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Preparation of Biodegradable Poly(±)lactide Microparticles Using a Spray-Drying Technique

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Abstract —Drug containing biodegradable poly(±)lactide microparticles were prepared by using a spray-drying technique. Formulations containing model drugs in either a dissolved (progesterone) or dispersed state (theophylline) were spray-dried. The spray-drying method was less dependent on the solubility characteristics of the drug when compared with traditional microencapsulation techniques such as phase separation or solvent evaporation techniques. Differential scanning calorimetry and scanning electron microscopy were used to characterize the microparticles. The drug release profiles were characterized by a rapid release phase (burst effect) followed by a slow release phase, the extent of each phase being dependent on the drug loading.

A wide variety of microencapsulation techniques exists for the formation of polymeric microparticulate drug delivery systems (Deasy 1984; Kondo 1979). Most microencapsulation techniques used to prepare biodegradable microcapsules or microspheres allow either the encapsulation of water-soluble or water-insoluble drugs with either hydrophilic or hydrophobic polymers. The choice of one particular method is governed to a great extent by the solubility characteristics of the active compound and of the wall-forming polymer. In addition, these methods are often time-consuming, dependent on many variables and difficult to scale-up to production size batches. An ideal method for the preparation of biodegradable microparticles should be simple, reproducible, rapid, little dependent on the solubility characteristics of the drug and polymer, and easy to scale-up.

The aim of this study was to investigate the potential use of a spray-drying technique (Masters 1976) in the preparation of biodegradable microparticles as an alternative method to the conventional microencapsulation techniques. The use of a spray-drying technique appears to be attractive and it seems to come close to the properties desired. The biodegradable polymer used as the drug carrier was poly(±)lactide (Kulkarani et al 1966).

Materials and Methods

Materials

Poly(±)lactide (PLA) (Southern Research Institute, Birmingham, Ala.) had an inherent viscosity of 1·7 dLg^{-1} in chloroform (5 mg mL^{-1}) at 30°C. The following chemicals were obtained from commercial suppliers and used as received: caffeine (MCB Manufacturing Chemist, Inc., Gibbstown, N.J.), progesterone (Sigma Chemical Co., St. Louis, Mo.) micronized anhydrous theophylline (Boehringer Ingelheim KG, Ingelheim, W. Germany), methanol and methylene chloride (J. T. Baker Chemical Co., Phillipsburg, NJ), polyethylene glycol 400 (PEG 400) (Fisher Scientific Co., Fair Lawn, N.J.).

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Methods

PLA and progesterone in mass ratios of 90:10, 80:20, 65:35, and 50:50, and PLA and theophylline in mass ratios of 75:25, 60:40, 40:60, and 25:75 were dissolved or suspended in methylene chloride. The solutions or dispersions were spray-dried with a Buechi Mini Spray Dryer-Model 190 to prepare the biodegradable microparticles. The process parameters were set as follows: inlet temperature (70°C); outlet temperature (40–45°C); aspirator setting (15); pump setting (10 mL min^{-1}); spray flow (600 NL h^{-1}); a 0·5 mm nozzle was used throughout the experiments.

In-vitro release profiles of the drugs from the microparticles were obtained by the rotating bottle apparatus at 37°C. Triplicate samples (20 mg) were suspended in test tubes containing 50 mL prewarmed medium and rotated at 26 rev min^{-1}. Particles were incorporated within dialysis bags (molecular weight cut off: 6000–8000; Spectrum Medical Industries, Inc., Los Angeles, CA) to avoid the removal of microparticles upon assaying. The dissolution fluid was isotonic pH 7·4 phosphate buffer for theophylline. For progesterone, a 40% (v/v) aqueous PEG 400 solution was used (Chiang et al 1986). The samples (1 mL) were withdrawn, assayed spectrophotometrically at the wavelength of maximum absorbance (theophylline, $\lambda = 273$ nm; progesterone, $\lambda = 250$ nm), and replaced with fresh medium.

The microparticles were coated for 70 s under an argon atmosphere with gold-palladium (Pelco Model 3 Sputter Coater) and observed by scanning electron microscopy (JEOL JSM 35C). Differential scanning calorimetry (Perkin Elmer Differential Scanning Calorimeter, Model DSC2; sample weight = 5 mg, scanning rate = 20°C min^{-1}, nitrogen atmosphere) on the microparticles and drugs was performed in order to characterize the physical state of the polymer and drugs after spray-drying.

Results and Discussion

Spray-drying is a versatile technique and microparticles can be formed from both homogeneous and heterogeneous systems. The preparation of spray-dried drug-poly(±)lac-

tide (PLA) microparticles from solutions and suspensions is described and discussed below.

In the case of solutions, the drug and PLA were co-dissolved in a common organic solvent and spray-dried. Progesterone-PLA solutions formed uniform microparticles, while caffeine-PLA solutions resulted in inhomogeneous microparticles (Fig. 1). Progesterone was entrapped within the polymeric matrix at all payloads (Fig. 1A–C). The actual progesterone content in the microparticles was within 1% of the theoretical drug content at all mass ratios. The particles were smaller than 5 μm and became more spherical and less deformed with increasing amounts of progesterone. The growth of needle-like crystals occurred after spray-drying caffeine-PLA solutions (Fig. 1D). Both the drug and the polymer precipitated during solvent evaporation. They have to be compatible to such a degree that they form homogeneous polymer-drug microparticles. The polymer-drug compatibility was tested by casting films from polymer-drug solution into a petri dish. Progesterone, although having a low solubility in PLA, resulted in milky but uniform films. Progesterone precipitated within the polymer matrix during solvent evaporation into small crystals which were homogeneously dispersed throughout the film. On the other hand, caffeine crystallized into large needles which interfered with the desired film forming process at concentrations above 2·5%.

The effect of progesterone loading on drug release from the microparticles is shown in Fig. 2. The microparticles released progesterone at a faster rate with increasing payload. A rapid drug release phase (burst effect) was followed by a slow release phase. The progesterone release was clearly retarded when compared with pure progesterone samples. Dialysis bags were not used for progesterone samples because progesterone had a high affinity for the dialysis membrane.

DSC thermograms of spray-dried progesterone and progesterone-PLA samples are shown in Figs 3 and 4. A second polymorph of progesterone developed during the spray-drying process. The crystal forms of progesterone have been reported in the literature, the α-form melting at 402 K and the β-form melting at 395 K (Theeuwes et al 1974). The presence of PLA influenced the crystallization process of the drug. The α-form was dominant when progesterone by itself was sprayed while the β-form was formed predominantly when spray-dried in combination with the polymer. The amount of the second polymorph increased with increasing temperature. The glass transition temperature of PLA is seen at approximately 330 K. Progesterone could not be detected at levels below 10 percent by differential scanning calorimetry as indicated by the absence of a peak.

Progesterone has been entrapped within PLA microspheres by the solvent evaporation method (Benita et al 1984; Bodmeier & McGinity 1987). One problem encountered with this method was the spontaneous crystallization of progesterone in the aqueous phase. Progesterone partitioned into the external aqueous phase and precipitated after the evaporation of the organic solvent was complete. The drug-loaded microspheres had to be prepared by an interrupted solvent evaporation method or they had to be separated from the free drug crystals by a washing step. This problem did not occur during the spray-drying of progesterone-PLA solutions. The external phase was hot air and the drug was not lost due to partitioning.

Micronized theophylline was used as the model compound

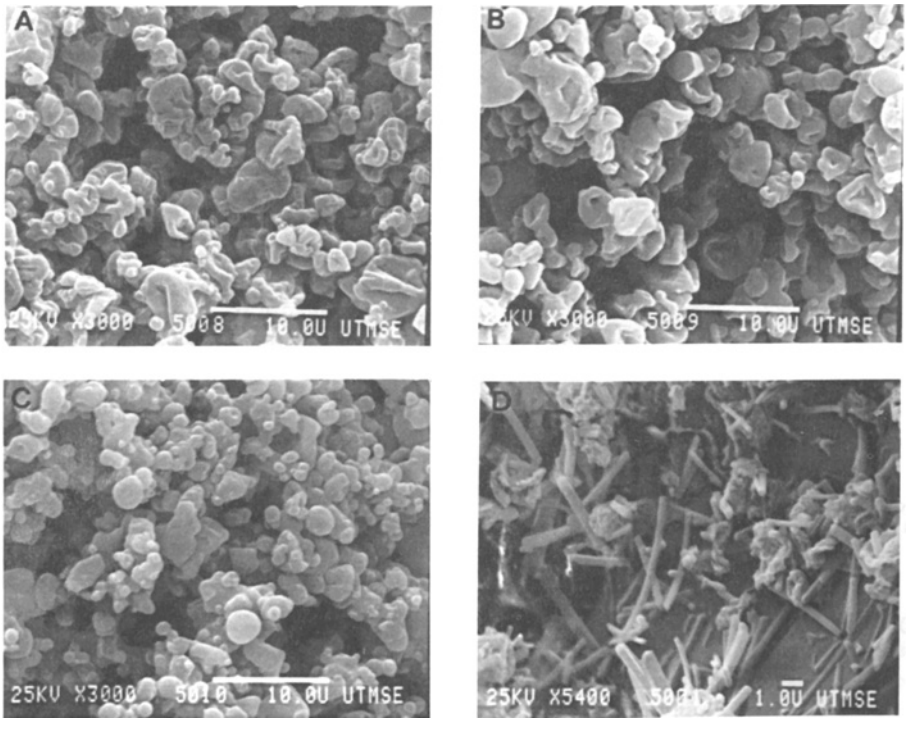

FIG. 1. Scanning electron micrographs of spray-dried poly(±)lactide microparticles: A, 20% progesterone; B, 35% progesterone; C, 50% progesterone; D, 50% caffeine.

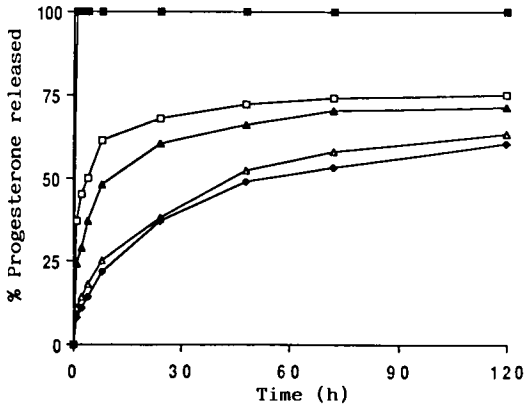

FIG. 2. Drug release from progesterone-poly(±)lactide microparticles; progesterone content: (■) 100%; (□) 50%; (▲) 35%; (△) 20%; (♦) 10%.

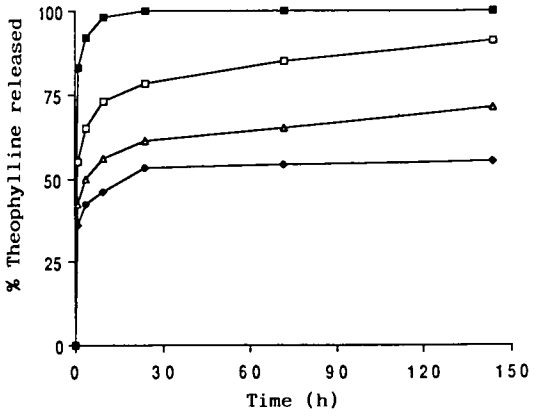

FIG. 5. Drug release from spray-dried theophylline-poly(±)lactide microparticles; theophylline content: (■) 75%; (□) 60%; (△) 40%; (♦) 25%.

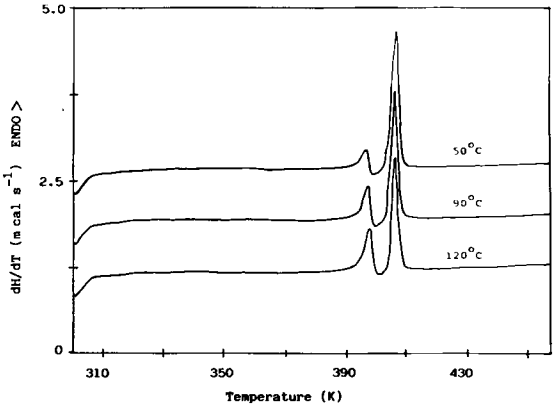

FIG. 3. DSC-thermograms of progesterone prepared by spray-drying at different inlet temperatures.

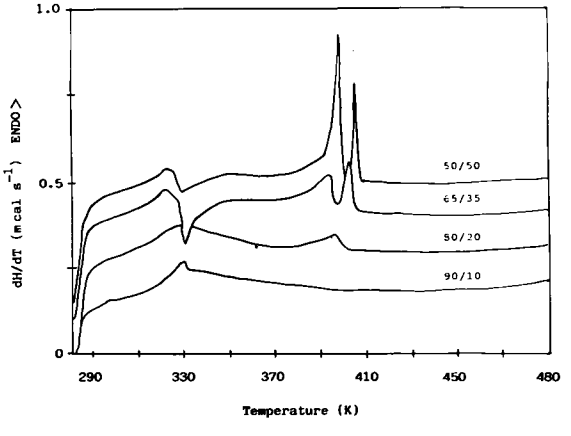

FIG. 4. DSC-thermograms of spray-dried microparticles prepared from different mass ratios of poly(±)lactide and progesterone.

for the spray-drying of drug suspensions. The polymer precipitated and encapsulated the dispersed particles upon solvent evaporation. The degree of encapsulation depended among other factors on the core to wall ratio. Empty PLA microparticles formed at high PLA : theophylline ratios. The amount of unencapsulated drug increased with an increase in the core material. The release of drug from spray-dried theophylline-PLA microparticles was clearly retarded and increased with increasing payload (Fig. 5).

The major problem we have encountered in the spray-drying of polymer solutions was the formation of fibres as a result of insufficient forces present to break up the liquid filament into droplets. Initial studies showed that the successful dispersion of the filaments into polymer droplets depended strongly on the type of polymer used and to a lesser degree on the viscosity of the spray solution. While ethyl cellulose solutions resulted in spherical droplets at concentrations as high as ten percent, PLA solutions of considerably lower viscosity resulted in fibres at concentrations as low as one percent in methylene chloride. Strong and extensive intermolecular bonds coupled with adhering stiffness of the polymeric chains lead to strong chain interactions and to a high degree of fibre formation (Dhingra & Lauterbach 1985). Linear macromolecules without bulky side groups such as PLA fall into this category. This could explain the difficult disruption of the liquid filament into individual particles even at low polymer concentrations.

Process parameters such as temperature, air-flow, and spraying rate had to be optimized in order to improve the yield. A spray-air movement through the dryer must be created which prevents the deposition of partially dried product at the walls and the discharge of the small particles with the exhaust. Product deposition on chamber walls can result from semi-wet particles or from sticky deposits caused by the nature of the product. The temperature in the drying chamber had to be kept below the softening temperature of the PLA microparticles.

In conclusion, the development of biodegradable microparticles by a spray-drying technique appears to be an attractive alternative to the conventional microencapsulation techniques. Spray-drying allows the preparation of microparticles from compounds with different physicochemical properties in a single operation.

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