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Review

Factors affecting the degradation and drug-release mechanism of poly(lactic acid) and poly[(lactic acid)-*co*-(glycolic acid)]

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Abstract: This paper reviews the most important factors affecting the degradation and drug-release rate of bio-erodible polymers for better control in biomedical applications. There are several factors that influence the overall rate of degradation, in addition to pH and copolymer composition. In general, polymer degradation is accelerated by greater hydrophilicity in the backbone or end groups, lesser crystallinity, lower average molecular weight, and smaller size of the finished device. At the moment, literature reflects contradictions about the role played by chemically reactive additives, crystallinity and degradation path. Factors affecting degradation and drug-release rate are discussed in their decreasing order of importance, including intrinsic properties of polymers and processing parameters.

Keywords: bio-erodible polymer; PLGA; limiting factors; degradation mechanism; drug-release mechanism

INTRODUCTION

Homopolymers and copolymers[1] based on L-lactic acid, D,L-lactic acid and glycolic acid have received interest in the medical and pharmaceutical field because of their biodegradability and toxicological safety. Poly[(lactic acid)-*co*-(glycolic acid)] (PLGA) is among the few synthetic polymers approved for human clinical use. An exciting application, for which biodegradable polymers offer tremendous potential, is drug delivery. 'Controlled release' refers to the use of polymeric materials to release incorporated drugs at a controlled rate for a desired period of time.[2]

Many other factors influence the degradation and drug release of PLGA polymers, including flow rate,[3] sterilization,[4–8] strain,[9–11] presence of plasticizers,[12,13] residual solvents,[14] buffer concentration,[15] porosity,[3,16,17] temperature,[18–20] size of the matrix,[21–26] crystallinity,[27–31] weight-average molecular weight (M_w),[32–38] composition[39–41] and enzymes.[16,42–46] The degradation kinetic pattern is further altered by the presence of additives such as salts, basic and acidic compounds.

Despite many investigations, the literature reflects contradictions at the moment about the role played by chemically reactive additives. A possible explanation is the existence of two opposite effects. First, basic compounds can catalyze ester-linkage scission and thus speed up polymer degradation.[23,24] On the other hand, they can neutralize carboxyl end groups and thus decrease the degradation rate, as a result of reduced acid catalysis.[47,48] In addition, the size of polymer samples has recently been recognized as an important factor affecting the degradation path.[22–24,49–54]

Other important properties of the polymer matrix that depend on the copolymer composition, such as the glass transition temperature (T_g) and crystallinity, can have additional indirect effects on degradation rates. Currently, there are confusing reports about the effect of crystallinity on the degradation rate. Finally, despite extensive investigation, controversial data are still found in literature, in so far as the degradation mechanism (hydrolytic *versus* enzymatic cleavage) is concerned.

Therefore, it is desirable to characterize the effect of these parameters on degradation and drug release from the bio-erodible matrices. The purpose of this critical review is to compare and explain the factors affecting the degradation process and, thus, the drug-release rate of selected bio-erodible polymers. In general, mechanistic details of the degradation and drug-release process for these polymers are sometimes contradictory. In addition to our work,[55,56] such a critical comparative review is important in the formulation development of controlled release devices. Various

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system parameters are reviewed, including copolymer composition, crystallinity, additives (drugs or plasticizers), average molecular weight and processing parameters (medium, size of the device, sterilization, strain, enzymes, temperature, porosity and flow rate).

Essentially, the process of 'degradation' for these polymers describes hydrolytic chain scission, during which polymer chains are cleaved into oligomers and, finally, monomers. When classifying degradable polymers, a distinction is made between surface (or heterogeneous) and bulk (or homogeneous) eroding materials. In the case of polymers that degrade in bulk, the rate of water penetration into the matrix is higher than the rate of polymer degradation. This process is a homogeneous one in which degradation occurs at a uniform rate throughout the polymer matrix. For surface-eroding polymers, hydrolysis of the polymer is confined to the outer surface, and the interior of the matrix remains essentially unchanged. In order to have purely erosion-controlled systems, polymer erosion has to be faster than water uptake or drug diffusivity.[57]

Furthermore, as the release of the drug is a direct consequence of the erosion process, release rates become predictable if the erosion process of the polymer is understood. The release patterns can be divided into those that release the drug with slow zero-order kinetics and those that provide an initial rapid dose followed by a non-release phase.[58] Formulations releasing the drug at a slow zero-order rate are more common than those containing a fast-release component.

The release of the drug from homogeneously eroding matrix is more complicated.[58] The Higuchi model (which assumes drug loading C_0 is greater than C_s, where C_s is the limit of solubility in the polymer) describes the release of the drug initially from the surface of the slab and progressively through a thicker drug-depleted layer. This is characterized by a two-phase drug-release pattern. In the case of over-loading the drug inside the polymer matrix, C_0 becomes greater than C_s (saturated concentration of drug inside polymer matrix) and a common early burst release is observed.

EFFECT OF COMPOSITION

The most important factor influencing the degradation rate is the composition of the polymer, which determines the hydrophilicity of the matrix. Wang and Wu[40] did a systematic study of the effect of the composition on polymer biodegradation. Three different samples with different compositions, PLGA 46/54 (number-average molecular weight $M_n = 990\,g\,mol^{-1}$), PLGA 63/35 ($M_n = 912\,g\,mol^{-1}$) and PLGA 72/28 ($M_n = 1317\,g\,mol^{-1}$), were used in this experiment. The results show that an increase of glycolic acid residue in the oligomers accelerates the weight loss. In addition, Li[41] reported a detailed study of the degradation mechanism and the effect of composition on the degradation of PLA/PGA polymers. PLGA 75/25 ($M_w = 111\,kDa$) exhibited a faster degradation than PLGA 85/15 ($M_w = 112\,kDa$) due to preferential degradation of GA units assigned by higher hydrophilicity, compared with LA units. PLGA 75/25 exhibited a half-life of 10 weeks compared with 20 weeks for PLGA 85/25. During a quantitative nuclear magnetic resonance (NMR) study[55] on PLGA 53/47, we found that the chain scission was specific to glycolic linkages and glycolic units were hydrolyzed much faster than lactic units due to their higher hydrophilicity. Furthermore, Wu and Wang[35] studied the effect of polymer composition. A series of polymers having similar molecular weights but different compositions were used in this set of experiments [PLGA 50/50, 65/35, 75/25, 85/15, and poly(L-lactic acid) (PLLA)]. The absolute value of the biodegradation rate constants increases with increasing glycolic acid content. The first-order biodegradation rate, k, varies from 0.0222 to $0.0544\,day^{-1}$ for PLLA to PLGA 50/50, with decreasing lactide content. Gümüsdereliod lu and Deniz[59] investigated the effect of lactide (LA) and glycolide (GA) ratios on mitomycin-C (MMC) release kinetics. The LA/GA ratio was varied from 70/30 to 90/10, keeping all other parameters constant. Increasing GA content resulted in an impressive increase in the release rate and release amount. After three months, PLGA 90/10 released only 30 wt% of MMC, as compared with 70 wt% of release from PLGA 70/30.

In summary, the amount of GA unit is a critical parameter to control the hydrophilicity of the polymer and, thus, the degradation and drug-release rate. The higher the GA content, the faster the degradation and drug-release rates.

EFFECT OF CRYSTALLINITY

Other important properties of the polymer matrix that depend upon the copolymer composition, such as glass transition temperature and crystallinity, have additional indirect effects on its degradation rate. Nakamura *et al*[28] reported that the decrease in M_w for both amorphous ($M_w = 201\,kDa$) and crystalline ($M_w = 156\,kDa$) PLLA, one month after *in vivo* implantation, was less than 20 % of the original. By the third month, the decrease in M_w for the amorphous sample was 30–40 %, while crystalline PLLA was 70–80 %. The amorphous sample retained over 90 % of its initial bending strength, whereas the crystalline PLLA lost more than 50 % of its initial value over the same period of time. The reason why the crystallized PLLA showed a higher degradation rate may have been due to the high processing temperature (200 °C) during crystallization. PLLA is known to be very sensitive to temperature, leading to extensive degradation when the processing temperature is higher than the glass transition. This was confirmed by the viscosity-average molecular weights (M_v) of PLLA

amorphous and semi-crystalline (201 and 156 kDa respectively) and the degradation was accelerated due to a heterogeneous path, increasing the hydrophilicity of the matrix. Unfortunately, no data were shown on the water uptake of the various polymers. Tsuji and Ikada[27] investigated the effect of initial crystallinity on the long-term *in vitro* hydrolysis of PLLA films ($M_w = 1300$ kDa). Polymer after melting were either annealed or quenched to prepare films with different degrees of crystallinity (0, 2, 30, 45 and 54 %). Within a period of hydrolysis of 24 months, it was observed that the rate of decrease in molecular weight was higher for samples with high initial crystallinity. Melting and glass transition temperatures of the PLLA films increased in the first 12 months of the study and decreased for the next 24 months. Weight-loss results are consistent with the decrease in molecular weight, with PLLA (54 % crystalline) losing 15 % after 36 months of incubation as against PLLA amorphous losing only 7 % of mass. This finding has been ascribed to the highly microporous structure or increased surface area per unit weight of PLLA films having a higher initial crystallinity, formed by removal of water-soluble oligomers. Another reason may be the crystallization protocol, and the results showed that the PLLA films annealed at 160 °C had a significant drop of M_w from 136 kDa to almost half of its value after treatment.

In contrast, Li *et al*[25] reported the effect of crystallinity on the degradation of PLLA ($M_w =$ 130 kDa). Specimens of similar size were processed by compression molding and made either amorphous by quenching or semi-crystalline by annealing. The mass of amorphous specimens remained unchanged during the first 18 weeks of study, and decreased by 4 % and 49 % at the end of 31 and 110 weeks, respectively. No weight loss was detected for the semi-crystalline samples until the 7th week, after which the weight loss was linear until the 31st week. A comparison between the 7th and 31st week showed that the weight loss was higher for the semi-crystalline samples. However, the opposite trend was observed from week 40. At week 110, PLLA semi-crystalline had lost only 24.6 % of its initial mass compared with 50 % for the amorphous PLLA. PLLA amorphous crystallized during degradation, in contrast to PLLA semi-crystalline and no additional data were shown for semi-crystalline PLLA due to brittleness. However, there was no significant difference in molecular-weight drop between the crystalline and amorphous samples after the 40th week. This is in clear disagreement with the results reported by Tsuji and Ikada[27] and this may be due to a different crystallization method. Li *et al*[25] annealed the films at a lower temperature (105 °C), thus avoiding early degradation of the polymer. This is inconsistent with Tsuji's samples, which were annealed at 100, 120 and 140 °C. Cai *et al*[29] showed the relationship between enzymatic degradation of PLLA as a function of heat of fusion (crystallinity). The weight-loss values were almost comparable below the heat of fusion of 20 J g^{-1}. This shows that the amorphous regions were easily accessible to enzymatic attack, as the limited extent of crystallinity (low heat of fusion) did not inhibit degradation. However, a sudden drop was observed in the weight-loss values beyond a heat of fusion of 20 J g^{-1}, which indicates that a critical amount of crystallinity inhibited degradation. In addition, Montaudo and Rizzarelli[30] reported that copolyesters exhibited greater rates of enzymatic degradation when the sample crystallinity decreased. We also found that crystallinity is a major factor controlling the degradation. PLLA (Intrinsic viscosity (IV) = 4.37 g dl^{-1}) degraded faster than its lower molecular weight PLLA ($IV = 2.04$ g dl^{-1}) due to a lower degree of crystallinity. In agreement, the amorphous poly(D,L-lactic acid) (PDLLA) ($IV = 2.4$ g dl^{-1}) degraded faster than semi-crystalline PLLAs ($IV = 2.04$ and 4.37 g dl^{-1}).[55]

At the moment, there are confusing reports on the effect of crystallinity on the degradation rate. Tsuji *et al*[14,27] are in disagreement with the *in vitro* findings reported by our study[55] and the Li *et al*[25] results. Crystallinity decreased the degradation rate. Nakamura *et al*[28] observed faster degradation *in vivo* of crystalline PLA, which is in disagreement with the findings reported by Montaudo *et al*.[30] However, Nakamura *et al* explained that the disagreement was due to the processing methodology.

Hurrell and Cameron[31] reported that the initial morphology did affect the release profiles of theophylline (5 wt% loading) from PLA matrices. Samples with higher initial crystallinity released more drugs at the earlier stages of the degradation. It was suggested that this might be due to a partitioning of drug molecules to the surfaces and an increase in the concentration of drug in the amorphous phase, as a result of the exclusion of drug molecules from the crystals. However, we observed the opposite effect in all the polymers studied to date.[56] We believe that this contradiction may be reconciled by the fact that we had intentionally kept the drug concentration (2 wt%) well below saturation limits, and the earlier report of enhanced release with increased crystallinity may be attributed solely to drug de-solvation, leading to leaching out of drug crystals.

EFFECT OF WEIGHT-AVERAGE MOLECULAR WEIGHT

Wang *et al*[33] used PLGA 72/28 having molecular weights of 1.317 and 3.025 kDa, respectively, to study the effect of molecular weight on biodegradation. The oligomer having high molecular weight had a lower biodegradation rate. Similarly, the degradation of the PDLLA microspheres (17 and 41 kDa) during the 53 days incubation period was greatly dependent on the initial molecular weight of the starting sample.[32] The lower molecular weight microspheres experienced significant degradation with reduced glass transition

temperature, while the higher molecular weight microspheres did not show any detectable change in the degradation until 53 days later due to their glassy state.

In contrast, Wu and Wang[35] investigated PLGA samples with the same composition but varying M_w, (166, 124, 66, 31 and 10 kDa), and they observed that the rate constant of degradation decreased from 0.0969 day^{-1} to 0.0472 day^{-1}, in that order. It was speculated that the longer the polymer chains, the more likely the chances of their being attacked by water molecules, a required condition for polymer chain hydrolysis and consequent degradation. Cam *et al*[34] investigated the effect of molecular weight on degradation for films made of PLLA (300, 450, 650 and 3000 kDa) in alkaline medium (pH 11.8). There was an increase in crystallinity from 3 to 30 % for samples from high to low molecular weight, in that order. Throughout the degradation process, PLLA samples of lower crystallinity lost weight more quickly, with little water absorption. On the other hand, PLLA of 3000 kDa lost almost 100 % of initial weight after 175 days, in contrast to 50 % for PLLA of 300 kDa. In conclusion, it is clear that crystallinity dominates the degradation rate and this is consistent with our findings.[55] It is worth noting that PLLA has been found to have a degree of crystallinity inversely proportional to its molecular weight.[34,55]

A study[36] on the effect of the molecular weight of PDLLA on the release of theophylline from tablets (25 wt% loading) showed that the rate decreased as molecular weight increased. Five molecular weight grades (3.5, 42, 92, 138 and 153 kDa) were investigated and the release slowed down progressively as the molecular weight increased. The difference in the rate of release became less significant and reached a limiting asymptotic value as the molecular weight increased to 138 kDa. Liggins and Burt[37] investigated PLLA microspheres having molecular weights of 2, 4, 10 and 50 kDa loaded with paclitaxel (about 30 wt%). As the molecular weight increased, the amount of drug released from microspheres over 14 days decreased. Based on the total content, between 11 and 76 wt% of the total paclitaxel was released over the 14 days of the release study. Wada *et al*[38] investigated the effect of molecular weight on the drug-release rate from PLLA microspheres loaded with insulin and doxorubicin hydrochloride (ADR). The release rate was greatly affected by the molecular weight (3.4, 4.7, 7.2 and 10 kDa). It was found that the remaining ADR amounts were 28.3 and 34 wt% of the initial loading for the 7.2 and 10 kDa polymers, respectively. As expected, the same effect of molecular weight was shown for insulin.

In summary, it is clear that the lower the molecular weight, the faster the degradation and drug release. However, this is the opposite for PLLA due to an inversely proportional degree of crystallinity with the molecular weight.

EFFECT OF THE ADDITION OF DRUG

At the moment, the literature reflects contradictions about the role played by chemically reactive additives. Giunchedi *et al*[60] investigated the degradation profiles of diazepam-loaded microparticles of PLGA 50/50 by a new high-performance liquid chromatography (HPLC) method. Diazepam (base)-loaded particles (2 wt%) have different polymer degradation behavior compared with those prepared without the drug. The rate of degradation was higher for drug-loaded microparticles. About 35 wt% of GA monomer was released from drug-loaded PLGA microspheres in 20 days, in contrast to 8 wt% released from blank microspheres. In a very interesting study, Li *et al*[24] examined the mechanism of hydrolytic degradation of PDLLA in the presence of caffeine (1, 2, 5 and 20 wt%) in order to elucidate the influence of this basic compound. For low contents (<2 wt%), it was suggested that caffeine was molecularly dispersed in matrices and considerably accelerated the matrix degradation compared with the caffeine-free device. During the early stages of degradation, the overall catalytic effect was larger for devices with low caffeine contents, as opposed to highly loaded ones where caffeine was in a crystallized state and hence less available for basic catalysis. According to the data reported, caffeine played a rather complex role in the degradation of PDLLA matrix. During the early stages, caffeine clearly catalyzed the hydrolysis, however, the lower loadings led to faster degradation of the matrix. Accordingly, caffeine should have acted catalytically according to its contents, a feature which was not observed experimentally. Therefore, the larger catalytic effect observed in the case of 1 and 2 wt% loadings, as compared with 5 and 20 wt% loadings, was ascribed to the solubility, with the drug in a dispersed form in the polymer matrix requiring a lag time to dissolve and catalyze the degradation. Zhang *et al*[61] investigated the effects of encapsulated metal salts (10 wt%) on water absorption and degradation properties of PLGA 50/50. It was found that the degradation was strongly influenced by the presence and nature of salts. The control films without incorporated salts showed initial water absorption of about 2 wt% during the first day. This was followed by a lag period during which there was negligible additional water uptake and a second phase of water uptake after 7 days. The effects of salts with low water solubility show an important initial increase of water absorption on the first day compared with the control film. Contrary to expectations, the increased uptake of water by encapsulated salt-containing films did not bring about an increase in the rate of degradation. It was speculated that the reduced degradation rates were due to the alkaline properties of hydroxide and carbonates salts. This was also expected to disrupt the autocatalytic degradation brought about by carboxylic acids generated during polyester hydrolysis. We found[56] that the effect of the chemistry of the drug on the matrix degradation

dominated the release pattern by influencing the rate of degradation. Contrary to other reported work, no effect of complexation of carboxylic end groups by base was found, leading to a slower release of the base drug. We believe that the reported complexation effects occur when dealing with low-M_w PLLA and its copolymers as the concentration of end groups is fairly high in low-M_w polymers. The presence of lidobase accelerated the hydrolysis of polyester links *via* a base-catalyzed reaction, and this effect dominated any other complexation. Polymer loaded with lidosalt degraded faster than the polymer, which was free of drug due to higher water absorption, a result of an osmotic effect.

Bodmeier *et al*,[62] while studying the system based on PDLLA loaded with caffeine (2.8 wt%), salicylic acid (6.7 wt%) and quinidine (12.5 to 22.5 wt%), reported different drug-release patterns. High molecular weight (120 kDa) PDLLA was blended in films of low-M_w PDLLA (2 kDa) containing drugs. Transparent and crystal-free films were obtained for salycilic acid and caffeine; however, the films containing quinidine increased in transparency. Low-M_w PDLLA films containing salicylic acid, caffeine and quidinine showed homogeneous dissolution of the drug so the data can be compared, and it is clear that caffeine released faster than salicylic acid, which in turn released faster than quidinine. The faster drug release was attributed to a reduction of the glass transition temperature, and quinidine exhibited a pattern of release complicated by interactions from carboxyl groups generated from degradation of PDLLA. On the other hand, Li *et al*[24] showed that at low content (<2 wt%), caffeine was dissolved in the matrix and acted catalytically to increase the rate of degradation. At higher loadings, caffeine was partially crystallized, and hence some of it was unavailable for catalytic action. Thus the drug release was dependent on caffeine loading in a complicated manner. The matrices with low caffeine content exhibited a diffusion phase for 11 days, and a degradation phase thereafter. Miyajima *et al*[47] reported the effects of the physico-chemical properties of a drug on its release properties from a matrix of PLGA 70/30 ($M_w = 4.5$ kDa). Five basic drugs (chlorpheniramine, papaverine, diltiazem, verapamil and nicardipine), an acidic drug (naproxen) and two neutral drugs (testosterone and griseofulvin) were investigated from PLGA cylindrical matrix. Incorporation of the various basic drugs raised the T_g of the PLGA rods from 30 °C to more than 41 °C, presumably due to interactions between the carboxylic group of the polymer and the drugs. This interaction kept these drugs dissolved in the matrix during the release studies and also shielded the polymer terminal carboxylic residues, resulting in slower matrix erosion. In contrast, acidic and neutral drugs had only weak interactions with PLGA. Naproxen and testosterone precipitated in the matrix as crystals within one day of immersion in the release medium. Thus, PLGA rods containing these drugs were transformed into a drug-dispersed matrix after water penetration into the matrix. However, the water absorption was shown only for the first day and at this point the drug release of acidic and neutral drugs were about the same. Therefore, it is difficult to consider the water absorption as a correlation and explain a faster release of the acidic drug. In addition, the weight loss was very similar for the matrices loaded with acidic and neutral drugs. It could be concluded that the factor controlling the drug release on the drug-dispersed rod was the solubility of the drug in the polymer matrix, and this is due to the higher solubility of the neutral and acidic drug. In comparing the drug-release rate, the acidic drug released faster than basic drugs, which in turn released faster than neutral drugs. However, it may be noted that a comparison with drug-release behavior of the base would be difficult because acidic/neutral drugs undergo crystallization to form a dispersed drug-matrix, in contrast to dissolved drug-matrix in the case of basic drugs. A comparison of the results reported in two other studies by Miyajima *et al* using PLLA rods ($M_w = 4$ kDa) made by heat compression and loaded with acidic/neutral[47] and basic drugs[48] showed that the extent of release of the basic drug was about 40 % of the initial loading, whereas the acidic and neutral drugs are released to the extent of 50 and 20 %, respectively, within two days of release. The release rate of acidic drugs was faster than that of basic drugs, whereas neutral drugs were found to release at the lowest rate. The reasons were again not very clear but it was suggested that it was due to the interactions between drugs and polymers and solubility of the drug in the polymer matrix. Unfortunately, no degradation data were shown to confirm the drug-release mechanisms proposed. Sung *et al*[63] reported the drug-release results from PLGA matrix of two different compositions, PLGA 75/25 and 50/50. Four nalbuphine prodrugs with various ester chains were incorporated into PLGA-based matrices by using a solvent-evaporation method. The results demonstrated that as the drug solubility decreased, the duration of drug release increased. Again, this study was carried out with implants made of 50 mg of drug and 100 mg of polymer corresponding to a dispersed drug-polymer matrix. However, the author attributed the differences in drug-release rate to the hydrophilicity of the drugs. In our study,[56] lidobase and lidoslat showed distinctly different drug-release profiles from poly[(D,L-lactic acid)-*co*-(glycolic acid)] (PDLLGA). Lidobase was released in a two-phase profile, in contrast to a distinct three-phase drug-release pattern of lidosalt from PDLLGA. Lidobase significantly accelerated the degradation by base catalysis, leading to an early breakdown of the matrix compared with a more stable PDLLGA film loaded with lidosalt. The drug was sustained for 2–3 weeks in a range of 10–20 % before breaking down and was totally released after one month. Semi-crystalline PLLA showed a very slow single diffusion-controlled release profile for both drugs due to its insignificant water absorption and degradation state.

It is clear that one should seriously take the effect of the chemical properties of the drug into consideration to explain the drug-release mechanisms of a particular system using biodegradable polymers.

EFFECT OF SIZE OF THE MATRIX

Degradation has been shown to be heterogeneous in the case of large-size devices, with the rate of degradation being greater inside than at the surface. However, the model also suggested that devices with dimensions smaller than the thickness of the outer layer should degrade less rapidly than larger ones. Basically, all the leachable oligomeric compounds formed within the matrix should be able to escape from the matrix as soon as they become soluble. Witt and Kissel[23] reported that the rates of PLGA 50/50 weight loss decreased with increasing surface to volume ratio, from tablets ($1.5\,mm^{-1}$) and rods ($2.8\,mm^{-1}$) to films ($7.3\,mm^{-1}$) and microspheres ($38.2\,mm^{-1}$). PLGA exhibited an apparent constant rate of degradation of 0.041, 0.093, 0.115 and $0.1035\,day^{-1}$ for microspheres, films, rods and tablets, respectively. However, the average molecular weight decreased faster for microspheres compared with tablets. Grizzi *et al*[22] showed that the degradation rate of various devices derived from the same PDLLA polymer depended very much on size, and it was the first report to propose a critical thickness. The hydrolytic degradation proceeds heterogeneously in the case of large-size devices, with the rate being greater inside than at the surface. The results show that plates had a lower water absorption and weight loss for the first 10 days, followed by a rapid increase of water absorption and weight loss to complete the degradation after 15 weeks. This is in contrast to films reaching only a weight loss of 25 % after 30 weeks of immersion. This weight-loss trend was consistent with the decrease of the average molecular weight. The authors proposed a value of 0.2–0.3 mm as a critical thickness above which the PLGA matrix is believed to undergo heterogeneous degradation. In agreement with Grizzi's work, Li *et al*[24] investigated the hydrolytic degradation of PDLLA pellets ($M_w = 65\,kDa$). At week 3 the specimens revealed heterogeneous cross-sections after breaking. A whitish outer layer appeared, whereas the inner part was yellowish and transparent. At week 5, the inner part of the specimens appeared as a very viscous liquid, whereas the outer layer was still rigid. A size-exclusion chromatography (SEC) analysis of the outer and inner parts of partially degraded specimens revealed that biodegradation was significantly larger in the inner part than at the surface. In another study, Li *et al*[25] reported a heterogeneous degradation path of semi-crystalline and amorphous PLA pellets. Amorphous PLA remained transparent for 18 weeks and then turned whitish. At week 40, cross-sections appeared white from the surface to the centre for the semi-crystalline, in contrast to PLA amorphous specimens exhibiting a heterogeneous degradation with a surface–centre differentiation. However, after 12 weeks there was little difference in molecular weight between the surface and the centre for both PLA polymers. Furthermore, Lu *et al*[21] demonstrated that thick films degraded faster than thin films of the same composition. Thickness levels were 5–10 μm for thin PLGA films and 85–100 μm for thick films. Thick films degraded faster than thin ones with the same copolymer ratio over the 10-week period and thus a greater extent of water uptake. This was evident from the accelerated profiles of mass loss and drop in molecular weight. It was suggested that faster degradation of thick films was due to the greater extent of autocatalytic effect. This was reported to be less evident for thin films, as expected. All the PLGA films degraded by heterogeneous bulk degradation mechanisms and this result disagrees with Grizzi's critical thickness and model of ease of diffusion of oligomers through thin films.[22]

In summary, one can expect a heterogeneous degradation from the bulk and the surface of the matrix with a thickness of more than 0.2–0.3 mm. This is characterized by an acceleration of degradation and drug-release rate due to acid catalysis of carboxylic end groups.

EFFECT OF pH OF *IN VITRO* RELEASE MEDIUM

Wu and Wang[54] used PLGA having an equal molar ratio of lactic to glycolic acid (50/50) to conduct a series of experiments. The effect of the pH of the *in vitro* release medium on the rate of biodegradation/hydrolysis of the PLGA was not obvious within the first two weeks of immersion. It was observed that the rate of degradation increased in acidic medium (pH 5), but slowed down when the medium was alkaline (pH 9.24). While the degradation in pH 9.24 reached a plateau after a certain period of time, in neutral (pH 7.4) and acidic media (pH 5.0) the polymer continued to degrade, with the fastest rate recorded at pH 5. The result suggests that the PLGA in a basic medium may degrade slower than in an acidic one. In the first few weeks, the integrity of the matrix is retained, although the polymer chains may have undergone hydrolytic scission, leading to a lowering of molecular weight. Presumably, the hydroxide ions from the medium outside and the hydronium (H_3O^+) ions generated by the initial matrix hydrolysis cannot diffuse in and out of the matrix freely, thus accounting for the non-obvious difference in the rate of degradation during the initial stage.

In contrast, Makino *et al*[15] reported that microcapsules of PLLA exhibited rapid weight loss in alkaline media (pH 8–9). Trends in the decrease of M_w indicated that such drops occurred more readily in alkaline media of pH 8–9. While there was no change in the distribution of molecular weight in neutral solutions, there was a broadening of the distribution in alkaline solutions. Apparently, depolymerization may

have been accelerated by production of intermediate molecular weight fractions. In a closely related study, Wang *et al*[33] showed that the degradation of PLGA was faster at pH 9.4 than at pH 7.4, indicating that base catalysis may be dominated in the alkaline range of pH 7.4–9.0. It is known that the hydrolysis of a carboxylic ester is an equilibrium reaction. In a study with 24 days of degradation of two samples of PDLLA, Belbella *et al*[18] reported that degradation of PDLLA ($M_w = 25$ kDA) appeared to be directly related to the pH value, whereas the degradation rate of PDLLA ($M_w = 95$ kDa) was highest at extremes of pH. PDLLA of M_w 25 kDa was more susceptible (than its high-M_w counterpart) in acid medium, losing more than 75 % of initial value. Conversely, in basic medium (pH 10.1) the degradation of PDLLA (95 kDa) was more pronounced. Thus, 102 days of study for the sample experienced 50 % reduction in nearly neutral body pH (7.4), whereas degradation was almost complete in both acidic (pH 2.2) and basic (pH 10.1) media. The different behavior between the two samples of PDLLA in acidic pH can be explained by the tail-spreading of the chromatogram of PDLLA (25 kDa) towards very low molecular weights, which indicates the presence of water-soluble oligomers, which possibly play a significant part in catalyzing the process of hydrolysis. On the other hand, with a basic medium, the degradation of low-M_w PDLLA (25 kDa) is lower at its early stages, in contrast to the trend in acidic medium. This can be explained by the adverse effect of the carboxylate ions, which form a negatively charged screen, hindering OH^- ions from penetrating into the polymer bulk. Thus the attack was concentrated on the surface at its early stages, which is in agreement with the moderate decrease of M_w and mass loss. Similarly, Holy *et al*[64] studied the *in vitro* degradation of macroporous PLGA 75/25, for application in tissue engineering, at 37 °C, over a period of 30 weeks and at one of three different pH values. The degradation profile of foams maintained at pH 5, 6.4 and 7.4 was similar until week 16, after which foams maintained at pH 6.4 and 7.4 had comparable degradation patterns whereas foams maintained at pH 5.0 degraded faster. However, Makino *et al*[15] observed a faster decrease of molecular weight of PDLLA microcapsules in a highly alkaline buffer solution (pH 9.6) than in a highly acidic pH (1.6–3) and slightly alkaline buffer solution (pH 7.4). No significant changes were observed during the immersion in the slightly acidic buffer solutions (pH 5). Since the cleavage of ester bonds takes place with different mechanisms depending on the pH of the medium (acid- and base-catalyzed reactions), large quantities of low-molecular weight PDLLA are produced in the highly alkaline solution by the de-esterification reaction, *via* production of polymers of intermediate molecular weights

It can be reasonably concluded that both alkaline and strongly acidic media accelerate polymer degradation. The difference between slightly acidic and neutral media, however, is less pronounced due to autocatalysis by the carboxylic end groups.

EFFECT OF PLASTICIZER

Kranz *et al*[12] investigated the mechanical properties of PDLLA and PLGA 50/50 films as a function of exposure time in buffer and in correlation with the degradation/erosion of the polymer. Triethyl citrate (TEC), a water-soluble plasticizer, leached from the films. This resulted in major differences in films with the more permanent water-insoluble acetyltributyl citrate (ATBC). Plasticized PDLLA films, which were above their glass transition temperature in the rubbery state, showed a faster decrease in M_w than plasticizer-free PDLLA ones, which were in the glassy state. The addition of plasticizer to the PLGA did not enhance the polymer degradation, whereas the plasticizer-free PLGA was already in the rubbery state. Andreopoulos[13] investigated the effect of plasticization (of propylene glycol) on low-molecular weight PDLLA tablets. It was clear that the rate of delivery of salicylic acid for the plasticized samples was higher than that of the pure polymer, at least for a period of 150 h. Interestingly, as the drug release proceeded, the delivery rate seemed to reach a level independent of the initial plasticizer content. A possible interpretation is the leaching of plasticizer by the surrounding medium, so that the composition of tablets eventually became similar for all.

EFFECT OF STERILIZATION

The most frequent method used for destroying all forms of microbial life is steam sterilization, but this process cannot be used with delivery systems based on PLGA/PLA for two reasons. First, the heating would cause a deformation of the matrix, and second, the penetrating high-pressure steam would initiate hydrolysis of the polymer. Therefore, radiation sterilization is still considered to be the technique of choice to produce sterile drug-polymer-matrices for clinical uses. Several authors have examined the influence of γ-irradiation on the degradation of LA/GA polymers. Gamma rays are known to induce structural changes, such as scission and crosslinking, in irradiated polymers. Such changes will in turn influence the drug-release characteristics and the rate of biodegradation, when these polymers are used as drug carriers. Doses of 2.5 Mrad are generally accepted as being satisfactory for sterilizing pharmaceutical products. An SEC analysis of the irradiated PLGA 75/25 and PLGA 50/50 showed that both M_n and M_w decreased. For high-molecular weight polymers gamma-sterilization resulted in degradation of the M_w (25 %).[4] Meanwhile, Hausberger *et al*[5] demonstrated a substantial effect of γ-irradiation on initial molecular-weight distribution and the onset of mass loss for PLGA. The first 1.5 Mrad of radiation produced the largest drop in M_w (14 %)

and a 26 % drop in M_n. Irradiation decreased M_n more drastically than M_w and the increase of the dose from 1.5 to 5.5 Mrad increased the degradation rate. The time required to reach 50 % of the initial mass decreased with increasing irradiation dose. Thus, the duration was approximately 8 weeks (0 Mrad), 7 weeks (1.5 Mrad), 6 weeks (2.5 and 3.5 Mrad), and 5 weeks (4.5 and 5.5 Mrad). In a detailed study, Nugroho *et al*[7] investigated the effect of γ-irradiation on degradation of PLLA. Melting point (T_m), glass transition temperature and M_n decreased with increasing irradiation dose. At low doses, T_m, T_g and M_n decreased sharply at first, followed by a slower rate. Up to a certain value, PLA was predominantly degraded by random chain-scission. Biodegradation of PLA was retarded with increasing dose due to the introduction of crosslinking during irradiation. Hooper *et al*[6] studied the effect of ethylene oxide and γ-irradiation on selected tyrosine-derived polycarbonates and PLLA. Ethylene oxide exposure of PLLA did not affect the molecular weight, surface exposition, mechanical properties or *in vitro* degradation rate. However, upon irradiation at 10.6 Mrad, PLLA retained only 29 % of its initial molecular weight. Irradiation of PLLA induced significant losses in the Young's modulus and strain at break.

Faisant *et al*[8] reported that the release of 5-fluorouracil (5-FU) from microparticles based on PLGA depended significantly on the applied γ-irradiation dose. Only the initial rapid drug release was accelerated by γ-irradiation; the subsequent zero-order phase was almost unaffected. This could be explained by the free-volume theory of diffusion: exposure to the γ-irradiation source resulted in random polymer chain-scission with a decrease in the average molecular weight. The subsequent free volume increased with increasing γ-irradiation dose, creating a more pronounced effect on drug release.

EFFECT OF STRAIN

Arm and Tencer[10] demonstrated that the rate of release of bovine albumin from PLGA 50/50 rods correlated with bending load. Cumulative drug release was significantly higher when a cyclic bending load was applied and increased with the magnitude of the load. Significant differences in the rates of release of drug for the three loading cases were observed at day 1, compared with unloaded specimens and specimens with 0.5 mm of deflection. With 1 mm of central deflection of the implant under load, release was complete after four days. The differences in release between deflection groups were significant up to four days, with the faster release observed in the more highly stressed implants. There were no differences measured between specimens subjected to the different loading regimes, and no differences were found on the average molecular weight with magnitude of deflection of the implant. However, pores on the surface of the polymer in the regions of highest stress were elongated into cracks, compared with pores in the low-stress region of the same implant, which were roughly circular. Presumably, these pores were responsible for the faster drug release observed. Edelman *et al*[11] proposed the use of mechanical deformation to modulate protein release in polymer matrices. The results showed self-diffusion through pores, rupture of the polymer matrix as a result of sorption of water by the hydrophilic protein, and polymer biodegradation. Pores that may be the result of protein dislodgement at the surface, from which cracks initiated, enhanced the rate of release.

In summary, the effect of strain induces the acceleration of degradation and drug-release rate due to the formation of cracks and pores.

EFFECT OF ENZYMES

Despite extensive investigation, controversial data are still found in literature, in so far as the degradation mechanism (hydrolytic *versus* enzymatic cleavage) is concerned. The suggestion has been made several times that enzymes may be involved in the degradation processes of polymers. Authors generally base their discussion on *in vitro* loss of radioactivity of ^{14}C radio-labelled polymers, and sometimes on the decrease of mechanical properties or the differences observed between *in vivo* and *in vitro* degradation rates. The polyesters were re-examined in the hope of gaining a better understanding of specific structural configurations in a polymer that favors biodegradability.[42] Lu *et al*[16] compared the *in vivo* and *in vitro* degradation of porous PDLLGA foams. A significant difference in half-life was found between *in vitro* and *in vivo* degradation. The *in vivo* degradation time was significantly shorter due to the autocatalysis effect of the acidic degradation products, which were released from the polymer matrix but accumulated in the medium surrounding the implants. This effect was minimized for foam degradation in phosphate buffer solution by the frequent change of the medium. Unfortunately the differences on degradation rate in this study did not explain the direct effect of the enzymes due to the frequent changes of the *in vitro* medium. Furthermore, Li *et al*,[43] in studies on amorphous film from L,D-lactide (10/90, 25/75 and 40/60 L/D), showed a remarkable dependence of L-lactyl unit content on the weight-loss rate. It was confirmed that proteinase K preferentially degrades L-lactyl units as opposed to D-lactyl ones. With only 10 % of L-lactyl units in its chains, PLA_{10} showed negligible enzymatic degradation, while degradation of PLA_{40} and PLA_{25} was much more pronounced. The higher water-uptake ratio in the case of PLA_{40} and PLA_{25} could also have facilitated the enzymatic attack. These results are consistent with other studies from the same author.[44]

In contrast, Hooper *et al*[45] reported the similarity of degradation rates of each polymer, confirming the absence of enzymatic involvement in the degradation

process. A comparison of molecular weight retention, water uptake, and mass loss *in vivo* with two commonly used *in vitro* systems of phosphate buffer solution (PBS) and synthetic body fluid (SBF) demonstrated that for PLLA the *in vivo* results were better simulated *in vitro* using PBS. While incubation in PBS did not lead to noticeable change in the surface roughness, incubation in SBF resulted in blistering at the implant surface. There were noticeable differences in mass loss. In spite of those differences, the rate of backbone degradation was identical. Furthermore, the curves of M_w retention *in vivo* and *in vitro* superimpose accurately. Thus, both PBS and SBF can be used to simulate the rate of backbone degradation of PLLA *in vivo*. However, PBS seemed to be the more appropriate incubation buffer for an accurate simulation of the *in vivo* water uptake and erosion behavior. Leeslag *et al*[46] investigated the *in vitro* and *in vivo* degradation of high-molecular weight PLLA polymers ($M_v = 680-950$ kDa). No significant differences between the *in vivo* and *in vitro* degradation were observed, which excludes the additional effect of enzymes for 39 weeks.

There is a clear difficulty in comparing and explaining the effect of enzymes due to the lack of standardization for *in vivo* studies, therefore, the choice of the enzymes is a predominant factor. However, as Li *et al*[43] suggested, water absorption might be the determinant factor and this is in agreement with the results reported by Hooper[45] and Leeslag,[46] showing no significant differences between the *in vivo* and *in vitro* environment due to little water absorption of high-M_w PLLA.

EFFECT OF DRUG LOADING

Drug content has a considerable effect on the rate and duration of drug release. Microgranules having higher drug content possess a larger initial burst release than those having lower content. This is due to the smaller oligomer–drug ratio. However, this drug content effect disappears when the drug content reaches a certain level. There is no significant release-rate difference between the microgranules having 15 and 20 wt% drug content.[40] Similarly, Wada *et al*[38] found that the release rate of drugs from PLLA ($M_w = 4.7$ kDa) microspheres was greatly affected by the initial loading. In the case of 20 wt% insulin-loaded microspheres, the burst effect reached 50 % of the initial amount of drug compared to about 20 % for 10 wt% insulin-loaded microspheres. Only 70 % of the total amount of drug was released after 15 days. Sampath *et al*[65] investigated PLLA microcapsules and cylindrical implants as localized antibiotic therapy. The release of gentamicin sulfate was strongly dependent on the loading (5, 10, 33, 50 and 67 wt%). The release profiles of microcapsules containing 50 and 67 wt% gentacymin were similar to that of microcapsules containing 33 wt% drug, while microcapsules with 20 wt% drug had a release profile similar to that with 10 wt% drug loading. Complete drug release occurred within three weeks. Microcapsules with higher drug loading, *eg* 33 wt% or greater, showed complete release of gentacimin in three days. Okada *et al*[66] investigated *in vivo* release mechanisms of PLLA (18.2 kDa) microspheres charged with different amounts of leuprorelin (9–18 wt%). The release rates were consistent with the loading of the drug in the microspheres. The release rates for the microspheres charged with 15 and 18 wt% were rapid because of an increase in the number of aqueous channels formed by the hydrophilic drug. After four weeks, microspheres loaded with 15 and 18 wt% of drug released 60 % of the initial loading. This is in contrast to 80 % for 9 and 11 wt% loading. Gümüsdereliod lu and Deniz[59] investigated the effect of drug loading on PLGA 70/30 ($IV = 0.6\,g\,dl^{-1}$) loaded with MMC on drug release. The results suggested that MMC release rates and total releasable fraction significantly increased with increasing initial drug loading (2:300, 1:300 and 0.5:300 mg drug:polymer). On the other hand, Miyajima *et al*[47] reported the fraction of drug release from PLGA 70/30 ($M_w = 4.5$ kDa) rods containing 5 and 10 wt% of the basic drug verapamil, and found that the release rate from the rod with 5 wt% loading was larger than that from the 10 wt% loaded one. Higher drug content resulted in higher glass transition, smaller water absorption and less weight loss. This relationship indicates that in the 10 wt% loaded rod, a larger fraction of the polymer carboxyl residues were held by the interaction with the basic drug, slowing the release. The glass transition of the 10 wt% loaded rod was higher than that of 5 wt% loaded rod, by at least 5 °C. This implies that the effect of drug content on the release has no significant impact on drug-release behavior. In another study, Miyajima *et al*[48] investigated the effects of drug content (5, 8, 10, 15 and 20 wt%) on the release of papaverine (PAP) from PLLA (4 kDa). A drug-dissolved matrix was prepared by heat-compression melting. In the case where the rods contained more than 15 wt% of PAP, the drug precipitated out to form crystals during release. Increasing PAP content up to 10 wt% resulted in a decrease of diffusion coefficient and a rise in T_g. Possible interactions between the polymer carboxyl residues and the drugs were suggested for causing an increase in matrix rigidity.

EFFECT OF FLUID FLOW

Agrawal *et al*[3] studied the effect of fluid flow on the *in vitro* degradation of biodegradable scaffolds using PLGA 50/50. These scaffolds were subjected to degradation in PBS for up to six weeks under two test conditions: static and flow ($250\,\mu l\,min^{-1}$). The results showed that the lower the porosity and permeability of the scaffolds, the faster their rate of degradation. Additionally, fluid flow decreased the degradation rate significantly. Weight loss and average molecular weight decreased much faster under static conditions

compared with flow conditions for all samples. If these degradation products are removed from the vicinity of the reaction in an expedient fashion, they lead to a slower rate of degradation and mass loss. It is likely that the acidic byproducts are washed away rapidly under flow conditions, thus impeding the autocatalytic process.

EFFECT OF FABRICATION PROCESSING

During the preparation of microspheres, Park[32] reported that hydrolysis occurred with the formation of oligomers. The process of solvent evaporation and the drying process permitted the polymer to have a relatively short exposure time with water, reducing the chances of the process parameters affecting the degradation. The average molecular weight decreased from 17 kDa to 12 kDa during the preparation of the poly(D-lactic acid) (PDLA) microspheres. Weiler and Gogolewski[67] reported that PDLA was amorphous after processing (extrusion, injection molding). The solid extrusion was carried out at temperatures in the range of 105–170 °C. Commonly used melt-processing led usually to extensive material degradation. The melt-extrusion of poly(D-lactide) bars showed a 40 % reduction in M_v as a result of thermo-oxidative degradation. The molecular weight decreased from 280 to 160 kDa. In agreement, Mainil-Varlet *et al*[68] showed that the raw material had a significant decrease in M_w from 202 to 55 kDa after injection molding.

In contrast, Rothen-Weinhold *et al*[4] reported that the effect of extrusion of PLGA 75/25 and PLGA 50/50 at 90 °C caused no significant decrease in M_w (less than 5 %). Surprisingly, for all polymers investigated, extrusion prior to γ-sterilization appeared to protect the polymer from molecular degradation.

EFFECT OF TEMPERATURE

Belbella *et al*.[18] reported that higher temperatures accelerated the degradation process of PDLLA. Results were based on the quantity of lactic acid released during the aqueous phase of the PDLLA nanosphere dispersion, after one month of conservation at three temperatures: −18, 4 and 37 °C. At pH 7.4, the degradation of the nanospheres is much faster at 37 °C than at 4 and −18 °C. Jamishidi *et al*[69] studied the long-term degradation behavior of PLLA fibers in PBS at 37 and 100 °C (30 °C higher than the *T*g of PLLA fibers). Tensile strength was reduced to half of the initial strength after 10 hours in PBS at 100 °C, in contrast to no changes at 37 °C. Aso *et al*[70] reported the effect of temperature (37 and 50 °C) on the degradation rate of PDLLA microspheres and discs at pH 12. The degradation of discs and microspheres showed temperature dependence. At 37 °C the molecular-weight change was negligible and appreciable weight loss was only observed by one week (8 %). This suggested that the degradation of PDLLA was restricted to the surface of the matrix. On the other hand, at 50 °C the molecular weight decreased rapidly and indicated a bulk process. In agreement, Hakkarainen *et al*[19] reported a dramatic effect of temperature (37 and 60 °C) on the degradation rate of PLLA and PLGAs. At 60 °C the hydrolysis was several times faster. After 60 days, 56 % of PLLA was lost compared with only 20 % at 37 °C. The molecular-weight decrease was consistent with the weight-loss results, showing a remaining molecular weight of about 50 % after 10 days at 37 °C, compared with 15 % at 60 °C. The same pattern was shown for PLGA polymers.

In summary, the degradation mechanism is strongly dependent of the temperature, which has a dramatic effect on the rate of mass loss. With a temperature higher than the glass transition temperature of the polymer, the rate of weight loss is drastic.

CONCLUSION

In general, polymer degradation and drug-release rate are accelerated by greater hydrophilicity in the backbone or end groups, greater reactivity among hydrolytic groups in the backbone, less crystallinity, and larger finished size of the device. Interestingly, the crystallinity dominates the effect of the molecular weight for PLLAs. All these parameters must be taken into account in order to control the degradation and drug-release mechanism for a targeted application. Thus, for a short-term release requirement (up to one month), an amorphous polymer with high hydrophilicity is recommended. For a longer-term release requirement (one to six months), the choice of an amorphous polymer with high molecular weight would be appropriate. Finally, for long-term release (more than six months), semi-crystalline polymer with a high degree of crystallinity can be considered. One should note that the burst release could be viewed from two perspectives. On one hand, it is often regarded as an undesirable consequence of creating long-term controlled release devices and to be due to the difficulties in obtaining repeatable results (local and systemic toxicity of the drug, short half-life of drugs *in vivo*, wastage and requiring more frequent dosing). On the other hand, in certain situations, it may be considered desirable (wound treatment, pulsatile release and targeted delivery) only for non-toxic drugs. In addition, ethylene oxide is still found to be the more suitable method of sterilization for such polymers. The major factors leading to an increase of degradation and drug-release rate can be summarized as follows:

- Hydrophilicity: high glycolic acid content, $M_w < 100$ kDa, amorphous state;
- Additives: basic drugs, plasticizers;
- Thickness: > 0.2 mm;
- Medium: $5 < pH < 8$;
- Processing: temperature $> T_g$, air, strain.

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