Controlled release of biofunctional substances by radiation-induced polymerization: 1. Release of potassium chloride by polymerization of various vinyl monomers

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The release behaviour of a drug from flat circular capsules obtained by radiation-induced polymerization at low temperatures and with different hydrophilic properties has been studied. The effect of various factors on release property was investigated. The release process could be divided into three parts, an initial quick release stage, stationary state release stage and a retarded release stage. Release behaviour in the stationary state was examined using Noyes–Whitney and Higuchi equations. It was shown that the hydrophilic property of polymer matrix expressed by water content was the most important effect on diffusion and release rate. Rigidity of the polymer may also affect diffusivity. The first quick release step could be attributed to rapid dissolution of drug in the matrix surface due to polymer swelling.

INTRODUCTION

In a previous publication the application of the radiation-induced polymerization method at low temperatures using glass-forming monomers was used to prepare polymer matrices comprising biofunctional substances[1]. This method consists of mixing the glass-forming monomer[2], biofunctional substances and solvent (usually water), cooling it to low temperatures and then irradiating. The characteristic of polymer matrices obtained was that they had a porous structure due to the crystallization of water or solvent. That is, at low temperature the glass-forming monomer acts as the supercooled suspension medium for the crystallizable solvent and rapidly polymerizes on irradiation to form a porous matrix membrane. The authors have found that this porous structure is effective for the diffusion of substrate and reaction product in the case of the immobilization of enzymes[1]. This characteristic can be applied to the controlled release of biofunctional substances such as drugs. It may be useful to control the porous structure of polymer matrices according to the purpose of the biofunctional substances. However, diffusion of low molecular substances in the matrices depends on diffusivity through matrix membrane swollen to various degrees by water, as well as on porous structure in polymer matrices.

In this report, the release behaviour of potassium chloride from radiation polymerized matrix capsules of various degrees of hydrophilicity, having no porous structure was studied in order to clarify the effect of diffusivity in the swollen matrix in relation to water content.

EXPERIMENTAL

Materials

Potassium chloride (~48 mesh powder) (Otsuka Pharmaceuticals Co. Ltd.) was dried over silica gel in vacuum. Commercial methyl acrylate, methyl methacrylate, and 2-hydroxyethyl methacrylate (Tokyo Kasei Kogyo Co. Ltd) were purified by distillation before use. Commercial polyethylene glycol #600 diacrylate, polyethylene glycol #400 dimethacrylate-diethylene, glycol dimethacrylate, trimethylolpropane triacrylate, and trimethylolpropane trimethacrylate (Shin–Nakamura Chemical Co. Ltd) were purified by washing with 1% aqueous sodium hydroxide, passed over Amberlyst A-27 (Rohm & Haas), and dried over Molecular sieve 4A.

Preparation of radiation polymerized flat circular capsules

In the preparation of radiation polymerized flat circular capsules comprising potassium chloride, 600 mg of potassium chloride was charged into a flat bottom glass ampoule 14 mm i.d., 0.5 ml of various vinyl monomers was added and the ampoule sealed off under a vacuum of 10^{-3} mmHg at a temperature of $-196°C$. In this case, potassium chloride in the ampoule was homogeneously coated by monomer. The sealed ampoule was irradiated at room temperature with γ-rays from ^{60}C source at a dose rate of 5×10^5 R/h. The polymerized matrix obtained by an irradiation dose of 4 MR as a flat circular capsule of 16 mm diameter, 4 mm thickness and 4.84 cm^2 surface area was used for the dissolution test. After irradiation, no monomer or other impurity was detected in the capsule by gas chromatographic techniques.

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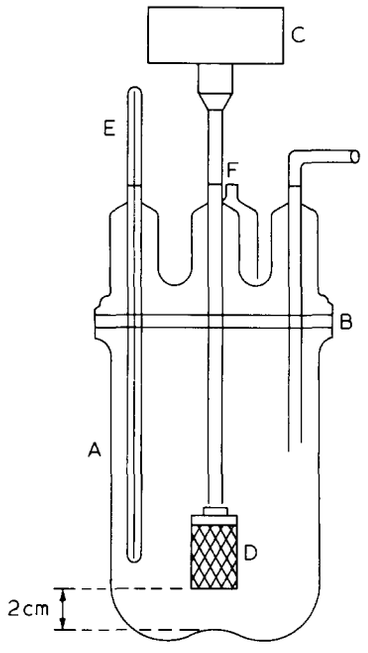

Figure 1 Apparatus for dissolution test. A, cylindrical vessel (1000 ml); B, fitted cover; C, motor; D, basket (40 mesh stainless steel cloth) 3.66 cm high and 2.5 cm in diameter; E, thermometer (37 ± 0.5°C); F, sampling

Dissolution of potassium chloride from the capsules

The dissolution test was carried out at 37° ± 0.5°C at a rate of 100 rpm with a Toyama Sangyo dissolution apparatus, Model TR-5S, based on United States Pharmacopeia XIX as shown in *Figure 1*. The basket was immersed in 1000 ml purified water, pH 6.0 and at selected time intervals over a total period of 480 min, 10 ml of the elution medium was sampled and potassium chloride assayed spectrophotometrically using a Shimazu double beam spectrophotometer, Model UV-200[3].

RESULTS AND DISCUSSION

Time–release curves from various matrix capsules containing potassium chloride

Potassium chloride, a known drug for oral treatment of hypopotassemia[4], was chosen as a model drug for the controlled release study. The amount of released potassium chloride was measured at various times and the results are shown in *Figure 2*. It was evident that the release property depended on the kind of polymer and this may be related to the hydrophilic property of the polymer as discussed later. It was also recognized that the release process could be divided into three parts – a relatively quick release process in the initial stage, followed by a stationary release process in the second stage, and a retarded slow release process in the later stage. The initial rapid process could be attributed to the quick dissolution of potassium chloride present on the surface of polymer caused by the rapid swelling of the polymer by water. The second step – a stationary state release process through the polymer matrix is analyzed in the next section. The last process is probably a release rate decreasing step caused by a shortage of potassium chloride in the matrix.

Analysis of stationary state release process by Noyes–Whitney equation

The Noyes–Whitney equation is applicable for the kinetic analysis of first order release from the matrix medium[5,6].

The release rate and the concentration (C) of the drug at a certain time t can be expressed as follows:

$$-\frac{dC}{dt} = K_r(C - C_1) \tag{1}$$

$$C = \frac{VC_0}{V_0 + V}\left\{1 + \frac{V_0}{V}\exp -\frac{-K_r(V_0 + V)t}{V_0}\right\} \tag{2}$$

where $C_1 = (C_0 - C)V/V_0$, C_1 is the drug concentration in fluid medium, C_0 is the initial drug concentration in the matrix, V_0 and V are the volumes of water used for release and of matrix per unit weight, and K_r is the rate constant for release. Since $V_0 \gg V$ (V_0 is 1000 ml and V is about 0.5 ml), equation (2) may be written:

$$K_r t = \ln\frac{\alpha C_0}{(\alpha C_0 - C_1)} \tag{3}$$

where α is V/V_0. The relation between t and $\log\alpha C_0/(\alpha C_0 - C_1)$ is shown in *Figure 3*. The three stages in the release behaviour are clearly shown. The linear relation in the stationary release stage shows that analysis by the Noyes–Whitney equation is approximately applicable to these matrices. Exact kinetic analysis for this release is complicated by the fact that the concentration of potassium chloride in the matrix changes as the matrix polymer swells with water. In addition the polymer swelling in the presence of a salt might be different to that in pure water and this difference may affect the drug concentration and diffusivity in the polymer matrix. However it was ascertained that the major step in the polymer swelling is completed within about 60 min; that is, within the initial, non-stationary, quick release stage, even in the most hydrophobic polymer used The linear relationship in *Figure 3* is therefore an approximate representation of experimental results using the value of

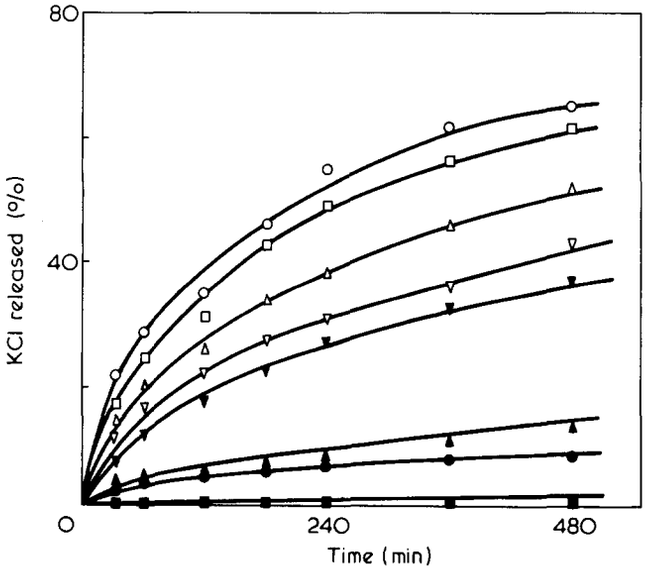

Figure 2 Relationship between the release of drug (%) from polymer capsules containing 600 mg of potassium chloride and the time. Monomer: (○), 2-hydroxyethyl methacrylate; □, polyethylene glycol #600 diacrylate; △, polyethylene glycol #400 dimethacrylate; △, methyl acrylate; ▲, methyl methacrylate; ▲, diethylene glycol dimethacrylate; ●, trimethylolpropane triacrylate; ■, trimethylolpropane trimethacrylate

drug concentration in polymer matrix saturated with pure water

Though the theoretical value of $\alpha C_0/(\alpha C_0 - C_1)$ must be unity at $t = 0$, the intersection of the straight line and the ordinate shows higher values This deviation is probably due to the quick dissolution of potassium chloride trapped on the surface of the matrix on swelling of the polymer. The values of intersection Z vary with the polymer used and probably depend on the hydrophilic property or swelling tendency of the polymer In order to estimate the hydrophilic property of the polymer, water content was determined as a rough measure of hydrophilicity, according to the following equation (though it might change in the presence of salt such as potassium, chloride):

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

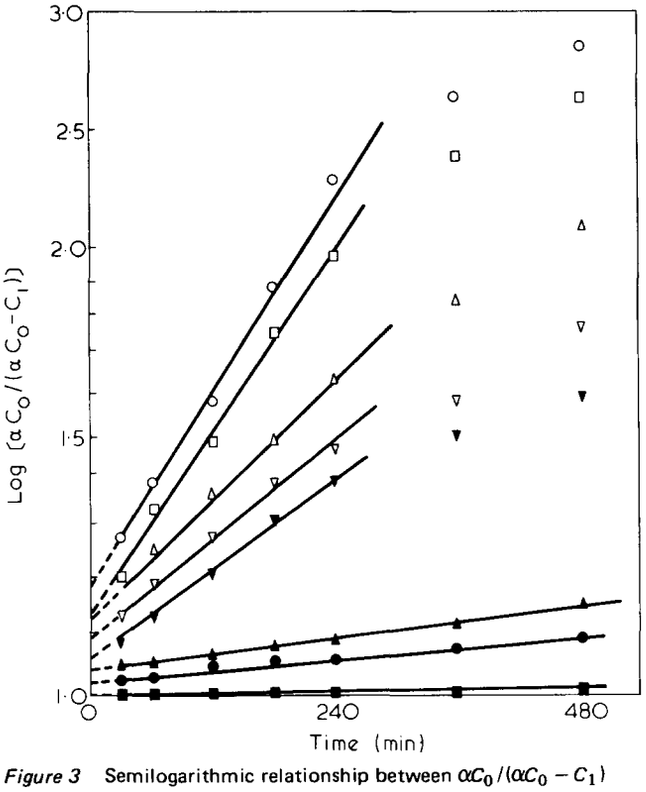

Figure 3 Semilogarithmic relationship between $\alpha C_0/(\alpha C_0 - C_1)$ and the time

where W_w and W_p are the weight of the water absorbed to saturate the polymer and of dried polymer, respectively. These values are listed in *Table 1*. Furthermore, the apparent diffusion coefficient of drug in the matrix capsules can be estimated according to:

$$D_p = \frac{K_r h}{S} \tag{5}$$

where h is the effective thickness of matrix membrane and S is the specific surface area. The values of D_p listed in *Table 1* show that Z increased in correspondence with the increase of water content and diffusion coefficient. It is clear that the rapid increase in rate in the initial release stage could be related to hydrophilic property and to the quick dissolution and release of drug on swelling of the aqueous polymer matrices.

Treatment of release property by the Higuchi equation

Higuchi proposed the following equation for the amount of drug released in non-capillary matrices[7]:

$$Q = (2A - C_s)\left(\frac{Dt}{1 + \frac{2(A - C_s)}{C_s}}\right)^{1/2} \tag{6}$$

For the common case of $C_s \ll A$, equation (6) can be simplified to:

$$Q = (2ADC_s t)^{1/2} \tag{7}$$

where A is the concentration of drug expressed in units/cm^3, C_s is the concentration of drug in the external polymer phase of the matrix, D is the diffusion constant of the drug in the external polymer phase of the matrix, t is the time, and Q is the amount of drug released up to time t per unit area of exposure.

Experimental results (*Table 1*) on the relation between Q and the square root of t show that the linear relation is obeyed within certain time ranges and then gradually changes to the saturated curve. It is clear that the main release step agrees approximately with equation (7). Although C_s and D in equation (7) depends on matrix swelling, values in saturated aqueous matrix can be used approximately for the stationary state release step in the linear parts of curves in

Table 1 Parameters for release of potassium chloride from the polymer–drug matrix capsules

Monomer	W (%)	Z (%)	K_r (x 10^{-3} min^{-1})	D_p (x 10^{-5} g/cm min)	A (mg/cm^3	C_s (mg/cm^3)	$Q/t^{1/2}$ (ng/cm^2 min$^{1/2}$)
Hydroxyethyl methacrylate	32.5	16	2.60	5.37	843	150	4.37
Polyethylene glycol #600 diacrylate	30.7	12	2.23	4.61	884	140	3.87
Polyethylene glycol #400 dimethacrylate	21.6	11	1.54	3.18	940	90	3.01
Methyl acrylate	7.6	9	1.14	2.35	1129	20	2.41
Methyl methacrylate	4.8	6	1.10	2.27	1185	10	2.06
Diethylene glycol dimethacrylate	3.8	3	0.22	0.45	1242	8	0.69
Trimethylolpropane triacrylate	3.3	1	0.21	0.43	1200	7	0.33
Trimethylolpropane trimethacrylate	2.4	0	0.04	0.08	1189	6	0.03

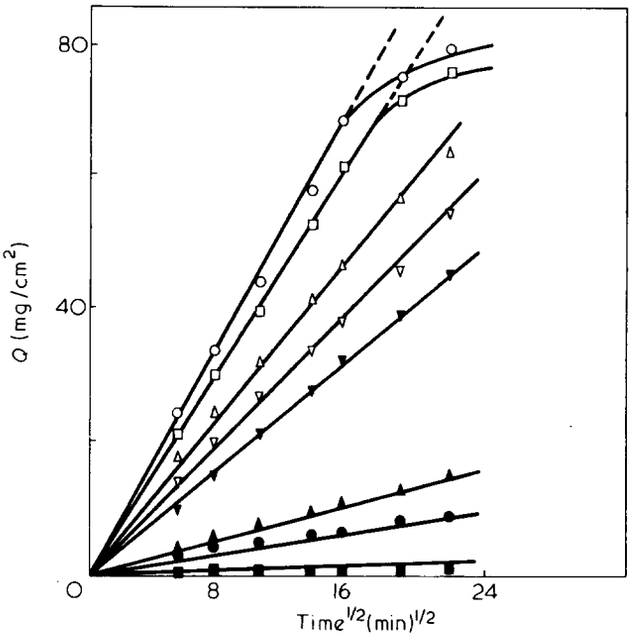

Figure 4 Linear relationship between the cumulative amount of drug release per unit surface area of polymer capsule and the square root of time

Figure 4 as well as in *Figure 3*. In later stages of release, deviation from linearity was observed owing to non-stationary state (non-first order) release.

It may be concluded that potassium chloride is effectively trapped and released with control in various acrylate and methacrylate polymers formed by radiation-induced polypolymerization. The hydrophilic property of these polymer matrices had the most important effect on release property, the release rate being very small in less hydrophilic or hydrophobic matrices. Practically it would be useful if the hydrophobic polymer had the preferable release rate and further, investigation on this point is reported in a following paper.

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