0032-3861(95)00632-X

Polymer Vol. 37 No. 17, pp. 3861–3869, 1996

0032-3861/96/$15.00+0.00

The precipitation of monomers during the erosion of a class of polyanhydrides

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(Received 12 September 1995)

The erosion mechanism of a class of bioerodible polyanhydride copolymers consisting of a fatty acid dimer (FAD) and sebacic acid was investigated *in vitro*. Special attention was given to the behaviour of the monomers that are released from the polymer matrix during the degradation process. The erosion of polymer matrix discs was followed by polarized light microscopy, differential scanning calorimetry, wide-angle X-ray spectroscopy and Fourier-transform infra-red spectroscopy. FAD, which is derived from erucic acid, was found to decrease the surface tension of the buffer significantly. Owing to its low solubility, however, as the polymer degrades, most of the FAD is deposited on the surface of the polymer matrix discs. There it forms an amorphous monomer film consisting of a mixture of FAD and FAD salts. The acid/salt ratio is pH-dependent and changes during erosion. Such films behave as diffusion barriers when these polymers are used as materials for the release of drugs from implants. Copyright © 1996 Elsevier Science Ltd.

(Keywords: polymer erosion; degradation; monomer release)

INTRODUCTION

In recent years, the interest in degradable polymers has spurred tremendous efforts in synthesizing polymers that degrade in a controlled way in a biological environment. In medicine and pharmacy, degradable polymers are used, amongst other applications, for the controlled delivery of drugs to a desired site of action[1]. Loaded with appropriate agents, degradable polymers are processed into implants and microspheres, which degrade during their application and release the drug in a controlled way. This principle has been applied for many therapies such as the systemic therapy of prostate cancer[2], the local treatment of microbial bone infections[3] and brain cancer[4].

In order for the release of drugs to be erosion-controlled, erosion has to be faster than other kinetic processes that might be involved in the release of drugs, such as drug diffusion and polymer swelling. A close correlation between erosion and drug release also ensures that the drug carrier essentially disintegrates when drug release is completed. Polyanhydrides offer these advantages. Many polyanhydrides erode faster on their surface than inside the polymer bulk[5], a phenomenon known as surface or heterogeneous erosion[6]. This mechanism is, however, subject to modifications and depends on the type of polyanhydride[7]. One of these polymers that has a more complicated erosion mechanism than pure surface erosion is poly(fatty acid dimer-*co*-sebacic acid), p(FAD-SA). The polymer is synthesized by melt polycondensation from sebacic acid and an erucic acid dimer (*Figure 1*). p(FAD-SA) has been reported to be biocompatible[8] and has already been applied for the local treatment of bone infections in the form of gentamycin-loaded implants[9]. p(FAD-SA) polymer matrix discs have been reported to accumulate degradation products on their surface, which is probably due to the poor solubility of the fatty acid dimer[10,11]. These films might substantially affect the release of drugs from these polymers by functioning as diffusion barriers. The intention of this article is to explore how these deposits develop and what their properties are. A better characterization of the polymer matrices during erosion could yield precious information for the development and optimization of drug delivery devices.

EXPERIMENTAL

Materials

Poly(fatty acid dimer-*co*-sebacic acid), p(FAD-SA), with a copolymer ratio of 30:70, 50:50 and 75:25 was manufactured by melt polycondensation[12] and obtained from Scios-Nova Pharmaceuticals, Baltimore, MD, USA. Fatty acid dimer was obtained from the same supplier. Sebacic acid was purchased from Fluka, Buchs, Switzerland.

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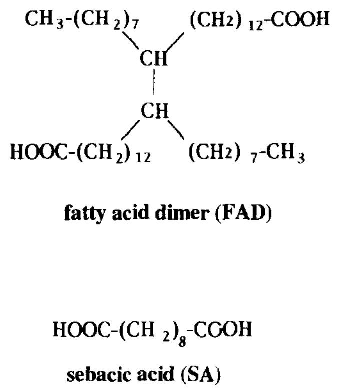

Figure 1 Monomers used for the synthesis of polyanhydrides investigated in this study

Polymer processing and erosion

Polymer matrix cylinders with a diameter of 8 mm and a height of 1 mm were manufactured using a melt casting method[13]. The discs were eroded at 37°C in 10 ml of a 0.1 M pH 7.4 phosphate buffer solution under gentle shaking (60 rpm). Eroded polymer samples were vacuum dried for 24 h in a desiccator, weighed and finally stored over phosphorus pentoxide to exclude any moisture until further investigation.

Scanning electron microscopy (SEM) investigations

The polymers were investigated before and after erosion by SEM using a model 1810T scanning electron microscope from Amray Inc., Bedford, MA, USA. Samples were prepared by breaking polymer matrix discs at −25°C using flact tweezers. The polymer pieces were fixed on the sample holders using conductive paint and gold sputtered.

Investigation of the buffer medium

The buffer was investigated for pH and surface tension whenever the buffer was changed. The surface tension was determined at room temperature using a K10 digital tensiometer from Krüss, Hamburg, Germany.

Investigation of surface layers by light microscopy

The surface deposits were investigated by polarized light microscopy for the presence of semicrystalline phases using a Diaphot-TMP Inverted Microscope from Nikon Inc., Tokyo, Japan. The deposits were transferred onto a glass slide and covered with a coverslip under gentle compression.

Differential scanning calorimetry (d.s.c.) investigations

D.s.c. spectra were taken with a PL-DSC, from Polymer Laboratories, Loughborough, UK. A 5–10 mg

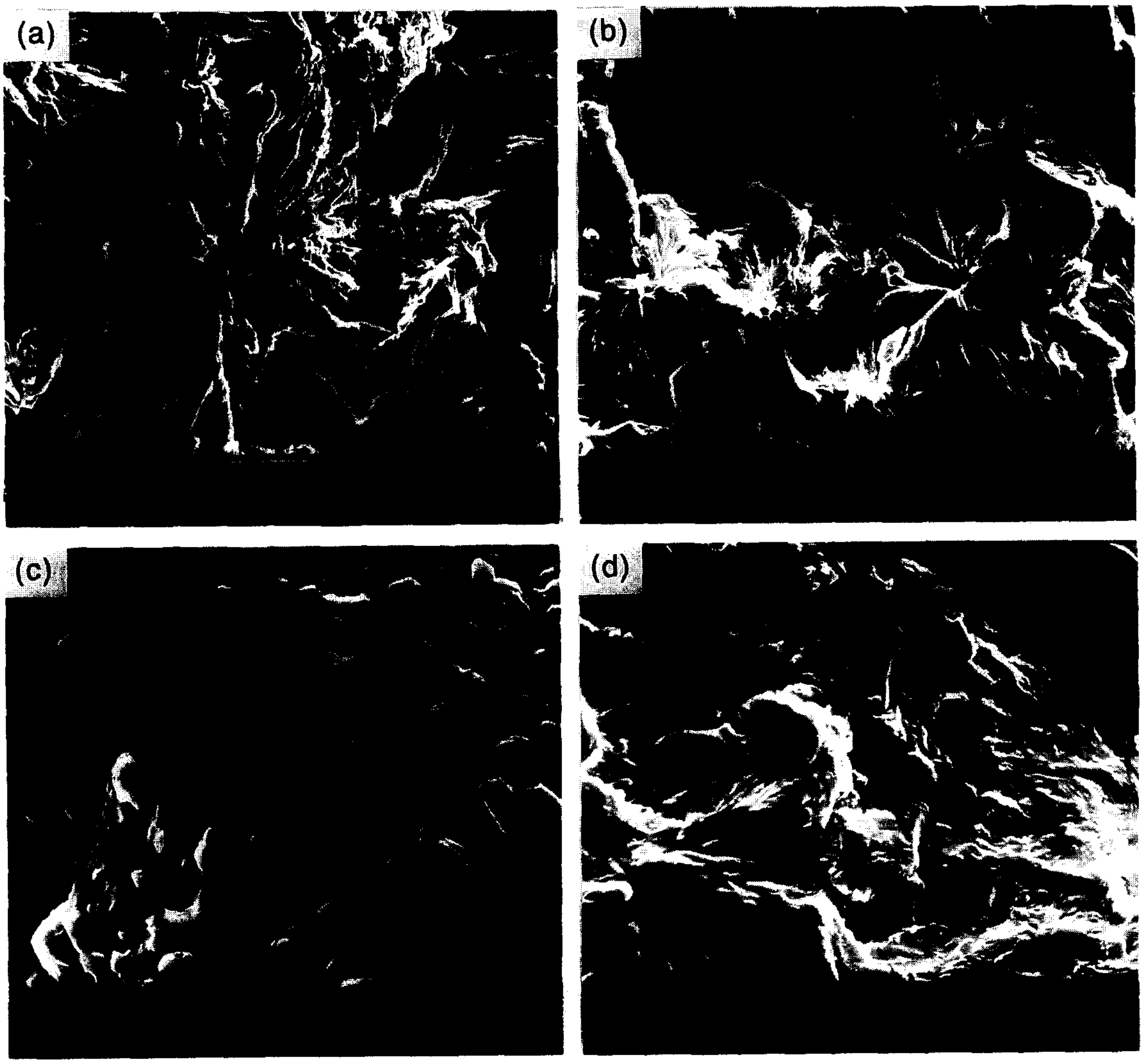

Figure 2 SEM micrographs of melt-processed polyanhydride matrix cross-sections: (a) p(FAD-SA) 30:70; (b) p(FAD-SA) 50:50; (c) p(FAD-SA) 75:25; (d) p(FAD-SA) 50:50 after 2 days erosion

sample representing a complete cross-section through a polymer matrix disc was sealed into a 40 μl aluminium pan from the same supplier. After keeping the temperature at 0°C for 5 min, spectra were recorded from 0 to 200°C at a heating rate of $10°C s^{-1}$.

Wide-angle X-ray spectroscopy investigations

For WAXS investigation a PW 1730 X-ray generator (nickel-filtered Cu Kα radiation, 40 kV, 30 mA) equipped with a PW 1050 vertical goniometer, a PW 1965/60 counter and a PW 1394 control unit, all from Phillips, Kassel, Germany, was used. Spectra were taken at room temperature with a step size of $S = 0.05°$ in $T = 4$ s time intervals.

Attenuated total reflectance Fourier-transform infra-red spectroscopy

*FT*i.r. spectra of the deposits that formed on the polymer matrix discs during erosion were recorded using the attenuated total reflection (a.t.r.) technique. The deposits were gently removed from the surface of the implants with a spatula and transferred onto a Zn-SE a.t.r. plate, from Nicolet Analytical Instruments, Madison, WI, USA. Spectra were taken using a Magna IR 550 spectrophotometer, also from Nicolet. Some 32 individual spectra were recorded from 400 to 4000 cm^{-1} with a resolution of 2 cm^{-1}. The spectra were averaged and corrected for background.

RESULTS AND DISCUSSION

Structural investigations by SEM

Prior to erosion we investigated polymer cross-sections by SEM. The cross-sections of the partially crystalline polymers contain spherulites, which are characteristic for melt-processed polymers. *Figures 2a–c* show such cross-sections for three different copolymer compositions. The ability to form these spherulites depends on the sebacic acid content. p(FAD-SA) 30 : 70 forms by far the most mature crystalline superstructures, whereas p(FAD-SA) 75 : 25 shows no signs of spherulites. The results agree with findings that the crystallinity of these polymers increases with increasing sebacic acid content[14]. *Figure 2d* shows that the spherulites of p(FAD-SA) 50 : 50 still exist inside the bulk after 2 days of erosion. The p(FAD-SA) 75 : 25 matrix discs were too soft to allow for SEM investigation after erosion.

Investigation of the degradation medium

The degradation medium was analysed for pH and surface tension. The pH profiles of the buffer medium revealed a substantial drop of pH during degradation. *Figure 3a* shows that the pH drops from 7.4 to 7.15 ± 0.03 during the first two days of p(FAD-SA) 50 : 50 degradation. It stays this low for 8 days, after which it recovers slowly and reaches its normal levels after approximately 16 days. The curve results from carboxylic acid release from the polymer matrix. The pH

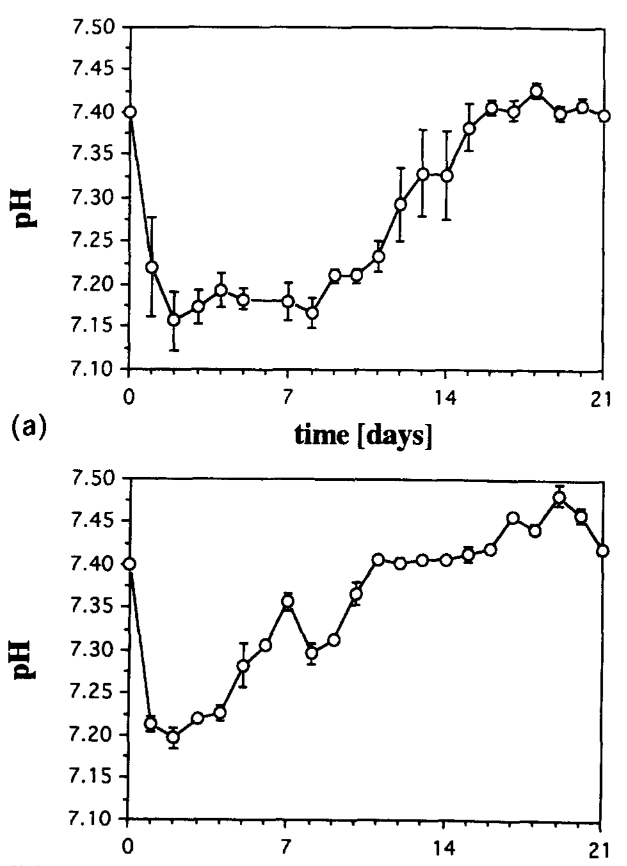

Figure 3 The pH in the buffer medium during polymer erosion: (a) p(FAD-SA) 50 : 50; (b) p(FAD-SA) 75 : 25

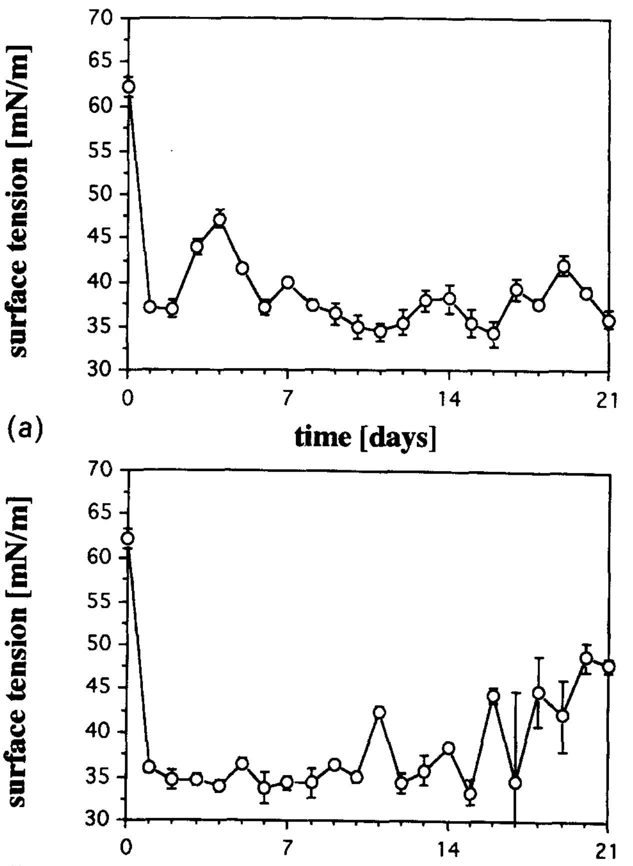

Figure 4 Surface tension of the buffer during polymer erosion: (a) p(FAD-SA) 50 : 50; (b) p(FAD-SA) 75 : 25

profile of the buffer during the erosion of p(FAD-SA) 75 : 25 is similar (*Figure 3b*). There is again a significant pH drop during the first 2 days. In contrast to p(FAD-SA) 50 : 50, however, the buffer pH increases again after 3 days. The results correlate very well with previous findings about the release of sebacic acid from the same polymers[11]. During the first week a fast release of monomer was observed from p(FAD-SA) 50 : 50, for example, followed by a release period during which sebacic acid was released at a slower rate. After 2 weeks, monomer release was completed from the matrices, which coincides with the return of the buffer pH to its nominal value.

The surface tension of the degradation medium of both copolymers is quite similar as *Figures 4a* and *4b* show. There is a substantial drop in surface tension of the buffer solution from 62 mN m^{-1} to approximately 37 mN m^{-1} during the first 2 days of p(FAD-SA) erosion. The surface tension does not recover after 2 weeks, which indicates that the drop is not caused by sebacic acid release. It can be concluded that mainly FAD is responsible for the surface tension changes during the erosion. This is not surprising because, based on its structure, FAD can be considered an amphiphilic molecule. To confirm our results, pure FAD was dispersed in 1 M sodium hydroxide solution and the surface tension was measured after separation from non-dissolved FAD. Values of 35 mN m^{-1} were measured, which compare very well with the values found for the buffer during erosion. The decrease of surface tension also indicates that FAD salts have some potential to dissolve in aqueous media, in contrast to FAD.

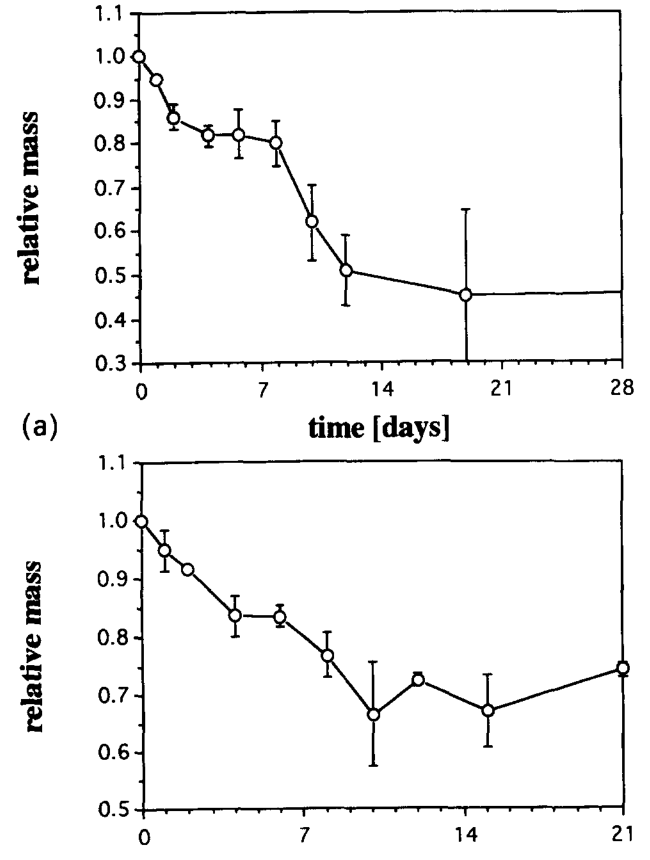

Figure 5 Mass loss from polyanhydride matrix discs during erosion: (a) p(FAD-SA) 50 : 50; (b) p(FAD-SA) 75 : 25

Loss of mass from eroding polymer matrix discs

The mass-loss profiles of p(FAD-SA) matrix discs are shown in *Figure 5*. The loss of mass from p(FAD-SA) 50 : 50 (*Figure 5a*) is complicated and proceeds in three phases. During the first phase, a fast drop in weight can be observed, which correlates well with the drop in pH. After that period, weight decreases only slightly for 5 days, after which a fast drop is again visible. After 21 days, the weight of the polymer stays at approximately 50%. The results for p(FAD-SA) 75 : 25, shown in *Figure 5b*, are similar. The only difference compared to the profile of p(FAD-SA) 50 : 50 is the duration of the phase with slow weight loss after 4 days. It now lasts only 2 days. Also p(FAD-SA) reaches a final constant weight after 21 days. From previous studies it is known that the release of sebacic acid is completed at this time[11]. Therefore, it can be concluded that FAD is released only in negligible amounts from the polymer matrices due to its low solubility.

Investigation of surface deposits by polarized light microscopy

The accumulation of FAD on the surface of the device in combination with its surface activity could possibly lead to the creation of liquid-crystalline systems during the erosion of p(FAD-SA) polymers. We therefore investigated the surface layers of eroded polyanhydrides using polarized light microscopy, which provides an easy method to check this hypothesis, as liquid-crystalline areas have a distinct appearance[15]. *Figure 6* shows a picture of a p(FAD-SA) 50 : 50 surface layer after 6 days of erosion. There is no indication that liquid-crystalline areas are present, which would show as brightly shining areas. Apart from some air inclusions, the FAD system seems isotropic. Similar results were obtained for p(FAD-SA) 75 : 25.

Investigation of matrices by d.s.c.

D.s.c. investigations were performed to elucidate further the erosion mechanism of the polymers. *Figure 7* shows the time series of p(FAD-SA) 50 : 50 erosion. Before its erosion p(FAD-SA) 50 : 50 shows only one endothermal transition at approximately 75°C. This

Figure 6 Polarized light micrograph of surface deposit on P(FAD-SA) 50 : 50 matrix discs after 5 days of erosion taken under polarized light

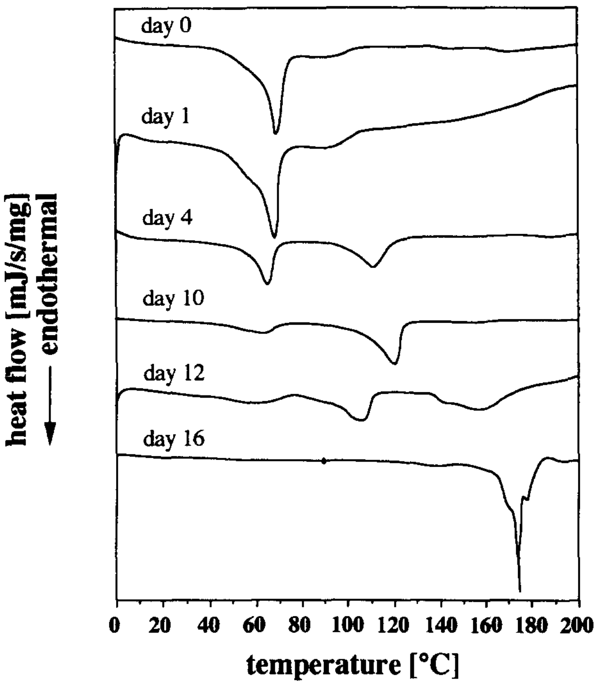

Figure 7 D.s.c. spectra of p(FAD-SA) 50:50 matrix discs during erosion

peak is due to the melting of the polymer and is in the same temperature range as for related polyanhydrides such as poly[1,3-bis(*p*-carboxyphenoxy)propane-*co*-sebacic acid][14]. The d.s.c. spectra change tremendously upon polymer degradation. The melting peak of the polymer, for example, shifts continuously to lower temperature and its melting enthalpy decreases with progressive erosion. Both are the result of polymer degradation. When the polymer crystallites are broken down, the total crystallinity decreases and the crystallites decrease in size. The first process reduces the melting enthalpy; the latter shifts the peak maximum to lower temperatures[16]. During erosion two new transitions appear in the d.s.c. spectra. After 4 days of erosion there is an additional endothermal transition in the spectrum at 110°C. After 10 days the melting enthalpy of this transition has increased and the melting temperature shifts to 120°C. Similar endotherms have been found before for p(FAD-SA) 25:75 microspheres and granules after 5 days of erosion[17,18]. After 12 days of erosion, the endotherm slowly disappears from the spectrum by again reducing its enthalpy and its peak temperature. Concomitantly a second broad and less well defined endothermal transition appears at 160°C and gains in enthalpy as well as peak temperature until the sixteenth day of erosion. Similar results were obtained for p(FAD-SA) 75:25. The peaks are less pronounced than in p(FAD-SC) 50:50 due to the lower crystallinity and the lower sebacic acid content.

To probe the nature of these peaks, d.s.c. spectra of the monomers were recorded (*Figure 8*). FAD, which is a viscous liquid, shows no transition. Sebacic acid, which is a crystalline solid, melted at 137°C. When FAD was neutralized to 50% using a 1 M NaOH solution, the dried mixture melts at 170°C, which is in the temperature range in which fatty acid salts melt[19]. These results indicate that the two unknown endothermal transitions are due to the presence of crystalline monomers in the dried eroded polymer matrix samples.

The kinetics of sebacic acid accumulation and polymer degradation can be followed by plotting the melting enthalpies against time as shown in *Figures 9a* and *9b*. The melting enthalpy of the sebacic acid crystals increases and the melting enthalpy of the polymer decreases during erosion. As the polymer crystallites consist of sebacic acid units only, the degradation of the polymer is representative for the release of free sebacic

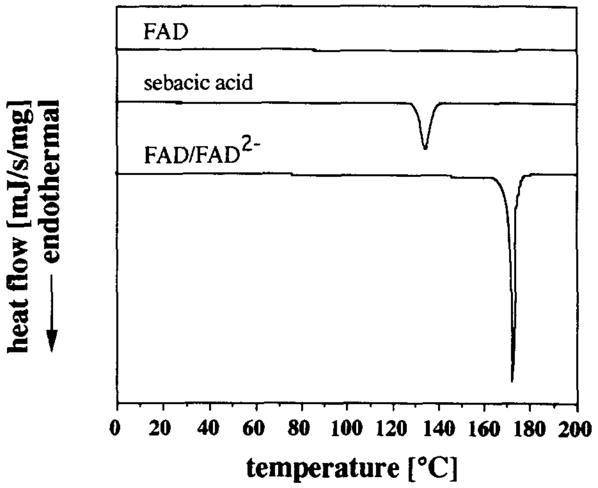

Figure 8 D.s.c. spectra of FAD, sebacic acid and a mixture of FAD with its sodium salts

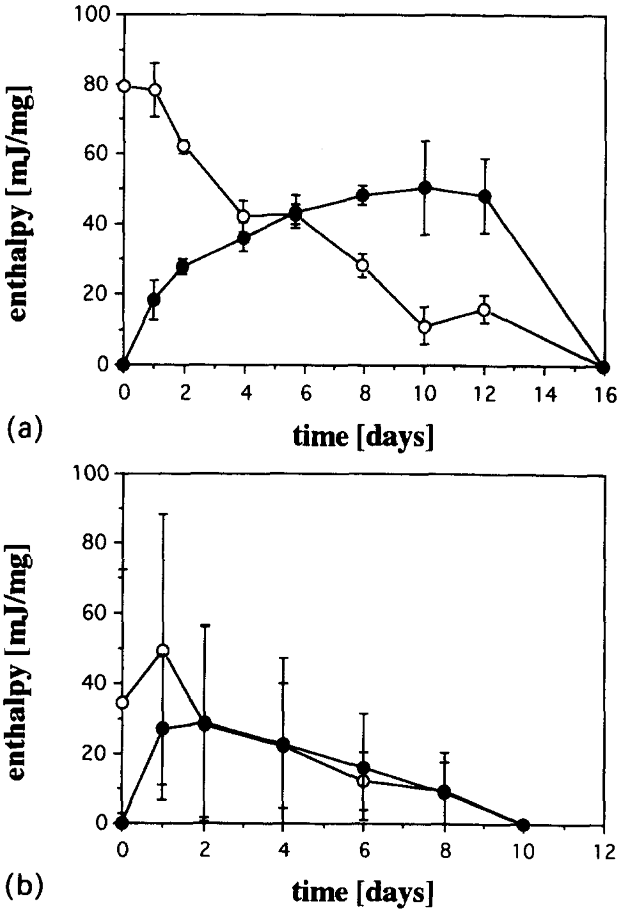

Figure 9 Melting enthalpies of polymer crystallites (○) and sebacic acid (●) determined from eroded polymer matrices: (a) p(FAD-SA) 50:50; (b) p(FAD-SA) 75:25

acid. This release leads to an increase of crystalline monomer during erosion. The disappearance of the melting endotherm after 16 days coincides with the completeness of sebacic acid release into the buffer[11] and the complete degradation of all polymer crystallites. In the case of p(FAD-SA) 75 : 25 the melting endotherm for polymer and sebacic acid are both lower, which is due to the lower sebacic acid content of this copolymer. The general shape of the curves is, however, similar to those of p(FAD-SA) 50 : 50.

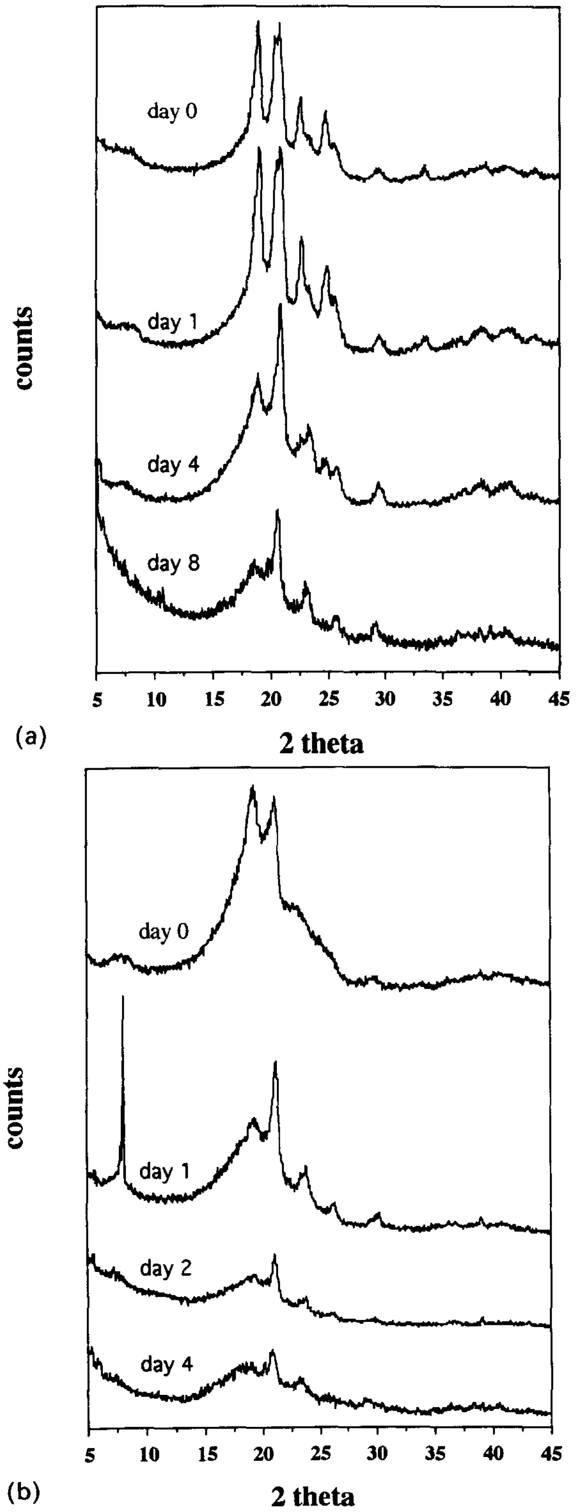

Figure 10 Wide-angle X-ray spectra of polyanhydride matrix discs during erosion: (a) p(FAD-SA) 50 : 50; (b) p(FAD-SA) 75 : 25

Investigation of eroded p(FAD-SA) matrix discs by WAXS

WAXS spectra were taken to confirm the results obtained by the d.s.c. investigations. *Figures 10a* and *10b* show the diffraction spectra of p(FAD-SA) 50 : 50 and p(FAD-SA) 75 : 25 as a function of time. The spectra prior to erosion are typical for a partially crystalline polymer, because the diffraction maxima overlap with a broad peak that stems from the amorphous polymer parts. The changes in the spectra reflect the changes of the polymer matrices during erosion. In the diffraction spectra of p(FAD-SA) 50 : 50, for example, all peaks become smaller with time. The peak pattern, however, is subject to individual changes for each peak. Of the two largest peaks at $2\theta = 19°$ and 20.75°, for example, which originally have the same height, the peak at $2\theta = 20.75°$ becomes relatively larger during erosion. The peaks at $2\theta = 22.7°$ and 24.9°, which have shoulders at $2\theta = 23.4°$ and 25.5°, undergo similar changes. During erosion, the shoulders become larger than the corresponding peaks. In the p(FAD-SA) 75 : 25 spectra these changes are even more pronounced. The peak at $2\theta = 20.75°$ increases even more relative to the other peaks compared to p(FAD-SA) 50 : 50. There is one additional peak visible at $2\theta = 8°$ after 1 day of erosion.

The WAXS spectra of the monomers, which are shown in *Figure 11*, help again to explain the behaviour of the polymers. The spectrum of a 1 : 1 mixture of FAD with FAD sodium salt shows only a broad diffraction signal. Sebacic acid, in constrast, shows several sharply defined diffraction maxima. The peak pattern agrees very well with the pattern of degraded polymer, in which all the peaks of the sebacic acid spectrum between $2\theta = 15°$ and 35° can be found. The diffraction peak at $2\theta = 8°$ in the diffraction spectrum of p(FAD-SA) 75 : 25 is most likely due to sebacic acid crystallites and has been found in a previous study for another batch of sebacic acid[20]. In summary, the findings confirm the d.s.c. results, which show that the monomers crystallize inside the polymer matrices either during erosion or during the drying process.

*Investigation of monomer precipitates by a.t.r.-*FT.*i.r.*

A.t.r.-*FT*.i.r. allows assessment of i.r. spectra of material surfaces and was used to investigate the

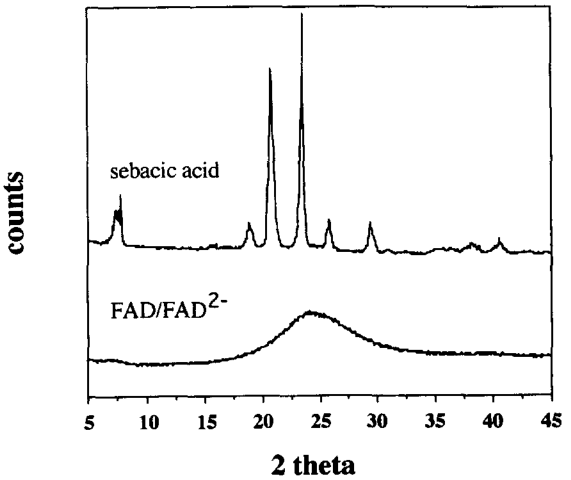

Figure 11 Wide-angle X-ray spectra of sebacic acid and a mixture of FAD with its sodium salts

monomer deposits on the surface of the eroding polyanhydride discs. *Figure 12* shows the *FT*.i.r. spectra that were recorded from eroded p(FAD-SA) 50 : 50. Two major changes can be observed. First, the two bands at 1710 and 1550 cm^{-1}, which represent the carbonyl stretching vibrations of the carboxylic acid group and the carboxylate group, change continuously. Secondly, the broad band between 3500 and 3000 cm^{-1}, which is due to the –OH stretching vibration of the carboxylic acid group[21] and is located underneath the sharp absorption bands of the C–H stretching vibrations, changes. At early erosion times, this band is clearly visible, but it disappears during the progressive erosion of the polymer. It could be suspected that these changes were due to the neutralization of the carboxylic acid groups of FAD. To support this hypothesis, a.t.r.-*FT*.i.r. spectra were taken of FAD and its sodium salt (*Figure 13*). The FAD spectrum indicates that only carboxylic acid groups are present in the system, which is visible from the missing $-CO_2-$ stretching vibration and the presence of the –OH stretching vibration. The partially neutralized fatty acid dimer, in contrast, shows a reduced –OH stretching vibration band, a reduced carbonyl stretching band and an additional band for the carboxylate group present in the system.

To determine the FAD/FAD^{2-} ratio in the surface layer, the *FT*i.r. spectra were evaluated quantitatively. For that purpose the spectra were integrated. As shown in *Figure 14* two areas were determined: the area *A* under the –CH stretching vibration peaks and the area *B* under the broad peak of the –OH stretching vibrations. When the areas *A* and *B* are expressed as double integrals of the *FT*i.r. curve *F*, the portion of carboxylic acid groups that are protonated was calculated from the following equation:

$$x = 100 \left. \frac{\iint_B F\,\mathrm{d}B}{\iint_A F\,\mathrm{d}A + \iint_B F\,\mathrm{d}B} \right|_{\mathrm{FAD}} \times \left. \frac{\iint_A F\,\mathrm{d}A + \iint_B F\,\mathrm{d}B}{\iint_B F\,\mathrm{d}B} \right|_{\mathrm{sample}}$$

Figure 15 shows the result of these calculations for p(FAD-SA) 50 : 50. Early during erosion, most of the carboxylic acid groups of FAD in the surface layer are protonated. This changes, however, during erosion. The degree of FAD protonation seems to depend on two factors: the presence of sebacic acid and buffer pH. During the first 2 weeks the presence of sebacic acid decreases the pH of the systems relative to the buffer pH. Therefore, most of the FAD will be protonated during this time. After sebacic acid has been released, the effect of the buffer takes over and leads to the partial neutralization of FAD.

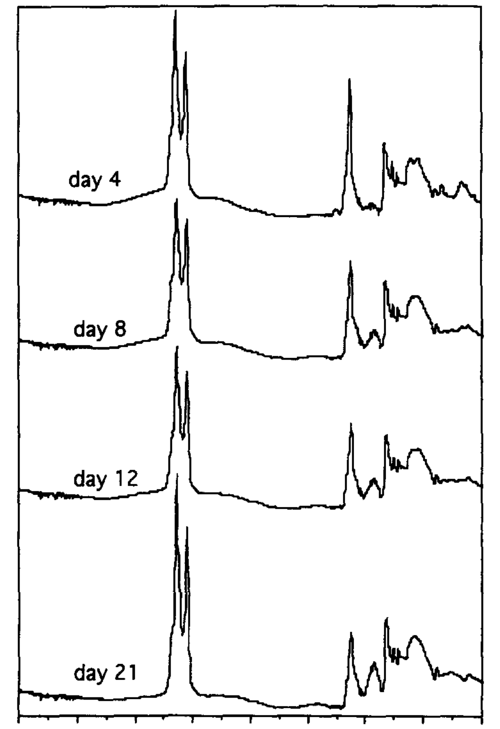

Figure 12 *FT*i.r. spectra of p(FAD-SA) 50 : 50 matrix discs during erosion

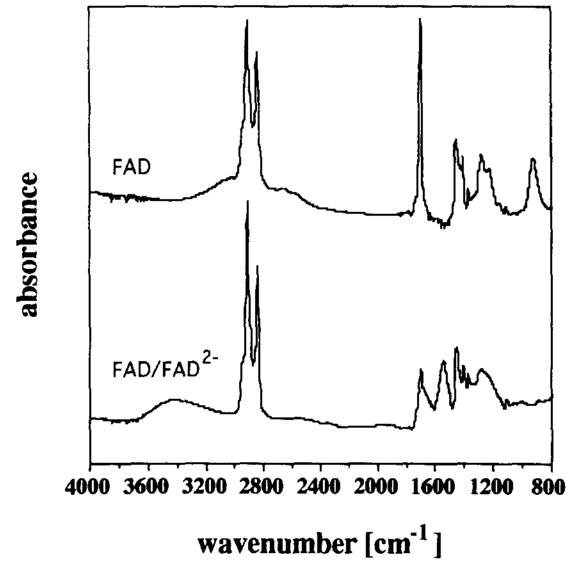

Figure 13 *FT*i.r. spectra of FAD, sebacic acid and a mixture of FAD with its sodium salts

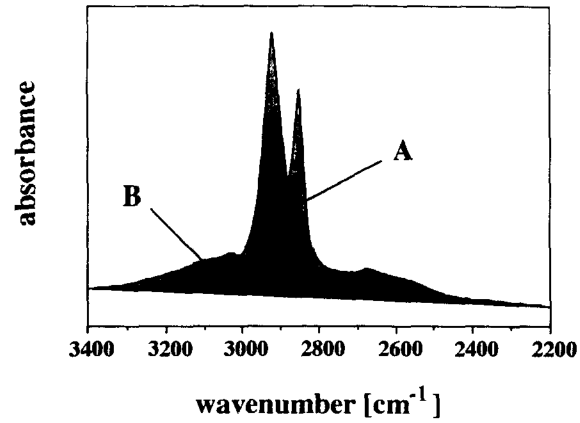

Figure 14 Schematic illustration of *FT*i.r. spectral evaluation

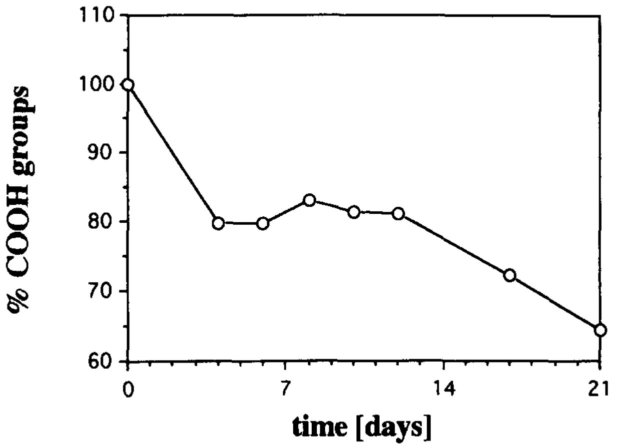

Figure 15 Percentage share of protonated carboxylic acid groups in the FAD film deposited on the surface of eroding p(FAD-SA) 50 : 50

Summary of the erosion mechanisms

The erosion of p(FAD-SA) polymers follows a clear mechanism. First, water intrudes into the polymer matrix, leading to the degradation of polymer chains. Many physicochemical parameters that are affected by erosion have a lag period. An example is the mass loss shown in *Figure 5*, which is slow during the first day and accelerates during the following days. At the beginning of the erosion process, the polymer chains on the surface of the polymer matrix have first to be degraded to such an extent that monomers, or at least soluble oligomers, are formed that can be released. This also explains the time lag during the release of sebacic acid from the devices observed in previous studies[10,11]. Another factor that is responsible for the observed lag periods is the intrusion of water into the polymer. Even for a surface eroding polymer, the zone in which degradation occurs is not infinitely thin. At the beginning of the erosion experiment this zone is not fully developed, so that the polymer volume in which erosion takes place has first to be established before constantly advancing erosion fronts can develop.

The two monomers play a major role during the erosion process. FAD is practically insoluble in water. FAD created by the degradation process does, therefore, dissolve in the buffer in trace amounts and deposits on the surface of the polymer matrix. Concomitantly FAD salts lower the surface tension of the buffer, which indicates that these substances are surface-active. This might explain the observed stabilization of enzymes after encapsulation into p(FAD-SA) microspheres[22]. At the end of the erosion process the matrices consist of FAD monomer only. This can be seen from the mass-loss profiles in *Figures 5a* and *5b*, which indicate that the final polymer matrix disc weight matches the weight of FAD due to the copolymer composition. The surface deposits are a diffusion barrier, which can easily be seen by comparing the release of low-molecular-weight compounds from different polyanhydride copolymers. For example, the release of indomethacin, a low-molecular-weight drug, from poly[1,3-bis(*p*-carboxyphenoxy)-propane-*co*-sebacic acid] 50 : 50, on which no dense diffusion barrier develops, is twice as fast as from p(FAD-SA) 50 : 50[23]. The FAD layer seems also to affect the release of sebacic acid from the polymer, which proceeds in two phases. At the beginning of the erosion experiment, the diffusion barrier is not fully developed and sebacic acid can leave the eroding polymer unhindered. This can be seen from the drop in the pH profile to low values for p(FAD-SA) 50 : 50 copolymer as shown in *Figure 3a*. The pH increases after a couple of days, because sebacic acid is hindered from diffusing fast enough from the surface of the device. Increasing the FAD content of the polymer to 75% causes this effect to set in earlier (*Figure 3b*).

The surface layer is composed mainly of FAD and temporarily also of sebacic acid. The pH is controlled by sebacic acid due to its higher solubility compared to FAD. This is illustrated by the d.s.c. and *FT*i.r. spectra of the surface layer. The sebacic acid melting endotherms of the d.s.c. spectra shown in *Figure 9a* indicate that substantial amounts of sebacic acid must be present inside eroding p(FAD-SA) 50 : 50 discs for at least 14 days. During this period the a.t.r.-*FT*i.r. spectra of *Figure 12* indicate that the functional groups of FAD consist of 80% carboxylic acid groups. After 14 days most of the sebacic acid has left the matrices, which is indicated by the disappearance of the sebacic acid peak in the d.s.c. spectra. Concomitantly the pH increases, leading to the formation of FAD salts that can be detected by *FT*i.r. as shown in *Figure 12*. The FAD salts also become detectable by d.s.c., as the thermograms of *Figure 7* show.

The partially crystalline polymers also change their crystallinity during erosion. Early during erosion there is only a slight increase in crystallinity detectable due to the preferential erosion of amorphous polymer regions, which is, however, substantially less pronounced than for poly(sebacic acid) for example[20]. As erosion proceeds, the crystallinity decreases, which is visible from the decreasing melting enthalpy (*Figure 9*) and the decreasing diffraction maxima in the WAXS spectra (*Figure 10*).

CONCLUSIONS

The erosion mechanism of poly(fatty acid dimer-*co*-sebacic acid) copolymers follows clearly defined rules, which makes it an ideal polymer material for drug delivery applications. The low solubility of the fatty acid dimer leads to the development of surface precipitates during *in vitro* erosion. These layers might affect the diffusion-controlled release of low-molecular-weight substances such as monomers or drugs and might also offer the opportunity to expand the drug release periods from polyanhydrides. FAD monomer was found to be surface-active, which might stabilize or destabilize macromolecular substances that are intended for release out of the polymers such as proteins and peptides.

ACKNOWLEDGEMENTS

Thanks are due to the German Research Foundation (DFG) and the National Institutes of Health who sponsored this project with Grants GO 565/3-1 and CA 52857.

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