.

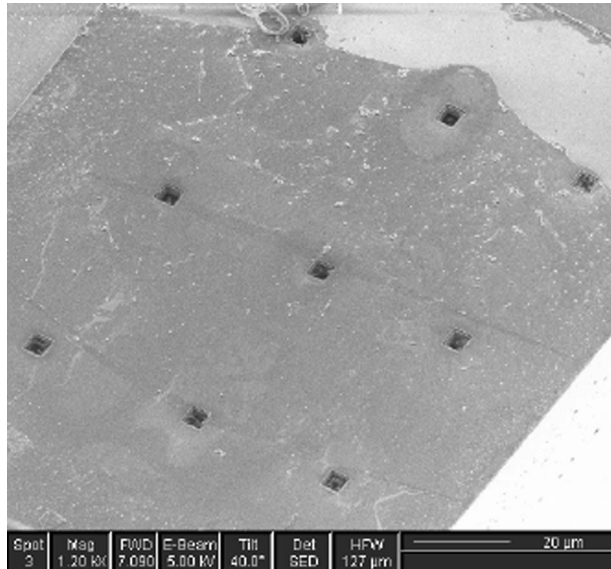


Fig. 1 A SEM image of the perforated Si membrane after the fabrication. The square perforations were fabricated by conventional photolithography processes and a focused ion beam patterning. The perforations were positioned far enough to avoid merging of the droplets.

$$R = \sqrt{\left(\frac{\sigma R_p^2}{10.2 \mu V}\right)} \quad (4)$$

where V is the tangential flow velocity of the continuous phase on the membrane, σ is the interfacial tension, and μ is the viscosity of the cross flow [13].

The PLGA droplet on the membrane is detached by the continuous phase cross flow generated by an agitator at the bottom of the glassware. The droplet on the perforated silicon membrane without the cross flow is shown in Fig. 5.

The velocity of the PLGA solution was 0.185 m/s, and a minimal pressure of 17.4 psi was applied through the pore. The speed of the agitator in the glassware was varied to optimize the capillary number. The desired microsphere diameter was reached at $Ca=0.15$. The detached PLGA droplets from the membrane were

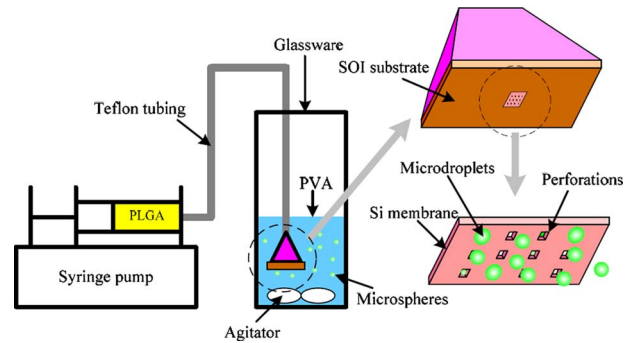


Fig. 3 Schematic view of the experimental setup. The PLGA is injected by a syringe pump, and passes through the perforations on the silicon membrane. The PLGA microsphere is forming when the droplet on the membrane is off by the cross flow on the membrane. The speed of the agitator determines the speed of the cross flow.

stabilized by PVA, underwent solvent evaporation, and transformed into microspheres. After the process, microspheres were separated by centrifugation, followed by the drying procedure.

Since the number of the collected microspheres at each experiment was not enough, a computational process was applied to measure the diameter of the spheres. Digital images of the microspheres were captured by an optical microscope connecting to a computer station, and 100 samples of microspheres were measured randomly at each experiment.

3 Results and Discussion

The major concern of this paper was to prove that a narrower distribution of microspheres can be achieved by using a silicon membrane with microsized perforations. The results of the experiment indicate a promising outcome. The size distribution of the microsphere is shown in Fig. 6 with different agitation speeds.

The results were achieved after three times of experiments at each agitation speed. The size distribution gives an average size of 1.56 μm and narrower size distribution with the definition of monodispersity. Table 1 shows the average diameter from the experiments and the theoretical results from the mathematical model

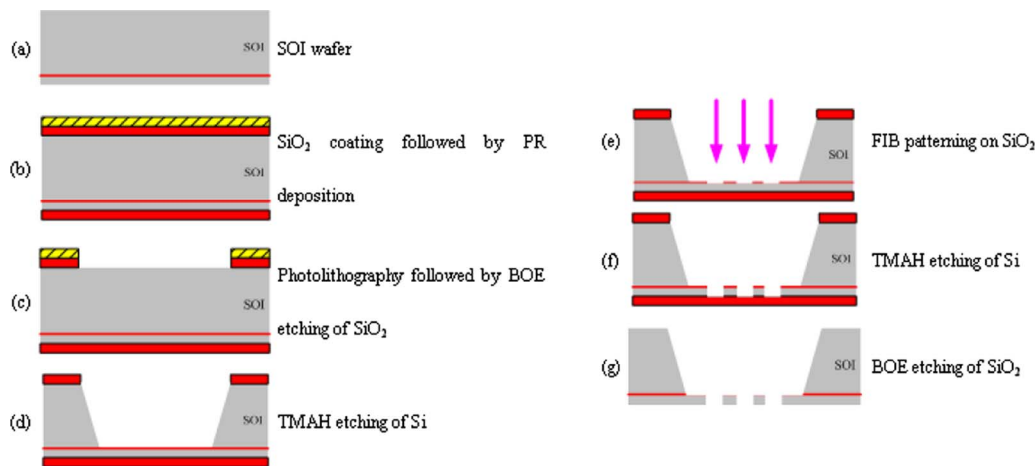


Fig. 2 Schematic view of the fabrication process (not drawn to scale). (a)–(d): The first conventional photolithography process with ultraviolet (UV) light and a wet chemical etching process with Tetramethylammonium hydroxide (TMAH). (e): The focused ion beam pattern squares on the exposed silicon dioxide. (f)–(g): The second conventional photolithography process with UV light and a wet chemical etching process.

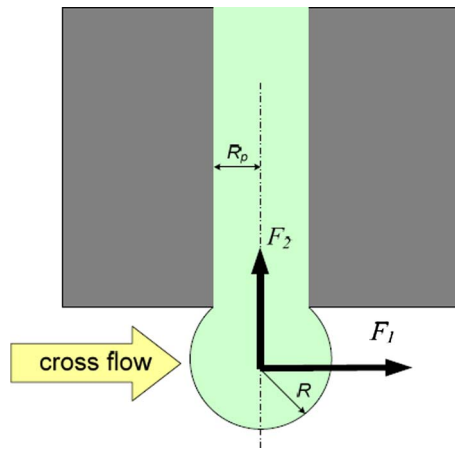


Fig. 4 Simplified acting forces on a droplet formed at perforation

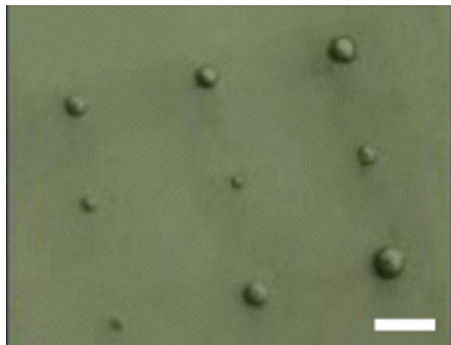


Fig. 5 The optical image of the droplets on the membrane without agitation. The white bar represents 25 μm .

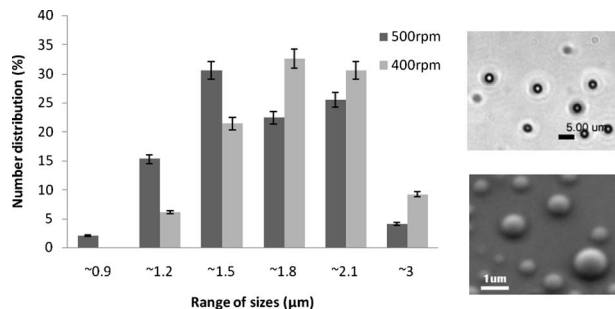


Fig. 6 Size distribution of the microspheres by two different agitation speeds (400 rpm and 500 rpm). Optical and SEM images of the microsphere are shown on the side.

of the microspheres by Eq. (4), where $\mu=1.7 \times 10^{-3}$ kg/m s and $\sigma=4.6 \times 10^{-3}$ N/m. The experimental results were very close to the outcome of the theoretical model.

4 Conclusion

In this paper, we described our work on developing a simple but very effective method to generate uniform microspheres using a

Table 1 The average diameters from experiments and the mathematical model

Agitation speed (rpm)	400	500
Measured (μm)	1.7	1.56
Theoretical (μm)	1.4	1.25

perforated silicon membrane. The device was fabricated and tested. With our device, only a slow stirring was applied to the continuous, compared with a vigorous stirring emulsion process such as a homogenizer that is applied by the devices developed by others, and this may then reduce the damage of the microspheres considerably. In particular, our device can achieve the production of microspheres with the diameter of $1 \sim 2 \mu\text{m}$ and the uniformity of about 90%. Although a specific size was targeted in this study, by varying the properties of PLGA and PVA solutions, and the size of perforation on the silicon membrane, other desired sizes of microspheres can be achieved.

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