

Title	Real-Time Observation of Hydrogen Peroxide Transport through the Oil Phase in a W/O/W Double Emulsion with Chemiluminescence Emission
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Real-time observation of hydrogen peroxide transport through oil phase in a W/O/W double emulsion with chemiluminescence emission

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KEYWORDS

W/O/W emulsion; mass diffusion; real-time measurement; shell permeability; chemiluminescence

Evaluation of the transport rates of hydrophilic substances is important in agricultural and pharmaceutical chemistries, and cosmetics and food-processing industries. Although there are some estimation methods focusing on the diffusion of the substances through the oil phase of W/O/W core-shell double emulsions (oil microcapsule), all of them take several hours or days. This long-time measurement has a risk of the rupture of the oil microcapsules, which causes the significant errors. If it were possible to measure the transport rate of substances in the oil phase of the oil microcapsules in real-time, the risk of the rupture could be reduced. Here, we propose a new estimation method of the transport rates of hydrogen peroxide (H_2O_2) in the oil phase of an oil microcapsule for real-time estimation by means of chemiluminescence (CL) emission of

luminol reaction. We theoretically give the relationship among CL emission intensity, diffusion coefficient, microcapsule size and experimental time, and successfully estimate the diffusion coefficient of H_2O_2 in the oil phase of the oil microcapsule from the experimental data. Moreover, we discuss the dependence of the permeation of H_2O_2 through the oil phase on the concentration of the oil-soluble surfactant; the difference in the permeation rate is likely to be attributed not to diffusion coefficient but to partition coefficient of H_2O_2 in the oil microcapsule.

INTRODUCTION

Encapsulated systems are useful to manipulate a small amount (nL- or pL-scale) of substances in the core region being protected from thermal, chemical, or mechanical degradation; e.g., water-in-oil-in-water (W/O/W) core-shell double emulsions (oil microcapsules), liposomes, colloidosomes, and polymersomes have attracted a great deal of attention as the encapsulated systems. Oil microcapsules, in particular, are one of the most promising structures for encapsulation, delivery, and controlled release of hydrophilic compounds: agricultural chemicals,¹ cosmetic components,² food additives,³ and pharmaceuticals.⁴⁻⁷ Control of transport of the substances through the oil phase of the oil microcapsules requires understanding the diffusion behavior of the substances in the oil phase. There are several methods to evaluate the transport of substances; the transport rate can be estimated from the volume change of inner phase,⁸ the viscosity change of W/O/W double emulsions,^{9,10} the variation of fluorescence intensity^{11,12} and the conductivity change of the outer phase.¹³⁻¹⁶ However, it takes several hours or days to measure the variation of the physical properties. Moreover, since the experiments take such a long time, the physical properties are more likely to be disturbed by the rupture of microcapsules; it is difficult

to distinguish the substances diffusing through the oil phase from those flowing out as a result of the rupture.¹⁷ If it were possible to measure the transport rate of substances in the oil phase of the oil microcapsules in real-time, we could distinguish between the two processes.

There are several methods to measure the transport rate of substances in real-time: the modulus of volume change,¹⁸ the change of X-ray fluorescence intensity,¹⁹ and chemiluminescence (CL) emission intensity.^{20,21} Owing to the high sensitivity of CL to the existence of substances, the methods including CL have been developed to characterize film inhomogeneity²⁰ and to estimate permeability of the liposomal membrane.²¹ The assumption that the CL emission intensity is proportional to the permeated amount of externally added reactant to the reaction field and reflects the permeation rate of reactant enables the real-time observation. We have recently reported that the CL emission occurs in microcapsules with an aqueous luminol solution as the inner phase when the microcapsules are placed in hydrogen peroxide (H_2O_2) solution.^{22,23} In this system, luminol reaction starts immediately after H_2O_2 reaches the inner phase. If we can track the amount of H_2O_2 that has passed through the shell phase by measuring the CL emission intensity, it should be possible to estimate the permeability to H_2O_2 in the shell phase. In addition, the rupture of microcapsules is likely to rarely disturb this method due to the reduction in the measurement time (several minutes ~ several tens of minutes).

In this paper, we demonstrate the utility of the CL method using oil microcapsules to estimate the permeability in the oil phase (Figure 1). First, we theoretically derive the time dependent CL emission intensity based on two assumptions of H_2O_2 permeation in an oil microcapsule; all of H_2O_2 molecules that reach at the inner interface react immediately, and CL emission intensity in an oil microcapsule is linear to the reacting amount of H_2O_2 per unit area and unit time. The derived relationship can account for the results of the time dependent CL emission intensity of the oil

microcapsules with an aqueous luminol solution as the inner phase (luminol microcapsules), and obtain the diffusion coefficient of H_2O_2 . Furthermore, the dependence of the permeation rates on the concentration of the oil-soluble surfactant enables us to discuss the H_2O_2 diffusion mechanism in the oil shell.

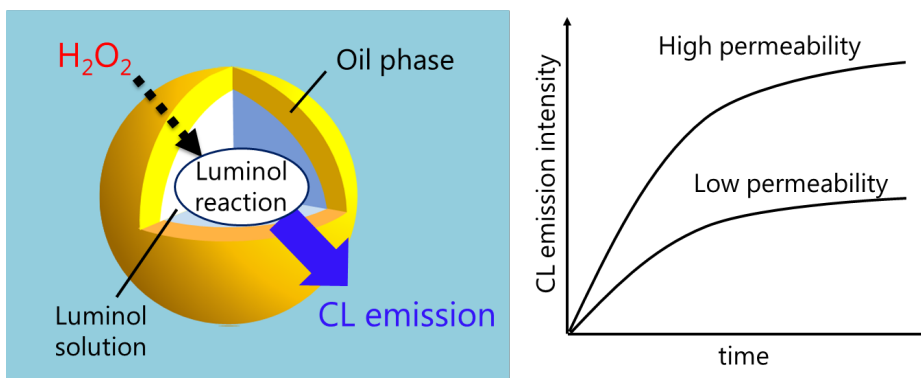


Figure 1. Schematic illustration of CL method using oil microcapsule consisting of aqueous luminol solution in the core phase. CL emission intensity reflects the permeability of the oil phase of the microcapsules.

MATERIALS AND METHODS

Luminol microcapsules were fabricated using glass microcapillary devices.²⁴ The inner and outer radii of the microcapsules are controllable by varying the size of the capillaries and the flow rates of the different phases. The inner phase was 8.4 wt% poly(vinyl alcohol) aqueous solution (PVA; Mw: 13000-23000 g mol⁻¹, 87-89% hydrolyzed, Sigma-Aldrich) dissolving 2.9 wt% sodium carbonate (Wako Pure Chemical Industries Ltd., $\geq 99.8\%$), 0.32 wt% sodium hydrogen carbonate (Wako Pure Chemical Industries Ltd., $\geq 99.5\%$), 4.2×10^{-2} wt% ammonium carbonate (Wako Pure Chemical Industries Ltd., $\geq 30.0\%$ as ammonia), 8.4×10^{-2} wt% luminol (Tokyo

Chemical Industry Co., Ltd., $\geq 98.0\%$) and 4.2×10^{-2} wt% $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (Wako Pure Chemical industries Ltd., $\geq 99.5\%$) as a catalyst. The middle phase was the mixture of 71 wt% poly(dimethylsiloxane) (PDMS; Acros-Organics) and 28 wt% bromobenzene (Tokyo Chemical Industry Co., Ltd., $\geq 99.0\%$) added 1 wt% Dow Corning 749 Fluid as an oil-soluble surfactant. The outer phase was 10 wt% PVA aqueous solution. Then, 15 wt% H_2O_2 aqueous solution was added to the outer phase of the luminol microcapsules to measure the CL emission intensity. Time-dependent CL emission intensity was measured using a photon counting head (H10682-201: Hamamatsu photonics) with photon counting unit (C8855-01: Hamamatsu photonics) attached to an optical microscope (BX51: Olympus).

RESULTS AND DISCUSSION

Theoretical model to estimate diffusion coefficient from time-dependent CL emission intensity. The permeation of substances from the outer phase to the inner phase through the shell region of the luminol microcapsule is attributed only to diffusion as long as the luminol microcapsule does not rupture. Radial diffusion can be expressed with a diffusion coefficient D according to Fick's second law²⁵ in the following equation:

$$\frac{\partial C}{\partial t} = D \left(\frac{\partial^2 C}{\partial r^2} + \frac{2}{r} \frac{\partial C}{\partial r} \right) \quad (1)$$

where $C(r, t)$ is the concentration of the concerned substance, t is time, and r is the distance from the center of a microcapsule.

If C at the inner interface ($r=a$) is C_1 , C at the outer interface ($r=b$) is C_2 , and C in the shell region ($a \leq r \leq b$) is initially C_0 , C in the shell region is expressed²⁵ in the following equation.

$$C = \frac{aC_1}{r} + \frac{(bC_2 - aC_1)(r - a)}{r(b - a)} + \frac{2}{r\pi} \sum_{n=1}^{\infty} \frac{b(C_2 - C_0) \cos n\pi - a(C_1 - C_0)}{n} \times \sin \frac{n\pi(r - a)}{b - a} \exp\{-Dn^2\pi^2 t / (b - a)^2\} \quad (2)$$

The total amount of substances reaching the inner interface from the beginning of the measurement ($t = 0$) to t_1 can be defined as $Q(t_1) = \int_0^{t_1} (4\pi r^2 D \partial C / \partial r)_{r=a} dt$. We assume that all of H_2O_2 molecules that reach the inner interface react with luminol at the inner interface. In this case, both C_0 and C_1 should be 0, and the total amount of H_2O_2 diffusing in the core region is expressed in the following equation:

$$\frac{Q(t_1)}{4\pi ab(b - a)C_2} = \frac{Dt_1}{(b - a)^2} - \frac{1}{6} - \frac{2}{\pi^2} \sum_{n=1}^{\infty} \frac{(-1)^n}{n^2} \exp\{-Dn^2\pi^2 t_1 / (b - a)^2\} \quad (3)$$

For Eq. (3), C_2 is the concentration of H_2O_2 at the outer interface in the shell region, but it is not measurable. Instead, the concentration of H_2O_2 at the outer interface in the outer phase, C_2' , is measurable. In general, H_2O_2 solubility in the aqueous phases is different from that of the oil phase; the partition coefficient, K , is not 1 for the oil and aqueous phases in the vicinity of each of the interfaces. When we assume that H_2O_2 concentration at the inner interface is 0, Eq. (3) can be derived as the following equation:

$$\frac{Q(t_1)}{4\pi ab(b - a)KC_2'} = \frac{Dt_1}{(b - a)^2} - \frac{1}{6} - \frac{2}{\pi^2} \sum_{n=1}^{\infty} \frac{(-1)^n}{n^2} \exp\{-Dn^2\pi^2 t_1 / (b - a)^2\} \quad (4)$$

Meanwhile, we can also estimate $Q(t_1)$ by comparing the CL emission intensity of the reaction in a luminol microcapsule with that in bulk luminol solution directly added H_2O_2 solution. The integrated CL emission intensity calculated using the experimental results for the bulk luminol solution should be linear to the amount of H_2O_2 added. In fact, the linearity is shown in Figure 2. Therefore, when CL emission intensity in the luminol microcapsule is I_{mc} , that in the bulk luminol solution is I_b , and the amount of H_2O_2 added directly to the luminol solution ($n_{H_2O_2}$), $Q(t_1)$ can be calculated as

$$Q(t_1) = \int_0^{t_1} \left(I_{mc} \frac{n_{H_2O_2}}{\int_0^\infty I_b dt} \right) dt. \quad (5)$$

By using Eqs. (4) and (5), we can determine the diffusion coefficient of H_2O_2 in the oil.

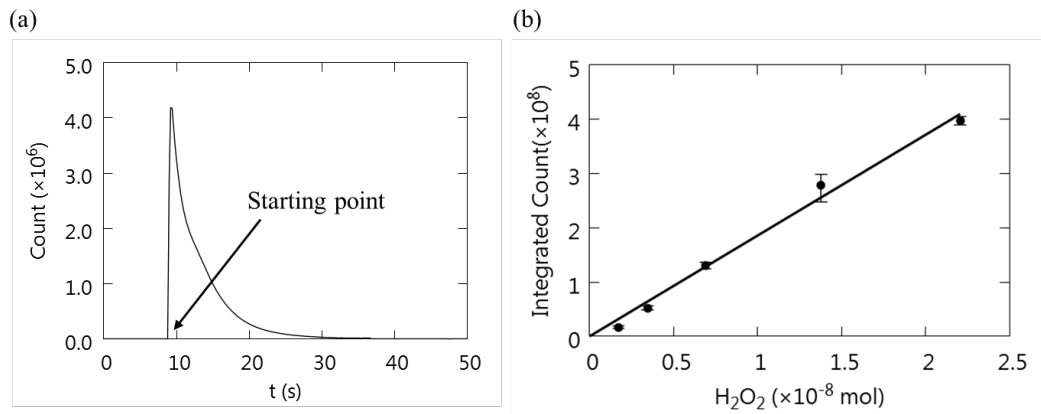


Figure 2. CL emission behavior for bulk luminol solutions. (a) Time dependence of CL emission intensity in experiments for a bulk luminol solution and (b) The integrated value of the CL emission intensity vs. the amount of H_2O_2 .

Validity of the assumption that CL emission occurs at the inner interface. To confirm the assumption that all of H_2O_2 molecules react with luminol at the inner interface, we observed the CL emission in a large luminol solution (the density is 1.065) droplet (W_1) in low-density PDMS oil with 1 wt% Dow Corning 749 Fluid (the density is 0.97), which was an oil-soluble surfactant, (O) on an aqueous H_2O_2 solution (W_2) phase as shown in Figure 3. We first put aqueous H_2O_2 solution in a vial, put PDMS oil with Dow Corning 749 Fluid on the H_2O_2 solution, and added the luminol solution in the oil phase. The luminol solution sank in PDMS oil and a thin PDMS oil layer was formed between the two aqueous phases. The CL emission occurs only at the W_1/O interface as shown in Figure 3. This result indicates that H_2O_2 can diffuse in the oil phase whereas luminol cannot, and all of H_2O_2 molecules coming from the W_2 phase react with luminol at the W_1/O interface. Therefore, the assumption that C_1 is 0 is valid for luminol microcapsules with an aqueous luminol solution as the inner phase.

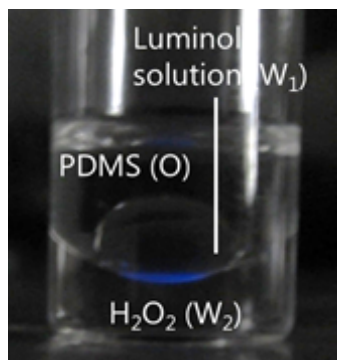


Figure 3. A large luminol solution droplet (W_1) in PDMS oil with Dow Corning 749 Fluid (O) on aqueous H_2O_2 solution (W_2). Luminol solution sank in oil phase and a thin oil layer was formed. The blue color at the W_1/O interface is CL emission light.

Estimation of diffusion coefficient from CL emission intensity in luminol microcapsule. To measure the CL emission intensity of the luminol reaction in luminol microcapsules, we fabricated mono-dispersed luminol microcapsules by using glass capillary microfluidic devices as shown in Figure 4. Bromobenzene with higher specific gravity is blended into the oil phase to bring the microcapsules into contact with H_2O_2 that sinks in the outer phase and to adjust the density of the oil phase (the density is 1.068) same as the inner phase (the density is 1.065). We used an alkaline buffer solution as the inner phase to enhance the emission intensity of the luminol reaction, whereas a neutral buffer solution was employed as the outer phase to inhibit luminol reaction in the outer phase. The inner and outer radii (a and b) and the shell thickness ($b - a$) of the luminol microcapsules obtained were several hundreds and several tens of μm , respectively. Since the above-mentioned theoretical equations assume centrosymmetric systems, we should confirm the location of the internal aqueous droplet in the oil droplet. When the interaction between the internal aqueous droplet and the external aqueous phase consisting of van der Waals and electrostatic interactions³⁴ is attractive or repulsive, the internal aqueous droplet should be located near the outer interface or at the center. Actually, the internal aqueous droplets is confined at the center of the oil droplet as shown in Movie S1. Therefore, the two aqueous phases are likely to be repulsive and the above-mentioned assumption could be adopted in this case.

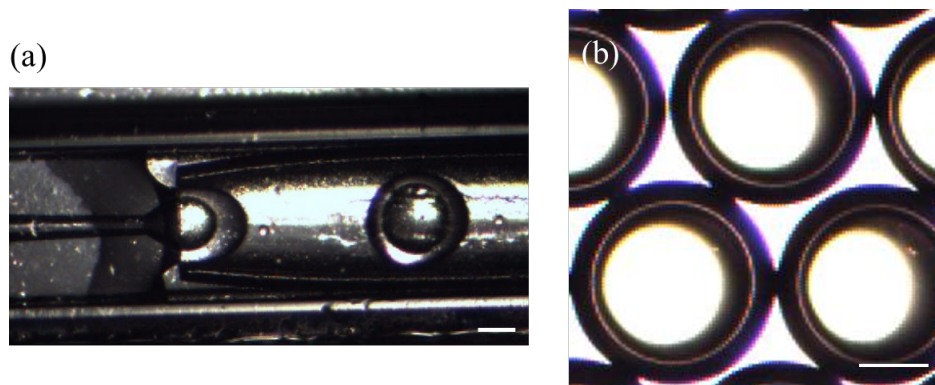


Figure 4. (a) Fabrication process of microcapsules consisting of an aqueous luminol solution as the inner phase and the oil mixture as the middle phase. (b) Bright-field microphotograph of the luminol microcapsules. Scale bars represent 200 μm .

To measure the time-dependent CL emission intensity for a luminol microcapsule, we added H_2O_2 solution to the outer phase, and then, measured the CL emission intensity in the core region using a photon counting head with photon counting unit; the experimental setup is schematically illustrated in Figure 5a. First, the CL emission intensity increased for about 15 seconds after the start of the CL emission, and then, decreased as shown in Figure 5b. Since the integrated CL emission intensity for the first 15 seconds is less than 1% of that for the whole measurement time, the concentration change of luminol in the core region can be negligible in this short period. Thus, the increase of the CL emission intensity reflects that of the permeation rate of H_2O_2 in the shell region. These results indicate that the amount of H_2O_2 that reached the inner interface gradually increased and became constant, while at the same time that of luminol was decreasing.

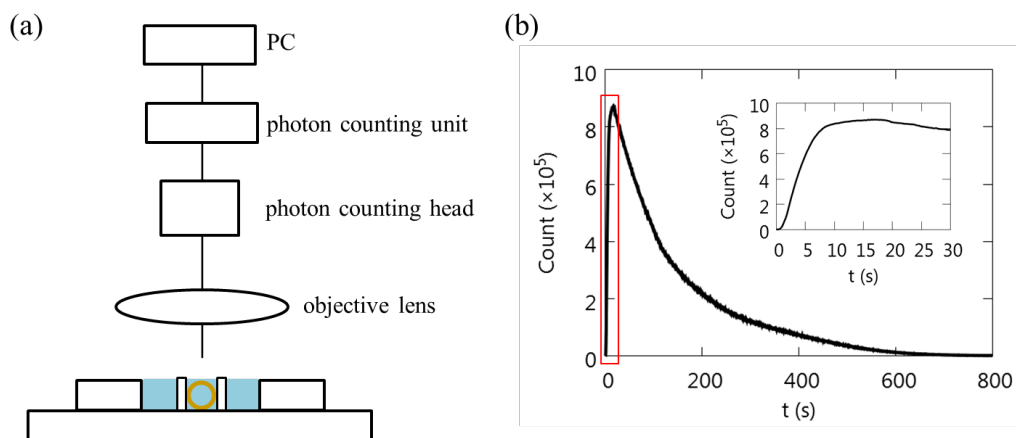


Figure 5. CL emission intensity of the luminol reaction in the luminol microcapsule. (a) Experimental setup for the CL emission intensity measurement of the luminol reaction in the luminol microcapsule. (b) CL emission intensity of the luminol reaction in the luminol microcapsule. The inset shows enlarged views of the whole CL emission intensity curve surrounded by a red rectangle.

Then, to estimate K of the mixture of 71 wt% PDMS and 28 wt% bromobenzene added 1wt% Dow Corning 749 Fluid (oil mixture) and the mixture of equal weights of 10 wt% PVA and 30 wt% H_2O_2 aqueous solutions (aqueous mixture), we measured the H_2O_2 concentration in the aqueous mixture. We added 0.2 ml of the oil mixture in a vial and then added 1.0 ml the aqueous mixture. The concentration of H_2O_2 in the aqueous phase of the vial achieved equilibrium 3 days later, and then, we measured the K . At this system, K was 0.308.

To examine the assumption, we estimate the diffusion coefficient in the oil shell of the luminol microcapsule by using Eqs. (4) and (5). The total amount of H_2O_2 reaching to the core region estimated from the CL emission intensity by Eq. (5) was plotted as shown in Figure 6. By fitting

the data with Eq. (4), H_2O_2 diffusion coefficient (D_{HP}) was estimated as $1.96 \times 10^{-10} \text{ m}^2/\text{s}$ for the oil phase of 71 wt% PDMS, 28 wt% bromobenzene, and 1 wt% Dow Corning 749 Fluid.

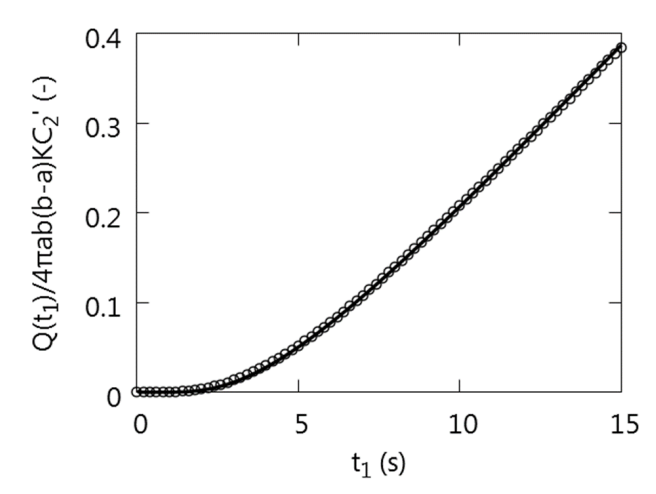


Figure 6. The total amount of H_2O_2 reaching to the core region estimated from the CL emission intensity (open circle) and the fitting curve by the right side of Eq. (4) (solid line).

To confirm the validity of this CL method for the estimation of the diffusion coefficient of H_2O_2 in the oil phase, we prepared three types of luminol microcapsules with different shell thicknesses at 60, 80, 140 μm . The total amount of H_2O_2 reaching to the core region estimated from the CL emission intensity was well fitted for each type of microcapsules by Eq. (4) as shown in Figure 7, and D_{HPS} are estimated as $1.80 \times 10^{-10} \text{ m}^2/\text{s}$, $1.75 \times 10^{-10} \text{ m}^2/\text{s}$, and $2.08 \times 10^{-10} \text{ m}^2/\text{s}$ for the microcapsules with 60, 80, and 140 μm of shell thickness, respectively. The difference is likely to mainly come from experimental errors, which consist of that of the measurement of luminol emission intensity (about 15%). Since the diffusion coefficient is constant as long as the oil shells have the same composition for all samples, we can conclude that this method enables us to estimate the diffusion coefficients of molecules in the oil phase by measuring the CL emission intensity.

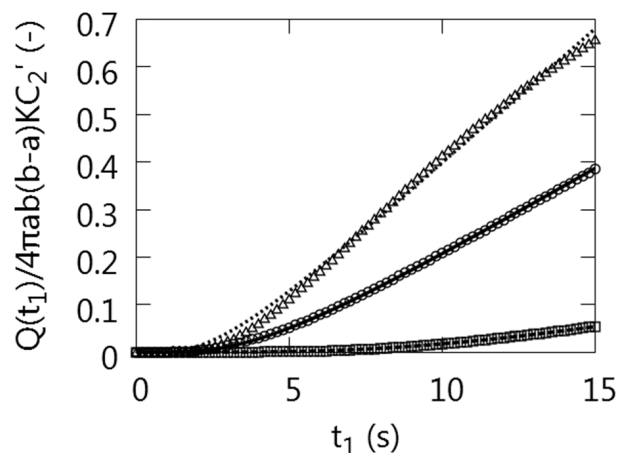


Figure 7. Left side of Eq. (4) estimated from the CL emission intensity for the microcapsules with different shell thicknesses: 60 (open triangle), 80 (open circle), and 140 μm (open square) shell thicknesses for the case of the mixture of 71 wt% PDMS and 28 wt% bromobenzene added 1 wt% Dow Corning 749 Fluid. Dotted line, solid line and dashed line are fitting curves by the right side of Eq. (4) for the microcapsules with 60, 80 and 140 μm shell thicknesses, respectively.

H₂O₂ diffusion mechanism in the oil shell. We assume that hydrophilic H₂O₂ behaves like water in the oil shell of the luminol microcapsule. Several possible scenarios have been proposed to account for the diffusive transport of water and hydrophilic molecules in the oil phase.^{8-10,12-18,26-31} In particular, for thick shells two scenarios have been proposed: (i) water is directly dissolved in the oil phase (for neutral molecules), (ii) water is solubilized by reverse micelles consisting of surfactant molecules in the oil phase.^{8-10,12-14,16,17,26-28} Therefore, to shed light on the diffusion mechanism of H₂O₂ in the oil shell, we measured the dependence of the H₂O₂ permeability on the concentration of the surfactant in the oil phase. We fabricated equally sized

luminol microcapsules with different concentrations of the surfactant in the oil phase to avoid the size effect of the reaction field. The more rapidly the CL emission intensity in the luminol microcapsule increases, the higher the concentration of the surfactant in the oil phase becomes as shown in Figure 8.

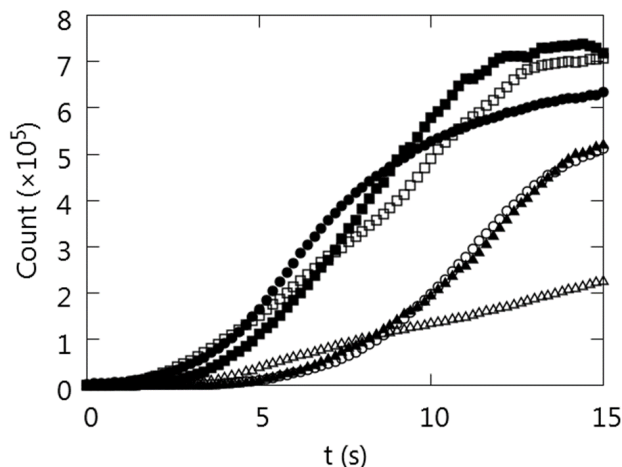


Figure 8. CL emission intensity in luminol microcapsules with different concentrations of Dow Corning 749 Fluid: 0.0 (open triangle), 0.25 (closed triangle), 0.50 (open circle), 1.0 (closed circle), 2.0 (open square) and 4.0 wt% (closed square) Dow Corning 749 Fluid.

This result indicates that the surfactant in the oil phase accelerates the permeation of H_2O_2 . There are two factors: diffusion coefficient, D , and partition coefficient, K . Our CL method can estimate D using K . First, we measured the dependence of K on the concentration of the surfactant in the oil phase as above mentioned as shown in Figure 9. Partition coefficient increases with increasing concentration of the surfactant in the oil shell; the surfactant is likely to induce the dissolution of H_2O_2 in the oil shell.

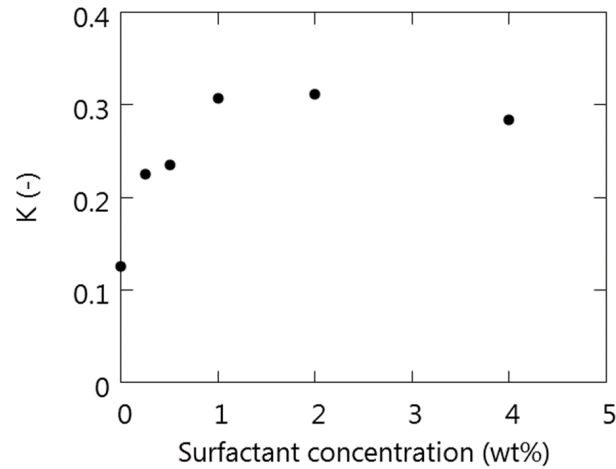


Figure 9. Partition coefficient with different oil-soluble surfactant concentrations of Dow Corning 749 Fluid.

Then, we measured the dependence of viscosity, density and diffusion coefficient on the concentration of the surfactant. The viscosity is 40 mPa s and density is 1.068, and these properties are independent of the concentration of the surfactant. Thus, these properties do not affect the dispersion of H_2O_2 in our experiments. Then, using Eq. (4), we estimate D for H_2O_2 in the oil phase of the luminol microcapsules with different concentrations of Dow Corning 749 Fluid as shown in Figure 10. The diffusion coefficient D estimated from the CL emission intensity in the core region looks independent of the concentration of the surfactant in the oil phase, and H_2O_2 permeates even in the oil shell without any surfactants.

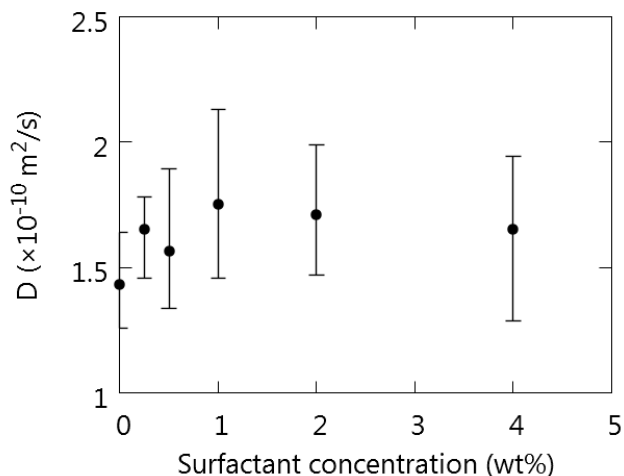


Figure 10. Diffusion coefficient estimated from the CL emission intensity for the microcapsules with different concentrations of Dow Corning 749 Fluid.

These results indicate that D of H_2O_2 in the oil phase of the luminol microcapsules is independent of the existence of the surfactant in the oil shell. H_2O_2 molecules and surfactant molecules with H_2O_2 molecules diffuse in the oil shell. When H_2O_2 molecules combine with the surfactant molecules, they diffuse slower than isolated H_2O_2 molecules because of the larger mean molecular diameter. When the oil phase contains Dow Corning 749 Fluid, simply dissolved H_2O_2 molecules are likely to mainly diffuse in the oil shell. The binding of the surfactant to H_2O_2 molecules should turn on and off. Therefore, most of H_2O_2 molecules could diffuse without surfactant molecules and reverse micelles containing H_2O_2 could work as the reservoir that virtually accelerate the transport as shown in Figure 11.^{8-10,12-14,16,17,26-28} Thus, we conclude that in W/O/W double emulsion, the permeation of hydrophilic molecules through the oil phase depends on the concentration of the surfactant stabilizing the inner interface, although not D but K affects the permeation rate.

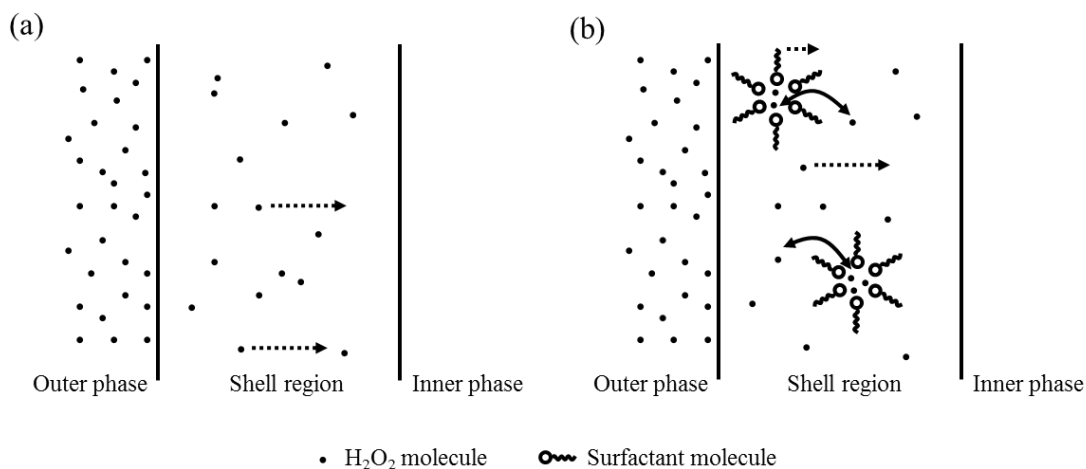


Figure 11. Possible diffusion mechanism of H₂O₂ in the oil shell. (a) Isolated H₂O₂ molecules can dissolve without surfactant molecules and H₂O₂ molecules can diffuse. (b) More H₂O₂ molecules can dissolve in the oil shell owing to isolated surfactant molecules or to reverse micelles. H₂O₂ molecules with surfactant molecules diffuse slowly. However, since the binding of the surfactant to H₂O₂ molecules should turn on and off. Isolated H₂O₂ molecules can diffuse faster. Dashed and solid arrows denote the transport of isolated H₂O₂ molecules and micelles in the oil phase, and the binding of the surfactant to H₂O₂ molecules and release, respectively.

CONCLUSION

We propose a permeability estimation method for oil shell using CL reaction in an oil microcapsule. We first theoretically derived the equations to estimate the diffusion coefficient of H₂O₂ in the oil shell of the luminol microcapsules. Moreover, we confirm that H₂O₂ concentration is negligible at the inner interface and CL emission in the luminol microcapsule is linear to the supplied amount of H₂O₂ by the observation of the CL emission in the system showing

macroscopic phase-separation. Next, we successfully estimated the diffusion coefficient of the liquid oil using the time-dependent CL emission intensity in microcapsule by means of the derived equations. The estimated diffusion coefficient D is independent of the shell thicknesses, which verifies the utility of our estimation method. Moreover, the dependence of D on the concentration of the surfactant in the oil phase indicates that in W/O/W double emulsion the permeation of H_2O_2 through the oil phase depends on the concentration of the surfactant due to the difference in K . We expect that our method is effective to estimate the release behavior of drug molecules in a microcapsule,⁴⁻⁷ to measure the anisotropy of the diffusion in liquid crystalline phases,²² and so on.^{32,33}

ASSOCIATED CONTENT

Supporting Information. Movie S1. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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