Morphological Characterization of Bioerodible Polymers. 3. Characterization of the Erosion and Intact Zones in Polyanhydrides Using Scanning Electron Microscopy

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ABSTRACT: This paper describes the morphological changes which occur during the preparation and degradation of polyanhydrides composing different solvent- and melt-cast devices. The following monomers were used to synthesize the various polymers: sebacic acid (SA); 1,3-bis(*p*-carboxyphenoxy)propane (CPP); 1,6-bis(*p*-carboxyphenoxy)hexane (CPH); (carboxyphenoxy)methane (CPM); and 5-(*p*-carboxyphenoxy)-valeric acid (CPV). The morphology of the films and the eroding and intact zones that developed during degradation were examined by scanning electron microscopy (SEM). Amorphous and semicrystalline polymers fabricated by melt-casting displayed well-defined eroding zones with specific spherulitic or lamellar structures typical for each copolymer composition. Solvent-cast devices displayed porous spherulitic structures and, in most cases, did not display any obvious erosion zone, as judged by SEM. Aromatic copolymers were found to have liquid crystalline regions and SEM displayed spherical morphology that is specific to these phases. Crystalline and liquid crystalline regions were found to be more resistant to hydrolysis and degradation than amorphous regions.

Introduction

Bioerodible polymers have been used as biomaterials for clinical applications and as drug carriers.[1-9] There are two limiting processes by which these polymers erode: (1) surface or heterogeneous erosion and (2) bulk or homogeneous erosion. Parts a and b of Figure 1 show schematics of these two erosion processes. In the former, degradation occurs only at the surface of the device and approaches the interior in a predictable way. In contrast, bulk erosion is characterized by degradation that occurs throughout the entire device. Five important factors control the type of erosion taking place: (1) bond stability, (2) crystallinity, (3) hydrophobicity of the polymer, (4) solubilities of the degradation products, and (5) porosity of the device.[10] In any erosion process, the first step is the penetration of water into the polymer. This is followed by hydrolysis of chemical bonds to yield degradation products (i.e. monomers or oligomers) which must then dissolve in the medium. The rates of these three steps will depend on the five factors mentioned above.

If water penetration is the rate limiting step, compared to the hydrolysis and/or dissolution, surface erosion will take place. If, however, water penetration is much faster than the hydrolysis and dissolution rates, bulk erosion will dominate. Typically, the behavior falls between these two extremes, with degradation occurring in a region of finite thickness at the outer portion of the device known as the erosion zone. Figure 1c shows a schematic of the development of the erosion zone. Throughout the paper, we refer to two main regions that exist during degradation: the intact and the eroding zones. The intact zone is the inner area where degradation either proceeds slowly or does not take place at all. The eroding zone is a dynamic region where erosion occurs. The moving interface is referred to as the erosion front and proceeds toward the center of the device as exposure to water progresses.

Other scientists have studied the erosion profiles of polymers[1,2,7,11] and correlated the degradation rates with the release kinetics of the incorporated material. In some cases a thin slab was used, and it was assumed that if surface erosion occurred, there would be zero order release of the drug since no change in surface area took place. In addition, the general assumption was that if both the drug and the degradation products appear at the same time and at the same rate, a pure surface phenomenon took place.[4,7] Despite all these studies, little work has been done on the characterization of the erosion zone by studying the morphology and following the development of the erosion zone as a function of time using SEM.

In previous publications,[12-14] we discussed several aspects in the development of surface-eroding polymer systems, specifically polyanhydrides. Previous studies of polyanhydride copolymers demonstrated that degradation rates are strongly influenced by copolymer composition.[7] In order to investigate this phenomenon, we have studied a series of copolymers before degradation using the following characterization methods: (a) NMR,[12] (b) X-ray diffraction,[13] and (c) FTIR.[14] NMR and FTIR studies permit determination of the degree of randomness and frequency of occurrence of specific comonomer sequences.[12,14] Combining X-ray powder diffraction with DSC[13] data enables the calculation of the degree of crystallinity of a series of polyanhydride copolymers. Crystallinity is important in understanding the physical properties of polymers, particularly when developing surface-eroding polymers. High crystallinity usually implies a low potential for diffusion of water, and thus the potential for bulk erosion is reduced.

The objective of this paper is to follow the development of the erosion zone by using SEM. In a separate contribution, we will characterize the same samples by DSC and FTIR.[15] Since surface phenomena depend on the fabrication procedure, this paper addresses some of the techniques used to fabricate delivery systems (melt- and solvent-cast films) and discusses which of them may lead to a system that reveals a well-defined erosion zone. What we expect to see by SEM from a material which erodes by bulk erosion are heterogeneous cracks or holes throughout the device. In the case of a purely surface eroding material, we expect to see a device which simply shrinks in size with no obvious eroding zone. As either extreme is difficult to achieve with polyanhydrides, we

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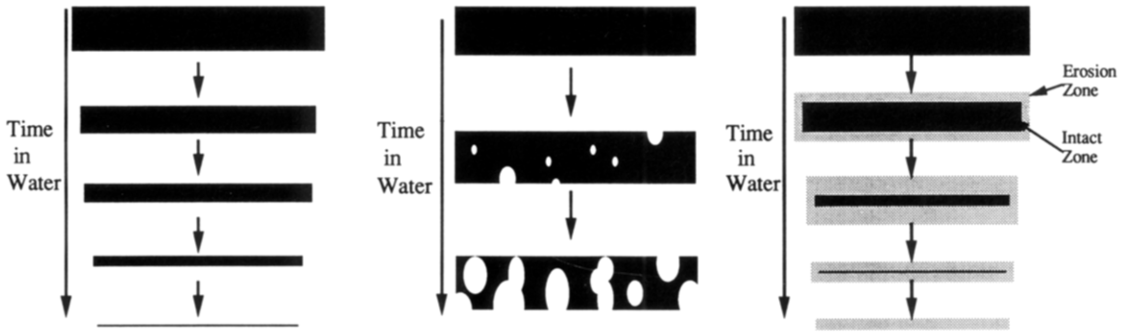
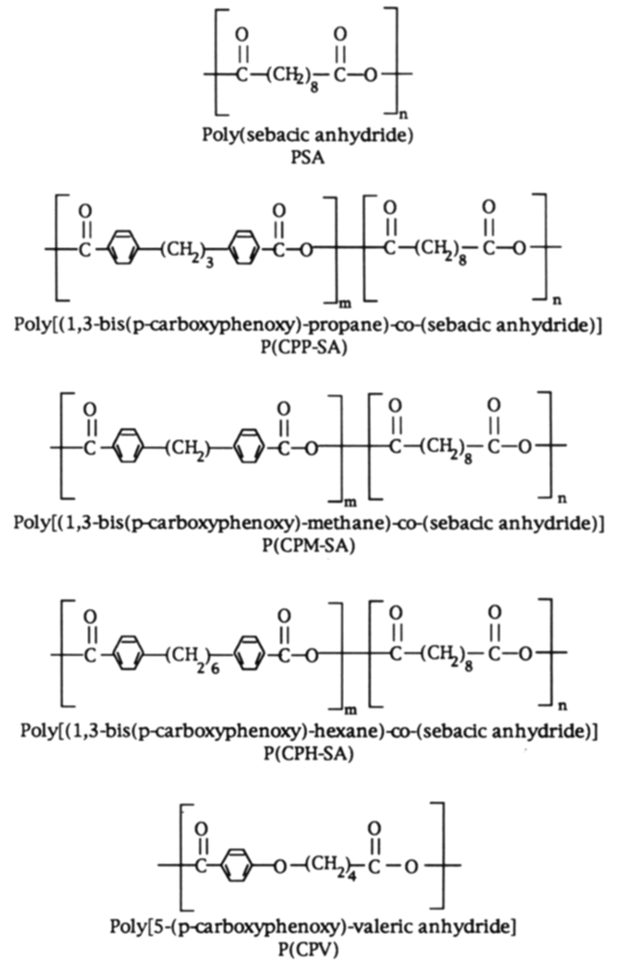


Figure 1. Schematic of (a) surface erosion, (b) bulk erosion, and (c) erosion front formation.

Table I. Chemical Structure of the Copolymers Studied


Poly(sebacic anhydride)
PSA

Poly[(1,3-bis(p-carboxyphenoxy)-propane)-co-(sebacic anhydride)]
P(CPP-SA)

Poly[(1,3-bis(p-carboxyphenoxy)-methane)-co-(sebacic anhydride)]
P(CPM-SA)

Poly[(1,3-bis(p-carboxyphenoxy)-hexane)-co-(sebacic anhydride)]
P(CPH-SA)

Poly[5-(p-carboxyphenoxy)-valeric anhydride]
P(CPV)

concentrated on characterizing the distinct morphologies of the intact and eroding zones. We also show in this paper that some polyanhydrides display liquid crystalline properties, a fact which is further supported by thermal analysis.[15]

Experimental Section

Polymer Synthesis. Sebacic acid, fumaric acid, 4-hydroxybenzoic acid, 1,3-dibromopropane, and 5-bromovaleric acid were all purchased from Aldrich Chemicals. The polyanhydrides were synthesized by melt polycondensation of mixed anhydrides of diacids and acetic acid. Poly(sebacic anhydride) (PSA), poly[1,3-bis(*p*-carboxyphenoxy)propane-*co*-(sebacic anhydride)] (P(CPP-SA)), poly[1,3-bis(*p*-carboxyphenoxy)methane-*co*-(sebacic anhydride)] (P(CPM-SA)), poly[1,3-bis(*p*-carboxyphenoxy)hexane-*co*-(sebacic anhydride)] (P(CPH-SA)), and poly(*p*-(carboxyphenoxy)valeric anhydride) (PCPV) were prepared according to the literature.[16,17] Table I lists the chemical structure of the copolymers. All the polyanhydrides were analyzed by GPC and had weight-average molecular weights (M_w) between 20 000 and 40 000. NMR studies showed that all the polymers were random copolymers with the sequence length distribution determined by the comonomer ratio.[12]

Equipment. The molecular weight of the polymers was estimated on a gel permeation chromatography (GPC) system (Perkin-Elmer) consisting of the Series 10 pump and the 3600 data station with the LKB 214-rapid spectral detector at a wavelength of 254 nm. Samples were eluted in alcohol-free chloroform through a PL gel 5-mm mixed column (Polymer Laboratories) at a flow rate of 1.0 mL/min and at 23 °C. Molecular weights of polymers were determined relative to polystyrene standards (Polysciences, molecular weight between 500 and 160 000) using CHROM 2 and GPC 4 computer programs (Perkin-Elmer).

Morphological characterization of polymers was performed on a scanning electron microscope Model Hitachi S-2700. Samples for SEM were freeze dried, mounted on metal stubs, and sputter-coated with a 50–100-Å layer of gold–palladium (Polaron Instrument E5100). A blade was used to cross-section the samples when necessary.

Film Preparation. Films of the different polymers were prepared as follows: 20% w/v solutions of polymers in methylene chloride plus 0.2% w/w mitomycin-C were cast in glass dishes. The dishes were placed on dry ice and immediately stored at −20 °C for 2 days to allow for solvent evaporation. Our experience shows that for the hydrophobic copolymers, residual solvent amounted to less than 0.5% by weight. A similar procedure was used for blank solvent-cast films. Blank melt-cast films were prepared in small Petri dishes, with the polymer allowed to slowly cool down to room temperature. Mitomycin-C was not incorporated into melt-cast devices since it is unstable at the high temperatures required for preparation.

Degradation Studies. Films containing drug or blank films were cut into 7-mm-diameter disks with a thickness of 1.2–1.4 mm. Weight loss studies were conducted for the various samples by introducing blank and drug-loaded films into a phosphate buffered saline solution at pH 7.4 and reweighing after time periods of 24, 48, 72, 146, and 192 h. Samples that did not completely disintegrate were characterized by SEM.

Polymer Morphology Studied by Optical Microscopy. Thin films were prepared by either melt- or solvent-casting between two glass slides to study the morphology of the polymers under crossed polaroids. To imitate the cold casting conditions, samples were cast on glass slides chilled on dry ice and stored at −20 °C for 1 h. All samples were studied under cross-polarized light to evaluate the morphology of the polymer films.

The second step in the study was to evaluate the different morphologies before and after degradation by optical microscopy. This was accomplished for all polymers with or without drugs. As a model drug for the solvent-cast devices, we used mitomycin-C. This is an anticancer drug with significant importance in clinical applications.[18] However, in our study it was mostly used since it was soluble both in organic and in aqueous solutions. It is a pink drug and was partially soluble in the polymer, thus allowing quick determination of the eroding zone by optical microscopy. White areas usually corresponded to the eroding zone where the drug had been released and pink regions corresponded to the intact zone. The work here focused on high magnification evaluation of the two regions using SEM.

Results and Discussion

Characterization of the Various Polymers by Cross-Polarized Light. Most delivery systems are fabricated

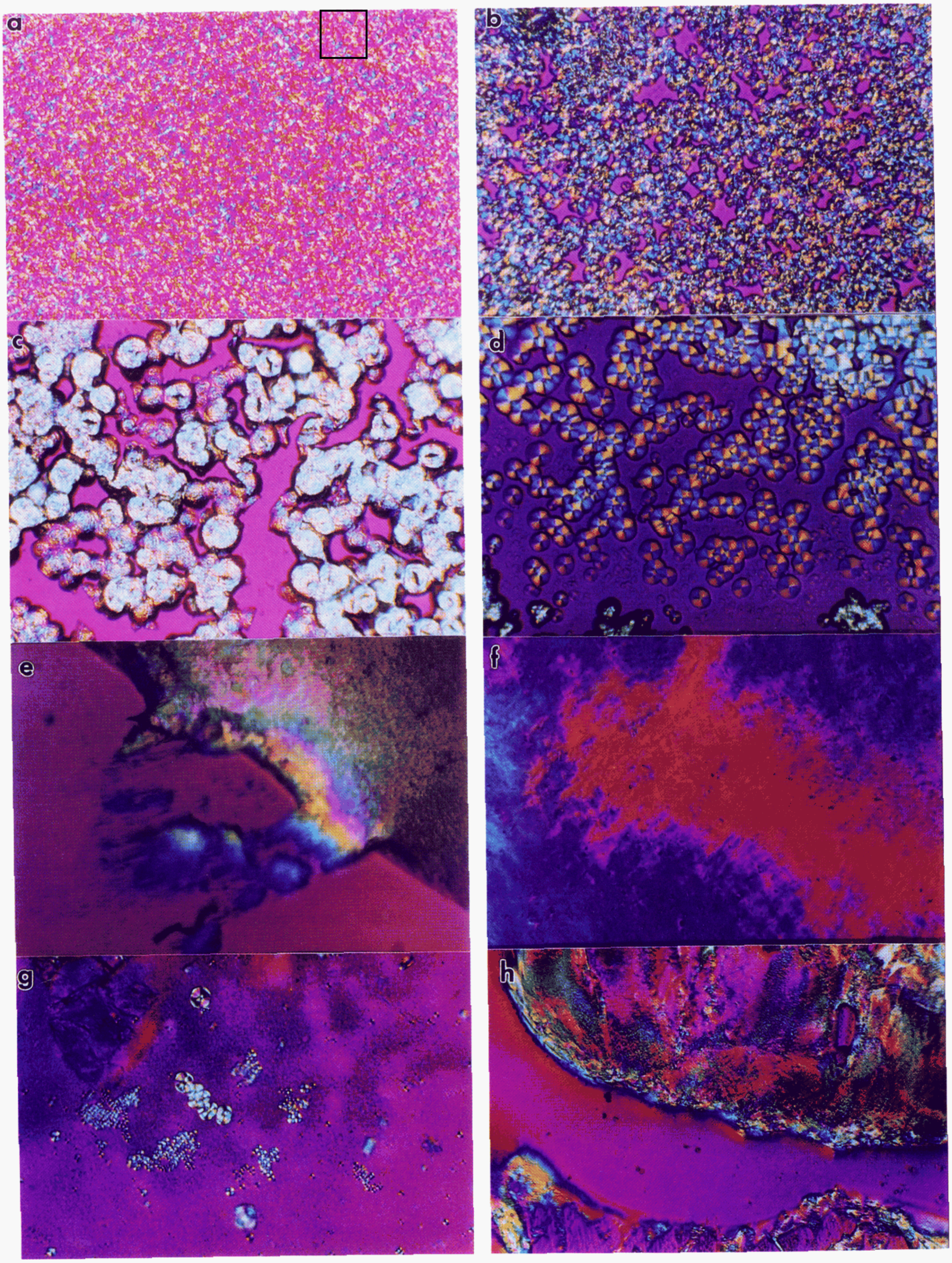


Figure 2. Morphology of thin film polymers using cross-polarized light: (a) small lamella forming from melt PSA; (b) spherulites growing in solvent-cast PSA; (c) banded spherulites in solvent-cast PSA; (d) classic spherulites growing in solvent-cast P(CPP–SA) 20:80; (e) liquid crystalline structure appearing in melt-cast P(CPP–SA) 50:80 polymer; (f) schlieren structures appearing in solvent-cast P(CPP–SA) 50:50 copolymer; (g) liquid crystalline as well as spherulitic structure appearing in P(CPM–SA) 50:50; (h) schlieren structures appearing in solvent-cast PCPV polymer.

by precipating the polymers from the molten state or from organic solvents. In melt-casting or hot-melt microencapsulation,[9] the polymer is first exposed to heating and then allowed to cool. In solvent-casting or microencap-

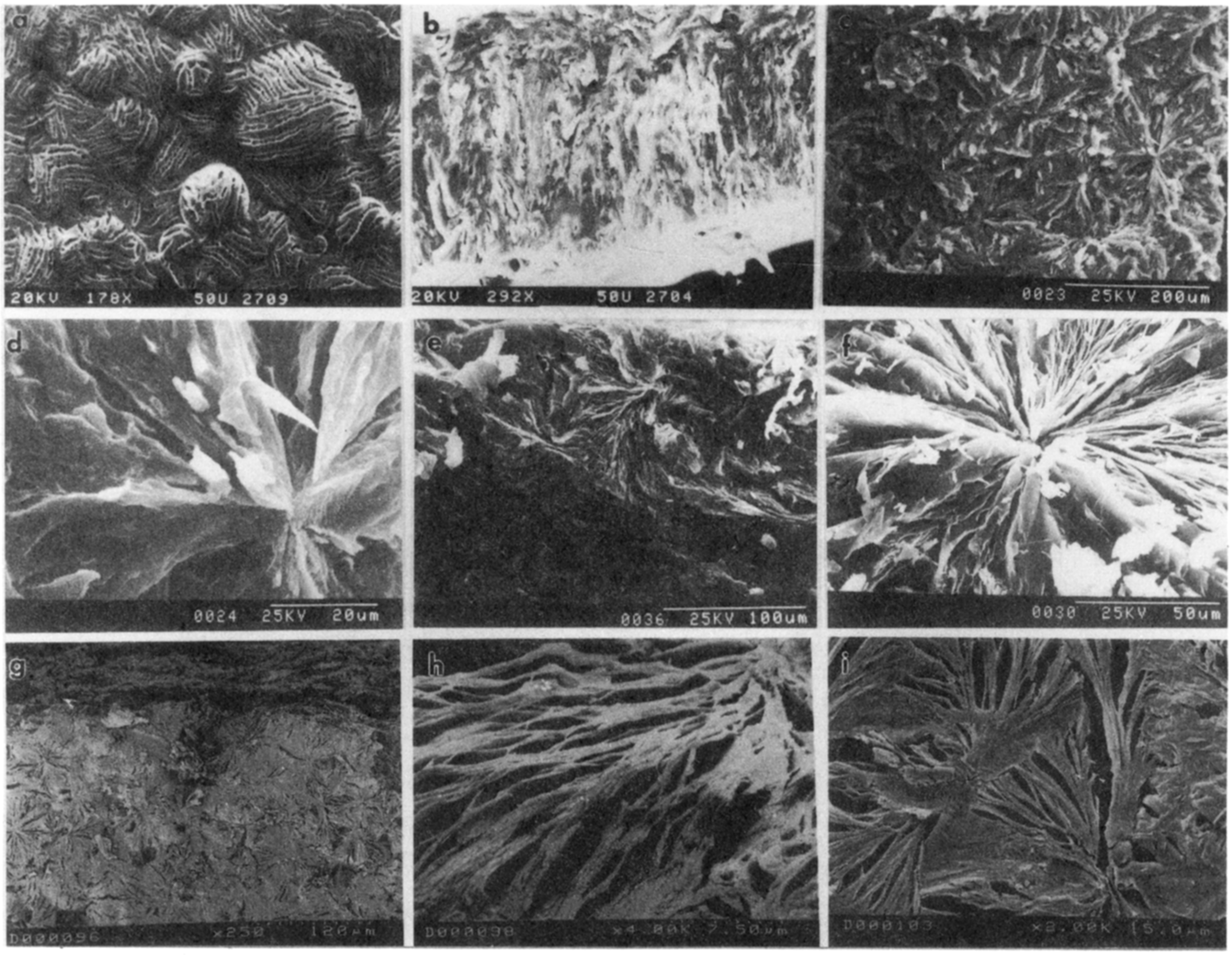


Figure 3. SEM of PSA polymer: (a) solvent-cast, external surface; (b) cross-section of the solvent-cast film; (c) internal structure of the melt-cast film; (d) higher magnification of a single spherulite; (e) interface between the eroded and noneroded zones, 3 h after degradation of the melt-cast film; (f) higher magnification of the partially eroded spherulite; (g) cross-section of the melt-cast film 24 h after degradation; (h) higher magnification of the eroding zone shown in (g); (i) higher magnification of the intact zone shown in (g).

sulation by solvent removal,[19] the polymer is precipitated out of the organic solvent. While polymer microspheres are being prepared, direct observation by optical microscopy is useful. However, once the polymer hardens and appears opaque, it is no longer possible to identify the morphology of the microspheres by observation between crossed polarizers. For this work, the various polymers were melt- or solvent-cast into thin films directly onto glass slides in order to study the morphology. Figure 2 displays the different structures that were found. PSA cast from the melt (Figure 2a) reveals thread shaped structures with coarse spiky microstructures. Occasionally, it was possible to see classical spherulitic structures. The relationship between the spherulites and crystallites is complicated but can be easily explained by following Ward's[20] explanation; the spherulite is made up of fibrils which are arranged in a radial pattern. The fibrils themselves are made up of crystallites with the chains folded at right angles to the fibril length. The fibrils contain a portion of noncrystalline defects, but the bulk of amorphous material which is rejected during the crystallization process is found between the fibrils. Other amorphous material is found between the spherulites themselves. When PSA was cast from solution, both spherulitic structures (Figure 2b), as well as banded spherulitic structure (Figure 2c), were found. In a classical spherulitic structure, the bright contrast is derived from birefringence and indicates a crystalline initiate. Superimposed on that is the black Maltese cross, with arms lying parallel to the extinction direction of polarizer and analyzer.[21] This structure usually implies that spherulites are made of radial fibrils which fill the entire space, with the polymer chain being perpendicular to the spherulite radius. Banded spherulites are more complicated spherulites which show concentric extinction rings in addition to the Maltese cross.[21] This indicates that the molecular axis is parallel to the illumination at the location of the rings.

The coarse spiky structure was also observed in melt-cast P(CPP–SA) 20:80 polymers. This structure could well be liquid crystalline in nature since it is similar to the smectic F phase described in the literature.[22] When this polymer was heated and quenched-cooled, a typical schlieren structure appeared. The crystallization of P(CPP–SA) 20:80 out of solution revealed a spherical structure (Figure 2d) and a classical spherulitic structure under cross-polarized light. The P(CPP–SA) 50:50 polymer displays classical schlieren structures either from cooling (Figure 2e) or from being solution-cast (Figure 2f). The same results were found with the P(CPH–SA), copolymers. The P(CPM–SA) 50:50 copolymer (Figure 2g) solidifies partially as crystalline and partially as liquid crystalline phases. This is evident by the existence of the Maltese cross, indicating the existence of spherulites as well as a schlieren structure. PCPV revealed a liquid crystalline state when cast from both melt and solution.

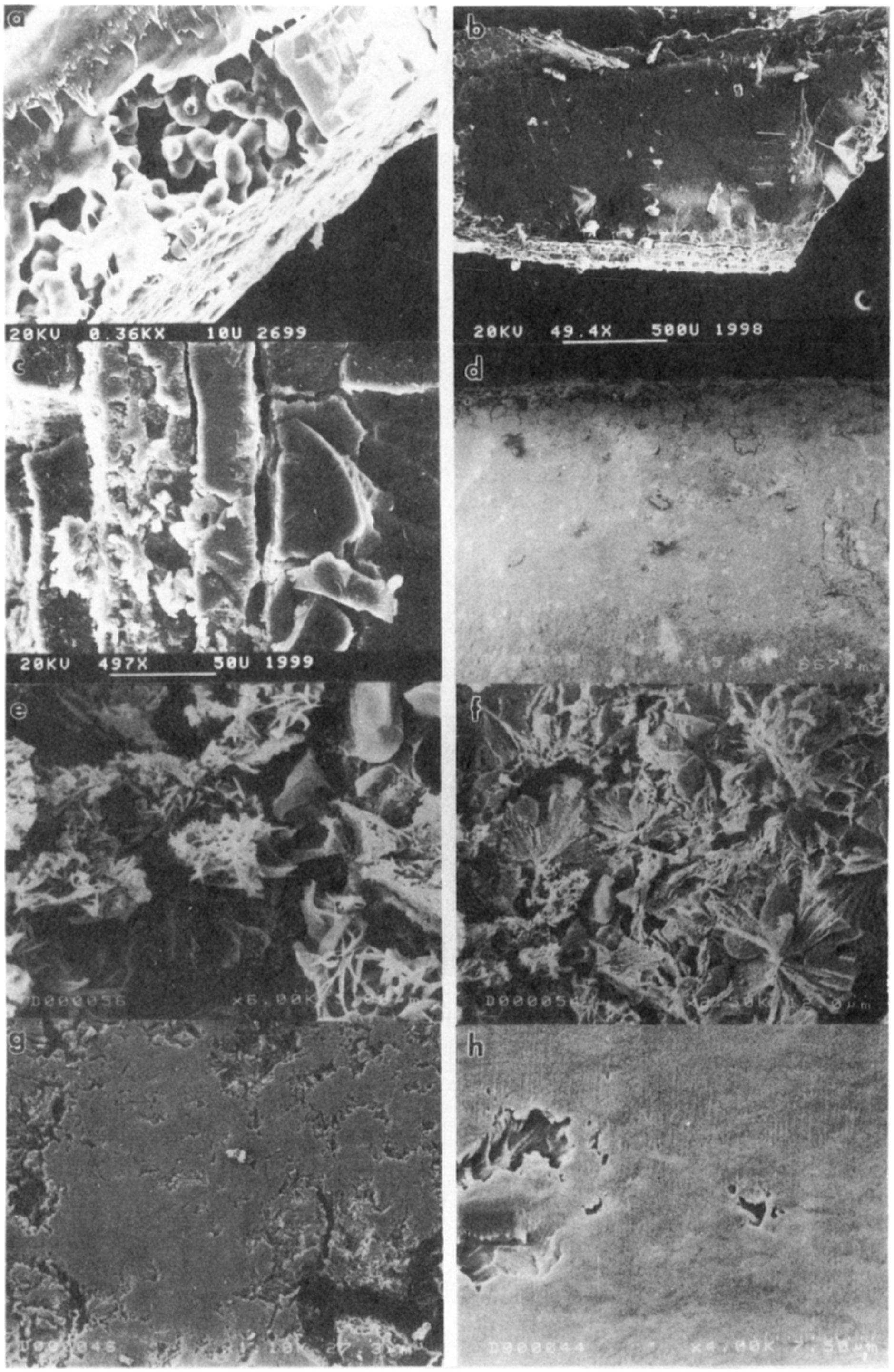


Figure 4. SEM of P(CPP–SA) 20:80 copolymers: (a) cross-section of the solvent-cast film loaded with mitomycin-C with a crystal of mitomycin-C shown in the upper right corner; (b) cross-section of the blank solvent-cast film 24 h after degradation; (c) higher magnification of the eroded zone of (b); (d) cross-section of the metal-cast film 48 h after degradation; (e) higher magnification of the eroded zone shown in (d); (f) the same eroding zone as in (d) but focused on spherulites; (g) higher magnification of the interface shown in (d); (h) higher magnification of the intact zone shown in (d).

Figure 2h displays a typical schlieren structure of that polymer.

The general conclusion from the entire optical study is that polyanhydrides can precipitate in a variety of physical states, including a liquid crystalline state. The last factor has never been considered in our previous analyses, but it could be of great importance, particularly in understanding erosion phenomena.

Surface Morphology of Solvent- and Melt-Cast Devices before and during Degradation As Studied by SEM. Studies were performed to understand the different degradation patterns of the various polymers using SEM. The work was divided into different sections, each corresponding to a different polymeric group. In each group, the polymers were first characterized by SEM. Then, samples that revealed the well-defined erosion zone were studied by DSC and FTIR.[15]

(a) PSA. Solvent-casting of the crystalline polymer PSA with mitomycin-C revealed a very porous structure, even before degradation. The fine structure of the various spherulites is shown in Figure 3a,b, with Figure 3a being one side of a film and Figure 3b the cross section. The spherulites contain lamellar ribbons and appear to branch and interpenetrate. The size of the spherulites ranges between 100 and 150 μm. The morphology revealed here is typical of polymers which crystallized from solutions[23]

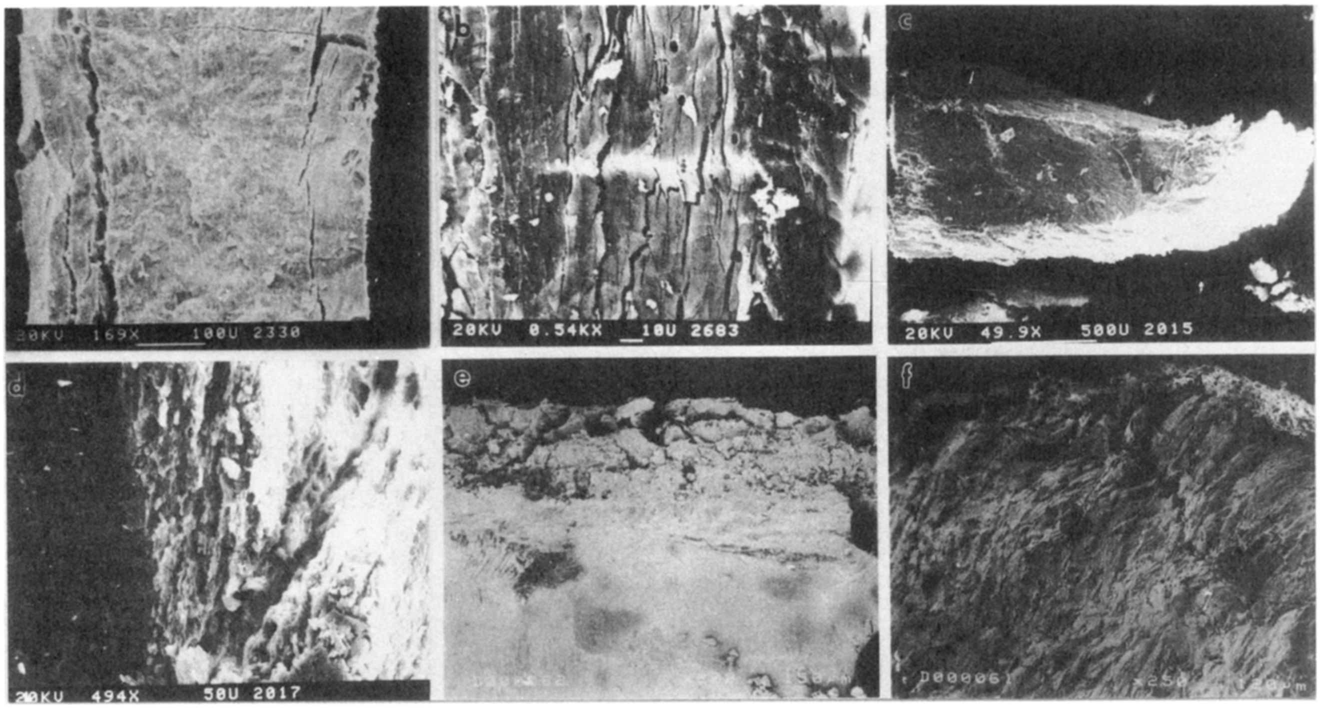


Figure 5. SEM of various P(CPP–SA) 50:50 copolymers: (a) cross-section of the solvent-cast film loaded with mitomycin-C; (b) high magnification of the eroding zone shown in (a); (c) cross-section of the blank solvent-cast film; (d) high magnification of the interface between the intact and eroded zones; (e) cross-section of melt-cast film 48 h after degradation; (f) higher magnification of the intact zone shown in (e).

and is further support for the optical observations (Figure 3b,c) which demonstrated the existence of spherulites. It is expected that this porous structure will erode by bulk erosion, since water will be able to penetrate the bulk of the polymer. In contrast, melt-cast PSA revealed a denser structure with radial spherulites (Figure 3c,d). The fibrils are filled with precipitated amorphous material (Figure 3d). When the film was allowed to erode for 3 h, a well-defined eroding zone appeared (Figure 3e). The eroding zone was very porous and full of spherulites which were shown at high magnification in Figure 3f. In this case, it is easy to identify the fine lamellar structure of the fibrils, because the amorphous material which filled the spherical structure of the spherulite is gone. These results are in agreement with the general knowledge that amorphous regions are more susceptible to degradation than crystalline regions.[20,21] After 12 h of degradation, the eroding zone is still separate from the intact zone and after 24 h of degradation at low magnification, it is easy to identify the eroding zone (Figure 3g) and the fragile lamellar structure inside it (Figure 3h) which reveals increasing porosity. The intact zone seems to be different in appearance; it is much denser than the eroding zone, but erosion has already started, dissolving the amorphous region and exposing more spherulites (Figure 3i). When PSA microspheres were fabricated by solvent removal, the microspheres precipitated as individual spherulites,[24] and as erosion proceeded, only the fine fibrils were left after the fast degradation of the amorphous material.

In conclusion, the PSA polymer with a high degree of crystallinity[13] crystallizes both from solvent and from melt in a semicrystalline form, which is characterized by spherulitic structures. The solvent-cast devices were crystalline but porous; thus no defined erosion was observed during degradation. The melt-cast samples revealed a denser structure and, as a result, it was possible to identify both the erosion and the inact zone. In the erosion zone, the amorphous material (which precipitated between the fibrils) seemed to disappear first, leaving spherulites to erode at a later time. The intact zone seemed to be eroding more slowly, but SEM revealed that even after only 24 h of degradation, hydrolysis was taking place. This was apparent by the open-structured spherulites. In both cases, the amorphous regions seemed to disappear first. The PSA polymer is the first example which shows that a high degree of crystallinity is not the only factor that needs to be considered when developing surface eroding polymers. The physical morphology must also be taken into consideration.

(b) P(CPP–SA) 20:80 Copolymers. P(CPP–SA) 20:80 is one of the most-studied polymers and has already been used for clinical applications. However, this is the first time that the morphologies of solvent-cast and melt-cast devices have been compared. Figure 4a displays the cross-section of solvent-cast P(CPP–SA) 20:80 loaded with 0.2% mitomycin-C. The structure reveals spherical spherulites which are typical to solvent-induced crystallization.[23] The results correlate with the structures that were obtained by optical microscopy (i.e. spherulitic structures). In addition, Figure 4a shows a crystal that precipitated during the evaporation. This is a mitomycin-C crystal that was also detected by X-ray powder diffraction.[15] No erosion zone was detected due to the porosity. When the same polymer was solvent-cast without any drug, a different morphology appeared. The cross-section revealed a dense structure, and after 24 h of degradation a well-defined erosion zone was observed (Figure 4b). Higher magnification of the erosion zone revealed longitudinal fractures with no signs of spherulites (Figure 4c). The degree of crystallinity of the solvent-cast polymer was almost as the melt-cast.[15] The results suggest that due to the presence of a drug the P(CPP–SA) 20:80 could precipitate into a different morphological state.

Melt-cast devices revealed a dense structure immediately after fabrication and all displayed erosion zones upon degradation. Figure 4d is a cross-section of a melt-cast device 48 h after degradation. At low magnification, the inact zone seemed to be very dense and the eroding zone looked porous and cracked. Higher magnification of the eroding zone reveals a porous structure with 20-μm size

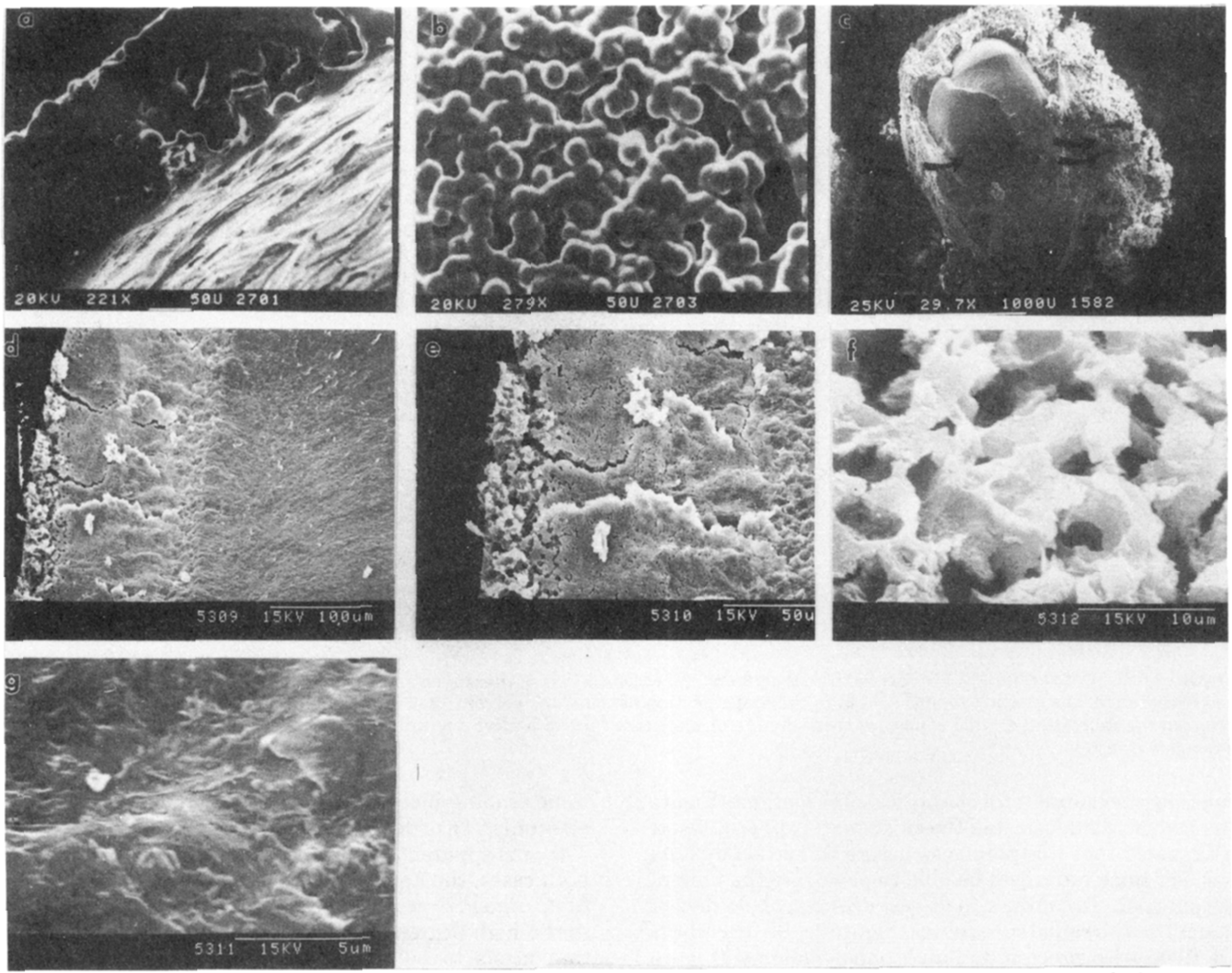


Figure 6. SEM of various P(CPM–SA) 50:50 copolymers: (a) cross-section of solvent-cast film loaded with mitomycin-C; (b) external surface of the same film; (c) cross-section of the melt-cast film 72 h after degradation; (d) cross-section of the melt-cast film 40 h after degradation, revealing three eroding zones; (e) high magnification of the eroding and intermediate zones shown in (d); (f) high magnification of the eroding zone shown in (d); (g) high magnification of the intact zone shown in (d).

spherulites (Figure 4f). The area of the eroding zone is also full of small crystals (Figure 4e) that could be broken dendrites or oligomers that are slowly degrading. The intact zone close to the eroding zone is less porous (Figure 4g), and the internal structure seems to be very dense (Figure 4h).

To summarize the results of this section, P(CPP–SA) 20:80, which is a semicrystalline polymer,[13] could precipitate into classical spherulitic structures from both solution and melt, or into dense, amorphous structures. Since this polymer displays liquid crystalline properties (Figure 2e), it well could be that the polymer in Figure 4b,c was frozen into a liquid crystalline state. Thus, the two samples that displayed erosion zones were the semicrystalline melt-cast film and the amorphous (or liquid crystalline) solvent-cast film. If we take into consideration just the morphological observation, it is strongly suggested that the erosion zone will contain crystalline, liquid crystalline, or even amorphous structures that exhibit dense structure before degradation. Once hydrolysis starts, the amorphous regions disappear first, leaving behind more crystalline structures. In the degradation of the P(CPP–SA) 20:80 copolymer, as in the case of PSA, we do not see pure surface erosion, but rather a process of degradation that proceeds with an erosion front approaching the center of the sample. We have already reported similar results when the same polymer was fabricated into microspheres using a hot-melt microencapsulation technique, which is analogous to melt-casting.[9] However, when polymers are fabricated into microspheres using the "hot-melt" technique,[9] they are usually cooled down rapidly. This rapid cooling may be the reason why no spherulitic structure was observed in our earlier study.[9]

(c) P(CPP–SA) 50:50 Copolymers. Figure 5 summarizes the morphology of different film and melt-cast devices of P(CPP–SA) 50:50. Solvent-cast devices with and without mitomycin-C displayed very dense structures before degradation. Figure 5a shows a cross-section of a film loaded with 0.2% mitomycin-C, 24 h after degradation. The eroding and intact zones are clearly seen, but it is also evident that the eroding zone displays mostly longitudinal cracks. No apparent spherulites are found, and after 48 h (Figure 5b), the cross-section revealed cracks throughout the entire device. Solvent-cast devices that were prepared without any drug revealed the same structure (Figure 5c,d). At higher magnification, the eroding zone (Figure 5d) revealed a more porous structure but still much denser than in the previous polymers that were studied. As time progressed, cracks appeared throughout the entire device with very little possibility of identifying the two zones. Melt-cast devices were more stable and the eroding zone was easy to identify throughout the entire study. Figure 5e reveals a cross-section of melt-cast film 48 h after degradation, and Figure 5f is a higher magnification of the intact zone revealing a very dense but wavy structure.

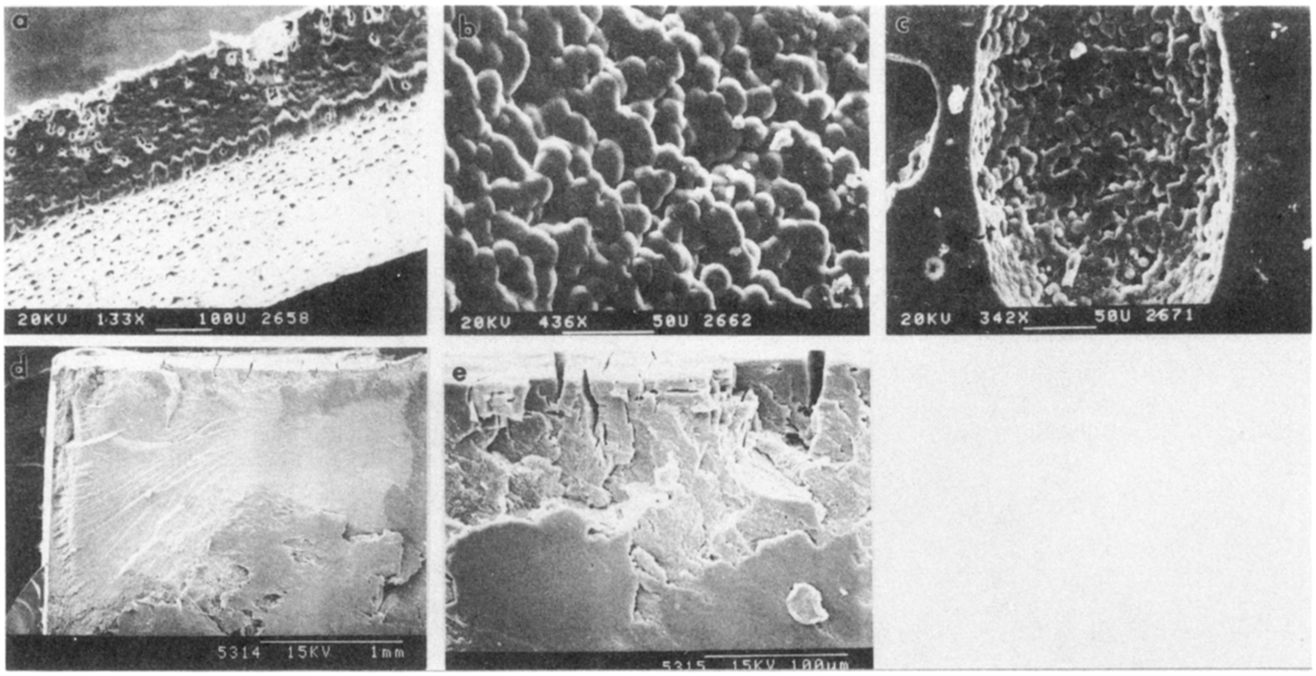


Figure 7. SEM of various P(CPH–SA) 50:50 copolymers: (a) cross section of solvent-cast film loaded with mitomycin-C; (b) external surface of the same film as in (a); (c) internal structure of the same film showing spherical shaped spherulites; (d) cross-section of the melt-cast film 48 h after degradation; (e) high magnification of the erosion zone shown in (d).

The P(CPP–SA) 50:50 polymer appeared amorphous by X-ray powder diffraction,[13] but we found that it displayed liquid crystalline properties when cast from solvent or melt. The high degree of order that the liquid crystalline state might introduce could be one explanation for having well-defined erosion zones. The erosion zones, as in most of our previous polymers were more pronounced in the melt-cast samples. We did not identify by SEM any specific morphological structure that could be directly attributed to the liquid crystalline state.

(d) P(CPM–SA) 50:50 Copolymers. Figure 6 displays the SEM study done on the P(CPM–SA) 50:50 copolymer. The cross-section of a solvent-cast film loaded with mitomycin-C is shown in Figure 6a. The structure is dense, but careful examination reveals a typical spherulitic structure which is more pronounced on the external surface of the film (Figure 6b). Cross-sections of the devices 24 and 48 h after degradation reveal a well-defined eroding zone (Figure 6c) and a dense intact zone. The eroding zone tends to disintegrate after 72 h, leaving a dense core and very loose particles that separate easily from the device. Figure 6c is an example of how the samples look if they are handled carefully. The sample in Figure 6c is a melt-cast film, but the solvent-cast films displayed the same morphological structure. Blank solvent-cast films revealed the same morphology as the drug-loaded ones.

Melt-cast films displayed very dense structures before degradation, and it was very easy to identify the eroding zones. A good example of a low magnification micrograph of a melt-cast film 72 h after degradation is shown in Figure 6c, which shows a dense intact zone and a porous eroding zone. For the sample degraded for 24 h, it was possible to identify three erosion zones after careful cross-sectioning. Low magnification of a 24-h sample is seen in Figure 6d. There is a very porous zone close to the external surface which measures approximately 20 μm and an intermediate zone which is less porous (approximately 100 μm). These two regions are seen more clearly in Figure 6e. Figure 6f is a higher magnification of the eroding zone, and Figure 6g is a higher magnification of the intact zone.

P(CPM–SA) 50:50 is one of the less studied polymers and, as such, it was interesting to visualize the development of the eroding zone. The intact zone was very dense and the eroding zone, particularly the part that was close to the surface, tended to disintegrate very easily. Compared to the other polymers where the erosion zone seemed to have more mechanical strength, the erosion zone in P(CPM–SA) 50:50 was more fragile. The three regions that were found in the sample that was eroded for 24 h strongly indicate that close to the surface the structure is more typical of small oligomers. In the intermediate zone which is porous, but to a smaller degree than the external surface, there are still traces of polymer left, while in the intact zone almost no degradation occurred. The interpretation of the three zones is supported by the FTIR and DSC examination.[15] On the basis of the results shown so far this polymer is the closest to showing pure surface erosion.

(e) P(CPH–SA) 50:50 Polymer. Solvent-cast devices of P(CPH–SA) 50:50, with or without mitomycin-C, revealed typical structures like those found in the P(CPP–SA) 20:80 polymers, which are typical of solvent-induced crystallization.[23] The cross-section of a P(CPH–SA) 50:50 film is shown in Figure 7a. Parts b and c of Figure 7 are external surfaces of one side of the film which exposes spherical structures, which are also found in craters (Figure 7c) all over the sample. These sperical structures could represent zones of phase separation instead of spherulites, since under the optical microscope we could not detect the classical Maltese cross structures that were found in P(CPP–SA) 20:80. Also, as degradation started, we could not detect a well-defined erosion zone and no classical spherulitic structures were found in the eroded samples. Melt-cast devices revealed a dense structure before degradation. At 40 h after degradation it was possible to see the eroding zone; however, it was characterized by cracks rather than the loss of structure (Figure 7d,e). After 48 and 72 h the sample was characterized by longitudinal cracks throughout the device with no well-defined eroding zone.

P(CPH–SA) 50:50 was found to display liquid crystalline properties that will be discussed further in a separate contribution.[25] The polymer is very hydrophobic due to the relatively high concentration of the aromatic monomer,

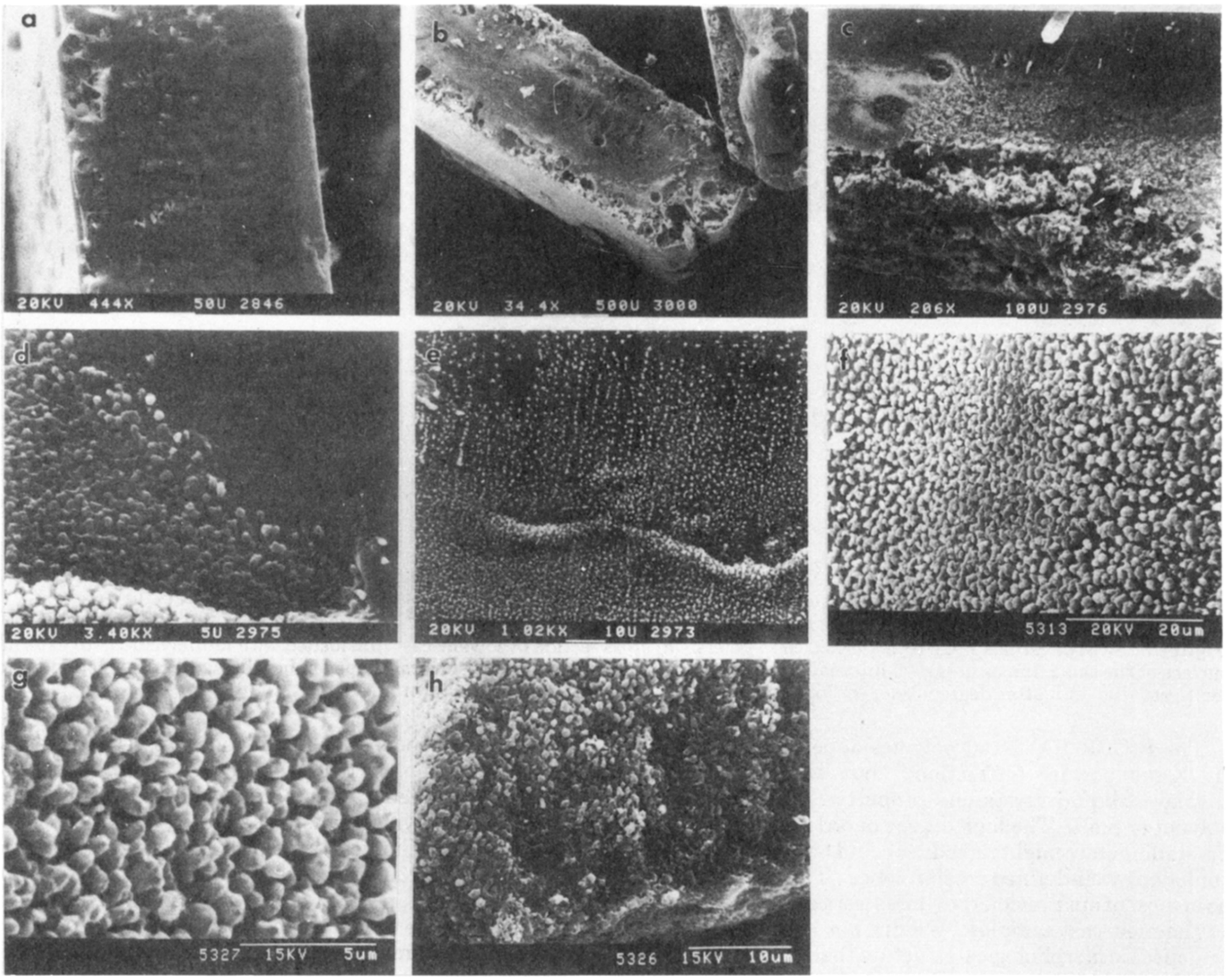


Figure 8. SEM of various PCPV polymers: (a) cross-section of the solvent-cast blank polymer before degradation; (b) cross-section of the solvent-cast film 24 h after degradation; (c) high magnification of the interfacial zone shown in (b); (d) high magnification of the eroding zone shown in (c); (e) high magnification of the erosion zone showing a high degree of order; (f) closeup of the erosion zone focused on the small globules; (g) same as (f); (h) eroding zone in the melt-cast film 24 h after degradation.

which makes it less susceptible to degradation. The monomers are also very insoluble[15] and as a result we observed heterogeneous degradation.

(f) PCPV Polymer. The last polymer that we studied was P(CPV) which is made out of one monomer that has both aliphatic and aromatic parts. This particular polymer was found to display lyotropic and thermotropic liquid crystal properties (Figure 2h). Solvent- and melt-cast devices before degradation displayed a very dense structure (Figure 8a). During erosion, a cross-section reveals a very dense internal structure and a very granular erosion zone (Figure 8b). High magnification of the erosion zone reveals a very bumpy structure (Figure 8c) that at high magnification seemed to have a spherical structure (Figure 8d–g). The structure is seen only in the erosion zone, and not in the intact zone (Figure 8d). It also has a very lined and organized structure (Figure 8e). These spheres are not spherulites of the type shown before. They have a very small size, less than 1 μm in diameter, while the spherulites that we have seen in the previous polymers were between 20 and 100 μm. We believe that these spheres could be liquid crystal regions that are exposed as the degradation proceeds.[15] The same typical structure was observed in a melt-cast film (Figure 8h). To our knowledge, this is the first time that liquid crystalline structures have been exposed during degradation of any polymer. It may well be that the amorphous material that surrounds the liquid crystalline regions erodes first, and only later do the more ordered structures degrade. The picture became clearer after studying the same samples using DSC and FTIR.[15] We find it quite exciting that through study of degradation it was possible to identify liquid crystalline states.

In conclusion, this study concentrated on the morphology of various polyanhydrides as studied by SEM. The study of bioerodible polymers is of great importance to the development of mathematical models since most current models rely mainly on release kinetics rather than on material science approaches. Many new studies dealing with polyanhydrides[9,15,24,26–28] as well as polylactides[29,30] are now emerging as more and more researchers become aware of the importance of this field. The study on polyanhydrides reveals that most of these polymers degrade by exposing the eroding zone. Existence of eroding zones depends, among other factors, on crystallinity and the degree of order that results from different fabrication techniques. It was found that crystalline polymers cast from solvent do not display eroding zones since the initial structure is very porous and water is capable of penetrating the entire device. Melt-cast systems are usually more dense, thus revealing well-defined eroding zones. The erosion zone is characterized by a very porous structure which is made of crystalline spherulites (in the case of PSA and P(CPP–SA) 20:80 polymers). Since those spherulites are made of polymer chains, the erosion zone has quite strong integrity. It was also found that the less crystalline polymers, such as P(CPP–SA) 50:50, P(CPM–

SA) 50:50, and PCPV, may solidify as liquid crystals. This may account for the dense structures obtained in the melt-cast film and for the well-defined erosion zones that appear in each sample. The PCPV sample revealed a very interesting structure that is attributed to the liquid crystalline regions. The general conclusion was that amorphous materials degrade faster than the liquid crystalline ones and the crystalline regions are the most resistant to degradation.

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