Spray Drying of biodegradable polymers in Laboratory Scale

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Introduction

Spray drying is a successfully employed method in pharmaceutical technology to prepare microspheres for controlled drug delivery systems [1, 2]. Other common methods to produce microspheres are emulsification solvent evaporation, emulsification solvent extraction, or phase separation. Comparing these methods, spray drying is a simple, rapid, reproducible and easy to scale-up technique [3]. It is a one stage process, allowing mild temperature conditions [4] and is less dependent on the solubility of the drug (e.g. hydro solubility) and the polymer [2].
In the last two decades, polymers based on lactic acid and glycolic acid and their copolymers have attracted much interest as carriers in the preparation of different medical devices and drug delivery systems. These polymers meet the necessary criteria of excellent biocompatibility, biodegradability, and non-toxicity in humans - either in surgery or in drug delivery systems.
In pulmonary applications, biodegradable polymers are interesting for inhalation therapy, where the particles sizes have to be smaller than 5.8 microns in aerodynamic diameter [5]. Spray drying has shown its potential use to achieve such small particle sizes.
The purpose of this study is to give an application help in spray drying of biodegradable polymers based on lactide and glycolide acids. In this work, the influence of inlet/outlet temperatures, polymer concentration and polymer type on the particles characteristics are studied. The results have been evaluated in terms of yield, shape of the microspheres, morphology and particle size. Spray drying was performed with the pure polymers and copolymers without drug encapsulation.

Drug	Application	Polymer	Solvent	Polymer conc.	pump rate	Tin	Tout	Yield	Particle size	Drug encapsu-lation	Drug release rate	Spray Dryer	Author and Reference
		lactide/glycolide ratio, viscosity [dl/g], molecular weight [g/mol]			[ml/min]	[°C]	[°C]	[%]	[micron]				
Diazepam	Lipophilic model drug	Res 203R (PDLLA 16000, 0.3 dl/g)	DCM/CFM (1:1)	3% (w/w) const.	2-7	44-63	36-51	20-55	5-14	70-85%	60-80% in 20h	B-190	Conte et al. 1994 [1]
Progesterone, Theophylline	Hormones, stimulants	PLA (1.7 dl/g)	DCM	20mg in 50ml (40%)	10	70	40-45	-	<5	-	70% in 60h	B-190	Bodmeier et al. 1988 [2]
Vitamin D3	Antitumoral activity, fortification of foods	Res 206 (PLLA 57000), Res 207R (PDLLA 209000), Res 206R (PDLLA 109000), Res 203R (PDLLA 16000), RG506 (PGLA 22000)	CFM, DCM/CFM	1-5%	2.5-4.5	51	34	35-46	<10	55-61%	30-60% in 300h	B-190	Pavanetto et al. 1993 [4]
Budesonid, Salbutamol	Aerosol therapy, inflammable respiratory disease	Res R202H (PLA, 14 000), Res RG 502H (PLGA 50:50, 14 000), Res RG 752-S (75:25, 17 000)	DCM	0.5%, 10% polymer 5-44% drug loading	9-11	55-60	<45	35-75	1.3-4.2	>90% Budesonid >73% Salbutamol	49-100% Budes, 14-85% Salbut. in 48h	B-191	Schrötle 2006 [5]
Human serum albumin, Tetanus toxoid	Controlled drug delivery	Res RG502H (PLGA 50:50, 14 kDa)	ethyl formate, DCM	7.5-20% + trehalose	0.9-4.6	45		31-59	2-14	18-67%	30% in 24h	B-191	Johansen et al. 2000 [6]
Superoxide dismutase (SOD)	Antioxidant, enzyme therapy	poly(e-caprolactone, 848 kD) Res R207 (PLA, 199.8 kD) Res RG756 (PLGA 75:25, 78.2 kD)	DCM	0.5% + sucrose	4.5-5.5	45	34	-	4-10	40-60%	100% in 48-72h	B-190	Youan 2004 [7]
Bovine serum albumin	Antigens, stabilizing protein	Res R207 (PLA, 209000)	DCM/CFM	0.5-3% (w/v)	3-5	44-54	34-40	-	3-9	2-18%	11-92% in 24h	B-190	Baras et al. 2000 [8]
Chlorambucil (CHL)	Chemotherapy, anticancer drug	PLA (90000-120000)	DCM/CFM (1:1)	1.0-2.5% CHL/PLA 1/1 - 1/4	10	65-85	-	10-51	2-12	98%	20-70% in 40h	B-191	Fu et al. 2001 [9]
Etanidazole	Radiotherapy, cancer treatment	PLGA (65:35, 40000-75000)	DCM	1-5% drug 0.5-3.0%	4, 11	45-70	38-52	30-40	1.5-2.5	67-96%	47% in 30 min, 80% in 5.5h	B-191	Wang and Wang 2002 [10]
5-fluorouracil	Cancer drug, treatment of tumours	PLA (40400), PLGA (50:50, 34400), PLGA (75:25, 57600)	DCM, CFM, Ethyl acetate	drug 1.8%, 0.2%	5	63-66	50-54	37-49	1-4	52-74%	70-90% in 28h	B-190	Blanco et al. 2005 [11]
Fluconazole	Fungal pulmonary infection	Res RG 502 (PLGA 50:50, 12000) RG 502H (PLGA 50:50, 12000) RG 504 (PLGA 50:50, 48000) HG 752 (PLGA 75:25, 22000)	DCM	2% polymer drug 2-40%	25%	58	37	-	7-14	86-100%	80% in 10 days, burst effect	B-191	Rivera et al. 2004 [12]
Prioxicam	anti-inflammatory drug	Res R206 (PLA, 1.0, 137000) PLGA (0.42, 36'000)	DCM	1% (w/v) + PVA	13	60	40	43-59	1-15	99%	PLA (20% in 10d), PLGA (50% in 5d)	B-190	Wagenaar and Müller 1994 [13]
Rifampicin	Antibiotic, respiratory disease of tuberculosis	PLGA (75:25, 82500)	DCM	0.5% (w/v)	16.7	60	40	34-41	3	20-30%	40-80% in 24h	B-100	O'Hara and Hickey 2000 [14]
Paclitaxel	Chemotherapy, cancer treatment	PLGA (50:50, 65:35, 40000-75000, 75:25, 66000-107000, 85:15, 50000-75000)	DCM	2% (w/v) drug 5-10%	20%	70	-	-	1-10	90-100%	25% in 30days	B-290	Lee et al. 2004 [15]

Table 1 : Literature review of spray dried PLA and PLGA biopolymers with the Mini Spray Dryer B-190, B-191 and B-290 from Büchi Labor technik AG. PLA: poly-L-lactide, PDLLA: poly-D,L-lactide, PLGA: polylactide-co-glycolide, DCM: dichloromethane, CFM: chloroform

Table 1 gives an overview of scientific research into the preparation of microparticles using different biodegradable polymers using the laboratory Mini Spray Dryer B-190, B-191 or B-290 from Büchi Labortechnik AG. The application range includes drug encapsulation for tuberculosis, infections, asthma, cancer or lung therapy. Proteins are stabilized well in the dried state of the powder by addition of glass forming stabilizers, such as trehalose [6], sucrose [7] or polyvinyl alcohol [8].
Polylactide (PLA) and polylactide-co-glycolide (PLGA) were mostly used as biodegradable polymers for drug delivery systems. The selection of the copolymer composition (e.g. lactide to glycolide ratio) and the molecular weight determines the degradation rate. PLGA with a higher glycolide ratio provides faster release of the drug. Water enters the more hydrophilic polymer chains faster compared to PLA. The microspheres start to swell and allow the encapsulated drug to be released by diffusion through aqueous pores. The reported particles sizes were between 1 to 15 micron, thus in the size range of inhalable particles. High encapsulation efficiencies close to 100% at a considerable yield of 50% are found [10, 11]. Short processing times make the bench-top spray dryer suitable for the first trials in the laboratory.

Materials and methods

In this study polylactide (PLA) and polylactide-co-glycolide (PLGA) biopolymers were used. The polymers were kindly supplied by Boehringer Ingelheim (Germany) and PURAC Biomaterials (The Netherlands). The biopolymers are a white, amorphous, odourless powder with neutral taste. The more hydrophilic types of polymer are indicated with a H at the end (free hydrogen bond). The glass transition temperature is an important parameter of the polymer, which depends on the glycolide content and decreases with higher glycolide amount.
The spray dried particles are amorphous due to the fast evaporation times they are subjected to and also due to the lack of ability to form crystalline structures [5].
The morphology of the produced microspheres was analysed by Scanning Electron Microscopy (Zeiss Leo Gemini 1500). The production yield is expressed as weight percent of product obtained with respect to the weight of polymer added to the solvent mixture to be sprayed. The powder was collected in the cyclone and in the collection vessel.

Polymer	Conc.	Tin	Tout	Pump feed	Yield
	g	°C	°C	ml/min	%
PDLLA 100:0 IV=0.23 dl/g Tg=51-55°C	1.5	55	38	4	54
	1.5	65	43	11	44
	1.5	75	45	11	42
	5	55	40	4	41
	5	65	41	11	37
	10	55	36	4	55
PLGA-H 50:50 IV=0.22 dl/g Tg=41-43°C	1.5	55	38	4	19
	1.5	65	40	11	83
	1.5	75	45	11	48
	5	55	37	4	45
	5	65	39	11	40
	10	55	38	4	31
PLGA 75:25 IV=0.20 dl/g Tg=38-45°C	1.5	55	32	4	33
	1.5	65	37	11	34
	1.5	75	46	11	58
	5	55	36	4	41
	5	65	37	11	43
	10	55	38	4	55
PLGA 50:50 IV=0.20 dl/g	1.5	55	34	4	31
	1.5	65	42	11	46
	5	65	36	11	53
	10	55	34	4	33
PLGA 50:50 IV=1.05 dl/g	0.5	35	25	9	52
	1.5	27	21	9	71

Table 2: Process parameters and polymer properties. Glass transition temp. (Tg) from literature [5, 12]. Aspirator rate 100% and gas spray flow of 600 liter/min kept constant. PDLLA: Poly-D,L-lactide, PLGA: Polylactide-co-glycolide, IV: Inherent viscosity (dl/g)

Figure 1: Mini Spray Dryer B-290 with High Performance Cyclone during spray drying of biodegradable polymers.

For the preparation of microparticles the biopolymers were dissolved in dichloromethane (DCM). DCM was chosen because of its high solvation capacity for PLA and PLGA biopolymers [7] and the low boiling point of 40°C. It is considered as one of the least toxic of the halogenated solvents [11]. Polymer type, concentration and inlet temperature were varied according to the process conditions listed in **Table 2**. The total weight of spray dried polymer solution was 100g. The Mini Spray Dryer B-290 and the two-fluid nozzle with the 0.7mm nozzle tip were used (**Figure.1**).

Results and Discussion

SEM pictures of spray dried microspheres of different polymer types show that the microparticles appear in general to be spherical with a relatively smooth and closed surface. **Figure 2** shows the influence of different concentrations (1.5%, 5% and 10% w/w) of PDLLA at 55°C inlet temperature on the morphology and particle size. The pictures reveal completely formed microspheres with spherical shape and smooth surfaces. The particle size distribution is homogeneous with some bigger individual particles. DCM evaporates quickly and renders microspheres spherical [10, 11]. Moreover, increasing the concentration from 1.5 to 10% resulted in a bigger particle size. Most of the particles are in the size range below 5 micron and so accessible to the alveoli in the lung.

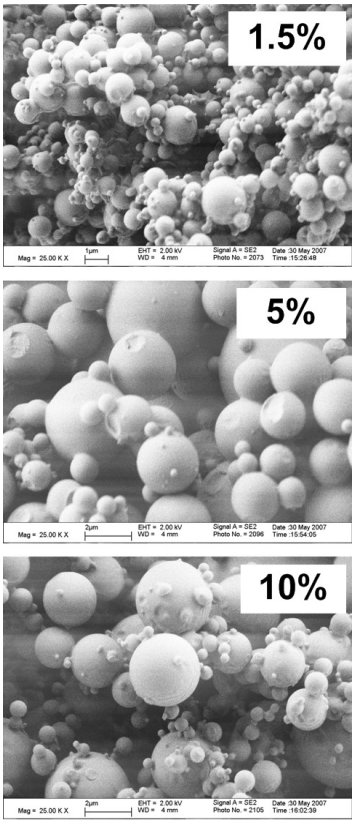

Figure 2 : SEM morphology of PDLLA microspheres prepared by spray drying at different polymer concentrations 1.5%, 5%, 10% (w/w).

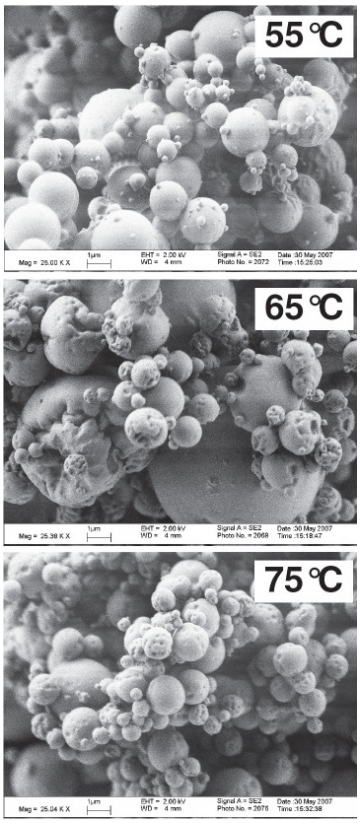

Figure 3: SEM observation of the PDLLA spray dried powders obtained at 55°C, 65°C and 75°C inlet temperatures.

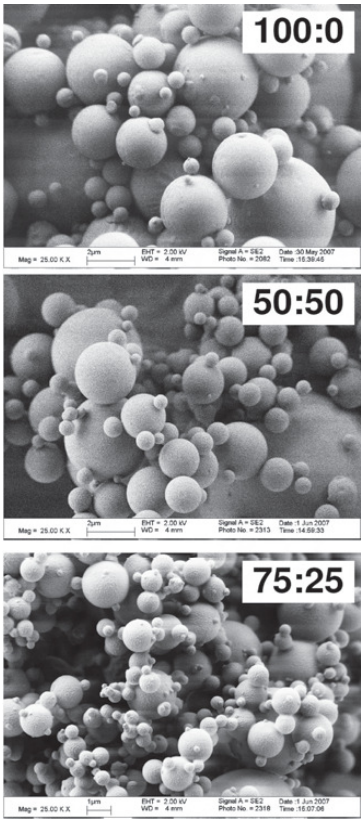

Figure 4: SEM pictures of spray dried biopolymers with different lactide to glycolide ratio. PDLLA (100:0), PLGA (50:50) and PLGA (75:25).

Figure 3 illustrates the morphology of the PDLLA microspheres prepared at different inlet temperatures (55°C, 65°C and 75°C). The surface of the spray dried particles at 55°C is spherical and smooth, whereas at higher temperatures the treated particles show some shrivelled surfaces, small craters and some have even collapsed. It is concluded that the inlet temperature has to be

sufficiently low to allow solvent evaporation (boiling point of DCM is 40°C) but not too high to prevent destruction of the polymer. The outlet temperature in the drying chamber has to be kept below the glass transition temperature of the polymer.
Figure 4 illustrates spray dried particles of the same molecular weight but different lactide to glycolide ratio. No significant difference in shape is noticed among the microspheres. However, as mentioned by other authors [4, 12] the ratio has influence on the drug release properties. With a higher glycolic acid content, both the amorphous and hydrophilic properties increase and facilitate the release of a loaded drug.
An average reproducible yield of 46% was achieved. These values are comparable with results obtained by other authors 37-49% [11], 30-40% [10] or 40% [1]. Most of the product loss is found as deposits in the spray chamber and in the outlet filter after the cyclone.
Product deposition on the spray chamber walls can result from semi-wet particles or from sticky deposits caused by the nature of the product, which has a high affinity to the glass walls.

Conclusions

The development of biodegradable microparticles by spray drying appears to be an attractive alternative to conventional microencapsulation technologies, like emulsification solvent evaporation, emulsification solvent extraction or phase separation. The advantage of spray drying is that it is a one step method allowing fast processing of small batches at reasonable yields. Spray dried microparticles have a suitable size and shape for inhalation applications. Process parameters are found for the production of spherical particles with a smooth or structured surface.
The feasibility of the Mini Spray Dryer B-190, B-191 and B-290 is further demonstrated by results from several literature studies. The collected data show the possibility to encapsulate different drugs into biodegradable microspheres for controlled drug delivery systems. Spray drying is promising to be the method of choice in preparing powders for new application fields in pulmonary therapy, cancer treatment or medical device applications.

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