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Polyanhydride degradation and erosion

A. Göpferich*, J. Tessmar

Faculty of Pharmacy and Chemistry, Pharmaceutical Technology Unit, University of Regensburg, Universitätsstrasse 31, D-93053 Regensburg, Germany

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Abstract

It was the intention of this paper to give a survey on the degradation and erosion of polyanhydrides. Due to the multitude of polymers that have been synthesized in this class of material in recent years, it was not possible to discuss all polyanhydrides that have gained in significance based on their application. It was rather the intention to provide a broad picture on polyanhydride degradation and erosion based on the knowledge that we have from those polymers that have been intensively investigated. To reach this goal this review contains several sections. First, the foundation for an understanding of the nomenclature are laid by defining degradation and erosion which was deemed necessary because many different definitions exist in the current literature. Next, the properties of major classes of anhydrides are reviewed and the impact of geometry on degradation and erosion is discussed. A complicated issue is the control of drug release from degradable polymers. Therefore, the aspect of erosion-controlled release and drug stability inside polyanhydrides are discussed. Towards the end of the paper models are briefly reviewed that describe the erosion of polyanhydrides. Empirical models as well as Monte-Carlo-based approaches are described. Finally it is outlined how theoretical models can help to answer the question why polyanhydrides are surface eroding. A look at the microstructure and the results from these models lead to the conclusion that polyanhydrides are surface eroding due to their fast degradation. However they switch to bulk erosion once the device dimensions drop below a critical limit.

Keywords: Bioerosion; Polyanhydride; Polymer degradation; Polymer erosion; Modeling

Contents

*Corresponding author. Tel.: +49-941-943-4843; fax: +49-941-943-4807.
E-mail address: achim.goepferich@chemie.uni-regensburg.de (A. Göpferich).

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1. Introduction

Degradable polymers have attracted significant attention for use in numerous medical and biomedical applications that require the presence of a material only for a limited period of time [1]. Especially after implantation into the body, it is highly desirable that the material 'disappears' to obviate the need for any post-application removal. Many current concepts in the pharmaceutical and biotechnological field depend significantly on this strategy [2,3]. A good example is parenteral drug delivery, by which a dose of drug is typically intended to be released over an extended period of time [4]. Biodegradable polymers can help significantly to overcome numerous problems inherent to this concept. The polymers can stabilize the drug reservoir from premature inactivation; concomitantly, the polymer can control the release of drug out of the reservoir and finally the degradability of the material helps to overcome the need for any post-application removal.

Based on the outlined advantage of degradable polymers there have been numerous polymers explored for their suitability to degrade in a biological environment. Since the 1970s a plethora of materials has been synthesized. Moreover, strategies are under way to provide polymers on the basis of combinatorial approaches [5]. Surprisingly, the class of hydrophobic biodegradable polymers has been dominated by poly(α-hydroxy acids) such as poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA) for more than 30 years. These materials are available in different compositions that allow to control degradation and, most importantly, they are approved as biocompatible which is a tremendous advantage over new degradable polymers that have to undergo time- and cost-intensive biocompatibility testing. There have been only a few cases in recent years, in which new degradable polymers were custom made for application in humans: polyanhydrides are one of these (Fig. 1).

Polyanhydrides were made with the intention to have a material at hand that fits to a paradigm as old as biodegradable materials themselves: the material should degrade within the time frame of their application. For degradables used in controlled release applications this means that the completeness of polymer erosion coincides with the end of drug release. This is hard to achieve with polymers that degrade over weeks such as PLA and PLGA when the drug is intended to be released for only a few days. Therefore in the early 1980s polyanhydrides were discovered for drug delivery applications [6]. The advantage of polyanhydrides is that they are made of the most reactive functional group available for degradation on the base of passive hydrolysis. How this translates to an enhanced degradation and in a further step to an accelerated drug release was subject to a careful characterization of polyanhydrides in the following decades.

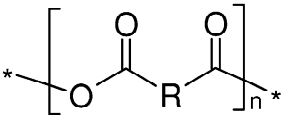


Fig. 1. General polyanhydride structure.

It is the intention of this review to shed some light on polyanhydride degradation and erosion in vitro to elucidate the consequences that result from their degradation and erosion behavior. First, both processes will be defined and methods will be presented by which we can investigate them. The erosion mechanism of some classes of polyanhydrides will be reviewed and finally theoretical models will be discussed that describe polyanhydride erosion.

2. Polymer degradation and erosion

Degradation in this review designates the process of polymer chain cleavage, a definition that was also adapted for polyanhydrides [7]. The prefix 'bio', thereby, usually indicates that in a biological system there are other mechanisms besides passive hydrolysis that contribute to the kinetics of the process. Such processes that are usually mediated by an enzymatic mechanism have been shown to affect the hydrolysis of poly(α-hydroxy acids) in vivo [8]. Whether they are of any enhancing effect for fast-degrading polymers such as polyanhydrides remains, however, questionable [9]. As polyanhydrides belong to the class of water-insoluble hydrophobic polymers, it is mandatory for these materials to degrade prior to erosion. *Erosion* in this review designates the sum of all processes that can lead to the loss of mass from a polyanhydride matrix irrespective of its geometry, such as slab, cylinder or microsphere. It is obvious that polyanhydrides need to undergo degradation prior to erosion. However, it must always be borne in mind that processes other than degradation can contribute to erosion as well. It has, for example, been shown for some polyanhydrides that cracks form early during degradation on the surface of polymers matrix discs [10], which might lead to the loss of pieces of non-degraded material due to mechanical instabilities. Furthermore some polyanhydride matrices turn into fragile and brittle materials so that parts of the matrix may wear off under the weak mechanical forces that are applied during in vitro erosion experiments.

Those who are active in the field of degradable polymers are familiar with the question for the optimal conditions that should be used to investigate polymer erosion in vitro. What we usually want to achieve with our experiments is to find at least a crude forecast of the in vivo degradation behavior. That this is not a trivial task is documented by numerous publications on this issue in the current literature. Polyanhydrides such as poly[1,3-bis(*p*-carboxyphenoxy) propane-*co*-sebacic acid] (p(CPP-SA)), for example, were found to erode substantially slower in vitro than in vivo [11]. Our efforts in vitro should, therefore, focus primarily on standardizing the experimental conditions rather than trying (usually in vain) to mimic in vivo conditions. The latter is usually only successful for a few materials and fails whenever we try to expand on a larger number of polymers. For purposes of comparing results we usually perform erosion experiments in buffer solutions. Many experiments are carried out in phosphate buffer solution of pH 7.4 at 37 °C. When erosion data are discussed below these will be the experimental conditions if not stated otherwise.

2.1. Surface erosion versus bulk erosion

The fast degradation of polyanhydrides based on their chemical structure has tremendous consequences for their erosion properties. In contrast to PLA and PLGA, polyanhydrides are undergoing *surface erosion* which is also termed *heterogeneous erosion*. The mechanism is schematically illustrated in Fig. 2. Typically, degradation and erosion are limited to the surface of a polymer only (Fig. 2a). In an ideal scenario, the mass loss kinetics are, therefore, linear. When degradation is the only mechanism that controls the erosion process the molecular weight of the polymer should be constant. *Bulk erosion* also termed *homogeneous erosion*, in contrast, reflects a different mechanism. Bulk eroding polymers degrade all over their cross-section and have erosion kinetics that are non-linear and are usually characterized by a discontinuity (Fig. 2b) [12].

Polyanhydrides usually undergo a linear mass loss during erosion, causing us to classify them as surface eroding. However, degradation is not strictly limited only to the surface of a polyanhydride matrix. This is illustrated by numerous experiments in which the molecular weight was found to drop exponentially [13,14].

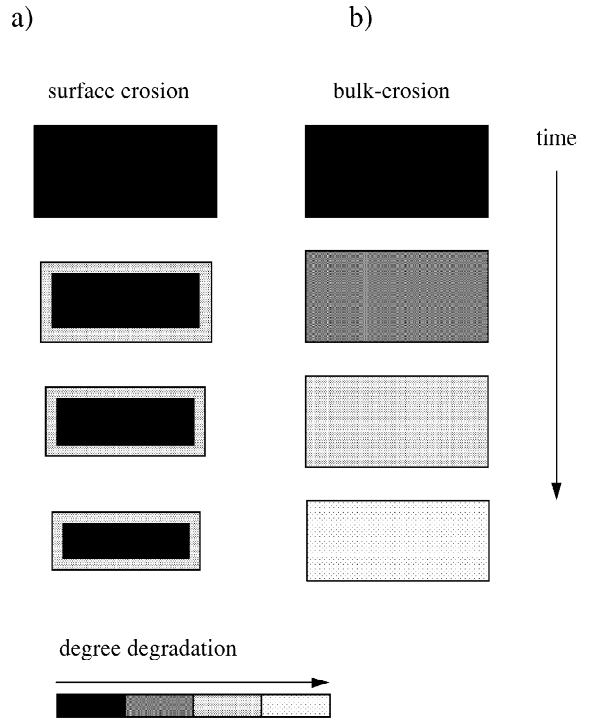


Fig. 2. Schematic illustration of surface erosion and bulk erosion.

2.2. Physicochemical characterization of polyanhydride degradation and erosion

The degradation of polymers in general, as well as the degradation of polyanhydrides, is not easy to investigate. What we are usually interested in is the degradation kinetics of individual bonds inside a polymer chain. As polyanhydrides are, however, essentially insoluble in water we, therefore, need organic solvents that contain at least traces of water to achieve this goal [15]. Although it may be possible to compare different polymers for their degradation rate under these well-defined conditions, it may not allow to predict the overall degradation of the chains once they are embedded in a polymer matrix. Therefore, polyanhydride degradation and erosion have been investigated by incubation of matrices in buffer solutions. In rare cases, water vapor also has been used to study the degradation of polymer particles [16]. The price of studying degradation in polymer bulk is that we cannot assume that at every point of the matrix identical conditions prevail. That this may have a tremendous impact was shown by investigating different zones of eroding polyanhydride matrices. Major differences existed between polymer areas on the surface and in the matrix center [7,17].

The methods that were used to investigate degradation of polyanhydride matrices are the classical ones used to determine polymer molecular weight. For reasons of simplicity and of automatization, gel permeation chromatography has been used extensively [10,13]. For some polyanhydrides such as p(CPP-SA), data on intrinsic viscosities may even be found [18], so that a universal calibration [19] may be possible. Other methods that have been used to investigate polyanhydride degradation are: infrared spectroscopy by which the anhydride and carbonyl signals of carboxylic acids can be monitored [20], ^{1}H NMR [21], ^{13}C magnetic angle spinning solid-state NMR [16] and differential scanning calorimetry (DSC) [22].

While the degradation of polyanhydrides can be unequivocally described on the basis of decreasing molecular weight of the polymer, erosion cannot be assessed based on a single parameter. By far the most important measure for polymer erosion is the mass loss of a polymer device [10]. Based on the definition of surface erosion one would expect, for a matrix with predominantly slab geometry, a linear mass loss profile. It is, however, important to realize that mass loss does not reveal anything of the mechanism of erosion. Techniques using spatial resolution, that allow further investigation into erosion mechanisms are: light microscopy techniques [17], scanning electron microscopy (SEM) [10], scanning confocal microscopy [10], atomic force microscopy [23,24] and surface plasmon resonance [24,25]. To investigate the composition of the polymer bulk under erosion, a number of physicochemical techniques have been applied, such as differential scanning calorimetry [10,22,26], wide-angle X-ray diffraction [10,26], nuclear magnetic resonance imaging (MRI) [27], electron paramagnetic resonance (EPR) [28], following the release of monomers or model compounds [29,30] and others.

3. Parameters affecting polyanhydride degradation and erosion

3.1. The impact of polymer composition on degradation and erosion

It is almost impossible to review the erosion behavior of all classes of polyanhydrides. In recent years, especially, the number of polyanhydrides has increased tremendously. While during the early years of their development they were mainly manufactured from linear diacids [31–33], they are now increasingly made of materials that deviate from that scheme. Examples are poly(anhydrides-co-imides) that hold promise for the development of vaccines [34–37], polyanhydride prodrugs [38–40], anhydrides that carry other degradable bonds in their backbone [41], block copolymers with poly(ethylene glycol) [42] and many others. Rather than reviewing all these materials the focus will be on major classes of materials for which a decent amount of degradation and erosion data exists and from which general rules of the two processes may be deducted. Fig. 3 lists some of the monomers that have been used for the manufacture of polyanhydrides. As the IUPAC names of monomers and polymers would sometimes be rather lengthy the abbreviations given in parentheses in Fig. 3 will be used to abbreviate monomer and polymer names. A copolymer made of 1,3-bis-(*p*-carboxyphenoxy)propane (CPP) and sebacic acid (SA), for example, will be abbreviated p(CPP-SA). The monomer ratio after the abbreviation of copolymers will indicate the percent (w/w) share of the monomers.

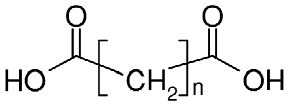
3.1.1. Aliphatic polyanhydrides

Aliphatic polyanhydrides were among the first materials to be investigated for the purpose of drug delivery. Homopolymers are often problematic materials as they are usually highly crystalline with unfavorable mechanical properties. p(SA) for example has a crystallinity of 66% [26]. Its microstructure is composed of crystalline and amorphous domains which is of utmost importance for the erosion mechanism. Erosion preferentially affects the amorphous parts of p(SA), which has been proven by measuring melting endotherms by DSC during erosion [10]. The crystalline polymer areas are embedded in spherulites, the structure of which becomes more apparent in AFM images after the surface has undergone erosion [23]. AFM images taken in situ provided additional evidence that amorphous polymer areas erode faster than crystalline ones. The erosion profile of p(SA) in phosphate buffer, pH 7.4, is linear, as expected from a surface eroding polymer (Fig. 4) [10].

Some authors have described the properties of other aliphatic polyanhydrides, such as those made of adipic, pimelic, suberic, azelaic, dodecanedioic and dodecanedicarboxylic acid [9]. All of these polymers were rigid, crystalline materials with melting points increasing with the monomer chain length. When rectangular matrices ($3 \times 7 \times 11$ mm) were eroded in vitro, polyanhydrides made of long chain monomers (7–10 methylene units) lost 20% while those made of short chain monomers (4–6 methylene units) lost 70% of mass during the first 48 h. The example illustrates that aliphatic polyanhydrides usually erode fast and are, therefore, not unequivocally useful for biomedical and pharmaceutical applications.

Some aliphatic polyanhydrides serve special applications such as p(FA-SA), i.e., copolymers derived from sebacic and fumaric acid (FA). p(FA-SA) polymers, for example, were proposed for the development of bioadhesive materials that interact with mucosal tissues [43]. When microspheres made of p(FA-SA) 20:80, p(FA-SA) 50:50 and p(FA-SA) 70:30 were degraded in vitro at pH 4.2, 7.4 and 8.8, the degradation rate at pH 8.8 was significantly higher than at neutral or acidic pH [20]. However, despite rapid degradation, long-lasting anhydride oligomers seemed to persist for extended periods of time. When p(FA-SA) 20:80 microspheres were loaded with 2% bovine serum albumin, the degradation of the polymer was accelerated [22], indicating that additives such as drugs can have a considerable effect on degradation and erosion.

In some cases, aliphatic polyanhydrides have been used for blending other polymers. As a fast degrading component, they are degradation accelerators for polymers by lowering pH during erosion. Blending poly(trimethylene carbonate) (PTMC) with poly-



n = 4 : adipic acid (AA)

n = 5 : pimelic acid (PA)

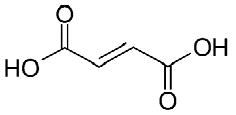
n = 6 : suberic acid (SU)

n = 7 : azelaic acid (AZ)

n = 8 : sebacic acid (SA)

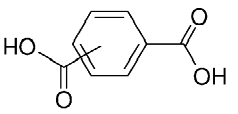
n = 10 : dodecanedioic acid (DD)

n = 12 : dodecanedicarboxylic acid (DX)



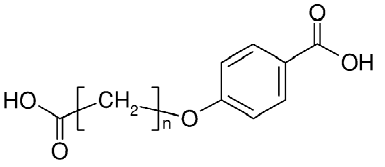
fumaric acid (FA)

aromatic polyanhydride monomers



meta : isophtalic acid

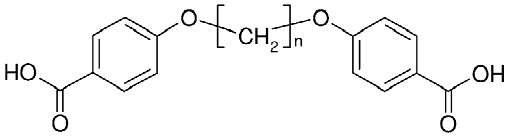
para : terephtalic acid



n = 1 : p-carboxyphenoxy acetic acid (CPA)

n = 4 : 5-(p-carboxyphenoxy) valeric acid (CPV)

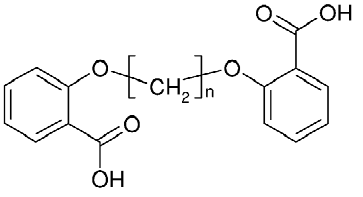
n = 7 : 8-(p-carboxyphenoxy) octanoic acid (CPO)



n = 1 : bis(p-carboxyphenoxy)methane (CPM)

n = 3 : 1,3-bis(p-carboxyphenoxy)propane (CPP)

n = 6 : 1,6-bis(p-carboxyphenoxy)hexane (CPH)



n = 6 : 1,6-bis(o-carboxyphenoxy)hexane (o-CPH)

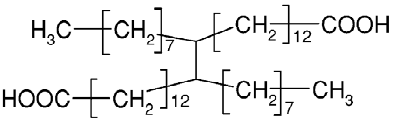
Fig. 3. Monomers that have been used for the synthesis of polyanhydrides.

(adipic anhydride) p(AA), for example, allowed control of the erosion of the blend. While matrices containing 20% p(AA) lost only approximately 18% weight over 25 days in PBS at pH 7.4, the mass of matrices containing 80% p(AA) dropped to approximately 25% of the original value [44]. While the enhanced mass loss may be mainly attributed to the polyanhydride component, an accelerated degradation of PTMC was caused by presence of the anhydride.

3.1.2. Aromatic polyanhydrides

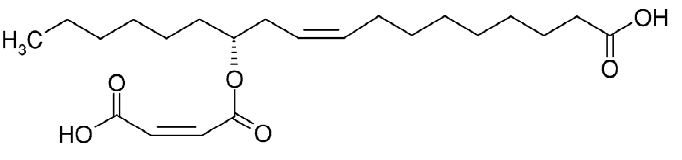
The development of aromatic polyanhydrides was slow over the last decades. One of the reasons is certainly their low degradation rates and their hydrophobic nature, which are disadvantageous for parenteral applications. p(CPP), for example, is an extremely slow eroding material [45] that has a very high melting point of approximately 240 °C [33], so that it is not readily processable. Furthermore, its solubility in organic solvents is poor.

Fatty acid dimer

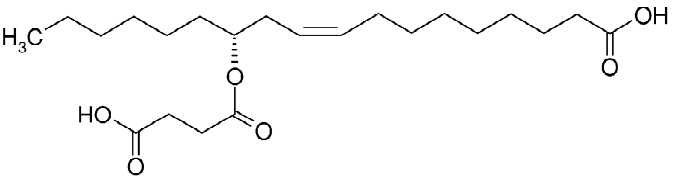


erucic acid dimer (FAD)

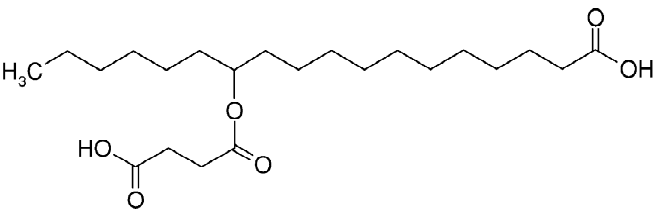
Ricinoleic acid-based monomers



ricinoleic acid maleate (RAM)



ricinoleic acid succinate (RAS)



12-hydroxystearic acid succinate (HSAS)

Fig. 3. (*continued*)

Materials that seem to overcome some of these drawbacks are aromatic, ortho-substituted polyanhydrides such as poly[1,6-bis(*o*-carboxyphenoxy)hexane] p(*o*-CPH) [46]. Compression-molded 13-mm diameter discs possessed elastic properties and degraded according to first-order kinetics. They eroded in a linear way over a time period of approximately 17 days, during which p(CPP) would erode only to less than 5% [45].

3.1.3. Polyanhydride copolymers derived from aromatic and aliphatic monomers

The examples above make it obvious that, from a historical perspective, the properties of polyanhydrides needed to be improved in order to obtain materials with superior properties, i.e., better mechanical characteristics and materials with adjustable erosion times. There have been numerous approaches to do so [33]; however, one of the most successful

Fatty acid terminated anhydrides

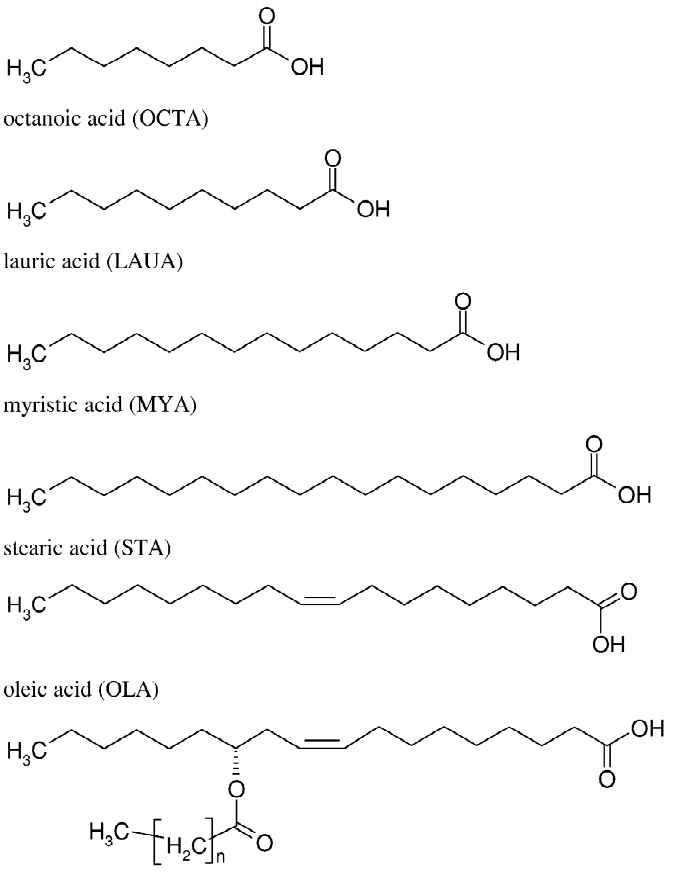
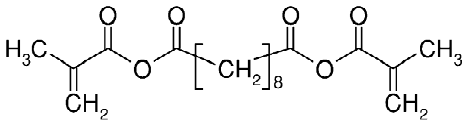


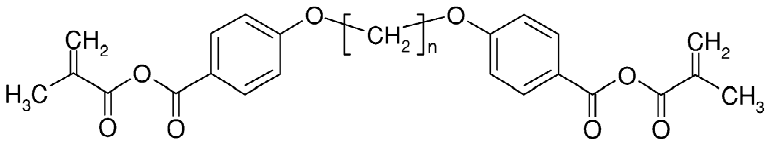
Fig. 3. (*continued*)

polymer types were copolymers made of sebacic acid and 1,3-bis(*p*-carboxyphenoxy)propane (p(CPP-SA)). First reports of using these polymers as a biomaterial go back to the early 1980s [6]. Since then, there have been numerous reports on their synthesis [15,33,47,48] and characterization [18]. This made p(CPP-SA) [16,18,26,27,32,45,49–51] probably the best characterized material in the family of polyanhydrides. This development was certainly spurred by the use of p(CPP-SA) 20:80 for the development of gliadel [52,53], a BCNU-loaded drug delivery system for the local therapy of malignant glioma [54,55]. For p(CPP-SA), a number of fundamental erosion and degradation data was raised. When the degradation of p(CPP-SA) matrices (cylindrical, 8 mm diameter/1.6 mm height) was investigated, it was observed that the molecular weight decreased according to first-order kinetics [14]. While varying the molecular weight between 10 and 65 kDa had no significant impact on the degradation kinetics, it was found that the erosion was delayed in a linear manner by 8–12 min. These results may be surprising as one would assume that polyanhydrides are surface eroding. However, experiments with polyanhydrides derived from fatty acid dimers (p(FAD-SA)), revealed a significant water uptake, a prerequisite to polymer degradation [56]. Once a polyanhydride matrix has taken up considerable

Photo polymerizable degradable polyanhydrides monomers



methacrylated sebacic acid (MSA)



n = 3: methacrylated 1,3-bis(p-carboxyphenoxy)propane (MCPP)

n = 6: methacrylated 1,6-bis(p-carboxyphenoxy)hexane (MCPH)

Fig. 3. (*continued*)

amount of water it is highly likely that all polymer parts in contact with it start degrading. That the degradation rate is a function of the polymer structure and also that of the the monomer, has been systematically studied by investigating homologous series of poly[bis(*p*-carboxyphenoxy)alkanes]. Increasing the number of methylene groups from one to six decreased the degradation rate by three orders of magnitude [45]. A general relationship that was derived from p(CPP-SA) and that may be extrapolated to other aliphatic/aromatic polyanhydrides is that anhydride bonds between aliphatic carboxylic acids degrade faster than those between aromatic ones. This was, for example, proven by using FTIR spectroscopy to follow the intensity of the anhydride bands that stemmed from SA-SA and CPP-CPP bonds [7]. These results were later confirmed by ^{1}H NMR [21] and solid state NMR [16]. These differences in reactivity were finally also confirmed with other polyanhydrides. In degradation experiments with poly(ω-(*p*-carboxyphenoxy) alkanoic anhydrides) derived from ω-(*p*-carboxyphenoxy)acetic acid, -valeric acid and -octanoic acid (CPA, CPV and CPO) [15] anhydride bonds between two aliphatic chains were cleaved faster than between bonds linking two aromatic ends. That the degradation of polyanhydrides is pH dependent was impressively shown with p(CPP) matrix discs eroded in phosphate buffer in the range of pH 7.4–10. Obviously the polymers were most stable at low pH (Fig. 5) [45].

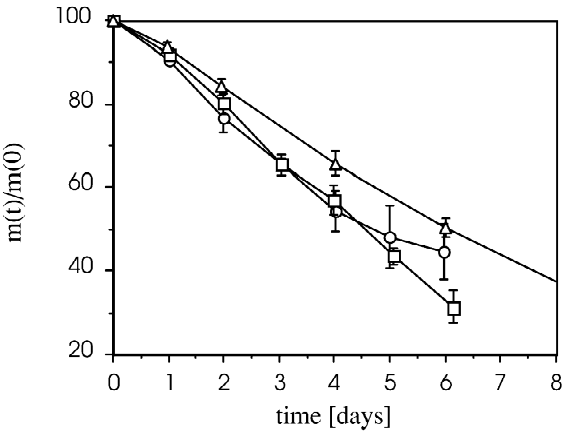


Fig. 4. In vitro erosion profiles of polyanhydride matrix cylinders. The cylindrical matrices (14 mm diameter/1 mm height) were eroded in phosphate buffer, pH 7.4, at 37 °C. Reproduced with permission from Ref. [10]. (a) p(SA), (b) p(CPP-SA) 20:80, (c) p(CPP-SA) 50:50.

In contrast to degradation, the erosion of p(CPP-SA) is substantially more complicated. As outlined above, erosion lags behind degradation by a couple of minutes [14]. The first changes that can be observed affect the polymer surface. By light microscopy, cracks became visible on the surface of p(CPP-SA) 20:80 matrices upon contact with water [10], which was also observed for p(FAD-SA) 50:50 matrices [56]. An observation that is unique for polyanhydrides, and that was reported quite early, is

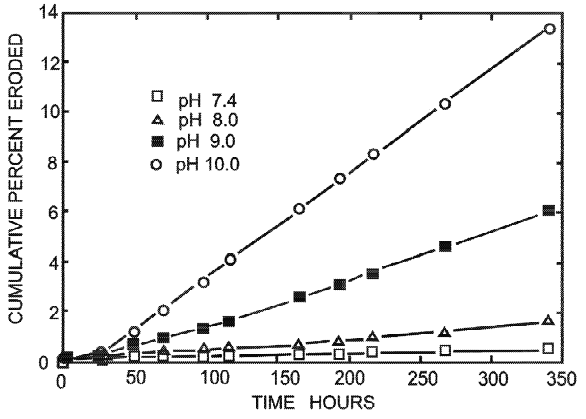


Fig. 5. Erosion of p(CPP) matrix discs as a function of pH. The cylindric matrices (14 mm diameter/1 mm height) were eroded in phosphate buffer, pH 7.4, at 37 °C. Reproduced with permission from Ref. [45].

their almost linear erosion kinetics. Polymers such as p(SA), p(CPP-SA) 20:80, p(CPP-SA) 50:50, p(CPP-SA) 85:15 and p(CPP) were reported to erode at an almost constant rate (Fig. 4) [10,45]. Due to the slower degradation of aromatic anhydride bonds, the erosion velocity decreases with increasing CPP content. A feature that is unique for p(CPP-SA) and many other polyanhydrides is the creation of erosion zones in which the polymer is undergoing erosion [7,29]. Erosion zones in p(CPP-SA) are separated from non-eroded polymer by erosion fronts, which move at constant velocity from the surface of a matrix into its center [10]. While the erosion zone was highly porous, the bulk showed no porosity at all. In the case of cylindrical p(CPP-SA) 20:80 and p(CPP-SA) 50:50 matrix discs (1.4 mm diameter, 1 mm height), 70 and 50% mass were lost after 6 days, while the overall geometry did not change [10]. This erosion behavior is based on the polymer microstructure which is composed of amorphous and crystalline polymer parts, of which the crystalline structures were significantly more erosion resistant than amorphous ones, and maintained a highly porous polymer skeleton in the erosion zone over a substantial period of time. Besides following the remaining mass of a matrix to assess erosion, the release of degradation products has been used extensively to follow erosion. This revealed very complex erosion patterns in the case of p(CPP-SA) [7] (Fig. 6). It was found that the release of SA from p(CPP-SA) 50:50 and p(CPP-SA) 20:80 matrices was similar to that from p(SA) and significantly faster than CPP release [10]. Fig. 6 reveals that the release velocity of CPP increases significantly once SA release is complete. It was hypothesized that these results are due to the solubility of monomers which is different for SA and CPP [10]. Both monomers are protolytes and, therefore, decrease the pH inside the porous erosion zone. EPR imaging of p(CPP-SA) 20:80 matrix discs eroded in vitro showed that a pH

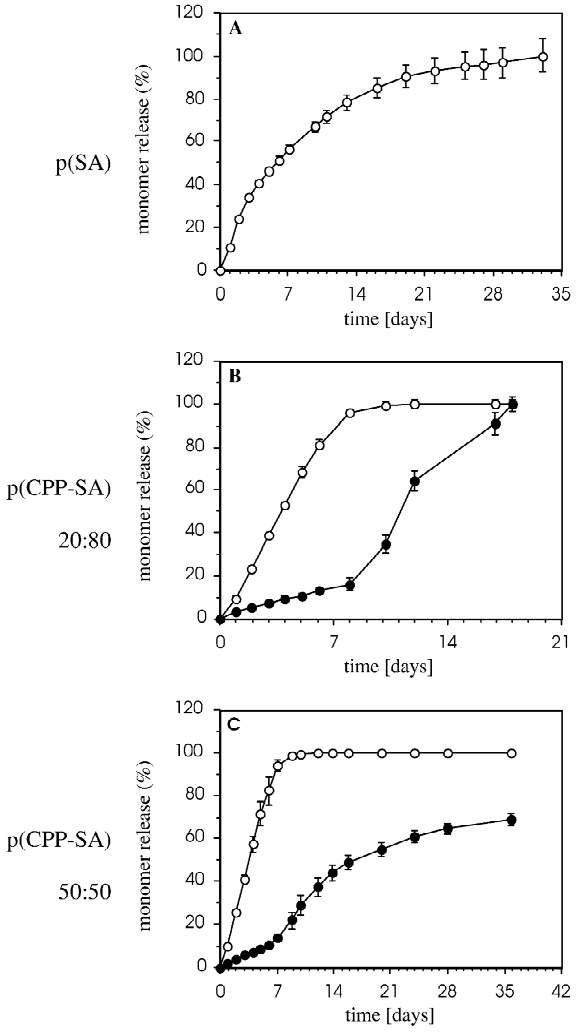


Fig. 6. Monomer release from polyanhydrides. The cylindric matrices (14 mm diameter/1 mm height) were eroded in phosphate buffer, pH 7.4, at 37 °C. Reproduced with permission from Ref. [10]. (A) p(SA), (B) p(CPP-SA) 20:80, (C) p(CPP-SA) 50:50.

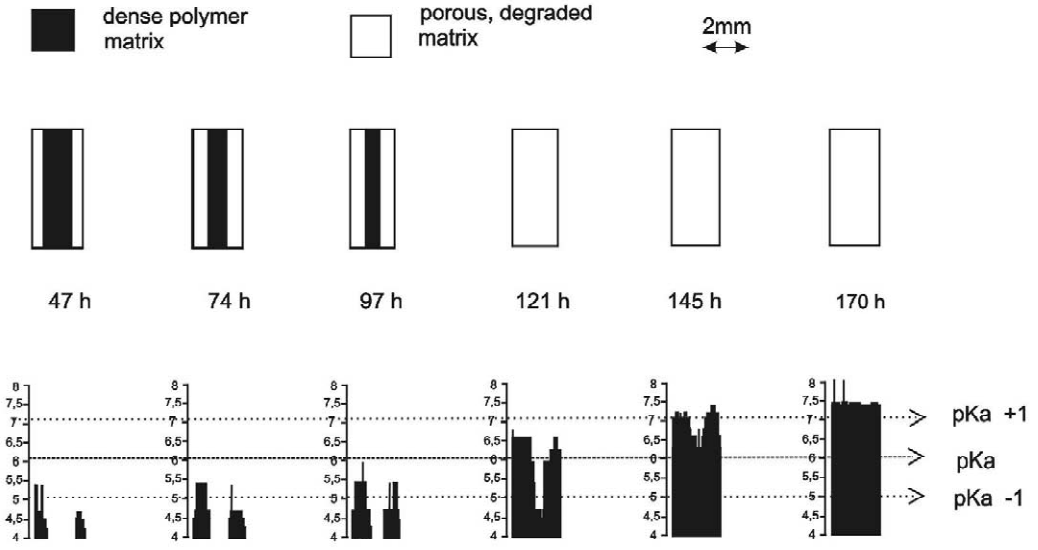


Fig. 7. pH profiles inside the erosion zone of p(CPP-SA) 20:80 (M_w 45 000) matrix discs. pK_a designates the pK_a of the pH sensitive spin probe. Reproduced with permission from Ref. [28].

gradient with a pH of 7.4 on the matrix surface to approximately 4.7 at the erosion front develops with time (Fig. 7) [28]. The pH inside the erosion zone seems, thereby, to be mainly controlled by SA that has an approximately five times higher solubility compared to CPP [10]. This suppresses the solubility and, therefore, the flux of CPP as long as significant amounts of SA reside in the matrix. After 7 days, however, when SA release is almost complete, the solubility and release of CPP increases significantly. This is also reflected by the monomer content of matrices during erosion (Fig. 8). The monomer content of p(CPP-SA) 20:80 after 4 days reaches a maximum of approximately 35%. This is more than the pores can dissolve. Therefore, one can assume that a good part of the monomer will exist in a crystalline state inside the erosion zone. This was supported by a diffusion/erosion models that were developed to describe the release of monomers from p(CPP-SA) matrices [57].

3.1.4. Polyanhydrides derived from fatty acids

The basic idea behind developing polyanhydrides from fatty acids was to obtain materials with a pronounced hydrophobic character and improved mechanical properties compared to materials such as p(CPP-SA). The hope was to increase the hydrolytic resistance of polyanhydrides and concomitantly slow down the intrusion of water into polymer matrices.

One of the first materials to be synthesized and by far the best investigated are copolymers made of sebacic acid and a erucic acid (fatty acid) dimer (FAD) [58]. When rectangular slabs (200 mg; $3 \times 5 \times 10$ mm) of the material were degraded in vitro, their molecular weight dropped again exponentially, similar to the degradation pattern of p(CPP-SA) [58]. Cylindrical discs (14 mm diameter/0.1 mm height) made of p(FAD-SA) 20:80 (M_w 30 000), p(FAD-SA) 50:50 (M_w 25 000) and p(FAD-SA) 70:30 (M_w 50 000) all had a molecular weight of less than 5000 after 24 h erosion in vitro [17]. Despite its unique chemical composition with long aliphatic chains, p(FAD-SA) erosion behavior resembles that of p(CPP-SA) in many ways. Polymers with an SA content of approximately 25% and more were found to be semi-crystalline [17,58]. The microstructure of crystallites revealed a spherulitic arrangement as in p(CPP-SA) [57]. The polymers also formed erosion zones during erosion. Due to the low solubility of FAD it consisted mainly of a semisolid mixture of FAD and FAD salts [57]. The semisolid layer can form a permeation barrier with significant influence on the release of SA as well as drugs [27]. Acid orange, for example, a hydrophilic dye, was released

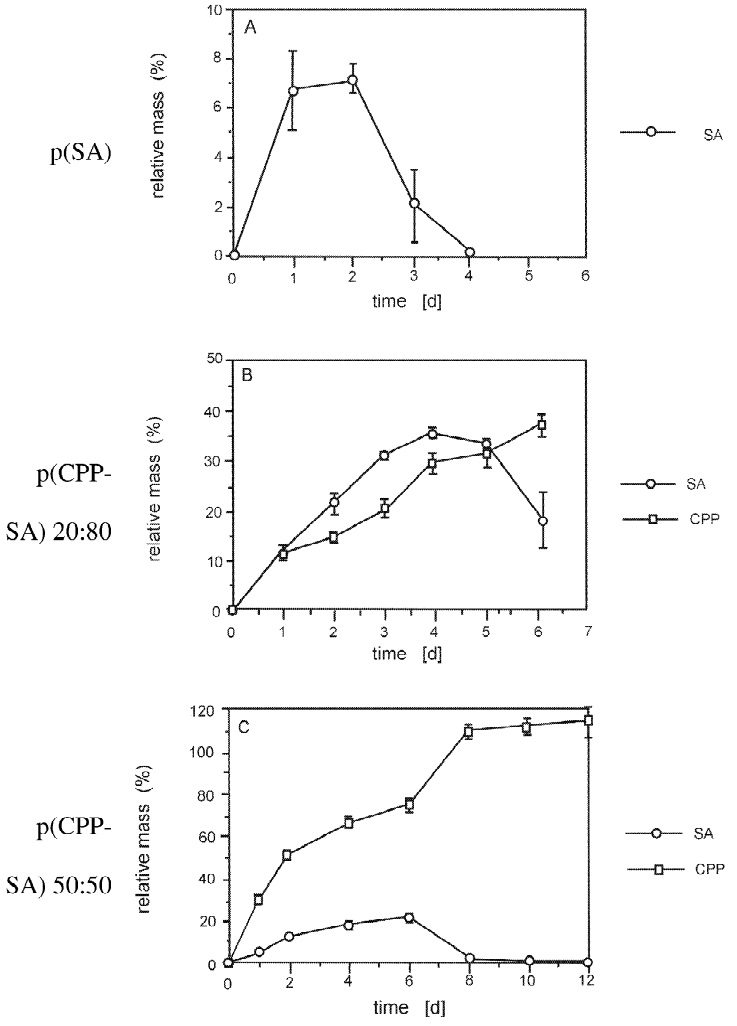


Fig. 8. Monomer content of polyanhydride matrix cylinders during erosion. The cylindrical matrices (14 mm diameter/1 mm height) were eroded in phosphate buffer, pH 7.4, at 37 °C. Reproduced with permission from Ref. [10]. (A) p(SA), (B) p(CPP-SA) 20:80, (C) p(CPP-SA) 50:50.

more slowly in vitro the higher the FAD content of the investigated p(FAD-SA) was [59]. The investigation of eroding p(FAD-SA) 50:50 and p(FAD-SA) 20:80 matrices by MRI and ESR shed some light on the changes of the polymer microstructure during the process [27]. When composed mainly of SA, the polymer was able to maintain a porous erosion zone, while at an equal amount of SA and FAD the erosion zone became more semisolid. Sebacic acid was found again to precipitate inside the erosion zone. Together with the formation of gel-like diffusion barriers, this might explain why the release of SA was the lowest for polymers made of equal amounts FAD and SA [60].

More recently, polyanhydrides were developed from non-linear hydrophobic fatty acid esters [61]. The development of these polymers was spurred by the long in vivo half-lives of FAD as well as the observation that matrices of p(FAD-SA) 20:80, for example, underwent significant tissue encapsulation in rats 65 days post implantation [27]. The polymers were synthesized from ricinoleic acid maleate

(RAM), 12-hydroxystearic acid succinate (HSAS) and 12-hydroxystearic acid maleate (HSAM) [61]. Copolymers, such as p(RAM-SA) 50:50, p(HSAM-SA) 50:50 and p(HSAS-SA) 50:50, were reported to undergo a sharp decrease of molecular weight during the first 24 h of erosion in vitro and lost 40% of their anhydride bonds in 48 h, as determined by FTIR [61,62]. Their erosion profiles were all similar with a weight loss of 40% after 2 days [61].

Polyanhydrides were also made of pure fatty acids that were not modified to carry a second carboxylic acid end [63,64]. These polymers were essentially polyanhydrides made of p(SA) chains terminated by fatty acids such as octanoic (OCTA), lauric (LAUA), myristic (MYA), oleic (OLA) or stearic acid (STA). When 300-mg slabs ($3 \times 7 \times 11$ mm) were eroded in vitro the degradation of all copolymers with a composition of 10 or 30% fatty acid and 90 or 70% sebacic acid, respectively, again showed an exponential loss of molecular weight. The same results were obtained for non-linear fatty acid anhydrides that were composed of sebacic acid and ricinoleic acid esterified with C8–C18 fatty acids at their alcohol function [64]. The erosion profiles of these polymers are intriguing. The mass of matrices under erosion remains stable for a couple of days before mass loss sets in [63]. This is usually typical of bulk eroding polymers. The more fatty acid these polymers contain, and the longer their chain length, the more pronounced this effect is. It seems, therefore, likely that the solubility of the fatty acids has a pronounced impact on erosion.

3.1.5. Cross-linked polyanhydrides

The often limited mechanical stability of polyanhydrides has always been a handicap to their use as biomaterials for orthopedic applications such as a temporary replacement in bone defects. To overcome these limitations unsaturated polyanhydrides that allow for cross-linking, such as p(FA) and p(FA-SA), have been synthesized [65]. In recent years unsaturated polyanhydrides were studied and developed more intensively [66–71]. Cross-linked polyanhydrides were synthesized from monomers such as SA, CPP or CPH after conversion to mixed anhydrides with methacrylic acid. The obtained methacrylated sebacic acid (MSA), methacrylated CPP (MCPP) and methacrylated CPH (MCPH) were then photopolymerized using UV light and appropriate photo initiators [71]. When discs of 16 mm diameter and 1.6 mm height were eroded in vitro, they showed linear erosion profiles. With increasing MCPH content, erosion slowed down significantly. While p(MSA) eroded completely in a few hours, p(MCPH) lost only approximately 20% weight in 80 days. Copolymers derived from MSA and MCPH showed erosion behavior between these extremes [71].

3.2. The impact of geometry on degradation and erosion

Most of the information that was collected on the degradation and erosion of polyanhydrides was collected from the investigation of macroscopic matrices. Doing so has the advantage that the polymer samples can easily be characterized. However, the use of polyanhydrides for drug delivery applications led to extensive research efforts to develop and investigate polyanhydride microspheres [72–77]. In the case of monolithic matrices the effect of geometry was also investigated.

3.2.1. Macroscopic matrices

The interest in investigating the effect of geometry of monolithic matrices on the erosion of polyanhydrides was spurred by the desire to better control the release of drugs from implants such as gliadel. Given that a polyanhydride undergoes perfect surface erosion it is obvious that the geometry of a device can significantly affect the release kinetics. A few studies focused on this issue. When for example cylindrical matrices (5 mm diameter/0.5 mm height, 9 mm diameter/0.8 mm height and 12.5 mm diameter/1.4 mm height) were prepared from p(CPP-SA) 40:60, the amount of water uptake of matrices in vitro was a function of size [13]. Concomitantly the molecular weight of matrices dropped in the usual exponential way, however, the rate for bigger matrices was lower than that for smaller ones. The erosion of matrices was also strongly related to their geometry and was highest for small matrices. These results indicate that the geometry can indeed affect the progress of degradation and erosion. This was also supported by release experiments with brilliant blue-loaded

p(CPP-SA) 20:80 matrix discs [30]. Erosion models confirmed that the changes in release that were obtained when the height of 6-mm diameter cylinders was increased from 1.5 to 2 mm were due to surface erosion. The example also illustrates, however, that taking advantage of device geometry for modulating erosion and drug release may lead to large devices that may not be useful for biomedical applications any more.

3.2.2. Microparticles

Obviously it is much harder to investigate microspheres, especially with respect to their microstructure. The erosion of microspheres is faster than the erosion of solid matrices. Microspheres made of p(FAD-SA) 8:92, p(FAD-SA) 25:75 and p(FAD-SA) 44:56 with average diameters below 100 μm released SA in approximately 100 h to 100% in vitro [78]. This suggests that the polymer is completely degraded after that time and that the release of acid orange that persisted for 400 h was mainly due to the semisolid erosion zone formed by FAD monomer. That polymer degradation and eventually also erosion depends on the microsphere size was demonstrated with some early work on p(CPP-SA) 21:79. Depending on the average microsphere size (between 50 and 1100 μm), the microspheres lost between approximately 90 and 75% of CPP when eroded in vitro [74], which is indicative of a similar degree of erosion. When p(CPP-SA) 20:80 and p(FA-SA) 20:80 microspheres with a size of less than 10 μm were manufactured by spray drying they degraded almost completely within 18 and 5 h, respectively [75]. These results illustrate that polyanhydride microspheres are very delicate systems that degrade and most likely erode very fast, which can make it hard to use them for long term drug delivery applications. This is most likely also one of the reasons why there have been few reports on polyanhydride nanoparticles [79].

4. Erosion-controlled drug release from polyanhydrides

One of the goals that we have in mind when using polyanhydrides is taking advantage of their surface erosion character. In drug delivery applications that means that we are interested in erosion-controlled release systems. This has sometimes, but not always been successful. Usually there are several mechanisms by which the release of a drug from a polymer can be controlled, such as diffusion, polymer swelling, erosion or the dissolution velocity of the drug. If we want to control the release of a drug exclusively by one of these mechanisms, which usually compete with one another, we have to make sure that it is the fastest process [80]. From the erosion mechanisms outlined above, it is obvious that polyanhydrides are ideal candidates for erosion-controlled release. There have been many reports that polyanhydride erosion and the resulting drug release kinetics are identical. For a surface eroding polymer this can mean that we have linear release kinetics which was, for example, found for drug release from p(CPP), p(CPP-SA) 20:80 matrix discs [54]. That the nature of the substance to be released and the way by which erosion is measured has a major impact on this correlation becomes obvious when examining some data for microspheres prepared from p(CPP-SA) 20:80 [74]. While the more hydrophilic acid orange exhibited a burst release, the more lipophilic *p*-nitroaniline correlated with CPP release, which was taken as a measure for erosion. From the erosion behavior of p(CPP-SA) matrices outlined above one can assume that the release of CPP lags significantly behind erosion. The release of lipophilic drugs seems, therefore, to be correlated to dissolution rather than erosion. To put polyanhydrides to the test on erosion-controlled release it seems, therefore, far better to use hydrophilic model compounds [30,81]. These model substances are not retained inside a polyanhydride by their hydrophobic character, but are released immediately upon erosion [82,83].

A sensitive issue is the incorporation of proteins and peptides into polyanhydrides. Although there have been numerous reports on the incorporation and release of proteins and peptides into polyanhydrides [84–86], the polymers may lead, similar to less reactive PLA and PLGA [87], to an acylation of nucleophiles such as primary amines or hydroxy groups [88]. This has to be carefully considered when proteins, peptides or drug-carrying amine or hydroxyl functions are to be released from polyanhydrides.

5. Polyanhydride erosion modeling

The intriguing advantage of polyanhydrides over most other degradable polymers is their clean-cut erosion behavior. As shown above, the erosion of these materials is characterized by a linear progression of erosion fronts associated with a strong correlation between erosion and drug release for a considerable number of drugs. This spurred the interest in the development of theoretical models, that allow to describe and predict the erosion behavior of polyanhydride matrices [89].

5.1. Empirical models

The first models that were developed were based on the assumption of a linear moving erosion front. They were empirical in a sense that they did not relate the erosion behavior of the polymer to measurable parameters with an exactly defined physical significance. Hopfenberg, for example, derived a general equation for describing erosion-controlled drug release that may also apply to describing the erosion polyanhydride spheres, cylinders and slabs [90]:

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_0 t}{c_0 a}\right)^n \quad (1)$$

where M_t and M_∞ are the polymer mass at time t and at infinite time, respectively, c_0 a uniform initial drug concentration or in the case of erosion a 'polymer concentration', a is the radius of a cylinder or sphere or the half-thickness of a slab and n is a 'shape factor' ($n=3$ for spheres, $n=2$ for cylinders and $n=1$ for slabs). According to Hopfenberg's model, only slabs erode with zero-order erosion kinetics.

Another model of heterogeneous erosion that may be used to describe erosion was developed by Cooney [91]. Cooney describes, like Hopfenberg, the erosion of polymer like a 'dissolution' process but assumes that there is an additional step involved, namely the release through an adjacent stationary solvent layer into the erosion medium. Cylindrical polymer matrices with an initial length L_0 and initial diameter D_0 erode according to Eq. (2) in which f designates the fractional 'dissolution' at time t (relative to $t=0$) and K is a rate constant.

$$f = \frac{(D_0 - 2Kt)^2 + 2(D_0 - 2Kt)(L_0 - 2Kt)}{D_0^2 + 2D_0 L_0} \quad (2)$$

Similar approaches were used later taking advantage of the individual erosion front velocities that were determined for polyanhydride matrix cylinders. This allowed to come up with simple predictions on the release kinetics of drugs [81].

5.2. Monte Carlo-based models

A different approach to polyanhydride erosion modeling was proposed in the early 1990s [92]. The concept offers the advantage, that the degradation of the polymer was modeled as a random event that obeyed first-order reaction kinetics. Rather than describing the degradation of individual bonds, the degradation of all bonds contained in a small volume of polymer was described. Similar approaches were used by Zygourakis and co-workers for modeling erosion-controlled drug release from eroding composite devices [93,94]. Polymer cross-sections were covered with two-dimensional grids by which the polymer matrix was divided into a multitude of pixels, each representing a small volume of polymer. To account for the existence of crystalline and amorphous areas inside most polyanhydrides, these pixels were randomly assigned one of these two qualities so that the relative number of pixels designated as crystalline were in agreement with the crystallinity of the polymer to be modeled. The 'life expectancy' of a pixel after contact with water was sampled at random from first-order Erlang distributions:

$$e(t) = \lambda\, e^{-\lambda t} \quad (3)$$

where λ is a degradation rate constant that is different for amorphous and crystalline polymer. $e(t)$ is the probability that a polymer pixel degrades at time t [95]. Applying direct Monte Carlo sampling techniques [96], values for t can be obtained at random so that all values are distributed according to Eq. (3). By applying this procedure to the two-dimensional grids, it is possible to simulate the erosion of polyanhydrides (Fig. 9). With these simulations it is possible to model the erosion profile or the porosity of polyanhydride matrices during ero-

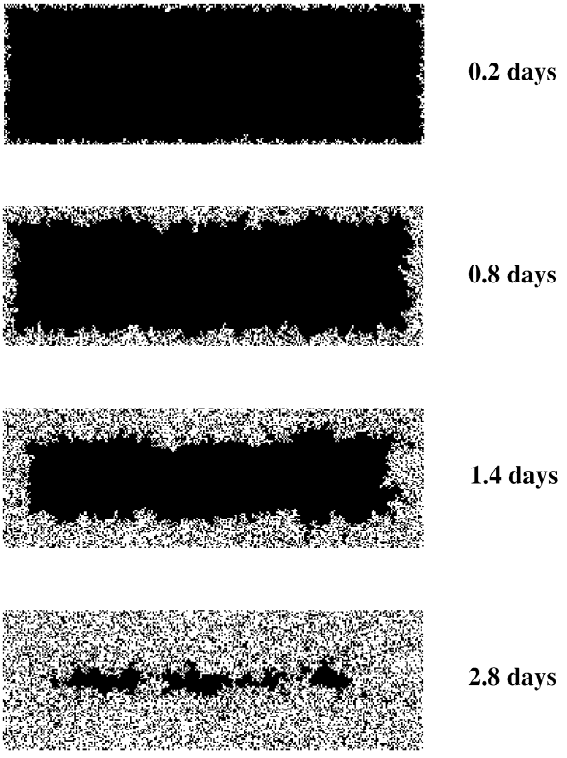


Fig. 9. Two-dimensional simulation of p(CPP-SA) 20:80 erosion. Reproduced with permission from Ref. [30].

sion. These data can then be used to fit the model to experimental data, which yields the erosion rate of crystalline and amorphous areas in p(CPP-SA) [92].

Originally the model was limited to two-dimensional simulations; however, it was also possible to expand it to three dimensions by assuming rotation symmetry [30]. This modification allowed to simulate the erosion of cylinders and concomitantly the release of drugs from such matrices. In combination with related models for bulk eroding polymers [12], it is also possible to simulate the erosion of composite devices that were developed for the manufacture of programmable release devices [83].

6. Why polyanhydrides undergo surface erosion

So far it has been widely accepted that polyanhydrides are surface eroding polymers. This is certainly true for macroscopic devices. However, a closer look at the microstructure of eroded matrices shows that this cannot be unequivocally true. Fig. 10a shows a pictures of the erosion fronts inside a p(CPP-SA) 20:80 matrix. Arrows identify the erosion fronts sharply separating eroded from non-eroded polymer. A look at the front at higher resolution shows that it is not a straight line any more. Rather than being well defined, it has the character of a transition zone in which the polymer changes from eroded to non-eroded within 5–20 μm.

Recently developed models can shed some light on the consequences of this uncertainty [97]. It was

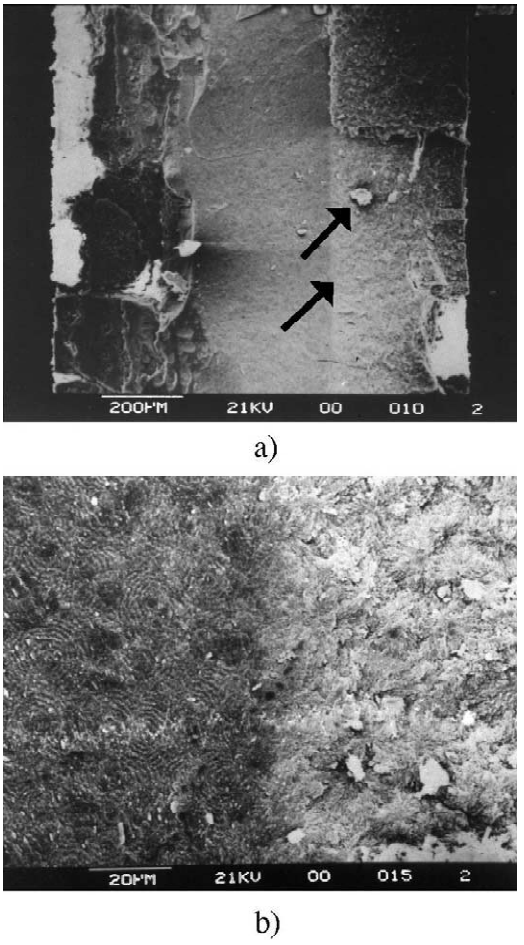


Fig. 10. Erosion front inside a p(CPP-SA) 20:80 matrix at two different magnifications (reproduced with permission from Ref. [10]): (a) survey on a cylinder cross-section (the arrow indicates the position of the erosion front), (b) erosion front at higher magnification.

assumed that a polymer matrix erodes according to a surface erosion mechanism if the velocity of water uptake, as described by diffusion theory, is lower than degradation rate of the polymer as described by Monte Carlo models [12,92]. A dimensionless 'erosion number' ε, which is the ratio of both processes indicates the mode of erosion:

$$\varepsilon = \frac{\left\langle x \right\rangle^2 \lambda \pi}{4D_{\text{eff}}\left(\ln[\left\langle x \right\rangle] - \ln\left[\sqrt[3]{\frac{\overline{M}_n}{N_A(N-1)\rho}}\right]\right)} \quad (4)$$

where D_{eff} is the effective diffusivity of water inside the polymer, $\langle x \rangle$ the device dimension, λ the degradation rate of the polymer, M_n the number average polymer molecular weight, N the average degree of polymerization, N_A Avogadro's number and ρ the polymer density. For $\varepsilon = 1$, the erosion mechanism is not defined and a critical device dimension L_{critical} can be calculated. If a matrix is larger than L_{critical} it will undergo surface erosion, if not it will be bulk eroding. L_{critical} values for polymers were estimated based on literature data. Polyanhydrides were estimated to be surface eroding down to a size of approximately $L_{\text{critical}} = 10^{-4}$ m, while poly(α-hydroxy acids) matrices need to be larger than $L_{\text{critical}} = 10^{-1}$ m to loose their bulk erosion properties. To support this theoretical findings it was shown experimentally that poly(α-hydroxy acid) matrices, which are considered classical bulk eroding materials, can also undergo surface erosion [97]. Although this model yields only a crude estimate for ε, it suggests that there is certainly a size limit to surface erosion, a fact that needs to be considered in design strategies involving polyanhydrides. Furthermore the theoretical value of ε is well in agreement with experimental findings regarding the width of the erosion front.

7. Summary and outlook

Polyanhydrides are materials that, based on their chemical nature degrade rapidly in a an aqueous environment. Passive hydrolysis seems, thereby, to be the most significant mechanism of polymer bond cleavage. Enzymatic degradation mechanisms seem to be of minor or no importance for polyanhydrides investigated so far. When the degradation of polyanhydride matrices is followed by monitoring polymer molecular weight, usually an exponential decay of molecular weight over time is observed.

Erosion in contrast is more complicated. Crystalline polymer areas were found to be more erosion resistant than amorphous ones. In many polyanhydrides such as p(CPP-SA) and p(FAD-SA), erosion fronts moved from the surface of polymer matrices to their center separating eroded from non-eroded polymer. These erosion zones may either be porous (Fig. 11a) such as in the case of p(CPP-SA), or semisolid (Fig. 11b) as was observed for p(FAD-SA). Inside the erosion zone, the pH values drop as determined by EPR to values close to the pK_a of the monomers. Some monomers such as SA may precipitate under these conditions.

The erosion zone is of utmost importance for the release of compounds from polyanhydrides as it may be a significant diffusion barrier to be overcome, as in the case of p(FAD-SA). The environment inside

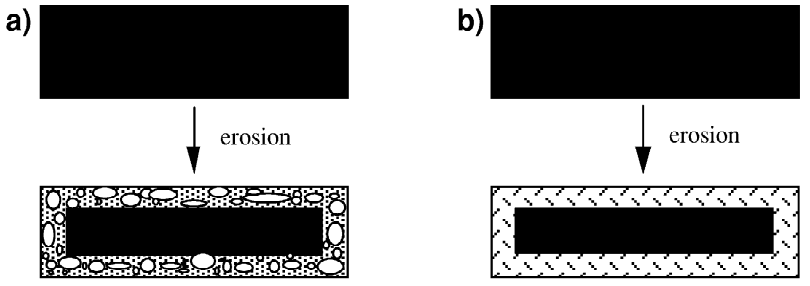


Fig. 11. Potential erosion mechanisms for polyanhydrides. (a) Erosion under the formation of porous erosion zones such as in p(CPP-SA). (b) Erosion under the formation of semisolid erosion zones such as in p(FAD-SA).

the erosion zone may be of significance for the stability of drugs. It can stabilize compounds such as BCNU which has a stability optimum at low pH [98], it can, however, also put the stability of proteins and peptide at risk due to the potential of anhydrides to acylate nucleophiles.

Erosion models helped to describe and understand the erosion behavior of polyanhydrides. Monte Carlo models that simulate erosion based on the erosion of small individual polymer areas after their contact with water allowed to explain the formation of erosion zones and erosion fronts. Models that compare the velocity of water diffusion into a polyanhydride matrix to the velocity of erosion allow to address why polyanhydrides undergo surface erosion. It seems that surface erosion is a characteristic that is strongly linked to the dimensions of a device and that, below a critical size limit, this property is lost. We should, therefore, examine, polyanhydride devices very carefully when they are smaller than 100 μm.

In summary polyanhydrides have unique degradation and erosion properties, that make them precious materials for numerous medical, biomedical and pharmaceutical applications. If we use them with the necessary circumspection they are ideal for all those applications in which we need degradable polymers that allow for a perfect erosion control.

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