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RESEARCH PAPER

Influence of Formulation Variables on the Morphology of Biodegradable Microparticles Prepared by Spray Drying

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ABSTRACT

The preparation of microparticles of the biodegradable poly-DL-lactide (PLA) and polylactide-co-glycolide (PLGA) polymers using spray-drying technology was studied. Formulation parameters investigated include polymer type, polymer molecular weight, polymer concentration, and viscosity. Microparticles were characterized using electron microscopy, particle size analysis, and gel permeation chromatography. Kinematic viscosity was determined for each of the sprayed polymer solutions. Polymer molecular weight and polymer concentration were found to be important parameters when preparing PLA and PLGA microparticles using spray-drying technology.

INTRODUCTION

Polylactide (PLA) and polylactide-co-glycolide (PLGA) microspheres have been widely investigated for the delivery of therapeutics ranging from conventional small molecules such as hydrocortisone (1) to macromolecules such as heparin (2) and BSA (3). These polymers are biodegradable, biocompatible, and FDA approved. Available parenteral products utilizing these polymers as the drug carrier include Zoladex (Zeneca), a depot system which releases goserelin acetate over a 1-month period and Lupron (TAP), an leuprolide acetate depot system. The production technology mainly employed in the manufacture of these polyester microparticles has been solvent evaporation/solvent extraction from emulsion systems. Problems encountered with this method of production include the use of high shear forces which may result in degradation of sensitive drug molecules such as proteins and peptides.

Preparation of microparticles by spray drying is an attractive alternative to conventional microencapsulation techniques. It is less dependent on the drug solubility than the solvent evaporation methods. The mild processing conditions employed during spray drying are particularly suited to the formulation of protein- and peptide-loaded microparticles. From a manufacturing viewpoint,

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spray drying offers the advantage of being a single-step process which can readily be scaled up. Spray drying is already widely used in the pharmaceutical industry for a range of applications (4–8) and has recently been investigated for the production of drug-loaded PLA and PLGA microspheres (9–11). The biodegradable depot product Parlodel (Sandoz), utilizes spray-drying technology for the preparation of bromocriptine-loaded microspheres for parenteral administration (12). However, factors influencing the formation and characterization of PLA/PLGA microparticles by spray drying have not been well studied.

The present paper reports the formation of PLA and PLGA microspheres by spray drying solution of the polymer in ethyl acetate. Two polymers, a low molecular weight and a high molecular weight, were selected from the hydrophobic poly-DL-lactide polymers and the more hydrophilic polylactide-co-glycolide polymers. The influence of formulation parameters including polymer composition, polymer molecular weight, and concentration/viscosity of the sprayed polymer solution on microsphere characteristics were investigated.

EXPERIMENTAL

Materials

The poly-DL-lactide polymers used were Resomer R203 (PLA1) of molecular weight 16,000 and inherent viscosity (i.v.) 0.27 dl/g and Resomer R206 (PLA2) of molecular weight 109,000 and i.v. 1.0 dl/g (Boehringer Ingelheim). The poly-DL-lactide-co-glycolide polymers used were the 75:25 lactide:glycolide polymers PLGA75-3 (molecular weight 18500, i.v. 0.246 dl/g) received from Mitsui Toatsui Chemicals, Inc., and Purasorb 75/25 (i.v. 0.97 dl/g) received from Purac Biochem. Ethyl acetate (HPLC grade) was obtained from Labscan.

Methods

Production of Particles

Solutions of each polymer in ethyl acetate at a range of concentrations were spray dried in a Büchi 190 mini spray dryer (Büchi Labortechnik AG, Flawil, Switzerland). The process parameters were: inlet temperature 58–64°C, outlet temperature 40–46°C, pump setting 5 ml/min, aspirator setting 10, and flow control 600–700.

The kinematic viscosity of the sprayed polymer solutions in ethyl acetate were determined using a Schott-Gerate Ubbelohde Viscometer, capillary number Oc, calibration constant 0.003097 mm^2/sec^2. The measurements were carried out at a temperature of $30.0 \pm 0.1°C$.

Characterization of Particles

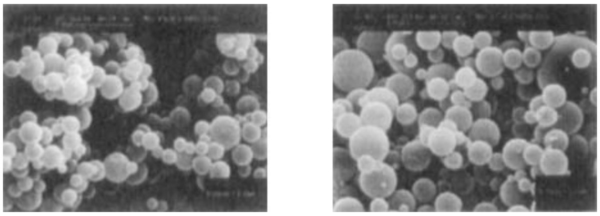
Microparticle morphology was examined using a scanning electron microscope (SEM, Leica Cambridge S360). Particle size analysis was carried out on a Malvern Mastersizer S 2.14. Polymer molecular weight was determined by gel permeation chromatography using a Waters HR4E column and tetrahydrofuran as mobile phase at a flow rate of 1 ml/min. Samples were dissolved in THF at a concentration of 0.5 mg/ml prior to analysis.

RESULTS AND DISCUSSION

PLA Polymers

Low Molecular Weight (lmw) PLA1 Polymer

When solutions of the lmw polymer PLA1 in ethyl acetate at concentrations of 2.0, 3.3, and 10% w/v were spray dried, microparticles were obtained at all polymer concentrations. Examination of microparticle morphology by SEM showed all particles to be well formed and spherical [Figs. 1(a) and 1(b)]. Particle size analysis (Table 1) showed little change in the mean particle size, D50%, with increasing polymer concentration. The D90% values were found to increase from 12.96 μm at 2.0% w/v PLA1 concentration to 26.98 μm at 10.0%


(a) 2.0% w/v PLA1 (b) 10.0% w/v PLA1

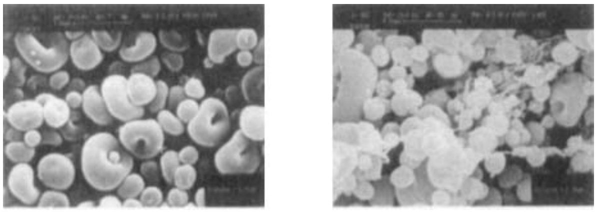

(c) 1.0% w/v PLA2 (d) 3.3% w/v PLA2

Figure 1. Photomicrographs for spray-dried PLA1 and PLA2 microspheres.

Table 1

Particle Size Analysis for Spray-Dried PLA and PLGA Microparticles

Polymer	Conc. (% w/v)	D90% (μm)	D50% (μm)	D10% (μm)	Span
PLA1	2.0	12.96 ± 0.75	5.19 ± 0.31	1.50 ± 0.06	2.21 ± 0.08
	3.3	18.12 ± 2.77	5.68 ± 0.28	1.56 ± 0.03	2.92 ± 0.54
	10.0	26.98 ± 8.89	7.58 ± 2.31	1.61 ± 0.13	3.43 ± 0.88
PLA2	1.0	15.28 ± 3.01	5.49 ± 1.07	1.65 ± 0.08	2.48 ± 0.05
	1.66	9.95 ± 1.54	4.14 ± 0.31	1.58 ± 0.03	2.01 ± 0.21
	1.8	9.70 ± 1.88	3.89 ± 0.33	1.60 ± 0.01	2.07 ± 0.31
	2.0	7.13 ± 0.71	3.27 ± 0.45	1.39 ± 0.10	1.77 ± 0.07
PLGA1	2.0	13.60 ± 2.99	5.35 ± 0.68	1.76 ± 0.06	2.17 ± 0.31
	3.33	14.34 ± 2.50	7.11 ± 1.04	2.99 ± 0.35	1.59 ± 0.09
	10.0	23.98 ± 0.32	10.00 ± 0.53	3.21 ± 0.25	2.07 ± 0.17
PLGA2	2.0	11.67 ± 6.31	4.63 ± 1.69	1.55 ± 0.12	2.08 ± 0.58
	3.3	18.30 ± 4.86	6.47 ± 1.10	1.66 ± 0.11	2.55 ± 0.30

w/v polymer concentration. This resulted in a widening of the particle size distribution as observed by the increase in span values from 2.21 at 2% to 3.426 at 10% w/v polymer concentration.

High Molecular Weight PLA2 Polymer

The preparation of microspheres of R206 by spray drying was investigated initially at concentrations of 2.0 and 3.3% w/v. At the higher concentration (3.3% w/w) microparticle formation was limited with the small quantity of microparticles recovered being concave rather than spherical in shape as shown by the photomicrograph [Figs, 1(c) and 1(d)]. The remainder of the product was fibrous rather than the fine free-flowing powder obtained with R203. At the 2% w/v polymer concentration microparticles were formed. Photomicrographs showed that while the product consisted mainly of well-formed spherical microparticles, there were some particles which were concave rather than spherical in shape. Subsequently, polymer solutions at the lower concentrations of 1.0, 1.6, and 1.8% w/v were spray dried. At these lower concentrations a fine free-flowing powder was obtained. Electron microscopy confirmed that microparticles were formed at all three concentrations. However, the microparticles were concave in shape. Particle size analysis (Table 1) showed a decrease in both D90% and D50% resulting in a narrowing in the particle size distribution with increasing polymer concentration. These observations were contradictory to the results obtained for the lower molecular weight polymer R203 (PLA1) and were unexpected since microparticle size has been reported to increase with increasing polymer concentrations (9).

The formation of fibers during spray drying of PLA polymers from solutions of the polymer in dichloromethane was reported by Bodmeier and Chen (13). They attributed this fiber formation to the insufficient forces present to enable the liquid filament to be broken into droplets. Dhingra et al. (14) reported that fiber formation results from a combination of strong and extensive intermolecular bonds and adhering stiffness of polymer chains and this may explain the fiber formation observed with linear polymers lacking bulky side chains, including the PLA and PLGA polymers.

PLGA Polymers

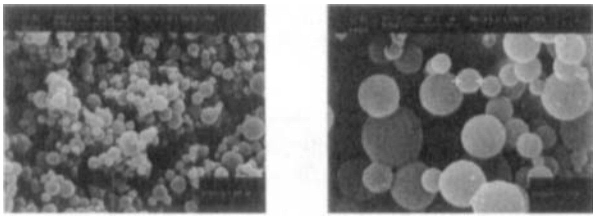
lmw PLGA1 Polymer

PLGA1 was spray dried from ethyl acetate at polymer concentrations of 2, 3.3, and 10% w/v. Well formed, spherical microparticles were obtained for all three concentrations investigated [Figs. 2(a) and 2(b)]. Particle size analysis (Table 1) showed that microparticle size (D90%, D50%, and D10%) increased with increasing polymer concentration. This observation is similar to that observed for R203 and is expected since the viscosity of the sprayed solution increases with increasing polymer concentration.

High Molecular Weight PLGA2 Polymer

The second polylactide-co-glycolide polymer investigated, PLGA2 with i.v. 0.97 dl/g, was spray dried at

(a) 2.0% w/v PLGA1 (b) 10.0% w/v PLGA1



(c) 2.0% w/v PLGA2 (d) 5.0% w/v PLGA2

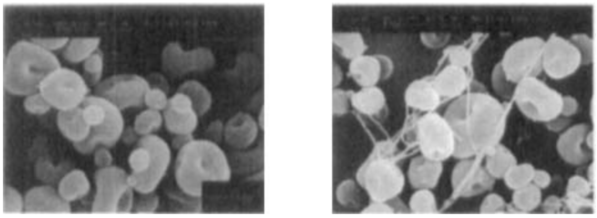


Figure 2. Photomicrographs for spray-dried PLGA1 and PLGA2 microspheres.

concentrations of 2.0, 3.33, 4.2, and 5.0% w/v. At the lower polymer concentrations of 2.0 and 3.3% w/v, spray drying resulted in the formation of microparticles many of which were concave rather than spherical in shape [Figs. 2(c) and 2(d)]. Increasing the polymer concentration from 2.0 to 3.33% w/v resulted in an increase in microparticle size distribution as indicated by an increase in both D50% and D90% with D10% remaining constant (Table 1). Spray drying the 4.2 and 5% w/v PLGA2 solutions resulted in the formation of fibers similar to that observed with the higher molecular weight polylactide polymer.

Gel permeation chromatography (GPC) analysis was carried out on all microparticles formed in order to establish if the conditions employed during the spray-drying process caused any polymer degradation. This data showed no/negligible change in polymer molecular weight (Mn or Mw) followed spray drying (Table 2). Previously, PLGA particles prepared by solvent evaporation from an emulsion system showed a decrease in polymer molecular weight suggesting some polymer degradation occurred during processing (15).

Comparison of Microparticle Formation by Spray Drying for the lmw Polymers PLA1 and PLGA 1

The formation of spherical, smooth microparticles of the low molecular weight polymers PLA1 and PLGA1 using spray-drying technology was possible at the three polymer concentrations investigated. At all three polymer concentrations, microparticles produced were larger for the PLGA polymer than for the PLA polymer. At 2% w/v polymer concentration the mean particle size, D50%, for the polymer PLA1 was 5.19 μm compared

Table 2

GPC Data for Spray-Dried PLA and PLGA Microparticles

Polymer	Conc. (% w/v)	Mw	Mn	Polydispersity
PLA1	Unprocessed	21905	12728	1.7213
	2.0	22855	13580	1.6839
	3.3	22970	13637	1.6904
	10.0	22752	13722	1.6589
PLA2	Unprocessed	106432	57047	1.8685
	1.0	101826	66263	1.5366
	1.66	99482	59414	1.6751
	1.8	96794	58061	1.6674
	2.0	108623	63863	1.7051
PLGA1	Unprocessed	18183	11213	1.6286
	2.0	18376	10982	1.6736
	3.33	17118	9984	1.7157
	10.0	17303	10238	1.6907
PLGA2	Unprocessed	73503	37324	1.9714
	2.0	72349	34858	2.0771
	3.3	73594	39676	1.8707

with 5.35 μm for the PLGA1 polymer at the same concentration. At 3.3 and 10% w/v polymer concentration the mean particle size, D50%, observed for PLA1 was 5.68 μm and 7.58 μm, respectively compared with a value 7.11 μm and 10.00 μm for the PLGA 1 polymer at similar polymer concentrations. For both polymers, the mean particle size was found to increase with increasing polymer concentration.

Comparison of Microparticle Formation by Spray Drying for the High Molecular Weight Polymers PLA2 and PLGA2

Microparticle formation for the high molecular weight polymers PLA2 and PLGA2 was successful only at low polymer concentrations. There was a critical polymer concentration, specific to each polymer, above which spray drying resulted in the formation of fibers rather than microparticles. This critical polymer concentration was lower for the hydrophobic PLA2 polymer than for the more hydrophilic PLGA2 polymer. For the PLA polymer a free-flowing powder was obtained at polymer concentrations up to 2.0% w/v. For the PLGA2 polymer microparticle formation was possible up to a polymer concentration of 3.3% w/v.

Kinematic Viscosity of Sprayed Polymer Solutions

The kinematic viscosity of the sprayed polymer solutions was found to increase with increasing polymer concentration as was expected (Table 3). For PLA1 and PLGA1 well-formed microspheres were obtained at all three polymer concentrations investigated, i.e., for solutions with kinematic viscosity of less than or equal to 2.3243 mm^2/sec.

Comparison of the kinematic viscosities of the hydrophobic PLA polymer with the more hydrophilic PLGA polymer showed that the kinematic viscosity values for the PLGA1 polymer solutions were slightly lower than the corresponding PLA1 solutions. This difference may be attributed to the difference in inherent viscosity of the two polymers. Inherent viscosity for PLA1 was 0.27 dl/g compared with a value of 0.246 dl/g for PLGA1.

For the high molecular weight polymers, microparticle formation was possible at lower viscosity and hence at lower concentration of the sprayed solution (Table 3). This suggests that the polymer molecular weight is a more important parameter than kinematic viscosity since microparticles were obtained with PLA1 solution of kinematic viscosity 2.3243 mm^2/sec whereas fibers were obtained with PLA2 solutions having a lower kinematic viscosity of 2.2206 mm^2/sec. For PLGA2 which is a lower molecular weight polymer than PLA2, microparticle formation was possible at the higher polymer concentration of 3.33% w/v than for PLA2 (2.0% w/v).

CONCLUSIONS

Our investigations showed that for PLA and PLGA polymers, polymer molecular weight and concentration of the polymer solution were important factors, and not viscosity of polymer solution, when using spray-drying technology for the production of PLA and PLGA microparticles. For the low molecular weight PLA/

Table 3

Kinematic Viscosities of PLA and PLGA Polymer Solutions

Polymer (Inherent Viscosity)	Concentration (% w/v)	Kinematic Viscosity (mm^2/sec)
PLA1	2.0	0.6679
(0.27 dl/g)	3.33	0.8487
	10.0	2.3243
PLA2	1.0	0.7898
(1.0 dl/g)	1.66	1.0874
	1.82	1.1750
	2.0	1.2738
	3.33	2.2206
PLGA1	2.0	0.6472
(0.246 dl/g)	3.33	0.8054
	10.0	2.1804

PLGA polymers, spray-dried microspheres were formed even at high polymer concentrations of 10% w/v in ethyl acetate. However, microparticle formation with the higher molecular weight polymers PLA2 and PLGA2 was possible at lower polymer concentrations of 2 and 3.3% w/v for PLA2 and PLGA2, respectively. Therefore significantly larger solvent volumes would be required for microsphere production by spray drying for the higher molecular weight PLA/PLGA polymers.

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