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ANALYSIS OF DEFORMATION PROCESS OF A BUBBLE IN A CAPSULE BY PRESSURE WAVE FOR DEVELOPING DRUG DELIVERY SYSTEMS

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Abstract. *This paper describes mathematical analysis of bubble deformation near free surface, which is the model of a gas bubble in a microcapsule collapsed by shock waves for drug delivery systems. By reviewing the previous investigations related to the disintegration of polymer capsules including gas bubbles by shock wave, it has been found that these modes depend on gas ratio in the liquid capsule, membrane thickness, pressure amplitude and frequency. This paper focuses on the effects of initial internal pressure of a bubble and gas ratio on the deformation process by simplified mathematical model, and it is compared with the previous experiments. The results showed that (1) the gas ratio does not affect oscillation amplitude of radius if the initial pressure is more than 0.4MPa; (2) the tendency of amplitude of radius with changing gas ratio in analysis is similar to the experimental averaged radius. It was concluded that the gas ratio and initial internal pressure are important parameters to control for making the micro capsule including a gas bubble.*

Keywords: Bubble dynamics, Free surface, Microcapsule, DDS, Pressure wave

1. Introduction.

Recently drug delivery systems are being widely developed in the research fields of medical, chemical, material engineering and pharmacy. There are many research works in these research fields, but the main topics of these works are production of carrier and drug release from the chemical point of view. As for the carrier, there are other approaches such as nanoparticle and micro-particle [1-4]. Regarding the drug release, there are also other approaches using temperature [5], ultrasonic and bubble [6-8].

On the contrary, shock wave phenomena in living tissues are also being applied in the fields of medical and chemical engineering, such as extracorporeal shock wave lithotripsy or bioprocess for environmental protection.

In the drug delivery systems using shock waves (called "shock wave DDS") [9-11], a microcapsule including a gas bubble is flown in the blood pipe, and then the shock wave generated outside human body works on the capsule. For developing microcapsules including a gas bubble, the penetration force of microjet should be controlled by shock wave strength (power), wave form of pressure, and capsule geometry and material properties. Especially the mechanical properties of membrane and geometry of the membrane are important parameters for changing the penetration strength of microjet in the microcapsule. This method is an efficient way to transfer drugs near the affected part in human body, because there are no thermal effects on the living tissue by using shock wave compared with that by the ultrasonic.

However, the relation of the penetration strength of microjet and the membrane thickness and elasticity is not clear even in the research field of bubble dynamics. It is difficult to optimize the design of microcapsule including gas bubbles because of their complicated mechanism of capsule disintegration. Then the mechanical properties of membrane and geometry of the membrane are important parameters for changing the penetration strength of microjet in the microcapsule.

In the previous investigations, the relations between the elasticity of capsule membrane and the probability of disintegration of polymer capsules by shock-induced microjet from a bubble were clarified [9-12]. However, the mechanism of the disintegration has not been elucidated yet, and the theoretical understanding of these phenomena should be needed for this elucidation. In the previous paper, the sine waves were used as working pressure. Then this paper focuses on the additional effects of gas ratio and the stepwise initial pressure on deformation process by using simplified mathematical model. By using this model, the complicated 3D problems, such as bubble deformation process in a capsule, will be able to be reduced to simplified 1D problems without changing of important parameters including flexibility of free surface.

In this paper, after reviewing previous experiments regarding the bubble deformation in a capsule (Section 2), the simplified mathematical model of deformation of a bubble in a capsule using free surface was constructed. Especially, the model of radius motion and translational motion was constructed from coupled oscillation equations (Section 3). Using these coupled oscillation equations, the radius and translation motion of a bubble near the free surface were solved by stepwise pressure waves. And the effects of gas ratio and the pressure on deformation process were obtained, discussed and concluded (Sections 4-5).

2. **Previous Findings of Deformation Process of a Bubble in a Capsule.** To observe the bubble deformation process in a capsule is very important work for understanding disintegration of microcapsules by shock wave or pressure wave in actual DDS. In the previous investigations, the bubble (less than 50μm) deformation is observed in a capsule by microscope. Polymer microcapsules were produced using alginic acid-sodium, PVA, and calcium chloride. The well mixed solution of gas and water was injected into the capsule by micro manipulation systems. Figure 1 shows important parameters of geometry for the microcapsule including gas bubble and liquid.

For generating pressure waves such as shock wave and sinusoidal wave, piezoelectric pressure generators have been used. Assuming the actual pressure conditions, maximum pressure is about 0.8MPa, M. I. (mechanical index) is 1.4 in these experiments. The piezoelectric sensor has resonance frequency of 414kHz. Figure 2 shows two types of still images of deformation process [10]. The left image shows before working pressure waves and the right one shows during working ones. It was found that the large deformation of the membrane can be found in the right image. In general, such large deformation induced micro-jet, and micor-jet penetrates the membrane of a microcapsule. This is so called "bubble collapse by pressure wave". Then it is very important for developing drug delivery systems to investigate how the deformation process is going by working pressure waves. By observing these capsules during working pressure waves, it was found that (1) deformation of a bubble in a polymer capsule is large with changing the proper parameters

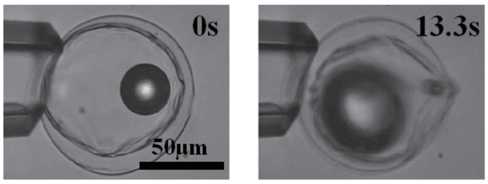
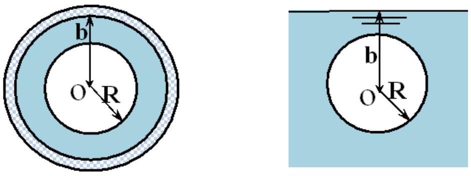


FIGURE 1. Observation of bubble deformation process in a capsule by pressure waves [9]



(a) (b)

FIGURE 2. Model of deformation process of a bubble in a capsule: (a) microcapsule including a gas bubble, (b) simplified mathematical model of a bubble near the free surface

such as gas ratio and thickness; (2) there are three modes of capsule deformation, that are damage, oscillation and non-oscillation.

And the other type of liposome capsule was developed using internal gas bubbles. It was also found that disintegration rate of 3 layers liposome capsule composed of gas, liquid and membrane by pressure wave is higher than that of 2 layers capsule composed of gas and membrane, and the effect of membrane elasticity is large [10].

Then this paper focuses on the effects of gas ratio and the pressure on deformation process by simplified mathematical model.

3. Mathematical Simplified Model of Bubble Deformation Process.

The mathematical model of deformation process of a bubble in a capsule is assumed to be a simplified model of a bubble near the free surface, as the membrane has soft elasticity in the case of actual DDS capsules (Figure 2).

In this case, the velocity potential of radial Φ_r, and tangential Φ_θ are used to express the flow filed by using mirror image beyond the free surface as follows (Figure 3) [13].

$$\Phi_r = R^2\dot{R}\left(\frac{1}{r} - \frac{1}{r_1}\right) \tag{1}$$

$$\Phi_\theta = \frac{R^2\dot{b}}{2}\left(\frac{\cos\theta}{r^2} - \frac{\cos\theta_1}{{r_1}^2}\right) \tag{2}$$

where b is distance from the surface (bubble position), and R is radius of a bubble (bubble diameter). Using these velocity potentials, the kinetic energy T by oscillation of radius and translational motion is described as follows.

$$\mathrm{T} = 2\pi\rho R^3\left(1 - \frac{R}{2b}\right)\dot{R}^2 - 2\pi\rho R^3\left(\frac{R}{2b}\right)^2\dot{R}\dot{b} + \frac{1}{3}\pi\rho R^3\left[1 - 2\left(\frac{R}{2b}\right)^3\right]\dot{b}^2 \tag{3}$$

Using Lagrange's equations related (3), the following coupled equations for R and b are derived;

$$\begin{aligned}\ddot{R} = \frac{1}{R\left[1 - \left(\dfrac{R}{2b}\right)\right]}\Bigg\{ &-\frac{1}{2}\left[3 - 4\left(\frac{R}{2b}\right)\right]\dot{R}^2 - \frac{7}{2}\left(\frac{R}{2b}\right)^2\dot{R}\dot{b} \\ &+\frac{1}{4}\dot{b}^2 + \frac{1}{\rho}\left[P_0\left(\frac{R_0}{R}\right)^{3k} - P_\infty - \frac{2\sigma}{R} - 4\mu\frac{\dot{R}}{R}\right]\Bigg\}\end{aligned} \tag{4}$$

$$\ddot{b} = \frac{1}{R\left[1 - \left(\dfrac{R}{2b}\right)\right]}\Bigg\{\frac{33}{2}\left(\frac{R}{2b}\right)^2\dot{R}^2 - 3\left[1 - \left(\frac{R}{2b}\right)\right]\dot{R}\dot{b}$$

$$+\frac{3}{4}\left(\frac{R}{2b}\right)^2 \dot{R}\dot{b}^2 + \frac{3}{\rho}\left(\frac{R}{2b}\right)^2 \left[P_0\left(\frac{R_0}{R}\right)^{3k} - P_\infty - \frac{2\sigma}{R} - 4\mu\frac{\dot{R}}{R}\right]\Bigg\} \tag{5}$$

where R_0 is initial radius of bubble, P_∞ is working pressure from surrounding fluid, σ is surface tension of liquid, k is heat capacity ratio and μ is viscosity. In this paper, these values are given in the case of water as follows. $\rho = 998.2$ [kg/m3], $P_0 = 9.8 \times 10^4$ [Pa], $\sigma = 72.75 \times 10^{-3}$ [N/m], $k = 1.31$, $\mu = 0$ [Pa·s], and $P_\infty = 0.86 \times 10^6$ [Pa]. Here gas ratio dg/dl is defined as R_0/b_0.

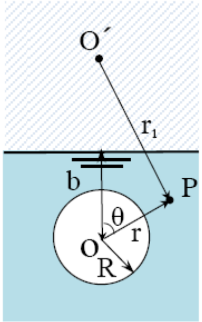
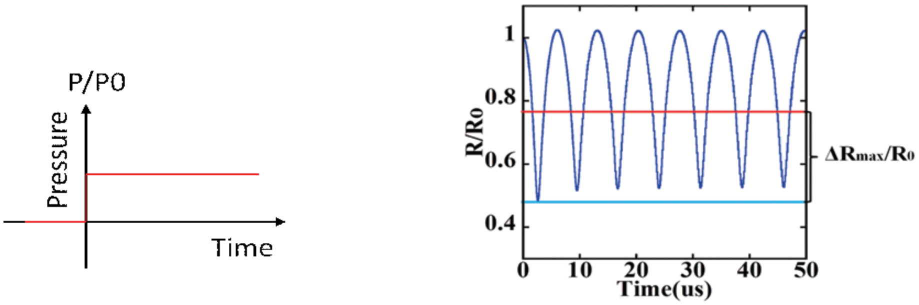


FIGURE 3. Mirror image of a gas bubble and related definition of variables

4. **Results and Discussions.** By integrating the above equations, time history of R and b are obtained. To solve above problems, the stepwise pressure wave is used as shown in Figure 4(a). Figure 4(b) shows the typical radius history and the definition of maximum amplitude of the oscillation by pressure wave is shown as $\triangle R_{\max}/R_0$. It is found that the oscillation of bubble starts just after working stepwise pressure.



(a) Stepwise pressure history

(b) Radius history of a bubble

FIGURE 4. Working pressure history on the bubble and an example of radius history with proper parameters

Figure 5 shows radius history with changing initial internal pressure. It is found that the effect of the internal pressure on amplitude of oscillation of a bubble is large. Figure 6 shows the maximum amplitude of radius with changing the gas ratio and initial internal pressure. From this figure, it is found that the variance of amplitude is small when the initial internal pressure is increasing up to 0.4-0.5MPa. It means that the amplitude varies well with changing gas ratio when the internal initial pressure is less than 0.2MPa. And it is also found that there are no such large variances for maximum amplitude when the initial internal pressure is 0.2-0.3MPa. Figure 7 shows the comparison of maximum amplitude of bubble radius between analysis and experiments. From this figure, it is found that the maximum amplitude at gas ratio 0.37 (damage in experiments) is larger than that at gas ratio 0.67 (oscillation in experiments). It is recommended that the internal initial pressure is properly controlled.

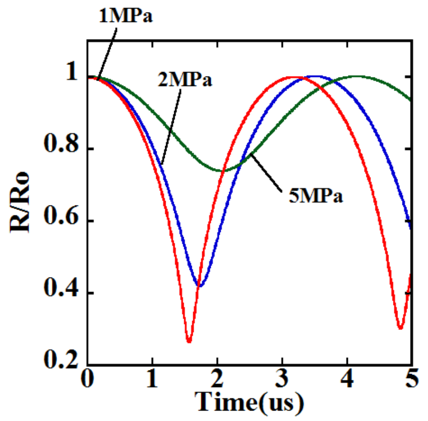


Figure 5. Effects of initial pressure and on radius history

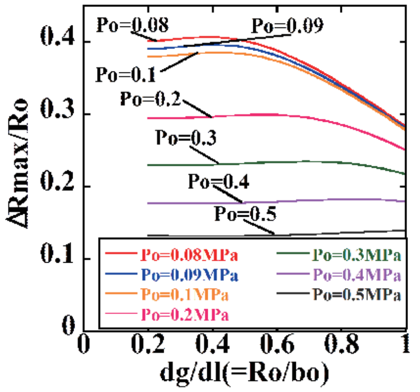
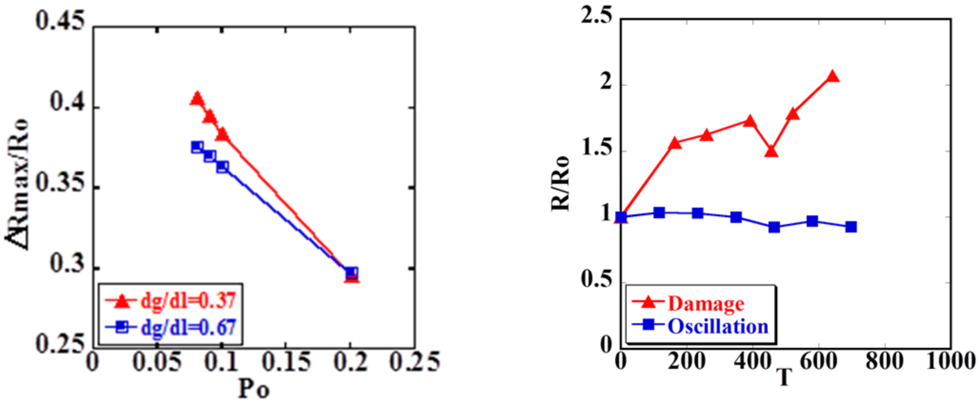


Figure 6. Maximum amplitude of radius with changing the gas ratio and initial internal pressure



(a) Mathematical model with initial pressure

(b) Experimental radius history with two cases

Figure 7. Comparison of maximum amplitude of bubble radius between analysis and experiments

5. **Conclusions.** In this paper, the effects of gas ratio and the pressure on deformation process by simplified mathematical model were focused on, and the simplified mathematical model was established for this analysis. The results showed that (1) the gas ratio does not affect oscillation amplitude of radius if the initial pressure is more than 0.4 MPa; (2) the tendency of amplitude of radius with changing gas ratio in analysis is similar to the experimental averaged radius. It was concluded that the gas ratio and initial internal

pressure are important parameters to control for making the micro capsule including a gas bubble. Further investigations related to the effects of elasticity of capsule membrane on the deformation process of a bubble will be needed for more precious modeling.

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