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Biodegradable controlled release tablets: II. Preparation and properties of poly(lactide-co-glycolide) powders

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Summary

A spray drying technique was adopted to prepare poly(lactide-co-glycolide) powders. Significant difficulties were encountered with the relatively high molecular weight polymers, the spray drying of which produced threads rather than particles, unless very dilute solutions were used (less than 2% w/v). The important factor for the successful 'spray powdering' of poly(lactide-co-glycolide) polymers appeared to be the molecular weight of the polymer and not the viscosity of the sprayed solution. The spray dried particles were porous, almost spherical agglomerates of tiny spheres. The agglomerated and rather loose texture of the particles probably enhanced the powder compressibility. Soft and ductile powders were obtained with yield pressure values ranging from 28 to 33 MPa. No correlation was found between polymer properties and yield pressure. The contact angle values between polymer compacts and water were in the range of 72–78°, indicating a moderate polymer hydrophobicity. The molecular weight of the polymers did not have any effect on the contact angle value, whereas an increase in glycolide content tended to lower the contact angle. Water uptake by poly(lactide-co-glycolide) matrices increased steadily as matrix hydrophobicity increased with time due to polymer degradation. The weight of the matrix increased with time but, when mass loss due to degradation outweighed the gain from water absorption, the weight of the matrix began to fall. An increase in glycolide content or a decrease in polymer molecular weight caused an increase in both the percent water uptake and water uptake rate. The polymers swelled considerably, although they absorbed relatively small amounts of water and this may have significant implications for drug release from poly(lactide-co-glycolide) matrix tablets.

Introduction

It has been shown that polymerisation conditions affect the characteristics of the produced polymer (Avgoustakis and Nixon, 1991). In the present work, larger batches of polymers having different composition and molecular weight (MW) were synthesised by a modified preparative procedure based on previously acquired data. These polymers were spray dried to give powders. The hydrophobicity and compaction behaviour of these powders, which might affect drug release from poly(lactide-co-glycolide) matrix tablets,

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were investigated. Wettability and water uptake experiments were conducted to assess the polymer hydrophobicity.

Materials and Methods

Materials

DL-Lactide (LE), m.p. 125°C, and glycolide (GE), m.p. 82°C, were purchased from Boehringer Ingelheim. The phosphate buffer (pH 7.4) was prepared from 1.19 g of potassium dihydrogen orthophosphate (BDH, GPR), 2.38 g disodium hydrogen orthophosphate (BDH, Analar) and 8.0 g of sodium chloride (BDH, GPR) in 1 l of distilled water. Chloroform (FSA), methanol (BDH, GPR), dichloromethane (FSA, analar), tetrahydrofuran (FSA, SLR), glacial acetic acid (FSA, SLR) and magnesium stearate (BDH, GPR) were also used.

Methods

Synthesis and characterisation of polymers 20 g batches of polymers were synthesised as described previously (Avgoustakis and Nixon, 1991). These were purified by precipitation from chloroform using excess methanol and dried under vacuum at 40°C to constant weight. The purification of 50:50 (LE:GE % mol) polymers was difficult due to their low solubility. Refluxing for 48 h in chloroform was used to dissolve them but some material remained undissolved, probably those polymer molecules containing a high proportion of glycolide blocks; this material was removed by filtration. The inherent viscosity (iv) of the samples was determined to express their MW on a relative basis. The composition of the samples was determined by ^{1}H-NMR spectroscopy. Details of these techniques are given elsewhere (Avgoustakis and Nixon, 1991).

Spray drying of polymers The polymers were dissolved in chloroform to form 2–5% w/v solutions and spray dried using a Buchi mini spray dryer (Model 190) to prepare powders. The process parameters were: inlet temperature, 60°C; outlet temperature, approx. 45°C; aspirator setting, 10; pump setting, 7–10 ml min^{-1}; spray flow, 400 ml h^{-1}. A 0.5 mm atomizer nozzle was used throughout the experiments. Material deposited on the walls of the drying chamber was retrieved by dissolving in chloroform and the process repeated. The morphology of the powders was examined using a Phillips EM501B scanning electron microscope. The spray dried polymers were stored in desiccators over silica gel.

Compaction behaviour of polymers The compaction behaviour of the spray dried powders was investigated as proposed by Heckel (1961a,b). The powders were compressed using a 10.55 mm diameter flat-faced punch and die system (prelubricated with a 1% suspension of magnesium stearate in chloroform) using a Dartec 100 kN M2501 Universal Testing Machine (Dartec Ltd). A maximum force of 10 kN was applied at a rate of 0.5 kN s^{-1} and the force and displacement of the upper punch continuously recorded with a digital storage oscilloscope (Nicolet 3091). The data were analysed using an Apple IIe computer to produce Heckel plots.

The particle density of the powders was measured with a Beckman air comparison pycnometer (Beckman Instruments, Model 930). The liquid content of the powders (due to residual spray drying solvent or moisture absorbed during storage), which might affect their compaction properties, was also determined before the compaction experiments using a Sartorius infrared dryer (Model YDU 01L, Germany). The liquid content of powders was low, ranging from 0.2 to 0.6% w/w.

Wettability of polymers Contact angle measurements were made to assess the wettability of spray dried polymer powders. The contact angles were determined by applying the h-ϵ method (Lerk et al., 1976).

The powders (63–150 μm) were compressed in a 20 mm diameter flat-faced punch and die system, using an RIIC (UK) hydraulic press. A load of 1 ton was applied. The dimensions and weight of each disc were measured, allowing the calculation of its porosity (ϵ). The disc was placed on a platform which could be adjusted to ensure the disc surface was horizontal. Deionized, distilled water was applied to the disc surface via an Agla microsyringe and readings of the drop height were taken with a cathetometer (Graticules Ltd, U.K.) until additional drops caused no increase in height. The contact angle was calculated from the formula (Lerk et al., 1976):

$$\cos\theta = 1 - \sqrt{\frac{2Bh^2}{3(1-\epsilon)}} \qquad (1)$$

where h is the height of the drop and $B = p_L g/2\,\gamma_{LV}$, where p_L is the density of water (1.0 kg l^{-1}), g the acceleration due to gravity (9.81 m s^{-2}) and γ_{LV} the water-vapour interfacial tension (0.072 N m^{-1}). All measurements were carried out at least in duplicate.

Water uptake by polymers Tablets were prepared by compressing spray dried powders (63–150 μm) in a 10.55 mm diameter flat-faced punch and die system using the Dartec apparatus. A 10 kN force was applied at a rate of 1 kN s^{-1} with a dwell time of 15 s. After their dimensions and weights had been measured, the tablets were placed in glass vials containing phosphate buffer, pH 7.4, and shaken in a water bath at 37°C. The weight change of the tablets with time was recorded over a period of 25 days. The dimensions of the tablets after 2 days and at the end of the incubation period were also measured.

Results and Discussion

Synthesis of polymers

Polymers having compositions ranging from 50 to 100 mol% LE were synthesised by polymerising the monomer mixtures shown in Table 1. Examination of the values in Table 1 shows that the proportion of LE units in the resulting polymer is smaller than that in the initial polymerisation mixture, probably because of the greater reactivity of GE during polymerisation. The MW of the samples synthesised was regulated by modifying the polymerisation conditions according to the results obtained in the study of poly (lactide-co-glycolide) synthesis (Avgoustakis and Nixon, 1991). Thus, polymers having iv in the range 0.3–0.4 were synthesised using 0.013–0.016% w/w stannous octoate at 190°C for 5 h, and polymers having iv in the range of 0.7–0.9 were prepared using 0.028–0.032% catalyst under the same polymerisation conditions. Relatively high MW polymers with iv > 1 were synthesised using 0.1–0.12% catalyst at 130°C for 5 h. 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.

TABLE 1

Composition of the polymers synthesized for spray drying

Lactide (% mol) in initial monomer mixture	Lactide (% mol) in polymer
100.0	100
87.5	85
76.5	75
51.4	50

Spray drying of polymers

The main problem encountered in spray drying was the production of threads, instead of particles, when relatively high MW polymers were sprayed unless very dilute solutions were used (less than 2% w/v). Thus, solutions of an 85(0.719) polymer in chloroform having a concentration higher than 2% w/v could not effectively be atomized, irrespective of the spray dryer operating conditions. Similar results were obtained using solvents such as methylene chloride, 2:1, 1:1 and 1:2 v/v mixtures of methylene chloride with chloroform, tetrahydrofuran and glacial acetic acid.

By applying the Solomon-Ciuta (1962) approximation to calculate the intrinsic Viscosity and the Mark-Houwink equation for poly(lactide-co-glycolide) proposed by Pitt and Gu (1987), it was found that the 85(0.719) sample has an M_n of 26000.

A lower MW 85:15 polymer, 85(0.358) sample, could successfully be 'spray-powdered' at concentrations as high as 10% in chloroform. The relative viscosity of a 3% solution of the 85(0.719) polymer, which would give threads, is 5.452, whilst the relative viscosity of a 10% solution of the 85(0.358) is 11.840, i.e., much higher; this indi-

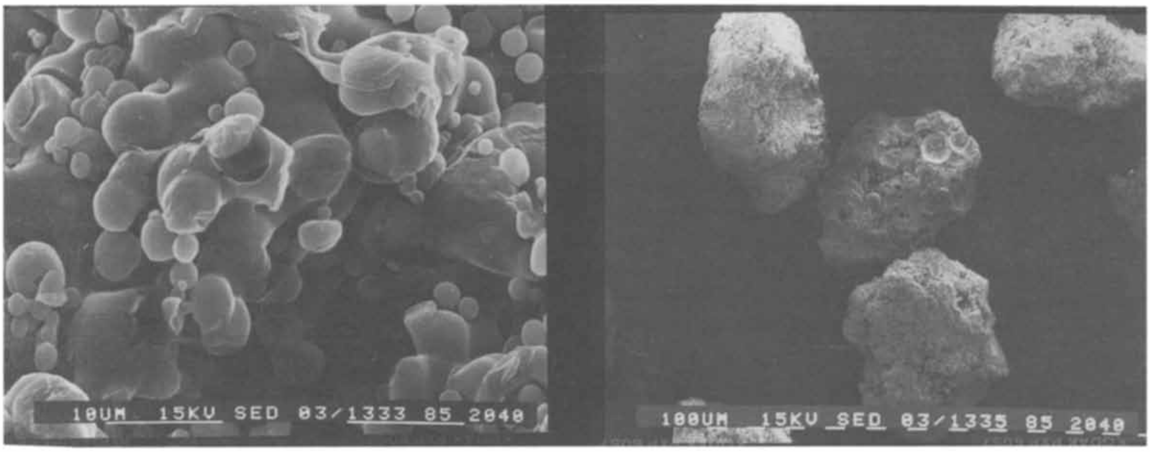

Fig. 1. Scanning electron micrographs of spray dried particles (the magnification is shown by the white bars at the bottom of the micrographs). 1335, particles (420–841 μm) of an 85(0.308) polymer; 1333, detail of the surface of one of the particles shown in 1335.

cated that the viscosity of the solution was not crucial for the successful spray drying of poly(lactide-co-glycolide). Bodmeier and Chen (1988) reported that the successful dispersion of liquid filaments into droplets depended strongly on the type of polymer used and only to a lesser degree on the viscosity of the sprayed solution.

Even more dilute solutions were required for the effective spray drying of polymers with higher MW, i.e., 1.5% w/v solutions for an 85(1.278) polymer. It appears that the important factor is the MW of the polymer, but this must be considered in conjunction with the polymer concentration in the sprayed solution. In linear polymers without bulky side groups, such as poly(lactide-co-glycolide), the higher the MW the stronger the intermolecular interactions, such as intermolecular attractive forces (Van der Waals forces) and the physical entanglement of the polymer chains. These might account for the increased difficulty in breaking up the polymer solution into individual droplets during spray drying as the polymer

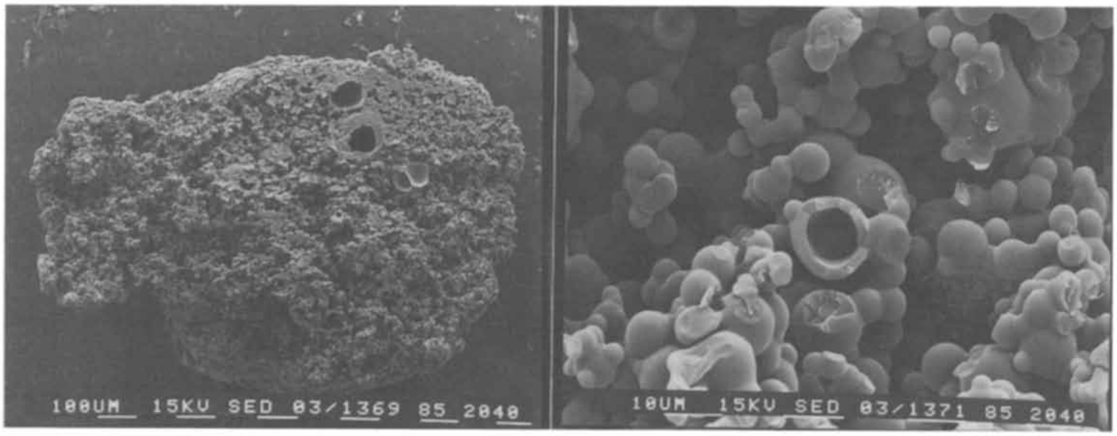

Fig. 2. Scanning electron micrographs of the interior of spray dried particles. 1369, mid cross-section cut of an 85(0.308) particle (420–841 μm); 1371, detail of the interior of the particle shown in 1369.

MW increases. Diluting the polymer solution reduces the intermolecular interaction by increasing the separation of the polymer chains and probably explains the successful 'spray-powdering' of high MW polymers using dilute solutions.

There was a significant deposition of partially dried material on the walls of the drying chamber, attributable to the tacky nature of the polymers at the drying temperature and to the characteristics, such as the small size of the drying chamber and the atomising method, of the spray dryer used. It was, therefore, necessary to recycle the deposited material twice in order that acceptable spray drying yields (70–80%) be achieved. The use of larger spray dryers with more efficient atomizing equipment, may improve the spray drying characteristics of poly(lactide-co-glycolide).

The spray dried particles appeared to be porous, almost spherical, agglomerates of tiny spheres. The agglomerates probably formed through droplets coalescing in the proximity of the atomizer and drying in this state, or alternatively, through partially dried droplets adhering to each other in the lower regions of the drying chamber, due to their sticky surfaces. The particle surface was porous and rough but without sharp edges (Fig. 1). Pictures of the particle interior showed that this had a similar texture to the surface, consisting of a large number of very small spheres attached to each other or fused together to form a porous irregular structure (Fig. 2).

Compaction behaviour of polymers

A typical Heckel plot for spray dried poly (lactide-co-glycolide) powders is shown in Fig. 3. The plot consisted of an initial curved region, during which densification occurred through particle slippage and rearrangement, followed by an essentially linear region during which densification through plastic deformation took place. The yield pressure (p_y) values of the polymers calculated from the slope ($p_y = 1/\text{slope}$) of the 1.5–3.5 kN part of the Heckel plots (1 kN of compaction force in the abscissa of the plot corresponds to 11.44 MPa of pressure) were in the range of 28–33 MPa, indicating a material of high plasticity (Table 2). The rather loose and porous texture of the spray dried particles, decreasing the resistance of the powder to deformation, probably contributed to the low p_y values observed.

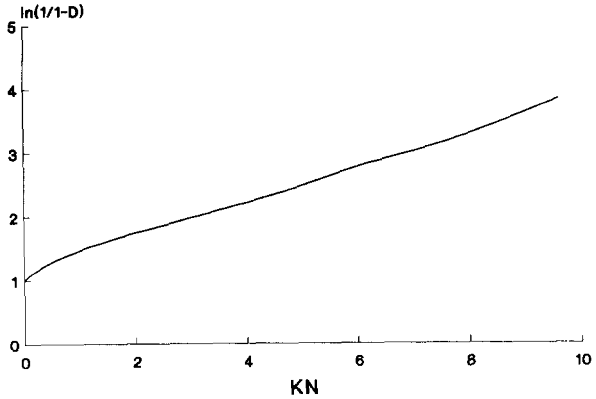

Fig. 3. Heckel plot of a 75(1.134) polymer(particle size of the polymer powder 63–150 μm, compaction rate 0.5 kN/s).

Even at low compaction pressures, a compact of high density results (Fig. 3). For example, at 5 kN (57.20 MPa) ln $[1/(1-D)]$ equals 2.5 and consequently $D = 0.918$ (D = relative density of the compact). This demonstrates the high ductility of the spray dried polymers and implies that even at low pressures, strong tablets should be produced, because high density values mean more intimate contact between the particles and strong interparticle bonding. The characteristics of the polymers, such as composition and MW, did not appear to have any significant effect on the yield pressure of the powders (Table 2).

Wettability of polymers

The contact angle values obtained with polymers of different composition and MW were in

TABLE 2

Effect of polymer composition and molecular weight on yield pressure, p_y

LE (% mol)	iv (dl/g)	p_y (MPa)	CV (%) [a]
100	1.178	33.24	2.51
85	1.278	30.27	1.22
85	0.727	28.43	0.15
85	0.334	31.35	6.21
75	1.134	31.61	7.57

The particle size range of the powders was 63–150 μm.

[a] Coefficient of variance.

TABLE 3

Effect of polymer composition and molecular weight on the polymer contact angle (θ) with water

LE (% mol)	iv (dl/g)	cos θ	θ (°)	CV (%) [a]
100	0.820	0.216	77.5	3.96
85	1.278	0.261	74.9	1.34
85	0.727	0.250	75.5	1.37
85	0.334	0.245	75.8	0.89
75	0.796	0.312	71.8	4.57

[a] Coefficient of variance.

TABLE 4

Analysis of variance of contact values obtained using polymers with different composition

Source of variation	Sum of squares	D.F. [a]	Mean square	F
composition	33.13	2	16.57	2.33
error	21.30	3	7.10	
total	54.43	5		

$F < F$ (d.f. = 2.3; level of significance = 0.05) = 9.55 → H_0 is valid.

[a] Degrees of freedom.

the range of 72–78° (Table 3), indicating a moderate polymer hydrophobicity. The positive values of cos θ imply that water would penetrate into a heterogeneous poly(lactide-co-glycolide) matrix, since a positive capillary pressure differential (Δp) would exist (Eq. 2) and this would draw water into the matrix:

$$\Delta p = \gamma \cos \theta / m \qquad (2)$$

where γ is the surface tension of the liquid, θ the liquid-solid contact angle and m the ratio of the cross-sectional area of the capillary to its perimeter (Ganderton and Selkirk, 1970).

The polymer MW did not appear to have any effect on poly(lactide-co-glycolide) wettability, in contrast to the effect of composition. Thus, an increase in GE content tended to increase the polymer wettability due to the decreased number of hydrophobic lactic acid methyl side groups in the polymer chains as the GE content increased (Table 3). However, the contact angle values obtained from polymers of different composition, but with similar MW, i.e., the polymers in Table 3 having iv ≃ 0.8, were not found to differ significantly (0.05 level of significance) when the analysis of variance (ANOVA) statistical method was applied (Table 4). ANOVA was carried out using KWIKSTAT version 2.00 (Texasoft/ Mission Technologies, TX, U.S.A., 1989) statistical software.

Water uptake from polymers

Gilding and Reed (1979) reported that the water uptake from poly(lactide-co-glycolide) polymers reached an equilibrium after 3–4 days of immersion in phosphate buffer, pH 7.4. However, because these polymers degrade in aqueous media, it might be expected that no equilibrium is ever really achieved. Indeed, water uptake from poly(lactide-co-glycolide) matrices increased steadily with time because degradation caused a continuous transformation throughout the experiment, causing the matrix to become more hydrophilic (Figs 4 and 5). Chain scission, occurring after the immersion of polymers in water, generates hydrophilic groups (hydroxyl and carboxylic acid end groups) which cause this increase in matrix hydrophilicity. The oligomers produced when extensive chain scission has occurred would create an osmotic pressure difference between the interior of the tablet and the surrounding

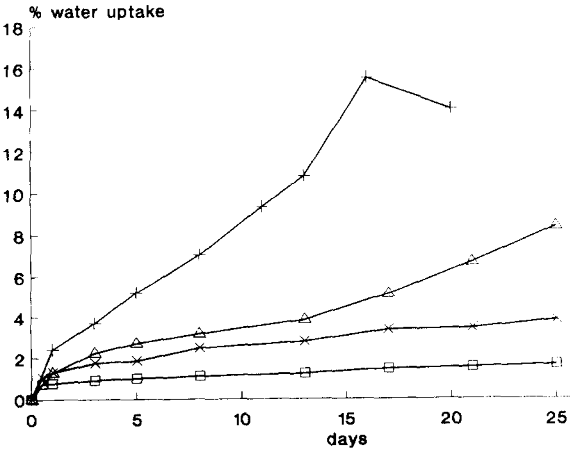

Fig. 4. Water uptake curves for polymers having different composition: (□) 100(1.178; (×) 85(1.278); (△) 75(1.134); (+) 50(0.343). Incubation medium: phosphate buffer pH 7.4, 37°C.

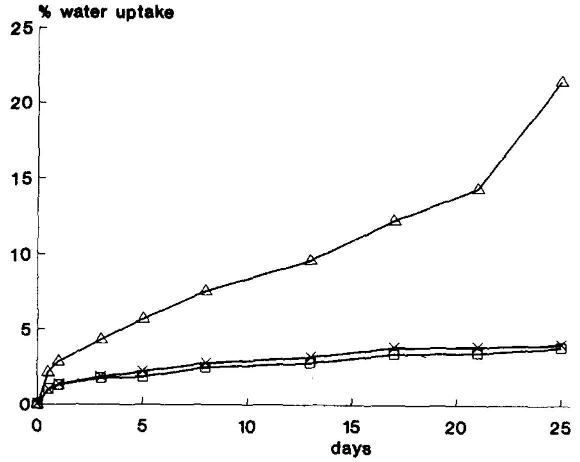

Fig. 5. Water uptake curves for polymers having different molecular weight: (□) 85(1.278); (×) 85(0.727); (△) 85(0.308). Incubation conditions as in Fig. 4.

liquid, because the oligomers formed in the interior diffuse out from the matrix at lower rates than those formed at the tablet surface. This would draw water into the matrix, the outer layers of the tablet functioning as a 'semipermeable membrane'. Thus, hydrolysis of the polymer causes water to be drawn continuously into the matrix and the weight of the matrix increases with time, but degradation is proceeding continuously and eventually, when mass loss due to this outweighs the gain from water uptake, the weight of the matrix begins to fall. The 50(0.343) polymer, which is the sample with the highest degradation rate, showed a mass loss half-life in vitro of approx. 26 days (Avgoustakis, 1992) and was the only matrix for which a weight reduction was observed during the 25 days of the water uptake experiment (Fig. 4).

TABLE 5

Effect of polymer composition and molecular weight on the swelling of polymers

LE (% mol)	iv (dl/g)	Swelling [a]
100	1.178	18.91 (12.71) [d]
85	1.278	21.49
85	0.727	26.93
85	0.308	35.3 [b]
75	1.134	32.05 (27.30) [d]
50	0.343	34.8 [c] (30.56) [d]

[a] % vertical expansion of tablet after 25 days of immersion in phosphate buffer pH 7.4, 37°C (mean of two replicates).

[b] Approximate value.

[c] Approximate value after 20 days of immersion.

[d] Swelling after 2 days of immersion.

An increase in glycolide content, or a decrease in polymer MW, caused an increase in both the percent water uptake and water uptake rate (as indicated from the slope of the water uptake curves) (Figs 4 and 5). This can be attributed to the increased polymer hydrophilicity and to the decrease in the glass transition temperature (T_g) of the polymer (Avgoustakis and Nixon, 1991), which would enhance the permeability of the polymer in water and would increase the amount of water that can be accommodated by the polymer.

The swelling (measured by the % increase in tablet thickness) of the matrices after immersion in the buffer increased with an increase in GE content, or a decrease in the MW of the polymer (Table 5). The increased polymer affinity for water, as hydrophilicity of the polymer increases, accounts for the observed increase in swelling. Significant swelling of the matrices had already occurred after 2 days of immersion (Table 5). The polymers swelled considerably, although they absorbed relatively small quantities of water. For example, the sample 100(1.178) absorbed only 1.67% water but swelled 18.31% over the 25 day period. A possible explanation for this might be the plasticisation of the polymer caused by the absorbed water, which would enhance the expansion of the polymer molecules and would increase the free volume in the polymer. Pitt and Gu (1987) observed that water uptake from a 70:30 (ρ-LE:GE % mol) polymer caused a decrease in the polymer T_g which they attributed to the plasticisation of the polymer by the absorbed water.

In conclusion, it was found that poly(lactide-co-glycolide) powders with good compaction properties can be prepared by spray drying. Contact angle measurements revealed a moderate polymer hydrophobicity and that water will penetrate through capillaries and pores of poly(lactide-co-glycolide) matrices. The continuous water uptake with time and the considerable swelling of the polymers may have significant implications for the release of drugs from poly(lactide-coglycolide) matrices.

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