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Biodegradable controlled release tablets: III. Effect of polymer characteristics on drug release from heterogeneous poly(lactide-co-glycolide) matrices

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Summary

Spray dried poly(lactide-co-glycolide) powders were used to prepare phenobarbitone matrix tablets. The release of phenobarbitone was significantly sustained, indicating the suitability of using poly(lactide-co-glycolide) matrix tablets for long-term controlled drug delivery. Drug release profiles consisted of three regions: these were an initial region of relatively high release rate (burst effect), followed by an extended region of lower and essentially constant release rate from approx. 20 to 80% of drug release. This steady state release region was followed by a final one in which the rate of drug release fell off as exhaustion of the drug in the matrix approached. A composite mechanism of drug release is proposed involving diffusion of the drug through water-filled pores in the matrix and drug diffusion through the swollen polymer. The rate of drug release increased with an increase in the glycolide content of the polymers. Decreasing the polymer molecular weight caused initially an increase but later a decrease in the release rate. These results are discussed in terms of degradation, water uptake and swelling of the polymers upon immersion in aqueous media.

Introduction

It has been shown that the polymerisation conditions affect the characteristics of the produced polymer (Avgoustakis and Nixon, 1991) and that larger batches of polymers, with specific properties, could be synthesised by judicious modifications of the normal preparative procedure. These polymers were spray dried to prepare powders which were found to have good compaction properties and moderate hydrophobicity. It was also shown that the polymers swell considerably in aqueous media, although they absorb relatively small amounts of water (Avgoustakis and Nixon, 1993). In the present work, the preparation of matrix tablets using spray dried poly(lactide-co-glycolide) as the matrix forming material is reported. The effects of changing the properties of the polymer on the release of the model drug phenobarbitone are investigated.

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Materials and Methods

Materials

The poly(lactide-co-glycolide) polymers (their in-house preparation was described in the preceding paper; Avgoustakis and Nixon, 1993) shown in Table 1 were used. Phenobarbitone (minimum assay 99%, Sigma), sodium phenobarbitone (minimum assay 99%, Fluka), magnesium stearate (BDH, GPR) and chloroform (FSA, Analar) were also used. The phosphate buffer, pH 7.4, was prepared from 1.19 g of potassium dihydrogen orthophosphate (BDH, GPR), 2.38 g of disodium hydrogen orthophosphate (BDH, Analar) and 8.0 g of sodium chloride (BDH, GPR) in 1 l of distilled water.

Methods

Preparation of tablets Drug and polymer powders (150–250 μg) were mixed in a tumbling blender (Pascall Engineering, U.K.). A mixing time of 30 min was found to produce homogeneous drug-polymer mixtures. These mixtures were compressed using a 10.55 mm diameter flat faced punch and die system (prelubicated with a 1% suspension of magnesium stearate in chloroform) in a Dartec 100 kN M2501 universal testing machine (Dartec Ltd). A compaction force of 10 kN was normally applied, the rate and dwell time being maintained at 1 kN s^{-1} and 15 s, respectively. The drug-polymer mixtures consisted of 25% drug by weight.

Drug release from tablets Drug release from tablets was investigated using the paddle dissolution method (USP XXII). 1 l of phosphate buffer, pH 7.4, was used as dissolution medium. The stirring rate was maintained at 50 rpm and the temperature at 37°C. Samples were withdrawn manually at predetermined intervals and assayed for phenobarbitone, or sodium phenobarbitone, at 240 nm. All release tests were carried out at least in duplicate. Pictures of tablets before and after dissolution were taken using a Phillips EM 501B scanning electron microscope (SEM).

TABLE 1

Polymers used in the preparation of tablets

LE (% mol)	iv (dl/g)
100	1.178
85	1.278
85	0.727
85	0.308
75	1.134

Results and Discussion

For convenience, the polymers will be referred to in the following discussion by the designation %LE(iv), i.e., an 85(1.278) polymer is a polymer containing 85% mol lactide with an inherent viscosity in chloroform of 1.278.

The effects of changing the polymer composition and molecular weight (MW) on the release, in vitro, of phenobarbitone was investigated. Drug release was followed for more than 30 days. The release of phenobarbitone was significantly sustained, indicating the suitability of using poly (lactide-co-glycolide) matrix tablets for long-term controlled drug delivery (Figs 1 and 2).

Drug release profiles consisted of three regions: an initial region of relatively high release rate, probably due to the rapid leaching of drug from surface layers of the tablet (burst effect), which was followed by an-extended region of lower and essentially constant release rate (steady

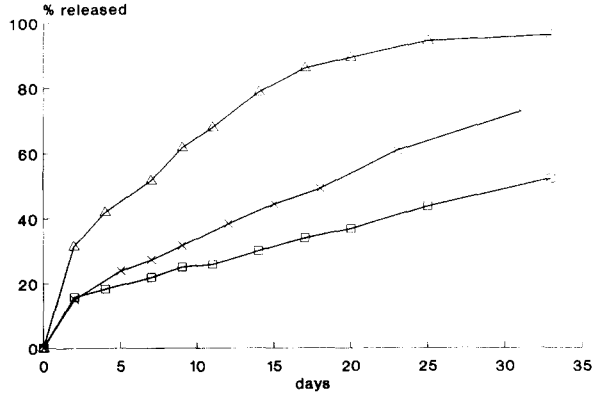

Fig. 1. Plots of phenobarbitone release from polymer matrices having different composition: (□) 100(1.178); (×) 85(1.278); (△) 75(1.134). Dissolution medium: phosphate buffer pH 7.4, 37°C: stirring rate, 50 rpm.

state release region). This usually lasted approximately from 20% drug release to 80% release. This steady state release region was followed by a final region in which the rate of drug release fell off as exhaustion of drug in the matrix approached. Release profiles of 75(1.134) and 85(0.727) matrices are shown in Figs 1 and 2, respectively.

The existence of the steady state release region indicates that the release of drug did not follow the matrix release mechanism suggested by Higuchi (1963). It was shown that water would penetrate into a heterogeneous poly(lactide-co-glycolide) matrix (Avgoustakis and Nixon, 1993). The pores in the matrix are believed to fill with water very rapidly, as indicated by the rapid release of sodium phenobarbitone, which is almost complete after 3 h of immersion of the tablets in the dissolution medium (Fig. 3). It has also been found that the polymers swell upon immersion in an aqueous environment (Avgoustakis and Nixon, 1993). Swelling of the polymer may reduce the volume of waterfilled pores and channels available for drug diffusion or may even create blind aqueous domains inside the matrix. Diffusion through the swollen polymer may then become the predominant release mechanism.

The rate of diffusion in the swollen polymer is much lower than that in water because polymer chains impose severe restrictions to drug movement and this, together with the decrease in drug diffusion rate via aqueous channels due to the decrease in pore volume caused by polymer swelling, probably accounts for the significantly sustained release of phenobarbitone from the matrix tablets.

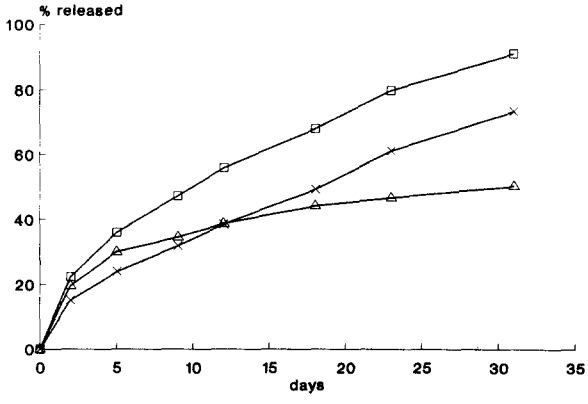

Fig. 2. Plots of phenobarbitone release from 85:15 (LE:GE %mol) matrices having different molecular weight: (×) 85(1.278): (□) 85(0.727); (△) 85(0.308). Dissolution conditions same as in Fig. 1.

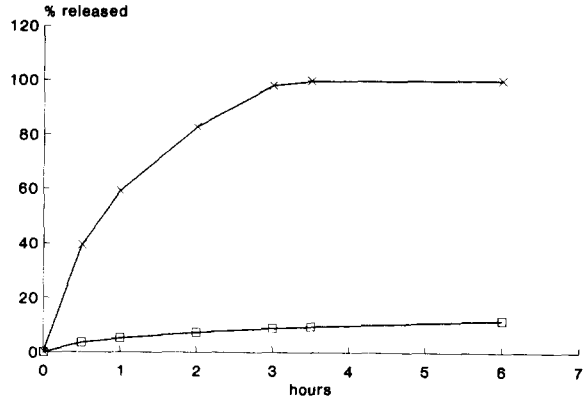

Fig. 3. Phenobarbitone (□) and sodium phenobarbitone (×) release from 75(1.134) matrices. Dissolution conditions same as in Fig. 1.

Degradation and water uptake with time both cause an increase in drug release rate (Avgoustakis and Nixon, 1993). Degradation generates aqueous channels through which drug diffusion and release can occur, whilst water uptake increases release rate because drug diffuses mainly through the aqueous regions of a polymer membrane (Langer and Peppas, 1981). The increase in drug release rate with time caused by degradation and water uptake compensated for the decrease in release rate caused by the increase in the distance with time which the drug has to travel to be liberated and so an essentially constant rate of drug release resulted, as exemplified by the steady state release regions of Figs 1 and 2.

An increase in the glycolide content of polymers having comparable MWs caused an increase in drug release rate (Fig. 1) due to the increased water uptake and swelling facilitating drug diffusion through the polymer (Avgoustakis and Nixon, 1993). A concomitant increase in the degradation rate (Miller et al., 1977; Avgoustakis, 1993) will also contribute. SEM pictures of mid cross-sectional tablet cuts after dissolution confirmed that

the 75(1.134) polymer had been more degraded than the 100(1.178) polymer (Fig. 4). Comparison of the steady state drug release constants, calculated by fitting the release data from the steady state region of the dissolution curves to zero order rate equations (of the general type: $\%m = k_{ss} \cdot t$, where $\%m$ is the percent drug released at time t and k_{ss} the rate constant), shows that the introduction of 25% glycolic acid units into the polymer chains increased the rate of drug release by a factor of 3 (Table 2).

A decrease in polymer MW was shown to increase swelling, water uptake and degradation rate (Avgoustakis 1992; Avgoustakis and Nixon, 1993) and it would, therefore, be expected that by decreasing the MW an increased drug release rate would result. This was indeed the case when the inherent viscosity (iv) of an 85 : 15 (lactide: glycolide %mol) polymer decreased from 1.278 to

TABLE 2

Steady state release rate constants (K_{ss}) of phenobarbitone from poly(lactide-co-glycolide) matrix tablets

Polymer	K_{ss} (% released/day)	r [a]
100(1.178)	1.19	0.9990
85(1.278)	1.93	0.9981
85(0.727)	2.37	0.9973
85(0.308)	0.78	0.9754
75(1.134)	3.50	0.9961

Each K_{ss} value is the mean of two determinations. [a] r: correlation coefficient.

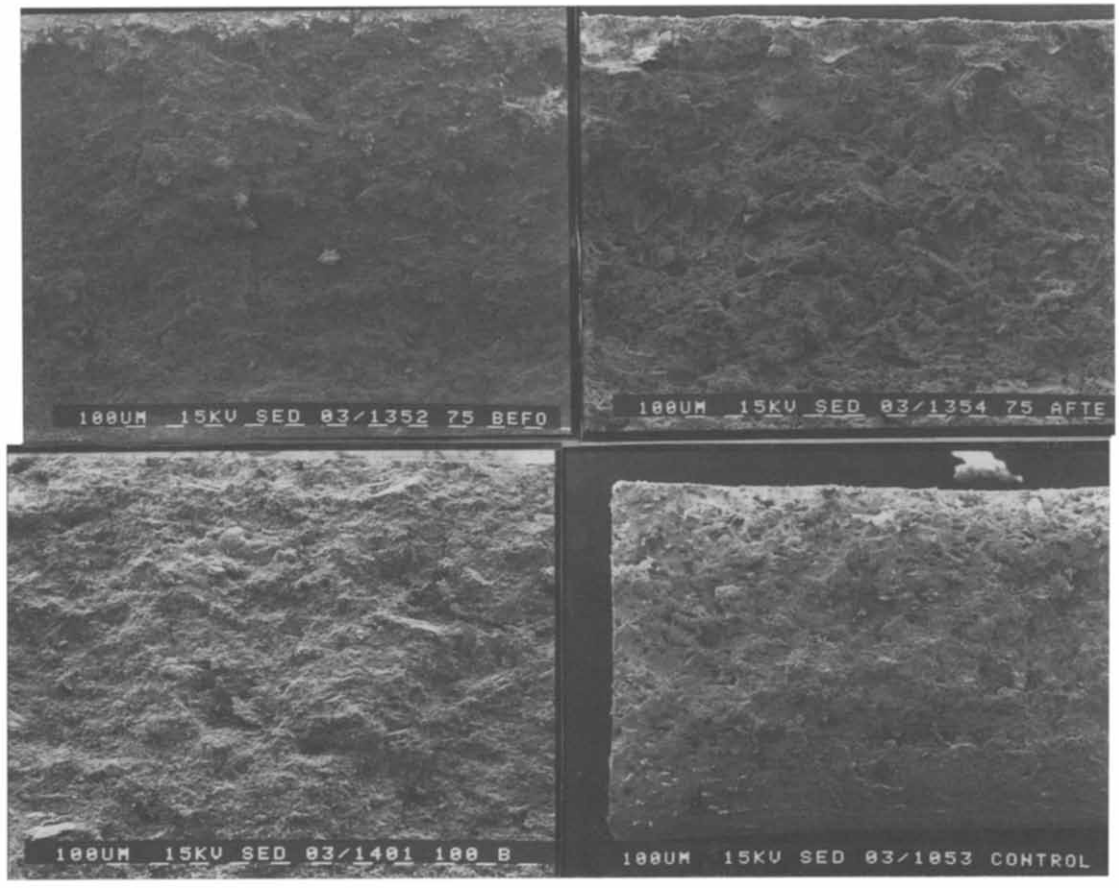

Fig. 4. Scanning electron micrographs of polymer-drug matrices before and after 33 days dissolution (the magnification is shown by the white bars at the bottom of the micrographs). 1352, mid cross-section cut of a 75(1.134) tablet before dissolution; 1354, mid cross-section cut of a 75(1.134) tablet after dissolution; 1401, mid cross-section cut of a 100(1.178) tablet before dissolution; 1053, mid cross-section cut of a 100(1.178) tablet after dissolution.

0.727, but a further decrease in the iv to 0.308 brought about the opposite effect, i.e., a decrease in the rate of drug release (Fig. 2). This can be attributed to the rapid hydrolysis of the low MW polymer, which gradually transformed the interior of the matrix to a 'hydrogel' (Fig. 5). For release to occur, the drug had to diffuse through this gel so that only one release mechanism operated. In the case of high MW polymers, drug release could occur by both diffusion through aqueous channels and diffusion through the swollen polymer. The 85(0.308) polymer exhibited the lowest rate of drug release from all polymers studied, having $k_{ss} = 0.78\%$ day (Table 2).

The transformation of the central portion of the tablet into a hydrogel had already started after 10 days dissolution. The gel area had cavities due to erosion of the polymer. After 20 days, the dimensions of the cavities had increased and a large number of tiny holes covered the gel area. Significant degradation of the surface layers of the matrix could also be observed. After 28 days immersion, gelation of the tablet centre was complete; the interior of the tablet was then a soft, gelatinous, sticky material (Fig. 5).

From the results obtained, it can be deduced that drug release from poly(lactide-co-glycolide) matrix tablets can be controlled by modifying the polymer properties. However, this can be more easily accomplished by modifying the composition of relatively high MW polymers rather than by changing the MW of the polymer. Drug release appears to involve, besides diffusion through the water-filled pores, diffusion through the swollen polymer where the size of the drug molecule may be expected to exert a significant influence on the release rate, because diffusion in polymers is much more sensitive to the MW of the permeant molecules than is diffusion in liquids.

Drug release from many poly(lactide-co-glycolide) systems has been reported as biphasic and discontinuous. Pitt et al. (1979) reported that the release of progesterone from films prepared from polymers with relatively high glycolide content increased abruptly and significantly after approx. 5% release had occurred, due to film fragmentation and exposure of a larger surface area. Beck et al. (1983) also found that the release of norethisterone from poly(lactide-co-glycolide) microcapsules was biphasic. Initially, the microcapsules released the drug by diffusion but later, degradation of the polymer induced a second phase of release producing increased norethisterone serum levels. The release of luteinizing hormone-releasing hormone (LHRH) analogues from poly(lactide-co-glycolide) depots was reported to be both biphasic and discontinuous. Initially, the polypeptide was released by leaching from the surface of the formulation and later by diffusion through aqueous channels generated by

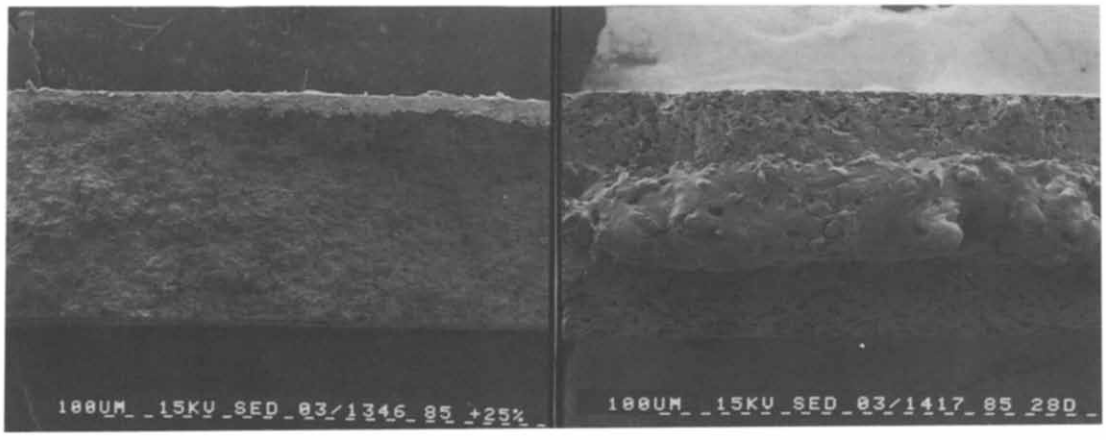

Fig. 5. Scanning electron micrographs of 85(0.308) drug matrices. 1346, mid cross-section cut of a tablet before dissolution; 1417, mid cross-section cut of a tablet after 28 days dissolution.

polymer degradation. The two phases were separated by a period of sub-effective or no polypeptide release, unless very low MW polymers with high glycolide content or high drug content were used (Hutchinson and Furr, 1985; Sanders et al., 1986). With respect to the above reports, the continuous and essentially constant release rate obtained with the poly(lactide-co-glycolide) matrix tablets would appear to provide a significant improvement.

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