Fabrication of Cyanoacrylate Hollow Particles using Microbubble Generation Technique

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Abstract: This paper describes the fabrication of hollow particles using microbubble generation technique. Conventional hollow particle generation techniques relate to several problems such as long synthesis time and complicated process. In this study, we succeeded in the fabrication of hollow particles having a diameter of <5 μm by simply blowing cyanoacrylate vapor into water in the form of microbubbles. However, in order to apply the hollow particles for medical applications, it is required to decreasing the diameter. Therefore, in the form of microbubbles and examined the effect of pH and gas supply on the fabricated particles. As a result, hollow particles fabricated in pH 3 condition were much smaller than those fabricated in pH 7 condition, and the use of poorly-soluble gas increased the ratio of hollow particles to solid particles. The CA particles prepared in this study would possibly have excellent thermal and sound insulation properties owing to the hollow structure. Furthermore, though further downsizing of hollow particles are required, CA particles can find the application for drug delivery to the targeted sites.

Keywords: Hollow particles, Cyanoacrylate, Ultrasonic oscillation, Microbubbles

1. Introduction

Fine bubbles, known as microbubbles, have attracted attention in recent years. Microbubbles have been widely used in agriculture, industry, fishery, and medicine because they possess unique characteristics, unlike millimeter- or centimeter-size bubbles. In particular, microbubbles have diameters of <100 μm, which are favorable for washing and sterilization of food, and decomposition of chemicals because of their unique properties such as low rising velocity, large surface area per unit volume, and absorption to the surface of microbubbles. Makuta et al. succeeded in generating microbubbles <100 μm in size by irradiating an ultrasonic wave to a hollow cylindrical ultrasonic horn (HUSH) that has a flow path inside [1]; they also applied this method for the production of hollow particles <10 μm in size with a cyanoacrylate shell [2]. This method with microbubbles is simple and short-time fabrication process because the removal process of the organic beads template from the solid core microcapsule generally is required for obtaining hollow structure in the conventional method for hollow particles [3]. Hollow particles with internal voids have favorable characteristics, including heat and sound insulation, and low specific gravity, which can be applied in the industry [4]. Furthermore, hollow particles having a diameter of <5 μm that show biocompatibility can pass through capillary vessels [5]. Therefore, they can be utilized in medicine as ultrasonic contrast agents and drug delivery agents. Cyanoacrylate (CA) is a biocompatible resin, which is the main component of instantaneous adhesive as the shell material of hollow particles. CA, which is biocompatible polymeric material, is also used for medical applications such as skin adhesion. Fig. 1 shows a polymerization model of CA. CA starts polymerization by reacting with water and forms a high polymer shell [9]. As a characteristic of CA, the reaction with water is very fast and it reacts with a trace amount of moisture in the air to complete polymerization in a few seconds. In addition, CA polymerizes faster under alkaline conditions and slower under acidic conditions [10].

![Polymerization model of cyanoacrylate](image)

2. Materials and Method

2.1 Materials

We used CA (Aron Alpha 201, Toagosei Co., Ltd., Minato, Japan) which is the main component of instantaneous adhesive as the shell material of hollow particles. CA, which is biocompatible polymeric material, is also used for medical applications such as skin adhesion. Fig. 1 shows a polymerization model of CA. CA starts polymerization by reacting with water and forms a high polymer shell [9]. As a characteristic of CA, the reaction with water is very fast and it reacts with a trace amount of moisture in the air to complete polymerization in a few seconds. In addition, CA polymerizes faster under alkaline conditions and slower under acidic conditions [10].
fabricated by these methods because CA vapor causes clogging of the porous media or is solidified before it is atomized by the shear flow nozzle. In this study, we used the hollow cylindrical ultrasonic horn (HUSH), which was connected to 15 kHz ultrasonic transducer to generate microbubbles. The HUSH includes a path of inner diameter φ3 mm for gas supply and amplifies the ultrasonic oscillation generated by the ultrasonic transducer. The gas-liquid interface is formed by supplying gas to the tip end of the HUSH placed in water. Ultrasonic oscillation severely disturbs the gas-liquid interface that generates microbubbles. Fig. 2 shows sequential images of microbubble generation using the HUSH. With the HUSH, microbubbles can be generated within a few milliseconds, before complete solidification.

![Sequential images of microbubble generation using the HUSH](image)

**2.3 Experimental apparatus**

Figure 3 shows the outline of the experimental apparatus. In this study, we used a microbubble generator device that consists of an HUSH connected to a bolt-clamped Langevin-type transducer (HEC-6015P4B, Honda Electronics Co. Ltd., Toyohashi, Japan) to generate microbubbles before the CA vapor completely solidified at the gas-liquid interface [1]. Furthermore, we used a cooling water circulation apparatus (LTC-450A, AS ONE Co. Ltd., Osaka, Japan) to control the temperature of the aqueous phase. The dry air supplied from the dry air generator (AT-20H, AS ONE Co. Ltd., Osaka, Japan) was heated using a water bath (TM-1, AS ONE Co. Ltd., Osaka, Japan) and a tube cover heater (SRX-6.35-10, AS ONE Co. Ltd., Osaka, Japan), and the flow rate of the supplied gas was adjusted using a flow meter (RK-1650, KOFLOCK Co. Ltd., Kyotanabe, Japan). CA was vaporized using a hot stirrer (RSH-IDN, AS ONE Co. Ltd., Osaka, Japan). Images of the CA hollow particles were recorded by a scanning electron microscope (JSM-7600FA, JEOL Co. Ltd., Akishima, Japan, hereinafter SEM) and transmission electron microscope (JEM-2100, JEOL Co. Ltd., Akishima, Japan, hereinafter TEM). The particle diameter was measured from the SEM images using image analysis software (Mac-View Ver. 4, Mountech CO. Ltd., Shinjuku, Japan).

![Experimental apparatus for the fabrication of CA hollow particles](image)

**2.4 Fabrication of CA hollow particles**

We fabricated CA hollow particles via the following four steps.

1. 0.04 g of sodium deoxycholate (Waco Pure Chemical Industries Co. Ltd., Osaka, Japan), which is a surfactant, and 0.2 g of tartaric acid (Waco Pure Chemical Industries Co. Ltd., Osaka, Japan), which is a pH regulator, were dissolved in 400 mL of pure water to obtain an aqueous solution. The aqueous solution was cooled using a cooling water circulation device.
2. 4.0 g of CA was placed in a 50-mL triangle flask with an air inlet and a mixed gas outlet, and then vaporized at 250 °C under stirring at 500 rpm by a hot stirrer.
3. Dry air was supplied to the triangle flask at a flow rate of 1100 mL/min and mixed with the CA vapor.
4. A mixture of CA vapor and dry air was supplied to the microbubble generator, and microbubbles were fabricated by irradiating ultrasonic waves in an aqueous solution for 10 min. CA hollow particles were fabricated when CA polymerized at the gas-liquid interface of the generated microbubbles.

**3. Results and Discussion**

**3.1 Influence of acid**

The pH of the aqueous phase was 7.0–7.5 (neutral condition) and was adjusted 3.0–3.5 (acidic condition) by adding tartaric acid. In this study, sodium deoxycholate was added to each aqueous phase to stabilize the generated microbubbles. Figs. 4 and 5 show SEM images of the CA hollow particles fabricated at neutral and acidic pH, respectively. As shown in Figs. 4 and 5, many spherical particles were observed under the acidic condition, however, few particles were observed under the
neutral condition. From Figs. 4(a) and 5(a), we observed that the diameter of the fabricated particles was ~4 μm under neutral conditions and ~800 nm under acidic conditions. Figs. 4(b) and 5(b) show the hollow structure of the CA particles. The mean diameter and standard deviation of the fabricated particles was 4.14 ± 1.20 μm (n = 20) under the neutral conditions and 0.91 ± 0.22 μm (n = 1000) under the acidic conditions. The diameter of the hollow CA particles decreased at pH 3.0–3.5 compared with pH 7.0–7.5, because the shell formation rate decreased under the acidic conditions. CA polymerizes and solidifies when in contact with water, but the polymerization proceeds slowly under acidic conditions. Furthermore, microbubbles undergo self-pressurization and hence shrink in a liquid because of surface tension [13]. Thus, the microbubbles decreased in size during the slow polymerization. The hollow CA particles became smaller in size under acidic conditions because the microbubbles with CA vapor shrank to a greater extent under the acidic conditions when compared with that under the neutral conditions.

![Fig.4 SEM images of fabricated CA hollow particles without tartaric acid (neutral condition)](image)

![Fig.5 SEM images of fabricated CA hollow particles with tartaric acid (acidic conditions)](image)

3.2 Influence of gas supply

Since the microbubbles acted as a template for the fabrication of the CA hollow particles, we hypothesized that the fabricated particles were influenced by the type of supplied gas in the microbubbles. Therefore, we fabricated the particles by changing the gas supplied with the CA vapor from dry air to carbon dioxide (CO₂), oxygen (O₂) and sulfur hexafluoride (SF₆). Figs. 6 to 8 show the SEM and TEM images of the CA hollow particles fabricated using CO₂, O₂ and SF₆, respectively. From the SEM images, the diameter of the fabricated particles was found to be ~700 nm, ~800 nm, and ~600 nm in the case of CO₂, O₂, and SF₆, respectively. Moreover, TEM images confirmed that the fabricated CA particles had a hollow structure with a bright center. The mean diameter and standard deviation of the fabricated particles was 744 ± 81 nm (n = 1000), 806 ± 180 nm (n = 1000), and 610 ± 127 nm (n = 1000) in the case of CO₂, O₂, and SF₆, respectively. Furthermore, the size of hollow part varied depending on the type of supplied gas. We believe that this is due to the difference in the solubility of the gas in water. As for the gas solubility in the dispersing aqueous solution, we assumed that it was approximately the same as that in pure water because the solution was composed of pure water and 0.01 % surfactant and acidic substance. Table 1 shows the solubility of each gas in water and the hollow ratio of the particles. The hollow ratio was obtained from the volume of the whole particle and the volume of the hollow. As shown in Figs. 6 to 8, the fabricated particles were almost-spherical, therefore the volume of the particle and its void was calculated from area-equivalent diameter measured by TEM image using Mac-View software. As shown in Table 1, the hollow ratio with SF₆ was higher compared that obtained with other gases. CA shell is formed with gas retained inside the microbubbles, resulting in CA hollow particles. At this process, CA membrane was thought to be in liquid state, and the gas inside microbubbles would be able to dissolve in the solution through the semi-solid shell. Therefore, the gas of low solubility stayed inside the microbubbles due to the difficulty in dissolving, and higher hollow ratio particles was fabricated accompanied with the final solidification of CA shell. SF₆ shows lower solubility in water than do the other gases. Therefore, the hollow ratio in the case of SF₆ was higher because of the larger amount of gas contained in the microbubbles as compared to that under the other conditions. In case of particle fabrication with CO₂ gas, void inside the particle was not located occasionally at the center of the particle. When gas dissolution rate is low, liquid layer on the bubble interface due to CA vapor condensation becomes uniform thickness with time. In case of dissolution rate being high like CO₂, the time required for the thickness uniformity is insufficient in some cases, and then local thin liquid layer enhances the gas dissolution to aqueous phase there.
supplied gas in the microbubbles. Therefore, we that the fabricated particles were influenced by the type of Since the microbubbles acted as a template for the 3.2 Influence of gas supply tartaric acid (acidic conditions)

Fig.5 SEM images of fabricated CA hollow particles with without tartaric acid (neutral condition)

Fig.4 SEM images of fabricated CA hollow particles under the neutral conditions.

under the acidic conditions when compared with that microbubbles with CA vapor shrank to a greater extent smaller in size under acidic conditions because the slow polymerization. The hollow CA particles became and hence shrink in a liquid because of surface tension Furthermore, microbubbles undergo self-pressurization polymerization proceeds slowly under acidic conditions. and the gas inside microbubbles would be able to dissolve and the shell formation rate with pH 7.0−7.5, because the shell formation rate compared = 20) under the neutral conditions and 0.91 ± 0.22 µm (deviation of the fabricated particles was 4.14 ± 1.20 µm (n hollow CA particles decreased at pH 3.0−3.5 c particles fabricated using CO\textsubscript{2}, O\textsubscript{2}, and SF\textsubscript{6}, respectively. Furthermore, the size of hollow gas of low solubility stayed inside the microbubbles due to in the solution through the semi-solid shell. Therefore, the gas inside microbubbles would be able to dissolve and the gas supply.

In this study, we observed that the hollow CA particles decreased in size when the pH of the aqueous phase is 3. This is because the shell formation is delayed under acidic conditions. Furthermore, the hollow rate of the fabricated CA hollow particles was affected when changing the gas supply. In particular, the hollow ratio was higher in the presence of SF\textsubscript{6}. The CA particles prepared in this study would possibly have excellent thermal and sound insulation properties owing to the hollow structure. Furthermore, though further downsizing of hollow particles are required, CA particles can find the application for drug delivery to the targeted sites.
References


