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Research Article

Porous Biodegradable Microspheres for Controlled Drug Delivery. I. Assessment of Processing Conditions and Solvent Removal Techniques

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Microspheres containing methylene blue and prednisolone acetate were prepared by one of three methods: freeze-drying, evaporation, and solvent-extraction-precipitation. An extremely porous structure was obtained by the freeze-dry and solvent-extraction-precipitation procedures. The specific surface area of 6.33-μm particles was 20.6 m^2/g, or 35 times that of a particle devoid of pores, and the void space was 59–61%. The sphericity, size, and yields of the microspheres were influenced by the preparation procedure, surfactant type and concentration, temperature of the continuous phase, polymer concentration in the dispersed phase, and ratio of marker to polymer. The most suitable processing conditions were a polymer concentration of 5–10%, a marker loading of 10%, 0.1% sorbitan sesquioleate as the surfactant, and temperature adjustment of the continuous phase from 15 to 50°C following the addition of the dispersed phase. Complete release of the highly water soluble methylene blue occurred within 72 hr, while the less soluble prednisolone acetate released much more slowly, i.e., 90% after 7 days. The microspheres remained relatively intact during the *in vitro* release of methylene blue, confirming that the incorporated agent was confined to the walls of the porous network. Collapse of the polymer structure was evident after 7 days. The release therefore was believed to be governed principally by the solubility of the drug and the porosity of the matrix.

KEY WORDS: drug delivery system; controlled drug delivery; poly(glycolic) acid; biodegradable microspheres; porous microspheres.

INTRODUCTION

While drug release from polymer systems has been limited mostly to oral, topical, or implantable systems, liposomes and albumin spheres have been used as drug delivery systems and their organ deposition has been studied following intravenous administration in animal models (1–5). Both the liposome and the albumin spheres are swellable type systems in which drugs are most commonly encapsulated. Although these systems have attracted considerable attention, they present control and stability problems. As an example, liposomes, unless the lipid bilayers are specifically stabilized, have a very short shelf life and the drug content is not uniform. This limits their use as a drug delivery system (6).

Recently, synthetic biodegradable polymers have been studied for various applications including controlled-release systems of drugs and agents. Sanders *et al.* (7) prepared poly(*d,l*-lactide/glycolide) microspheres containing a luteinizing hormone-releasing hormone analogue by a microencapsulation technique. In this technique the polymer precipitated around the drug during solvent removal. Benita *et al.* (8), Wakiyama *et al.* (9), and Beck *et al.* (10) prepared polylactide microspheres by emulsifying a drug/polymer/solvent mixture in an aqueous phase and then removing the solvent by evaporation.

The current methods of preparing microspheres, including those of Fong (11) and Morishita *et al.* (12), generally encapsulate the agents in a relatively nonporous matrix, thereby requiring erosion of the matrix and diffusion through the polymer or across a membrane for release of the incorporated agent. The purpose of this investigation was to search for a method which would produce a highly porous matrix so that erosion kinetics would not be a factor in the release and to determine the most suitable processing parameters for preparing small microspheres in suitable yields. To this end, three recovery techniques were evaluated: evaporation, freeze-drying, and solvent-extraction-precipitation.

Poly(glycolic acid) (PGA) was selected as the matrix material because it has received attention as a drug carrier. Additionally, it is nontoxic, non-tissue reactive, and bioerodible and has found particular application in surgical sutures. The degradation products are mainly carbon dioxide and water excreted via the kidney (13,14). Meth-

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ylene blue and prednisolone acetate were selected as model agents for incorporation because they represent highly and lowly soluble compounds and release could be followed easily by spectrophotometry.

MATERIALS AND METHODS

Materials

All materials were obtained commercially: poly(glycolic acid) (PGA) (American Cyanimid Co.) as compressed pellets, methylene blue (American Cyanimid Co.), hexafluoroacetone sesquihydrate (HFA) (Polysciences, Inc.), carbon tetrachloride (Fisher Scientific Co.), 1,4-dioxane (Fisher Scientific Co.), acetone (MCB Manufacturing Chemists, Inc.), sorbitan sesquioleate (SO-15) (Nikko Chemicals Co.), polyoxyethylene sorbitan (TWEEN, HLB 2) (Atlas Chemical Industries, Inc.), and prednisolone acetate (DM Pharmaceutical Company). The reagents are all analytical grade and were used without further purification.

Preparation of Microspheres

Using the procedure illustrated in Fig. 1, the various factors which influence microsphere properties were evaluated. Initially, principal attention was given to assessing the yield, shape, and size. Two surface active agents (SAA), SO-15 and TWEEN, were assessed over a concentration range of 0.1–1.0% (w/w) in the continuous-phase solvent, carbon tetrachloride (CCl_4). The temperature of the continuous phase during the addition of the dispersed phase was studied at 15, 22, and 50°C and by adjusting from 15 to 50°C. The PGA concentration in the dispersed phase solvent, HFA, was studied at 1.7, 2.5, 5, and 10% (w/w). The loading of marker in the PGA was studied at levels of from 4 to 50%, i.e., 1:25 to 1:1 loading ratios.

The PGA and methylene blue or prednisolone acetate were dissolved separately in HFA and combined to give the desired ratio of marker to polymer. The resulting solution was warmed to 37°C and dispersed into the continuous phase, CCl_4, containing SAA, in a double-jacketed glass vessel. Temperature control was effected during the dispersion process by means of a water bath and circulator. Agitation of the continuous phase was effected by either a vibromixer (Type E1, Chemap AG) or a dispersator (Premier Mill Corp), and it was found that the latter gave a smaller and narrower size distribution of microspheres. The emulsified droplets of the dispersed phase were formed in the continuous phase and the solvent was removed from the dispersed droplets by one of three methods.

1. Freeze-Dry Method. The temperature was cooled to −20°C while agitating to effect solidification of the dispersed-phase droplets, then the mixture was rapidly cooled to −40°C in dry ice and acetone to freeze the continuous phase, CCl_4. The frozen continuous phase and the solvent of the dispersed phase were removed by freeze-drying in two steps in a Pilot Freeze Dryer (Model X8F12, Hull Corp). First, the continuous phase, CCl_4 (m.p., −23°C) was removed at a drying temperature sufficiently low to maintain the product below −25°C and then the drying temperature was increased to 15–20°C to remove the HFA. The resulting microspheres were washed with acetone twice followed by filtration and air-dried.

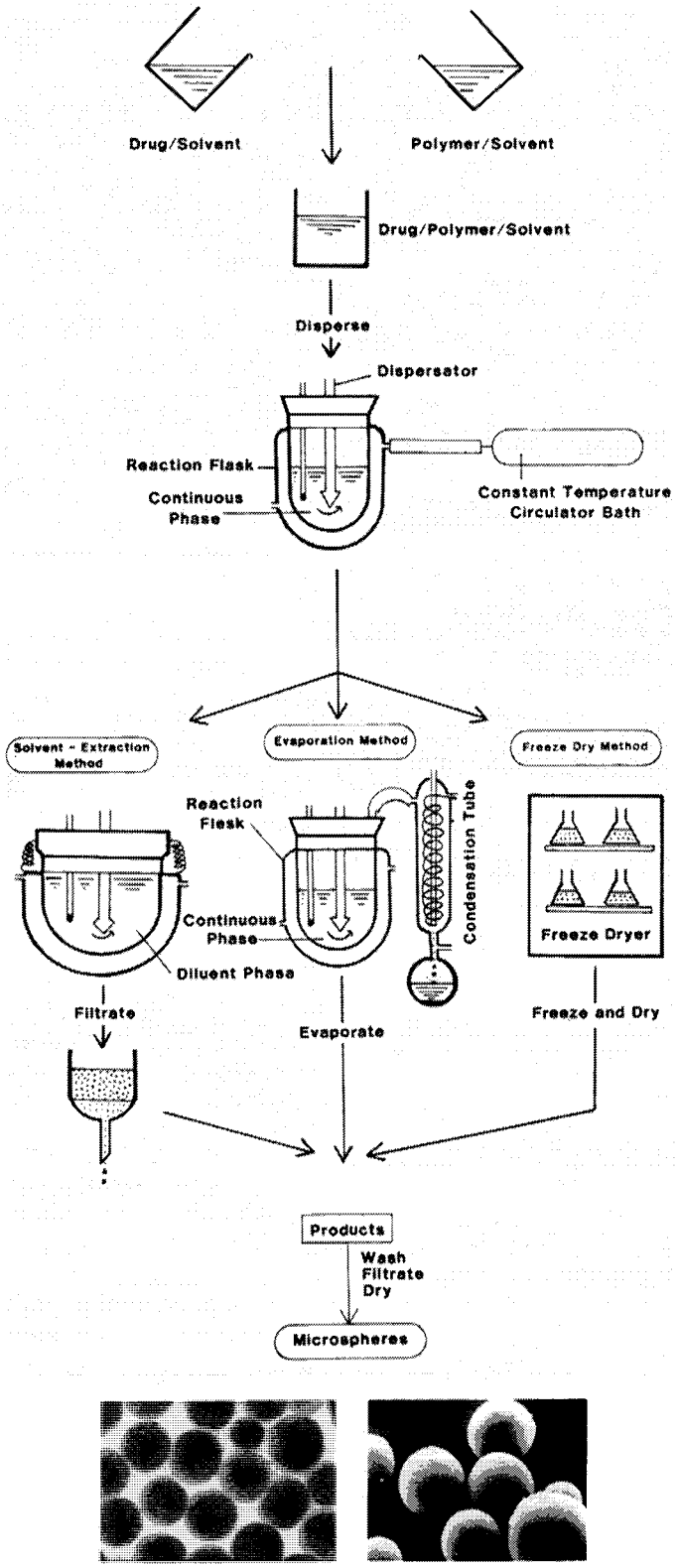

Fig. 1. Schematic diagram for microsphere preparation by three methods of solvent removal.

2. Evaporation Method. The emulsion was stirred continuously in a water bath at 40–60°C to allow the simulta-

neous evaporation of the solvents of dispersed and continuous phases. The resulting spheres were washed and recovered as in the freeze-dry method.

3. Solvent-Extraction-Precipitation Method. The mixture was rapidly added to a miscible nonsolvent (1,4-dioxane) and stirred by a vibro-mixer for about 30 min to extract HFA from the dispersed phase and cause precipitation of the spheres. The spheres were washed and recovered as before.

Characterization of Microspheres

Shape and Size. The shape of the spheres was observed by optical microscopy (Zetapan Research Microscope, C. Reichert AG) and by scanning electron microscopy (SEM) (StereoScan Mark IIA, Cambridge). The size, size distribution, and area were determined using a πMC Particle Measurement Computer System (Millipore, Inc.).

Zeta Potential Measurement. Zeta potential of microspheres was measured in distilled water using a Zeta Meter (Zeta-Meter, Inc.) equipped with a Nikon SMZ-2 stereoscopic microscope. Velocity measurements were performed on 10 individual particles at a voltage of 200 V and the zeta potential was calculated using the average velocity of three runs.

Porosity and Specific Surface Area. The porosity in terms of pore size, pore distribution, pore volume, and pore volume distribution was determined by a porosimeter (Autoscan-60 Porosimeter, Quantachrome Corp.). Based on the data obtained from a single batch, a void space was calculated. Specific surface area was determined with a B.E.T. analyzer (Monosorb, Quantachrome Corp.) using nitrogen gas.

In Vitro Release Studies

An appropriate amount of spheres containing 1.0 mg of the incorporated agents was dispersed in 10 ml of aseptically filtered phosphate buffer solution at pH 7.4 in screw-top test tubes, then the tubes were incubated at 37°C and gently agitated on an end-over-end shaker at a rate of 22 rpm. Sampling was performed under aseptic conditions in a laminar flow hood until essentially all of the incorporated drug was released. Samples were centrifuged at 3000 rpm for 2 min and the supernatant was analyzed at wavelengths of 630 and 245 nm for methylene blue and prednisolone acetate, respectively. A study to assess the effect of centrifugation on drug release from the pores revealed that, at a force of 3000 rpm, there was no difference in release between centrifuged and filtered samples.

RESULTS AND DISCUSSION

Preparation of Microspheres

Effect of Surfactant Type and Concentration. Surfactant type and concentration have been found to be important in stabilizing microparticulate systems and emulsion microencapsulation processes. As shown in Table I, at the lower SAA concentrations in the continuous phase, the yield of microparticles was higher, there was less tendency of adherence to the walls of the preparation vessel and the size distribution was toward the smaller size range. On the other hand, sphericity appeared to be compromised at the lower SAA levels. With SO-15, completely spherical particles were obtained at 0.5 and 1.0% concentrations of SAA, while with TWEEN, nonspherical particles were evident even at the 1.0% concentration. Sphericity was based on observation of at least 100 particles randomly viewed with a microscope. The term "spherical" was used when a percentage of completely spherical particles to nonspherical particles was greater than 95%, while "nonspherical" represents a percentage of greater than 50% of nonspherical particles. The yield of spheres determined by weight after drying was >90% at concentrations of 0.1% SO-15 and 0.25% TWEEN. While sphericity was favored at the higher SAA concentrations, some of the marker leached into the continuous phase at 0.5% concentrations of either SO-15 or TWEEN (Table II).

Effect of Temperature During Dispersion. The temperature of the continuous phase during introduction of the polymer-marker solution influenced the shape and size of the particles. The data listed in Table II show that more spherical and larger particles are formed at higher temperatures. Maintaining the temperature at 15°C produced small particles in the range of 1–20 μm but of not entirely spherical shape. Sphericity was improved by raising the temperature of the continuous phase, but the size also increased. At

Table I. Effect of Surfactant Concentration in the Continuous Phase on Characteristics of Particles[a]

Surfactant concentration (%)	Relative level of spherical particles (%)	Tendency of adhering to the vessel wall	Yield (%)	Size distribution (%)		
				<10 μm	10–50 μm	>50 μm
HLB 2						
0.25	>70		92	12	78	10
0.5	>70		82	10	81	9
1.0	>90	Greater	74	7	74	19
SO-15						
0.1	>90		91	15	83	2
0.5	100		86	10	76	14
1.0	100	Greater	80	8	81	11

[a] Temperature of continuous phase, 22°C; polymer concentration in dispersed phase, 5%; methylene blue in dispersed phase, 1%; ratio of dispersed phase to continuous phase, 1:40; method of particle recovery, freeze-drying.

Table II. Effect of Temperature on Physical Characteristics of Particles[a]

Temperature (°C)	Shape and size characteristics		
	0.1% SO-15	0.5% SO-15	0.5% HLB 2
15	Nonspherical, <1–20 μm	>70% sphericity, <1–20 μm	>70% sphericity, <1–20 μm
22	>90% sphericity, 5–150 μm	Complete sphericity, 5–150 μm	>70% sphericity, 5–150 μm
50	Complete sphericity, 60–80 μm	Complete sphericity, 60–80 μm	>90% sphericity, 40–50 μm
15, then increased to 50	Complete sphericity, 1–30 μm	Complete sphericity, 1–30 μm (marker leached)	>90% sphericity, 1–30 μm (marker leached)

[a] Polymer concentration in dispersed phase, 5%; methylene blue concentration in dispersed phase, 1%; ratio of dispersed phase to continuous phase, 1:40; method of particle recovery, Freeze-drying.

22°C, the size distribution was broad (5–150 μm). At 50°C, entirely spherical particles, 60–80 μm in diameter, were obtained with SO-15. At 0.1% SO-15 there was no evidence of leaching of the marker into the continuous phase. By adding the dispersed phase to the continuous at 15°C, then increasing the temperature to 50°C over a 2-min period of time, smaller microspheres, in the range of 1–30 μm, were obtained.

Effect of Polymer Concentration in the Dispersed Phase. As shown in Table III, spherical particles were obtained in good yields at 5 and 10% concentrations of PGA in the dispersed-phase solvent, HFA. The range of particles was 1–30 μm for the 5% PGA and 5 to 50 μm for the 10% concentration. The critical concentration for sphericity appeared to be 5%. At 10% the yield was slightly less as a result of a discernible adherence of particles to the wall of the container.

Effect of Loading of Marker. As shown in Table IV the ratio of methylene blue to PGA did not seem to influence the sphericity and yield of microspheres over the range studied. Using the freeze-dry method the yields of spherical particles were ≥86% over a range of 4–33% dye. With the solvent-extraction-precipitation technique the yields were 78–86% for 10–50% loading. Slightly larger spheres were obtained at the higher loading and some aggregation was evident at the 50% loading level.

Summary of the Most Appropriate Conditions. From the results of the experiments to determine suitable processing parameters, the most appropriate conditions were selected to evaluate the three methods and assess *in vitro* release of marker or drug. The conditions selected were as follows:

PGA concentration in dispersed phase, 5% (w/w);
marker loading, 10% (w/w);
surfactant in continuous phase, 0.1% SO-15; and
temperature of continuous phase, 15°C increased to 50°C over 2 min.

Comparison of the Three Methods. The characteristics of spheres containing methylene blue made by the three methods with the most appropriate conditions are listed in Table V. Yields were good for the freeze-dry and solvent-extraction-precipitation techniques but poor for the evaporation method. In all cases, completely spherical particles were obtained, although aggregation was evident in the evaporation technique, which required appropriate sieving before use. Slightly smaller particles were obtained by solvent-extraction-precipitation as compared to freeze-drying. Particles obtained by solvent evaporation were much larger. The time of preparation was shortest for the solvent-extraction-precipitation method (1 hr) and longest by freeze-drying (1–2 days). The spheres obtained by the three solvent removal methods were subjected to scanning electron microscopy for topographic observation. Qualitatively, the porosity was high by the freeze-drying and solvent-extraction methods (Figs. 2A–D) and low by the evaporation technique. Further studies are under way to quantitate porosity as a function of processing method and processing parameters. From the results of these experiments, the solvent-extraction-precipitation method was felt to be the most appropriate.

Table III. Effect of PGA Concentration in the Dispersed Phase on Characteristics of Particles[a]

	PGA concentration (%, w/w)			
	1.7	2.5	5	10
Shape of particles	Nonspherical	Nonspherical	Spherical	Spherical
Size range of particles	1–30 μm	1–30 μm	1–30 μm	5–50 μm
Yield	70%	75%	>90%	>87%

[a] Temperature of continuous phase, 15°C increased to 50°C; ratio of methylene blue to polymer, 1:10; ratio of dispersed phase to continuous phase, 1:40; SO-15 concentration, 0.1%; method of particle recovery, solvent-extraction-precipitation.

Table IV. Effect of the Ratio of Marker/PGA in the Dispersed Phase[a]

Marker:PGA ratio	Preparation method	Shape	Yield (%)	Size range (μm)
1:25 (4%)	Freeze-dry	Spherical	90	1–30
1:10 (10%)	Freeze-dry	Spherical	98	1–30
1:2 (33%)	Freeze-dry	Spherical	86	5–50
1:10 (10%)	Solvent-extraction-precipitation	Spherical	82	1–30
1:2 (33%)	Solvent-extraction-precipitation	Spherical	78	5–50
1:1 (50%)	Solvent-extraction-precipitation	Spherical	86	5–75

[a] Temperature of continuous phase, 15°C increased to 50°C; polymer composition in dispersed phase, 5%; ratio of dispersed phase to continuous phase, 1:40; SO-15 concentration, 0.1%; method of particle recovery, solvent-extraction-precipitation.

Surface Characterization of Microspheres

Specific Surface Area and Surface Charge. Using microspheres containing 10% methylene blue prepared by the solvent-extraction-precipitation technique, the surface area and porosity were assessed for a batch of spheres having a mean diameter of 6.33 ± 2.93 μm. The specific surface area determined by nitrogen gas adsorption on two samples was found to be 20.6 m^2/g. This high value is indicative of either very small or highly porous particles. The specific surface area of 6.33 μm particles completely devoid of pores and having a density of 1.64 g/ml is 0.58 m^2/g. Therefore, the high value obtained (35 times that of a nonporous particle) confirms the very porous feature of the microspheres. The surface charge or zeta potential for three different batches of microspheres was found to be −26.5 ± 0.5 mV. This high value confirmed the low tendency for aggregation, which was observed to be minimal throughout the experiments.

Porosity. Figure 3 shows a plot of cumulative specific pore volume as a function of pore size for a single run. The initial short plateau was considered as an interspacial volume between particles and read as 0.62 cm^3/g. The curve gradually increased as the pores were being filled with mercury under pressure. This began at a pore radius of 4×10^3 Å (or 0.8-μm diameter) and continued until it reached a second plateau at a pore radius of 1.2×10^2 Å (0.024-μm diameter). This suggested that the pores were filled and corresponded to a maximum value of 1.59 cm^3/g. The pore volume of the microspheres, which is the difference in the two plateau values, was 0.97 cm^3/g. Mercury porosimetry was not felt to have altered the pore structure since Fig. 3 suggests no increase in pore volume above a pore radius of 1.2×10 Å.

The pore size distribution can be obtained by plotting the pore size distribution function, $D(r)$, against radius, r,[6] as shown in Fig. 4. The volume distribution range indicated in Fig. 3 was approximately 4×10^3 to 1×10^2 Å. The maximum pore volume occurred at a pore radius of 2×10^2 Å (0.04-μm diameter). The curve showed no pores smaller than 100-Å radius (0.02-μm diameter), suggesting this as a minimum size for hexafluoroacetone sesquihydrate molecules to leach out freely from the matrix under the solvent extraction procedure. Another solvent used in the dispersed phase under the same extraction conditions could render a different pore size. Nevertheless, the rate of solvent extraction is believed to be a factor influencing pore size.

The void space was calculated to be 59–61% (v/v) based on the pore volume determined experimentally and the volume of nonporous microspheres theoretically calculated using the PGA density, which varied from 1.50 to 1.64

[6] $$D(r) = \frac{p}{r} \cdot \frac{d(V_t - V)}{dp}$$

where $D(r)$ is the pore size distribution function, r is the pore radius, $(V_t - V)$ is the pore volume in which the total volume of all pores, V_t, is diminished by the volume, V, of pores smaller than r, and p is the pressure (15).

Table V. Characteristics of Microspheres Prepared by Three Methods with the Most Appropriate Conditions

	Method		
	Freeze-dry	Evaporation	Solvent-extraction-precipitation
Shape	Spherical	Spherical	Spherical
Size, diameter	27.6 ± 10.0 μm	47.6 ± 18.2 μm	24.6 ± 13.5 μm
Qualitative porosity	High	Low	Very high
Yield	Good	Poor	Good
Time period of preparation	Ca. 1–2 days	2 hr	1 hr

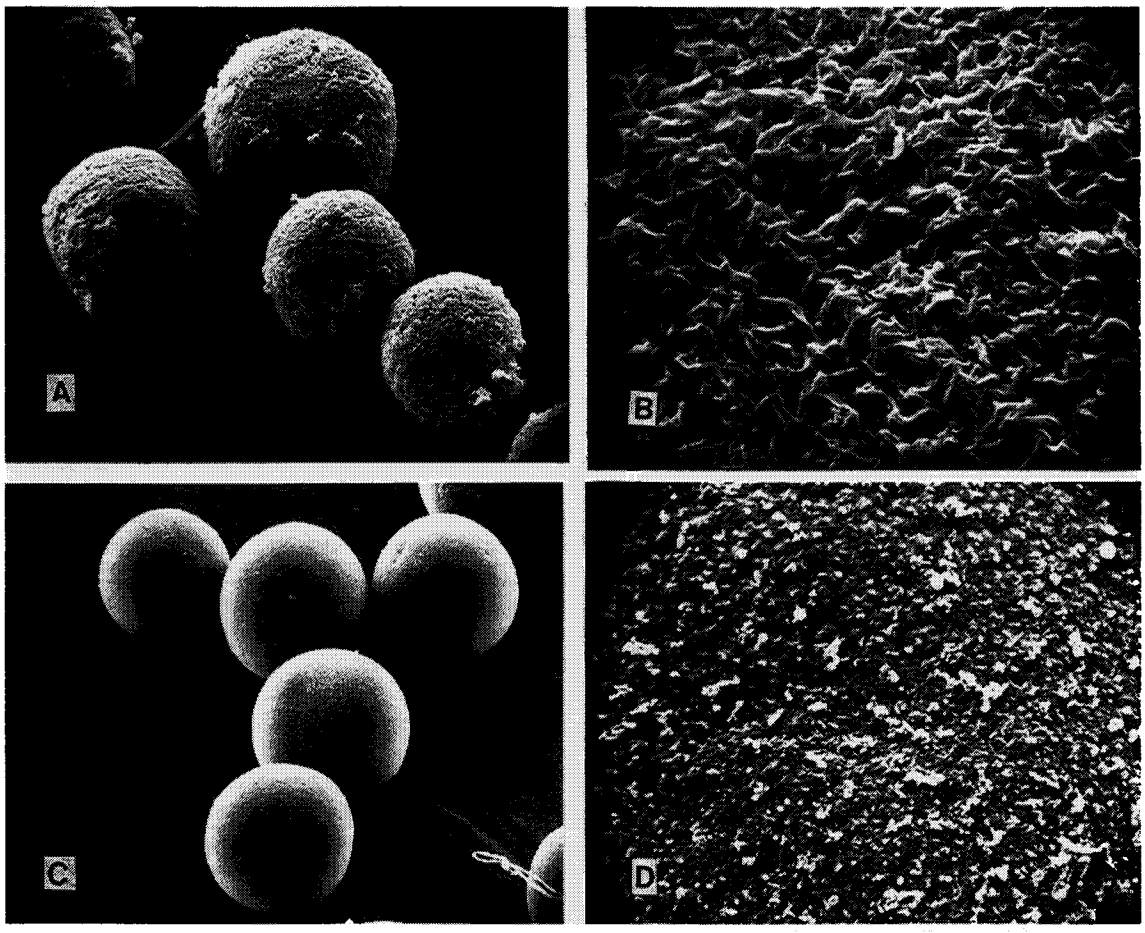

Fig. 2. Scanning electron photomicrographs of PGA–methylene blue microspheres prepared by freeze-drying (A and B) and solvent-extraction-precipitation (C and D) procedures. B and D are 10-fold magnifications of A and C, respectively.

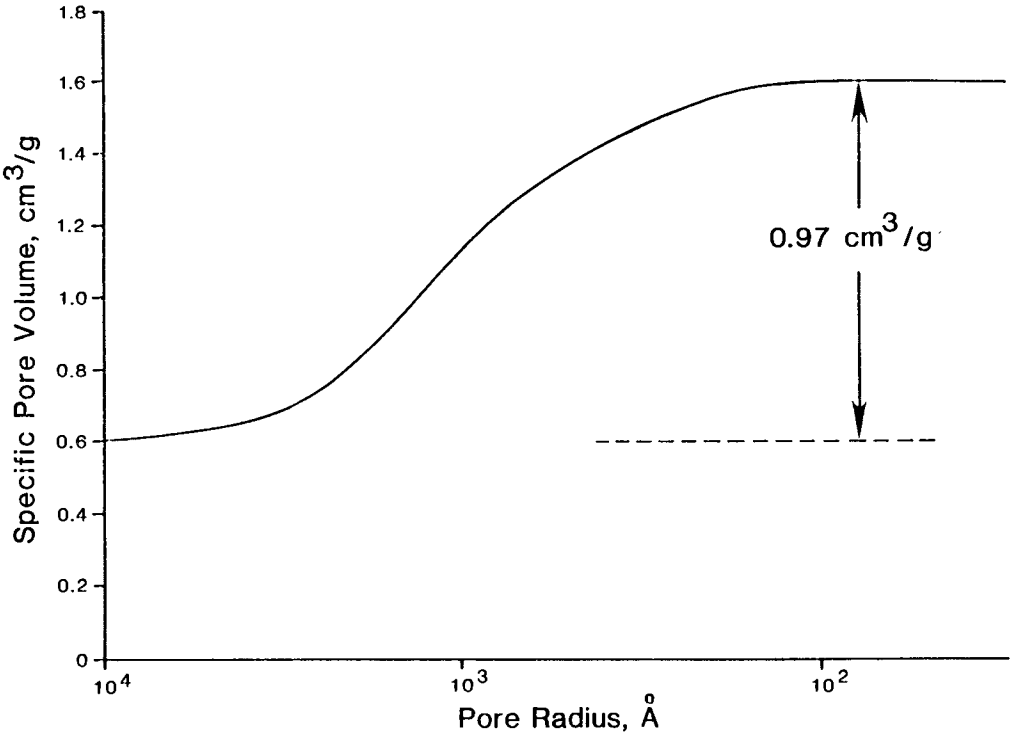

Fig. 3. A cumulative plot of specific pore volume as a function of pore size obtained by porosimetry measurements of PGA–methylene blue microspheres prepared by the solvent-extraction-precipitation method.

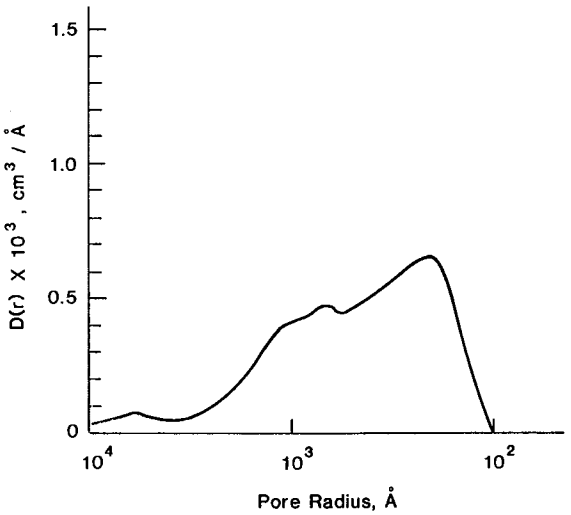

Fig. 4. Pore size distribution obtained by porosimetry measurements for PGA–methylene blue microspheres prepared by the solvent-extraction-precipitation method.

g/ml depending upon the degree of polymerization. A void space of approximately 60% by volume and an average pore size of 40 nm further confirm the porous structure. The high specific surface area confirms the porous structure and SEM suggests an interconnecting feature.

In Vitro Release

Methylene Blue Marker. Figure 5 shows the release of methylene blue from spheres prepared by freeze-drying at loading levels of 4 to 33%. The burst effect was high for the 33% concentration and essentially all of the dye was released in the first hour. However, at the lower loading levels slower release was observed and the burst effect was reduced. The results show that for a given preparation technique the polymer–drug ratio influences the release. A sample of spheres devoid of marker after 72 hr was removed for SEM (Fig. 8A). Figure 6 shows the release from spheres prepared by the solvent-extraction-precipitation technique and loaded with 9 to 50% methylene blue. A burst effect of 80–90% was observed. At 33 and 50% loading, the methylene blue was totally released within 48 hr. With the 9% loading, after an initial release of 80%, the remaining portion is released uniformly over a 120-hr period. Again, the lower the marker content, the slower the release. A sample of spheres devoid of marker after 120 hr was removed for SEM (Fig. 8B).

When comparing the microspheres containing 9% methylene blue prepared by the solvent-extraction-precipitation and freeze-dry methods, the release was found to be faster from the spheres prepared by solvent-extraction-precipitation. This can be attributed to a higher porosity with the solvent-extraction technique. This difference, while not very significant with highly soluble drugs, should be more pronounced with slightly soluble drugs.

Prednisolone Acetate. Figure 7 shows the release of prednisolone acetate, a slightly soluble drug in water, from microspheres prepared by the freeze-dry technique with 9% loading. A burst effect of about 25% release occurred, after which the release was almost zero order. Approximately 90% of the drug released after 168 hr, at which time the study was discontinued and a sample of the spheres was removed for SEM (Fig. 8C).

Degradation of Spheres. Figure 8 shows the scanning electron photomicrographs of spheres removed from the dissolution media after the release studies had been com-

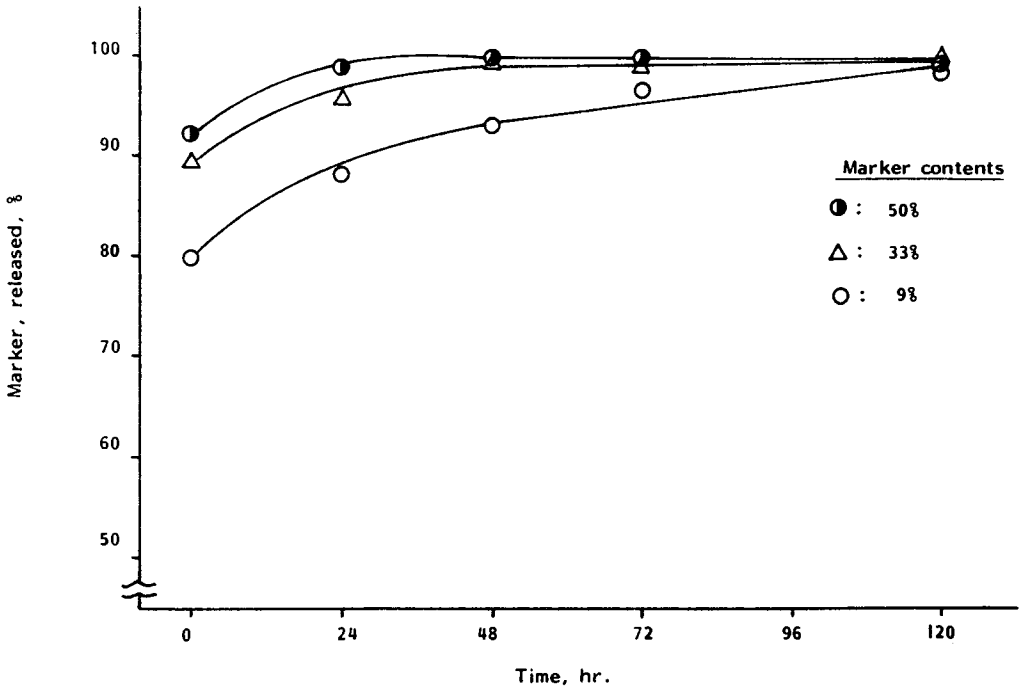

Fig. 5. Release of methylene blue from PGA microspheres prepared by the solvent-extraction-precipitation method. Each point represents the mean of three runs.

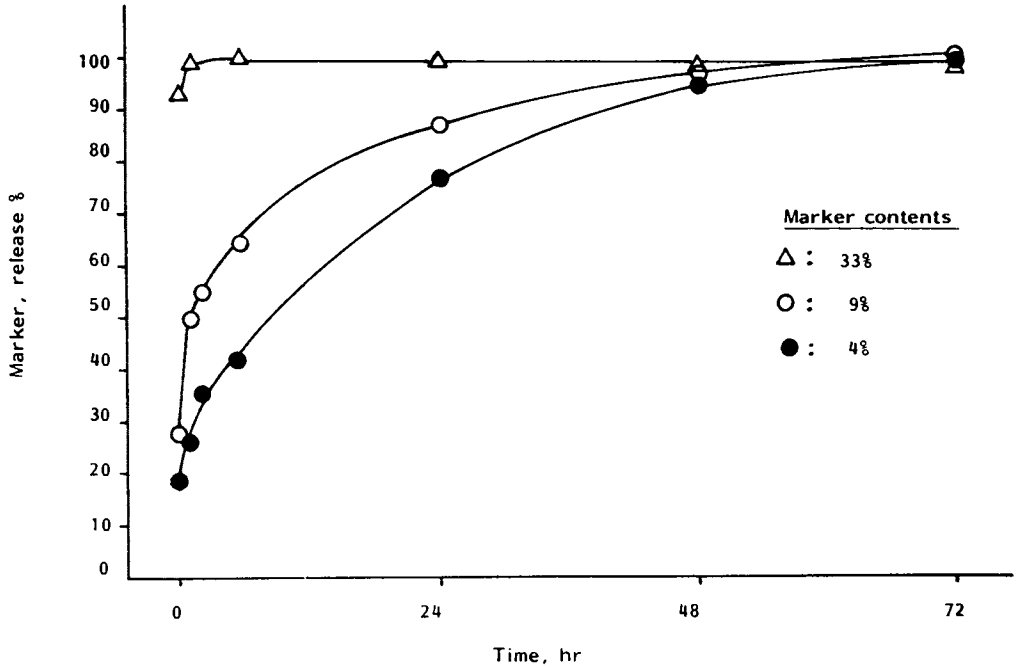

Fig. 6. Release of methylene blue from PGA microspheres prepared by the freeze-dry method. Each point represents the mean of three runs.

pleted. After 3 days the spheres remained intact, while after 5 days erosion could be discerned, and after 7 days the matrix had collapsed into fragments. Such collapse would be expected to result in an increase in release of drug due to the accessibility of new surfaces.

Effect of Polymer Concentration. Figure 9 shows the release of methylene blue in human plasma from matrices in which the polymer content in the dispersed phase was varied but the drug:polymer ratio was maintained constant. The release was directly related to the polymer concentration in the dispersed phase, decreasing as the concentration was increased. This is attributed to a lower porosity in the matrix. At 10% polymer an almost linear release was observed.

Release Mechanism. Figure 10 represents an illustration of the microporous polymeric network of intercon-

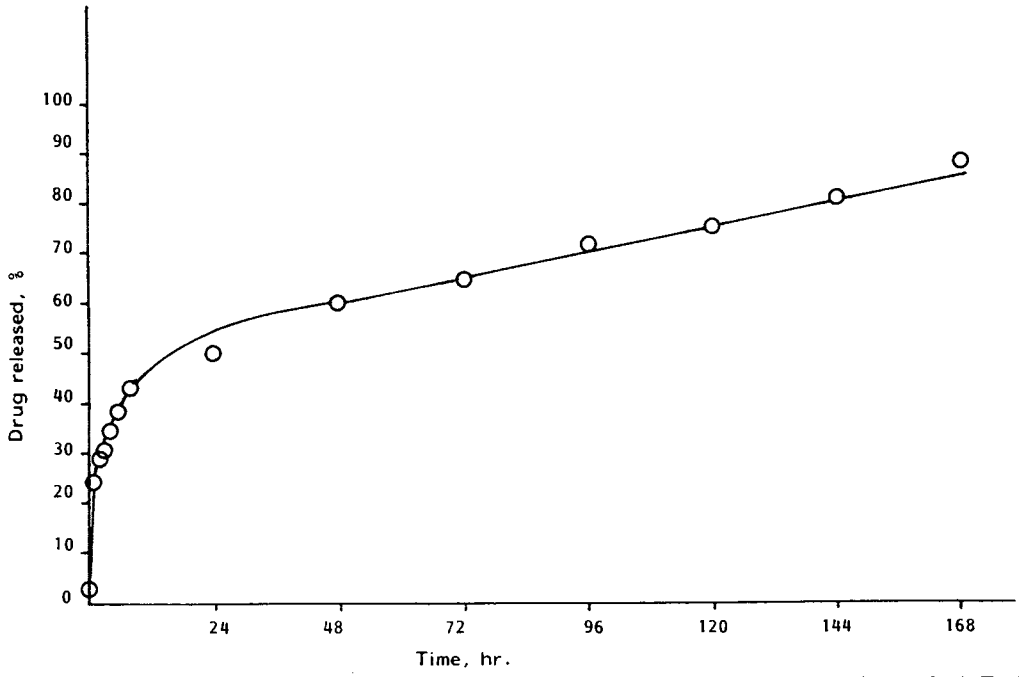

Fig. 7. Release of prednisolone acetate from PGA microspheres prepared by the freeze-dry method. Each point represents the mean of three runs.

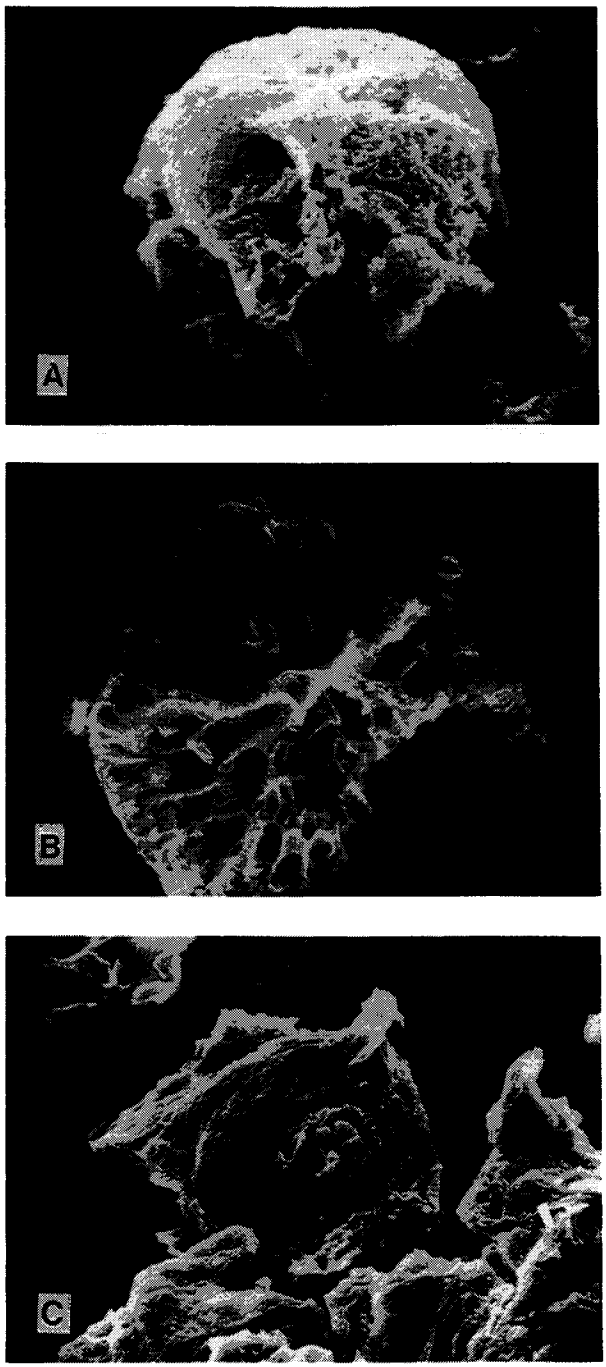

Fig. 8. Scanning electron photomicrographs of PGA microspheres after release of contents: (A) 72-hr release; (B) 120-hr release; (C) 168-hr release.

necting channels resulting from the solvent-extraction-precipitation and freeze-dry techniques. The unique features of the microspheres prepared by solvent-extraction and freeze-drying include a very porous structure in which the drug resides predominantly on the surface of the pores. Prior technology which utilized solvent evaporation and distillation or microencapsulation by phase separation resulted in a nonporous or relatively pore-free matrix in which the drug is either encapsulated or distributed homogeneously throughout the polymer matrix. The release from such

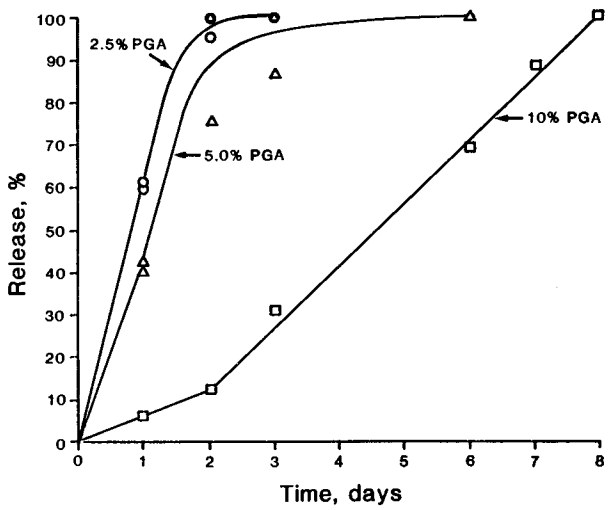

Fig. 9. Release of methylene blue from PGA microspheres in plasma. Labeled concentrations of polymer reflect that in the dispersed phase. [Methylene blue concentration, 4% (w/w) of total matrix.] Each point represents the mean of three runs.

systems, which have been described previously (7–12), occurs via erosion of the polymer or diffusion through the hydrated matrix. Sanders *et al.* (7) described the drug release by three stages, i.e., an initial diffusional release from the superficial region of the microspheres, followed by a slower release due to polymer hydrolysis and diminishing molecular weight, and then, finally, a rapid release resulting from polymer erosion. On the other hand, in the present study accessibility of the drug or incorporated agent is dependent not upon physical or chemical erosion of the polymer for release, but on dissolution of the drug within the fluid-filled pores and diffusion through the pores. The rate-determining step in such a system is the solubility of the drug. The porosity of the microspheres plays a role in restricting the permeation of fluids into the pores and the specific surface area influences the amount of drug accessible per unit of surface area available.

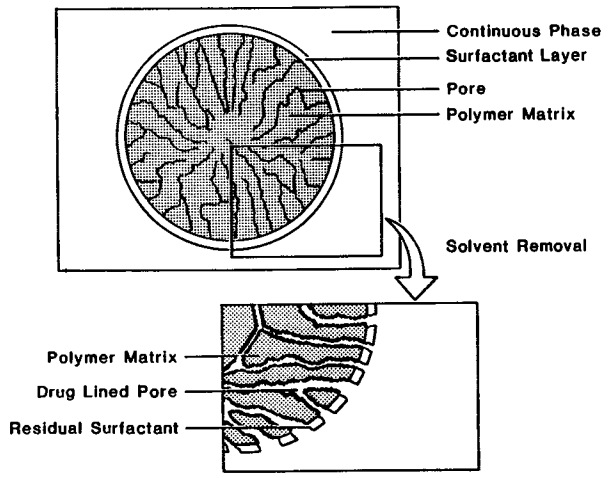

Fig. 10. Illustration of the microporous polymeric network resulting from the solvent-extraction-precipitation and freeze-dry techniques before washing.

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