CONTROL OF THE DOMAIN MICROSTRUCTURES OF PLGA AND PCL BINARY SYSTEMS
Importance of Morphology in Controlled Drug Release

Z. G. Tang*, N. P. Rhodes and J. A. Hunt

UK Centre for Tissue Engineering, Clinical Engineering, University of Liverpool, Liverpool, UK.

Abstract: Ratio blends of PLGA/PCL: (0:10), (1:9), (2:8), (3:7), (4:6), (5:5), (6:4), (7:3), (8:2), (9:1), and (10:0) were spin-coated to produce thin films; surface topographies were determined using interferometric microscopy. It was demonstrated that micro-wells of a defined size (150 μm) were present in all PCL dominant PLGA/PCL systems. Stratification of PLGA with PCL enabled the formation of that size of micro-well independent of the percentage of PLGA in a PCL dominant system. Perforation of the amorphous PCL solid layer with PLGA liquid introduced the conglomerates of micro-pits of PLGA with a PCL solid skin. A 20% PLGA liquid in a PCL dominant PLGA/PCL system produced the largest conglomerates and the roughest surface of film. These conglomerates of PLGA together with intact micro-well PCL framework could be considered as an ideal structure for the controlled release of proteins.

Keywords: PLGA/PCL binary system; spin coating; evaporation model; lateral phase separation; stratification; drug carrier.

*Correspondence to:
Dr Z.G. Tang, UK centre for Tissue Engineering, Clinical Engineering, University of Liverpool, Liverpool, UK.
E-mail:
z.g.tang@liverpool.ac.uk

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INTRODUCTION

The extensively investigated poly(hydroxyl acids) for drug delivery comprise poly(2-hydroxy acid) such as poly(lactide-co-glycolide) (PLGA) and poly(6-hydroxy acid) like poly(ε-caprolactone) (PCL). PLGA is a copolymer of lactic acid (LA) and glycolic acid (GA) having the advantage of being able to tailor the degradation by manipulating the ratio of LA/GA (Engelberg and Kohn, 1991; Miller *et al.*, 1977). The PLGA in this copolymer family with the fastest degradation rate is that with a LA/GA ratio of one, or so-called 5050. It is amorphous and has a half life of approximately one week *in vivo*. PCL is a semi-crystalline polymer with characteristic longer hydrocarbon segments and slower hydrolytic degradation (Sinha *et al.*, 2004). Both are extensively used as carriers for drug delivery (Baldwin and Saltzman, 1998; Dai *et al.*, 2005; Hans and Lowman, 2002; Hatefi and Amsden, 2002; Jiang *et al.*, 2005; Sinha *et al.*, 2004; Tamber *et al.*, 2005; Whittlesey and Shea, 2004; Winn *et al.*, 1998; Zisch *et al.*, 2003).

Developing carriers for personalized DNA and protein drugs is a topic of academic and commercial value following on from the functional genomic project (Tang, 2006). PLGA is favourable for protein release; having the capacity to control the release of peptides and proteins slowly and continuously from one to four months (Jiang *et al.*, 2005). However, this polymer degrades relatively quickly and potentially introduces an acidic environment which raises issues for the use of protein drugs that favour a high pH environment. Using bases within the polymer to act as an acid neutralizer is one solution to controlling the pH of the polymer degradation products. PCL is also suitable for controlled drug delivery due to its high permeability to many drugs and non-toxicity (Sinha *et al.*, 2004). Slow degradation of PCL makes it useful for long-term delivery extending over a period of more than one year. In addition to its high permeability to small drug molecules it does not generate an acidic environment during degradation. Sustained release of proteins using PCL is reported in a recent review by Sinha *et al*. (2004). Candidate drugs include antigen, bovine serum albumin, nerve growth factor and insulin. PCL, compared to PLGA, is more economic; it has longer term sustained release and degradation profiles and as a consequence impacts less on the maintenance of homeostasis.

PCL in combination with polymers such as cellulose propionate, cellulose acetate butyrate, polylactic acid (PLA) or PLGA is used to manipulate the rate of drug release from microcapsules. Among these, PLGA/PCL systems could be utilised for the controlled release of growth factors for tissue regeneration. PCL is a hydrophobic polymer with a surface contact angle of approximately 90° (Tang *et al.*, 2004). Adding PLGA into PCL enhances the hydrophilicity of films (Tang *et al.*, 2005). PLGA modified PCL films have the capacity of controlling degradation of PLGA and enhancing adhesion and growth of osteoblast cells (Tang *et al.*, 2005; Tang and Hunt, 2006). PLGA/PCL binary system has been used in encapsulation of ovalbumin (OVA) and nerve growth factors (NGF) (Cao and Shoichet, 1999). PCL in this system played a role in the control of mass loss of PLGA and therefore the release of OVA. Sung *et al.* (2005) produced a series of polymer films through demixing of PLGA/PCL binary system. The surfaces were investigated from the AFM topology images in terms of roughness and height and they found the strong influence of surface roughness on the adhesion of murine vascular smooth muscle cells. Singh *et al.* (2006) produced nanoparticles loaded with diphtheria toxoid for use as mucosal vaccine delivery systems. They found that antibody responses were correlated with hydrophobicity of the nanoparticles.

Polymer demixing of partially miscible binary polymeric systems provides an economic and convenient approach to produce polymer surfaces of nano-features (Affrossman *et al.*, 1996). It is a fascinating area worth consideration in the design and manufacture of carriers for drugs of small molecules and macromolecules. In this study, spin coating has been applied to produce thin films of PLGA/PCL. Under a controllable fast evaporation, the topology of the polymer demixing film is supposed to be influenced by the composition of the binary PLGA/PCL system, the mechanisms of demixing, and the nature of the preferable solidification, which are of interest for pharmaceutical manufacturing processes such as spray drying, freeze drying and solvent extraction in the double emulsion.

EXPERIMENTAL

PCL (MW 65 k, Aldrich, Poole, UK) and PLGA (65:35, MW 40–75 k, Sigma, Poole, UK) dissolved in chloroform (6% w/v) was dropped onto cover glass (22 mm × 22 mm, borosilicate glass). Chloroform was evaporated using a spin-coating process (Single Wafer Spin Processor, Model WS-400A&B/500 Series, Laurell Technologies Corporation) with a spin speed of 1000 rpm and duration of 30 s. The spin-coated films were placed in six-well cell culture plates and stored in silica gel monitored desiccators before evaluation. The morphology of PLGA/PCL systems was observed using interferometric microscopy (WYKO NT 3300 surface profilometer). The surface structures of PLGA/PCL systems were evaluated using the 2D analysis, contour plot, and 3D interactive plot—the analytical components in WYKO Vision software. Systematic studies of surface topology of PLGA/PCL systems were carried out on samples of PLGA/PCL—(0:10), (1:9), (2:8), (3:7), (4:6), (5:5), (6:4), (7:3), (8:2), (9:1) and (10:0) by weight. Roughness and maximal height of the surfaces were measured and used to evaluate the self-assembly of the polymers under unstable environments with extremely high speeds of solvent evaporation. For comparison, PCL solution cast films were produced using PCL (MW 65 k, Aldrich) chloroform solution (6% w/v) which was a slow and uncontrollable process (Tang *et al.*, 2004).

RESULTS AND DISCUSSION

Figure 1 presents morphologies of entities of PLGA or PCL frozen in PCL or PLGA at an area of 92 μm × 121 μm. The pure PCL - PLGA/PCL-(0:10) displayed a surface covered with small raised islands, the pure PLGA - PLGA/PCL-(10:0) presented a more continuous wave-like rippled pattern. Adding 10% PLGA into PCL introduced a complex surface feature with many long raised extensions which also contained microsphere pits. Increasing the percentage of PLGA in PLGA/PCL systems produced enlarged conglomerates (20% PLGA) and coarsened the line connection of the entity cores (30% PLGA). These groups, PLGA/PCL systems of (1:9), (2:8) and (3:7) are defined as phase I and have distinctive surface features—conglomerates of microspheres and line connections between the conglomerates. Progressing to a higher percentage of PLGA in PCL resulted in the line connection between conglomerates disappearing. The line connection could be traced in PLGA/PCL-(4:6), which was still a PCL dominant system. A chaotic surface with minimal conglomerates and without line features was the summary for PLGA/PCL-(5:5) until the density and size of conglomerates increased in PLGA/PCL-(6:4). The (4:6), (5:5) and (6:4) groups were defined as phase II and had distinctive surface features—conglomerates of micro- and nanospheres without line connections between the conglomerates. When PLGA existed as the dominant phase in PLGA/PCL systems, the topologies of these polymers were completely different from those of the PCL dominant PLGA/PCL systems. The surface features—conglomerates of micro- and nano-spheres in PLGA/PCL (6:4) were more prominent in these than in any other PLGA/PCL systems in phase II. The shortest distance between two conglomerates approached zero. Joining two or more conglomerates and forming a complex branched network in the PCL dominant phase was a definite feature of surface topology of PLGA/PCL (7:3). This became a characteristic feature for PLGA/PCL (8:2) and (9:1). These groups—PLGA/PCL systems of (7:3), (8:2) and (9:1) were defined as phase III and had distinctive surface features—a belt-like PCL dominant phase without clear domains of micro-spherical conglomerates.

Figure 2 presents changes in surface roughness and maximal height of PLGA/PCL films (92 μm × 121 μm). The root-mean-squared surface roughness (Rq) displayed a zigzag progression with the greatest surface roughness generated by PLGA/PCL (2:8) and the least roughness from PLGA/PCL (10:0). The mean peak-to-valley height difference (Rt) of PLGA/PCL systems displayed a similar zigzag progression. The roughest surface of the PLGA/PCL mixture (2:8) also had the maximal height difference.

Figure 3 presents morphologies of PLGA/PCL films in broad view (1.8 mm × 2.4 mm). The results showed that PLGA/PCL (2:8) had the roughest surface in all the PLGA/PCL systems. Micro-wells were distinguished from the PCL dominant PLGA/PCL systems— (1:9), (2:8), (3:7) and (4:6) in a size of approximately 118 μm × 12 μm in *x*-axis and 130 μm × 11 μm in *y*-axis ($n = 6$, 70% PCL). This was a surface feature of the new paradigm which covered much larger areas in macro-scale. Although in phase II, PLGA/

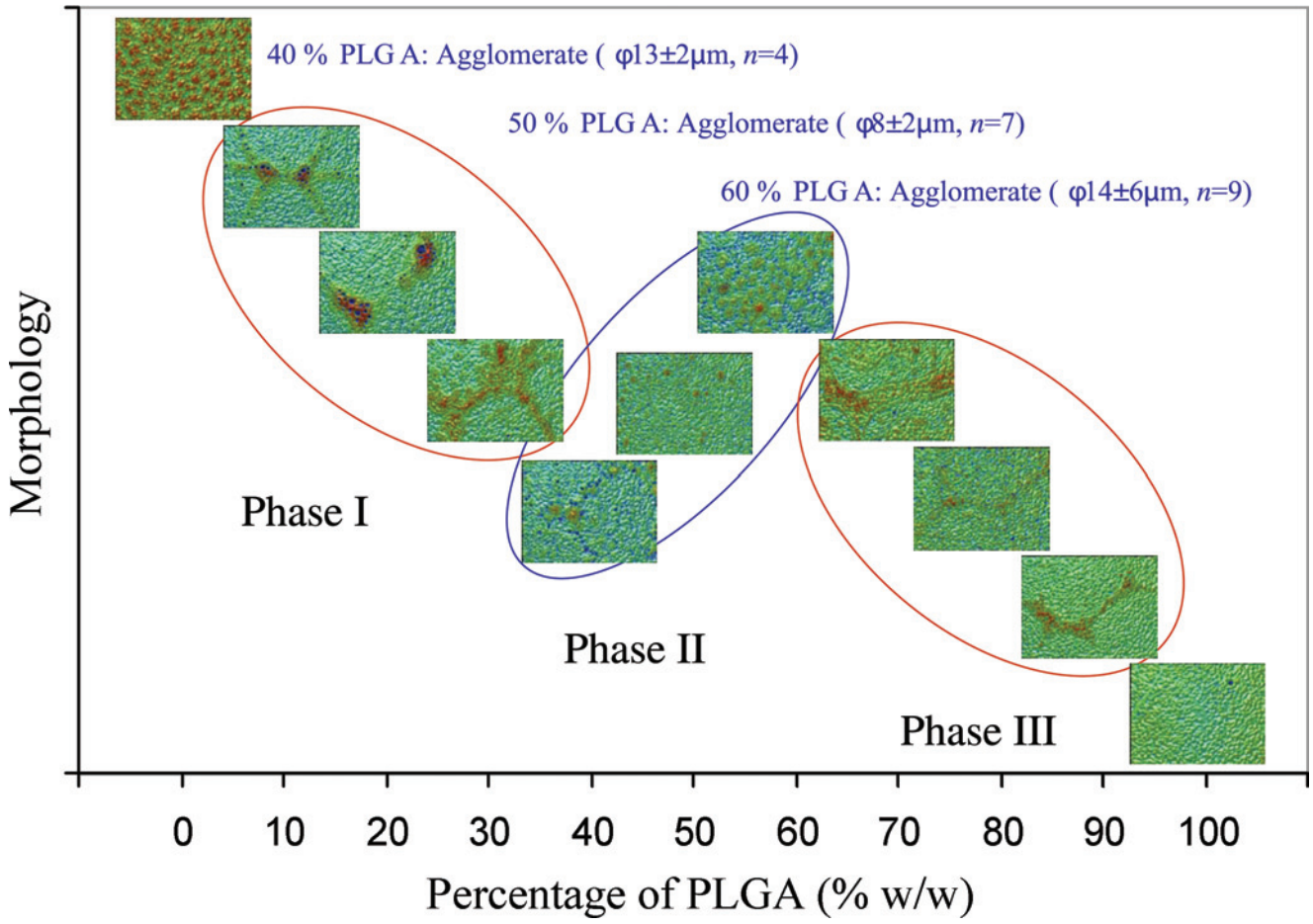

Figure 1. Morphologies of entities of PLGA or PCL frozen in PCL or PLGA (92 μm × 121 μm). This figure is available in colour online via www.icheme.org/cherd

PCL (5:5) and (6:4) demonstrated a chaotic surface feature compared to PLGA/PCL (4:6). It represented a transition from one order to the other. The other order was 'micro-well free' being more spread out and indicated a less constrained flow of the PCL phase in a PLGA dominant system, which was different from the more constrained flow of the PLGA phase in a PCL dominant system. The phase III displayed more such spread out features with less interconnection between the individual islands.

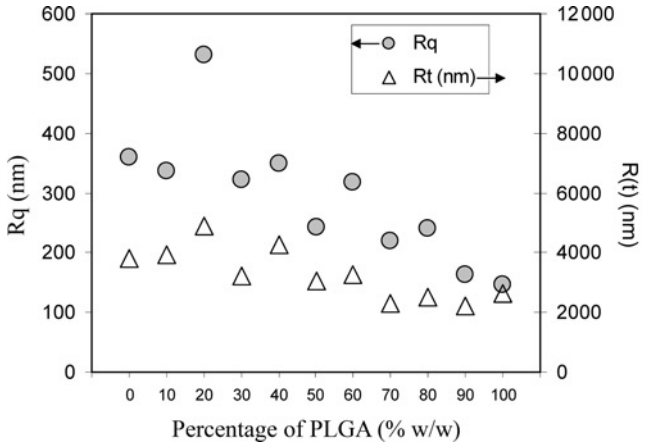

Figure 2. Changes of surface roughness (Rq) and maximal height (Rt) of PLGA/PCL films (92 μm × 121 μm).

Figure 4 presents changes of the root-mean-squared surface roughness (Rq) and the mean peak-to-valley height (Rt) of PLGA/PCL films (1.8 mm × 2.4 mm). The results demonstrated that PLGA/PCL (2:8) produced the roughest surface in the whole PLGA/PCL system. In this macro-scale, PLGA/PCL (5:5), PLGA/PCL (8:2) and PLGA/PCL (10:0) had the distinctive low roughness and smooth surface.

It was interesting that spin-coating appeared to be a fast, convenient and economic tool for evaluating binary systems for consideration as drug carriers having controlled release. The available information before this investigation was:

(1) PLGA and PCL are miscible polymers and can be dissolved in chloroform
(2) PLGA (65:35) is an amorphous polymer while PCL is a semi-crystalline polymer (Tang *et al.*, 2005)
(3) PLGA has a contact angle that varied with fabrication method, while PCL has an almost consistent contact angle (Tang, unpublished data)
(4) PLGA is relatively hydrophilic while PCL is relatively hydrophobic
(5) PCL controlled the degradation of PLGA when PLGA/PCL films were produced using solution casting (Tang *et al.*, 2005; Tang and Hunt, 2006)

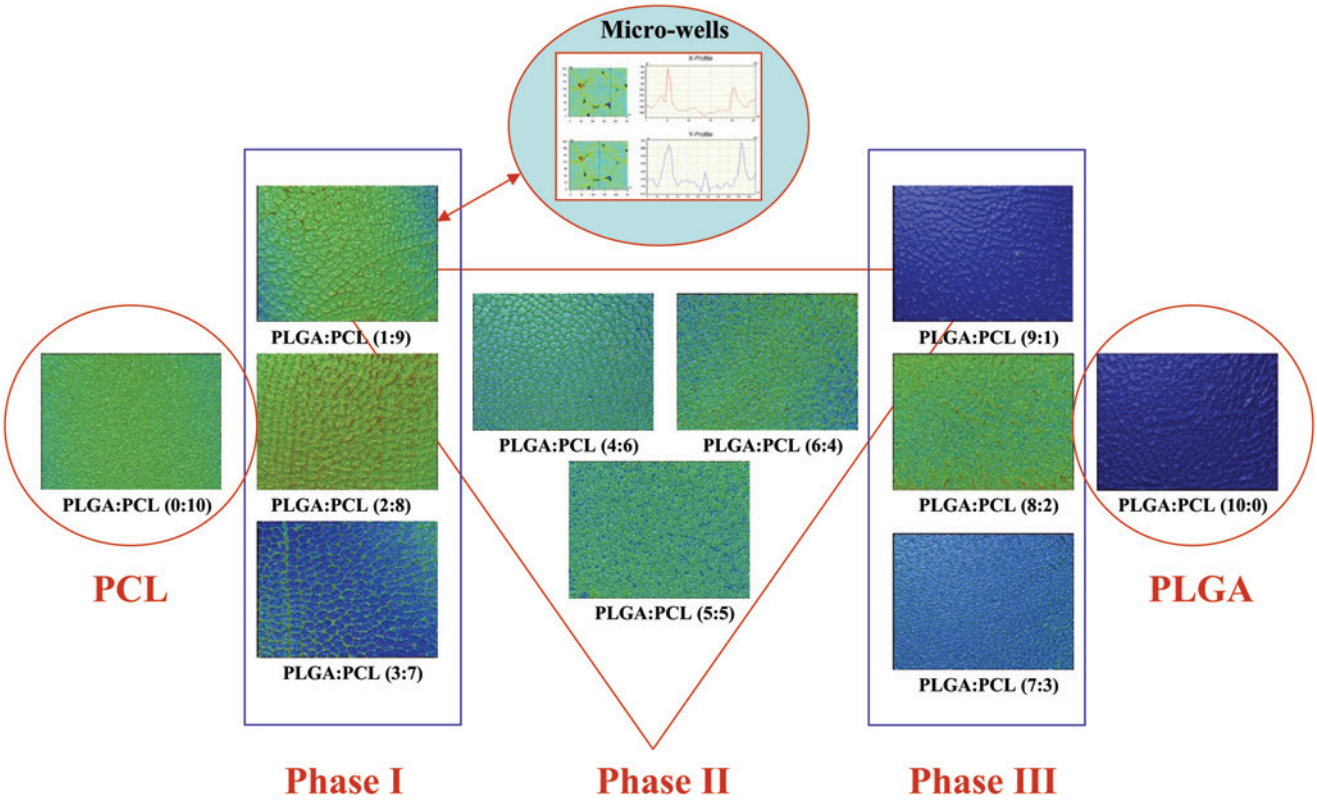

Figure 3. Morphologies of PLGA/PCL films in broad view (1.8 mm × 2.4 mm). This figure is available in colour online via www.icheme.org/cherd

(6) PLGA is an important vehicle for controlled release of proteins while PCL is not fully accepted as a vehicle for encapsulation of protein (Sinha *et al.*, 2004; Tamber *et al.*, 2005)
(7) PLGA is expensive while PCL is more economic
(8) PLGA is not a good vehicle for long term controlled release while PCL is a promising candidate for the long term release of proteins

The questions raised from this research are

(1) What is the mechanism for PLGA/PCL (2:8) to produce the roughest surface?

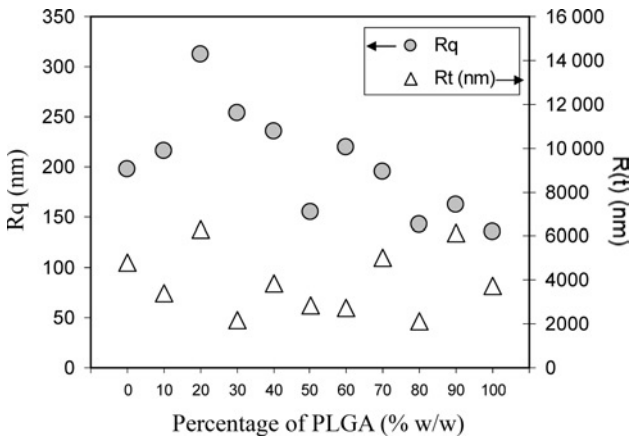

Figure 4. Changes of surface roughness (Rq) and maximal height (Rt) of PLGA/PCL films (1.8 mm × 2.4 mm).

(2) Why do micro-wells with a defined size appear in PCL dominant systems?
(3) Which PLGA/PCL system is a promising candidate for controlled release of proteins?

PLGA/PCL (2:8) produced the roughest surface at a small area of 92 μm × 121 μm and a large area of 1.8 mm × 2.4 mm. This was substantial evidence from a relatively homogeneous surface, which could be used as a template for the evaluation of the molecular physics and the related chemistry of drug carriers. In a PCL dominant PLGA/PCL system, conglomerates of microspheres were one of the major elements that defined the roughness of the surface of PLGA/PCL (2:8) film. The PLGA/PCL (2:8) system produced the largest conglomerates with the biggest micro-pits of PLGA.

Spin-coating is a process extensively used in producing uniform thin films of photoresists. Detailed studies have been carried out on the structural formation of polymer films using spin-coating (Walheim *et al.*, 1997). Bulk demixing of binary polymer mixtures demonstrated that the molecules with lower solubility would precipitate out first and form the higher part of the film and the solvent favourable molecules would precipitate out later and form the lower part. These phenomena have been supported with atomic force microscope (AFM) images after selective component etching. The exemplar binary polymer mixture is polystyrene (PS) and poly(methyl methacrylate) (PMMA), two immiscible polymers. The proposed mechanism for surface structure formation is that the demixing occurs immediately upon solvent evaporation during the spin-coating process. Depending on the relative solubility of the

two polymers in their common solvent, one of the phases is more rapidly depleted of solvent and solidifies earlier than the other phase. Subsequent evaporation of the remaining solvent leads to a further collapse of the more soluble phase.

The mechanism for surface structure formation in a spin-coating process, although supported with convincing AFM evidence, did not provide real time observations. A time-resolved small-angle light scattering technique has been used subsequently to detect the light reflectivity during the spin-coating process (Heriot and Jones, 2005). It provided a tool for a real time study of the development of the structure formation. Those results favoured the mechanism proposed above with slight modification by adding in self-stratification of two immiscible polymers. The solvent at the film surface evaporated at a faster rate than the solvent in the bulk which could diffuse through the film. At a specific point, there was a rapid movement of the contact lines to yield the laterally phase-separated structure as the earlier mechanism proposed. The new mechanism explained why it was possible to obtain final morphologies that were either self-stratified or laterally phase separated. However, the new mechanism did not answer the question of which film substrate interactions influenced the final morphology of the polymer blend films.

By extending the surface structure formation mechanism for a binary mixture of two immiscible polymers to that of two partially miscible polymers, we have developed the understanding of why PLGA/PCL (2:8) produced the roughest surface. PCL is a relatively hydrophobic and less dense polymer. Self-stratification would place the PCL phase on top of the PLGA phase. Solid PCL formed first; which was wetted by diffusion of the solvent from the PLGA phase continuously until the depletion of solvent from the PLGA phase.

Considering PLGA/PCL (0:10), PCL is a semi-crystalline polymer. Single phase spin coating produced a surface structure of PLGA/PCL (0:10) with small raised features. The small features had a mean size of 13 μm $\pm$ 5 μm and 11 μm $\pm$ 4 μm ($n = 11$). The lower flatter surface was where the weaker amorphous phase was located and from where the solvent was eventually depleted. Compared to the size of micro-spheres of PCL (MW 65 k) formed in a solution casting process, the small areas of PCL (MW 65 k) ($\sim$10 μm) from a spin-coating process were approximately one tenth of the size of the micro-spheres of PCL (MW 65 k) ($\sim$100 μm) formed from a solution casting process (Figure 5). The X- and Y-profiles of the micro-domains demonstrated that spin coating was an unstable and dynamic process. PCL molecules could assemble into a circle of size 19 μm $\times$ 16 μm in 30 s. Solution casting was a slow and stable process. PCL molecules assemble and build up a dome-like domain (70 μm $\times$ 80 μm).

During the spin-coating process, PCL behaved like a binary mixture of crystalline and amorphous phases. The mechanism of thin film formation followed the lateral phase separation model (Figure 6) and can be described briefly. There were five steps involved in generating a spin-coated PCL thin film. Step I: a drop of PCL in chloroform was placed on the cover glass; Step II: a layer of PCL in chloroform was generated from the spinning; Step III: solidification of PCL from the top via evaporation of chloroform; Step IV: PCL chloroform leaching out from the amorphous PCL solid; and Step V: depletion of chloroform and formation of the spin-coated PCL thin film. This model was also applicable to solution casting. The differences between spin coating and solution casting were that spin coating produced a circular cake-like micro-domain which could fold up on the surface, whereas solution casting demonstrated a wet-etching valley.

Formation of the unique micro-wells in all the PCL dominant PLGA/PCL systems was a striking phenomenon. The defined size of micro-wells in these systems was similar to each other (approximately 150 μm) regardless of the quantity of PLGA in the mixture and was equivalent to the micro-domains of PCL formed in the solution casting process.

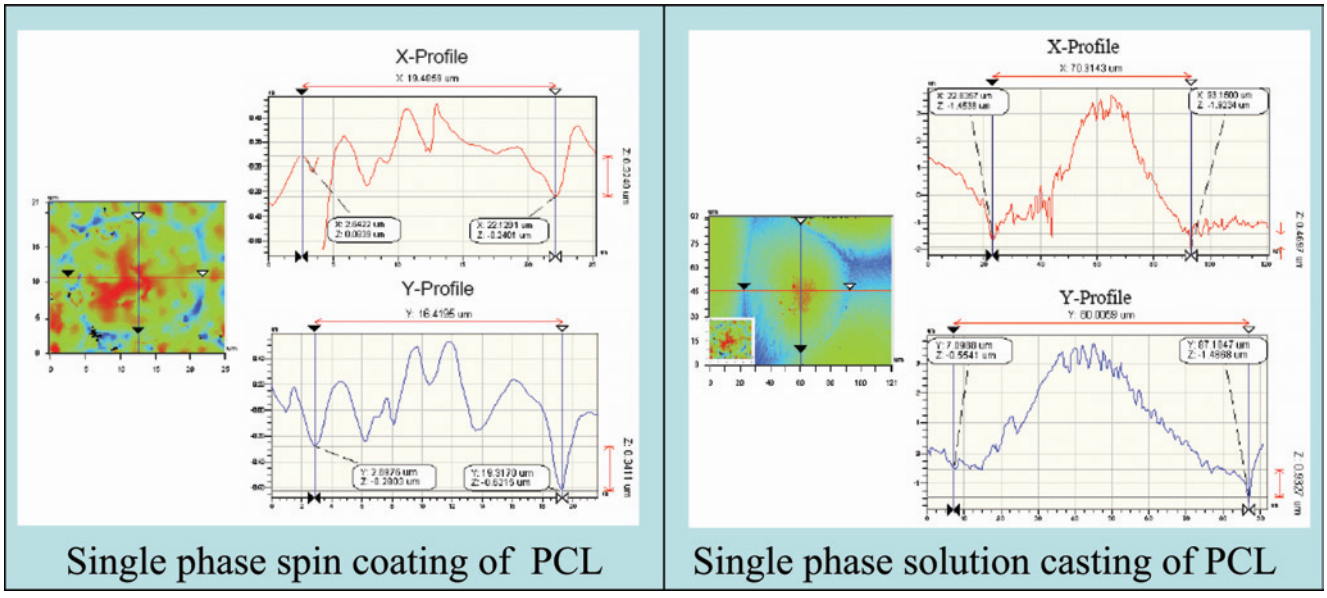

Figure 5. Comparison of micro-domains of PCL between spin coating (image size: 21 mm $\times$ 25 mm) and solution casting (image size: 92 mm $\times$ 121 mm). Left corner on the right image is the actual size of the left image compared to the right image. This figure is available in colour online via www.icheme.org/cherd

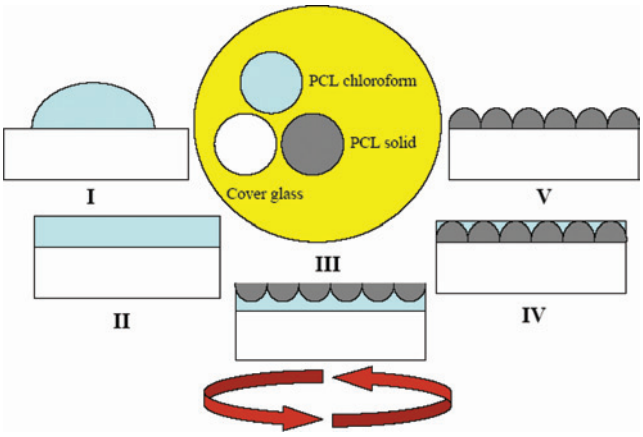

Figure 6. Lateral phase separation model for single phase spin coating of PCL. I, a drop of PCL chloroform; II, a layer of PCL chloroform; III, evaporation of solvent on top of the layer and generation of solid PCL; IV, solid PCL touching the bottom and solvent leaching out from perforation of solid amorphous PCL; and V, depletion of solvent. This figure is available in colour online via www.icheme.org/cherd

Figure 7 demonstrates the effect of the evaporation of solvent from a PCL dominant PLGA/PCL system. A stratification and lateral phase separation model was proposed for the process. Briefly, there were seven steps involved in forming the PLGA/PCL film. Step I to Step V are equivalent to the lateral phase separation model in Figure 6 based on the assumption chloroform did not diffuse too much into the amorphous liquid and solid PCL. This diffusion started at Step VI and introduced perforation of amorphous PCL solid until the solidification of PLGA. This is true for a PCL dominant PLGA/PCL system.

The favourable condition for micro-wells keeping constant sizes in all the PCL dominant PLGA/PCL systems was the stratification of the PLGA liquid. Liquid PLGA uses chloroform to maintain the size of the primary layer of growth. This liquid did not exist in a pure PCL system which was drawn out by amorphous PCL through molecular capillary force. The lateral phase separation in a pure PCL system forces the primary layer of growth to shrink into a size approximately one-tenth of that before.

With the increase of liquid PLGA, perforations of amorphous PCL become bigger and bigger and eventually break the micro-wells of the PCL primary growth layer. Perforations of amorphous PCL induced the formation of micro-pits of PLGA surrounded by PCL solid skin. The maximal size of the micro-pits was found at the surface of PLGA/PCL (2:8) film. This indicated that the PCL solid skin for the micro-pits of PLGA might break down when the presence of PLGA liquid was increased to 30% PLGA. The roughest surface was formed from PLGA/PCL (2:8) and was the result of perfect perforations until they burst under the influx of more PLGA liquid. The immediate effect was illustrated in Figure 1 with minimized PCL solids and much smoother surface for PLGA/PCL (3:7).

The phenomenon of PCL solid skin breakdown continued through the binary system. A slurry of submicron PCL particles in PLGA liquid formed, leaving traces of line connections in PLGA/PCL (4:6) system. As the events prevailed, the number of conglomerates with PCL solid skin reduced to a minimum (50% PLGA). The submicron PCL solids mixed with PLGA solids and micro-domain composites emerged (60% PLGA). Diluting the composite layer with more liquid PLGA introduced belt composites as a consequence of merging the micro-domain composites (70% PLGA). The higher percentage of PLGA actually dissolved PCL solids and eventually made them invisible (80–100% PLGA).

Figure 8 shows PLGA chloroform erosion of PCL solids in PLGA/PCL phase II and III. Erosion and composite formation were dominant events in PLGA dominant PLGA/PCL systems, that started when PCL was completely solidified (Step I), followed with PLGA liquid perforation (Step II) that leached out more PLGA liquid, eroded more PCL solids and formed a slurry-like PLGA-PCL composite until the PCL solids became completely invisible.

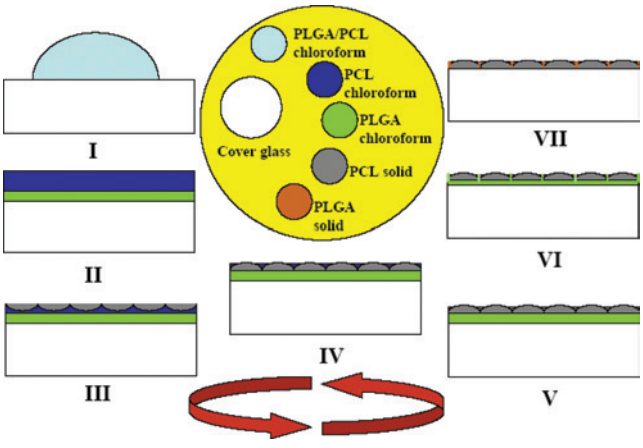

Figure 7. Stratification and lateral phase separation model for PLGA/PCL. Step I to Step V are equivalent to lateral phase separation model in Figure 6 assuming chloroform does not diffuse too much into the amorphous liquid and solid PCL. Step VI introduces perforation of amorphous PCL solid until solidification of PLGA. This figure is available in colour online via www.icheme.org/cherd

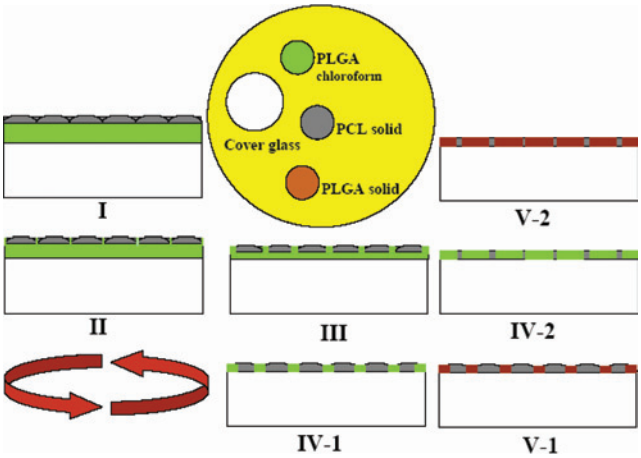

Figure 8. PLGA chloroform erosion of solid PCL in PLGA/PCL phase II and III. Step I, solidification of PCL; Step II, perforation of PLGA liquid through amorphous PCL; Step III, leached out more PLGA liquid; Step IVs, eroded more PCL solids and formed slurry-like PLGA-PCL composites; and Step Vs, depletion of the solvent. This figure is available in colour online via www.icheme.org/cherd

A PCL framework with a PLGA coating would be the best candidate for controlled release of proteins. Theoretically, a binary PLGA/PCL system that produced PCL solid skin for PLGA micro-pits would be ideal in consideration of the integrity of the structures and the stability of proteins. Therefore, PLGA/PCL (2:8) was the best candidate for the controlled release of proteins.

CONCLUSIONS

Evaporation of solvent through a single phase spin coating strictly followed the lateral phase separation if a semi-crystalline polymer such as PCL was used. Perforation of the amorphous PCL solid layer with PLGA liquid and formation of conglomerates of micro-pits of PLGA with a PCL solid skin produced the roughest surface of PLGA/PCL (2:8) film. Stratification of PLGA/PCL chloroform and evaporation of chloroform layer by layer maintained the constant sizes of microwells in a PCL dominant PLGA/PCL system. The formation of a slurry of PLGA and PCL and etching the PCL solids were dominant events in Phase II and Phase III PLGA dominant PLGA/PCL systems. Finally, PLGA/PCL (2:8) was the best candidate for controlled release in consideration of the integrity of the structures and the potential for stabilizing proteins.

REFERENCES

Affrossman, S., Henn, G., O'Neill, S.A., Pethrick, R.A. and Stamm, M., 1996, Surface topography and composition of polystyrene-poly(bromostyrene) blends, *Macromolecules*, 29: 5010–5016.

Baldwin, S.P. and Saltzman, W.M., 1998, Materials for protein delivery in tissue engineering, *Adv Drug Delivery Rev*, 33: 71–86.

Cao, X. and Schoichet, M.S., 1999, Delivering neuroactive molecules from biodegradable microspheres for application in central nervous system disorders, *Biomaterials*, 20: 329–339.

Dai, C., Wang, B. and Zhao, H., 2005, Microencapsulation peptide and protein drugs delivery system, *Colloids Surface B: Biointerfaces*, 41: 117–120.

Engelberg, I. and Kohn, J., 1991, Physio-mechanical properties of degradable polymers used in medical applications: a comparative study, *Biomaterials*, 12: 292–304.

Hans, M.L. and Lowman, A.M., 2002, Biodegradable nanoparticles for drug delivery and targeting, *Current Opinion in Solid State Mater Sci*, 6: 319–327.

Hatefi, A. and Amsden, B., 2002, Biodegradable injectable in situ forming drug delivery systems, *J Controlled Release*, 80: 9–28.

Heriot, S.Y. and Jones, R.A.L., 2005, An interfacial instability in a transient wetting layer leads to lateral phase separation in thin spin-cast polymer-blend films, *Nature Materials*, 4: 782–786.

Jiang, W., Gupta, R.K., Deshpande, M.C. and Schwendeman, S.P., 2005, Biodegradable poly(lactic-co-glycolic acid) micro-particles for injectable delivery of vaccine antigens, *Adv Drug Delivery Rev*, 57: 391–410.

Miller, R.A., Brady, J.M. and Cutright, D.E., 1977, Degradation rates of oral resorbable implants (polylactates and polyglycolates): rate modification with changes in PLA/PGA copolymer ratios, *J Biomed Mater Res*, 11: 711–719.

Singh, J., Pandit, S., Bramwell, V.W. and Alpar, H.O., 2006, Diphtheria toxoid loaded poly-(ε-caprolactone) nanoparticles as mucosal vaccine delivery systems, *Methods*, 38: 96–105.

Sinha, V.R., Bansal, K., Kaushik, R., Kumria, R. and Trehan, A., 2004, Poly-ε-caprolactone microspheres and nanospheres, *Int J Pharm*, 278: 1–23.

Sung, H.J., Su, J., Berglund, J.D., Russ, B.V., Meredith, J.C. and Galis, Z.S., 2005, The use of temperature-composition combinatorial libraries to study the effects of biodegradable polymer blend surfaces on vascular cells, *Biomaterials*, 26: 4557–4567.

Tamber, H., Johansen, P., Merkle, H.P. and Gander, B., 2005, Formulation aspects of biodegradable polymeric microspheres for antigen delivery, *Adv Drug Delivery Rev*, 57: 357–376.

Tang, Z.G., 2006, Invited lecture on *Pharmaceutics Research in the 21st Century*, for School of Pharmacy and Biomedical Sciences, University of Portsmouth, 7 September.

Tang, Z.G., Black, R.A., Curran, J.M., Hunt, J.A., Rhodes, N.P. and Williams, D.F., 2004, Surface properties and biocompatibility of solvent-cast poly(ε-caprolactone) films, *Biomaterials*, 25: 4741–4748.

Tang, Z.G., Callaghan, J.T. and Hunt, J.A., 2005, The physical properties and response of osteoblasts to solution cast films of PLGA doped polycaprolactone, *Biomaterials*, 26: 6618–6624.

Tang, Z.G. and Hunt, J.A., 2006, The effect of PLGA doping of polycaprolactone films on the control of osteoblast adhesion and proliferation in vitro, *Biomaterials*, 27: 4409–4418.

Walheim, S., Böltau, M., Mlynek, J., Krausch, G. and Steiner, U., 1997, Structure formation via polymer demixing in spin-cast films, *Macromolecules*, 30: 4995–5003.

Whittlesey, K.J. and Shea, L.D., 2004, Delivery systems for small molecule drugs, proteins, and DNA: the neuroscience/biomaterial interface, *Experimental Neurology*, 190: 1–16.

Winn, S.R., Uludag, H. and Hollinger, J.O., 1998, Sustained release emphasizing recombinant human bone morphogenetic protein-2, *Adv Drug Delivery Rev*, 31: 303–318.

Zisch, A.H., Lutolf, M.P. and Hubbell, J.A., 2003, Biopolymeric delivery matrices for angiogenic growth factors, *Cardiovasc Pathol*, 12: 295–310.

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