Controlled Drug Dissolution by Radiation-Induced Polymerization in the Presence of Dimethylaminoethyl Methacrylate–Methyl Methacrylate Copolymer or Methacrylic Acid–Methyl Acrylate Copolymer

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Received July 24, 1978, from the *Takasaki Radiation Chemistry Research Establishment, Japan Atomic Energy Research Institute, Takasaki, Gunma, Japan.* Accepted for publication January 11, 1979.

Abstract □ Polymer-containing tablet preparation was studied using radiation-induced polymerization of glass-forming monomers at low temperatures in the presence of dimethylaminoethyl methacrylate–methyl methacrylate copolymer or methyl acrylate–methacrylic acid copolymer. Drug dissolution from tablets was in the pH 3.0–8.0 range. A copolymer contained in the tablets dissolved in the dissolution medium at a specific pH. Drug dissolution from tablets took place rapidly at pH >6.0 in the presence of methyl acrylate–methacrylic acid copolymer and at pH <5.0 in the presence of dimethylaminoethyl methacrylate–methyl methacrylate copolymer. The polymers had fibrous or capillary pore structures in contrast to the spherical pore structures formed in the presence of polyethylene glycol 600.

Keyphrases □ Dosage forms—controlled-release delivery devices, radiation-induced polymerization of glass-forming monomers, low temperature, in the presence of dimethylaminoethyl methacrylate–methyl methacrylate or methacrylic acid–methyl acrylate copolymers, for various drugs, dissolution rate from tablets □ Tablets—drug dissolution rate, radiation-induced polymerization of glass-forming monomers in the presence of dimethylaminoethyl methacrylate–methyl methacrylate or methacrylic acid–methyl acrylate copolymers, various drugs □ Copolymers—anionic and cationic, controlled-release tablets, dissolution rate, various drugs □ Dissolution rates—various drugs, tablets containing radiation-induced polymers of glass-forming monomers in the presence of cationic and anionic copolymers

Recent studies reported enzyme immobilization by polymer entrapment (1–3). Controlled drug dissolution by polymer entrapment is attractive due to durable and moderately controlled pharmaceutical effects (4–6).

Radiation-induced polymerization using glass-forming monomers (7) at low temperatures for the preparation of polymer matrixes containing biofunctional substances (8–10) such as enzymes, microbial cells, and drugs has been reported. Glass-forming monomers are a suitable entrapping matrix because they supercool to highly viscous liquids or amorphous solid at low temperatures and because they polymerize even at low temperatures. The polymer matrixes produced by this method were characteristic in porous structure due to crystallized solvent or crystallized water in the matrix at low temperatures; this porous structure facilitates substrate or drug diffusion in and out of the matrix.

However, controlled drug dissolution often requires dissolution of a drug in a solvent within a specific pH range. The entrapping method permits the mixing of various additives with drugs and polymer in the matrix. This paper describes drug dissolution from solid tablets prepared by radiation-induced polymerization in the presence of dimethylaminoethyl methacrylate–methyl methacrylate copolymer or methacrylic acid–methyl acrylate copolymer for controlled dissolution at pH 3.0–8.0.

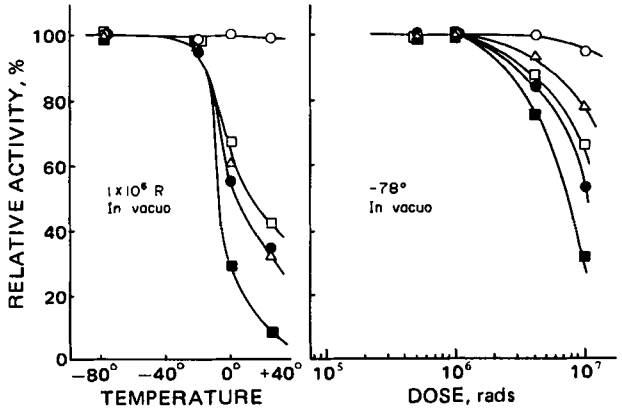

Figure 1—*Effect of irradiation conditions on native drug activity. Drug was dissolved in distilled water (pH 6.0) and put into a glass ampul. The ampul was sealed under a vacuum of 10^{-3} mm Hg. Irradiation was carried out at 1 × 10^6 rads (R)/hr* in vacuo. *The native drug activity was taken ds 100%. Key (drug concentration): ○, 60 μg of potassium chloride/ml; □, 25 μg of salicylic acid/ml; △, 8 μg of sulfanilamide/ml; ●, 60 μg of aspirin/ml; and ■, 20 μg of colchicine/ml.*

EXPERIMENTAL

Monomers—2-Hydroxyethyl methacrylate[1], hydroxyethyl acrylate[1], and glycidyl methacrylate[1] were used.

Drugs—Aspirin[2], sulfanilamide[3], salicylic acid[3], colchicine[3], and potassium chloride[4] were used.

Copolymers—Copolymer[5] of dimethylaminoethyl methacrylate–methyl methacrylate (cation-type copolymer) and copolymer[6] of methacrylic acid–methyl acrylate (anion-type copolymer) were used. The cation-type copolymer was dissolved only in a medium corresponding to the gastric juice at pH <5.0; the anion-type copolymer was dissolved in a medium corresponding to the intestinal juice at pH >6.0.

Porous Polymer–Drug Tablet Preparation—Polymer tablets containing drugs were made as follows. Drug, 600 mg, was put in a flat-bottom glass ampul, 14 mm i.d., and then 0.5 ml of the copolymers–glass-forming monomer mixture was added. Powdered copolymers, such as anion- and cation-type copolymers, completely dissolved at 30–80° in glass-forming monomers such as 2-hydroxyethyl methacrylate, hydroxyethyl acrylate, and glycidyl methacrylate. The ampul was sealed under a vacuum of 10^{-3} mm Hg at −196° (liquid nitrogen) and was irradiated for 2 hr at 5 × 10^5 rads/hr at −78° with γ-rays from a ^{60}Co source. After irradiation, the polymer–drug matrix was obtained as a homogeneous tablet, 14 mm in diameter and 4 mm thick.

Drug Dissolution from Tablets—The dissolution test was made with the dissolution apparatus[7] at 37° at a rate of 100 rpm according to USP XIX. The basket containing the tablet was immersed in 1000 ml of dissolution medium at various pH values. At time intervals over 480 min, 5 ml of the dissolution medium was sampled. The dissolved drug was

[1] Tokyo Kasei Kogyo Co., Ltd. Monomers were purified by distillation according to conventional methods.
[2] Nipponkayaku Co.
[3] Kanto Chemical Co.
[4] Otsuka Pharmaceuticals Co. (~48-mesh powder).
[5] Eudragit E, Röhm Pharma GMBH.
[6] Eudragit L, Röhm Pharma GMBH.
[7] Model TR-5S, Toyama Sangyo.

0022-3549/79/0700-0860$01.00/0

Table I—Parameters for Drug Dissolution from Polymer Tablets, 14 mm in Diameter and 4 mm Thick, in the Presence of Anion-Type Copolymer

Sample	Composition, wt. % Anion-Type Copolymer	Monomer	Drug (mol. wt.)	W, %	k, $\times 10^{-3}$ min^{-1}
1	—	100% Hydroxyethyl methacrylate	Aspirin (180.16)	31.2	0.89
2	5	95% Hydroxyethyl methacrylate	Aspirin (180.16)	34.9	1.24
3	10	90% Hydroxyethyl methacrylate	Aspirin (180.16)	39.3	1.99
4	20	80% Hydroxyethyl methacrylate	Aspirin (180.16)	47.4	3.41
5	10	90% Hydroxyethyl acrylate	Aspirin (180.16)	57.9	7.26
6	10	90% Glycidyl methacrylate	Aspirin (180.16)	7.2	0.50
7	10	90% Hydroxyethyl methacrylate	Potassium chloride (74.55)	37.6	4.31
8	10	90% Hydroxyethyl methacrylate	Salicylic acid (138.12)	40.1	2.88
9	10	90% Hydroxyethyl methacrylate	Sulfanilamide (172.21)	37.2	2.36
10	10	90% Hydroxyethyl methacrylate	Colchicine (399.45)	38.6	1.00

assayed spectrophotometrically[8] at 460 nm by a mercury thiocyanate method for potassium chloride (11), at 258 nm for sulfanilamide, at 296 nm for salicylic acid, at 273 nm for aspirin, and at 353 nm for colchicine.

Measurement of Tablet Porosity—Polymer–drug matrix porosity was observed by scanning electron microscopy[9].

The polymer–drug matrix water content (W) was defined as:

$$W\ (\%) = \frac{W_w}{W_p + W_w} \times 100 \qquad \text{(Eq. 1)}$$

where W_w and W_p are the weights of water absorbed in the polymer and of dried polymer, respectively.

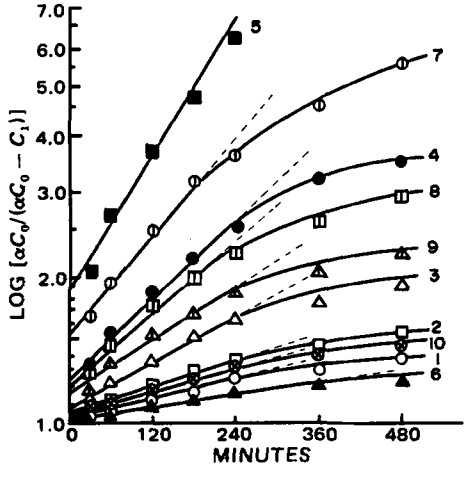

Figure 2—*Semilogarithmic relationship between $\alpha C_0/(\alpha C_0 - C_1)$ and dissolution time for polymer tablets in the presence of an anion-type copolymer. Sample number refers to compositions in Table I. The dissolution medium was at pH 8.0. Key (tablet system and drug): ○, 100% hydroxyethyl methacrylate (aspirin); □, 95% hydroxyethyl methacrylate–5% anion-type copolymer (aspirin); △, 90% hydroxyethyl methacrylate–10% anion-type copolymer (aspirin); ●, 80% hydroxyethyl methacrylate–20% anion-type copolymer (aspirin); ■, 90% hydroxyethyl acrylate–10% anion-type copolymer (aspirin); ▲, 90% glycidyl methacrylate–10% anion-type copolymer (aspirin); ⊙, 90% hydroxyethyl methacrylate–10% anion-type copolymer (potassium chloride); ⊡, 90% hydroxyethyl methacrylate–10% anion-type copolymer (salicylic acid); ◭, 90% hydroxyethyl methacrylate–10% anion-type copolymer (sulfanilamide); and ⊗, 90% hydroxyethyl methacrylate–10% anion-type copolymer (colchicine).*

[8] Shimazu double-beam spectrophotometer, model UV-200.

[9] Model JSM-03, Japan Electron Optics Laboratory Co.

RESULTS AND DISCUSSION

Effect of Irradiation on Drugs—It was necessary to know the irradiation effect on drug activity before polymer tablet preparation. The relation between native drug relative activity and the irradiation conditions used in experimental tablet preparation is shown in Fig. 1. Under the present experimental temperature, energy, and irradiation duration, there was no detectable drug decomposition. Since drug radiation damage is enhanced in the presence of oxygen, the irradiation in a vacuum is desirable.

Drug Dissolution–Time Curves of Tablets in Presence of Anion-Type Copolymer—Potassium chloride, salicylic acid, sulfanilamide, aspirin, or colchicine was entrapped in the polymer matrix by radiation-induced polymerization of a glass-forming monomer at low temperature in the presence of an anion-type copolymer. The dissolved drug in the dissolution medium at pH 8.0 was measured at certain time intervals.

First-order drug dissolution kinetics were investigated using the Noyes–Whitney equation (12, 13). The rate constant for dissolution (k) and the drug concentration at time t were expressed as:

$$kt = \ln \frac{\alpha C_0}{(\alpha C_0 - C_1)} \qquad \text{(Eq. 2)}$$

where α represents V/V_0, V and V_0 are the volumes of tablet per unit weight and medium used for dissolution, C_1 is the drug concentration in the dissolution medium, C_0 is the initial drug concentration in the tablet, and k is the dissolution rate constant.

The relation between t and $\alpha C_0/(\alpha C_0 - C_1)$ in tablets of various anion-type copolymer concentrations and various polymer matrixes and drug components is shown in Fig. 2. The dissolution rate constant (k) was calculated from the initial slope of linear graphs (Table I).

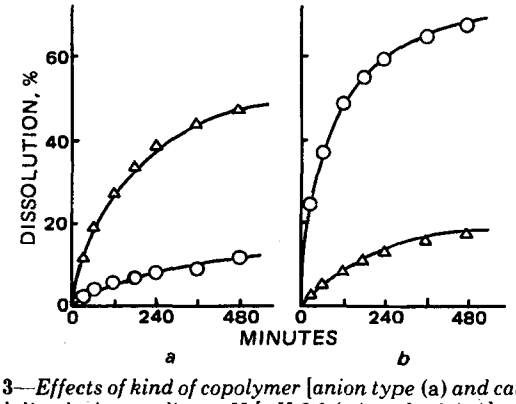

Figure 3—*Effects of kind of copolymer [anion type (a) and cation type (b)] and dissolution medium pH [pH 3.0 (○) and 8.0 (△)] on aspirin dissolution from polyhydroxyethyl methacrylate tablet. Tablet composition was 90% hydroxyethyl methacrylate–10% copolymer.*

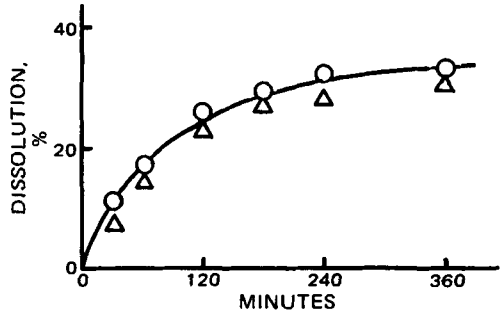

Figure 4—*Effect of dissolution medium pH [pH 3.0 (○) and 8.0 (△)] on aspirin dissolution from polyhydroxyethyl methacrylate tablet in the presence of polyethylene glycol 600.*

For Samples 1–4 (Fig. 2), aspirin dissolution from the tablet increased with anion-type copolymer concentration. This increase was attributed to anion-type copolymer dissolution in the tablet at pH 8.0, although the copolymer barely dissolved in 2-hydroxyethyl methacrylate monomer at concentrations above 30%. The results for Samples 3, 5, and 6 in Fig. 2, showing aspirin dissolution from various polymer tablets, depended on the kind of glass-forming monomer or matrix. This dissolution was related to the hydrophilic property of the matrix, which is indicated in Table I in relation to the polymer matrix water content (W).

Drug dissolution from tablets in the presence of a 10% anion-type copolymer is shown for Samples 3 and 7–10 in Fig. 2. Dissolution decreased in the order potassium chloride, salicylic acid, sulfanilamide, aspirin, and colchicine, perhaps due to differences in drug molecular weights (Table I). The larger the molecular weight of the trapped substances, the smaller was the dissolution rate from the matrix.

The intersections of the straight lines and the axis of the ordinates show values higher than unity (Fig. 2). This deviation was probably due to the rapid dissolution of drugs and anion- or cation-type copolymers trapped on the matrix surface by polymer swelling.

Effect of Medium pH on Aspirin Dissolution from Polyhydroxyethyl Methacrylate Tablet—The anion-type copolymer dissolved in the medium only at pH >6.0, while the cation-type copolymer dissolved only at pH <5.0. Aspirin dissolution from tablets containing various copolymers was investigated for dissolution media at various pH values (14, 15) (Fig. 3). The dissolution rate at pH 8.0 was larger than that at pH 3.0 for anion-type copolymer tablets, while the pH dependency of dissolution in the presence of the cation-type copolymer was the opposite to that in the presence of the anion-type copolymer. Therefore, dissolution of the formulation was markedly influenced by pH in the presence of a copolymer.

Aspirin dissolution from a porous polyhydroxyethyl methacrylate tablet prepared with polyethylene glycol 600 instead of with a copolymer also was investigated. Dissolution of the formulation was hardly influenced by dissolution medium pH (Fig. 4).

Porous Structure—Polymer tablet structure was observed by scanning electron microscopy after complete removal of additives such as aspirin, polyethylene glycol 600, and copolymers (Fig. 5). Since the porous structure is hardly observable in Fig. 5*a*, it must have been a consequence of the dissolution of copolymers or polyethylene glycol 600. The porous polymer matrix obtained in the presence of a copolymer is shown in Figs. 5*b* and 5*c*, and the porous polymer matrix obtained in the presence of polyethylene glycol 600 is shown in Fig. 5*d*. The porous structures in Figs. 5*b* and 5*c* are quite similar but are different from the structure in Fig. 5*d*. The reason may be the difference in dispersion form of those additives (copolymer and polyethylene glycol 600) in hydroxyethyl methacrylate monomer before polymerization. That is, the anion- or cation-type copolymer may be dispersed in the monomer in the fibrous molecular form, and the pore structure forms in the polymer after polymerization as shown in Figs. 5*b* and 5*c*. On the other hand, polyethylene glycol 600 may be dispersed in the monomer in the spherical form owing to its crystallization at low temperatures, and then the pore structure in Fig. 5*d* forms. Consequently, porous structure in the tablets can be controlled by varying the kinds of additives and their concentrations.

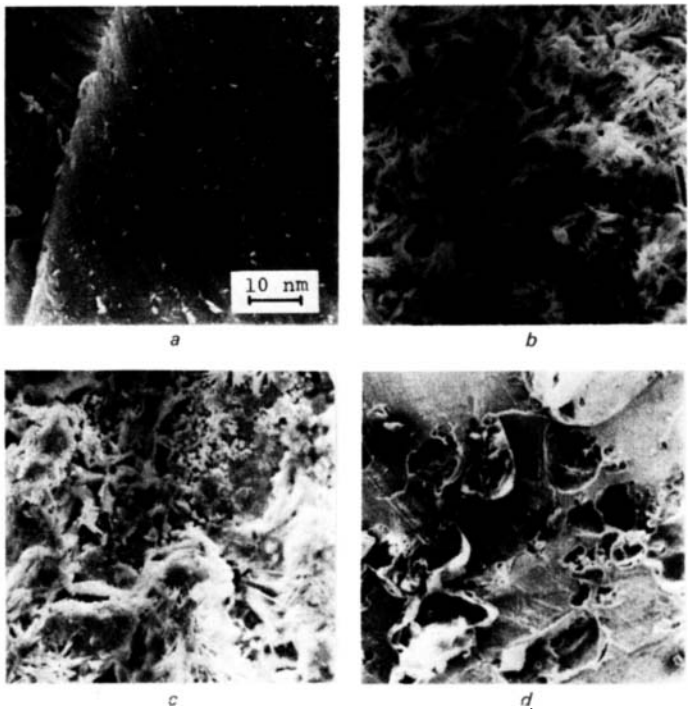

Figure 5—*Scanning electron microphotographs of porous structure of polyhydroxyethyl methacrylate tablets containing aspirin in the presence of various additives. The specimens were dried for 4 days at room temperature* in vacuo *(10^{-4} mm Hg) and then fractured at room temperature. The fractured surface was coated by gold in a vacuum evaporator. Key:* a, *tablet in the presence of 10% anion-type copolymer before treatment with dissolution medium;* b, *tablet in the presence of 10% anion-type copolymer after treatment with dissolution medium at pH 8.0;* c, *tablet in the presence of 10% cation-type copolymer after treatment with dissolution medium at pH 3.0; and* d, *tablet in the presence of 10% polyethylene glycol 600 after treatment with dissolution medium at pH 3.0.*

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ACKNOWLEDGMENTS

The authors thank Dr. T. Seguchi for help with electron microscopy.