

Observation of the degradation due to irradiation of CR 39 polymer by long-term monitoring of mass loss

Laurence Faiman

Physics Department, Birkbeck College, University of London, Malet street, London WC1E 7HX, UK

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Abstract

We γ -irradiated CR 39 of three thicknesses with 51–3311 kGy. Mass loss *during* irradiation repeated the three-step pattern observed by Li et al. [Li, S.M., Garreau, H., Vert, M., 1990. Structure-property relationships in the case of the degradation of massive aliphatic poly(α -hydroxy acids) in aqueous media. *J. Mater. Sci.: Mater. Med.* 1, 123–139.] from thick PLA50. Mass loss *following* irradiation in thin CR 39 repeated the observations of Grizzi et al. [Grizzi, I., Garreau, H., Li, S., Vert, M., 1995. Hydrolytic degradation of devices based on poly(D,L-lactic acid) size-dependence. *Biomaterials* 16, 305–311.] in thin PLA50, whereas in thicker samples, it followed second-order kinetics. The graph of total mass loss per unit dose against dose absorbed displays the step-wise pattern from ESR spectroscopy [Nara, S., Shimada, S., Kashiwabara, H., Sohma, J., 1968. Relation of the decay of free radicals in irradiated polyethylene to the molecular motion of the polymer and the configuration of the free radicals. *J. Polym. Sci., Polym. Phys. Ed.* 6, 1435–1449.]. The implications for drug release from γ -irradiated microcapsules is discussed.

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1. Introduction

Controlled release of drug incorporated into the matrix of a polymeric material is now being widely investigated for use as a device for drug delivery (Alexis et al., 2005). Particular interest lies in bio-resorbable polymer microcapsules, examples being poly(L-lactic acid) (PLA) and poly(glycolic acid) (PGA) and the co-polymer poly(L-lactic acid)–CO–(glycolic acid) (PLGA). The fundamental mechanisms underlying release from these polymers were outlined by Li et al. (1990) for 2-mm thick plates (a three-step process), and by Grizzi et al. (1995) for 0.3-mm thin films and microcapsules. In thick films, mass loss is initially delayed (step 1); auto-catalytic reactions then transform the interior of the plate (step 2); finally in step 3, the surface becomes permeable to oligomers in the interior. Grizzi, Garreau, Li and Vert (1995) observed no initial delay in mass loss in 0.3-mm thick films, this “initial burst” being followed by a 23-week “plateau” period after which mass

loss resumed for a period termed by Grizzi the “final burst”.

Before delivery to the patient, microcapsules require sterilization. The only practical means by which sterilization can be carried out is by γ -irradiation, the dose usually being 25 kGy. But this dose will initiate polymer degradation, and consequently release of drug. The effect of γ -irradiation on microcapsules, therefore, requires investigation. Several authors have reported on the effects of γ -irradiation (a brief review can be found in Alexis (2005)). In particular, Nugroho et al. (2001) reported that the *rate* of degradation of PLA decreased as dose absorbed increased from 0 to 200 kGy, and suggested that this was due to cross-linking at higher doses. This problem has previously been extensively investigated in a different substrate, namely polyethylene, where ESR spectroscopy revealed that the intensity of the free radicals (primarily alkyl radicals generated by chain scission) decreases in a step-like pattern, three plateau regions being interspersed by three decay regions (Nara et al., 1968). Fujimura et al. (1979) identified the first decay region as arising from the

E-mail address: gfailm01@students.bbk.ac.uk

decay of alkyl radical pairs (often labeled the δ -mechanical dispersion). Fujimura et al. (1982a, b) found this to be the predominant chemical reaction in lightly irradiated polyethylene (PE) (127 kGy). The second and third decay regions, on the other hand, appear to correspond closely to two different motions of the polymer matrix, the γ - and α -mechanical dispersions, respectively. According to Fujimura, in samples irradiated *in vacuo*, greatly increasing the dose increases the degree of cross-linking, and consequently, the rigidity of the polymer matrix, and slows the decay of alkyl and allyl radicals. In samples irradiated in air, on the other hand, the effects of cross-linking are canceled out by oxidation-induced chain scission (Fujimura et al., 1982b). Films and plates can be treated as irradiated *in vacuo*. Hence, in films and plates irradiated with very high doses, the frequency with which free-radical decays occur decreases, the same phenomenon observed by Nugroho et al. (2001) in poly(L-lactic acid) powder samples irradiated both *in vacuo* and in air, the frequency of free-radical decays decreasing faster in samples irradiated *in vacuo* than in samples irradiated in air, as found by Fujimura. We concluded from these results that if the rate of desorption is proportional to the frequency of decays, then heavy irradiation might also slow desorption, and, therefore, the rate of release of incorporated drug. Such a slowing of the rate of desorption could be detected by monitoring weight changes (gravimetry) in irradiated samples. Since the decay of alkyl radicals is frequently observed by gravimetry, it is possible that in irradiated samples, the entire step-like pattern revealed by ESR spectroscopy might also be observable by gravimetry at ambient temperatures.

It is likely that results from other substrates may be relevant to investigations of drug release from bio-resorbable polymers. We had been investigating the behavior of a particular polymer, CR 39, the monomer of which is diethylene glycol bis(allyl carbonate) (chemical formula is $C_{12}H_{18}O_7$), and, therefore, oxygen-rich like PLA50. It is an optically transparent, glassy, brittle thermo-set, widely used for lenses for spectacles, in the electronics industry as a resist, and also as a track-etch detector (Faiman, 1986). In particular, we had been measuring the rate of mass loss during and following irradiation. We demonstrate from our data that the three-step process observed by Li et al. (1990) in thick samples, and the “initial” and “final” bursts observed by Grizzi et al. (1995) in thinner samples, are repeated for CR 39 samples exposed to large doses of ionizing radiation when their weight was monitored over long periods. We also demonstrate that by estimating the total mass loss, and graphing the total mass loss per unit dose against the dose absorbed, we derive an ESR-type spectrum from which we can identify free-radical decays and the occurrence of phase transitions. We suggest that these results may account for many of the different phenomena observed by Nugroho et al. (2001), Hausberger et al. (1995) and Faisant et al. (2002).

2. Experimental methods

The methods in this work are very similar to those used by Charlesby (1952), and Black and Charlesby (1959). CR 39 polymer of all thicknesses was supplied (by Pershore Plastics, Pershore, Worcs, UK) already cut up into squares 2.49 cm \times 2.49 cm. The thickness of most of the samples varied between 0.45 and 0.65 mm, but samples 1.4 and 0.24-mm thick were also used in this work. All samples, therefore, had effectively the same surface area. Samples, when not being subjected to a procedure (irradiation or weighing), were stored in a dessicator (anhydrous aluminum hydroxide), not under vacuum. This dessicator was stored at room temperature in a basement room with no windows whose ambient temperature was $20 \pm 3^\circ\text{C}$. Samples were weighed with a Stanton unimatic balance that had a resolution of ± 0.1 mg, and an accuracy of ± 0.25 mg when tested over several days. This error would also include any fluctuations in moisture content of samples. The samples were gauged with a dial gauge that had an accuracy of ± 0.0042 mm. By calculating the thickness-to-weight ratio, we were able to test for any variation in density between samples. We found the thickness-to-weight ratio of the samples from one sheet varied by $\pm 0.24\%$. The density of our samples was, therefore, highly uniform.

Samples were irradiated at room temperature in the chemical engineering department of Imperial College, University of London. The facility consisted of up to six ^{60}Co γ -ray sources arranged in a circle 15 cm in diameter, the samples being placed at the center of the circle. Irradiation was virtually continuous, any intermissions being few and of short duration. The dose rate was calibrated whenever new sources were loaded, by means of a Fricke dosimeter, and varied, after allowing for source decay, between 5 and 18 kGy/h, depending on the number of sources used. The error in dose rate is the principal error in dose absorbed. We do not believe this error to be greater than $\pm 5\%$. In order to be irradiated, between 10 and 20 samples were formed into a block that was wrapped in aluminum foil that also served to establish electronic equilibrium. All samples were weighed before irradiation. Return to our laboratory occurred between 2 and 20 h following the end of irradiation. The block was then broken up, and four or five of the samples were weighed, and these continued to be weighed at various intervals thereafter.

3. Results and discussion

3.1. Morphology

Despite mass loss from the samples that increased with dose, irradiation had no effect on the dimensions of samples, even at the highest doses. This is what we might expect from a thermo-set where extensive cross-linking gives the solid an extremely robust matrix. Equally, the

surfaces were not roughened by mass loss, indicating that irradiation had a uniform effect on the surface, and no localized erosion had occurred. However, as dose increased, samples displayed an increasing tendency to bow. Also, as dose increased, samples ceased to be transparent, the surfaces became progressively more yellow in color and the inner layers became white, indicating significant changes in internal chemical composition and morphology. Hence, degradation appears to have been *heterogeneous* rather than *homogeneous*, the surface remaining relatively unaffected compared to the core. Samples in a block became increasingly more difficult to separate as dose increased. Adjacent samples each appeared to develop a “skin” that strongly adhered to its neighbor, as Charlesby (1952) observed on his polyethylene samples. In our samples, adhering “skins” were always easily separated.

3.2. Mass loss before first weighing

We denote mass loss during irradiation and up to the time of the first weighing, by m_I (where I stands for irradiation). The pre-irradiation, or virgin, mass is denoted by m_v . The errors in all figures are smaller than the size of the symbols used to plot the points. Sample-to-sample fluctuations in mass loss (± 0.4 mg) were found to be independent of the dose absorbed, which is denoted in this work by d_t . Table 1 compares the mass loss from samples from three different blocks. We can immediately conclude from the table that m_I is not proportional to thickness in any of the blocks. Hence, mass loss in CR 39 is, as Charlesby observed in polyethylene, a surface effect. Charlesby suspected that oxidation most likely explained the formation of “skins”. To demonstrate explicitly that mass loss is independent of thickness, we calculated $m_I/m_v/d_t$. In each block, the thinnest samples had the highest value. The possibility that oxidation might play a role in mass loss in CR 39 is also suggested by the work of Giberson (1962).

Fig. 1 charts, for samples 0.45–0.65-mm thick, the mass loss that occurred during irradiation, and subsequently while samples remained in the block in which they were irradiated, up to the time of the first weighing. The different symbols used to plot the points in Fig. 1 represent

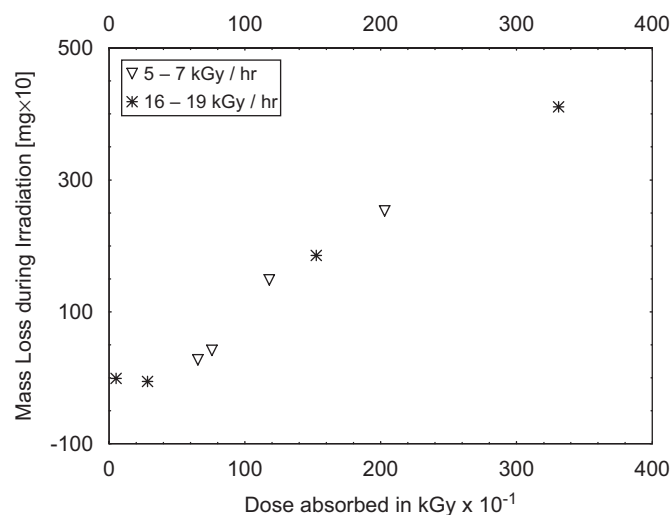


Fig. 1. Mass loss before first weighing m_I as a function of dose absorbed.

two different dose rates. All points appear to lie on one continuous “S”-shaped curve, suggesting that dose rate has no effect on mass loss. It is widely accepted that, to a first approximation, the extent of cross-linking and chain scission is dose-rate independent (Singh, 1992), and in our work, the difference in dose rates is, in any case, less than an order of magnitude.

Our analysis of Fig. 1 below will demonstrate that three different phases can be discerned to have occurred. The first two points on the left represent an apparent mass gain, though this mass gain is significant only in the case of the second point. Hence, mass gain increases with dose. This was also observed by Charlesby, who explained it in terms of the radio-oxidation of the surface layers of his samples. The mass gain indicates that our samples are likely to have similarly undergone radio-oxidation. This is the first phase.

As the dose increases, the samples begin to lose mass. Between 758 and 1180 kGy, there is a sudden acceleration in the rate of mass loss. This is the second phase. We see, therefore, that during any prolonged irradiation, mass loss is *delayed*. This delay is, moreover, dose-rate independent. Hence, this delay is not a delay in *time*, but until a sufficient concentration of free-radical moieties will have been generated in the matrix that moiety–moiety reactions can occur.

Charlesby found that the points of the first and second phases, were well fitted by the parabola $m_I = (\alpha_1 d_t^2 + \beta_1 d_t)m_v + (\alpha_2 d_t^2 + \beta_2 d_t)A$, where A is the surface area of a sample. m_I in Charlesby’s work is due to both a whole-body and a surface effect. In our work, the surface area is effectively constant for all samples. We found that the four points $d_t = 51.8, 282, 654$ and 1180 kGy were very closely fitted by a parabola. According to Table 1, when d_t is increased from 654 to 758 kGy, the change in m_I of samples whose $m_v = 0.2$ and 0.4 g is 14.3 ± 1.8 and 14.0 ± 3.7 (mg x 10), respectively. It appears, therefore, that for CR 39, $\alpha_1 = \beta_1 = 0$, m_I is independent of m_v , and

Table 1

Dependence of mass loss during irradiation (dose rate = 5.5 kGy/h) on sample thickness

Mass of virgin sample, m_v (g)	Dose absorbed, d_t (kGy)	m_I (mg x 10)	$m_I/m_v/d_t$
1.1577	1180	209.5 ± 6.4	0.153
0.4084	1180	150.3 ± 1.2	0.311
0.4034	758	43.3 ± 3.7	0.142
0.2042	758	53.0 ± 1.2	0.342
0.4101	654	29.3 ± 0.3	0.109
0.2060	654	38.7 ± 1.4	0.287

mass loss during the first and second phases is a purely surface effect.

Finally, the last four points to the right of the graph can be closely fitted ($r = 0.9926$) by the straight line $m_t = ad_t + b$, where $a = 0.1236 \pm 0.0021$ and $b = 2.0 \pm 4.3$. This line effectively passes through the origin. Hence, the samples that these points represent appear to have lost mass during irradiation at a rate proportional to the dose absorbed. Mass loss in this third phase has become, therefore, a *whole body effect*, rather than a surface effect. As pointed out by Matsuo and Dole (1959), the intercept at $d_t = 0$ is an estimate of the quantity of molecular oxygen absorbed. In our samples, this appears to be relatively insignificant. The constant rate of mass loss would agree with our expectation that the free radicals, from which the moieties that desorb are formed, are generated by irradiation at a rate proportional to the dose rate. But it ignores the existence of the first two phases. The sudden change at $d_t = 1180$ kGy from m_t being a surface to a whole-body effect, therefore, appears to suggest that the moieties that desorb, or their precursors, were somehow “stored up” in the solid following generation, until a “catastrophic event” occurred on which they were released. This release would have to be completed by $d_t = 1180$ kGy. Hence, the “three steps” observed by Li et al. (1990) when “ageing” PLA50 plates are repeated when samples of CR 39 are irradiated. In addition, here we have been able to greatly extend by a mathematical analysis of our own data in Fig. 1, the qualitative observations of Li et al. (1990) of the heterogeneous degradation of their PLA50 plates. But we cannot know whether the fine detail of our model is equally valid for ageing in buffered solutions. This needs to be determined experimentally. Since Fig. 1 shows mass loss during irradiation to be dose-rate independent, the occurrence of the “catastrophic event” must be explained by a concentration-driven decay of free radicals. This is exactly what Fujimura et al. (1982a, b) found from ESR spectroscopy of lightly irradiated polyethylene.

Auto-catalytic reactions will not be initiated in samples that are sufficiently thin so that soluble oligomers can diffuse out even from the centre of a sample. Equally, the initial delay in mass loss that occurs in thicker samples will not occur in thin samples. (The same reasoning also applies to thicker samples that are porous.) This is what we observed in Table 1. However, no explanation was offered by Grizzi et al. (1995) for the occurrence of the plateau period and the final burst in thin films. We shall attempt to explain these phenomena below.

3.3. Mass loss from samples after their first weighing and estimation of total mass loss

Significant mass loss continued many months after irradiation had been terminated, probably due to auto-catalytic reactions. Fig. 3 charts on a log–log graph the mass loss (denoted here by m_{AI}) over time (t measured in days), since the first weighing following the break-up of the

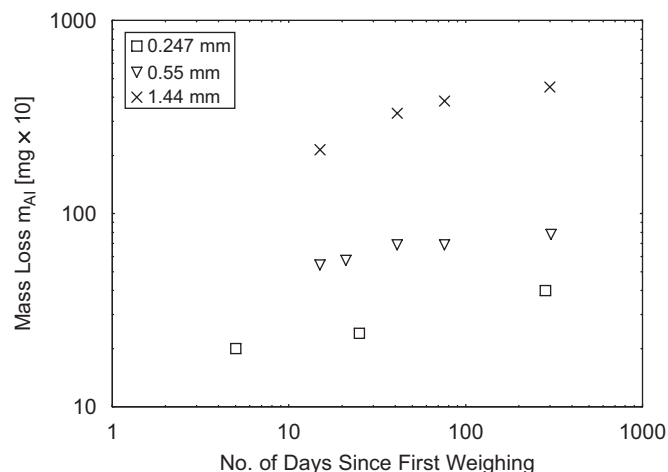


Fig. 2. Mass loss after first weighing: \times , samples 1.44-mm thick exposed to 1180 kGy at 5.5 kGy/h; ∇ , samples 0.55-mm thick exposed to 1180 kGy at 5.5 kGy/h; \square , samples 0.27-mm thick exposed to 758 kGy at 6.1 kGy/h.

blocks, from samples of three different thicknesses. The mass loss in Fig. 2 indicated by crosses is from two samples 1.4-mm thick that had been exposed to 1180 kGy at 5.5 kGy/h. We found that the shape of the curve that passes most closely through all four points is that given by the second-order reaction kinetics formula (Atkins, 2000), i.e., $m_{AI} = At/(t+B)$. The correlation coefficient r for the fit to the four points in Fig. 2 is 0.9998. An exponential cannot fit all four points, but both second-order kinetics and an exponential will fit the first three ($t = 15, 41$, and 76 days). The work of Grizzi et al. (1995) suggests an alternative interpretation for the fourth point ($t = 299$ days), namely that the fourth point represents a “final burst” of mass loss following a plateau period. If we consider the five points in Fig. 2 indicated by inverted triangles, that represent mass loss from samples 0.55-mm thick, these points are successfully fitted by the formula for second-order reaction kinetics ($r = 0.9669$). But if we observe this data closely, we see that there is nevertheless a plateau region (mass loss did not increase between $t = 41$ and 76 days), while the mass loss at $t = 304$ days is significantly higher. Hence, a plateau region followed by a final burst is an alternative interpretation of this data, both second-order kinetics and “final burst” interpretations of this data being equally valid. Finally, the points representing mass loss from samples 0.24-mm thick, and indicated by open squares, cannot be fitted by the second-order reaction kinetics formula, as is obvious by inspection of the graph. Rather, mass loss from samples 0.247-mm thick follows the pattern observed by Grizzi et al. (1995) from PLA50 films.

We now attempt to explain the nature of the “final burst”. The long plateau period might be a period during which product molecules accumulate, but do not desorb until their concentration reaches a critical value. (The “catastrophic event” followed such a “plateau period” during which gas molecules accumulated.) The occurrence

of a plateau period indicates that the concentration of product in the polymer has fallen below the critical concentration, probably because the *rate of formation* of product has suddenly decreased, for example, due to stiffening of the polymer matrix. Eventually, sufficient product would accumulate for the critical value to be reached, so that desorption could be resumed, “the final burst”, indicating that a second-order phase transition had occurred, probably a mechanical dispersion.

We used the second-order kinetics formula on our data for m_{AI} from samples 0.55-mm thick, and derived values for A ($\text{mg} \times 10$) and B (days) for each dose. The values of A and B are tabulated against dose in Table 2. We observe that the two sets of samples that *gained* mass during irradiation (see Fig. 1), both suffered significant mass loss after the blocks in which they were irradiated were broken up, indicating that the reactions leading to mass loss began in these samples post-irradiation. The peak in A must be associated with the occurrence of the “catastrophic event” during irradiation, since at that point, samples are loaded with product remaining to be released. At higher doses, product is released during irradiation, so A decreases.

Ignoring the first line in Table 2, examination of the five remaining data points shows that there is a significant inverse correlation between the inverse of the rate constant for second-order reactions and the dose rate ($r = -0.9308$). In fact k is proportional to the dose rate. This is evidence of a close connection between generation of free radicals by radiation and desorption of gaseous molecules.

We can estimate the total mass loss m_T by adding m_I and A . m_T is graphed against dose in Fig. 3. We observe that the graph in Fig. 3 has an “S” shape similar to the graph for m_I in Fig. 1. We conclude that m_T , like m_I , is likely to be dose-rate independent. It follows that the data for A is also likely to be dose-rate independent. The third linear phase of Fig. 1 shows that a “radiation equilibrium” has been established between product formation and desorption (hence the linearity of k with the dose rate). We might, therefore, expect that A would tend to a constant value at very large doses. Instead, it is clear from Table 2 that at moderate doses (800–3000 kGy), A decreases as dose increases. This decline in A is evidence for the occurrence of a further mechanical dispersion, and this will be

Table 2

Values of A and B from fitting $m_{AI} = At/(B+t)$ to data for samples 0.55-mm thick

Dose (kGy)	Dose rate (kGy/h)	A ($\text{mg} \times 10$)	B (days)	$AB = 1/k$
51.8	17.3	46.3 ± 2.1	23.1 ± 1.6	1070 ± 89
282	16.7	57.6 ± 0.9	3.07 ± 0.25	177 ± 15
654	5.5	96.0 ± 1.6	7.76 ± 0.38	745 ± 39
758	5.5	97.7 ± 5.4	5.18 ± 0.91	506 ± 93
1180	5.5	79.2 ± 5.3	6.83 ± 2.20	541 ± 178
1521	16.6	66.5 ± 1.7	3.14 ± 0.10	209 ± 9
3311	18.0	55.7 ± 3.8	3.77 ± 1.20	210 ± 68

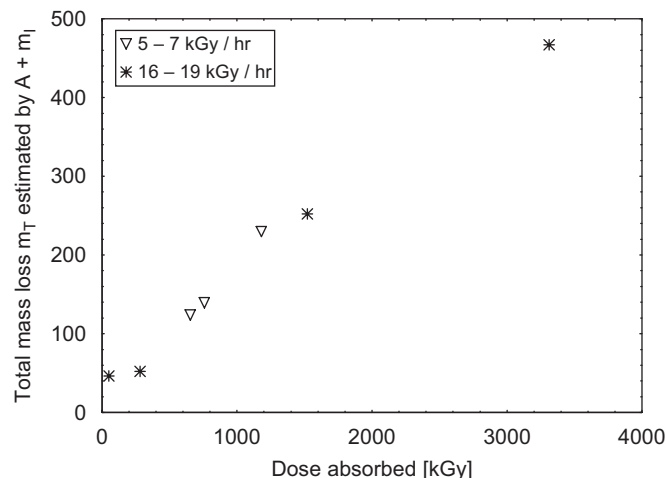


Fig. 3. Total mass loss m_T from samples due to irradiation, estimated by adding m_I and A .

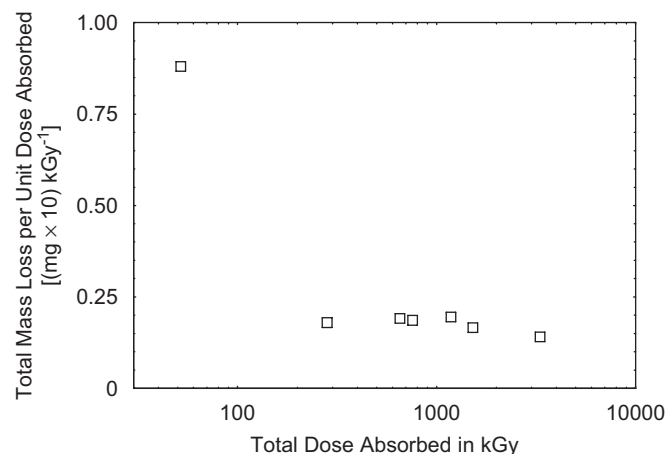


Fig. 4. Graph of mass loss per kGy absorbed (m_T/d_t), against dose absorbed in kGy.

demonstrated more formally below. Our data, therefore, clearly shows that the observation in polyethylene by Fujimura et al. (1982a, b), that as dose absorbed increases the frequency of decay of free radicals decreases, does indeed apply to the oxygen-rich thermo-set CR 39 polymer. Our results in irradiated CR 39 together with those of Nugroho et al. (2001) in irradiated PLA would suggest that the observation of Fujimura is likely to be true for polymers in general.

Following the observation of Fujimura, we calculated the rate of total mass loss m_T per unit kGy absorbed d_t (i.e. m_T/d_t). The quantity m_T/d_t is graphed against d_t in Fig. 4. Initially, m_T/d_t is undergoing a steep decline, but for $d_t > 282$ kGy, it enters a plateau region. The last two points indicate the onset of a slight, but significant, decline in m_T/d_t . Fig. 4, therefore, reproduces the pattern of plateaus and decays characteristic of ESR spectroscopy of irradiated polymers. We observed in Table 2 that the half-life B

for desorption of product from samples irradiated with 51.8 kGy (23.1 ± 1.6 days) is longer than B for samples absorbing higher doses (mean value 5.0 ± 2.0 days). Hence, the most likely reason why m_T/d_t is much larger for 51.8 kGy than it is for 282 kGy is that free-radical decays continued for a much longer period in samples irradiated with 51.8 kGy. This would indicate that free-radical mobility is greater in lightly irradiated polyethylene than it is in heavily irradiated polymer. A stiffening of the polymer matrix, a *mechanical dispersion*, will occur *post-irradiation* in those samples exposed to 282 kGy. In samples exposed to higher doses, this phase transition *might* occur during irradiation. It might possibly be associated with the occurrence of the “catastrophic event”. When, $d_t > 1180$ kGy, m_T/d_t is gradually declining, although the half-life B is unchanged. The mobility of free radicals does not, therefore, appear to change significantly at higher doses. This is consistent with the formation of metastable radical pairs observed by Fujimura. This decline suggests a further mechanical dispersion has occurred post-irradiation.

Recent results from the irradiation of bio-resorbable polymers have confirmed our observations from CR 39. In the thicker samples we found degradation to be heterogeneous rather than homogeneous, a similar conclusion to that reached by Hausberger et al. (1995) from the γ -irradiation of bio-resorbable polyesters. The pattern of mass loss from the thinnest CR 39 samples post-irradiation followed the pattern observed by Grizzi et al. (1995), whereas the post-irradiation pattern of mass loss from thicker samples could be fitted *either* by a second-order reaction kinetic model, *or* by the pattern of Grizzi. Faisant et al. (2002) monitored the percentage of drug released from their irradiated PLGA microparticles, equivalent to our monitoring post-irradiation mass loss. They found that their data could be fitted by a biphasic pattern of an initial burst followed by a zero-order kinetics phase. We believe that careful inspection of the actual data in both Figs. 1 and 2 of their paper suggests that the pattern of an initial burst followed by a plateau period, followed by a final burst, is an equally valid interpretation of their data. We conclude that our results from CR 39 are likely to provide a valid model for drug release due to irradiation.

4. Conclusions

We have irradiated both thin and thick CR 39 samples, and monitored their mass loss. We found that mass loss from thick samples *during* irradiation, and from thin samples *post-irradiation* followed the pattern of mass loss observed when the respective thick and thin samples of PLA50 were aged in a buffered solution. We conclude that drug release following irradiation of microcapsules is likely to be determined by the same processes that determine mass loss. Equally, our use of mass loss as a technique for observing phase transitions suggests that phase transitions

are likely to play a significant role in drug release from irradiated microcapsules.

Acknowledgments

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