Polyanhydride Microspheres. IV. Morphology and Characterization of Systems Made by Spray Drying

EDITH MATHIOWITZ,[1,2] HOWARD BERNSTEIN,[3] STEVE GIANNOS,[1] PHILLIP DOR,[1] TOM TUREK,[1] and ROBERT LANGER[1,*]

[1]Massachusetts Institute of Technology, Department of Chemical Engineering, 45 Carlton Street, Cambridge, Massachusetts 02139, [2]Section of Artificial Organ, Biomaterials, and Cellular Technologies, Brown University, Providence, Rhode Island 02912, and [3]Enzytech, Cambridge, Massachusetts 02139

SYNOPSIS

The morphology of bioerodible polyanhydride microspheres produced by spray drying is described. Microspheres prepared from a variety of homo- and copolymers were studied and characterized using X-ray powder diffraction, differential scanning calorimetry (DSC), and scanning electron microscopy (SEM). Crystalline polymers, such as poly(sebacic anhydride) (P(SA)) and poly(fumaric acid) (P(FA)), yielded microspheres with a crenelated and porous surface, as judged by SEM. Polymers, with lower crystallinity, such as copolymers of carboxyphenoxypropane and sebacic acid P(CPP-SA), yielded microspheres with a smooth external surface. Polymer crystallinity decreased after spray drying, for both blank and drug loaded microspheres.

INTRODUCTION

In previous publications[1-3] we developed methods to prepare polyanhydride microspheres. The methods, based on hot melt microencapsulation[2] and solvent removal,[1,3] offered several advantages; they enabled the preparation of microspheres made from polymers with different physical properties, which in turn corresponded to different degradation rates. In the hot-melt method, the microspheres were fabricated at the melting point of the polymer; this method was specifically useful for polymers with low melting points, especially when developing systems for temperature sensitive drugs. The solvent removal method was conducted at room temperature and were carried out in organic solvents only. This was advantageous for hydrolytically labile polymers such as polyanhydrides. In this method, the drug was dispersed or dissolved in a solution of the polymer in a volatile organic solvent. This mixture was then suspended in an organic oil, into which the organic solvent is extracted, thus forming microspheres. In all of these methods the morphology of the final product depended on a variety of properties, including the nature of crystallization, the type of solvent used, the temperature of crystallization, and the type of polymer used.[3,4]

In the current article we report the use of spray drying, a reproducible, rapid, and easy-to-scale-up method, for preparing polyanhydride microspheres. The target of the current study was to examine the influence of spray drying on polymer properties, such as crystallinity (by X-ray and DSC) or external morphology (by SEM) and release kinetics. Model drugs, including the dyes, acid orange 8 and methyl red, and the protein, bovine somatotropin (STH), were examined with a variety of polyanhydride homo- and copolymers.

The following polymers were studied: poly(sebacic anhydride) (P(SA)), copolymers of 1,3 bis-(carboxyphenoxypropane) (CPP) with sebacic acid (SA), with molar ratios of 20 : 80 and 50 : 50, copolymers of 1,6 bis-(carboxy-phenoxy hexane) (CPH) with sebacic acid (SA), with a molar ratio of 50 : 50, and copolymers of fumaric acid (FA), with sebacic acid (SA), with a molar ratio of 20 : 80 and poly valeric anhydride (PCPV).

* To whom correspondence should be addressed.

Journal of Applied Polymer Science, Vol. 45, 125–134 (1992)
 CCC 0021-8995/92/010125-10$04.00

EXPERIMENTAL

Materials

Sebacic acid (SA) and fumaric acid (FA) (Aldrich), were recrystallized from ethanol. Acid orange 8 (Aldrich) and methyl red (Fluka AG) were available as solid particles. Bovine somatotropin (STH) was from Upjohn, Michigan. P-carboxy-benzoic acid (Aldrich) was crystallized from an acetone/water mixture. All solvents were analytical grade or better.

Instrumentation

Polymer molecular weight was determined by Gel Permeation Chromatography (GPC), using a Perkin–Elmer instrument 10 pump and a 3600 Data Station with the LKB 214-rapid spectral detector at 254 nm. Polystyrene standards (Polysciences, Pennsylvania, molecular weight range 500–1,600,000) in chloroform (10 mg/mL) were used for calibration. The thermal properties of the polymers and microspheres were determined on a Perkin–Elmer DSC-7 differential scanning calorimeter, employing a heating rate of 15°C/min. Wide-angle X-ray diffraction of polymers and microspheres, in the form of pressed discs (1 mm thick), was recorded on a Rigaku RU300 X-ray diffractometer using a nickel-filtered CuK source. Morphology of polymers was studied on a Hitachi S 530 scanning electron microscope. Samples for SEM were dried under vacuum, mounted on metal stubs, and sputter-coated with gold–palladium for 30 to 60 sec (Polaron Instrument E5100).

Methods

Polymer Synthesis

Polyanhydrides were synthesized by melt polycondensation.[5–7] The following homo- and copolymers were prepared: P(SA), P(CPP-SA) 50 : 50, P(CPP-SA) 20 : 80, P(CPH-SA) 50 : 50, P(FA-SA) 20 : 80 and P(CPV).

Microencapsulation

Production of Small Particles for Microencapsulation. (a) Acid orange 8: Three g of acid orange 8 were dissolved in 500 mL of water. The solution was spray-dried with the Buechi Mini Dryer-Model 190. The process parameters were as follows: inlet temperature 154°C; outlet temperature 72–80°C; aspirator setting 20; pump setting 10 mL min^{-1}; spray flow 600 NLh^{-1} and 0.5 mm nozzle.

(b) STH (spray-dried by Upjohn), with a particle size of 1–2 microns, was used as received.

Spray-drying of Polyanhydrides Together with Model Compounds. Polyanhydrides were dissolved in methylene chloride (0.04 g/mL). When acid orange or STH was used, a known amount of the spray-dried powder was suspended in the polymer solution. Soluble drugs, such as methyl red, were codissolved in the polymer solution. The solution or the dispersion was then spray-dried. The process parameters were as follows: polymer concentration was 0.04 g/mL, inlet temperature 24°C; outlet temperature 13–15°C; aspirator setting 15; pump setting 10 mL min^{-1}; spray flow 600 NLh^{-1} and a 0.5 mm nozzle.

Polymer Degradation and Drug Release Studies. Polymer degradation and release studies were performed in 0.01 M phosphate buffer pH 7.4. Twenty mg of microspheres were suspended in 400 mL buffer solution that was stirred throughout for the entire release study. Periodically, samples were removed and analyzed spectroscopically for the degradation products and drug.[1,2]

STH Release from Spray-Dried Poly(CPP:SA) 20 : 80. Twenty mg of Poly(CPP:SA) 20 : 80 (5% w/w) was added to 250 mL or 400 mL of 0.1 M potassium phosphate pH 7.4. The mixture was slowly agitated by hand for 3–5 min to resuspend the spray-dried material. Aliquots of this mixture (1.5 mL) were taken every 15 min initially, during the first hour, and every 1 to 3 h thereafter. Aliquots were immediately filtered through a 45 μm filter and stored at 4°C until analyzed by HPLC. STH determination: STH concentrations were determined with a Waters 840 HPLC, equipped with a Wisp-712 auto-injector, and a 490 programmable multi-wavelength detector at 217 nm. The mobile phase

Table I Physical Properties of Polyanhydrides[a]

Polymer	T_m °C	T_g °C	Crystallinity %
PSA	86	60	66
P(CPP-SA) 20 : 80	72	47	40
P(CPP-SA) 50 : 50	185	2	14
P(FA-SA) 20 : 80	74	45	38
P(FA-SA) 50 : 50	69	45	42
P(CPH-SA) 50 : 50	50	11.5	32
PCPV	74	12	Amorphous

[a] All numbers, except for the PCPV, were taken from Ref. 8.

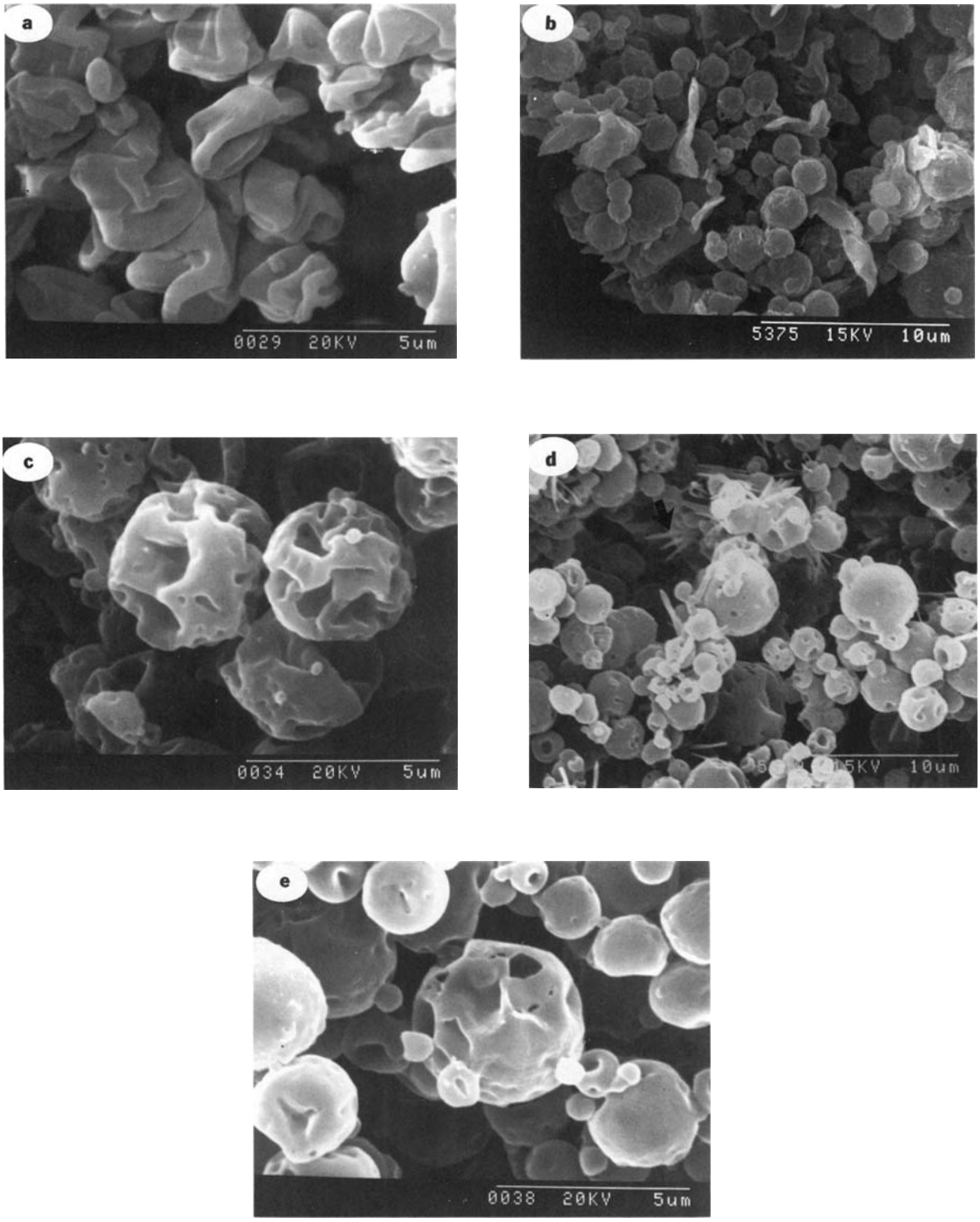

Figure 1 SEM of (a) External surface spray dried acid orange particles, note the raisin type surface, (b) Blank PSA microspheres, note the rough external structure, (c) P(CPP-SA) 20 : 80 microspheres loaded with 3% acid orange, (d) P(CPP-SA) 20 : 80 microspheres loaded with methyl red and collected in the trap of the spray drier, note the pure methyl red crystals, and (e) P(CPP-SA) 20 : 80 microspheres loaded with STH.

was 0.02 M NaH_2PO_4 adjusted to pH 6.8 with NaOH at a flow rate of 1.0 mL/minute. Quantification was performed using external standard peak area and height comparison.

Microsphere Loading. The actual loading of microspheres was obtained by summation of the total amount of drug released (after complete release) in each release study and normalized by the weight of microspheres used. Expected loading was the initial amount of drug used divided by the total weight of the polymer and the drug used during the formation of the microspheres.

RESULTS AND DISCUSSION

Polymer Characterization

The polymers used for this study have been extensively characterized[8,9] Table I summarizes some of their physical characteristics. The aliphatic polymers degrade in 1 to 6 days (depending on the size of the device),[1] are soluble in organic solvents,[3] have low melting points (70–80°C), have glass transition temperatures about 45°C,[7] and have high degrees of crystallinity.[8] Polymers made of aromatic monomers degrade more slowly (weeks), are insoluble in organic solvents, have high melting points, and their degree of crystallinity varies from polymer to polymer.[8] Copolymers made of aliphatic and aromatic monomers display degradation rates ranging from one day to several weeks, are soluble in organic solvents, and their melting points, glass transition temperatures, and crystallinity depend on the ratio of the aliphatic to aromatic monomers,[8] which results in random copolymers.[9]

Microsphere Preparation

In order to create a delivery system using spray drying, it is essential to dissolve the polymer matrix

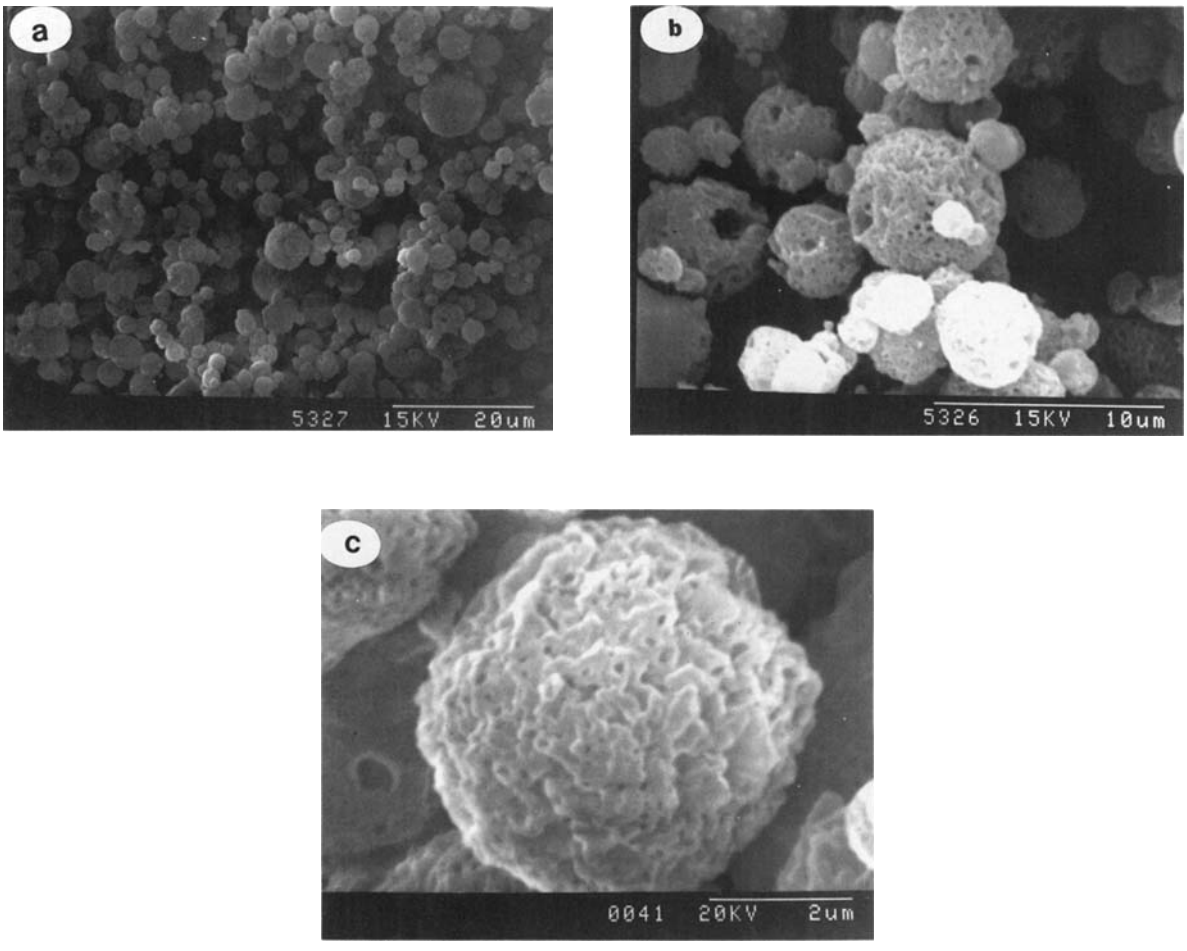

Figure 2 SEM of (a) P(FA-SA) 20 : 80 microspheres. Note the spherical external surface with sizes smaller than 10 micron, (b) Higher magnification then in (a), reveals a highly porous structure, and (c) higher magnification of (b).

in a volatile liquid. Polyanhydrides degrade in aqueous solution and it is preferable to process them in organic solvents. Using volatile solvents, such as methylene chloride, makes it possible to encapsulate various heat sensitive drugs, including proteins, at low temperature. For this particular study we used only polymers that were soluble in methylene chloride. The polymer is first dissolved in methylene chloride, and the drug can be either dissolved (e.g., methyl red) or suspended as particles (e.g., acid orange 8 and STH). Since the spray dryer nozzle was 0.5 mm, it was important to obtain very small particles of the insoluble drug when a suspension was spray dryed. This was achieved by first spray drying the acid orange in a dilute aqueous solution to obtain particle sizes ranging from 1 to 5 microns. Figure 1(a) shows the external surface of such particles. They are raisin-shaped and their size ranges from 1 to 5 microns. These particles were subsequently suspended in the polymer solution and sprayed as described above. STH (the pure drug) had a narrow size distribution (1 to 2 μm). Methyl red was soluble in the organic solvent and was sprayed as a solution. Throughout this work, the conditions of spraying were kept identical: the same organic solvent and the same polymer concentration were used. This fact allows us to correlate the morphology of a series of polymers, spray dried under the same conditions. In general, it was possible to spray the crystalline polymers PSA, P(CPP-SA) 20 : 80, P(FA-SA) 20 : 80, and P(FA-SA) 50 : 50. However, each polymer displayed a different morphology as judged by SEM (see the next section). When using more hydrophobic polymers—P(CPP-SA) 50 : 50, P(CPH-SA) 50 : 50, and PCPV—some aggregation occurred during spraying. This could have been a result of the more viscous solutions of these polymers as well as their low glass transition (see Table I).

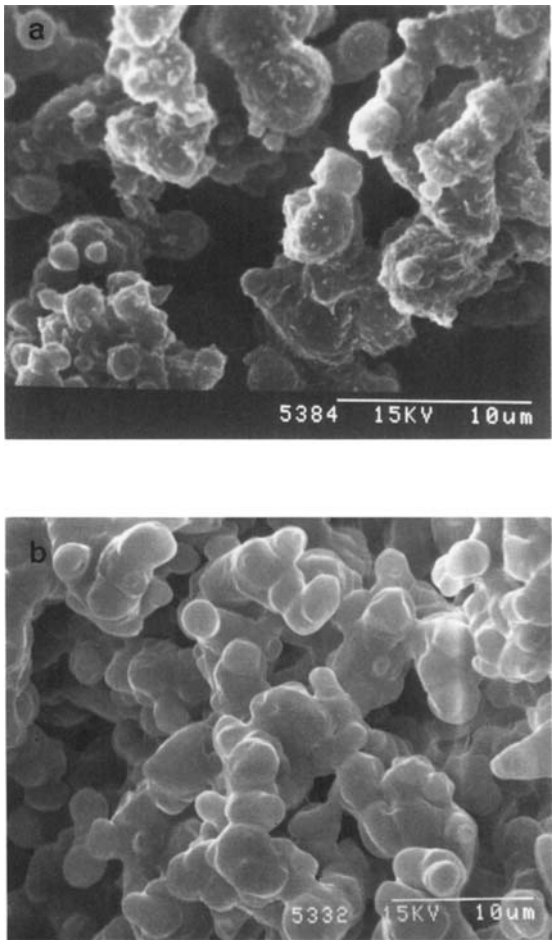

Figure 3 (a) External surfaces of the amorphous P(CPP-SA) 50 : 50 microspheres. Note the smooth and dense structure and the tendency to fuse with each other. (b) The same as in (a), only for PCPV microspheres.

Morphological Characterization of Microspheres Using SEM

Scanning electron micrographs of blank microspheres made of PSA are shown in Figure 1(b). The microspheres displayed a rough external structure: they are spherical in shape with few aggregates. Some of the polymer precipitated as long rods. This could be a result of fast precipitation that is typical of the PSA polymer. Microspheres, made of P(CPP-SA) 20 : 80 polymers, exhibited a crenelated external surface (Fig. 1c), with size distributions ranging from 1 to 5 microns. The same external surface appeared when microspheres, loaded with 3% acid orange in P(CPP-SA) polymer, were prepared. Note that the raisin-type surface, typical of the acid orange particles (Fig. 1a), was not observed. This suggests that the drug was successfully coated with the polymer solution. When methyl red was encapsulated, the external surfaces of the individual microspheres were spherical in shape with few pores on the surfaces (Fig. 1d). In this particular preparation, some of the spheres accumulated in the spray-drier trap. An SEM micrograph of the those microspheres is shown in Figure 1(d). The crystals in Figure 1(d) are pure methyl red, which crystallized during the evaporation process. The aggregation, caused by crystallization of methyl red during the evaporation process, prevented some of the spheres from reaching the final collecting tube and they accumulated in the trap of the spray-drier. However, the microspheres, which were found in the collecting tube, were spherical in shape with the same appearance as the P(CPP-SA) 20 : 80 microspheres loaded with methyl red, but they were completely different from

Table II Characterization of Microspheres by DSC

Polymer	Drug	% Loading	T_m °C	ΔH cal/g	T_m (drug)
P(SA)	Pure		86.00	31.00	—
P(SA)	Blank MS		81.00	23.4	—
P(SA)	AO	5.0	81.00	21.90	—
P(CPP-SA) 20 : 80	Pure	—	72.00	19.3	—
P(CPP-SA) 20 : 80	Blank MS	—	58.45	15.00	—
P(CPP-SA) 20 : 80	AO	7.0	56.64	16.52	123
P(CPP-SA) 20 : 80	MR	5	56.23	9.48	125
P(CPP-SA) 20 : 80	STH	5	58.3	15.52	—
P(FA-SA) 20 : 80	Pure	—	76–86	25.8	—
P(FA-SA) 20 : 80	AO	5	60–68	17.6	—
P(FA-SA) 20 : 80	MR	5	50–75	20.9	—

AO = Acid Orange; MR = Methyl Red; MS = Microspheres; — = Not Measured.

the P(CPP-SA) microspheres that were loaded with acid orange (Fig. 1c). The difference may be due to the fact that the methyl red is soluble in the organic solvent. During the spraying process, some of the dye precipitated within the polymer and some precipitated outside the microspheres as crystals.

The P(CPP-SA) 20 : 80 microspheres loaded with STH (Fig. 1e) were spherical in shape with a smooth external surface and few pores on the surface of some of the capsules. In this case, the drug was supplied as fine particles with sizes ranging from 1 to 2 μm. It is possible that some of the spheres are single particles of drug encapsulated by a continuous polymer membrane.

P(FA-SA) 20 : 80 was the next crystalline polymer that was studied. In this case, the microspheres displayed a spherical external surface with sizes smaller than 10 μm (Fig. 2a). High magnification reveals a highly porous structure (Fig. 2b,c). This porous structure was typical of all spray dried fumaric polymers—both blank and loaded microspheres.

The external surfaces of the amorphous P(CPP-SA) 50 : 50 and P(CPH-SA) 50 : 50 microspheres were smooth and dense. However, the microspheres tend to fuse with each other before the final drying (Fig. 3a). The same phenomenon was observed with PCPV microspheres (Fig. 3b). The aggregation can

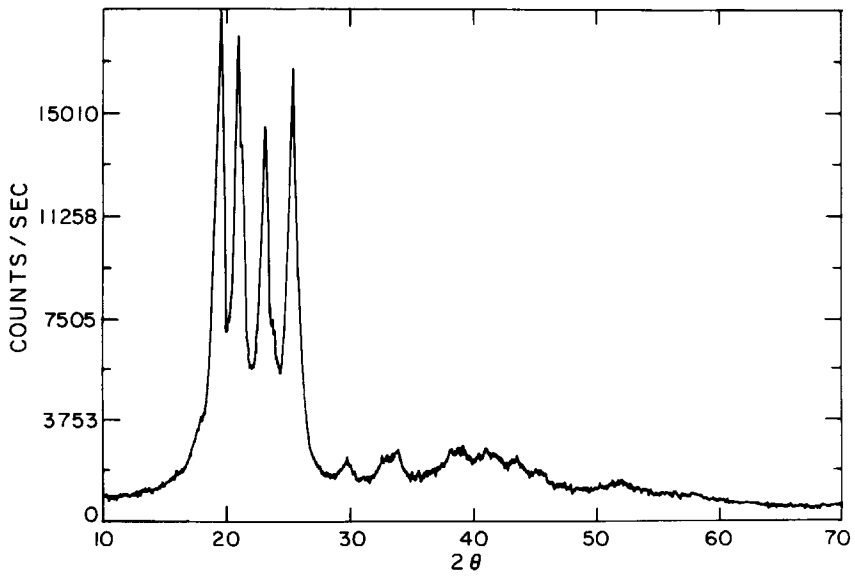

Figure 4 Typical X-ray diffraction of PSA polymer.

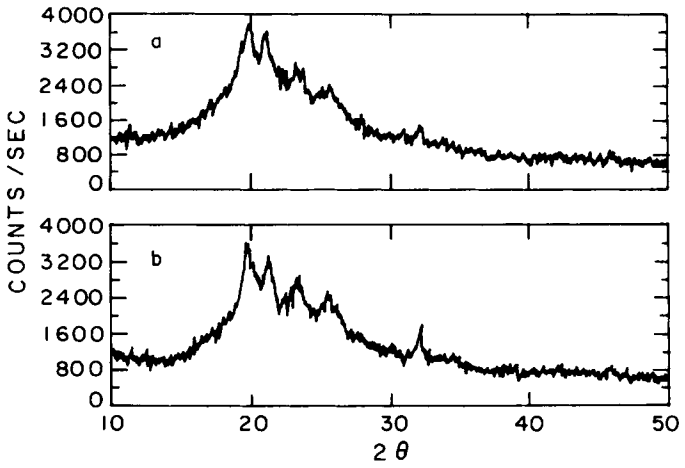

Figure 5 X-ray diffractions of two different loadings of acid orange in P(CPP-SA) 20 : 80 microspheres. (a) 3% acid orange and (b) 10% acid orange.

be prevented by lowering the concentration of the polymer solution. However, as shown in Table I, the glass transitions of these polymers are very low and it is possible that this is the main reason for the high degree of fusion during spray drying.

Characterization of Microspheres by DSC and X-Ray Diffraction

DSC and X-ray analyses of the spray dried polymers loaded with dyes and drugs were performed in order to characterize the physical state of the polymers after microencapsulation. We monitored the melting points of the dyes and polymer before and after encapsulation. A sharp endotherm was observed for free acid orange and methyl red (119.4, 181–2°C, respectively) corresponding to the melting phase transitions. The "blank" spray dried PSA microspheres displayed a sharp endotherm at 81°C, corresponding to the melting of the crystalline regions of the polymer (Table II). The crystallinity of the P(SA) microspheres was lower than the crystallinity of the original polymer (Table II, decrease of 7.6 cal/gr). However, the crystallinity is not completely destroyed and the typical powder diffraction of the P(SA) units[7] was still retained. A typical X-ray diffraction pattern of the PSA polymer is shown in Figure 4. After acid orange is incorporated, the crystallinity of the polymer remains almost unchanged (see, for example, the heat of fusion in Table II). In order further to study the behavior of the spray dried microspheres, we examined the P(CPP-SA) 20 : 80 microspheres. Data shown in Table II indicated a dramatic decrease in the melting point of the blank microspheres (58.5°C) compared to the pure polymer (72°C). The melting was broad and the numbers reported represent the peak maxima. This was true for microspheres loaded with acid orange (56.6°C), methyl red (56.2°C), and STH (58°C). The decrease in melting point could be a

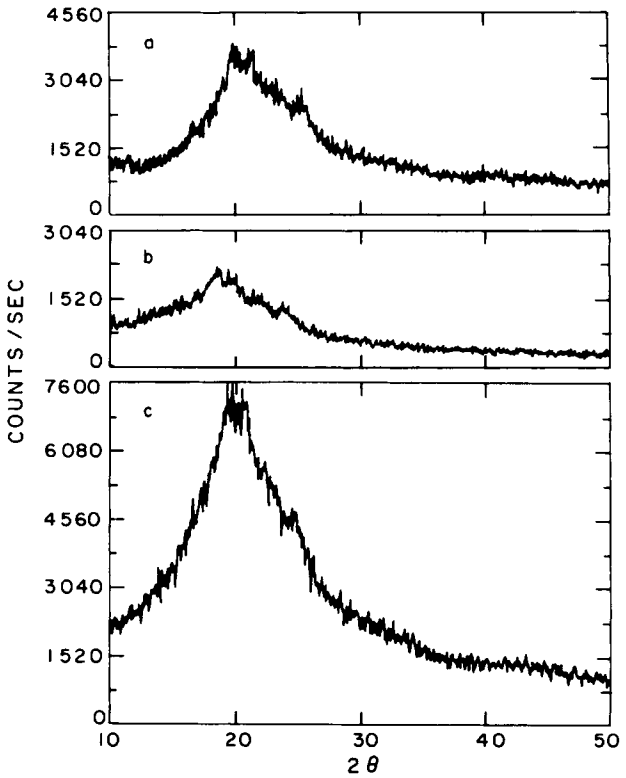

Figure 6 X-ray diffraction of P(CPP-SA) 20 : 80 microspheres. (a) Blank, (b) Loaded with methyl red, and (c) Loaded with acid orange.

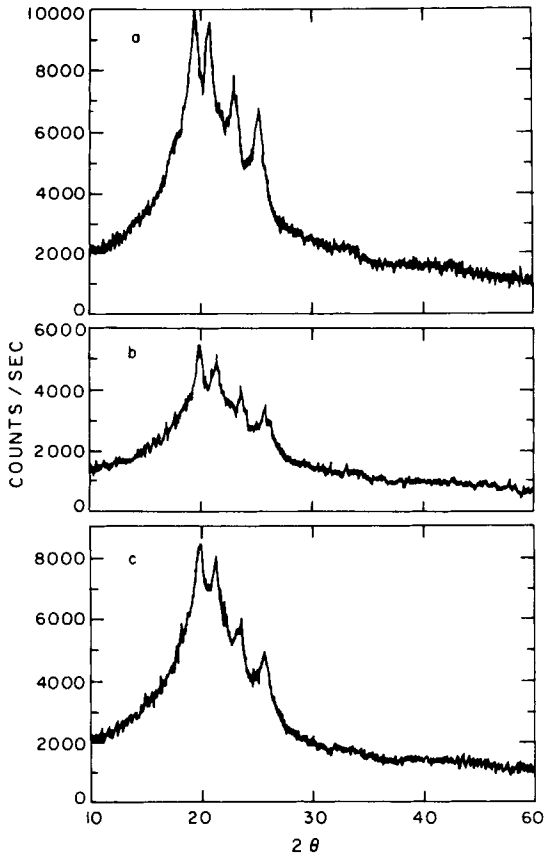

Figure 7 X-ray diffraction of P(FA-SA) 20 : 80 microspheres. (a) Blank, (b) Loaded with acid orange, and (c) Loaded with methyl red.

result of residual solvent (up to 5% by weight) in the microspheres, which acts as a diluent. There was also a pronounced decrease in the heat of fusion, which directly reflects a decrease in crystallinity. X-ray diffractions of two different loadings of acid orange in P(CPP-SA) 20 : 80 microspheres are shown in Figure 5. The four, well-defined diffraction pat-

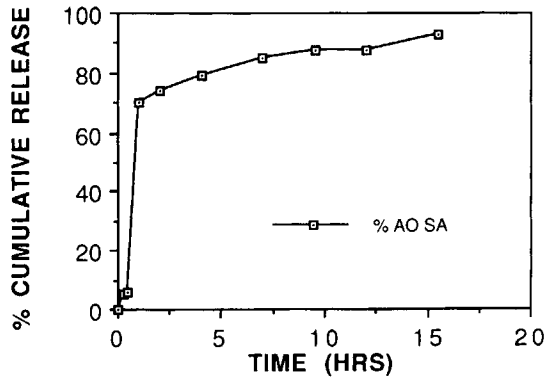

Figure 8 Acid orange released from PSA microspheres.

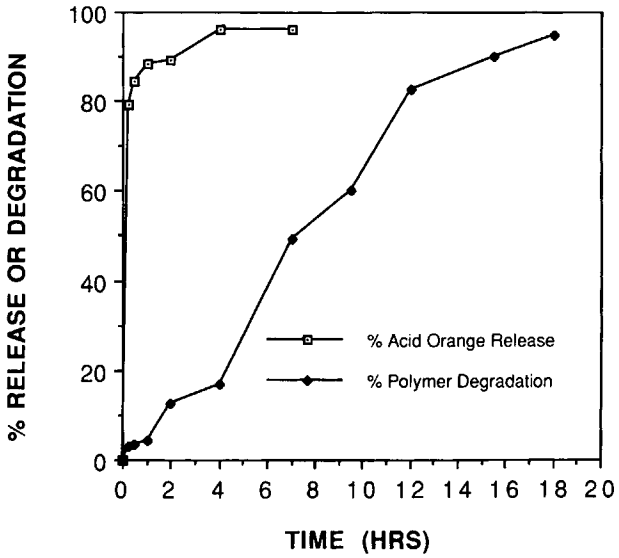

Figure 9 Acid orange released from P(CPP-SA) 20 : 80 microspheres.

terns, which correspond to the P(CPP-SA) 20 : 80,[8] are hardly seen and are replaced by broad bands, indicating a pronounced decrease in the degree of crystallinity. The blank microspheres seemed to be less crystalline than the loaded spheres, as judged by X-ray diffraction (see Figs. 5 and 6a). This difference was not as pronounced in the DSC studies (see Table II; the difference is 1.5 cal/g). This fact may be a result of the action of the drug particles as nucleating centers for the polymer, however, this observation was different for methyl red microspheres. A comparison of blank P(CPP-SA) 20 : 80 microspheres to microspheres loaded with acid orange, as well as methyl red, is shown in Figure 6. As mentioned previously, the polymer still retains some crystallinity, but the fine structures of the crystalline

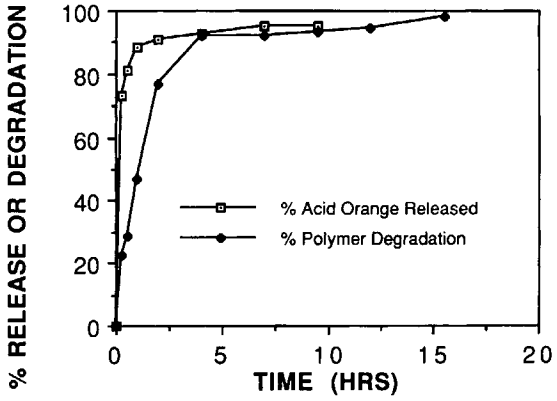

Figure 10 Acid orange released from P(FA-SA) 20 : 80 microspheres.

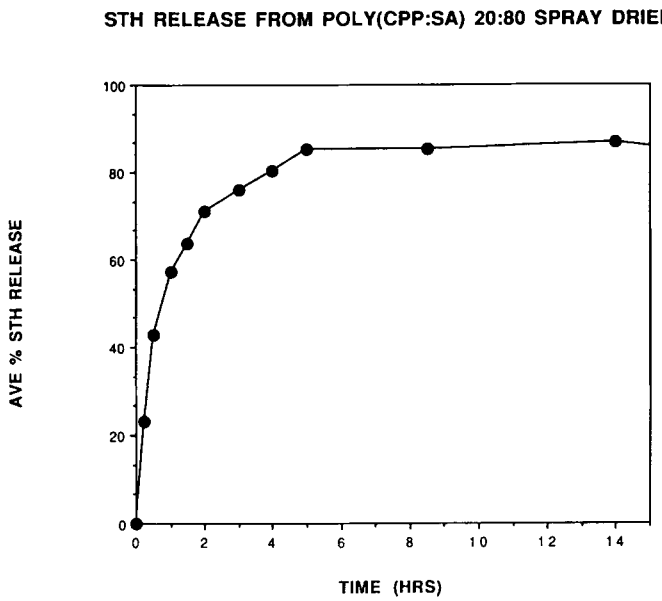

Figure 11 STH released from P(CPP-SA) 20 : 80 microspheres.

areas are gone. The lower degree of crystallinity is more pronounced in the methyl red sample and is also supported by the lower heat of fusion (Table II; the decrease is 5.5 cal/g). Previous publications, describing different encapsulation systems, indicated that methyl red may form solutions with polyanhydrides, resulting in a lower degree of crystallinity.[3]

P(FA-SA) 20 : 80 behaved differently. The melting point, as well as the heat of fusion, was lowered for both loaded and unloaded microspheres (Table II). However, the fine structure of the P(FA-SA) 20 : 80 polymer was retained (Fig. 7). This indicates that the polymers crystallized during the spray drying process.

It was evident from the X-ray powder diffraction, as well as from thermal studies, that the polymers tend to lose their degree of crystallinity during spray drying. This phenomenon is known in spray drying of both polymers as well as small molecules.[8,9] The fast drying process provides very short times for the polymer to precipitate, resulting in a more amorphous structure. Addition of drugs, especially those soluble in the organic solvents, further decreases the degree of crystallinity.

Release Studies

Acid orange release from PSA microspheres is shown in Figure 8. The release occurs over a period of 15 h. Release rates of acid orange released from P(CPP-SA) 20 : 80 microspheres are shown in Figure 9. The polymer degraded completely over a period of 24 h. Similar release rates were observed from P(FA-SA) 20 : 80 microspheres, where polymer degradation was more closely correlated to release rates. In this case, both the porous structure and the good solubility of the degradation products resulted in a better correlation between the release and degradation products. Release of STH (Fig. 9) lasted over 24 h and resulted in the release of about 90% of the drug. The short release rates (24 h) that were obtained are expected. First the degradation time of the P(CPP-SA) 20 : 80 polymer is very fast.[2] In addition, the size of the microspheres is very small (1–5 μm). This type of delivery system may find application in cases were fast release is needed, for example, in oral delivery systems.

The release of the incorporated material can occur via two independent processes. The first is diffusion of the drug through fluid-filled pores, formed by the dissolution of the incorporated drug particles; the second is via erosion of the polymer matrix as the anhydride bonds are hydrolyzed. The total release of drug will be the sum of these two release rates.

Table III Diffusion Coefficients D_s (Saline), D_e (Polymer), and Retardation Factors for P(CPP-SA) 20 : 80 Microspheres

Drug	D_s cm^2/s	D_e cm^2/h	R
Acid Orange	1.0×10^{-5}	6.3×10^{-9}	5.7×10^{6}
STH	1.0×10^{-6}	8.0×10^{-10}	4.5×10^{6}

For most of the polymer types utilized, the erosion of the polymer is less than 15% over the first 4 h. During this time period, cumulative drug release is in the range 60–70%. Thus, to compare the effect of different polymers and drug loadings, the release over this early time period was modelled as a diffusion process, since the release due to erosion is low.

The following mass balance applies for the drug within the microspheres:

$$\frac{\partial C}{\partial t} = D_e \nabla^2 C \qquad (1)$$

where C is the concentration of drug in the particle, t is the time, D_e is the effective diffusion of the drug in the polymer matrix, and ∇^2 is the Laplacian.

Equation 1 can be integrated, and the cumulative fraction of the drug released as a function of time can be computed as follows:

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left(-n^2 \pi^2 D_e \frac{t}{r_0^2}\right) \qquad (2)$$

where $\frac{M_t}{M_\infty}$ is the cumulative fraction released, and r_0 is the sphere radius.

The effective diffusion coefficient will be governed by the fabrication parameters, such as the quantity of drug loaded, the size of the drug particles loaded, the crystallinity of the polymer, and the porosity of the system. The release curves are fitted to eq. (2) using a least squares fitting method and an estimate of the effective diffusion coefficient (D_e) is obtained. Knowing the diffusion coefficient of the drug in saline (D_s), a retardation factor can be calculated as follows: $R = D_s/D_e$.

The degree of retardation will provide information as to whether the drug or dye was successfully encapsulated. Diffusion coefficients were calculated for the 20 : 80 polymer for both acid orange and STH. The diffusion coefficients in saline for acid orange and STH (D_s) were estimated as 1×10^{-5} cm^2/s and 1×10^{-6} cm^2/s, respectively. The estimated effective diffusion coefficients and the net retardation factors are summarized in Table III.

The microspheres produced have approximately the same diameter as the drug particles that were incorporated. Thus, it is likely that only a single drug particle is contained within each microsphere. The retardation factors for acid orange and STH are on the same order of magnitude, despite the large difference in molecular weight. This supports the notion that the individual drug particles are completely entrapped within the polymers as the initial release is not a function of the characteristic properties of the drug.

This study describes some morphological as well as release characteristics of spray-dried polyanhydride delivery systems. The method is useful in that it involves only very mild temperatures, presumably making it possible to encapsulate even sensitive molecules, for example, proteins. The morphology of the system depends on the polymer used and results in microspheres ranging from 1 to 10 microns.

This study was supported by a grant from NOVA Pharmaceuticals.

REFERENCES

1. E. Mathiowitz, W. M. Saltzman, A. Domb, Ph. Dor, and R. Langer, *J. Appl. Poly. Sci.*, **35,** 755–774 (1988).
2. E. Mathiowitz and R. Langer, *J. Contr. Rel.*, **5,** 13–22 (1987).
3. E. Mathiowitz, Ph. Dor, C. Amato, and R. Langer, *Polymer*, **31,** 547–555 (1990).
4. E. Mathiowitz, D. Kline, and R. Langer, *J. Scan. Microsc.*, **4,** 329–340 (1990).
5. A. J. Domb and R. Langer, *J. Polym. Sci. Part A*, **25,** 3373–3386 (1987).
6. A. Domb, E. Mathiowitz, E. Ron, S. Giannos, and R. Langer, *J. Polym. Sci. Part A Polym. Chem.*, **29,** 571–579 (1991).
7. A. Domb, C. Gallardo, and R. Langer, *Macromolecules*, **22,** 3200–3204 (1989).
8. E. Mathiowitz, E. Ron, G. Mathiowitz, and R. Langer, *Macromolecules*, **23,** 3212–3218 (1990).
9. E. Ron, E. Mathiowitz, G. Mathiowitz, and R. Langer, *Macromolecules*, **24,** 2278–2282 (1991).

Received March 8, 1991
Accepted July 19, 1991