ACOUSTICALLY EXCITED MICRO MASS TRANSPORT FOR REMOTELY DOSE-CONTROLABLE DRUG RELEASING

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ABSTRACT

Remotely activated drug release strategy with controllable dosage is the key factor of various targeting drug delivery methods as minimal invasive treatment. This article describes mass transport in liquid in microscale with a controllability of releasing amount, which is wirelessly excited by an external acoustic excitation. A liquid droplet (releasing agent, or drug in application) is trapped in the middle of a one-end open microtube which has a ratchet-structure on its inner wall. The droplet is trapped in the tube and neighbored by two gaseous air bubbles on both sides. In the presence of acoustic wave, the air bubbles oscillate and resonate. The air bubble near the tube opening segregates the liquid droplet into smaller ones and transport them on the ratchet-surface wall of the microtube. This mass transport occurs in both directions at similar rates: from the surrounding fluid to the trapped droplet and vice versa. As a result, the overall mass of droplet remains similar. Meanwhile, the other bubble positioned back in the tube sealing side enhances mixing between incoming mass from the surrounding and existing mass in the droplet. This mass transport is significant only when the inner wall of the tube has rachets. The exchanging mass between the surrounding and droplet is monotonically proportional to the excitation period, showing high controllability of mass transport. This mass transport phenomenon possibly provides a new mechanism of *in vivo,* on-demand, dose controllable drug delivery.

KEYWORDS

Microbubble oscillation, Drug delivery, Micro ratchet surface

INTRODUCTION

Drug delivery aims to administer a pharmaceutical compound to pathological sites, a specific organ or tissue, in body as a therapy. Traditional drug delivery routes include oral administration, inhalation, hypodermic or transdermal injection. However, there exist several drawbacks in the above routes. Drug is usually released at the location distant from the targeting location, resulting in loss and degradation. Therefore, higher dosage or concentration than actually required at the targeting location is used for the treatment and may cause toxicity to the healthy tissue [1, 2]. An ideal drug delivery must be capable of maintaining drug levels within a therapeutic window and adequate fluctuation over a desired period to maximize the therapeutic efficacy and minimize the systemic toxicity. To address this issue, the localized drug delivery system has been applied in order to release drug on targeting site with a desired profile via drug loaded carrier or implantable microsystem [3, 4]. These microsystems are capable of storing and releasing drug by either passive or active methods. Passive release is usually based on diffusion by drug-infused porous material or drug-permeable membrane, which provides a long and continuous release with less fluctuation. On the other hand, for certain therapy, it requires pulsatile release by active control that mimics the natural body's function such as insulin or hormone-based drug [1]. Microfluidic system is a preferable method for active drug release due to its ability of precise manipulation of fluid in small quantity.

An active microfluidic drug release system generally consists of three components: a drug reservoir, an actuator or pump and a membrane [1, 5] and incorporates with a strategy to drive the actuator on-demand. The simplest demonstration is actuated by manually pressurizing, opening the valve and releasing the drug from the reservoir [6]. However, this strategy is lack of flexibility to arbitrary release profile and only accessible within a certain depth. Making up for this lack, various stimuli-response reaction mechanisms have been developed to control releasing rate and time in microfluidic system. Electrochemical reaction can be employed by embedding two electrodes on the gold membrane and reservoir. Electrolysis by applied potential dissolves the gold membrane, pressurizes the reservoir, and releases the drug [7]. Local heating by a micro-resistor also generates a bubble and rupture the membrane that sealed the reservoir [8]. However, both methods require a power supply connected to the system and have only one-time release due to one-time membrane rupture, which are suitable only for emergency treatment. They may also cause damage to local cells or tissue by high electrolysis or high temperature. Changing pH was one of the stimuli applied to drug release mechanism. By functionalizing the surface of asymmetric nanopore with pH sensitive group, the nanopore can perform ionic selectivity and favor the passage of counter ions [9]on the site of tumor or inflammation since they cause lower pH than normal tissues and blood do. However, inducing pH change in a timely manner to achieve certain release profile may not be practical. For a more delicate control of release profile, magnetic deformation was incorporated to the microfluidic system. By inducing an inward movement of magnetic membrane with a pre-drilled orifice, drug can be released from the reservoir whenever an external magnetic field is applied [10]. Meanwhile, Jeong et al. used an acoustically oscillating bubble to release liquid from a microtube [11]. However, this method is also suitable for one-time burst and not for dosage control.

This article presents an on-demand, dose controllable active method to transport mass via acoustically oscillating gaseous bubble. This method only requires a microtube as a reservoir with the interior wall patterned with micro ratchets. A liquid (water) droplet is placed in the middle of the microtube as a replacement of a liquid drug in application. Then, when the entire microtube is submerged into liquid, two gaseous bubble automatically form inside the microtube on both sides of the droplet, as shown in Fig. 1. The gaseous bubbles serve as a membrane, valve and

pump at the same time. In the absence of external acoustic excitation, the outer gaseous bubble near the tube opening acts as a membrane that isolates the liquid drop from the liquid surrounding the tube. When an external acoustic wave is applied to the microtube, the outer bubble (bubble 1 in Fig. 1) oscillates. In a specific frequency window of the external acoustic wave, the oscillation of the outer gaseous bubble segregates the liquid droplet into smaller ones and transport them to the surrounding. Similarly, the surrounding liquid is segregated into small droplets, which are then delivered into the microtube. The ratchet structure on the microtube inner wall enhances the mobility of segregated liquid droplets. The inner bubble near the tube sealing side (bubble 2 in Fig. 1) also oscillates and promotes mixing within the liquid droplet to achieve an efficient and complete delivery. The rate of acoustic bubble induced mass release is controllable by the duty cycle of the external acoustic wave. Since the release rate and amount is controllable, arbitrary release profiles can be achieved. This present releasing mechanism is promising for either continuous or pulsatile drug release strategy in implantable devices.

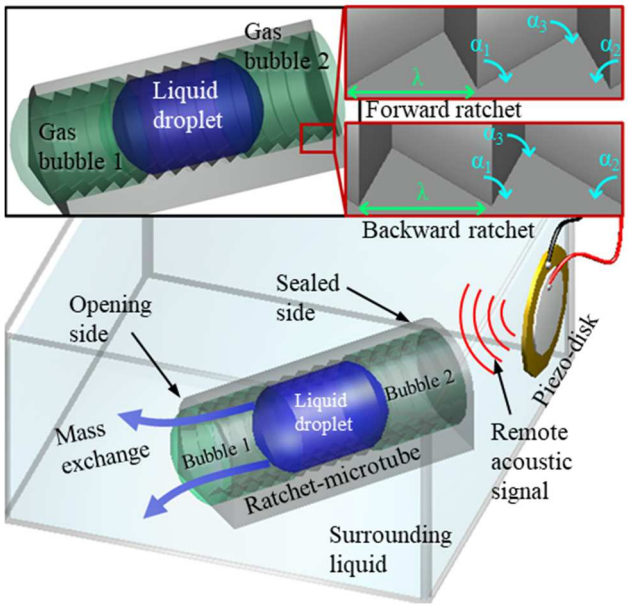

Fig. 1. Physical configuration for mass transport between the liquid droplet and surrounding liquid by two acoustically oscillating gaseous bubbles. The liquid droplet is sandwiched by the two bubbles. The one-end opening microtube has ratchets on the inner surface. Bubble 1 in the opening side not only serves as a barrier between the liquid droplet and surrounding liquid but also an actuator to transport mass, while bubble 2 in the sealing side enhances mixing in the liquid droplet.

EXPERIMENTAL

The microtube with ratchet structure on the inner wall was fabricated by a 3D laser printer utilizing two-photon polymerization (Nanoscribe® GmbH, Germany). First, a drop of photoresist (IP-S) was placed on an ITO-coated substrate and cured into designed conformation by the laser beam. Afterwards, the excessive photoresist was removed by SU8-developer (MicroChem Corp., USA), followed by a rinse of isopropanol (Sigma-Aldrich, USA). After the microtube is completely dried, 2% Teflon is coated on the interior wall.

The configuration of the microtube is shown in Fig. 1. A 0.1-μL blue-dyed water with the volume concentration of 2.4 % is first injected to the middle of the microtube by a microliter syringe (Hamilton, USA) to form a liquid drop, and a gaseous bubble is simultaneously trapped in the sealed end (Bubble 2). Then, by submerging the tube into the tank filled with water, another gas bubble (Bubble 1) is automatically trapped in the opening side due to the hydrophobicity of the tube interior. As a result, the water droplet is sandwiched between the two bubbles in the microtube. The two bubbles are acoustically excited by a piezo-disk glued to the wall of testing water tank.

RESULTS

Design of the Ratchet-Patterned Microtube

The microtube has an average diameter of 400 μm and 2000 μm in length with one end opened and the other one sealed as shown in Fig.1 (left inset). The inner surface of the microtube is structured with ratchet pattern, which has the base of period = 60 μm and the top angle $_3$ is 90 •. Two different directions of ratchet are designed to verify the impact on mass transport from ratchet geometry. (1) forward and (2) backward have leading ratchet angles $_1$, pointing to the opening end, at 30• and 60•, receding angle $_2$, pointing to the sealed end, at 60• and 30• respectively as shown in Fig. 1 (right insets). Six grooves of width at 5 μm are embedded in the ratchet pattern along the axial direction to assist the communication of gas between two bubbles for smoother mass transport result.

Mass Transport between Droplet and Surrounding

The fabricated ratchet microtube is displayed in Fig. 2(a) (left) where the transparent parts on two sides are the air bubbles and the blue part in the middle is the dyed-water droplet. The excitation signal is given at 2.4 kHz, 5.5 V with the duty cycle of 50% and the period of 2 seconds. After 15 effective cycles, the droplet inside ratchet microtube has a significant fade in color with negligible volume change (Fig. 2(a), right). On the other hand, the microtube of the same size but without ratchet pattern (flat inner wall instead) has no change under the same excitation input (Fig. 2(b)). Therefore, it implies that the content of the original droplet (blue dyed water) is delivered to the outside of the ratchet microtube while the clear water of similar amount was transported from the surrounding fluid to the location of the droplet inside the microtube. These two cases show the ratchet structure is the key factor of this phenomenon.

The process of the mass transport is quantified by measuring the change in dye intensity (color) of the droplet after each cycle. The intensity change in the droplet for the forward ratchet wall (Fig. 2(a)) and flat inner wall (Fig. 2(b)) are plotted in Fig. 2(c). The concentration of the liquid droplet inside the ratchet-microtube is decreased monotonically with increasing the actuation cycle. In contrast, the concentration remains almost the same for the droplet in the flat-microtube. A slight fluctuation may be attributed to the vibration and deviation of the location where the intensity is measured. Moreover, the amount of mass released from the ratchet microtube can be controlled

by the duty cycle, as shown in Fig. 2(d). Actuation signals have the period of 1 second with duty cycles at 50%, 37.5%, 25%, and 12.5%, respectively. With 50% duty cycle, mass transport can be completed in 3 cycles of actuation, which is suitable for pulsatile release. Shorter duty cycles such as 37.5% and 25% need longer time, 19 and 22 cycles, to complete mass exchange. In particular, the shortest duty of 12.5% needs up to 28 cycles to transport all the content of the liquid droplet out. The 12.5% duty cycle also expressed a steady and uniform release with less fluctuation, which is optimal for continuous release.

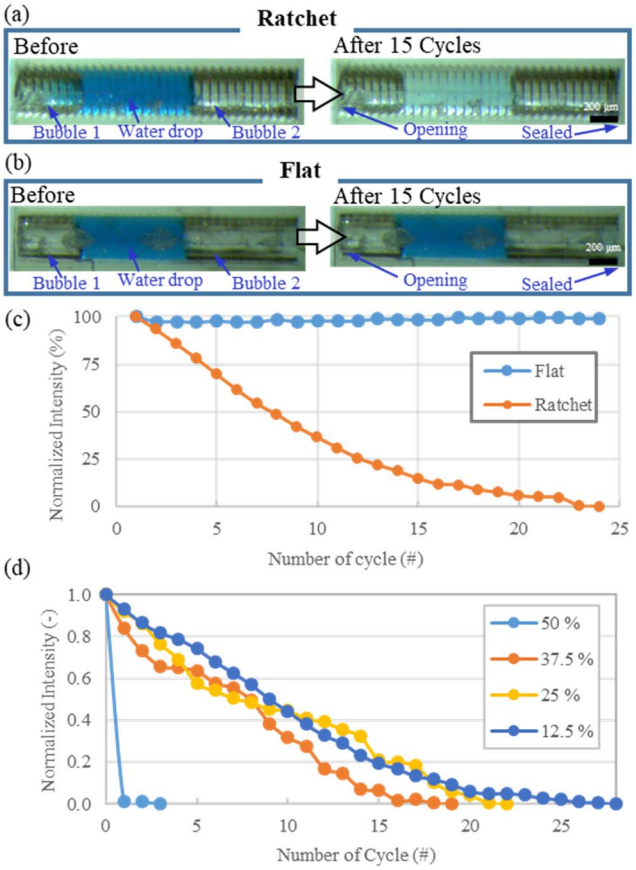

Fig. 2. Snapshots before and after acoustic actuation. The blue water droplet in (a) ratchet-patterned microtube turns transparent while the droplet in (b) flat-wall microtube remains the same in color. (b) The change in normalized intensity (color) with respect to the number of actuation cycle for ratchet-patterned and flat inner wall microtube and (c) for different duty ratios in ratchet-patterned microtube.

Effect of Ratchet Geometry and Gaseous Bubble

The above results indicate that the ratchet structure is a crucial factor to enable mass transport in such a gas-liquid-gas configuration. Hence, the effect of ratchet direction is studied by changing the ratchet structure. In Fig. 3(a), it shows that both forward and backward ratchets can generate mass exchange although the forward ratchet has higher exchange rate with less dye left in the droplet after the same excitation cycles. This indicates that the geometry of ratchet affects the mass transport rate to a certain extent. The functions of two air bubbles are demonstrated in Fig. 3(b) by removing bubble 2 from the microtube and filled the microtube with dyed water droplet all the way to the sealed end. When the external acoustic wave is applied, bubble 1 oscillates and initiates the mass exchange of the droplet from the left side, where it turns transparent. After more actuation cycles, the mass exchanged part is limited to the area closer to bubble 1 and the deeper part of the droplet remains unchanged. It is different from the previous case with two air bubbles where mass exchange occurs thoroughly within the entire droplet. It infers that bubble 2 enhances mixing within the droplet while bubble 1 exchanges mass.

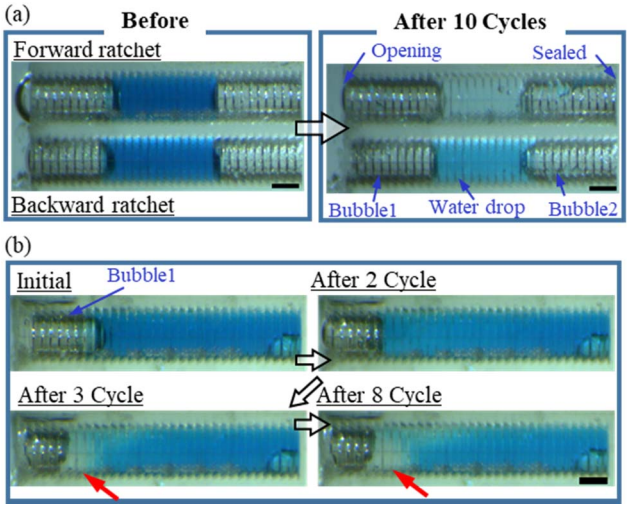

Fig. 3. (a) Effect of ratchet pattern (forward and backward). Both show significant color changes in water droplets (mass exchanges) although the forward pattern is slightly more efficient (b) Mass transport without bubble 2. The color change is limited to the vicinity of the bubble (red arrows), and there is almost no change in the deep sealed side.

Mechanism of Ratchet-Induced Mass Exchange

It was observed that the above stable mass exchange occurs only within a narrow window of frequency between 2.4 and 2.5 kHz. Out of this window, neither significant nor repeatable mass exchange was observed under similar oscillating amplitudes. Increasing the amplitude at other frequencies sometimes initiates the mass transport but is less stable, easily changes the volume of the droplet during mass exchange, and even splits the bubbles or droplet, thus destroys the original configuration. To study the mechanism of acoustic bubble induced mass transport, the elevated oscillating motion of bubble 1 under higher input voltage (2.4 kHz, 7.7 V) was captured by a high-speed camera. When the bubble is excited by the frequency within 2.4-2.5 kHz, the large bubble oscillation segregates liquid into smaller drops, as shown in Fig. 4(a). On the other hand, the excitation out of this window results in a mild back and forth movement of the liquid-air interface in the cross-section area only. No segregated droplet passage was observed under the actuation of off-frequency input. A sketch shows the concept of how the liquid is transported via the oscillation of the bubble in Fig. 4(b). Liquid from the trapped droplet is stretched and segregated by the deformation of oscillating bubble 1 and eventually forming smaller droplets between the ratchet surface and bubble 1.

Then, the undulating motion of the oscillating bubble 1 transports the smaller droplets out of the microtube. Simultaneously, the liquid from the surrounding is also separated into smaller drops and transported into the microtube. To confirm the motion of the segregated drop, 20 μm plastic particles were seeded into the trapped droplet. Fig. 5 shows that the particles are ejected out of the microtube opening as soon as the oscillation starts, which proves that the constituent of the droplet inside the microtube is delivered out.

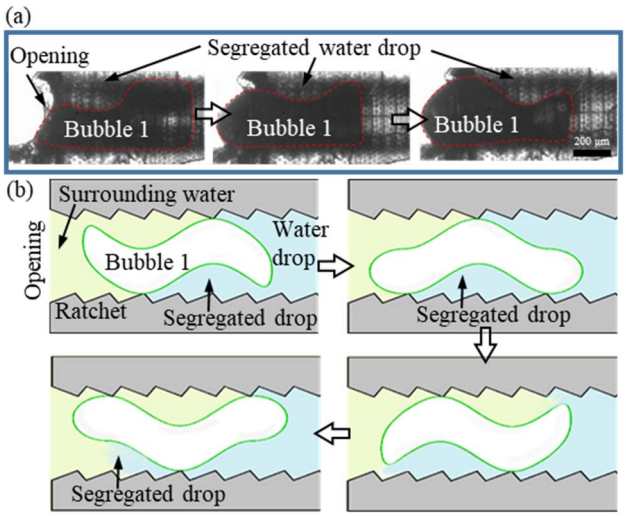

Fig. 4. (a) Sequential high-speed snapshots of bubble 1 (outlined by red dashed line) and water droplet under high-amplitude oscillation where smaller droplets segregated from the liquid droplet or surrounding water. The bubble oscillation with large amplitude stretches and segregates water into smaller droplets. The undulating motion of the bubble transports the segregated droplets on ratchet surface. All these processes occur in both directions (from the water droplet to the surrounding water or vice versa) (b) Simplified sketches of the high-speed images to clarify the mass transport mechanism.

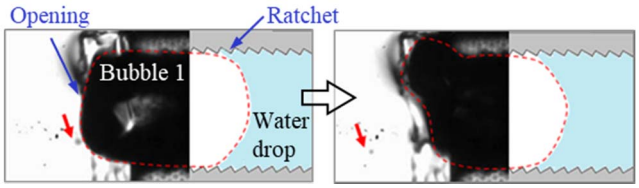

Fig. 5. High-speed images near tube opening. Microparticles initially seeded in the water droplet are ejected out of the tube (red arrows) when bubble 1 (outlined by red dashed line) oscillates.

CONCLUSION

This article describes a physical principle of microscale mass transport of liquid, which can be remotely activated and precisely controlled by an external acoustic field. When a liquid droplet neighbored by two gaseous bubbles are trapped in a one-end sealed microtube with ratchet-patterned interior wall, the outer bubble transports the liquid in the droplet to the outside and the inner bubble enables thorough mixing over the droplet to achieve effective mass transport. The mass transport is realized by specific oscillation mode of the outer bubble, which can be selectively activated by a certain frequency of acoustic input. Furthermore, the rate of release (mass transport) can be tuned by the duty cycle of actuation, and the total amount of release can be controlled by the number of actuation cycles. This allows either pulsatile or continuous drug release profile with on demand control for different type of therapy.

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