Table II—Pharmacokinetic Parameters for the Disappearance of Dog Plasma Pentazocine following an Intravenous Dose of 0.3 mg/kg

Animal Weight, kg, and Sex	Rate Constants, hr^{-1}			Plasma Clearance Rate, liters/hr	Apparent Distribution, Volume, Steady State, liters	$t_{1/2}^{a}$, min	Area under the Curve, ng hr/ml
	K_{12}	K_{21}	K_{10}				
17.2 F	2.27	1.89	1.05	2.88	6.04	100.2	99.6
9.6 F	2.02	3.41	0.65	3.99	9.80	106.8	80.7
12.6 M	14.6	5.26	1.67	2.68	6.07	99.6	107
Mean	6.29	3.52	1.12	3.18	7.30	102.2	95.9
±*SEM*	±4.15	±0.97	±0.29	±0.41	±1.25	±2.3	±7.95

[a] Calculated from $\frac{0.693}{1/2[(K_{12}+K_{21}+K_{10})-\{(K_{12}+K_{21}+K_{10})^2-4K_{12}K_{21}\}^{1/2}]}$.

ported pentazocine terminal elimination half-life of 150 min in dogs is in good agreement with the present estimate (102 min, Table II). The two-compartment model was used recently to describe pentazocine pharmacokinetics in healthy humans (18) where the average terminal disposition half-life was 203 min.

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Drug Entrapment for Controlled Release in Radiation-Polymerized Beads

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Received June 20, 1978, from the *Takasaki Radiation Chemistry Research Establishment, Japan Atomic Energy Research Institute, Takasaki, Gunma, Japan.* Accepted for publication October 31, 1978.

Abstract □ The preparation of beads including polymer, vinyl monomer, and drug was carried out by low temperature, radiation-induced polymerization. Complete spherical particles were obtained when ethanol was the precipitation medium. Polymers such as polymethyl methacrylate and polystyrene were dissolved in various glass-forming monomers, and the drug was dispersed in the mixture. The mixture was dropped into cold precipitation media. The formed monomeric particle was irradiated at low temperatures to produce polymerization. The drug release profiles from polymerized particles were changed by varying the glass-forming monomer and the precipitation medium.

Keyphrases □ Dosage forms—controlled-release delivery devices, radiation-polymerized beads, potassium chloride □ Potassium chloride—controlled-release delivery devices, radiation-polymerized beads □ Polymers—controlled-release delivery devices, beads, potassium chloride

Controlled drug release may improve effectiveness and safety in drug use (1–3). Drug entrapment in polymerized matrixes may be an effective way to control release. Various bioactive materials, such as enzymes or microbial cells, could first be attached effectively to a carrier surface and then incorporated into a polymer by means of radiation-induced polymerization at low temperatures (4, 5). This method can be performed using monomers that form stable glass-like states when supercooled and that can be readily polymerized at low temperatures (6).

This method can be applied to entrapping low molecular weight drugs for controlled release as well as high molecular weight bioactive substances. Entrapping drugs in fine polymer particles, such as microspheres, could have practical advantages. Trapping enzymes or microbial cells on a carrier surface is desirable for the contact with the substrate (7). Immobilized enzyme or microbial cell microspheres were obtained by suspension polymerization of a hydrophobic glass-forming monomer and a buffered enzyme solution at low temperatures or by polymerization

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Table I—Properties and Preparation of Polymer, Glass-Forming Monomer, and Potassium Chloride Beads in Low Temperature Polymerization

Sample	Polymer-Monomer Composition, wt. %	Precipitation Condition			Property of Beads		
		Medium	Temperature	W, %	Shape	D_{av}, mm	C_{KCl}, mg/particle
1	100% Diethylene glycol dimethacrylate	Methanol	−78°	3.8	Nonparticle (block composite)	—	—
2	5% Polymethyl methacrylate–95% diethylene glycol dimethacrylate	Methanol	−78°	3.3	Ellipsoid	—	19
3	10% Polymethyl methacrylate–90% diethylene glycol dimethacrylate	Methanol	−78°	3.6	Ellipsoid	—	21
4	20% Polymethyl methacrylate–80% diethylene glycol dimethacrylate	Methanol	−78°	3.1	Ellipsoid	—	23
5	10% Polymethyl methacrylate–90% diethylene glycol dimethacrylate	Ethanol	−78°	2.7	Sphere	2.2 ± 0.1	18
6	10% Polymethyl methacrylate–90% diethylene glycol dimethacrylate	n-Butanol	−78°	3.6	Ellipsoid	—	20
7	10% Polymethyl methacrylate–90% diethylene glycol dimethacrylate	n-Hexane	−78°	3.4	Ellipsoid	—	19
8	10% Polymethyl methacrylate–90% diethylene glycol dimethacrylate	Ethanol	−24°	—	Nonparticle (block composite)	—	—
9	10% Polymethyl methacrylate–90% hydroxyethyl acrylate	Ethanol	−78°	64.5	Sphere	2.1 ± 0.1	16
10	10% Polymethyl methacrylate–90% glycidyl methacrylate	Ethanol	−78°	4.2	Sphere	1.9 ± 0.1	17
11	10% Polymethyl methacrylate–90% hydroxyethyl methacrylate	Ethanol	−78°	32.0	Sphere	2.0 ± 0.1	17
12	10% Polymethyl methacrylate–90% trimethylolpropane trimethacrylate	Ethanol	−78°	2.6	Sphere	2.1 ± 0.1	20
13	100% Glycidyl methacrylate	Ethanol	−78°	4.0	Nonparticle (block composite)	—	—
14	10% Polystyrene–90% glycidyl methacrylate	Ethanol	−78°	3.8	Sphere	2.0 ± 0.1	23
15	20% Polystyrene–80% glycidyl methacrylate	Ethanol	−78°	3.5	Sphere	2.2 ± 0.1	21

of the salted-out hydrophilic glass-forming monomer and a buffered enzyme solution.

Drugs also can be entrapped inside the microsphere polymer matrix, because low molecular weight substances leach too rapidly from the surface-sorbed state. In this report, a new method for small solid particle preparation incorporating drugs inside the matrix by means of radiation-induced polymerization at low temperatures was investigated.

EXPERIMENTAL

Materials—Potassium chloride[1] was the drug used.

2-Hydroxyethyl methacrylate[2], diethylene glycol dimethacrylate[3], trimethylolpropane trimethacrylate[3], glycidyl methacrylate[2], and hydroxyethyl acrylate[2] were the glass-forming monomers. Methyl methacrylate[2] was the nonglass-forming monomer.

Reagent grade methanol[2], ethanol[2], n-buthanol[2], n-hexane[2], and 1,4-butanediol[2] were the precipitation media. Polymethyl methacrylate[4], polyethylene glycol 600[2], and polystyrene[5] were the polymers used.

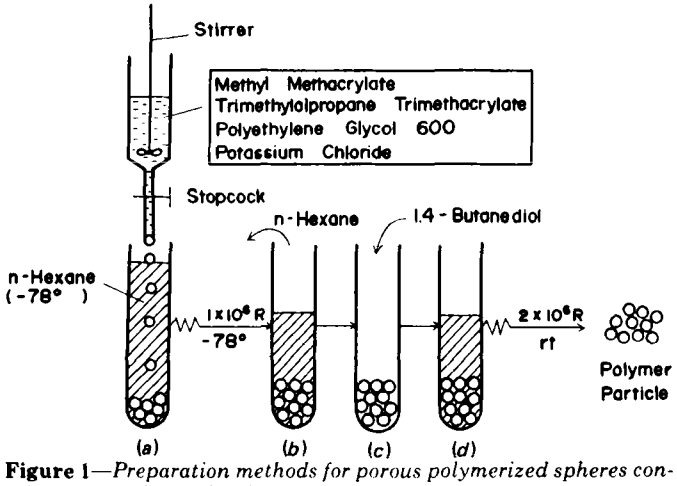

Figure 1—*Preparation methods for porous polymerized spheres containing potassium chloride.*

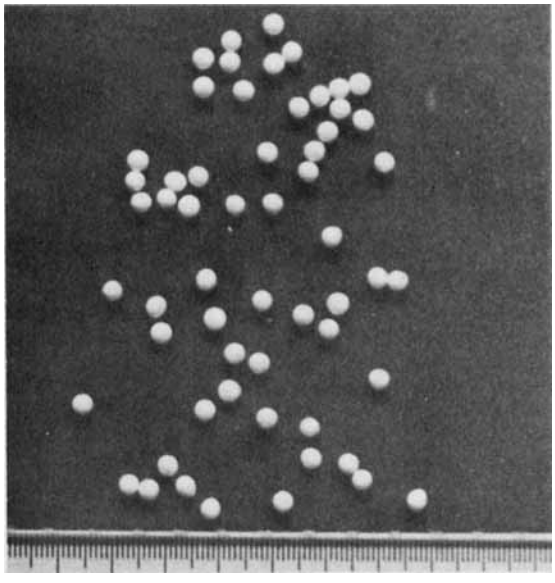

Figure 2—*Photograph of spherical particles.*

Preparation of Radiation-Polymerized Beads—Drops of polymer, monomer, and drug (potassium chloride) mixtures were allowed to fall into a cold (−78°) precipitation medium with the equipment shown in Fig. 1*a*. The solid globules were irradiated at −78° (dry ice–methanol) or −24° for 2 hr at 1×10^6 rads/hr with ^{60}Co γ-rays. After irradiation, the polymerized spheres were removed and dried. When polyethylene glycol 600 replaced the polymers polymethyl methacrylate or polystyrene, the solidified globules were irradiated for 1 hr at 1×10^6 rads/hr. Then the original n-hexane precipitation medium was replaced by cooled 1,4-butanediol, and polymerization was continued for 2 hr at room temperature at the same rate.

Properties of Spheres—The mean particle diameter, D_{av}, was measured by optical microscopic observation[6], and the mean potassium chloride amount, C_{KCl}, was estimated from the potassium chloride released from the beads. To estimate the polymer hydrophilicity, water content, W, was determined according to:

[1] About 48-mesh powder, Otsuka Pharmaceuticals Co.

[2] Tokyo Kasei Kogyo Co. Monomers were purified by distillation according to conventional methods.

[3] Shin-Nakamura Chemical Co. Monomers were purified by washing with 1% NaOH, passing over Amberlite A-27 (Rohm & Haas), and drying over molecular sieves 4A.

[4] Mitsubishi Rayon Co.

[5] Denki Kagaku Co.

[6] Model SMZ-6, Nippon Kogaku Co.

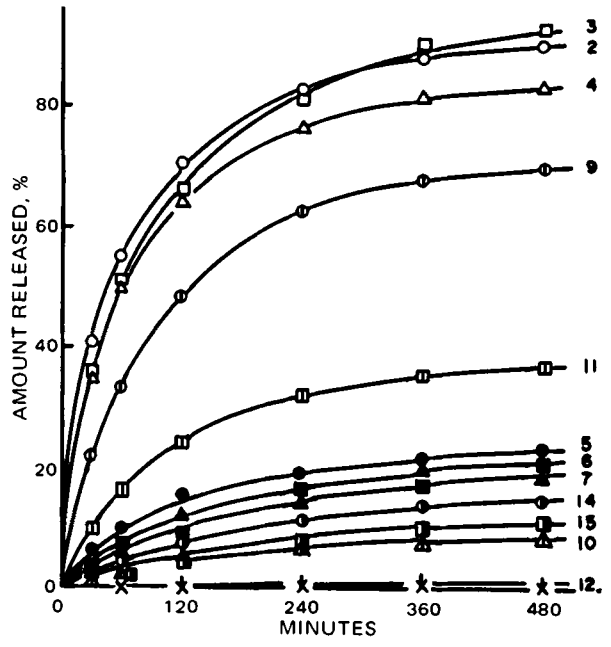

Figure 3—*Potassium chloride release profile from polymerized particles. Numbers refer to compositions (Table I).*

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

where W_w and W_p are the weights of the water required to saturate the polymer and of the dried polymer, respectively.

Dissolution of Potassium Chloride from Polymerized Spheres—The dissolution test was carried out at 37°, 100 rpm, with the dissolution apparatus[7] based on USP XIX. The basket was immersed in the vessel containing 1000 ml of dissolution medium, usually water at pH 6.0. At selected intervals over 480 min, 5 ml of the dissolution medium was sampled and the released potassium chloride was assayed spectrophotometrically[8] (8).

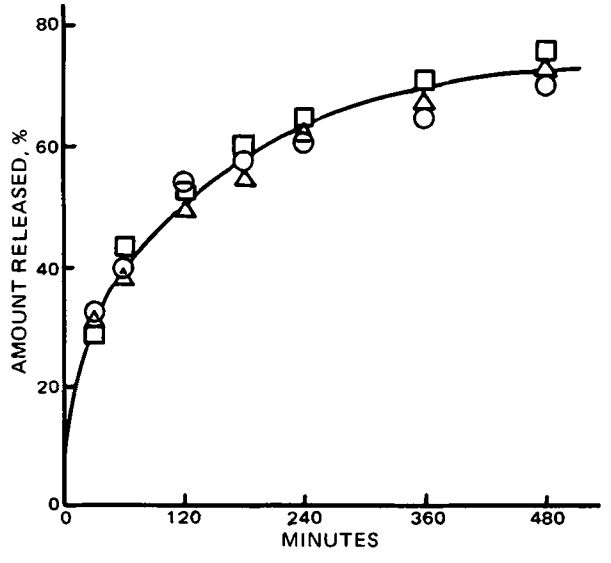

Figure 4—*Potassium chloride release from spheres as a binary monomer composition function in 30% monomers–70% polyethylene glycol 600. Key (monomer composition): ○, 70% methyl methacrylate–30% trimethylolpropane trimethacrylate; □, 50% methyl methacrylate–50% trimethylolpropane trimethacrylate; and △, 30% methyl methacrylate–70% trimethylolpropane trimethacrylate.*

[7] Model TR-5S, Toyama Sangyo Co.
[8] Model UV-200 Shimazu double-beam spectrophotometer.

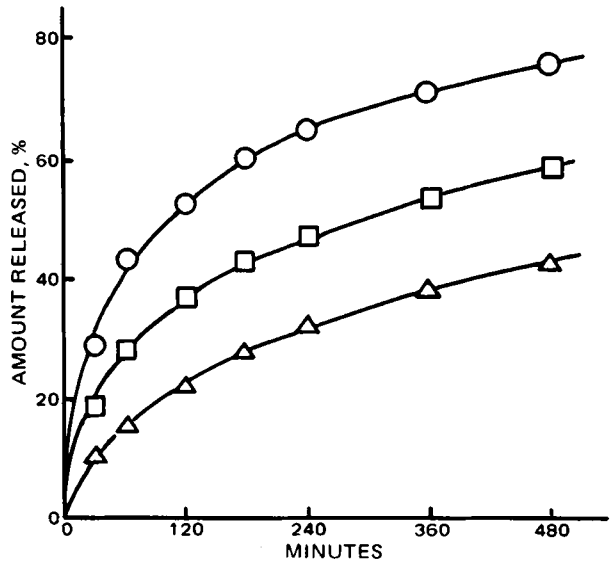

Figure 5—*Potassium chloride release from spheres as a function of polyethylene glycol 600 concentration in 50% methyl methacrylate–50% trimethylolpropane trimethacrylate monomer system. Key (polyethylene glycol 600 concentration): ○, 70%; □, 50%; and △, 30%.*

RESULTS AND DISCUSSION

Nonglass-Forming Monomers—Methyl methacrylate required at least 6% polymethyl methacrylate to form stabilized globules when dropped into cold methanol. Otherwise, the monomer-polymer-drug mixture formed threads or simply coalesced into an immiscible layer. Other precipitation media produced similar results. Methyl methacrylate polymerization did not yield solid spheres at cold temperatures and merely coalesced above 0°.

Glass-Forming Monomers—These monomers gave well-formed solid globules when mixed with polymer and potassium chloride and supercooled. They were easily polymerized by irradiation at the low temperatures used.

Globule Formation—Ethanol as the supercooled precipitation me-

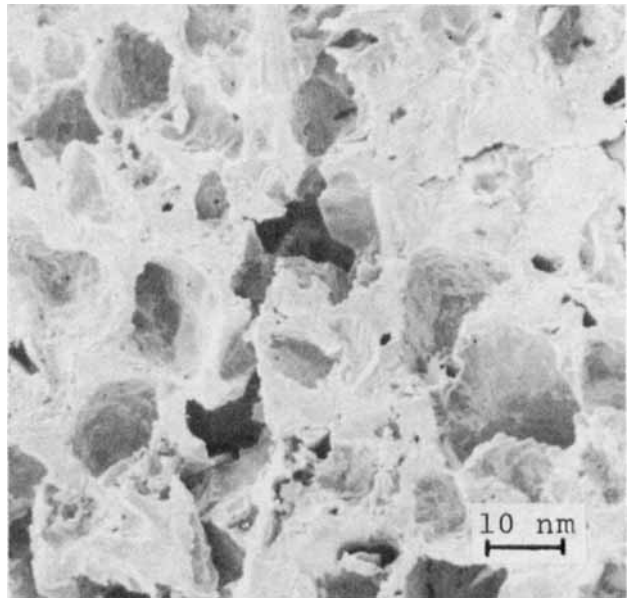

Figure 6—*Scanning electron micrograph of sphere structure. The spheres (2.4 ± 0.2 mm in diameter) were prepared with 30% (methyl methacrylate–trimethylolpropane trimethacrylate)–70% polyethylene glycol 600, a monomer composition of 50% methyl methacrylate–50% trimethylolpropane trimethacrylate, ethanol as the precipitation medium, and a precipitation temperature of −78°. Irradiation was carried out under the conditions shown in Fig. 1.*

dium yielded spherical globules (Fig. 2[9]). Methanol, *n*-butanol, and *n*-hexane formed ellipsoidal globules. Globule formation seemed dependent on the polymer present in the mixture and on a precipitation medium temperature not above −24°. When these conditions were not met, coalescence but not stabilization occurred.

Release of Potassium Chloride—In the spheres containing polymethyl methacrylate as the polymer and diethylene glycol dimethacrylate as the monomer (Samples 2–7), the methanol precipitation medium increased potassium chloride release (Fig. 3). In nonmethanol precipitation media, release from relatively strongly hydrophilic beads (Samples 9 and 11) was faster than that from less hydrophilic matrixes.

The binary monomer spheres containing polyethylene glycol 600 in place of polymer showed a release rate independent of the methyl methacrylate–trimethylolpropane trimethacrylate proportions (Fig. 4). The polyethylene glycol 600 concentration strongly affected potassium chloride release (Fig. 5). Larger polyethylene glycol 600 proportions together with 1,4-butanediol in the final polymerization step yielded spheres with a markedly porous internal structure (Fig. 6[10]).

[9] Nikon F, Nippon Kogaku Co.
[10] Model JSM-U3, Japan Electron Optics Laboratory Co.

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UV Studies of Nucleic Acid Base Complexation with Isoproterenol in Different Solvents

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Abstract □ Charge transfer complex formation between nucleic acid bases and isoproterenol was demonstrated from UV absorption measurements. The solvent polarity effects on equilibrium constants were investigated. The solvent systems containing 0.1 *N* HCl were 20% aqueous ethanol, water, and water containing sodium chloride. The equilibrium constants, calculated from UV absorption data by the application of the Benesi–Hildebrand equation, were small and increased with increasing ionic strength. Equilibrium constant wavelength dependence was demonstrated in some cases.

Keyphrases □ Complexes, charge transfer—nucleic acid bases with isoproterenol, various solvents, UV absorption study □ Nucleic acid bases—charge transfer complex formation with isoproterenol, various solvents, UV absorption study □ Solvents, various—charge transfer complex formation, nucleic acid bases with isoproterenol, UV absorption study

Catechol forms the catecholamine aromatic nucleus and anchors these molecules to their receptors (1). The adrenergic sites and the biogenic amine storage granules are known to contain adenosine triphosphate, phosphate, and magnesium ions (2, 3). Complex formation between these ions and catecholamines has been demonstrated (4, 5). Evidence for charge transfer complex formation between catechol, epinephrine, and nucleic acid bases has been presented (6–8).

The present study was undertaken to trace the catecholamine action mechanism, to obtain more information about adrenergic receptors, and to investigate adenosine triphosphate-like action of some other storage granule nucleoside triphosphates. UV absorption was used to study the interactions between the nucleic acid bases and isoproterenol in the following solvents containing 0.1 *N* HCl: 20% aqueous ethanol, water, and water containing sodium chloride.

EXPERIMENTAL

Isoproterenol sulfate dihydrate[1], thymine[2], cytosine[2], standard hydrochloric acid solution[2], adenine[3], uracil[3], and sodium chloride[4] (BP) were the highest commercially available purity (>99%) and were used without further purification.

Solutions containing a fixed nucleic acid base concentration (0.02 *M*, except cytosine-containing solutions in 20% alcohol, fixed at 0.01 *M*) and different isoproterenol sulfate concentrations (0.3–0.8 *M*) were prepared by dilution from concentrated standard solutions.

The solvents used were 20% aqueous ethanol containing 0.1 *N* HCl, 0.1 *N* aqueous HCl, and water solutions containing 0.1 *N* HCl and different amounts of sodium chloride.

All solutions were freshly prepared, and their spectra were recorded within 6 hr in 1-cm path length rectangular cells with stoppers. Most experimental work was carried out in subdued light to avoid isoproterenol light oxidation and at room temperature (20–25°).

The spectrophotometers[5] were checked and calibrated with an oxide film[6]. Cell holders were thermostated to maintain the temperature at 25°. The baseline was recorded before the experiments with the same solvent in the reference and in the sample compartments.

[1] Aldrich Chemical Co., Milwaukee, Wis.
[2] BDH Chemical Co., Poole, England.
[3] Hopkin and Williams Chemical Co., Chadwell Heath, Essex, England.
[4] Evans Medical Ltd., Liverpool, England.
[5] Perkin-Elmer model 402 and Pye Unicam model SP 800 UV-visible.
[6] Holmium.

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