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# Permeation-induced chromatic change of a polydiacetylene vesicle with nonionic surfactant

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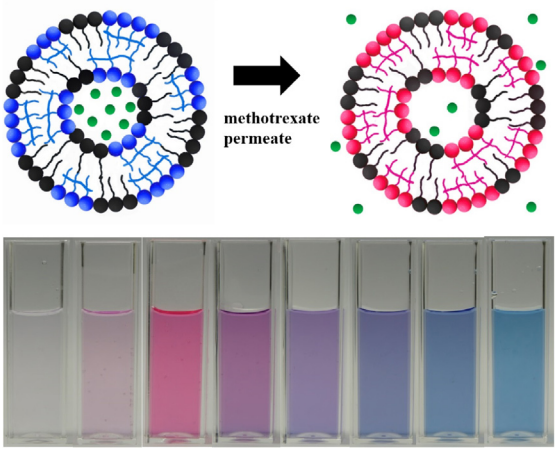
## HIGHLIGHTS

- A color change was achieved by substrate permeation in a polydiacetylene vesicle.
- The color change from blue to red due to MTX permeation occurred only with the mixed vesicle with tetra(ethylene glycol) monooctadecyl ether.
- The color change occurred due to the permeation of a substrate with a high molecular weight.

## GRAPHICAL ABSTRACT

The color change from blue to red due to MTX permeation was clearly shown when the AEPCDA: TEGOE ratio was 4:6.

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## ABSTRACT

A color change could be achieved by substrate permeation in a polydiacetylene vesicle formed with nonionic surfactant. The polydiacetylene vesicle was formed with *N*-(2-aminoethyl)pentacosa-10,12-diynamide (AEPCDA), tetra(ethylene glycol) monooctadecyl ether (TEGOE) was used as a nonionic surfactant, and methotrexate (MTX) was used as a substrate. The color change from blue to red due to MTX permeation was clearly shown when the AEPCDA: TEGOE ratio was 4:6. The change in color occurred only with the mixed vesicle with TEGOE. The change color could occur through permeation of a substrate with a high molecular weight, for example gentamicin and neomycin, but it could not occur with a substrate with low molecular weight, for example ethylamine and butylamine.



## 1. Introduction

Polydiacetylene is a polymeric material for which the double bond and triple bond are alternately conjugated [1,2], and the color

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of polydiacetylene can change by applying an external stimulus through changes in the temperature [3] or exposure to acid [4], base [4], organic solvent [5,6], metal ions [7,8], physical stress [9,10], or contact with biological compounds [11–13]. Many researchers have reported that polydiacetylene can be implemented as a sensor to detect the above external stimuli [14–19]. 10,12-Pentacosadiynoic acid (PCDA) is usually used as a source material to form polydiacetylene because PCDA can easily form the vesicle through sonication, and polymerization can be easily performed in the vesicle using UV irradiation. Like this, polymerization can proceed only in the structure in which the molecules are regularly arranged, so we refer to this polymerization as topopolymerization [20–23].

Nonionic surfactants exhibit a low toxicity compared to ionic surfactants. Therefore, these can be widely applied in biological systems [24–26]. Tetra(ethylene glycol) monooctadecyl ether (TEGOE) is known to form a vesicle by sonication, and this vesicle can contain drugs inside and can be used as a drug delivery vehicle [27–32]. Nonionic surfactants are well known to be useful in forming drug delivery systems [33–36].

Several studies on polydiacetylene have been conducted in our lab [37–40], and we have reported that the color of polydiacetylene in vesicles could changee according to the permeation of the substrate [40]. In our previous work [40], vesicles were formed with *N*-(2-aminoethyl)pentacosa-10,12-diynamide (AEPCDA) and dimethyldioctadecylammonium chloride (DODAC). The results showed that the polymerized vesicle clearly exhibited a change in color as the ratio of AEPCDA: DODAC was 1:1. In that study, we revealed that the color of the vesicle could change due to the permeation of the substrate, but the mechanism for the change in color was not discussed.

Therefore, in this study we form the vesicle using a nonionic surfactant that has good compatibility with AEPCDA, and we investigate the change in color of the vesicle due to MTX permeation, and discuss the mechanism for this change in color.

## 2. Experimental

### 2.1. Materials

10,12-Pentacosadiynoic acid (PCDA), tetra(ethylene glycol) monooctadecyl ether (TEGOE), methotrexate (MTX), *N*-hydroxysuccinimide, *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide, and ethylenediamine were obtained from Aldrich.

The *N*-(2-aminoethyl)pentacosa-10,12-diynamide (AEPCDA) was synthesized by using reported method [20,41,42].

NMR data: 0.88 (t, 3H), 1.28 (s, 26H), 1.45-1.52 (m, 6H), 2.14 (t, 2H), 2.24 (t, 4H), 2.81 (m, 2H), 3.36 (m, 2H), 4.48 (s, 2H), 6.42 (s, 1H).

### 2.2. Characterization

The Bruker DRX 300 spectrometer (Germany) was used to obtain the 1H NMR spectra. A sonic VC-505 ultrasonic processor (Newtown, CT, USA) was used to form the vesicle, and the dialysis membrane was purchased from Sigma-Aldrich (St. Louis, MO) (Molecular weight cut-off: 14,000 g/mol). The ELSZ-2 instrument (Photal Otsuka Electronics, Japan) with a laser diode was used to measure the size of the vesicle via dynamic light scattering (DLS), and the LEO-912 OMEGA instrument (Carl Zeiss, Germany) was used to obtain the transmission electron microscopy (TEM) photos. Differential scanning calorimetry (DSC) was measured using a differential scanning calorimeter (Scinco DSC N-650) under a nitrogen atmosphere. The DSC studies were performed from 5 °C to 95 °C at a heating rate of 10 °C/minute.

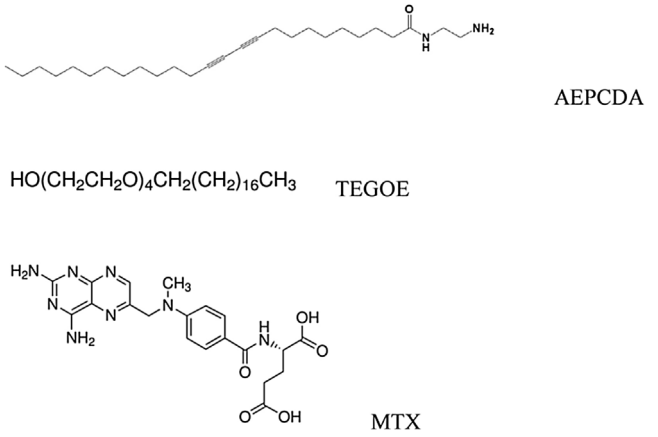


**Fig. 1.** Chemical structures of AEPCDA, TEGOE, and MTX.

### 2.3. Preparation of the AEPCDA/TEGOE vesicles

The case of a 4: 6 mol ratio (AEPCDA: TEGOE) is described below. 16.7 mg ($4.00 \times 10^{-5}$ mol) of AEPCDA and 26.8 mg ($6.00 \times 10^{-5}$ mol) of TEGOE were dissolved in 10 mL of chloroform. The solution was dried at 40 °C under vacuum, and a film was formed at the bottom of a flask. After all chloroform was removed, 50.0 mL of 0.01 M phosphate buffer solution (PBS) (pH 7.4) were added into the flask. 2.0 mM concentration (0.8 mM of AEPCDA + 1.2 mM of TEGOE) of vesicle solution was formed by sonication of the film at the bottom of the flask at 70 °C for 20 min in the buffer solution. The vesicle solution was cooled to room temperature, and the vesicle could be polymerized by irradiation with UV light (254 nm) for 20 s.

### 2.4. MTX release from the vesicle

The MTX release was performed from the vesicles formed with AEPCDA and TEGOE. The vesicles with MTX entrapped in the cavity were prepared to obtain samples with a 4: 6 mol ratio of AEPCDA: TEGOE. 16.7 mg ($4.00 \times 10^{-5}$ mol) of AEPCDA, 26.8 mg ($6.00 \times 10^{-5}$ mol) of TGEOE, and 5.00 mg ($1.10 \times 10^{-5}$ mol) of MTX were dissolved in 15 mL of chloroform. The vesicle formation process was the same as that mentioned above. After the vesicle solution had been formed with MTX, it was cooled down to room temperature. Since MTX may exist both inside and outside the vesicle, Sephadex G-50 column (20 cm length x 2 cm diameter) was used to separate out the MTX present outside the vesicle. Finally, the vesicle part which have got MTX inside the vesicle was gathered. In order to polymerize the vesicle, the vesicle part could be irradiated with a UV lamp (254 nm) for 20 s. The dialysis of the polymerized vesicle in a semi-permeable bag was performed to measure the amount of MTX release using 100 mL of 0.01 M PBS. The MTX release was measured by detecting the UV absorption of the dialyzed solution at 303 nm, and the chromatic change of the vesicle due to MTX permeation was detected.

## 3. Results and discussion

### 3.1. Formation of vesicle

Fig. 1 shows the chemical structures for the AEPCDA, TEGOE, and MTX. In this study, the vesicles were formed with AEPCDA and TEGOE, and the size of the vesicle was measured via DLS, with the results shown in Fig. 2.

In our previous work, the vesicle was formed using AEPCDA and DODAC. In the case with 1:9 or 2:8 ratios of AEPCDA: DODAC, the formed vesicles had two sizes. The reason for this is that DODAC