Controlled release of biofunctional substances by radiation-induced polymerization: 2. Release of potassium chloride from porous poly(diethylene glycol dimethacrylate)

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The controlled release of potassium chloride from flat circular matrices made by radiation-induced polymerization of a glass-forming monomer at low temperatures has been studied. The water–particle phase content formed in a poly(diethylene glycol dimethacrylate) (polyDGDA) matrix was controlled by the addition of polyethylene glycol #600 (PEG 600). The dispersed water-particle phase content in the matrix was estimated directly and by scanning electron microscopic observations. The release of potassium chloride from the matrix increased linearly with the square root of time. The water content of the matrix had an important effect on the release rate which increase roughly in proportional to water content. This effect can be attributed to the apparent increase of the rate of drug diffusion.

INTRODUCTION

Recently, immobilization of enzymes by the polymer entrapping method has been studied[1,2] and also controlled release of drugs by polymer entrapping has been examined from the viewpoint of durable and moderately controlled pharmaceutical effects[3,4]. The authors have studied the characteristics of low temperature radiation-induced polymerization of monomers which have stable supercooling properties and high polymerizability at low temperatures[5]. The application of low temperature polymerization in the supercooled state to the entrapping of various enzymes has also been tried[6]. It was found that the polymerized matrix consisting of a heterogeneous proous structure formed due to crystallized water in the matrix showed a considerably leakage of enzyme from the porous matrix depending on the content of water. This property is applicable to the controlled release of drugs.

In the previous paper[7], the authors investigated the release property of potassium chloride as a model drug from various polymer matrices formed by radiation-induced polymerization. In this work, the release property of the same drug from polyDGDA prepared by low temperature polymerization in the presence of PEG 600 was studied in relation to the heterogeneous water–particle phase (porous structure) formed in the matrix.

EXPERIMENTAL

Materials

Potassium chloride (~48 mesh powder) (Otsuka Pharmaceuticals Co., Ltd.) and diethylene glycol dimethacrylate (DGDA) (Shin-Nakamura Chemical Co. Ltd.) were purified by the method described in the previous paper[7]. Polyethylene glycol #600 (PEG 600) obtained from Wako Pure Chemical Industries Ltd. was not purified.

Preparation of the polymer-drug composite having a heterogeneous disperse phase

The polymer–drug composite was prepared as described in Part 1 but using DGDA–PEG 600 mixtures. The ampoule was irradiated for 8 h at a dose rate of 5×10^5 R/h at a temperature of −78°C (dry ice–ethanol) with γ-rays from a ^{60}Co source. No DGDA remaining in the matrix was detected by gas chromatographic techniques. The polymer–drug composites obtained from a composition of 30%DGDA–70%PEG 600, 50%DGDA–50%PEG 600. 70%DGDA–30%PEG 600, and 100%DGDA were flat circular composites of 14 mm diameter and 4 mm high having 4.84 cm^2 surface area.

The dissolution examination of potassium chloride from the polymer–drug composite was carried out as described in Part 1[7].

Measurement of porous structure in the matrix

The porous structure of the polymer–drug composite was observed under a scanning electron microscope (Model JSM-U3, Japan Electron Optics Laboratory Co. Ltd) and the average area of dispersed water–particle phase read directly from the microscopic photograph. The average diameter of this phase D_{av} was determined from equation (1):

$$D_{av}(\mu m) = 2\left\{\frac{\text{Average area of a particle phase}}{\pi}\right\}^{1/2} \quad (1)$$

The apparent density of dispersed particle phase W_a' in the

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matrix was estimated from microscopic observation and defined as equation (2):

$$W_a'(\%) = \frac{\text{Total area of particle phase}}{\text{Total area of visual field in microscopy (particle phase and polymer matrix)}} \times 100 \quad (2)$$

RESULTS AND DISCUSSION

Time–release relations in the matrix having various dispersed water–particle phase

In Part 1[7] the release property in polymer matrices having no heterogeneous dispersion phase was studied in relation to the diffusivity in the matrix and its dependence on the water absorption of the polymer. The characteristic property of the polymer–enzyme composite obtained by low temperature polymerization of the mixture consisting of glass-forming monomers, enzymes and solvent (water) is that the polymer formed had a porous structure[2]. The porous structure in the matrix can be varied by changes in the composition of monomer and solvent. In this study, in order to make a similar heterogeneous dispersed particle phase in the matrix the crystallizable solvent PEG 600 was added in polymerization of DGDA. The amount of potassium chloride released from the polymer, measured against time, is shown in *Figure 1*. The results show that release rate increases with decreasing monomer concentration. It was also clear that the release property could be controlled by changing the composition of monomer and crystalline component.

Treatment of release property by Higuchi equation

According to the Higuchi equation (equation 7, Part 1), the amount of drug Q released from a suspension-type matrix is proportional to the square root of the amount of drug per unit volume, the diffusion constant, the drug solubility and time, respectively:

$$Q = (2ADC_s t)^{1/2} \quad (3)$$

The plot of Q against the square root of time was linear (*Figure 2*) through the origin.

In order to estimate the effect of the PEG 600 on the heterogeneous dispersed phase, the water content (W) was measured according to:

$$W(\%) = \frac{W_w}{W_p + W_w} \times 100 \quad (4)$$

where W_p is the dried capsule weight and W_w is the weight of the water absorbed to saturate the capsule. In this case, W_w is composed of water in that part of the heterogeneous dispersed phase caused by the crystallized PEG 600 (A_w), water absorbed in the polyDGDA matrix itself (B_w) and water in the part of the matrix formed by the dissolution of potassium chloride (C_w). For W_p = 1g, W_w values in 30%, 50%, 70% and 100%DGDA systems are 1.42, 0.85, 0.33 and 0.04 g, respectively. As W_w in the case of 100% DGDA represents the contribution of B_w and C_w, an increase of W_w resulting from increased PEG 600 can be attributed to the increase of A_w. According to this result, contribution of B_w and C_w to W_w is much lower than that of A_w. The values of W (*Table 1*) show that the major part of the water content is due to the water replacing and being contained in the heterogeneous dispersed phases of the matrix formed by

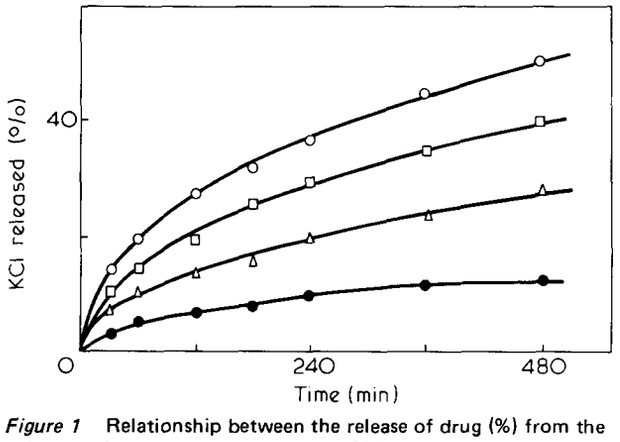

Figure 1 Relationship between the release of drug (%) from the polymer–drug composite containing 600 mg of potassium chloride and time. Composition; ○, 30% DGDA–70% PEG 600; □, 50% DGDA–50% PEG 600; △, 70% DGDA–30% PEG 600; ●, 100% DGDA

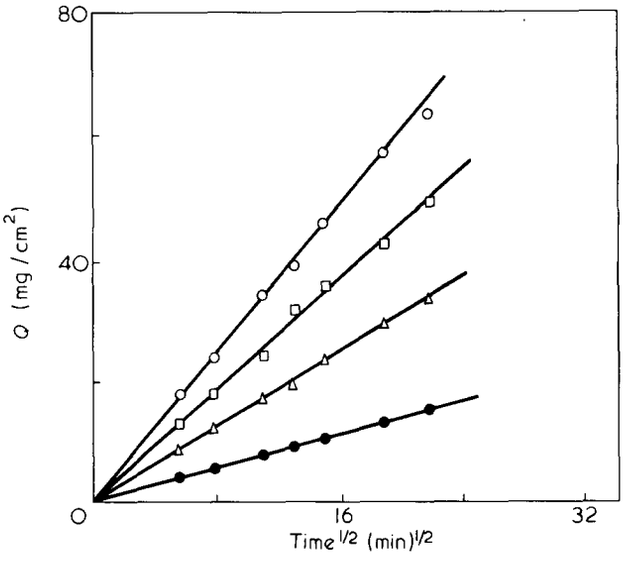

Figure 2 Linear relationship between the cumulative amount of potassium chloride per unit surface area of the composite and the square root of time

Table 1 Effect of porous structure on the $Q/t^{1/2}$ of potassium chloride from the polymer–drug composite

No.	Compositon (vol %)		W(%)			Porous structure		
	DGDA	PEG 600		(mg/cm²/min$^{1/2}$)	(x 10^{-4} cm²/min)	D_{av}(μm)	Number of D_{av} (pieces /cm²)	W_a'(%)
1	30	70	58.7	3.00	4.43	15.5	2.2 x 10^5	41.7
2	50	50	46.1	2.31	2.63	5.6	1.2 x 10^6	30.7
3	70	30	24.8	1.54	1.17	2.2	2.9 x 10^6	11.4
4	100	0	3.8	0.69	0.23	–	–	–

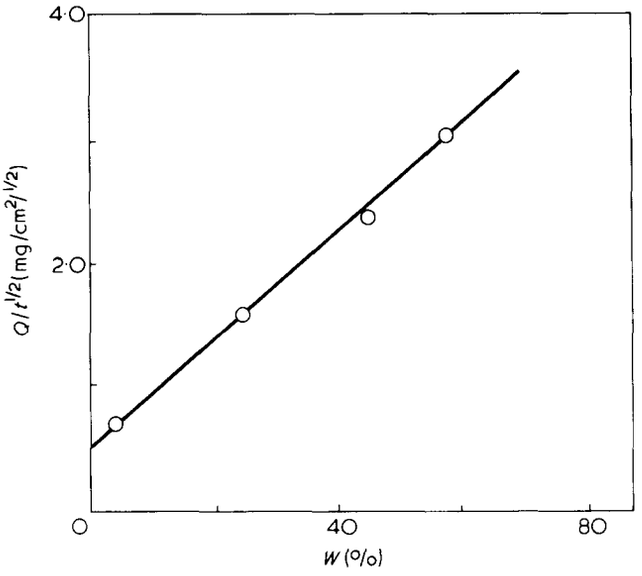

Figure 3 Relationship between the flux of potassium chloride ($Q/t^{1/2}$) and the water content (W)

PEG 600 The value of water content (W) may be used as a rough estimation of the dispersed water–particle phases. It is suggested that encapsulated water in the matrix is more im portant for diffusion and release of drugs than absorbed water in the matrix itself.

From the slope of linear relation between Q and the square root of t in *Figure 2*, the magnitude of drug release profile ($Q/t^{1/2}$) can be estimated. Values $Q/t^{1/2}$ (*Table 1*) plotted as a function of water content (W) (*Figure 3*), gave a linear plot, showing that the release rate ($Q/t^{1/2}$) increases roughly in proportion to the water content (W). Furthermore, the apparent diffusivity (D) of drug in the porous matrix calculated from equation (3) are shown in *Table 1*. The diffusivity in the matrix itself should not change appreciably since the polymer matrix is always methacrylate and its water absorption is hardly changed by the PEG 600. However, apparent diffusivity in *Table 1* increased markedly with increasing PEG 600 and the results support the conclusion that dispersed water–particle phases made by PEG 600 markedly promote the release rate. It is certain that this promoting effect is due to the apparent increased effect of drug diffusion in the matrix due to the presence of the dispersed water phase as well as to the decrease in thickness of matrix membrane by decreased monomer concentration. Clearly, the release rate can be controlled by the composition of monomer and PEG 600.

Observation of porous structure by microscopic method

The structure of the polymerized matrix observed by scanning electron microscopy, after complete leaking of potassium chloide and PEG 600 is shown in *Figure 4*. As the dispersed water–particle phase could be hardly observed in *Figure 4d*, it is clear that the dispersed phase is formed by the addition of PEG 600 which crystallized at temperatures below 0°C. The PEG 600 crystals dispersed in supercooled DGDA monomer at low temperatures formed a heterogeneous dispersion structure in the matrix by melting and leaking out (replacing by water) after polymerization. These structures consisted of independently closed cells as seen clearly in *Figure 4*. The formation of such a heterogeneous dispersion structure is the most characteristic property of polymers obtained by low temperature polymerization of supercooling monomer containing a crystallizable solvent.

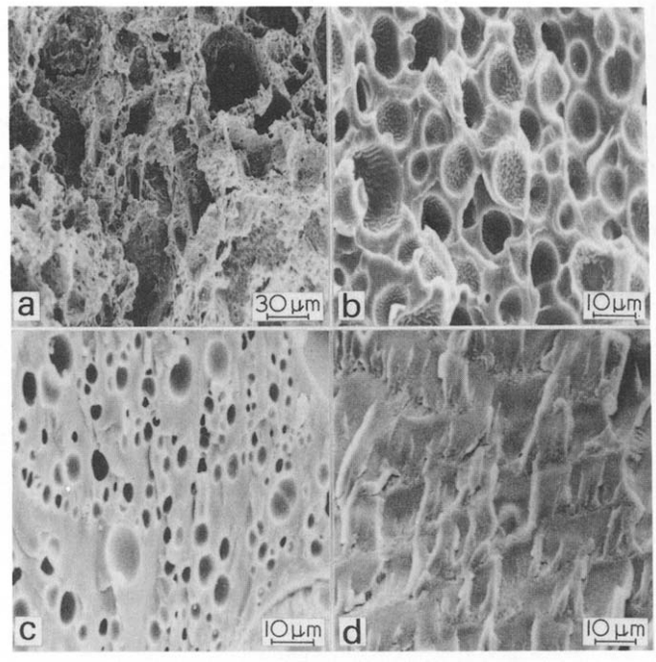

Figure 4 Scanning electron microphotographs of porous structure in the polymer–drug composite. Composition: (a) 30% DGDA–70% PEG 600; (b) 50% DGDA–50% PEG 600; (c) 70% DGDA–30% PEG 600; (d) 100% PEG 600

The distribution of average diameter of dispersed phases and their number determined by microscopic observation was shown in *Table 1*. These distributions can be controlled by changing the combination and composition of supercooling and crystallizing components. The average diameter of dispersed phase decreased but their average number increased with decreasing PEG 600 concentration. This fact might be due to the nature of the crystal growth at low PEG 600 concentration. The apparent content of dispersed water–particle phase W_a' was estimated also from the result of microscopic observation and compared to W_a obtained from water content in *Table 1*. The value from microscopic observation was smaller than that from water content, but its dependence on monomer concentration agreed with the trend observed in the water content study. This difference might be attributed to a low estimation of average diameter in the visual field of electron microscopy in *Figures 4b* and *4c*, because relatively few water–particle phase will be sliced at their maximum length or diameter.

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