Microfluidic fabrication of monodisperse microcapsules with gas cores†

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A facile strategy for efficient and continuous fabrication of monodisperse gas-core microcapsules with controllable sizes and excellent ultrasound-induced burst performances is developed based on droplet microfluidics and interfacial polymerization. Monodisperse gas-in-oil-in-water (G/O/W) double emulsion droplets with a gas core and monomer-contained oil layer are fabricated in the upstream of a microfluidic device as templates, and then water-soluble monomers are added into the aqueous continuous phase in the downstream to initiate rapid interfacial polymerization at the O/W interfaces to prepare monodisperse gas-in-oil-in-solid (G/O/S) microcapsules with gas cores. The sizes of both microbubbles and G/O/W droplet templates can be precisely controlled by adjusting the gas supply pressure and the fluid flow rates. Due to the very thin shells of G/O/S microcapsules fabricated via interfacial polymerization, the sizes of the resultant G/O/S microcapsules are almost the same as those of the G/O/W droplet templates, and the microcapsules exhibit excellent deformable properties and ultrasound-induced burst performances. The proposed strategy provides a facile and efficient route for controllably and continuously fabricating monodisperse microcapsules with gas cores, which are highly desired for biomedical applications.

Introduction

Gas microcarriers refer to microstructures with gas cores, usually formed by embedding or encapsulating bubbles with sizes ranging from several micrometers to hundreds of micrometers within liposomes1–4 or polymer microcapsules.5–8 Encapsulated microbubbles can respond to external ultrasound9,10 and are commonly used in biomedical fields such as drug delivery11–15 and ultrasound contrast.16–22 Above all, gas microbubbles that can act as endogenous gaseous biological messengers to mediate diverse physiological functions have therapeutic effects on tumors.23–25 The gas microcarriers not only prevent microbubbles from merging, but also have a certain fluidity to transport microbubbles to the target positions.26–28 In most applications, the size distribution of the microbubbles plays an important role.29,30 However, the microbubbles prepared by common shearing methods usually have wide size distributions, which limit the applications for precise treatments.31 Therefore, the controllable preparation of monodisperse gas-core microcarriers is of great significance.

To date, several methods have been developed for preparing gas-core microcarriers, mainly including stirring emulsification,10,32–34 ultrasonic emulsification3 and microfluidic emulsification.7,35–37 The stirring emulsification and ultrasonic emulsification methods mainly use mechanical stirring or ultrasound to mix a gas with a liposome solution, and then form liposome microstructures that encapsulate microbubbles. For example, Kheirolomoom et al.10 added a buffer diluent consisting of 100 mM Tris, glycerol and propylene glycol to dried lipids to create a solution of multilamellar vesicles at a temperature above the lipid phase transition temperature of the lipids, and then decafluorobutane gas was slowly introduced into the liposome solution. The microbubble–liposome conjugation was formed via mechanical agitation of the liposome solution using a shaker. Ibsen et al.3 dissolved lecithin and cholesterol in chloroform, evaporated and removed the chloroform under an argon flow, and then added ethanol solution to prepare a liposome solution. Next, a mixture of boron trifluoride and air was introduced into the liposome solution, and a probe sonar was inserted into the solution for ultrasound to form microbubble-filled lipospheres. However, both of the above-mentioned stirring and ultrasonic emulsification methods still face certain problems, such as low gas loading, poor

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stability and non-uniform bubble sizes. Compared with the stirring and ultrasonic emulsification methods, microfluidic emulsification can generate microbubbles of uniform sizes through controllable flow shear. For instance, Abbaspourrad et al.\textsuperscript{35} used microfluidic technology to prepare water-in-oil-in-water (W/O/W) double emulsions, and then prepared hard-shell microcapsules filled with water through ultraviolet photopolymerization of ethoxylated trimethylolpropane triacylate (ETPTA). Subsequently, gas-filled microcapsules are prepared by drying to evaporate the core moisture and allowing air to enter into the microcapsules. Nevertheless, this method is limited by the type of gases that can be loaded in the microcapsules. Chen et al.\textsuperscript{7} used microfluidic technology to prepare gas-in-oil-in-water-in-oil (G/O/W/O) triple emulsions to load air. The polyethylene glycol diacrylate in the aqueous phase was then polymerized by irradiating ultraviolet light outside the microfluidic device to prepare particles with gas-in-liquid-in-solid (G/L/S) structures. However, the polymerization process of the G/O/W/O triple emulsions initiated by ultraviolet irradiation should be operated carefully in batches. To date, it is still challenging to efficiently achieve controllable and continuous fabrication of monodisperse gas-core microcapsules.

Here, we propose a facile strategy based on droplet microfluidics and interfacial polymerization to achieve controllable and continuous preparation of monodisperse microcapsules with gas cores. First, monodisperse gas-in-oil-in-water (G/O/W) double emulsions are fabricated in the upstream of a polydimethylsiloxane (PDMS) microfluidic device as templates, and then interfacial polymerization is initiated at the O/W interfaces in the downstream of the microfluidic device to prepare gas-in-oil-in-solid (G/O/S) microcapsules (Fig. 1a). To prepare the G/O/W double emulsions in the upstream, the water phase containing polyvinyl alcohol (PVA) is used as the continuous phase, the oil phase is soybean oil containing terephthaloyl chloride, and the gas phase is nitrogen as the model gas. Then, the water reaction phase containing PVA and ethylenediamine are added in the downstream. Ethylenediamine in the water phase and terephthaloyl chloride in the oil phase undergo rapid interfacial polymerization at the O/W interfaces of the G/O/W double emulsion droplets to form G/O/S microcapsules (Fig. 1b). The sizes of microbubbles and double emulsion templates as well as the resultant gas-core microcapsules can be effectively controlled by adjusting the supply pressure of the gas phase and the flow rates of the

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**Fig. 1** (a and b) Schematic illustration of the PDMS microfluidic device (a) and the principle of interfacial polymerization (b) for the preparation of monodisperse microcapsules with gas cores. (c) Design details of the PDMS microfluidic device. (d) Optical micrograph of the microchannel structure.
water and oil phases. Because the solid shells of the G/O/S microcapsules fabricated with the interfacial polymerization method are very thin, the prepared microcapsules exhibit excellent ultrasound-induced burst performances for delivering the encapsulated gas cores.

Materials and methods

Materials

Nitrogen (N₂) with a purity of 99.9% was purchased from QYG (Sichuan). Poly(vinyl alcohol) (PVA1799, Mₜ = 44.05) was purchased from Aladdin (Shanghai). Terephthaloyl chloride was purchased from Macklin. Ethylenediamine was purchased from Sinopharm. Polyisobutylene succinimide (T154) and soybean oil were purchased from Chengdu Kelong Chemicals. All other chemicals were of analytical grade and used as received without further purification. Deionized (DI) water was obtained from a Milli-Q water purification system (Millipore).

Fabrication of the microfluidic device

A self-designed PDMS microfluidic device was used to fabricate gas-core emulsions and microcapsules. The microfluidic device, which consists of an upstream part for forming monodisperse G/O/W double emulsions and a downstream part for initiating the interfacial polymerization to prepare G/O/S microcapsules (Fig. 1a), was fabricated with PDMS. The structures of the microchannels were first fixed on the silicon plate, and then the PDMS precursor and the cross-linker were poured into the mold at a ratio of 10:1. After vacuuming at room temperature for 30 min to remove bubbles from the solution, PDMS was further cured completely at 98 °C. The prepared PDMS device was used by fitting it on a glass sheet and modifying the surface wettability of microchannels with a hydrophilic PVA solution. In the upstream part, the width of the microchannel for the gas phase was 120 μm, and the widths of microchannels for the oil and water phases were 230 μm and 370 μm, respectively (Fig. 1c). The height of the entire microchannel was 120 μm. The prepared microchannels of the PDMS device exhibited regular structures with smooth surfaces (Fig. 1d).

Fabrication of monodisperse microcapsules with gas cores

Monodisperse gas-core microcapsules were prepared by generating monodisperse G/O/W double emulsions as templates first, and then forming thin solid shells at the O/W interfaces via interfacial polymerization (Fig. 1). The nitrogen gas phase was injected into the device through a cylinder connected to a constant pressure pump. 10 g of soybean oil dissolved with 0.4 g of T154 and 0.05 g of terephthaloyl chloride was used as the oil phase. T154 is an oil-soluble surfactant that can stabilize the gas core inside the oil phase. DI water dissolved with 5% (w/v) PVA and 0.5% (v/v) ethylenediamine was used as the water reaction phase in the downstream. The oil and water phases were respectively injected into the PDMS device using syringe pumps (LSP01-1A, Baoding Longer). Monodisperse microdroplets containing microbubbles were generated by controlling the gas pressure and the flow rates of the oil and water phases (Movie S1 in the ESI†). When the gas-core emulsions got into the downstream of the PDMS device, terephthaloyl chloride in the oil phase and ethylenediamine in the water phase came into contact, and interfacial polymerization occurred rapidly at the O/W interfaces of the emulsions, forming the polymer shells encapsulating the oil solution and microbubbles. The principle of interfacial polymerization was shown in Fig. 1b. The obtained monodisperse gas-core microcapsules were washed with DI water to remove the residual chemicals for subsequent experiments.

Regulation and control of the sizes and structures of gas-core emulsions and microcapsules

Using the microfluidic devices, gas-core emulsion templates with different sizes were obtained by adjusting the gas pressure and the flow rates of oil and water phases. The gas pressure was adjusted to 107 mbar and 120 mbar respectively, and the corresponding flow rates of oil and water phases were adjusted in both cases to obtain microbubbles and gas-core emulsions with different sizes. In addition, when the flow rates of oil and water phases were constant, the number of encapsulated microbubbles in each emulsion droplet could be controlled by adjusting the gas pressure. The gas-core emulsion droplets with different sizes were then used as templates for fabricating gas-core microcapsules via interfacial polymerization reaction at the O/W interfaces of emulsion droplets. According to previously reported results,39,40 the sizes of microbubbles and emulsion droplets can be determined primarily by the balance between viscous shear force and surface tension, which can be described by the capillary number (Ca):

\[
Ca = \frac{u_c \mu_c}{\gamma}
\]

(1)

where \(u_c\) and \(\mu_c\) are the velocity and viscosity of the continuous phase respectively, and \(\gamma\) is the interfacial tension.

Thus, by combining the flow rates of the gas, oil and water phases, the prediction of the sizes of microbubbles and emulsion droplets can be expressed by the following equations:

\[
\frac{d_{gas}}{d_i} = K_1Ca^\alpha \left( \frac{Q_o}{Q_g} \right)^\beta + C_1
\]

(2)

\[
\frac{d_e}{d_m} = K_2Ca^\alpha \left( \frac{Q_g + Q_o}{Q_w} \right)^\beta + C_2
\]

(3)

where \(d_{gas}\) and \(d_e\) are the diameters of microbubbles and emulsion droplets; \(Q_o\), \(Q_g\) and \(Q_w\) are the flow rates of the gas, oil and water phases, respectively; \(K_1\), \(K_2\), \(C_1\) and \(C_2\) are constants for the built microsystem; \(d_i\) and \(d_m\) are the
equivalent diameters of the microchannel outlets for gas and oil phases, respectively; and α and β are the indices of capillary numbers and flow rate ratios, respectively.

**Study on the stability of gas-core emulsion droplets**

To study the stability of the gas-core emulsion droplets, the prepared droplets were collected in different collection baths, which were DI water, DI water containing 3 wt% SDS and DI water containing 5 wt% PVA. The stability was determined by calculating the encapsulation rates at different time periods in different solution environments, and the encapsulation rates of the microbubbles in the droplets were examined from 0 to 30 min. In addition, the thermodynamic stability was investigated with the spreading parameter (S), which is defined and calculated with eqn (4):

$$S = \gamma_w - (\gamma_o + \gamma_{wo})$$

where S is the spreading parameter, γ_w is the water–gas interfacial tension, γ_o is the oil–gas interfacial tension, and γ_{wo} is the water–oil interfacial tension.

**Test of the elasticity of microcapsules**

The elasticity of the microcapsules was measured using a microparticle strength tester (Microforce Measurement Ltd, UK). The principle of the tester is based on the compression of a single microcapsule into different deformations or ruptures between two parallel surfaces and the simultaneous measurement of the corresponding forces.⁴¹,⁴² A 400 μm glass probe was mounted on a force transducer (Model 405A, Aurora Scientific). The force transducer was mounted on a 3D micromanipulator to precisely control the position of the probe. The prepared microcapsules were compressed to various degrees at room temperature. The force–displacement curves of the microcapsules with different polymerization time periods were plotted, and the elasticities of the microcapsules can be calculated by analyzing the curves.

**Investigation of the ultrasound-induced burst performances of gas-core microcapsules**

To explore the ultrasound-induced burst performances of gas-core microcapsules, the effects of the ultrasonic power, distance and interstitial oil thickness on the burst behaviors of gas-core microcapsules were investigated. A medical ultrasound probe with adjustable power from 1 to 5 W was used, a glass slide was fixed on the probe and the microcapsules were placed at positions with different distances from the probe. In addition, a rat’s back skin was placed between the probe and the glass sheet to test the effect of ultrasound penetrating the skin on the burst performance of the microcapsules. Furthermore, the effect of interstitial oil thickness of gas-core microcapsules on the ultrasound-induced burst performances were investigated by introducing an index called interstitial oil ratio (φ), which was defined and calculated with eqn (5):

$$\varphi = (d_p - d_{gas})/d_p$$

where φ is the interstitial oil ratio, d_p is the diameter of microcapsules, and d_{gas} is the diameter of gas core.

The optical micrographs of the burst processes of gas-core microcapsules at different distances triggered with different powers were recorded using a high-speed camera.

Furthermore, a self-designed in vitro embolization chip was constructed using 3D printing with transparent resin to simulate the embolization behavior of the bifurcated microchannels of vascular networks. The maximum diameter of the microchannel in the embolization chip was set as 800 μm, and the diameter of each bifurcation was uniformly reduced with a proportional coefficient of 0.6. The minimum diameter of the microchannel in the embolization chip was 170 μm. An amplifying chamber was constructed at the end of the smallest channel. The prepared gas-core microcapsules were injected into the in vitro embolization chip with a constant flow pump to simulate the embolization in the microchannels in the chip, and the chip was placed on the ultrasound generating platform with the medical ultrasound probe to investigate the ultrasound-induced burst behaviors of the gas-core microcapsules in the microchannels.

**Results and discussion**

**Effects of gas pressure and flow rates of oil and water fluids on the sizes of gas-core droplet templates**

In various applications, microbubbles and microcapsules with different sizes are usually desired. Within the above-mentioned PDMS microfluidic device, the G/O/W droplets are generated with controllable sizes of both the gas cores and the droplets. The effects of gas pressure and flow rates of oil (Q_o) and water (Q_w) fluids on the sizes of microbubbles and gas-core droplets are investigated (Fig. 2). When Q_o and Q_w are fixed, both the size of the microbubble (d_{gas}) and the droplet size (d_e) increase with increasing gas supply pressure (Fig. 2a and b). The increase of the gas pressure results in the increase of the microbubble size, and then the size of the G/O/W droplet increases accordingly. When Q_o increases while the flow rates of other phases remain constant, both d_{gas} and d_e decrease (Fig. 2a and b), because the shear force on either the gas phase or the oil phase increases with increasing flow rate of the outer fluid. When Q_o increases while the flow rates of other phases remain constant, d_{gas} decreases and d_e increases linearly (Fig. 2c and d). That is, d_e is proportional to Q_o and d_{gas} is inversely proportional to Q_o. By adjusting the flow rates and gas pressure, monodisperse G/O/W droplets with adjustable sizes of droplets and gas cores can be obtained easily (Fig. 2e).

Furthermore, it is possible to adjust the number (N) of encapsulated microbubbles in each droplet (Fig. 3). When Q_o and Q_w are fixed, if the gas pressure is too low, no microbubbles can be generated in the droplets (Fig. 3a1). With increasing gas pressure, the number of encapsulated microbubbles in a single droplet can increase from 1 to 5
By fitting the experimental data of $\frac{d_{\text{gas}}}{d_i}$ and $K_1 \text{Ca}^{1.15} \left( \frac{Q_g}{Q_o} \right)^{1.89}$ in eqn (2), the average size of microbubbles ($d_{\text{gas}}$) can be predicted with eqn (6) (Fig. 4a):

$$\frac{d_{\text{gas}}}{d_i} = 292.76 \text{Ca}^{1.15} \left( \frac{Q_g}{Q_o} \right)^{1.89} - 2.01 \quad (6)$$

By analyzing and comparing the differences between the sizes of the microbubbles obtained from the experimental data and those calculated by eqn (6), the results show that all the relative errors are within ±5% (Fig. 4b).

Similarly, by fitting the experimental data of $\frac{d_e}{d_m}$ and $K_2 \text{Ca}^{0.94} \left( \frac{Q_g + Q_o}{Q_w} \right)^{0.74}$ in eqn (3), the average size of G/O/W droplets ($d_e$) can be predicted with eqn (7) (Fig. 4c):

$$\frac{d_e}{d_m} = 1.99 \text{Ca}^{-0.014} \left( \frac{Q_g + Q_o}{Q_w} \right)^{-0.74} - 0.48 \quad (7)$$

By analyzing and comparing the differences between the sizes of G/O/W droplets obtained from the experimental data and those calculated by eqn (7), the results show that all the
relative errors are within ±5% (Fig. 4d). The results confirm that eqn (6) and (7) can be used to precisely predict the sizes of microbubbles and G/O/W droplets generated in the designed microfluidic device.

Effect of the collection bath environment on the stability of G/O/W droplets

To prepare gas-core microcapsules, it is crucial to study the stability of G/O/W droplets. The stability of G/O/W droplets in different collection bath environments is investigated in this study (Fig. 5). With DI water as the collection bath, the G/O/W droplets have good stability in the first 5 min (Fig. 5a and b). However, as time goes on, the G/O/W droplets get more and more unstable, and the percentage of the stable G/O/W droplets remains about only 50% after 30 min (Fig. 5b). Because DI water in the collection bath dilutes the PVA concentration in the continuous phase, the stability of the G/O/W droplets gets worse and worse with time going on. In the DI water environment, the interfacial tension values of $\gamma_w$, $\gamma_o$ and $\gamma_{wo}$ are 70.8, 26.3 and 38.4 mN m$^{-1}$ respectively, and the resultant spreading parameter ($S$) is 6.1 (>0), which means that there is thermodynamic stability in this environment. With SDS solution in the collection bath, the microbubbles tend to escape from the G/O/W droplets rapidly (Fig. 5c and d). After 5 min, no stable G/O/W droplets are left in the SDS solution anymore (Fig. 5d). Because the SDS molecules have strong affinity for microbubbles, the existence of SDS molecules in the environmental aqueous solution causes the escaping of gas cores from the G/O/W droplets, thus resulting in instability of the G/O/W droplets. In the SDS solution, the $\gamma_w$, $\gamma_o$ and $\gamma_{wo}$ values are 40.4, 26.3 and 18.4 mN m$^{-1}$ respectively, and the resultant $S$ value is $-4.3$ (<0), which means that there is thermodynamic instability in the SDS solution. With PVA solution in the collection bath, the G/O/W droplets exhibit excellent stability in the experiments (Fig. 5e and f). With PVA molecules as the stabilizers in the continuous phase, the G/O/W droplets remain completely stable even after 30 min (Fig. 5f). In the PVA solution, the $\gamma_w$, $\gamma_o$ and $\gamma_{wo}$ values are 79.7, 26.3 and 37.5 mN m$^{-1}$ respectively, and the resultant $S$ value is 15.9 (>0), which means that there is thermodynamic stability in the PVA solution. Therefore, in the water reaction solution in the downstream of the microfluidic device, PVA is added to ensure the stability of G/O/W droplets for template fabrication of gas-core microcapsules. In addition, the stability of gas-core microcapsules depends on the solubility of the gas cores in the oil solution. Since the gas core is insoluble in oil solution in this study, the gas-core microcapsules have good stability in the experiments.
Relationship between the sizes of G/O/W droplets and gas-core microcapsules

Gas-core microcapsules are fabricated from the G/O/W droplets as templates; therefore, the sizes of the polymerized microcapsules strongly depend on the sizes of the G/O/W droplets. The relationship between the sizes of G/O/W droplets and those of polymerized microcapsules is investigated (Fig. 6). Using monodisperse G/O/W droplets with different sizes as templates, uniform gas-core microcapsules with different sizes can be successfully obtained (Fig. 6a). The results show that the average diameter of microcapsules ($d_p$) is almost the same as that of the G/O/W droplet templates ($d_e$) (Fig. 6b). Because the polymer shells of microcapsules formed at the O/W interfaces of G/O/W droplets via interfacial polymerization are as thin as 2–3 μm (Fig. 6c and d), and the shell thickness is uniform and is not influenced by the buoyancy of the gas, there is no obvious change in the sizes when the G/O/W droplets are converted into gas-core microcapsules.

Elastic property of gas-core microcapsules

The elastic properties of gas-core microcapsules are tested in an ethyl alcohol environment using a 10 g force transducer. In the ethyl alcohol environment, gas-core microcapsules can sink to the platform to contact probe for measurement. First, the microcapsules are compressed to 30% by the microprobe, followed by withdrawing the force immediately. The results show that the microcapsules can immediately recover from the compressed state (Fig. 7a), and the polymer shell of the microcapsule sticks to the probe during the recovering process because there exist hydrogen bonding forces between the amide bonds in the polyamide shell and the hydroxyl groups on probe surface, and the alcohol–water environment also strengthens the hydrogen bonding force. Next, the microcapsules are compressed by the microprobe until rupture, followed by withdrawing the force immediately (Fig. 7b). The results show that the microcapsules are completely crushed. The elastic properties of gas-core microcapsules prepared with different polymerization time
periods are obtained by measuring the force–displacement curves. By analyzing the force–displacement curves, the Young’s moduli ($E$) of gas-core microcapsules prepared with different polymerization time periods are determined. The results show that the polymerization time nearly does not affect the Young’s moduli of gas-core microcapsules, and the Young’s moduli of gas-core microcapsules prepared with polymerization time varying from 10 min to 50 min are all 0.1 MPa (Fig. S1 in the ESI†). Because the interfacial polymerization reaction is extremely fast, and the time period needed for the complete polymerization reaction is generally much less than 10 min. Therefore, the thickness of the microcapsule shell does not significantly change with the polymerization time in this study (Fig. 6d). As mentioned above, the polymer shells of microcapsules formed at the O/W interfaces of G/O/W droplets via interfacial polymerization

![Fig. 5](image-url)
Fig. 6 The diameters and the shell thicknesses of polymerized microcapsules. (a) Optical micrographs of monodisperse polymerized microcapsules with average diameters of 440 μm (a1), 522 μm (a2), 561 μm (a3), and 578 μm (a4). (b) Relationship between the sizes of G/O/W droplets (d_e) and those of polymerized microcapsules (d_p). (c) SEM images of parts and fragments of freeze-dried microcapsules prepared with polymerization time of 10 min (c2), 20 min (c1 and c3) and 50 min (c4). (d) Relationship between the shell thicknesses of polymerized microcapsules and the polymerization time periods.

Fig. 7 The compressing and recovering processes of gas-core microcapsules when the microcapsules are compressed by the microprobe to 30% (a) and until rupture (b). t = 0, 9, 14, 17 and 20 s in a1, a2, a3, a4 and a5, and t = 0, 24, 29, 32 and 34 s in b1, b2, b3, b4 and b5.
are very thin; as a result, the Young's moduli of gas-core microcapsules are very low. Actually, the elasticity of the gas-core microcapsules is lower than the minimum detection limit of the instrument, so the elasticity value 0.1 MPa is the minimum detection limit. Nevertheless, the results confirm that gas-core microcapsules have good compressibility and deformation performances.

**Ultrasound-induced burst performances of gas-core microcapsules**

One of the main advantages of gas-core microcapsules is that the gas core inside can respond to ultrasound. Upon ultrasonic triggering, the gas cores inside the microcapsules generate resonating to cause the rupture of the microcapsule shells; as a result, the gas cores can be released from the microcapsules. Recorded with a fast camera, the optical micrographs show that the ultrasound-triggered burst process of gas-core microcapsules is finished in a sudden moment (Fig. 8a, Movie S2 in the ESI†). To quantitatively explore the ultrasound-triggered burst performances of gas-core microcapsules, the effects of ultrasonic power, ultrasonic distance and interstitial oil thickness on the average breaking time of ultrasound-triggered burst of gas-core microcapsules are investigated. The results show that as the ultrasonic power increases from 1 to 5 W, the average breaking time decreases.

![Fig. 8](image-url)

**Fig. 8** Ultrasound-triggered burst of gas-core microcapsules. (a) Optical micrographs showing the ultrasound-triggered burst process of a gas-core microcapsule triggered with an ultrasonic power of 5 W and a distance of 2 cm. t = 0, 1000, 1050, 1100, 1200 and 1600 ms in a1, a2, a3, a4, a5 and a6. (b) Effect of the ultrasonic power on the average breaking time of ultrasound-triggered burst of gas-core microcapsules. (c) Effects of ultrasonic distance and medium on the average breaking time of ultrasound-triggered burst of gas-core microcapsules. (d) Effects of interstitial oil thickness on the average breaking time of ultrasound-triggered burst of gas-core microcapsules with an ultrasonic power of 5 W and a distance of 2 cm. (e) Optical image of the in vitro embolization chip. (f) Optical micrographs of the gas-core microcapsule in the microchannel (f1), and the ultrasound-triggered burst of the gas-core microcapsule in the microchannel (f2).
Adding water-soluble monomers into the aqueous continuous phase in the downstream of the microfluidic device to prepare monodisperse G/O/S microcapsules with gas cores. The sizes of microbubbles and G/O/W droplet templates can be precisely controlled by adjusting the supply pressure of the gas phase and the flow rates of the oil and water phases. Because the solid shells of the G/O/S microcapsules fabricated via the interfacial polymerization method are very thin, the sizes of the resultant G/O/S microcapsules are almost the same as those of the G/O/W droplet templates. Due to the thin shells, the prepared gas-core microcapsules exhibit excellent deformable properties and ultrasound-induced burst performances. The proposed strategy and the results in this study provide valuable guidance for controllable and continuous fabrication of monodisperse gas-core microcapsules with controllable sizes, which are highly promising in biomedical applications for developing novel formulations for embolic and gas-mediated therapy of cancer.

Data availability
The data supporting this article have been included as part of the ESI.

Author contributions
The manuscript was written through contribution of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

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