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ANALYSIS OF A BUBBLE DEFORMATION PROCESS IN A MICROCAPSULE FOR DEVELOPING DRUG DELIVERY SYSTEMS USING UNDERWATER SHOCK WAVES

Masaaki TAMAGAWA
Kyushu Institute of Technology, Fukuoka, Japan
tama@life.kyutech.ac.jp

ABSTRACT
This paper describes development of microcapsule using underwater shock waves, especially (1) the trial of making smaller microcapsules including a bubble for shock wave drug delivery systems, and analysis of a bubble deformation process to have higher efficiency of disintegration by shock wave, and (2) the effects of gradient of cytokine concentration on neutrophile motion in liquid by observing the concentration transport process with adding cytokine for developing drug delivery systems

INTRODUCTION
Shock wave is a discontinuous wave that has high pressure and short rise time. We have proposed drug delivery systems (DDS) using shock waves to apply micro/nano technology in the fields of biomedical engineering. In this system, a microcapsule including a gas bubble is flown in the blood vessel, and it is broken by shock induced microjet, then drug is reached to the affected part in the body as same as conventional DDS. This method is efficient way to transfer gene and drugs near the affected part in human body, because there are no thermal effects on the living tissue by using shock wave comparing with that by the ultrasonic. 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 is important parameter for changing the penetration strength of microjet in the microcapsule. But 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, it is necessary to obtain the new design method for making capsule inside a gas bubble even though this difficulty.

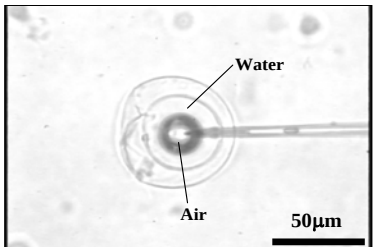


Fig.1 Prototype of microcapsule including gas and liquid

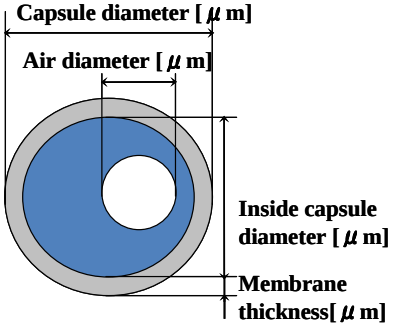


Fig.2 Parameter of geometry for the microcapsule including gas bubble and liquid

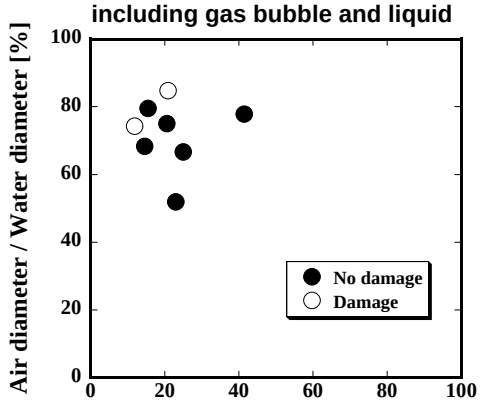


Fig.3 Geometrical mapping between membrane thickness and air diameter of microcapsule

In our previous investigations [1], the prototype of microcapsules including gas bubbles were made for tests. Then, to clarify the relation between the visco-elasticity of capsule membrane and the probability of disintegration of membrane by shock-induced microjet from a bubble, the elasticity of membrane was determined. As for estimation of elasticity and visco-elasicity of microcapsules, the apparent Young's modulus of membrane was determined using finite element method (FEM). The threshold of disintegration of membrane was rearranged by using apparent Young's modulus.

In this paper, after new prototype pf microcapsule is shown, the results of disintegration experiment and bubble deformation process in a capsule are discussed.

By the way, inflammation reaction is very important role as immune response in human body. In this reaction, once the inflammation occurred, the cytokine (chemokine) is delivered from the inflammation place, then neutrophile accesses at the place to cure. The neutrophile moves the place that has large gradient of cytokine concentration. This is so called chemotaxis of neutrophile, but the driving force of this motion in liquid is not elucidated yet. Generally, the particulate in liquid on the gradient of concentration has the force by Marangoni effects. So the neutrophile has the driving force of the motion in liquids by Marangoni effects. It is necessary to control of neutrophile motion in liquid by concentration gradient for drug delivery systems.

In our previous experiments [2], the effects of gradient of cytokine concentration on chemotaxis of neutrophile were investigated by observing the motion in liquid with adding cytokine concentration. Using PTV measurements, the average velocity of neutrophile was obtained with changing the cytokine concentration.

In this paper, the model of membrane for sensing cytokine concentration is constructed by comparing with inorganic particulate model such as a bubble in water. Then the cytokine with fluorescent material (FITC) is observed in the microscope and the motion of neutrophile is analyzed on the membrane and around the membrane (surrounding fluid).

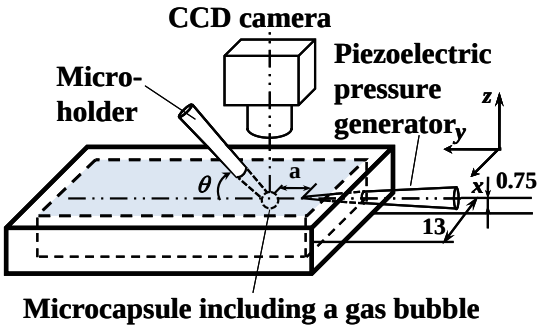
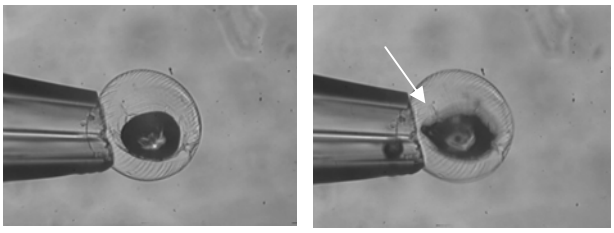


Fig. 4 Experimental apparatus for observation of deformation process of a bubble inside a capsule



(a) Initial status of a bubble **(b) Typical deformation of a bubble**

Fig. 5 Bubble deformation inside a capsule (43kHz)

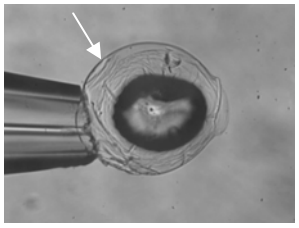


Fig. 6 Bubble deformation inside a capsule (77kHz) when the gas diameter ratio to diameter of capsule is almost 1.0

MAKING SMALLER POLYMER MICROCAPSULES FOR SHOCK WAVE DDS

To investigate possibilities for making polymer microcapsules in small scale, the prototype capsules in micro scale are produced using alginic acid-sodium (0.3-0.7 %), PVA, and calcium chloride. The well mixed solution of gas and water is injected into the capsule by micromanipulation systems. In this process, the pressure and temperature during injection should be controlled. In figure 1, three-layer capsule (membrane, water and bubble) can be shown. The diameter of this capsule is about 50μm and bubble diameter is about 20μm, which is smaller than old type.

Figure 2 shows parameter of geometry for the microcapsule including gas bubble and liquid. Figure 3 shows mapping of microcapsules between membrane thickness and bubble diameter. From this mapping, it is found that membrane thick ness and mixing ratio between gas and liquid should be controlled exactly in our method.

ANALYSIS OF A BUBBLE DEFORMATION PROCESS IN A SMALLER 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 this investigation, the bubble (less than 50μm) deformation is observed in a capsule by microscope. Figure 4 shows experimental apparatus for observing the bubble deformation process. The micro-holder is used not to move on the microscope. To work shock wave or pressure wave on this preparation slide, we developed small size piezoelectric pressure generator with horn type adapter. In this experiment, maximum pressure is about 0.16MPa, which is under the disintegration of capsule, but it is enough to observe deformation process.

In this paper, only sinusoid wave is shown. We are using resonance frequency of this system (44 kHz, 77 kHz). As an observation result, figure 5 shows the typical bubble deformation process. In this figure, the bubble has large acute angle part in a capsule. In this case, the ratio (air diameter/water diameter) is 0.53, and then the volume ratio of gas bubble in the capsule is 0.15. Compared with this gas ratio, figure 6 shows the deformation process in the case that the diameter ratio is almost 1, which means almost gas inside capsule. It is clear found that there are no acute-angle parts of a bubble. From these results, it is considered that microjet should be generated around this scale (50μm) with proper gas ratio.

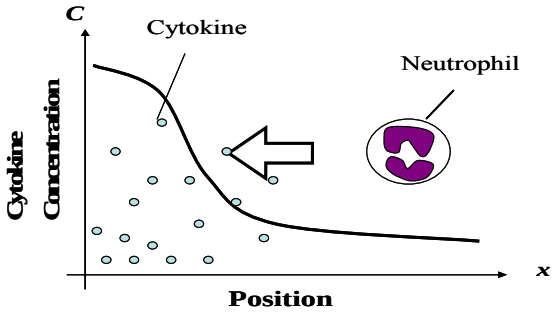


Fig. 7 Concept of chemotaxis using concentration Marangoni effect

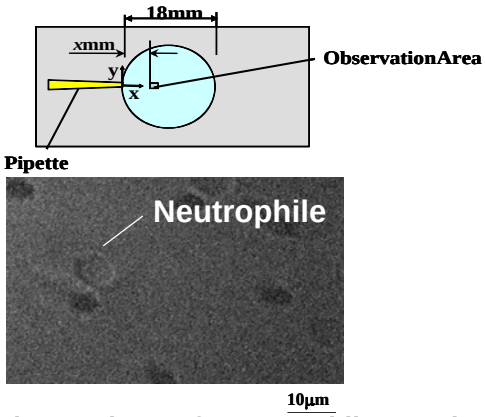


Fig. 8 Observation of neutrophile motion by concentration (cytokine) gradient on the prepared slide

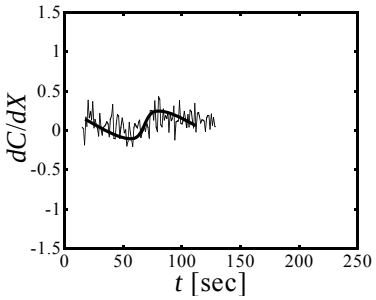


Fig.9 Concentration gradient history on the membrane after passing incident concentration gradient

OBSERVATION OF CONCENTRATION GRADIENT ON THE MEMBRANE BY FLUORESCENCE

Supposing that the particulate sphere is in liquid under the surface tension gradient, the driving force F in liquid is caused by the concentration (the surface tension) gradient. This is so called Marangoni effect (Fig.7).

To prove the neutrophile motion by concentration gradient, the experimental observation was done using the simple system as shown in Fig. 8. In this system, after dropping the cytokine IL-8 at the liquid area of neutrophile suspension, the concentration of cytokine is diffusing in the suspension liquid. The motion of neutrophile is taken by the video movie. The cytokine with fluorescent material (FTTC) is observed as intensity level in CCD image. Figure 8 shows diffusion process of cytokine and motion of neutrophile. It is found that the high intensity region can be observed around the neutrophile. Then it is considered that the cytokine with fluorescence is attached to the membrane of neutrophile. Figure 9 shows intensity gradient (concentration gradient) history on the membrane of neutrophile. It is found that gradient is changing from negative to positive value, and oscillating.

COMPUTATIONAL MODEL FOR TRANSPORT PROCESS OF CONCENTRATION ON MEMBRANE

To confirm the negative and positive gradient of concentration on the membrane, the transport of concentration is analyzed by using FEM software, ANSYS10. In this case, by changing the diffusion coefficient of membrane, the gradient of concentration can be checked. Figure 10 shows two dimensional model of transport process of concentration without advection, initial concentration profile. Figure 11 shows the typical result of concentration contour after 60 seconds and concentration gradient at membrane. It is found that the sign of gradient changes due to the diffusion ratio. This result means that the driving force is obtained by concentration gradient alternatively if the diffusion of the membrane is different from that of surrounding fluid. Figure 12 shows concept of the mechanism of driving force by concentration gradient with alternative sign.

CONCLUSIONS

It is concluded that there should be optimum parameter to have micro-jet even in less than 100μm scale). In the next step, the instantaneous disintegration process should be analyzed by higher CCD camera. From the experimental and the analytical results of driving force of neutrophile, the driving force is considered to be obtained due to the differences of the force in each gradient case

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[2] Tamagawa M., Mukai, K., Furukawa, Y., , Proc. of Fifth East Asian Biophysics Symposium & Forty-Fourth Annual Meeting of the Biophysical Society of Japan, 2006

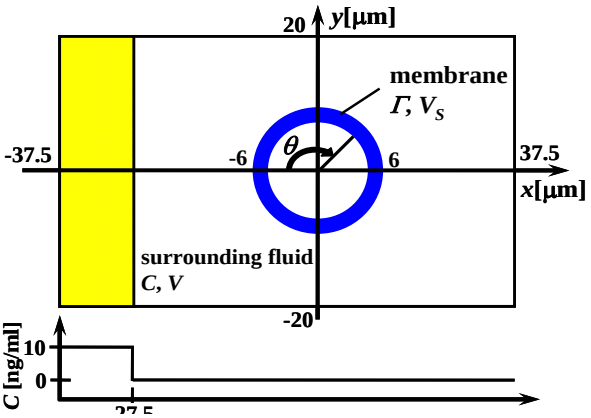

Fig.10 Computational model for analyzing the transport process of concentration around the neutrophile with membrane and initial concentration profile along x axis

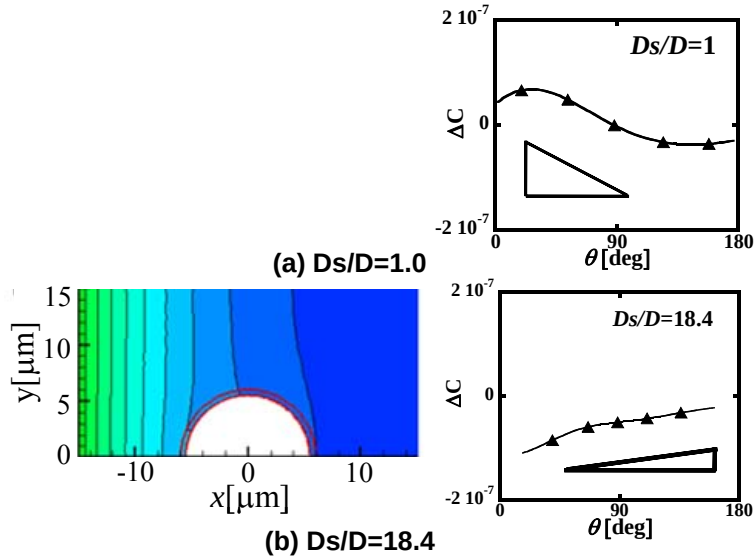

Fig.11 Computational result for (1) concentration contour after 60 seconds and (2)concentration profile by changing the diffusion coefficient on membrane and surrounding fluid; (a)Ds/D=1 and (b)Ds/D=18.4.

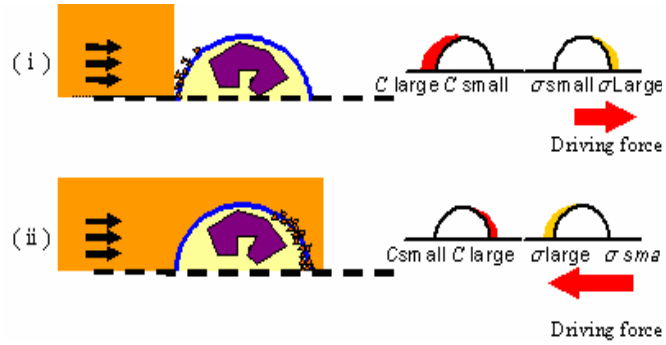

Fig.12 Concept of driving force by alternative change of concentration gradient on the membrane; (i)first stage, the concentration is high at front (ii) second stage, the concentration is high at the end