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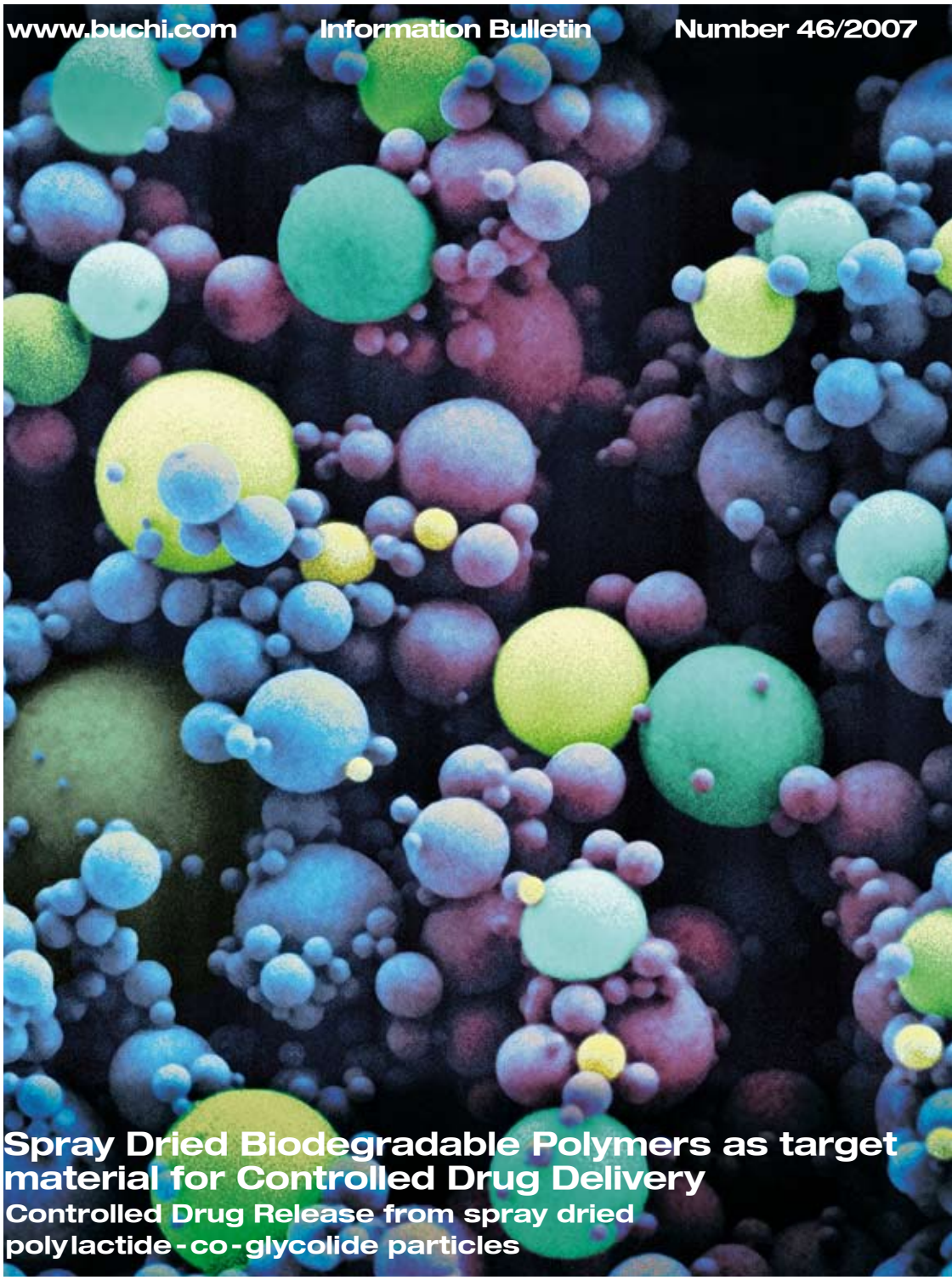

Spray Dried Biodegradable Polymers as target material for Controlled Drug Delivery

Controlled Drug Release from spray dried polylactide-co-glycolide particles

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Spray dried biodegradable polymers as target material for controlled drug delivery

Abstract:

Biodegradable polymers based on polylactide (PLA) and its co-polymers polylactide-co-glycolide (PLGA) were successfully spray dried with the Mini Spray Dryer B-290. Process parameters are found to prepare spherical particles with a smooth or structured surface.
A literature review demonstrates the feasibility to encapsulate different drugs in biodegradable microspheres for controlled drug delivery systems.
Spray dried microparticles have a suitable size and shape for new application fields in pulmonary therapy, cancer treatment or medical devices.

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]. The spray drying technique 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.

Goal of this study

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.
The morphology of the produced microspheres was analysed by Scanning Electron Microscopy (Zeiss Leo Gemini 1500). The particle size distribution was analyzed by laser diffraction (Sympatec Helos Disperser) with a dry powder disperser. 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.

Literature overview

The potential use of the laboratory Mini Spray Dryer B-190, B-191 or B-290 from Büchi Labortechnik AG is reported in scientific literature.
Table 1 gives an overview of research into the preparation of microparticles using different biodegradable polymers.
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 particles sizes of the microspheres prepared in these studies 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 reported [10, 11].
Short processing times make the bench top spray dryer suitable for the first trials in the laboratory.

Materials

In this study polylactide (PLA) and polylactide-co-glycolide (PLGA) biopolymers were used. The properties are shown in ***Table 2***. 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].

Drug	Application	Polymer	Solvent	Polymer conc.	pump rate	Tin	Tout	Yield	Particle size	Drug encapsulation	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	Schöttle 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, 648 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	65-65	-	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. 2006 [11]
Fluconazole	Fungal pulmonary infection	Res RG 502 (PLGA 50:50, 12000) RG 502H (PLGA 50:50, 12000) RG 504 (PLGA 50:50, 48000) RG 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%	40-60% in 24h	B-190	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 Labortechnik AG. PLA: poly-L-lactide, PDLLA: poly-D,L-lactide, PLGA: polylactide-co-glycolide, DCM: dichloromethane, CFM: chloroform*

Process conditions

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***). The flow type is co-current with mixing of air and liquid at the nozzle head. The air spray flow and aspirator rate were kept constant at 600 l/h and 100%, respectively. The liquid feed rate was set to maintain a constant outlet temperature during the spray drying process.

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

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. Values for the glass transition temperatures (Tg) are from literature [5, 12]. The aspirator rate 100% and gas spray flow of 600 liter/min were kept constant.*
PDLLA: Poly-D,L-lactide, PLGA: Polylactide-co-glycolide, IV: Inherent viscosity (dl/g)

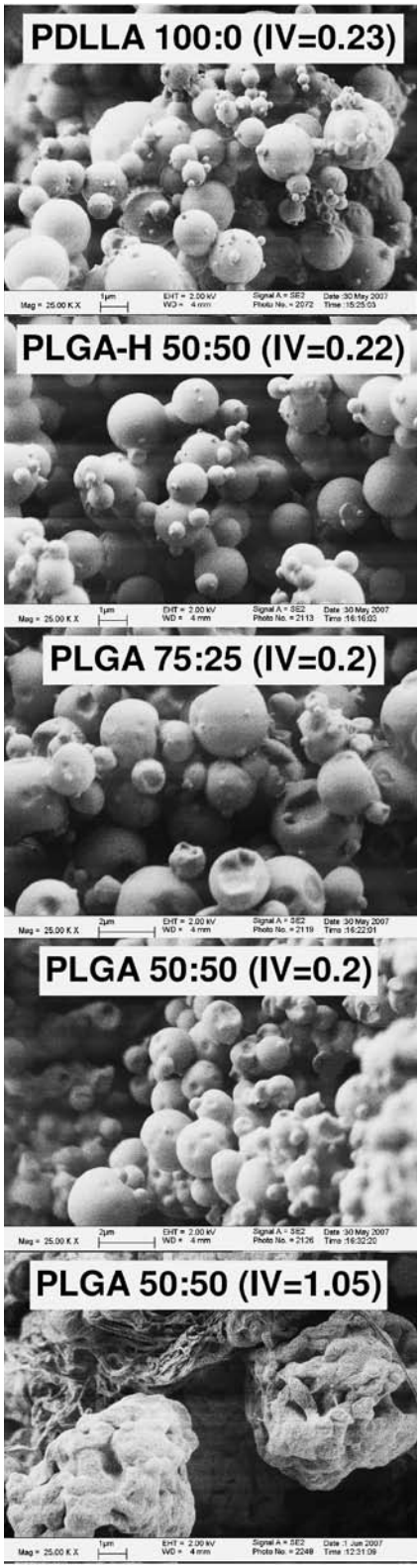

***Fig. 2**: SEM micrographs of spray-dried microspheres of different polymers.*

Results and discussions

Influence of polymer type on microsphere morphology

As the SEM pictures of spray dried microspheres of different polymer types show, the spray dried microparticles of the IV ≈ 0.2 dl/g polymers appear in general to be spherical with a relatively smooth and closed surface (***Figure.2***). The surfaces of the IV = 1.05 dl/g microspheres show some irregularities, incompetently formed particles and big agglomerates.

This is probably due to the high molecular weight of the latter polymer [4]. The particles have a tendency to build up agglomerates (up to 100 micron size) due to the adsorption force of the small particles on the surface. This is a sign of a high surface energy of the amorphous spray dried material.

Influence of polymer concentration on particle size and morphology

Figure 3 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.

Figure 4 illustrates the influence of concentration on the morphology of microspheres prepared from PLGA 50:50 biopolymer. At 1.5% polymer concentration, the obtained microspheres have some dents. This deformation can result during solvent evaporisation and hardening at low solid concentration [10]. Dichloromethane evaporates quickly and renders microspheres spherical [10, 11].
Increasing the polymer concentration to 5% results more spherical shape of the prepared microspheres. Moreover, increasing the concentration from 1.5 to 10% resulted in a bigger particle size.

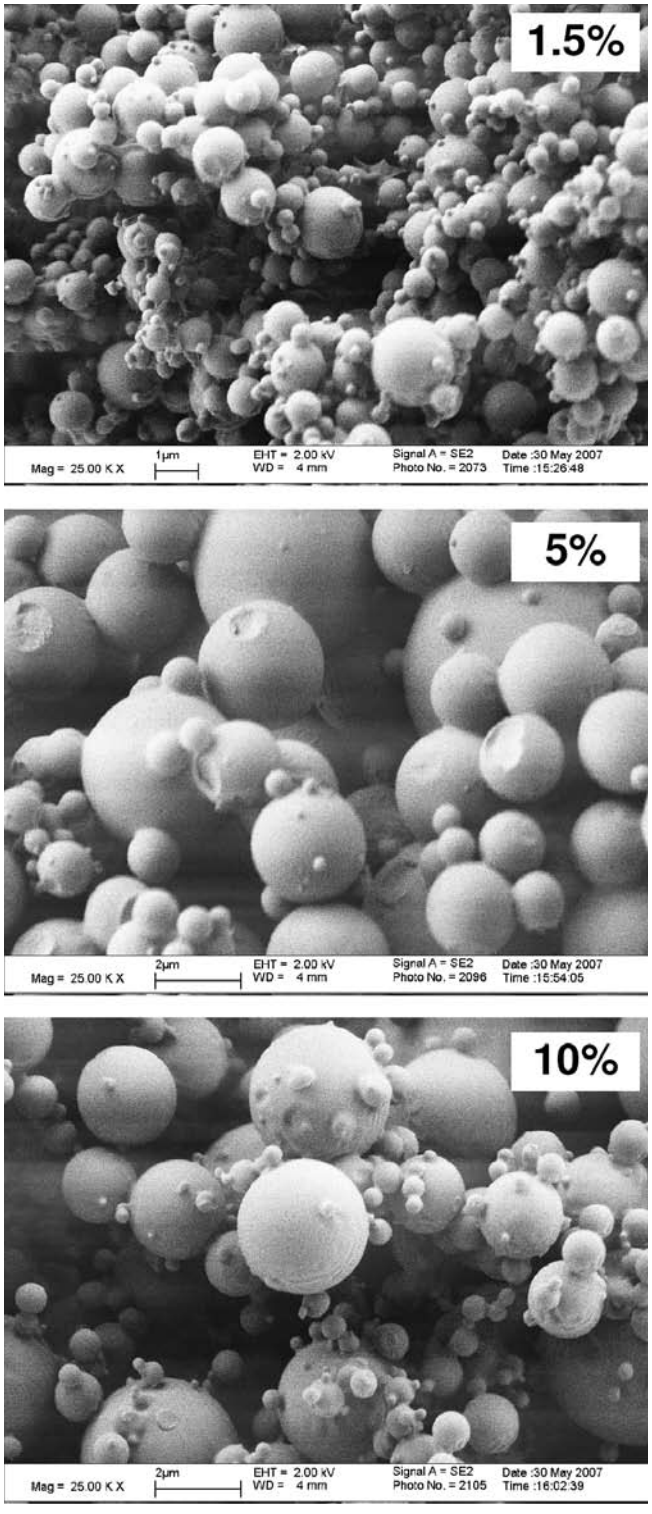

Fig. 3*: SEM morphology of PDLLA microspheres prepared by spray drying at different polymer concentrations 1.5%, 5%, 10% (w/w).*

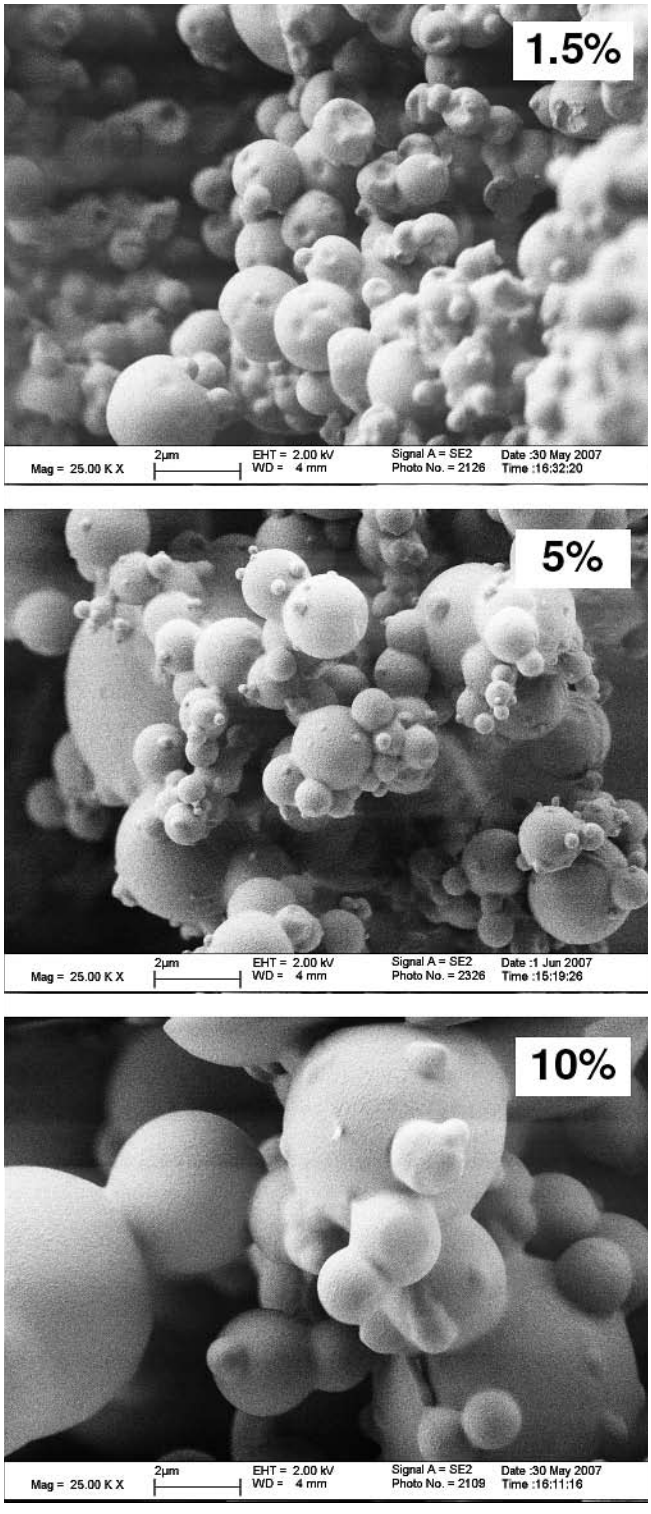

Fig. 4*: SEM pictures showing PLGA (50:50) particles at different concentrations 1.5%, 5% and 10% (w/w).*

Figure 5 shows the particle size distribution of spray dried microspheres at different polymer concentrations of the PDLLA biopolymer.
The mean diameter of the particles is around 5 microns and is varied only slightly with the change of the polymer concentration. The particle size distribution is almost identical.
The fine particle fraction, e.g. less than 6 micron is in the range of 40% to 60%. So, most of the particles are in the size range accessible to the alveoli in the lung.
SEM pictures (***Fig. 2 to 4***) reveal smaller sizes compared to the laser diffraction measure. This is attributed to agglomerated particles during the size measurement, which shifted the mean values to higher numbers. The obtained particles sizes are in the range of literature values in ***Table 1***.

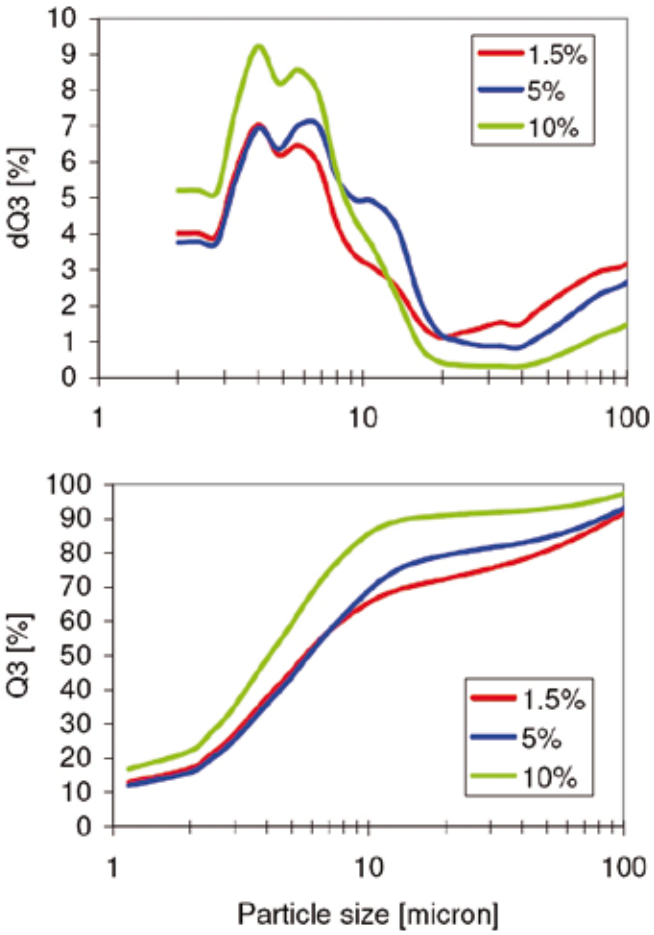

Fig. 5*: Effect of different polymer concentrations (1.5%, 5% and 10%) for the PDLLA biopolymer on particle size.*

Influence of inlet temperature on microsphere morphology

Figure 6 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 dichloromethane 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 (see ***Table 2***).

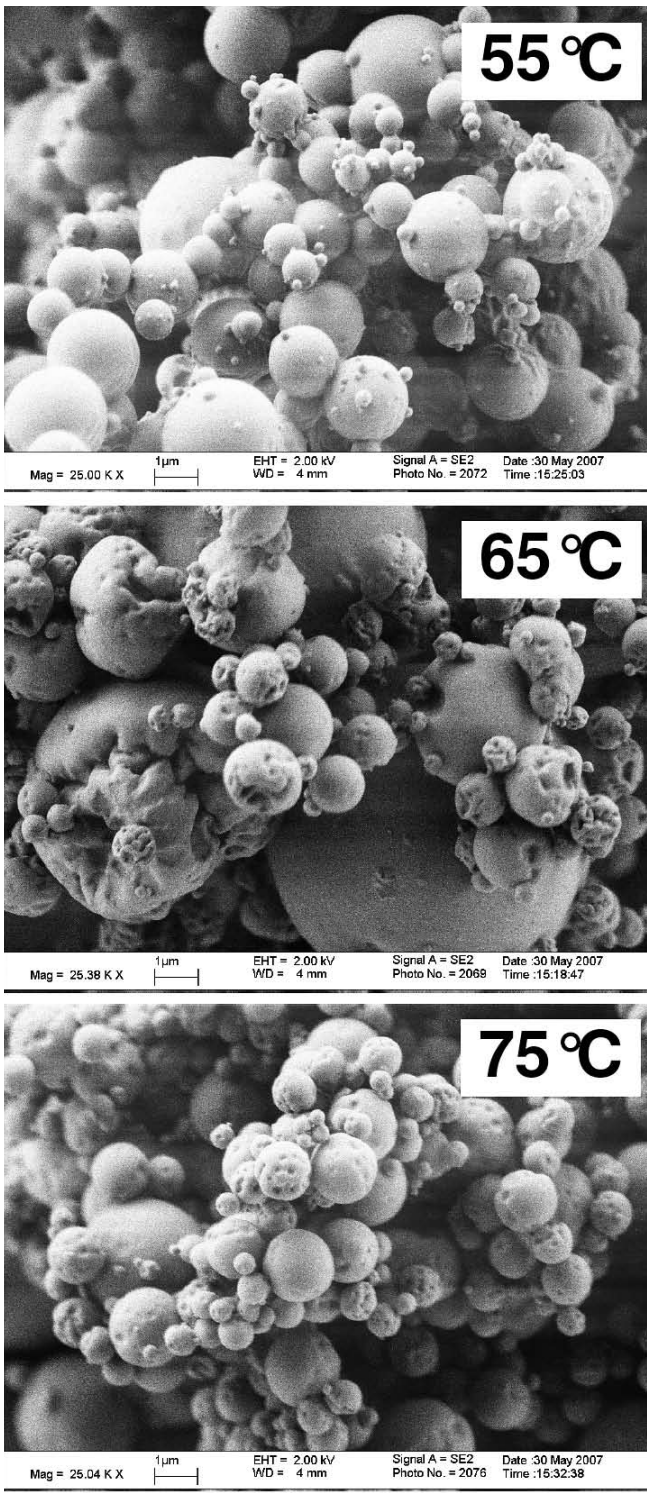

Fig. 6*: SEM observation of the PDLLA spray dried powders obtained at 55°C, 65°C and 75°C inlet temperatures.*

Influence of viscosity and molecular weight on particle morphology

Figure 7 shows the influence of the viscosity and molecular weight on the morphology of PLGA 50:50 biopolymers at a constant concentration of 1.5%.
The results show an increased particle size with higher viscosity, which has also been found by other authors [4, 5].
At high molecular weights, the forces required to break up the liquid filament into droplets are insufficient, which leads to incomplete formation of particles and big agglomerates [2].

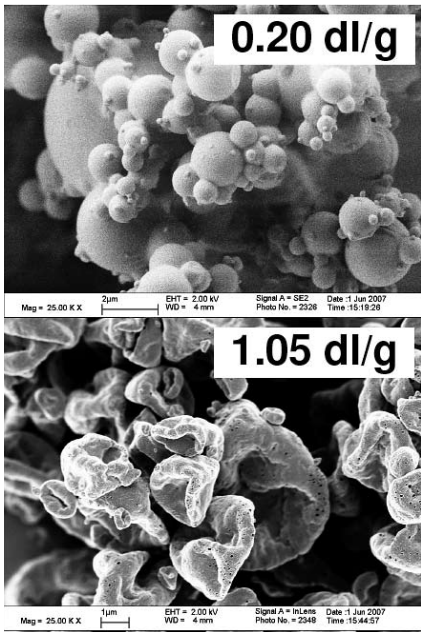

Fig. 7*: SEM pictures of PLGA 50:50 polymers at two different molecular weights and inherent viscosities (0.2 and 1.05 dl/g).*

Influence of lactide to glycolide ratio on particle shape

Figure 8 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.

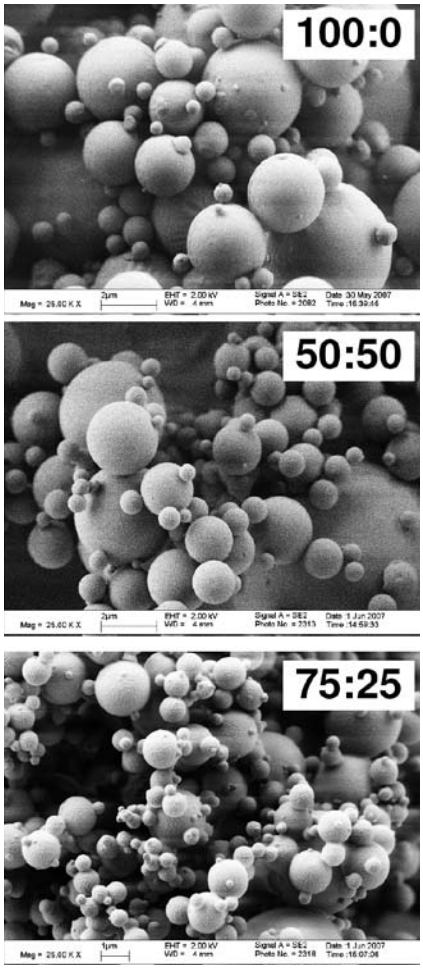

Fig. 8*: SEM pictures of spray dried biopolymers with different lactide to glycolide ratio. PDLLA (100:0), PLGA (50:50) and PLGA (75:25).*

Reported drug release rates

Literature data [4, 9, 10, 11, 13] reveal that the drug release profile typically exhibits two phases. At the beginning there is a steep increase (so called "burst effect"), which is followed by a second sustained release period. The "burst effect" in the first 12 to 24 hours is attributed to the release of drug of the more superficial area of the microspheres. Initial bursts of 20 to 60% are reported in the literature.
The second phase of release is determined by diffusion of the drug through small pores or channels in the polymer matrix [14]. Drug release data clearly proves retarded profiles compared to pure drug samples.
The high loading efficiency from 50% up to 100% is typical for spray drying [15]. The reason for this is that the drug cannot separate into an external phase, as is the case of solvent evaporation [14]. Highest encapsulation efficiencies are obtained with the lowest amount of drug added to the polymer [4, 10]. In vitro drug release from the particles can be altered by the selection of the used copolymer [15].
Drug release studies from literature reveal typically lower drug release rates at higher inlet temperatures (denser polymer matrix), higher air flow rates (smaller particle sizes), lower polymer concentrations (reduced porosity) and lower drug loading (fewer pores, less diffusion).

Yield as a function of polymer type, concentration and inlet temperature

Figure 9 shows the yield of different spray dried powder samples as a function of polymer type, temperature and concentration. The collected product was weighed as the sum of a fraction in the cyclone and in the collection vessel.

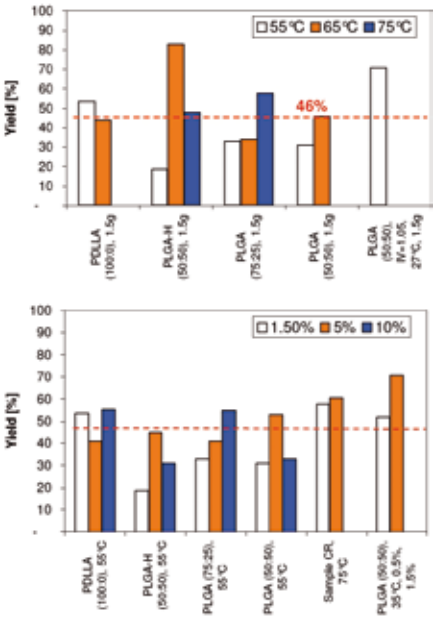

Fig. 9*: Yield as a function of polymer type, temperature and polymer concentration.*

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.
Small particles of less than 1 micron go directly to the filter from the separation cyclone. The centrifugal forces are too low for separation. Setting the aspirator rate at 100% gives reproducible results. A high spray air movement through the dryer enhances the separation efficiency in the cyclone.
A higher air spray flow through the nozzle increases the shear force between the gas and the liquid. This higher atomizing energy leads to smaller droplets and consequently to smaller solid particles. Increasing the air spray flow rate from 400 to 800 l/h reduced the mean particle size from 8 to 4 microns [9].

Conclusions

The development of biodegradable microparticles by spray drying of polylactide (PLA) and its copolymers polylactide-co-glycolide (PLGA) 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.

Acknowledgments

The authors would like to thank Mr. Weingärtner from Boehringer Ingelheim (Germany) and Mr. Van Alst and Mr. Krul from Purac Biomaterials (The Netherlands) for the supplied biodegradable polymers.
We gratefully thank Mr. Huber from the Institute of Process Engineering at ETH Zurich for his valuable assistance with the scanning electron microscopy work. We acknowledge Dr. Schöttle from Sanofi-Aventis (Germany) for her helpful comments to establish this brochure.

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