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Preparation of Polymer Membranes with Responsive Function for Amino Compounds

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SUMMARY

Polymeric membrane having responsive function for the concentration change of amino compounds was prepared by introduction of dinitrophenyl group into hydrophilic polymer and release behavior of methyl orange from the polymeric membrane to aqueous medium was studied. The release rate of methyl orange was increased by addition of amino compounds to the aqueous medium. This result is attributed to the specific interaction between dinitrophenyl group and amino compounds.

INTRODUCTION

It is well known that many skillful systems having responsive functions for external physical signals or concentration change of some chemical substances exsist in the body. With attention to such functions, research is under way in our laboratory for the purpose of achieving the functions in the artificial systems.

We have already reported that the synthesis of photo-responsive polymers containing azobenzene group in their side chain which has responsive function for light and the regulation of their properties by light such as conformation (ISHIHARA et al., 1981), wettability and binding ability of low-molecular-weight compound (ISHIHARA et al., 1982).

In this report, we will describe the preparation of polymeric membrane having responsive function for the concentration change of amino compounds as a chemical signal. If the permeability of the polymeric membrane is controlled by the concentration change of amino compounds, it is expected that such polymeric membrane can apply for the controlled release of drugs.

Generally, since amino compounds act as a electron donor, they form charge transfer complexes between electron acceptors. The charge transfer complex is typically characterized by a weak bond. However, the formation is often accompanied by remarkable changes in the physical and chemical properties of the two spacies of which they are composed.

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In order to gain a basic knowledge to design the useful polymeric membrane, hydrophilic polymer containing dinitrophenyl group (DNP), which is known as one of the electron acceptor, was synthesized and release behavior of methyl orange (MO), which is a model compound of drug, from the polymeric membrane was investigated.

EXPERIMENTAL PART

Materials

2-Hydroxyethyl methacrylate (HEMA) was distilled under a reduced pressure in a nitrogen atmosphere and the fraction of bp 67°C/2.5mmHg was used. 2-Propanol was purified by distillation from magnesium under nitrogen atmosphere and fraction of bp 82°C/760mmHg was used. 3,5-Dinitrobenzoyl chloride, MO of reagent grade were used without further purification. 2,2'-Azoisobutyronitrile (AIBN), N,N-dimethylformamide (DMF), pyridine, triethylamine (TEA), and aniline 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 an initiator and 2-propanol as a chain transfer agent at 60°C for 2h. The reaction mixture was poured into an excess of diethyl ether. The precipitated polymer, poly(HEMA), was filtered off and dried in vacuo. P(HEMA-DNP) was synthesized as following procedure. A 30ml of a DMF solution containing 11.53g (0.05mol) of 3,5-dinitrobenzoyl chloride was added to 70ml of a DMF solution containing 6.56g (0.05unit mol) of poly(HEMA) and 10ml of pyridine. After the mixture was stirred for 40h at room temperature, it was poured into diethyl ether. The precipitate was filtered off and washed with water and dried in vacuo. Degree of introduction of dinitrophenyl group was 0.119, which was determined by the elemental analysis.

Preparation of Polymeric Device Containing MO

1g of P(HEMA-DNP) and 0.104g (3.18mmol) of MO were dissolved in 10ml of DMF. Polymeric membrane was cast from the solution on tefron plate, evaporating the solvent slowly in an oven at 60°C for 3 days and then dried in vacuo. Polymeric device (1cm x 1cm) was prepared by cutting the membrane obtained.

Measurement of the Release Amount of MO from the Polymeric Device

The polymeric device was put into aqueous solutions of various organic compounds of specific concentration and the amount of MO released from the polymeric device was determined spectrophotometrically using a Union Giken SM-401 spectrophotometer.

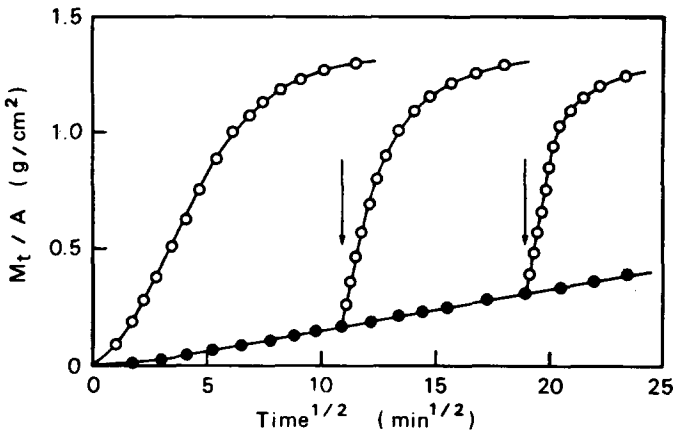

Fig. 1. Release behavior of MO from the device of P(HEMA-DNP) at 25°C ; (●) in pure water, (○) in 1vol-% aqueous solution of TEA. The arrows represent the addition of TEA. M_t ; amount of MO released, A ; surface area of the device.

RESULTS AND DISCUSSION

The release behaviors of MO from the device of P(HEMA-DNP) in pure water and in aqueous solution of TEA (1vol-%) were represented by the relation between the amount of MO released per surface area of the device and the square root of time, and they were shown in Fig. 1. It is clear that the release rate of MO from the device in aqueous solution of TEA was much faster than that in water. Moreover, after MO had been released in water for 2h or 6h, the addition of TEA induced the increment of the release rate of MO.

In general, the release behavior of solute from monolithic device which is prepared by disperison of solute homogeniously in polymer matrix follows Higuchi equation (eq. 1), when the swelling degree of the device for solvent is not appreciably large (HIGUCHI et al., 1961)

$$M_t/A = (2DC_0C_{device}t)^{1/2} \quad , \quad \text{(eq. 1)}$$

where M_t is amount of solute released, A is surface area of device, D is diffusion coefficient of solute in device, C_0 is initial concentration of solute in device, C_{device} is solubility of solute in device, t is time.

However, since the swelling degree of the device of P(HEMA-DNP) for solvent was not negligible and the solubility of MO for solvent was larger than that for polymer matrix, the solubility of MO for the device was represented by the product of the swelling degree and the solubility for solvent as eq. 2. Therefore, eq. 3

was obtained from eq. 1 and eq. 2

$$C_{device} = HC_{solvent} + (1-H)C_{polymer} \simeq HC_{solvent} \quad \text{(eq. 2)}$$

$$M_t/A = (2DC_0HC_{solvent}t)^{1/2} , \quad \text{(eq. 3)}$$

where H is the swelling degree of device, $C_{solvent}$ is solubility of solute in solvent, $C_{polymer}$ is solubility of solute in polymer.

According to eq. 3, when the plots of M_t/A against the square root of time are linear, the diffusion coefficient of solute in the device can be calculated from the slope of the straight line.

The diffusion coefficient of MO in the device of P(HEMA-DNP) was calculated by eq. 3 in the range that the MO release curve in Fig. 1 was regarded as straight line. Also the diffusion coefficients of MO were calculated when other organic compounds were added in the aqueous medium, and these values were summarized in Table 1 with the swellind degree of P(HEMA-DNP).

Table 1. Diffusion coefficients of MO in the device of P(HEMA-DNP) in aqueous solution containing various organic compounds at 25°C.

Solvent	Swelling degree	D x 10^7 (cm^2/sec)
water	0.287	0.17
water-TEA[a)]	0.837	7.17
water-pyridine[a)]	0.783	7.01
water-aniline[a)]	0.344	0.49
water-dopamine[b)]	0.348	0.47
water-tryptophan[b)]	0.287	0.39
water-DMSO[a)]	0.287	0.24
water-THF[a)]	0.287	0.24
water-acetone[a)]	0.287	0.24
water-urea[b)]	0.287	0.24

a) 1vol-% solution, b) [solute] = 0.05mol/l
Swelling degree : weight of solvent in the device at equilibrium hydoration per weight of swelling polymer membrane.

It can be seen from Table 1 that the diffusion coefficients were increased with increasing the swelling

degree of P(HEMA-DNP) in the case of the aqueous medium containing amino compounds. However, when water soluble organic compounds other than amino compounds, such as dimethylsulfoxide (DMSO), tetrahydrofuran (THF), etc. were added in the aqueous medium, the swelling degree and the diffusion coefficient were approximately equal to those in water.

According to the free volume theory of diffusion, the relation indicated as eq. 4 between the free volume in the device which served as diffusion pathway for solute molecule and the diffusion coefficient is valid (YASUDA et al., 1968)

$$D \propto \exp(- V^*/V_f) \quad , \quad \text{(eq. 4)}$$

where V^* is characteristic volume required to accommodate the diffusing molecules in device, V_f is free volume in device.

In the case in which the solute molecules diffuse in swelling membrane, the free volume in the device is represented as eq. 5 based on assumption that the interaction between polymer network and diffused molecule is negligible and V_f is proportional to the swelling degree, H

$$\begin{aligned} V_f &= HV_{f(solvent)} + (1-H)V_{f(polymer)} \\ &\simeq HV_{f(solvent)} \quad , \quad \text{(eq. 5)} \end{aligned}$$

where $V_{f(solvent)}$ is free volume of solvent, $V_{f(polymer)}$ is free volume of polymer.

From eq. 4 and eq. 5, finally, eq. 6 is followed (YASUDA et al., 1968)

$$\log D = \log D_0 - K(1/H - 1) \quad , \quad \text{(eq. 6)}$$

where D_0 is diffusion coefficient in solvent, K is proportionality coefficient related to V^* and $V_{f(solvent)}$.

It is found from eq. 6 that the logarithm of the diffusion coefficient of solute is proportional to the reciprocal of the swelling degree.

Fig. 2 shows the relation between the logarithm of the diffusion coefficient of MO in the device of P(HEMA-DNP) and the reciprocal of the swelling degree, when amino compounds were added in the aqueous medium immersing the device of P(HEMA-DNP). It can be seen from the figure that eq. 6 could be applied, since the relation between log D and 1/H was linear. Therefore, the assumption in eq. 5 considered to be applied in this case. It is considered that the interaction between P(HEMA-DNP) and MO was negligible, and the free volume of the device which is effective for the diffusion of MO was proportional to the swelling degree of the device, in other wards, the amount of

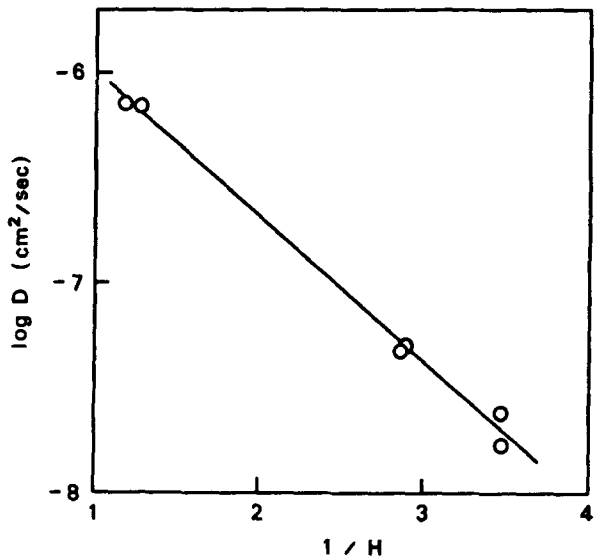

Fig. 2. Diffusion coefficient of MO in the device of P(HEMA-DNP) as a function of reciprocal of the swelling degree at 25°C.

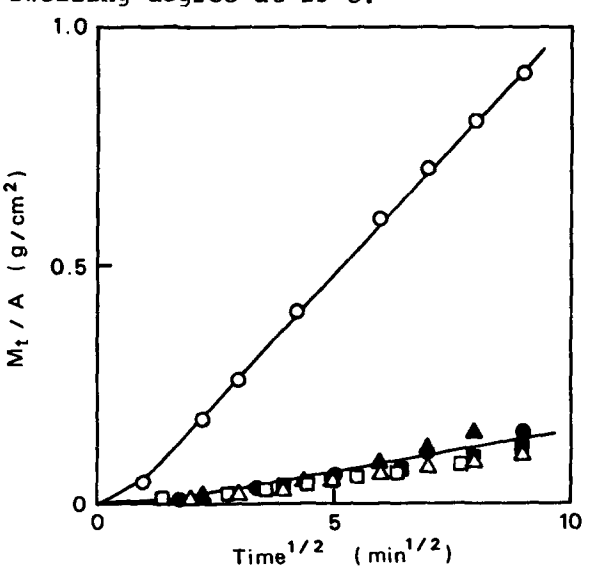

Fig. 3. Release behavior of MO from the device of P(HEMA-DNP) at 25°C ; (○) in 0.1vol-% aqueous solution of TEA, (●) in water : pH 10.62, (△) pH 8.95, (▲) pH 6.94, (□) pH 5.40, (■) pH 4.62. M_t ; amount of MO released, A ; surface area of the device.

solvent in the device.

This result suggests that the increment of release rate of MO from the device of P(HEMA-DNP) was explained by the increment of the swelling degree of the device, when amino compounds were added to the aqueous medium.

On the other hand, the value of pH of aqueous solution is increased by the addition of amino compounds. For example, the value of pH of aqueous solution containing 0.1vol-% of TEA was about 10. Thus, 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. Fig. 3 shows the release behavior of MO from the device of P(HEMA-DNP) to water at various pH. It was found that the rate of MO release was constant in the pH range from 4.6 to 12.0.

Moreover, it is confirmed that the solubility of MO in aqueous medium was not changed by addition of organic compounds tested below 1vol-%.

From these results, it seems that the increment of the swelling degree accompanying the increment of release rate of MO from the device was caused by the interaction between dinitrophenyl group in P(HEMA-DNP) and amino compounds.

Further work is needed to clarify this interaction.

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