Aerosol solvent extraction system – a new microparticle production technique

J. Bleich, B.W. Müller and W. Waßmus

Department of Pharmaceutics and Biopharmaceutics, Christian Albrecht University, Kiel (Germany)

Summary

The aerosol solvent extraction system (ASES) utilises the extraction properties of supercritical gases for the production of microparticles. Extraction with supercritical gases is frequently used in the food industry and in analytical chemistry. In the ASES process drug and polymer are dissolved or dispersed in an organic solvent which is sprayed into a supercritical gas phase (e.g., carbon dioxide). The organic solvent is soluble in the supercritical gas phase and is extracted resulting in the formation of solid microparticles. Different biodegradable polymers, poly(DL-lactide) (PDLA), poly(DL-lactide-co-glycolide) (PGLA) with lactide/glycolide ratios (50:50) and (75:25), poly(L-lactide) (PLA) and poly(β-hydroxybutyric acid) (PHB) were tested for their suitability in ASES. The polymers PDLA and PLGA (75:25) were extracted. The use of PLGA (50:50) led to partial extraction and a polymer film in the collecting vessel. Microparticles were obtained using PLA and PHB. The particles were spherical and the particle size range ($X_{50\%}$) was 1–10 μm.

Introduction

Various microencapsulation techniques exist for the formation of polymeric microparticulate drug delivery systems (for reviews see Bornschein et al. (1989) and Jalil and Nixon (1990)). A new microencapsulation technique was developed by employing the extraction properties of supercritical gases. The fact that compressed gases can dissolve solids was first demonstrated by Hannay and Hogarth in 1879, who dissolved potassium iodide in supercritical ethanol and reprecipitated the salt by reducing the pressure. Little above the critical temperature of a gas, densities similar to those of solvents can be reached within the range of 1–3 times the critical pressure. Density and dielectric constant can be changed by varying the pressure (Hubert and Vitzhum, 1980). The influence of pressure and temperature variations on the density is shown in Fig. 1. Materials which are dissolved in a supercritical gas can be recovered by decreasing the density either by reducing the pressure at constant temperature or by raising the temperature at constant pressure (Zosel, 1980). Supercritical gases are used in industrial processes for the extraction of natural products (Hubert and Vitzhum, 1980; Rajamaran et al.,

Correspondence to: B.W. Müller, Department of Pharmaceutics and Biopharmaceutics, Christian Albrecht University, Kiel, Germany.
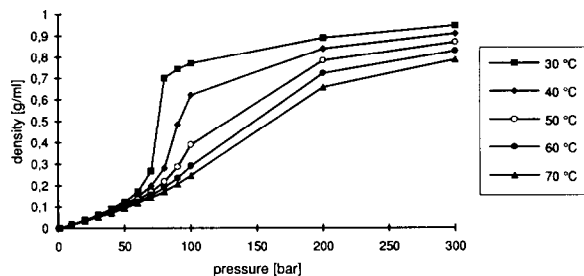
Fig. 1. Dependence of the density of carbon dioxide on pressure and temperature.

1984; Gährs, 1985), residual solvents (Kamihira et al., 1987) and for polymer purification (Braun et al., 1985). Extraction with supercritical gases can also be used as a milling technique for the micronization of drugs (Glatz, 1985; Loth and Hemgesberg, 1986; Ghang and Randolph, 1989). For this purpose, the material is dissolved and subsequently precipitated from supercritical gas (with or without cosolvents). A similar method for particle formation is the rapid expansion of supercritical solutions (RESS) (Tom and Debendetti, 1991).

The gas used is usually carbon dioxide, since it has a low critical temperature, is inexpensive, inflammable, non-toxic, non-combustible, readily available in large quantities and purity and non-corrosive. Supercritical fluid extraction also works with other supercritical gases, but it is important that the critical temperature is not too high in order to avoid decomposition in heat-sensitive substances which are to be extracted. A list of gases with a critical temperature below 50°C is given by Glatz (1985). Special extraction problems are discussed by Gährs (1985).

Materials and Methods

Separation with supercritical gases

The principle of a high-pressure extraction apparatus with extract separation by pressure variation is shown schematically in Fig. 2. The apparatus consists of a pump, a high-pressure column, a pressure regulation valve (V_2) and a separation vessel. The separation vessel is cooled below the critical temperature of the gas. The raw material is filled into the column. In the extraction step the soluble components are solved by the compressed gas. The homogeneous critical gas phase is decompressed as it passes through the pressure regulation valve (V_2) into the separation vessel, with the result that the density of the gas decreases and the extract/solvent mixture separates into its component parts. The gas is compressed again and returned to the extraction process. In one case, the aim may be to obtain an extract and the remaining matrix or carrier may be of no value (spices) and, in another, the carrier substance may be desired (tobacco) while the extracts are of secondary interest (Hubert and Vitzhum, 1980).

Aerosol solvent extraction system (ASES)

The ASES process (Müller and Fischer, 1989) uses the extraction properties of supercritical gases for organic solvents. The process (Fig. 3) works with a carbon dioxide cycle. Liquid carbon dioxide is filled into a cooled condenser (< 10°C) and is pumped with a diaphragm pump (P_1) (LEWA Herbert Ott & Go., Leonberg, Germany) through a heater into a high-pressure column (ZWAG Zschokke Wartmann., Zoettingen, Switzerland). The temperature in the column can be adjusted with another heater and is controlled by an iron-constantan thermoelement in the middle of the column. The pressure is regulated by a magnetic valve (V_3) which is controlled by a pressure gauge (Hydrotechnik, Limburg, Germany). The carbon dioxide is expanded to subcritical conditions into the separation vessel (separator) where it is vaporized and supplied to the condenser where it is liquified again. It is possible to work with a carbon dioxide continuous-current, counter-current or with a static carbon dioxide phase (V_2 and V_3 closed) during the spraying time. To produce microparticles, drug and polymer are dissolved or dispersed in an organic solvent and sprayed through a nozzle into the column with the supercritical gas phase (in this case carbon dioxide). The organic solvent is soluble in the supercritical gas phase and is extracted, leading to the formation of solid microparticles (Fig. 4). The column is equipped with an inlet and outlet metal-sinter filter (Pressmetall Krebs-
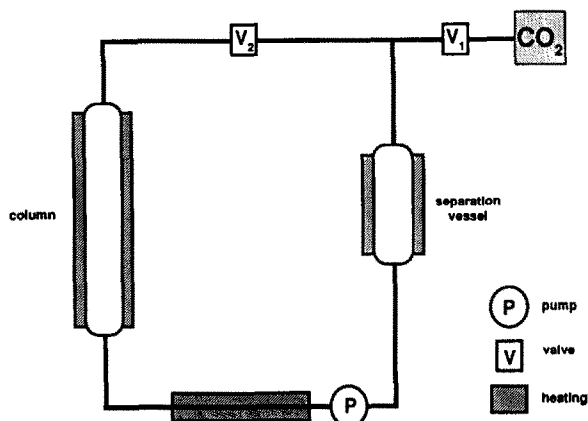
Fig. 2. High-pressure extraction apparatus.

Fig. 4. Flow sheet of the ASES process.

böge, Radevordemwald, Germany) to ensure that the particles remain in the column. After microparticle formation the carbon dioxide is discharged and the microparticles are collected.
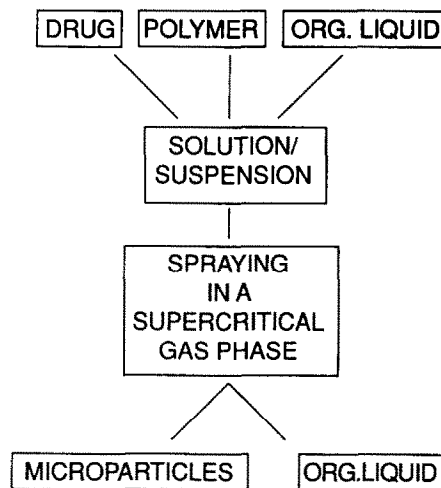
Polymers

Poly(DL-lactide) (PDLA) of low and high molecular weight and poly(DL-lactide-co-glyco-
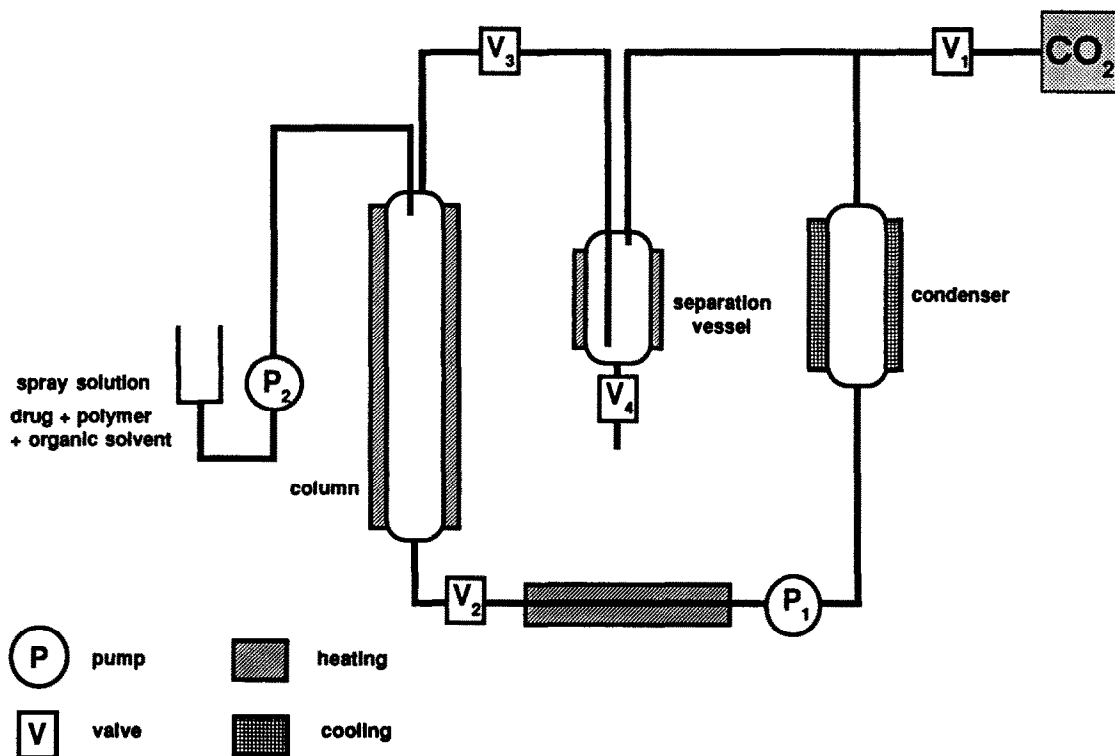

Fig. 3. ASES apparatus.

TABLE 1

Intrinsic viscosity and molecular weight determined with GPC

Polymer		Intrinsic viscosity (dl/g)	Mol. Wt GPC
R-203	PDLA	0.3	28 000
R-207	PDLA	1.5	236 000
RG-506	PGLA 50:00	0.8	98 000
RG-755	PLGA 75:55	0.8	98 000
L-206	PLA	1.0	102 000

lide) (PGLA) of different lactide-glycolide ratios (PLGA (75:25) and PLGA (50:50)) and poly(L-lactide) (PLA) were purchased from Boehringer Ingelheim, Germany. The intrinsic viscosity and molecular weight (declaration of the manufacturer) are listed in Table 1. Poly(β-hydroxybutyric acid) (PHB) (Mol. Wt 54 000) was obtained from ICI, Frankfurt, Germany. PDLA and PLGA are amorphous polymers while PLA and PHB are semicrystalline polymers (Schindler et al., 1977; Juni and Nakano, 1987).

Thermoanalysis

The glass transition temperatures and melting temperatures were determined with a Perkin Elmer DSC 7 (Perkin Elmer, Norwalk, CT, U.S.A.). The heating rate was 10°C/min.

Microparticle production

In order to investigate particle formation using the ASES process different polymers were tested. The polymers were used as a 1.5% solution in methylene chloride and were tested under two different conditions: 90 bar/40°C and 200 bar/40°C. These conditions were chosen because of

TABLE 2

Glass transition temperatures and melting points of the used polymers

Polymer		T_g (°C)	T_m (°C)
R-203	PDLA	42.6	–
R-207	PDLA	49.7	–
RG-506	PDLGA 50:00	44.8	–
RG-755	PDLGA 75:55	44.5	–
L-206	PLA	53.6	152.1
PHB		–	160.7

the large difference in gas density at 90 and 200 bar (Fig. 1). The temperature was adjusted below the glass transition temperature of the polymers. The carbon dioxide flow was 6.4 kg/h in counter-current. The solutions were sprayed through a 0.4 mm nozzle at a rate of 3 ml/min. The drying time was 3 h after the spraying process was finished.

Scanning electron microscopy (SEM)

The particles were fixed using a conductive tape (Plano, Marburg, Germany) and were coated for 60 s under an argon atmosphere with gold (Mini Coater Commonwealth Scientific, Alexandria, VA, U.S.A.). The shape and the surface characteristics of the microspheres produced were examined with Stereoscan S4-10 (Cambridge Instruments, Cambridge, U.K.).

Particle size measurement

The particles were suspended in a 0.01% solution of Pluronic F68, stirred for 30 s and were measured with a laser diffractometer (Sympatec, Clausthal-Zellerfeld, Germany). Using another testing method the particles were suspended in a 0.01% solution of Pluronic F68, stirred for 30 s and treated by ultrasonication (80 W, 35 kHz) for 30 s before measurement. The volume size distribution was calculated with a computer program

TABLE 3

Results of the particle size measurement by laser diffractometry

	X10	X50	X90	X90–X10	(X90–X10)/X50
Particle size					
L-206:90 bar	1.17	3.49	12.45	11.28	3.23
L-206:200 bar	1.07	3.51	34.82	33.75	9.62
Particle size (after ultrasonic treatment)					
L-206:90 bar	1.04	2.29	4.47	3.43	1.50
L-206:200 bar	0.74	1.76	3.41	2.67	1.52
Particle size					
PHB/90 bar	1.53	6.45	13.59	12.06	1.87
PHB/200 bar	1.16	2.75	5.85	4.69	1.71
Particle size (after ultrasonic treatment)					
PHB/90 bar	1.47	5.77	10.66	9.19	1.59
PHB/200 bar	1.08	2.23	4.23	3.15	1.41

(HELOS-Sympatec). The values $X_{10\%}$, $X_{50\%}$ and $X_{90\%}$ of the size distribution are listed in Table 3. $X_{90\%}$ minus $X_{10\%}$ was calculated to express the distribution width and $X_{90\%}$ minus $X_{10\%}$ divided by $X_{50\%}$ was used to describe the relation between distribution width and average size.

Results and Discussion

No particle formation was obtained using the amorphous polymer PDLA (R-203) of low molecular weight. The polymer was extracted from the column and precipitated in the separator and in the duct between the column and separator. The same result was obtained when the PDLA (R-207) of higher molecular weight was used. The PGLA polymers of different lactide/glycolide ratios led to the partial extraction of the polymer. In the vessel at the base of the column there was a polymer film when the PLGA (50:50) RG 506 was used. The behaviour did not change when preparation was carried out under different conditions. The use of PLA (L-206), however, led to the formation of spherical microparticles under both experimental conditions (Figs 5 and 6). The particles obtained were different in size and shape
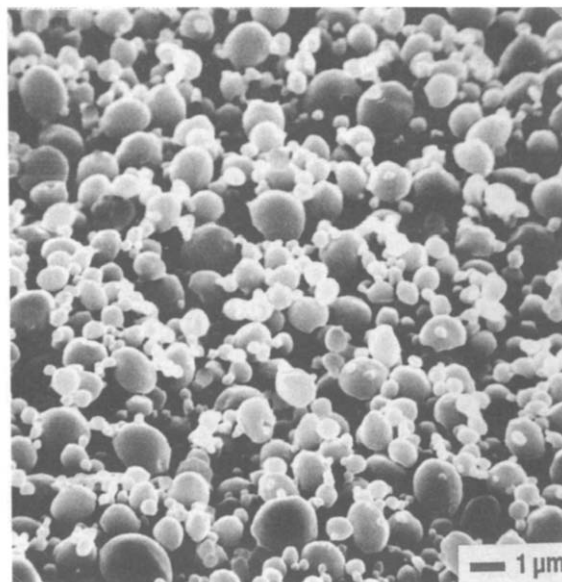

Fig. 6. PLA particles: 200 bar/40°C.

under the two experimental conditions when PHB was used. When the process was carried out under conditions of 90 bar/40°C particles with a porous surface were produced (Fig. 7). Other conditions led to smaller particles with a closed surface (Fig. 8). The results of the particle size
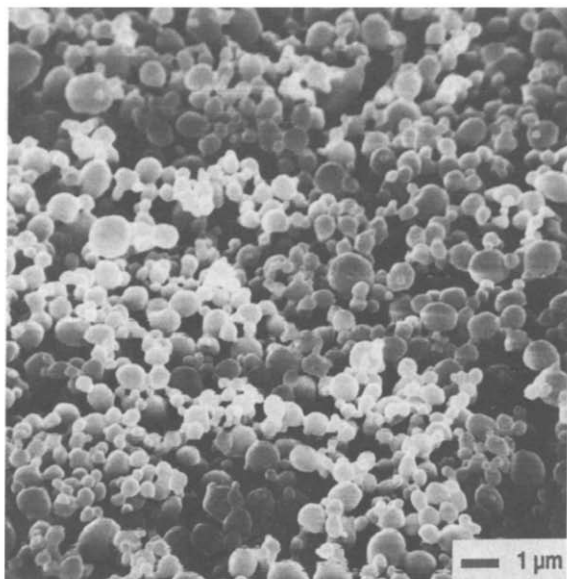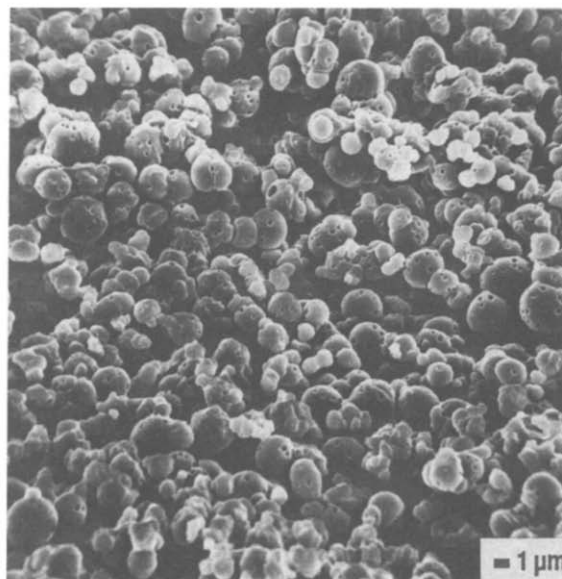

Fig. 5. PLA particles: 90 bar/40°C.

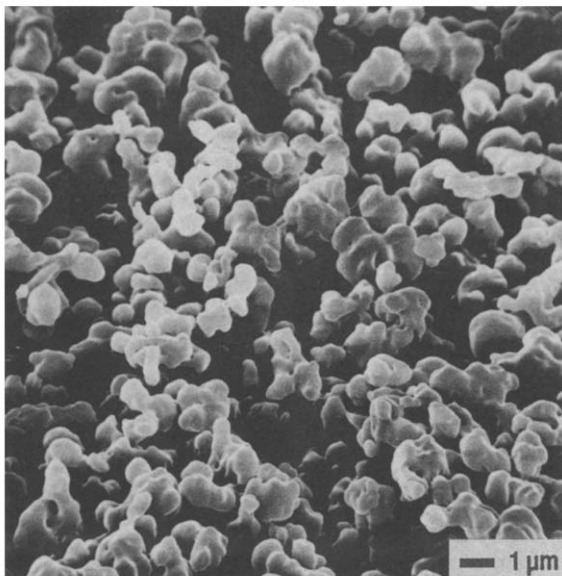

Fig. 7. PHB particles: 90 bar/40°C.

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Fig. 8. PHB particles: 200 bar/40°C.

measurement are listed in Table 3. The $X_{50\%}$ values are lower than 10 μm for PLA and PHB under both production conditions. When the PLA particles were measured without ultrasonic treatment, the disintegration of agglomerates was not observed. This can be seen by comparing the values of the different measurement conditions (e.g., PLA without ultrasonic treatment $X_{90\%} =$ 34.82 μm/distribution width = 33.75 μm and with ultrasonic treatment $X_{90\%} = 3.41$ μm/distribution width = 2.67 μm). When PLA was used the particles produced were smaller under higher pressure. The same results were achieved with the PHB particles. The two production conditions led to different particle sizes but the differences between them were smaller compared with the data on PLA. The influence of ultrasonic treatment on measured particle size and size distribution is, however, greater in the case of the PLA particles which can readily be seen from the $X_{90\%}$ values.

Conclusions

The present results indicate that the reported method can be used for production of microparti-

cles using the semicrystalline polymers PLA and PHB. The particles produced were spherical and the $X_{50\%}$ of the particle size distribution was below 10 μm. The use of PDLA and PGLA led to polymer extraction and not to particle formation.

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