# Controlled Release of Organic Substances Using Polymer Membrane with Responsive Function for Amino Compounds

KAZUHIKO ISHIHARA, NAOHIRO MURAMOTO, and ISAO SHINOHARA, *Department of Polymer Chemistry, Waseda University, Ohkubo, Shinjuku-ku, Tokyo 160, Japan*

## Synopsis

In order to regulate the release of a water-soluble organic substance from a polymer device, an amphiphilic polymer membrane having a dinitrophenyl group was prepared and the effects of an amino compound on the release of such a substance in an aqueous medium were investigated. When the amino compound, triethylamine (TEA), was added to the medium, the release rate of methyl orange (MO) in solution from the polymer device increased; the same was noted with an increase in the concentration of TEA. However, on removal of the TEA from solution, the rate resumed its initial level of that in water. These results were explained by the change in the swelling degree of the polymer membrane induced by the addition of TEA. This change was considered to result from the formation of a charge transfer complex between the dinitrophenyl group in the polymer membrane and the added TEA, since a charge transfer spectrum was observed in the polymer membrane–TEA system.

## INTRODUCTION

Recently, efforts have been directed to the development of a method for the administration of drugs, which is more effective and safer than conventional methods such as an oral administration and injection in a chemotherapy using drugs. Special attention was directed to a means for regulating the amount of drug release by means of a polymer membrane so as to maintain a therapeutically desirable concentration and avoid unfavorable side effects.[1] In dealing with these problems, much research has been carried out. The release rate of a drug, in order for it to be compatible with the surrounding environment, must be controlled.

In the body, there are many systems which respond to stimulation from the outside. For instance, the amount of insulin released is determined by changes in the glucose concentration in the blood. The sense of taste and sight require external chemical and physical signals. These systems are of interest from the release rate of a drug can be regulated by external signals; it should be possible to develop some system or method by which the release of a drug can be regulated with respect to amount and time.[2,3]

For the realization of this objective, an attempt was made to prepare a polymer membrane whose permeability would respond to changes in the concentration of external amino acids and amino compounds. In a previous paper, it was shown how electron donating amino acids could be separated by column chromatography using a polymeric adsorbent having an electron accepting dinitrophenyl

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group.[4] Furthermore, it was reported that the swelling degree of an amphiphilic polymer membrane with a dinitrophenyl group changed on the addition of amino compounds.[5] These results suggest that amino compounds interact with the dinitrophenyl group in the polymer matrix in an aqueous medium.

In this paper, we describe the effects of concentration change of amino compounds on the release in solution of MO, a model drug compound. From our experiments, we obtained basic information regarding the application of a polymer membrane responsive to amino compounds to a system for controlling drug release.

## EXPERIMENTAL

**Materials.** 2-Hydroxyethyl methacrylate (HEMA) was distilled under reduced pressure in a nitrogen atmosphere and the fraction of bp 67°C/2.5 mm Hg was used. 2-Propanol was purified by distillation from magnesium under nitrogen atmosphere and the fraction of bp 82°C/760 mm Hg was used. 3,5-Dinitrobenzoyl chloride and MO of reagent grade were used without further purification. 2,2′-Azoisobutyronitrile (AIBN), *N*,*N*-dimethylformamide (DMF), pyridine, and TEA were purified by conventional methods.

**Synthesis of HEMA–Methacroyl-β-Hydroxyethyl-3,5-Dinitrobenzoate Copolymer [P(HEMA–DNP)].** The homopolymerization of HEMA was carried out using AIBN as the initiator and 2-propanol as a chain transfer agent at 60°C for 2 h. The reaction mixture was cooled and poured into an excess of diethyl ether. The precipitated polymer, poly(HEMA), was filtered off and dried *in vacuo*. The molecular weight of poly(HEMA) was $5.7 \times 10^5$ according to viscosity measurement.[6] P(HEMA–DNP) was synthesized by the following procedure. 30 mL of a DMF solution containing 11.53 g of 3,5-dinitrobenzoyl chloride was added to 70 mL of a DMF solution containing 6.56 g of poly(HEMA) and 10 mL of pyridine. After being stirred for 40 h at room temperature, the mixture was poured into diethyl ether. The precipitate was filtered off and washed with water and dried *in vacuo*. The degree of dinitrophenyl group introduction was 0.119 mole fraction as determined by elemental analysis.

**Preparation of Polymer Device Containing MO.** 1 g of P(HEMA–DNP) and 0.104 g of MO were dissolved in 10 mL of DMF. The polymer membrane was cast from the solution onto a Teflon plate; the solvent was slowly evaporated in an oven at 60°C for 3 days and the membrane was dried *in vacuo*. The polymer device (1 cm × 1 cm) was obtained by cutting it out of the membrane. The thickness of the polymer device was 0.3 mm.

**Measurement of the Amount of MO Released from the Polymer Device.** The polymer device was placed in an aqueous solution of TEA and the amount of MO released from the polymer device was determined spectrophotometrically, using a Shimadzu UV-240 Spectrophotometer.

**Measurement of the Swelling Degree of the Polymer Membrane.** The polymer membrane which did not contain MO was immersed into 100 mL of aqueous solution of TEA and swollen in a vessel thermostated at 25°C. The swollen membrane was removed from the aqueous solution at regular time intervals, and the excess solution on the swollen membrane was observed by gentle tamping between filter papers and weighed. Four measurements were made

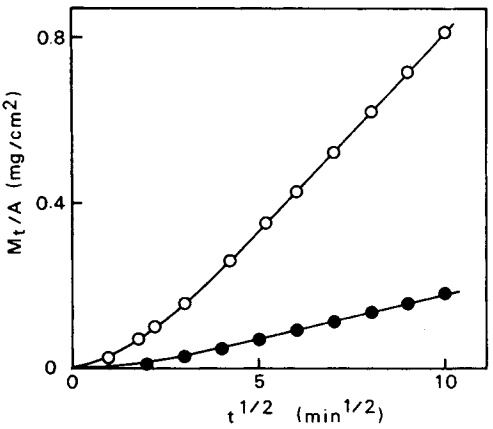


Fig. 1. The release of MO from the P(HEMA–DNP) device at 25°C: (●) in pure water; (○) in 0.06 vol % TEA aqueous solution. $M_t$ = amount of MO released; $A$ = surface area of the device; $t$ = time.

and the mean value was used to indicate the swelling degree, calculated from the following equation:

$$\text{swelling degree } H = \frac{(\text{wt of swollen membrane}) - (\text{wt of dry membrane})}{\text{wt of swollen membrane}}$$

## RESULTS AND DISCUSSION

### Effects of TEA Concentration on the Release Rate of MO from the Polymer Device

Figure 1 shows the amount of MO released from the polymer device in 0.06 vol % of TEA aqueous solution compared with that in pure water. This amount for each unit of surface area of the device ($M_t/A$) either in a TEA aqueous solution or pure water was linearly proportional to the square root of time. Moreover, it is clear that the amount of MO released in the TEA aqueous solution was much larger than in pure water.

Figure 2 shows the relation between the slope of the release curve, $M_t/A/t^{1/2}$, representing the apparent release rate,[7] and the concentration of TEA in the solvent. The apparent release rate increased linearly with increasing concentration of TEA. Therefore, it is considered that the property of the polymer device continuously changed TEA concentration. According to Higuchi, the released amount of solute from a polymer device prepared by dispersion of solute homogeneously in polymer matrix is proportional to the square root of time, provided the swelling degree of the polymer device in the solvent is not appreciably large.[8] However, since in the case of P(HEMA–DNP) device, this is not negligible, we propose the following equation.[5]:

$$M_t/A = (2DC_0C_{\text{solvent}}Ht)^{1/2}$$

where $M_t$ is the amount of solute released, $A$ is the surface area of the polymer

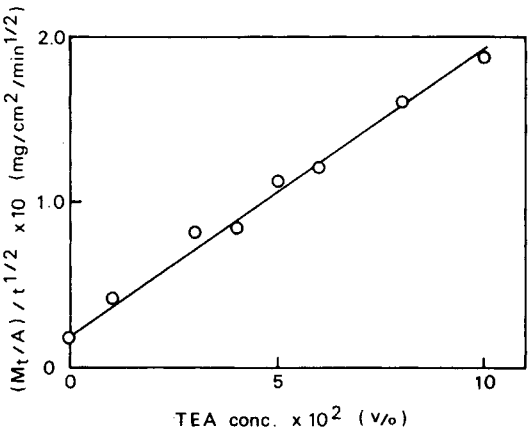


Fig. 2. Relation between the apparent release rate of MO from the P(HEMA–DNP) device and the concentration of TEA in solution.

device, $D$ is the diffusion coefficient of solute in the polymer device, $C_0$ is the initial concentration of solute in the polymer device, $C_{solvent}$ is the solubility of solute in solvent, $H$ is the swelling degree of the polymer device, and $t$ is time. It is obvious from this equation that the swelling degree of the polymer device influences the apparent release rate of solute. It has already found that the swelling degree of the P(HEMA–DNP) membrane increased selectively by the addition of amino compounds such as TEA, pyridine, aniline, and dopamine.[5]

Figure 3 shows the relation between the swelling degree of a P(HEMA–DNP) membrane in a TEA aqueous solution and the concentration of TEA. The swelling degree increased with increasing concentration of TEA. Thus, it is considered that the increase in the apparent release rate of MO from the polymer device with increasing concentration of TEA corresponds to the increase in the swelling degree of the polymer device.

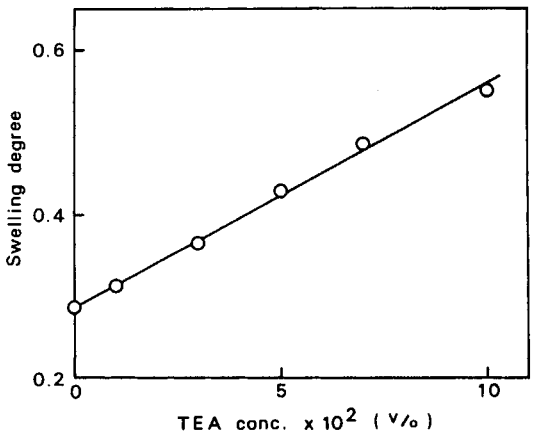


Fig. 3. Relation between the swelling degree of the P(HEMA–DNP) membrane and the concentration of TEA at 25°C.

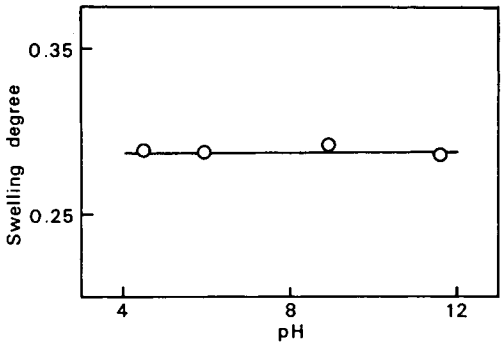


Fig. 4. The pH dependence of the swelling degree of the P(HEMA–DNP) membrane at 25°C.

## Interaction between TEA and Dinitrophenyl Group in the Polymer Membrane

The swelling degree of the poly(HEMA) membrane did not change on addition of TEA. Moreover, the dinitrophenyl moiety in the P(HEMA–DNP) was not hydrolyzed by the addition of TEA. Therefore, this change in the swelling degree as observed in P(HEMA–DNP) membrane seems to be induced by an interaction between the dinitrophenyl group and TEA. When amino compounds are added to water, the pH value of the solution increases. For example, the pH value of a 0.1 vol % TEA aqueous solution is about 10. However, when the pH dependence of the release rate of MO from the device of P(HEMA–DNP) was examined by changing the pH of the aqueous medium, the release rate of MO remained the same in a pH range from 4.6 to 12.0.[5] Figure 4 shows the pH dependence of the swelling degree of P(HEMA–DNP) membrane. It can be seen from this figure that the swelling degree was constant from a pH of 4.5 to 11.5. From these results, the increase in the release rate of MO was not due to an increase in the pH of the solution on addition of TEA.

In order to analyze the interaction between the dinitrophenyl group and TEA,

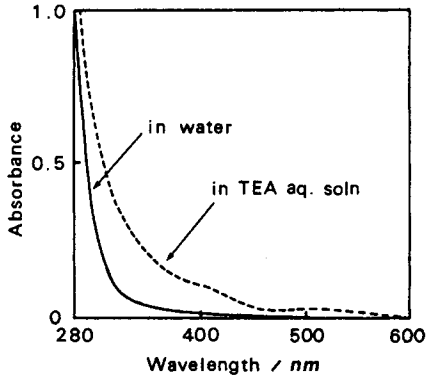


Fig. 5. Absorption spectra of the P(HEMA–DNP) membrane in pure water and in a 0.05 vol % TEA aqueous solution.

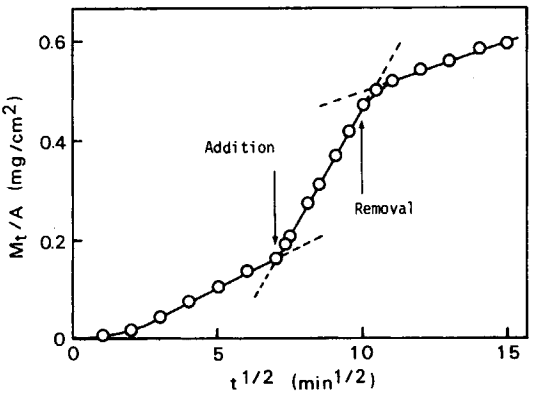


Fig. 6. The effect of addition and removal of TEA in solution on the release of MO from the P(HEMA-DNP) device at 25°C.

the electronic spectra were measured. Figure 5 shows the spectra of the P(HEMA-DNP) membrane in pure water and that in a 0.05 vol % of TEA aqueous solution. The absorption of TEA was not observed in the range from 280 nm to 600 nm. In the TEA aqueous solution, new absorption was found in a longer wavelength region compared with that in pure water. It is well known that when an electron donor and acceptor form a charge transfer complex, a new absorption can be observed in a wavelength region longer than their own absorption wavelength.[9] Since the dinitrophenyl group is typically an electron acceptor and TEA is an electron donor, the newly observed absorption of P(HEMA-DNP) membrane in the TEA aqueous solution was caused by a charge transfer interaction between them. Thus, the increase in the apparent release rate of MO from the polymer device in the TEA aqueous solution was possibly caused by an increase in the swelling degree of the membrane, as induced by the formation of the charge transfer complex between the dinitrophenyl group and TEA in the polymer membrane.

## Reversible Control of the Release Rate of MO in Response to Concentration Change in TEA

Figure 6 shows the effect of the addition and removal of TEA in solution on the release of MO from the polymer device. After the polymer device was immersed and MO released in pure water, the addition of TEA (0.01 vol %) was found to cause an increase in the release rate of MO. However, when TEA was removed from the solution by means of placing the device in pure water, the release rate of MO resumed its former level of that in pure water. Therefore, a reversible change in the release rate of MO from the polymer device is possible by the response to concentration change of TEA. This lead us to the conclusion that the release of solute from the device prepared by P(HEMA-DNP) can be regulated continuously and reversibly by the concentration change of amino compounds.

A polymer membrane with the properties mentioned above will prove useful for the controlled release of drugs. For example, it may be applied to controlling

the release of an antihistamine in response to concentration change in histamine, a biooriginated amino compound causing an allergie disease present in an excess amount in the body. Further study about this application is now continued in this laboratory.

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