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Effect of poly-hydroxy aliphatic ester polymer type on amoxycillin release from cylindrical compacts

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Abstract

The objective of the work was to investigate the effects of a range of poly-hydroxy aliphatic esters (poly-lactide (PLA) and poly-lactide-co-glycolide (PLGA)) of different molecular weight and composition on the release and stability of the amphoteric drug amoxycillin. The effect of this amphoteric drug on the extent and kinetics of polymer degradation was also investigated. The polymers were used to prepare drug-free and drug-loaded cylindrical discs. Drug release profiles were determined while changes in polymer composition were monitored by weight loss and molecular weight change. The extent of drug release was highly dependant on polymer molecular weight and composition, with earlier complete release occurring with the lower molecular weight and lower lactide containing polymers. A larger proportion of drug was released by polymer degradation control with the higher lactide containing polymer. The proportion of drug released intact was influenced by the polymer molecular weight, with a greater proportion of intact drug being released from the higher molecular weight systems. The inclusion of amoxycillin influenced polymer degradation and resulted in slower polymer hydrolysis. Model parameters obtained for polymer degradation indicated that this retardation effect increased with increasing lactide content of the polymer. The results suggest that small amounts of amoxycillin or its degradation products may bind or cross link with the polymers, thus retarding their degradation.

Keywords: Poly (D,L-lactide-co-glycolyde) (PLGA); Amoxycillin; Polymer degradation-controlled release; Amphoteric drugs; Drug degradation; Glass transition temperature

1. Introduction

Previously we reported that amoxycillin release from poly (D,L-lactide-co-glycolide) (RG 503) compacts showed two distinct phases separated by an induction period (Mollo and Corrigan, 2002). Thus, both diffusion and polymer degradation mechanisms were involved in drug release, the relative importance of each depending on processing type and drug loading. The fraction of total drug released, in the initial release phase, increased with drug loading and was much larger for compressed physical mixtures than for compressed composites prepared from co-evaporate films. Significant drug degradation also occurred and this was associated with antibiotic release at later times. Release data suggested accelerated amoxycillin degradation during the polymer degradation-controlled release phase, consistent with changes in pH in the microenvironment of the eroding compact (Mollo and Corrigan, 2002).

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The development of extended release antibiotic formulations using biodegradable polymers has been previously reported, for example PLA-ampicillin films for maxillary sinusitis (Min et al., 1995) and PLGA-gentamicin systems for osteomyelitis associated infections (Zhang et al., 1994). Ampicillin poly (D, L-lactide-co-glycolide) microcapsules were also developed (Setterstrom et al., 2001). Since the antibacterial spectrum of penicillins is usually broad, controlled release systems containing them have potential applications in a range of human and veterinarian areas.

The aim of this work was to investigate the release of amoxycillin from a range of poly-hydroxy aliphatic ester matrices, to explore the impact of polymer type on the relative contributions of dissolution, diffusion and polymer degradation to drug release, in order to reduce the extent of drug degradation and to evaluate further the impact of the presence of drug on polymer degradation.

2. Materials and methods

Amoxycillin trihydrate was purchased from Sigma. The polymers were purchased from Boehringer Ingelheim. Their specified intrinsic viscosities (i.v.) were, for the lactide-co-glycolide copolymers, RG 503 i.v. approximately 0.4, RG 504 i.v. approximately 0.5, RG 755 i.v. approximately 0.6, and for the pure lactide, R 203 i.v. approximately 0.3.

Cylindrical 13-mm discs were prepared by the solvent evaporation (SE) method, with compression of the films formed as previously described. The films were formed on a Teflon® plate while the solvent (acetone and dichloromethane) evaporated at room temperature in a vacuum dessicator. An amount of film of similar weight to the desired final disc weight (120 mg on average) was employed and compressed at 10,000 kg/cm^3 for 10 min under vacuum in the preheated 13-mm hydraulic press (Mollo and Corrigan, 2002).

Drug release and polymer mass loss experiments were conducted in phosphate buffer pH 5.9 in a shaking water bath (95 rpm and 37 °C), as previously described (Mollo and Corrigan, 2002).

Total drug release (intact amoxycillin plus degraded) was analysed by UV spectroscopy at 230 nm as outlined previously (Mollo and Corrigan, 2002). Intact amoxycillin was quantified by a HPLC stability indicating method based on the drug monograph (USP XXIII, 1995) and drug absorbance was measured at 230 nm. A Novapack C18 column (Waters) was used, the mobile phase involving a compositional gradient whereby an aqueous potassium phosphate solution (6.8 g/l) was gradually converted to a solution containing 10% acetonitrile (Mollo and Corrigan, 2002).

Polymer loss was calculated from the difference between the total mass loss and the total amount of drug released at a given time, during a release experiment. Polymer loss was also determined for drug-free discs (Fitzgerald and Corrigan, 1996; Gallagher and Corrigan, 2000). In all the cases, the disc was removed from the release medium at a given time and dried in a desiccator until constant weight was achieved. In order to determine entrapped drug and establish its chemical integrity, dried discs were extracted with dichloromethane and analysed.

The software package Scientist version 1.05 (Micromath Scientific Software 1995) was employed to fit a particular model to the data. Estimated parameters, 95% confidence levels and standard deviations (S.D.), were generated by the software. The ability of an equation to describe the experimental data was assessed using the coefficient of determination (r^2) and model selection criterion (MSC) (Micromath Scientific Software, 1995), the most appropriate model being that with the highest MSC.

Amoxycillin and polymer systems were characterised by DSC in the temperature range 0–180 °C at a rate of 10 °C/min. The amount of sample used varied from 5 to 15 mg depending on the type of sample analysed. DSC analyses were performed in duplicate, utilising 40 μl aluminium crucibles that were sealed and pierced at the top, under N_2 atmosphere. The heating cycle was repeated twice in all samples. Glass transition temperatures, T_g, were determined using the STAR^e Software (Mettler Toledo), on the basis of the second heating scans.

Polymer molecular weights were determined by GPC using a Waters Styragel column with THF as the mobile phase (Waters 510 pump) and a Refractive Index Detector RI 410 (Waters). Millenium Chromatography software version 2.0 was employed to integrate the peaks and calculate the results. Samples were evaluated against a series of polystyrene standards of M_w 2500, 13,000, 90,000 (Aldrich)

and 5970, 37,900 (Tosoh, Japan). Baseline values of weight-average molecular weight (M_w) and the number-average molecular weight (M_n) as defined by Painter and Coleman (1994) were determined for the co-polymer powders RG 503, RG 504, RG 755 and the pure lactide R 203. The polydispersity P of a polymer was calculated as $P = M_w/M_n \geq 1$.

The sample preparation for nuclear magnetic resonance (NMR) studies involved the dissolution of approximately 5 mg polymer samples in 2 ml $CDCl_3$, aided by sonication if required. The ^{13}C NMR data was processed at 100.61 MHz and the ^{1}H NMR at 400.13 MHz.

3. Results

3.1. Effect of polymer type on amoxycillin (20%) release from poly-hydroxy aliphatic ester compacts

The effect of polymer type on total drug released from PLA/PLGA discs containing 20% drug was investigated during long-term release experiments (~4 months). Significant differences were seen in the release profiles depending on the polymer employed (Fig. 1). As the proportion of lactide in the polymer increased, the overall release time also increased. The amoxycillin release versus time profiles showed an initial release phase followed by a plateau and then the second release phase. These phases varied greatly in magnitude and/or duration and in the proportion and rate of drug released in each phase. In the case of RG 504, the two phases overlapped. The proportion of drug released in the initial phase was greatest for the highest molecular weight polymer, RG 755, followed by RG 504. Consequently, there was a lower amount of total drug released in the final, polymer degradation-dependant phase as the molecular weight increased. The data in Fig. 1 were fitted to Eq. (1) and the drug release related parameters obtained for the different polymers are summarised in Table 1.

$$F_{tot} = F_{b\infty}(1 - e^{-k_b t}) + (1 - F_{b\infty})\left(\frac{e^{kt - kt_{max}}}{1 + e^{kt - kt_{max}}}\right) \quad (1)$$

where k_b is the burst rate constant, $F_{b\infty}$ is the total burst fraction at time infinity, t_{max} is the time for maximum rate and k is the rate constant of the polymer degradation release phase (Gallagher and Corrigan, 2000). Drug release data from the earlier RG 503 systems (Mollo and Corrigan, 2002) is also included in Fig. 1 for comparison. The R 203 polymer gave the longest t_{max}, reflecting the longest delay until the onset

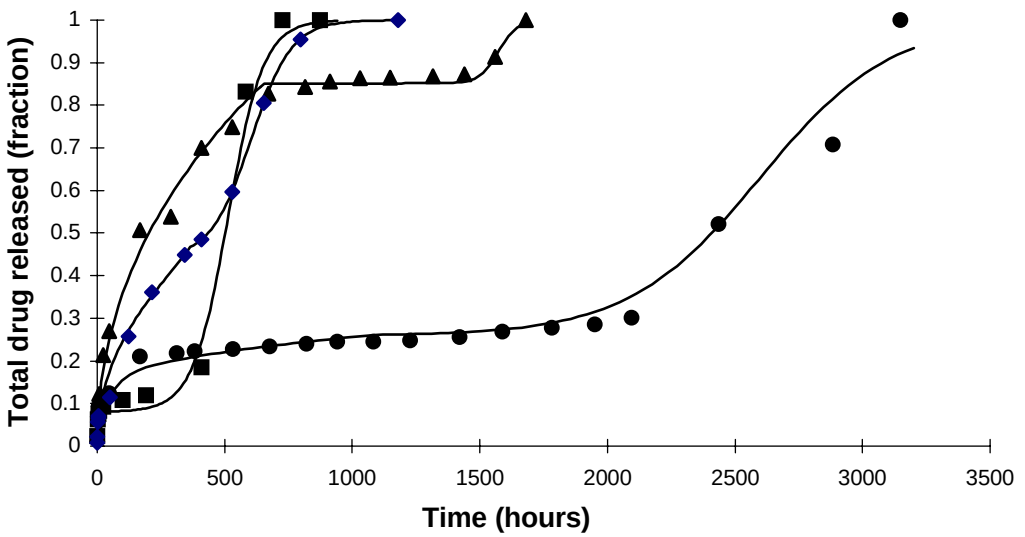

Fig. 1. Fraction of total drug released vs. time from amoxycillin (20%) loaded SE discs, RG 503 (■), RG 504 (◆), RG 755 (▲) and R 203 (●). Fitted lines where obtained using Eq. (1).

Table 1
Estimated parameters obtained using Eq. (1), for drug release profiles of RG 504, RG 755 and R 203 SE systems loaded with 20% amoxycillin trihydrate

Parameter	System		
	RG 504	RG 755	R 203
$F_{b\infty}$ ± S.D.	0.488 ± 0.078	0.629 ± 0.063	0.262 ± 0.015
k_b ($h^{-1} \times 10^3$) ± S.D.	61.9 ± 1.92	5.44 ± 1.20	6.64 ± 2.12
k ($h^{-1} \times 10^3$) ± S.D.	13.1 ± 3.47	1.69 ± 0.45	4.15 ± 0.60
t_{max} (h) ± S.D.	611 ± 25	718 ± 104	2660 ± 46
r^2	0.9946	0.9899	0.9695
MSC	4.65	4.19	3.07

of the degradation-controlled drug release phase. The model fit was poorest for this polymer. The RG 755 polymer gave the largest non-polymer degradation dependant phase encompassing ~63% of the drug load.

The release profiles of intact amoxycillin, determined using the HPLC method, are shown in Fig. 2. Evaluation of the chemical integrity of the drug was attempted beyond 700 h, however, quantifiable levels of intact drug were not detected beyond this time. The release profiles of intact drug were less complex than those for total drug. Initial release was rapid from all systems, the rate declining with time. A degradation-controlled drug release phase was absent, indicating that the later drug release phases observed in Fig. 1 was due to degraded drug. Similar findings were observed previously with RG 503 (Mollo and Corrigan, 2002). Those formulations prepared with RG 755 and RG 504 offered greater recovery of intact amoxycillin, i.e. the higher molecular weight formulations resulted in higher proportion of intact drug release and also showed the greatest duration of release of intact drug. A maximum of approximately 60% intact drug release was achieved with the RG 755 and RG 504 formulations, while less than 20% was recovered intact from the RG 503 and R 203 formulations. The polymer degradation data (Section 3.3) also support the concept that the majority of intact drug is released prior to onset of the polymer degradation/mass loss phase.

Polymer matrix-controlled drug release data, for example, for dihydroisoandrosterone-PLA microspheres (Ramtoola et al., 1991) or loaded pentamidine-PLA nanoparticles (Paul et al., 1997), were fitted to the general Eq. (2) (Ritger and Peppas, 1987):

$$F_{tot} = Bt^n \quad (2)$$

where F_{tot} is the fraction of drug released at time t, B and n are constants. The diffusional exponent, n, is indicative of the release mechanism. A value of 0.5 corresponds to matrix type release from a planar

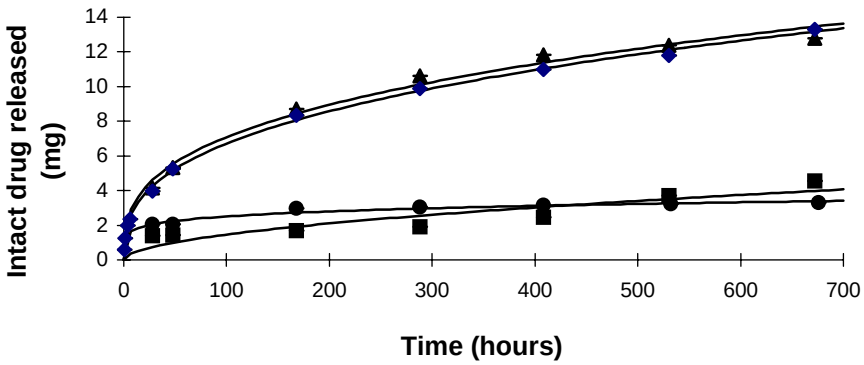

Fig. 2. Intact amoxycillin release (mg) vs. time profiles from SE discs containing amoxycillin (20%) in RG 503 (■), RG 504 (◆), RG 755 (▲) and R 203 (●). Fitted lines where obtained using Eq. (2).

surface. Eq. (2) is applicable to the first 60% of the drug released ($F_{tot} \leq 60\%$). In Fig. 2, the quantity of intact drug released for each of the four polymers systems, at 20% drug loading, was fitted to Eq. (2). In fitting the data to Eq. (2), the *fraction* of intact drug released (relative to the drug load) was used. Fractional values were then converted to amounts released. The fit to Eq. (2) was best for those polymers releasing the greater proportion of intact drug, RG 755 and RG 504 and gave n values of 0.34 and 0.35, respectively.

3.2. Effect of drug loading on release of amoxycillin from RG 755 formulations

As RG 755 gave the greatest proportion of intact drug release, amoxycillin release versus time profiles were obtained from systems loaded with 10 to 60% drug. The results are shown in Fig. 3 and are fitted with Eq. (2) (for fractional drug release <60%). The fits were reasonably good ($r^2 > 0.99$). The values of the parameter n were 0.44–0.46 for drug loadings in the range 40–60% and were lower (range 0.34–0.13) for the lower loadings (10–30%). The lower n values may reflect the lower recovery of intact drug at the lower loadings. Drug release rate increased systematically with increased drug loading. The proportion of intact drug recovered was greater at the higher loadings. Release evidently occurred over shorter time periods prior to onset of polymer degradation. Thus, by increasing the loading more intact drug is made available and degradation minimized.

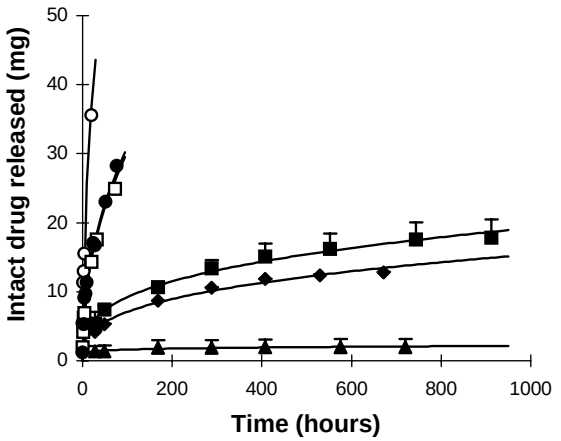

Fig. 3. Intact amoxycillin released (mg) from RG 755 SE discs containing 10% (▲), 20% (◆), 30% (■), 40% (□), 50% (●), 60% (○) initial drug load. Fitted lines where obtained using Eq. (2).

3.3. Polymer mass loss for drug-free and amoxycillin loaded PLA/PLGA discs

The polymer mass loss profiles, both in the absence and presence of 20% amoxycillin (the latter corresponding to the drug release profiles in Fig. 1), were determined for all four polymers and fitted by Eq. (3):

$$\ln\left(\frac{x}{1-x}\right) = k_P t - k_P t_{\max P} \quad (3)$$

where x is the fraction of polymer loss over time t, k_P is the acceleratory coefficient and $t_{\max P}$ represents the time to maximum rate. Eq. (3) was previously employed (Gallagher and Corrigan, 2000; Dunne et al., 2000) to describe the degradation/erosion of poly-hydroxy aliphatic ester polymers. The parameter estimates obtained are summarised in Table 2. It is evident from Table 2 that the $t_{\max P}$ increases with the proportion of lactide in the polymer and also that the presence of drug increases the $t_{\max P}$, and decreases the k_P, reflecting retardation of the polymer erosion process. Thus, inclusion of the amphoteric drug amoxycillin had a major retarding effect on the onset of mass loss of the PLA/PLGA systems, particularly RG 755 and R 203.

The trend in polymer degradation/erosion, in the order RG 503 > RG 504 > RG 755 > R 203 (Table 2), is qualitatively consistent with the findings reported by Sanders et al. (1986) during in vitro and in vivo studies involving a series of PLGA-controlled release implants of the peptide nafarelin, a luteinizing hormone-releasing analogue.

The values of t_{max} estimated for RG 503, RG 504, RG 755 systems from drug release data (Table 1) were smaller than the corresponding values obtained from polymer mass loss profiles ($t_{\max P}$). The smaller values suggest that the polymer degradation related amoxycillin release phase reached its maximum release rate at a time prior to the time for maximum rate of polymer mass loss ($t_{\max P}$). Estimation of the onset of mass loss, by subtraction of four half-lives from $t_{\max P}$, gave times which were lower than the values for the drug release parameter t_{max} of the corresponding polymers, consistent with polymer degradation being a pre-requisite for the release of entrapped amoxycillin

Table 2
Parameters and statistics obtained for polymer mass loss profiles of 20% amoxycillin and drug-free SE discs prepared with RG 503, RG 504, RG 755 and R 203 employing Eq. (3)

System	k_P ($h^{-1} \times 10^5$) ± S.D.	$t_{max\,P}$ (h) ± S.D.	r^2	MSC
RG 503 drug-free[a]	1050 ± 83	669 ± 7	0.9945	4.76
RG 503 20% drug[a]	1008 ± 51	707 ± 7	0.9960	5.10
RG 504 drug-free	1230 ± 140	674 ± 9	0.9941	4.64
RG 504 20% drug	820 ± 50	886 ± 10	0.9922	4.45
RG 755 drug-free	1160 ± 170	993 ± 16	0.9824	3.68
RG 755 20% drug	340 ± 60	2099 ± 94	0.9899	4.15
R 203 drug-free	690 ± 120	1310 ± 39	0.9997	7.73
R 203 20% drug	320 ± 62	2042 ± 211	0.9948	4.70

[a] Mollo and Corrigan (2002).

from the polymeric discs. It is possible then that the final phase of drug release was triggered by the commencement of polymer mass loss and further facilitated by an ingress of water into the system. For R 203, the value of t_{max} estimated from drug release profiles was slightly higher than the corresponding parameter estimated from polymer mass loss data ($t_{max\,P}$) and may indicate that, for the pure lactide, the drug is more tightly bound to the polymer than in the case of the co-polymers.

The magnitude of the effect of the drug on the retardation of polymer degradation appeared to increase both with increasing molecular weight and with increasing lactide content of the polymer. Table 3 shows the ratio of $t_{max\,P}$ from drug-free discs versus $t_{max\,P}$ from 20% drug-loaded discs for each of the four polymers. The corresponding k_P ratios are also included in Table 3. In the case of RG 503 and RG 504, both (50:50) PLGA, the magnitude of the effect of the drug on the degradation kinetics of the polymer was greater for the higher molecular weight system (RG 504). Comparison of RG 503 and R 203, which are the two systems of lowest molecular weight (determined as 35,000 and 26,600, respectively) suggests that the increase in lactide content resulted in an increase of the $t_{max\,P}$ ratio. On this basis, a higher $t_{max\,P}$ ratio for RG 755 (75:25) PLGA systems compared to RG 503 and RG 504 systems was expected, as shown in Table 3. The results of the k_P ratios were consistent with the $t_{max\,P}$ ratios. Thus, the presence of amoxycillin caused a retardation of the kinetics of polymer degradation, the retarding effect being greater the larger the molecular weight and lactide content of the polymer employed.

Table 3
Ratio of $t_{max\,P}$ and k_P for 20% drug-loaded (DL) to drug-free (DF) SE discs prepared with RG 503, RG 504, RG 755 and R 203, from polymer mass loss studies

System	$t_{max\,P}$ DL/$t_{max\,P}$ DF	k_P DL/k_P DF
RG 503	1.058	0.93
RG 504	1.315	0.66
RG 755	2.114	0.293
R 203	1.559	0.464

These results, with the amphoteric drug amoxycillin contrast with those previously obtained with basic compounds. Basic drugs were reported to affect polymer hydrolysis through pH changes, in studies on a series of four amines incorporated in poly-alpha-hydroxy-aliphatic esters (Cha and Pitt, 1989). Formulations of various basic drugs with poly-alpha-hydroxy-aliphatic esters (Ramtoola et al., 1992; Fitzgerald and Corrigan, 1993, 1996) resulted in drug release in a much shorter period of time than corresponding systems in the current work. In addition, drug-free PLA/PLGA discs eroded in less time than equivalent amoxycillin loaded discs, as shown from polymer mass loss profiles and GPC studies. Miyajima et al. (1998), using low molecular weight (M_w 1500–4500) PLGA systems, showed that increasing the proportion of either verapamil or papaverine contained in the polymeric matrix resulted in lower in vitro percent release rates. These workers attributed such effect of the drug to a significantly larger number of polymer/drug interactions due to

increased drug content, likely to give rise to an increase in the glass transition temperature (T_g) of the polymer making the matrix more rigid. Higher T_g values were observed by these authors when the drugs were incorporated in the polymer.

In the current work, the inclusion of amoxycillin (20%) resulted in a slight increase of the T_g of the glycolide copolymers when compared to the corresponding drug-free systems. For example, RG 503 mechanical mixes (MM) at 20% drug load showed a T_g value of 46.8 °C compared to 45.0 °C for the pure copolymer powder. In the case of RG 503 SE systems, the T_g was found to be approximately 45.5 °C for 20% drug-loaded systems compared to 44.2 °C for drug-free systems prepared by the solvent evaporation method. Similar trends were seen in the results obtained for RG 504 and RG 755 when 20% drug-loaded systems were compared to similarly processed drug-free systems, although the trend was not observed in the case of the pure lactide systems R 203.

3.4. Polymer molecular weight changes in drug-free and drug-loaded PLA/PLGA discs

The process of polymer mass loss is preceded by a considerable reduction of the M_w of the polymer, which commences on contact with the dissolution/release medium, the molecular weight apparently declining exponentially during the first phase of degradation (Kenley et al., 1987; Dunne et al., 2000). Limited GPC analysis was performed on drug-loaded discs in which degradation was suspected, on the basis of the polymer mass loss and/or drug stability profiles.

Table 4
Molecular weight determinations (M_n and M_w) of RG 503, RG 504, RG 755, R 203 systems obtained by GPC

Sample	M_n	M_w (Da)	P
RG 503 20% SE 0 h	24740	36686	1.48
RG 503 drug-free SE 676 h	2199	5130	2.33
RG 503 20% SE 676 h	5754	10295	1.79
RG 504 20% SE 0 h	29471	42614	1.45
RG 504 drug-free SE 676 h	770	1474	1.91
RG 504 20% SE 676 h	9293	16385	1.76
RG 755 20% SE 0 h	43361	76938	1.77
RG 755 drug-free SE 288 h	10973	20980	1.91
RG 755 20% SE 288 h	19051	40859	2.15
RG 755 drug-free SE 1084 h	759	1197	1.58
RG 755 20% SE 1084 h	15071	25851	1.72
R 203 20% SE 0 h	17266	26541	1.54
R 203 drug-free SE 1084 h	2681	7458	2.78
R 203 20% SE 1084 h	12348	19077	1.54

The molecular weight changes observed for the four polymers, both in the presence and absence of 20% drug are given in Table 4. The decrease of molecular weight in the drug-free discs was considerably greater in all the cases investigated. A semi-log plot of the RG 755 and R 203 data are shown in Fig. 4, consistent with an exponential decline in molecular weight with time. Apparent half-lives for the molecular weight decrease are summarised in Table 5. It is evident that the presence of amoxycillin (20%) retards the rate of polymer molecular weight reduction for all four polymers, the effect being greater the more lactide present. Changes in the polymer molecular weight parameters were consistent with the polymer mass

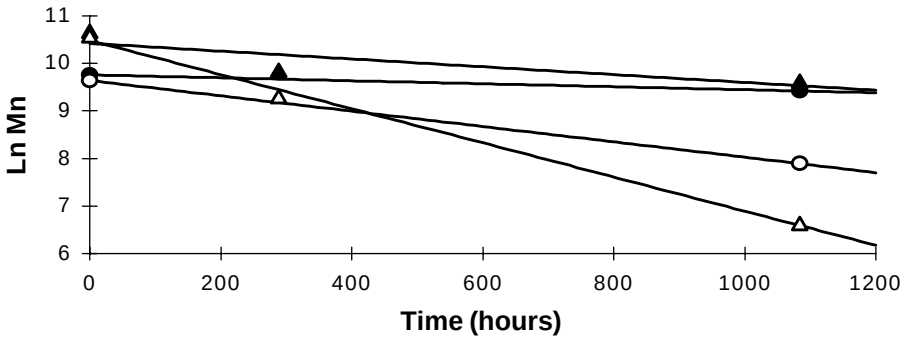

Fig. 4. Logarithm of number average molecular weight as a function of time for drug-free and 20% drug-loaded systems. Drug-loaded: RG 755 (▲) and R 203 (●); drug-free: RG 755 (△) and R 203 (○).

Table 5
Apparent half-lives estimated from M_n changes observed in RG 503, RG 504, RG 755 and R 203 drug-free and amoxycillin loaded systems

System	$t^{1/2}$ (h) drug-free	$t^{1/2}$ (h) drug-loaded
RG 503	204	315
RG 504	124	408
RG 755	193	845
R 203	433	2235

loss data of Table 2, the inclusion of the drug had a retarding effect on the kinetics of polymer hydrolysis. For RG 755, comparison with the data from polymer mass loss (Table 2) show that polymer degradation occurred earlier than mass loss, both for drug-loaded and drug-free discs. The onset of mass loss for these systems was not earlier than 700 h, while there was at least a 50% reduction of the initial molecular weight by approximately 300 h in the release medium.

RG 755 SE discs loaded with 50% amoxycillin were also analysed after 1700 h of dissolution. At this time, the discs were apparently depleted of drug and a relatively large amount of solid polymer was still available for further erosion. Interestingly, the M_n (8925) and M_w (16,826) of these discs are comparable to those of drug-free SE discs when exposed to only 288 h of dissolution.

^{13}C NMR spectra, of drug-free SE discs having undergone 600 h of dissolution and 20% drug-loaded discs undergone 1000 h of similar release, suggested that breakdown of the polymer backbone was greatest in drug-free SE discs. Similar NMR findings during PLA hydrolysis were reported by Shih (1995). The methyl group at approximately 16 ppm is considered to correspond to the lactic acid subunits in the polymer backbone. Chain scission with generation of free lactic acid was suggested by the appearance of a methyl related peak at approximately 20.35 ppm. Similarly, it appears that at 70 ppm the methine groups of the polymer backbone displayed a signal which shifts to 66.6 ppm upon chain scission. Signals obtained at 175.1 and 177.6 ppm (in both drug-loaded and drug-free discs used in drug release studies), displayed a significantly wider distribution of signals suggesting a higher degree of backbone breakdown in the drug-free discs compared to the 20% drug-loaded systems. Presence of the drug or its degradation products was not detectable in by ^{13}C NMR or ^{1}H NMR analysis. ^{1}H NMR results were consistent with those obtained by ^{13}C NMR, i.e. increased polymer breakdown in drug-free discs compared to 20% drug-loaded discs. In the ^{1}H NMR spectra, drug-loaded discs displayed two signals that were absent in the drug-free systems. These two new signals (2.321 and 5.032 ppm) may reflect a drug/polymer interaction. Given the apparent absence of drug from the discs at the later sampling times one might expect the degradation rate/mass loss of the polymer to increase if the physical presence of drug were responsible for the retarded polymer degradation. Consequently, the possibility of small amounts of the drug or its degradation products binding or cross linking with the polymer and thus retarding polymer degradation is likely.

4. Conclusions

The stability of the amphoteric drug amoxycillin formulated with poly-alpha-hydroxy aliphatic esters was found to be dependant on the type of polymer employed. Where higher molecular weight polymers were employed, a greater proportion of intact amoxycillin was released. A model reflecting drug release by surface dissolution and polymer degradation, adequately described the total drug release profiles. The results indicated that those systems showing a greater proportion of drug released by diffusion were less affected by the acidic microenvironment created upon the release of the polymer constituent sub units. Thus, increasing the amoxycillin loading such that drug release occurs in advance of the polymer degradation phase will optimise release of intact amoxycillin.

It was found that the amphoteric drug amoxycillin retarded the rate of polymer degradation and thus increased the onset time of polymer erosion. The interaction between drug and polymer was greater in those systems with the larger proportion of lactide content and the higher polymer molecular weight. It was considered that this effect may reflect binding or cross linking of the drug and/or its degradation products with the polymer.

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