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Evaluation of ibuprofen-loaded microspheres prepared from novel copolyesters

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Abstract

The utility of two novel linear random copolyesters to encapsulate and control the release of ibuprofen, via microspheres, was investigated. Various manufacturing parameters, including temperature, disperse phase volume and polymer:ibuprofen ratios were altered during the microsphere production. The effects of these changes on the morphological characteristics of the microspheres, yield, drug loading, encapsulation efficiency and drug release rates were examined. The diameter of the microspheres ranged from 36 to 89 μm and showed both smooth and ridged surfaces. Microsphere diameter was probably determined by the internal phase volume, while surface morphology was controlled by manufacturing temperature. Greater encapsulation efficiency was obtained by increasing the polymer:ibuprofen ratio and by reducing the internal phase volume. For all batches there was an initial burst drug release into phosphate buffer (pH 7.4) over the first 2–4 h, which was followed by a much slower release rate over the remaining time period. Drug release rates during both these phases were dependent upon the amount and nature of the polymer in the microspheres, noting that the more hydrophilic polymer provided faster release rates. Ibuprofen solubility appeared to play a dominant role in controlling release, although both encapsulation efficiency and microsphere morphology were also contributing factors.

Keywords: Polyesters; Microspheres; Emulsion solvent evaporation; Manufacturing parameters

1. Introduction

The process of microencapsulation has been used to produce microspheres containing both hydrophilic drugs, such as propranolol hydrochloride (Hombreiro-Pérez et al., 2003), 5-fluorouracil (Lin and Vasavada, 2000) and cephradin (Ustariz-Peyret et al., 2000) and hydrophobic drugs, such as nifedipine (Guyot and Fawaz, 1998; Hombreiro-Pérez et al., 2003), beclomethasone (El-Baseir and Kellaway, 1998) and ibuprofen (Bodmeier and Chen, 1989) entrapped within biodegradable polymers. The purpose of producing microspheres is to obtain controlled release of the drug and thus maintain therapeutic drug levels over a specified time period (Benoit and Puisieux, 1986; Prescott, 1989; Flandroy et al., 1993; Leroux et al., 1996; Mathiowitz et al., 1999). Short half-lives and poor bioavailability of certain drugs can be overcome by implanting the microspheres within the target tissue area thus minimising absorption into the systemic circulation (Benoit and Puisieux, 1986; Prescott, 1989; Flandroy et al., 1993; Leroux et al., 1996; Mathiowitz et al., 1999). Reduced drug plasma levels could minimise the incidence and severity of adverse side effects (Prescott, 1989; Mathiowitz et al., 1999).

Microspheres may be produced by several methods utilising emulsion systems (oil-in-water, oil-in-oil, water-in-oil-in-water), as well as by spray drying (Bakan, 1986; Watts et al., 1990; Giunchedi and Conte, 1995; Mathiowitz et al., 1999). The most common emulsion system used is oil-in-water (o/w), with the microspheres being produced by the emulsion solvent evaporation (ESE) method. This relatively simple method enables the entrapment of a wide range of hydrophobic drugs (Conti et al., 1992; Flandroy et al., 1993; Whateley, 1993). The main disadvantage of this method is its limited ability to encapsulate hydrophilic drugs (Watts et al., 1990; Conti et al., 1992; Whateley, 1993; Mathiowitz et al., 1999; Jain, 2000) as partition-

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ing into the aqueous phase of the emulsion readily occurs. The effect is to reduce the drug loading compared with hydrophobic drugs (Watts et al., 1990; Conti et al., 1992; Whateley, 1993; Mathiowitz et al., 1999; Jain, 2000). A further effect of partitioning is the accumulation of drug crystals on the surface of microspheres which produces burst release of the drug on administration (Jain, 2000). The degree of burst release will generally depend upon the nature of the polymer, the polymer:drug ratio (Bodmeier and Chen, 1989; El-Baseir and Kellaway, 1998; Guyot and Fawaz, 1998; Hombreiro-Pérez et al., 2003; Karasulu et al., 2003) and the relatively affinities of the drug for the polymer and the aqueous phase (Tice and Cowsar, 1984).

The aliphatic semi-crystalline polyester, poly-ε-caprolactone (PCL), has been used in the field of controlled drug release. When used alone PCL produces controlled release over extended periods of up to 1 year (Sinha et al., 2004). However, due to its hydrophobic and semi-crystalline nature, the degradation of PCL is much slower than the established polymers based on poly(lactic acid) (PLA) derivatives. Both PCL and the PLA polymers tend to produce drug-loaded microspheres with an initial burst drug release. PLA derivatives also have the limitation that their properties cannot be varied beyond copolymer composition and molecular weight, and they have no chemical functionality which can be modified post-polymerisation, to enhance drug incorporation and release.

The two novel polyesters, used in this study, were enzymatically prepared from equimolar quantities of three monomers: ω-pentadecalactone, divinyl adipate and either propane-1,3-diol or glycerol (Namekawa et al., 2000). Due to the specificity of the chosen hydrolytic enzyme a linear random copolyester was prepared which has a chemical composition similar to PCL, but this time has a greater degree of disorder. The polyester prepared using glycerol, as one of its monomers, allows for a slight increase in the hydrophilicity of the polymer, as well as providing a functional group for possible covalent bonding or hydrogen bonding of the drug molecules (Thompson et al., 2006).

The objective of this work was to produce microspheres by the emulsion solvent evaporation (ESE) method using these novel polymers and incorporate ibuprofen, as a model hydrophobic drug. Ibuprofen was selected because of its capability to undergo conjugation to polymer SH-L510. The conjugated material will be the focus of future work and therefore allowing comparison of drug release between conjugated and non-conjugated batches. The morphological characteristics and the in vitro drug release rates from these microspheres were thus examined.

2. Materials and methods

2.1. Materials

The two polyesters were prepared in our laboratories (Liverpool John Moores University, UK), and their synthesis and analysis was detailed in our earlier work (Thompson et al., 2006). Specifically, the polymer prepared from: ω-pentadecalactone, divinyl adipate and propane-1,3-diol (code name SH-L509) had a $M_w = 15.7$ kDa, whereas the polymer prepared from: ω-pentadecalactone, divinyl adipate and glycerol (code name SH-L510) had a $M_w = 12.2$ kDa. These polymers were similar to those previously used to produce drug-free microspheres (Thompson et al., 2006). Ibuprofen, polyvinyl alcohol (PVA) (average molecular weight 30,000–70,000), sodium phosphate, sodium acid phosphate, sodium chloride and polysorbate 20 were purchased from Sigma–Aldrich Co. Ltd., UK. Dichloromethane (DCM) and chloroform (C), both of analytical grade, were obtained from Fisher Chemicals (Fisher Scientific UK Ltd., England).

Table 1
Manufacturing parameters used in production of microspheres

Batch	Temperature (°C)	DCM volume (mL)
1	24	2.5
2	24	1.5
3	37	2.5

2.2. Microsphere production

Ibuprofen-loaded microspheres were produced in triplicate at polymer:ibuprofen ratios of 4:1, 6:1 and 10:1 using both polymers. Briefly, the method involved co-dissolving 150 mg of polymer and selected weights of ibuprofen in DCM. The solution was dispersed in an aqueous phase consisting of 80 mL of a 0.2% (w/v) solution of PVA. The resulting emulsion was stirred for 30 min at 1000 ± 10 rpm on a magnetic stirrer at different temperatures. The manufacturing parameters used are shown in Table 1. Microspheres were then collected by filtration and dried at room temperature under vacuum until required for use.

2.3. Yield, drug loading and encapsulation efficiency

Dried microspheres were accurately weighed and the yield calculated as a percentage using Eq. (1):

$$\text{Yield} = \left(\frac{\text{weight of microspheres}}{\text{weight of polymer} + \text{weight of ibuprofen}}\right) \times 100 \quad (1)$$

A microsphere sample (10 mg) was dissolved in 10 mL of chloroform. The UV absorbance of the solution was measured using a Biomate 5 UV spectrophotometer (Thermo Spectronic, England) at 273 nm. Drug loading and encapsulation efficiency were determined in duplicate for all batches using Eqs. (2) and (3), respectively. Values were expressed as percentage:

$$\text{Drug loading} = \left(\frac{\text{weight of ibuprofen in microspheres}}{\text{microspheres sample weight}}\right) \times 100 \quad (2)$$

$$\text{Encapsulation efficiency} = \left(\frac{\text{actual weight of ibuprofen in sample}}{\text{theoretical weight of ibuprofen}}\right) \times 100 \quad (3)$$

2.4. Differential scanning calorimetry

Microsphere samples (5–7 mg) from each batch were placed in hermetically sealed aluminium pans. Thermal analysis was carried out in a Q100 differential scanning calorimeter (TA instruments, USA). Samples were heated from 20 to 90 °C, cooled to −90 °C and then heated to 90 °C at 20 °C min^{-1}. Thermal data was determined from the second heating cycle using the supplied software.

2.5. Scanning electron microscopy

Microspheres were mounted on copper stubs and coated with a gold–palladium mixture in a sputter-coater (Polaron SC7640). Samples were then scanned using a Cambridge Stereoscan S90B electron microscope (Cambridge Instruments, UK). Micrographs were taken of each batch at a range of magnifications in order to determine morphology as well as be able to calculate particle mean diameter and standard deviation around the mean.

2.6. In vitro release of ibuprofen

Microsphere samples (20 mg) were suspended in 20 mL of pH 7.4 phosphate buffer (at 37 ± 0.5 °C) in a Grant OLS 200 shaking water bath (Grant Instruments, Cambridge, England) at 75 oscillations/min in sealed glass jars. Samples (5 mL) were withdrawn at regular time intervals, filtered using a syringe and Millex GP 0.22 μm filter (Millipore, USA) and UV analysed at 273 nm. The withdrawn volume was replaced with 5 mL of fresh buffer to maintain sink conditions.

2.7. Statistical analysis

Quantitative data were reported as mean ± standard deviation (S.D.). Statistical analysis was performed using a one-way analysis of variance (one-way ANOVA). Comparison between the two means was determined using the Tukey's test with statistical significance evaluated at $p < 0.05$.

3. Results and discussion

3.1. Yield

The results of the determination of microsphere yield for various polymer:ibuprofen ratios are shown in Table 2. This shows that batches 2 and 3 produced consistently higher yields than batch 1. This may have been due to their faster rates of solidification resulting from the use of a lower volume of DCM (batch 2) and a higher manufacturing temperature (batch 3). Moreover, a fast solidification rate may reduce partitioning of drug and polymer into the external phase of the emulsion.

3.2. Drug loading and encapsulation efficiency

The results of the variation in drug loading and encapsulation efficiencies with polymer:ibuprofen ratio are shown in Tables 3 and 4, respectively. Consistent with the higher yields

Table 2
Microsphere yield (%) at various polymer:ibuprofen ratios (±S.D., $n = 3$)

Batch	SH-L509			SH-L510		
	4:1	6:1	10:1	4:1	6:1	10:1
1	48.61 (±0.56)	47.51 (±0.84)	47.48 (±2.27)	47.86 (±1.84)	46.82 (±0.44)	45.36 (±1.41)
2	57.25 (±1.99)	65.42 (±7.43)	60.12 (±1.71)	55.92 (±3.13)	54.45 (±1.37)	53.81 (±2.05)
3	56.69 (±0.60)	53.20 (±4.12)	52.87 (±1.41)	47.60 (±3.35)	52.11 (±3.23)	50.24 (±0.42)

Table 3
Drug loading (%) at various polymer:ibuprofen ratios (±S.D., $n = 3$)

Batch	SH-L509			SH-L510		
	4:1	6:1	10:1	4:1	6:1	10:1
1	11.90 (±0.14)	8.35 (±0.21)	5.60 (±0.56)	12.10 (±0.14)	8.20 (±0.14)	5.30 (±0.14)
2	13.45 (±0.49)	8.95 (±0.49)	6.15 (±0.35)	13.65 (±0.49)	8.70 (±0.42)	5.85 (±0.21)
3	12.25 (±0.21)	8.55 (±0.07)	5.45 (±0.07)	12.45 (±0.21)	8.40 (±0.28)	5.25 (±0.35)

Table 4
Encapsulation efficiency (%) at various polymer:ibuprofen ratios (±S.D., $n = 3$)

Batch	SH-L509			SH-L510		
	4:1	6:1	10:1	4:1	6:1	10:1
1	59.50 (±0.70)	58.75 (±1.48)	61.60 (±6.22)	60.50 (±0.70)	57.70 (±0.98)	58.30 (±1.55)
2	67.25 (±2.47)	62.95 (±3.46)	67.65 (±3.88)	68.25 (±2.47)	61.20 (±2.96)	64.35 (±2.33)
3	61.25 (±1.06)	60.15 (±0.49)	59.95 (±0.77)	62.25 (±1.06)	59.10 (±1.97)	57.75 (±3.88)

for batch 2, higher drug loadings and encapsulation efficiencies were also produced from this batch. A possible reason for this is that the internal phase of batch 2 was more viscous and therefore solidified at a faster rate (Bodmeier and McGinity, 1988; Bodmeier and Chen, 1989). However, the average drug loading was in the rank order of batch 2 > batch 3 > batch 1. Although the higher processing temperature used in batch 3 might have produced a rapid rate of solidification, the average drug loading for batch 3 was a little lower than batch 2. It may be that at 37 °C the solubility of ibuprofen would be greater than at 24 °C possibly causing an increase in the rate of drug partitioning into the aqueous phase.

Reduced viscosity of the internal phase by a reduction in the initial amount of ibuprofen used did not cause a reduction in the encapsulation efficiency. In fact, in some cases, ibuprofen encapsulation efficiency increased slightly with increased polymer:drug ratio. This improved encapsulation efficiency may be simply due to the greater proportion of polymer with respect to the amount of drug.

To further increase the drug loading, solvents in which the polymers are less soluble may be used. Using a solvent in which the polymer is less soluble could result in the polymer solidifying more quickly and hence result in a higher drug loading (Bodmeier and McGinity, 1988).

3.3. Differential scanning calorimetry

Single melting peaks were found for all batches, with peaks at 57–59 °C and 65–68 °C for microspheres produced using SH-L509 and SH-L510, respectively (see Fig. 1). This was lower than the peak found for ibuprofen alone (78 °C) and higher than those found for the polymers alone (Thompson et al., 2006). A molecular dispersion may have been produced as the polymers and ibuprofen behaved as a single species on melting. This may have been caused by the polymers and ibuprofen being dissolved in a common solvent during manufacture. In other words the ibuprofen was dissolved, not dispersed, in the polymer matrix (Dubernet, 1995). The scans are similar for all batches of microspheres produced using both polymers at all ratios and hence not all scans are shown.

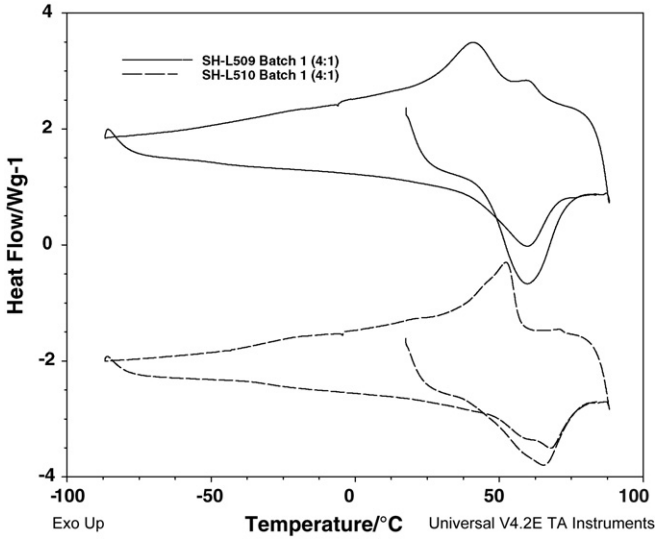

Fig. 1. DSC scans of microspheres produced using batch 1 at a polymer:ibuprofen ratio of 4:1 using polymers SH-L509 or SH-L510.

3.4. Scanning electron microscopy

Fig. 2 shows that microspheres from batch 1 using polymer SH-L509 at a polymer:ibuprofen ratio of 4:1 had crystals present on the surface while at a ratio of 10:1 these crystals were absent. These crystals were presumed to be ibuprofen. The precipitation rate of the polymer and the drug may have been approximately equal at a ratio of 10:1 thus reducing accumulation of drug crystals on the microsphere surface (Bodmeier and Chen, 1989). Moreover, the higher proportion of polymer at the 10:1 ratio may have been sufficient to entrap the drug completely (Fu et al., 2001; Lagarce et al., 2002). However, the microspheres from batch 3 did not display surface crystals at any ratio (see Fig. 3). This may be due to the increased solubility of ibupro-

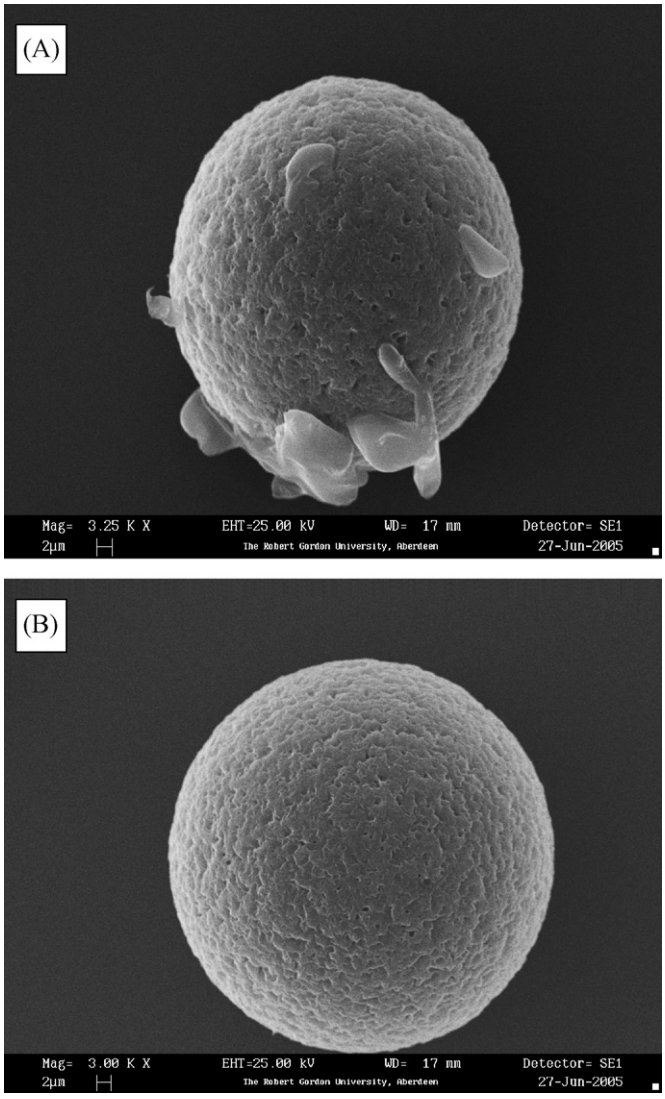

Fig. 2. Scanning electron micrographs of microspheres from batch 1 using polymer SH-L509:ibuprofen ratios (A) 4:1 and (B) 10:1.

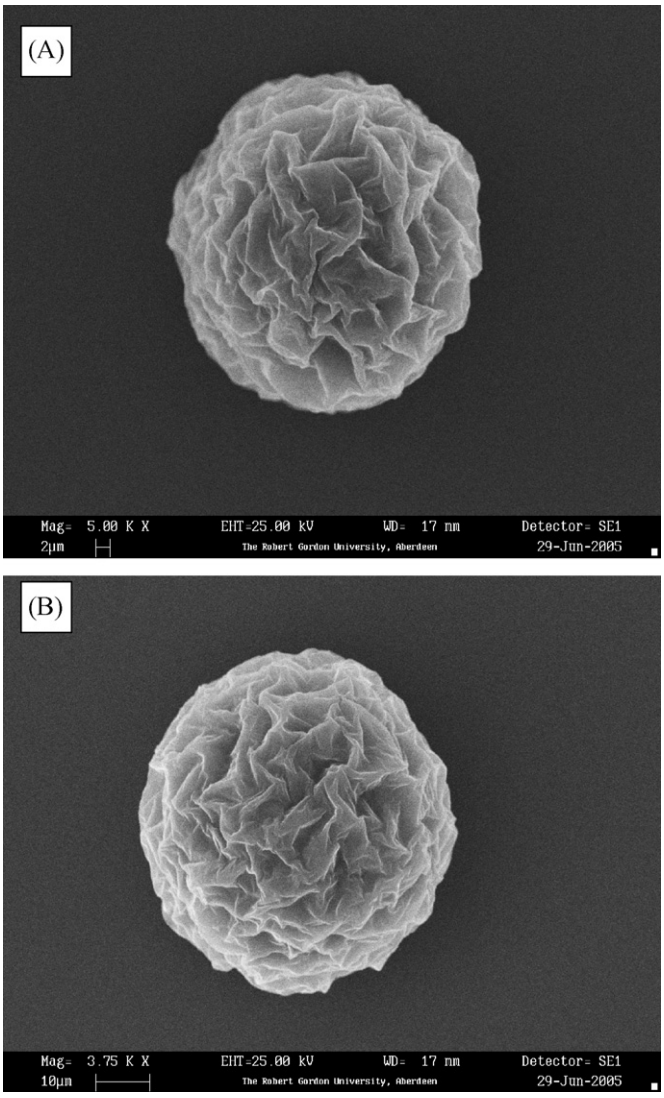

Fig. 3. Scanning electron micrographs of microspheres from batch 3 using polymer SH-L509:ibuprofen ratios (A) 4:1 and (B) 10:1.

fen in the external phase of the emulsion at 37 °C. Any surface drug crystals may have dissolved in the external phase prior to microsphere collection. This could also account for the lower drug loadings obtained in batch 3 compared with batch 2.

Microspheres from batch 3 produced at a higher temperature (37 °C) showed extensive ridges over the entire surface at both polymer:drug ratios (4:1 and 10:1) (see Fig. 3). Drug-free microspheres produced in earlier work (Thompson et al., 2006) also displayed these surface ridges. These drug-free microspheres had a melting range (39–47 °C) similar to the polymer from which they were formed while the ibuprofen-loaded microspheres had a slightly higher melting point (57–68 °C). Hence it is unlikely that microsphere melting point alone is responsible for this ridged morphology. Morphology at higher processing temperatures may also be determined by a combination of polymer molecular weight, solubility, relative hydrophilicity, as well as melting point. Ibuprofen-loaded microspheres produced at 24 °C using polymers SH-L509 and SH-L510 had relatively smooth surfaces. Although polymer SH-L510 was more hydrophilic than polymer SH-L509 (Thompson et al., 2006), the inclusion of ibuprofen, a poorly water soluble drug, may have increased the hydrophobicity of the internal phase of the emulsion sufficiently to make the factor of polymer water solubility almost negligible.

As seen in Table 5, the mean diameters of microspheres from batch 2 at all polymer:drug ratios were significantly greater than those produced from batches 1 and 3 ($p < 0.05$). In addition, the mean microsphere diameters produced from polymer SH-L509 were significantly larger than those produced using polymer SH-L510 ($p < 0.05$). Batch 2 used a smaller volume of DCM and this could result in an increased rate of microsphere hardening. An increased hardening rate would also tend to reduce the time available for subdivision of larger globules into smaller ones during stirring. As a result the globules of the internal phase were larger in diameter than the other batches on solidification. In the case of batch 3 where the mean microsphere diameters were significantly lower than batch 2, but significantly higher than batch 1, the increased processing temperature (37 °C) possibly increased the rate of polymer and drug solidification ($p < 0.05$). However, the temperature seemed to have a lesser affect on diameter than the internal phase viscosity.

The mean microsphere diameter decreased with increasing polymer:ibuprofen ratio, although the differences between ratios were not statistically significant ($p > 0.05$). This could be due to the changes in viscosity resulting from changes in total weight of solids dissolved in the internal phase. A reduction in viscosity may result in an increased solidification time. The increased stirring time associated with it may have reduced the overall globule diameters and consequently produced smaller microspheres.

3.5. In vitro release of ibuprofen

Microspheres from batch 1 showed surface crystals, probably of ibuprofen (see Fig. 2A). They produced an initial burst release of drug (Fig. 4) similar in magnitude to the burst shown from microspheres of batch 3 where drug crystals were absent (see Fig. 3). This was surprising as surface drug crystals would have been expected to increase initial burst release to some degree

Table 5
Mean diameter (µm) of microspheres at various polymer:ibuprofen ratios (±S.D., $n \geq 50$)

Batch	SH-L509			SH-L510		
	4:1	6:1	10:1	4:1	6:1	10:1
1	55.4 (±19.3)	46.3 (±13.3)	45.5 (±22.8)	38.3 (±13.8)	36.0 (±14.4)	36.0 (±15.2)
2	89.4 (±39.2)	79.2 (±38.3)	74.7 (±31.6)	64.6 (±33.3)	64.1 (±37.3)	59.3 (±34.4)
3	62.3 (±31.1)	55.5 (±21.5)	52.4 (±27.6)	47.0 (±30.6)	43.2 (±16.0)	44.1 (±23.6)

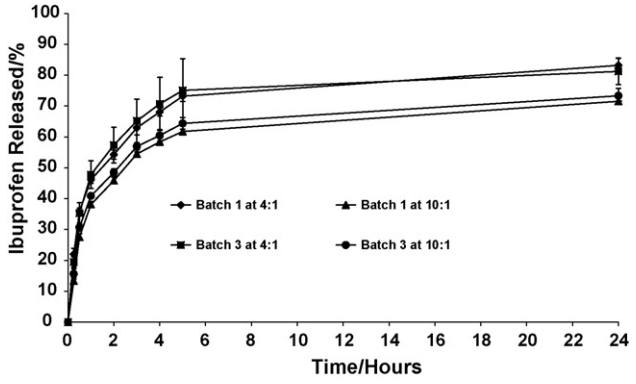

Fig. 4. Release of ibuprofen from microspheres into pH 7.4 phosphate buffer at 37 °C from batches 1 and 3 using polymer SH-L509: drug ratios of 4:1 and 10:1 (±S.D., $n = 3$).

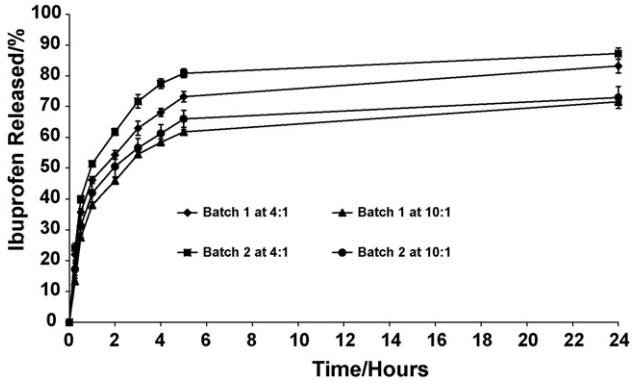

Fig. 5. Release of ibuprofen from microspheres into pH 7.4 phosphate buffer at 37 °C from batches 1 and 2 using polymer SH-L509: drug ratios of 4:1 and 10:1 (±S.D., $n = 3$).

(Perumal et al., 1999; Tunçay et al., 2000; Huang and Brazel, 2001; Perumal, 2001). It may be that ridges on the surfaces of microspheres from batch 3 afforded them an increased surface area compared to smooth microspheres of similar size (Guiziou et al., 1996). Minute pores may also have formed as a result of the diffusion of residual DCM through the polymeric matrix on drying. This solvent diffusion during hardening could form a porous internal structure and result in faster drug release rates (Mathiowitz et al., 1999; Huang and Brazel, 2001).

A fast rate of solvent removal can also contribute to a heterogeneous distribution of drug within the internal phase as it hardens which would further explain the biphasic release profile (Mathiowitz et al., 1999; Huang and Brazel, 2001). Any remaining DCM, as well as any water that entered the internal phase during manufacture, could have exerted a plasticizing effect on the polymer matrix, particularly at elevated manufacturing temperatures, causing further disruption in the internal structure (Guiziou et al., 1996) and giving rise to the ridged morphology found (Blanco-Prieto et al., 2000; Mu and Feng, 2001; Passerini and Craig, 2001; Pistel et al., 2001). Again this would have contributed to the release pattern found in Fig. 4 (Aso et al., 1994; Ricci et al., 2005). There was no evidence of a plasticizing effect from the DSC data. The T_g values for each batch did not vary with the initial volume of DCM or mass of ibuprofen used and were similar to those found previously with the polymer alone (Thompson et al., 2006). However the transitions were of such low energy that they did not produce clearly identifiable peaks. This could mean that any T_g values are inaccurate.

Microspheres from batch 2 had faster initial drug release rates at all polymer:drug ratios compared with microspheres from batches 1 and 3 (see Figs. 5 and 6). Initial fast drug release from the batch 2 product probably resulted from the higher encapsulation efficiency of this batch.

The rate of drug release from microspheres produced using polymer SH-L510 was consistently faster than from those produced using polymer SH-L509. This may be due to the greater hydrophilic nature of polymer SH-L510, with the presence of an extra hydroxyl group in every repeating unit (Thompson et al., 2006), compared to polymer SH-L509. A more hydrophilic

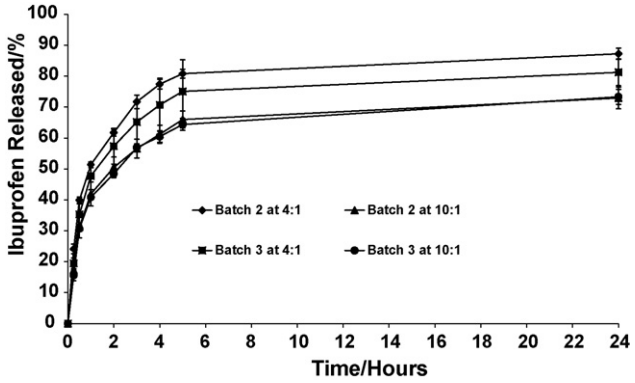

Fig. 6. Release of ibuprofen from microspheres into pH 7.4 phosphate buffer at 37 °C from batches 2 and 3 using polymer SH-L509: drug ratios of 4:1 and 10:1 (±S.D., $n = 3$).

matrix will result in a faster ingress of aqueous fluid and so produce a faster rate of drug dissolution. Another reason for this effect could be the smaller spheres, and hence larger surface area, of the product from polymer SH-L510 (see Fig. 7). The smaller particle size of batches prepared from polymer SH-L510 may also have made the matrix more susceptible to drug percolation (Leuenberger et al., 1987; Tzafriri, 2000).

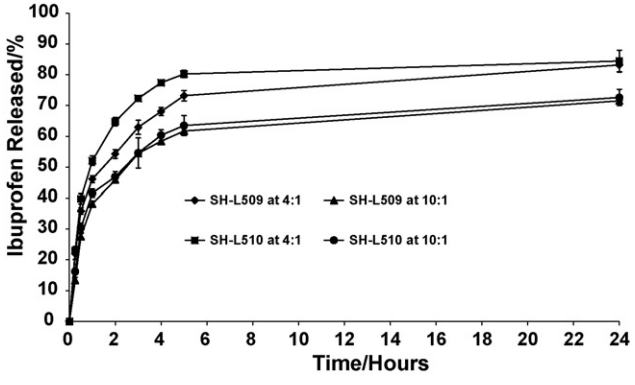

Fig. 7. Release of ibuprofen from microspheres into pH 7.4 phosphate buffer at 37 °C from batch 1 using polymers SH-L509 and SH-L510: drug ratios of 4:1 and 10:1 (±S.D., $n = 3$).

The low glass transition temperature (T_g) of both novel polymers (Thompson et al., 2006) would suggest that buffer ingress would be rapid since the diffusion of aqueous fluid is inversely proportional to the T_g (Bodmeier et al., 1989; Flandroy et al., 1993). At 37 °C the polymer chains would have been relatively more mobile thus rendering the matrices more permeable to buffer (Pitt, 1990; Engelberg and Kohn, 1991; Faisant et al., 2002; Sinha et al., 2004). Moreover, the relatively low molecular weight of ibuprofen (206 Da) (Clarke's Isolation and Identification of Compounds, 1986) would also have the effect of increasing the release rate. The increased permeability of the matrix at 37 °C would allow the more rapid transit of relatively small ibuprofen molecules through the matrix and so contribute to the burst release found (Huang and Brazel, 2001; Faisant et al., 2002).

All batches of microspheres at polymer:ibuprofen ratios of 4:1 and 6:1 showed rapid burst release. Burst release was reduced at the 10:1 ratio partly due to the absence of ibuprofen crystals on the surface, as well as the fact that the ibuprofen particles within the matrix should have been more evenly distributed. However, as burst release occurred at all polymer:drug ratios, even in products without surface crystals, it suggests that the drug particles may have been heterogeneously distributed within the matrix even at a ratio of 10:1. Ibuprofen may be confined to the area near the peripheral surface of the microspheres, the drug being released by leaching and diffusion mechanisms as suggested by Sato et al. (1988). However the polymer and drugs used in their work are different from those used in this work. Leaching would have occurred if the amount of ibuprofen present exceeded its solubility within the polymers (Langer, 1980). Thin films produced using the same polymer:ibuprofen ratios that were used in microsphere production were opaque, whereas pure polymer films were transparent (data not shown). This suggests that the amount of ibuprofen used exceeded its solubility in the polymers at all polymer:ibuprofen ratios, thus leaching was probably a mechanism involved in drug release. The higher manufacturing temperature used in batch 3 could account for a heterogeneous distribution of ibuprofen within the microspheres produced from that batch (Yang et al., 2000; Blanco et al., 2003). It is also possible that the ibuprofen particles might have migrated toward the matrix surface carried by residual solvent during the drying stage (Kishida et al., 1998; Mathiowitz et al., 1999; Huang and Brazel, 2001). A further cause of heterogeneous distribution of ibuprofen could be the semi-crystalline nature of the polymers. Ibuprofen would only have been encapsulated within the amorphous regions of the microsphere (Tice and Cowsar, 1984; Jain et al., 1999; Youan et al., 1999) which could have been located mostly around the microsphere surfaces. This might explain the high initial burst release followed by the more constant release thereafter. As a result of the semi-crystalline nature of the matrix, it may not be possible to achieve zero order drug release from microspheres produced using these polymers. It has been suggested that the rate of polymer degradation needs to control the release rate from biodegradable microspheres (Tice and Cowsar, 1984; Langer, 1995). However, the results of this work using polymers SH-L509 and SH-L510 suggest that the aqueous solubility of ibuprofen (not polymer degradation) was the major factor in controlling drug release from these polymers.

These findings are in general agreement with the conclusions of other workers who produced ibuprofen-loaded microspheres (Bodmeier and Chen, 1989; Perumal et al., 1999; Tunçay et al., 2000; Leo et al., 2000; Perumal, 2001; Zhu et al., 2005). Release generally showed a large burst (up to 90% release in 1 h with 16 kDa poly(lactic acid)) (Leo et al., 2000), followed by a period of sustained release. Both burst and subsequent rate of ibuprofen release was dependant upon the polymer:ibuprofen ratio (Perumal et al., 1999; Perumal, 2001). These authors concluded that it was drug solubility, not polymer degradation, which controlled drug release. However, other workers have shown that there are other ways to modify ibuprofen release, such as making the microsphere more hydrophobic by the addition of Labrifil® (Fernandez-Carballido et al., 2004) or the use of hydrophobic copolymers (Gallardo et al., 1998).

4. Conclusions

Manufacturing temperature appeared to be the main factor influencing the surface characteristics of ibuprofen-loaded microspheres produced by emulsion solvent evaporation using these polymers. At the same time, higher processing temperature prevented the formation of drug crystals on the microsphere surface.

The rate of ibuprofen release from these microspheres into phosphate buffer appeared to be dependant upon a number of factors including differences in encapsulation efficiency, drug solubility, microsphere surface area, surface morphology, hydrophobic nature and crystallinity of the polymer. The rate of polymer solidification appeared to be the main factor that determined the efficiency of drug encapsulation.

Burst release of ibuprofen occurred with all formulations, declining with increasing ratios of polymer:ibuprofen. This suggests that the level of drug loading was the main factor that controlled the extent of burst release. Other possible causes of burst release included the heterogeneous distribution of ibuprofen within the matrix, the plasticizing effect of residual solvent and drug as well as, possibly, the presence of surface pores which were too small to be seen even at high magnifications. All of these could have increased the instability of the matrix.

Future work will involve the covalent attachment of ibuprofen to the backbone of the novel polymer in order to improve encapsulation efficiency and the control of the drug release rate.

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