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A novel spray-drying technique to produce low density particles for pulmonary delivery

Hartwig Steckel*, Heike G. Brandes

Department of Pharmaceutics and Biopharmaceutics, Christian Albrecht University Kiel, Gutenbergstraße 76, 24118 Kiel, Germany

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Abstract

To date, all marketed DPI products rely on jet-milled, micronized drugs. Micronization often leads to drug powders exhibiting a large hydrophobic surface area resulting in strong cohesive forces, agglomeration and unsuitable aerosolization properties. In the current study, a new approach to prepare low density drug particles is described. Briefly, an oil-in-water emulsion consisting of an aqueous phase containing the dissolved model drug salbutamol sulphate, suitable surfactants, such as poloxamer or phosphatidylcholine, and optionally a bulking agent like lactose or a cyclodextrin derivative, and a lipid-phase that essentially consists of a liquefied propellant is spray-dried. By means of this process particles of very low density (0.02 g/cm^3) and a drug load of 40% were prepared. The particle exhibit a porous to hollow structure, are thin-walled and of irregular shape. Depending on the composition of the aqueous phase, mean geometric particle sizes of <5 μm were obtained. It could be shown that a higher amount of poloxamer in the feed emulsion resulted in particles with improved dispersibility. Reducing the vapour pressure of the inner propellant phase by addition of dichloromethane decreased the agglomeration tendency of the powders as a result of the irregular particle morphology and, hence, resulted in higher fine particle fractions.

Keywords: Dry powder inhaler; Spray-drying; Fine particle fraction; Efficiency; Phosphatidylcholine; Dipalmitoylphosphatidylcholine; Emulsion-spray technique

1. Introduction

There are a number of different inhalation devices available on the market. The most commonly used device is the pressured metered-dose inhaler (pMDI) (Brocklebank et al., 2001), but one major limitation of drug delivery to the lungs by a pMDI is the relatively poor efficacy of these devices. Several studies have shown the coordination difficulties and problems patients have when administering an aerosol with the current pMDI devices (e.g. Crompton, 1982). A different approach of delivering drugs to the lung is the formulation of a dry powder inhalation product which is activated and driven by the patients' inspiratory flow. They proved to be as effective as pMDIs in clinical trials (Bronsky et al., 1987). In some cases they deliver even a higher amount of drug to the lungs leading to the conclusion that lower drug doses delivered with certain DPI devices are as effective as pMDIs (Borgstrom et al., 1996; Toogood et al., 1997; Goldberg et al., 2002).

Drug deposition in the lungs ranges from 20 to 40% of the emitted dose with the current generation of DPI devices (Anderson, 2001). The percentage of the

* Corresponding author. Tel.: +49-431-880-1333; fax: +49-431-880-1352.
E-mail address: steckel@pharmazie.uni-kiel.de (H. Steckel).

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emitted dose deposited in the lungs is dependent on the powder dispersibility which is controlled by interparticle cohesive forces. Strong interparticulate forces result in poor powder flow, as well as in poor powder dispersion from passive DPI devices followed by decreased drug deposition in the lung. These forces are proportional to the area of contact and separation distance between the particles (Weers, 2000). To date, all marketed DPI products rely on jet-milled, micronized drugs. The micronisation process leads to small and also flat particles. The smaller the particles are, the stronger are the cohesive forces (French et al., 1996). Additionally, the flat surface promotes large contact areas resulting in increased adhesion forces between the particles. Micronized powders with a high energetic surface show poor flow properties (Feeley et al., 1998). By jet-milling disordered regions in the crystal lattice are produced that cause thermodynamical instability (Ticehurst et al., 2000). Due to a decreased glass transition temperature of amorphous or disordered surface areas the tendency to re-crystallization is increased (Elamin et al., 1995). The re-crystallization process is followed by a gradual conversion of crystalline solid surfaces into partially amorphous, hydrophobic solid surfaces with surface energy changes (Ward and Schultz, 1995). This dynamic changes in the crystal habit show an influence on the processing properties like the powder flow as higher surface energy promotes higher cohesivity (Buckton, 1997). Accordingly, the micronization process using mills is extremely inefficient (Parrott, 1990) and, in addition, may create a safety issue due to dust formation during the process.

Also, micronized but spherical particles can be prepared by spray-drying. The amorphous particles are characterized by a low area of contact and a smaller and more homogeneous particle size distribution resulting in a higher respirable fraction than mechanically micronized drugs (Vidgrén et al., 1987; Chawla et al., 1994; Dellamary et al., 2000). Spray-drying also allows a control over particle shape, morphology and density dependent on the spray-drying conditions (Hickey et al., 1996).

In this paper a new particle engineering technology is presented with the aim to design low density and aerodynamically suitable particles for inhalation. During the last decade growing interest of improving pulmonary drug deposition and drug absorption could be observed. Several authors report about the production and characterization of large and porous aerosol particles with low bulk density. The related particles were prepared by solvent evaporation, solvent extraction and by conventional spray-drying (Edwards et al., 1997, 1999). Edwards et al. make use of a blowing agent to produce porous particles for inhalation. However, the power of an evaporating propellant that disrupts the shell of the particles during the drying step was not yet reported. The particles are prepared by spray-drying an oil-in-water-emulsion where a liquefied propellant is used as the oil-phase, leading to particles with a network-like morphology and irregular shape. This specific particle nature provides a low area of contact between the particles compared with commonly spray-dried powders. The idea was that due to decreased cohesive forces between the particles a much lower aggregation tendency might be obtained. This lower surface energy was thought to increase the flowability and, finally, the respirable fraction of the powders.

2. Materials and methods

2.1. Materials

Salbutamol sulphate (Polfa S.A. Poznan, Poland) was used as a water soluble model drug. Water was used in double-distilled quality. 1,1,1,2,3,3,3-Heptafluorpropan (Solkane® 227 Pharma, Solvay AG, Hannover, Germany) and dichloromethane (VWR International GmbH, Darmstadt, Germany) were used as lipid-phase and emulsified with hydrated egg phosphatidylcholine (PC) (Phospholipon® 100 H, Nattermann Phospholipid GmbH, Cologne, Germany) or dipalmitoylphosphatidylcholin (DPPC) (Lipoid GmbH, Ludwigshaven, Germany). Employed stabilizing agents were poloxamer 188 (Lutrol® F 68, BASF AG, Ludwigshaven, Germany) and calcium chloride dihydrate (VWR International GmbH, Darmstadt, Germany). Other ingredients like lactose and 2-hydroxypropyl-beta-cyclodextrine (HPCD) (both VWR International GmbH, Darmstadt, Germany) were also used to modify powder characteristics.

The chosen batch numbers for the different formulations (Table 1) indicate the composition of the used formulations (e.g. HPCD-20-MeCl$_2$-30-Pol-1

Table 1
Composition of the investigated formulations

Ingredients	Batch no.												
	Pol-0.7	Pol-1	Pol-1.5	DPPC-Pol-0.7	DPPC-Pol-1	Lact-20-Pol-0.7	Lact-20-Pol-1.5	HPCD-20-Pol-1	HPCD-20-Pol-1.5	$MeCl_2$-30-Pol-1	$MeCl_2$-30-Pol-2	HPCD-20-$MeCl_2$-30-Pol-1
Salbutamol sulphate	+	+	+	+	+	+	+	+	+	+	+	+
Phospholipon® 100 H	+	+	+	–	–	+	+	+	+	+	+	+
DPPC	–	–	–	+	+	–	–	–	–	–	–	-
Calcium chloride	+	+	+	+	+	+	+	+	+	+	+	+
Poloxamer 188 (%)	0.7	1	1.5	0.7	1	0.7	1.5	1	1.5	1	2	1
HPCD (%)	–	–	–	–	–	–	–	20	20	–	–	20
Lactose (%)	–	–	–	–	–	20	20	–	–	–	–	–
Dichloromethane (%)	–	–	–	–	–	–	–	–	–	30	30	30
Solkane® 227	+	+	+	+	+	+	+	+	+	+	+	+
Water	+	+	+	+	+	+	+	+	+	+	+	+

Ingredient is included (+), ingredient is not included (–).

contains HPCD 20%, dichloromethane and poloxamer 1%).

2.2. Methods

2.2.1. Preparation of the respirable particles

An emulsion was prepared for the spray-drying process, where the aqueous phase contained 1.015 g hydrated egg phosphatidylcholine, 0.7854 g salbutamol sulphate, 0.0196 g poloxamer 188 and 0.14 g calcium chloride dihydrate. The aqueous phase was homogenized three times with an Ultra-Turrax T25 (IKA-Labortechnik, Staufen, Germany) at 8,000 rpm and was then stirred for 8 h at room temperature for hydration of the phosphatidylcholine. The aqueous phase was then weighed into a pressure-resistant glass can and sealed with a continuous-spray valve. For formulations containing dichloromethane, dichloromethane was also added into the glass container before crimping. Solkane® 227 pharma was then added into the crimped vessel by means of a pamasol P2016 filling machine (pamasol W. Mäder AG, Pfäffikon, Switzerland) and emulsified with the aqueous phase by gentle shaking.

The prepared emulsion was then spray-dried with a Büchi 190 Mini Spray-Dryer (Büchi AG, Flawil, Switzerland) equipped with a spraying nozzle that fits to the pressurized canister. The following conditions were used during spray-drying: inlet temperature = 120 °C, outlet temperature = 59 °C, aspirator = 100%. The spray-dried powder had a calculated drug load of 40.1%.

2.2.2. Particle size

The volume particle size distribution was measured with a Sympatec HELOS laser diffractometer (Sympatec GmbH, Clausthal Zellerfeld, Germany) in dry powder form after dispersing with compressed air (2 bar). The particle size distribution is characterized by the x_{10}, x_{50} and the x_{90} value, giving the percentage undersize. Values presented are the average of at least 3 determinations, error bars indicate the standard deviation (S.D.).

2.2.3. Scanning electron microscopy (SEM)

Visualisation of particle size and morphology was achieved by scanning electron microscopy. Scanning electron micrographs were taken using a Philips XL 20

(Philips, Eindhoven, The Netherlands). Samples were fixed on a aluminium stub with conductive double-sided adhesive tape (Leit-Tabs; Plano GmbH, Wetzlar, Germany) and sputter-coated with gold in an argon atmosphere (50 Pa) at 50 mA for 50 s (Sputter coater; Bal-Tec AG, Liechtenstein).

2.2.4. Bulk density

Bulk density was measured by filling the powder in a 10 ml-measuring cylinder with a funnel (Ph. Eur., 2004).

2.2.5. Specific surface area

The specific surface area was determined by gas adsorption, the BET multipoint method, in relative pressure range of 0.05–0.25 (p/p_0). The surface area analyzer Gemini-2360 (Micrometrics Instrument Corporation, Norcross, USA) was used. Powder samples were prepared under Helium atmosphere for 24 h at 25 °C and 1.2 bar.

2.2.6. Aerodynamic particle-size analysis

The aerodynamic particle size distribution was determined with a multi-stage liquid impinger, MSLI (Erweka GmbH, Heusenstamm, Germany). The powder was delivered into the impinger by means of an application system (Fig. 1). The flow rate was adjusted to a pressure drop of 4 kPa as typical for inspiration by a patient (Shekunov et al., 2001) resulting in a flow rate of 82 l/min. Without using any inhaler or excipients the pure powder characteristics were analyzed with this method. Drug deposition in the throat, the four stages and the filter (stage 5) was determined by high-pressure liquid chromatography (HPLC) analysis. All samples were analyzed in triplicate.

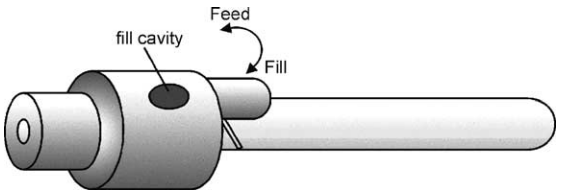

Fig. 1. Application system for drug application into the MSLI. The powder is dispersed into the air stream by rotating the fill cavity from the “fill” to the “feed” position.

2.2.7. HPLC

The HPLC system consisted of a Gynkotek High Precision Pump model 300 (Gynkotek, Munich, Germany), a Kontron HPLC Autosampler 360, a Kontron HPLC Detector 430 (Kontron Instruments, Milano, Italy) and a LiChrospher 100 RP 18 column (5 μm, 125 mm; VWR International GmbH, Darmstadt, Germany). The peak areas were integrated using a computer-controlled software (Data System 450; Kontron Intruments). Samples of 80 μl volume were injected. A methanol/water mixture was utilized as the mobile phase, consisting of 61.5 ml phosphate buffer (0.1 M H_3PO_4 + 0.2 M NaH_2PO_4), 1.1 g 1-heptanesulfonic acid sodium salt monohydrate, 400 ml methanol and 538.5 ml water. Methanol (VWR International GmbH, Darmstadt, Germany) was of HPLC and water of double-distilled quality. Using a flow of 1.2 ml/min salbutamol sulphate was detected at 280 nm after a retention time of 2.5 min. The calculation of the drug on each stage was done by using an external standard.

3. Results

Different powder compositions were formulated with particular focus on the influence of the excipients on the physicochemical and aerodynamic characteristics of the powders. Table 1 gives an overview of all powder formulations compared. All batches include the drug salbutamol sulphate and the emulsifier Phospholipon® 100 H in the same amount, except for the batches DPPC-Pol-0.7 and DPPC-Pol-1, where dipalmitoylphosphatidylcholine is employed instead of Phospholipon® 100 H in order to analyze the effect of these emulsifiers on the particle properties. Calcium chloride as a stabilizing agent is also included in a fixed concentration as it elevates the glass transition of the solid material. Some batches are produced by using further excipients like lactose in Lact-20-Pol-0.7 and Lact-20-Pol-1.5 (20% lactose) or 2-hydroxypropyl-beta-cyclodextrine in HPCD-20-Pol-1 and HPCD-20-Pol-1.5 (20% HPCD). Lactose and HPCD should function as bulking excipients in these batches, so that the effect of a filling agent on the Phospholipon® 100 H-or DPPC-composed particles could be seen. Another stabilizing agent is poloxamer 188. As preliminary results indicated that

poloxamer plays a special role concerning the particle morphology, it was added in increasing amounts to the formulations.

The spray-drying emulsion was always composed of the same amount of Solkane® 227 and water, except for the batches $MeCl_2$-30-Pol-1, $MeCl_2$-30-Pol-2 and HPCD-$MeCl_2$-30-Pol-1 which additionally contained 30% dichloromethane in order to see the effect on the particles by reducing the vapour pressure of the propellant.

3.1. Physicochemical characteristics

The particle size distribution measured in compressed air (Fig. 3) looks nearly similar for all powder formulations exhibiting an x_{50} value below 5 μm, except for the powder containing 2% poloxamer 188 which is prepared with the help of dichloromethane ($MeCl_2$-30-Pol-2) and shows an x_{50} value of 6.7 μm. Spray-dried powders containing DPPC instead of Phospholipon® 100 H show a significantly ($P < 0.01$) tighter particle size distribution as it is represented by the x_{10} and x_{90} values (DPPC-Pol-0.7, DPPC-Pol-1), as well as the powders containing lactose or HPCD (Lact-20-Pol-0.7, Lact-20-Pol-1.5, HPCD-20-Pol-1). Fig. 2 exemplarily presents the cumulative size and density distribution of the powder batch HPCD-20-$MeCl_2$-30-Pol-1 (two consecutive batches). The turning-point of the cumulative size distribution as well as the maximum of the particle size density distribution support the related x_{50} value given in Fig. 3 where the x_{10}, x_{50} and x_{90} quantiles of the particle size distribution are listed. The size distribution data are confirmed by the SEM photographs (Fig. 4). Morphologically, the particles including 0.7% poloxamer (A) and 1.5% poloxamer (B) have a spherical but also deformed shape. The exchange of Phospholipon® 100 H for DPPC results in more spherical particles which are less deformed (C and D). Moreover the latter particles (C and D) are less thin-walled leading to heavier particles with less flowability as it is described later.

Particles were also prepared with the addition of HPCD (E and F). The resulting particles are deformed and have a very thin shell, ruptured by a large blow-out hole. Due to this kind of morphology the particles become very light as it is confirmed by the bulk density measurements (Fig. 5). Creating even lighter particles was possible by lowering the vapour–pressure of the lipid-phase with the addition of 30% dichloromethane. The resulting particles (Fig. 4 G) show a spherical and also network-like texture. They exhibit even a translucent appearance on SEM photomicrographs. The bulk density of this powder was about 0.02 g/cm3 (Fig. 5,

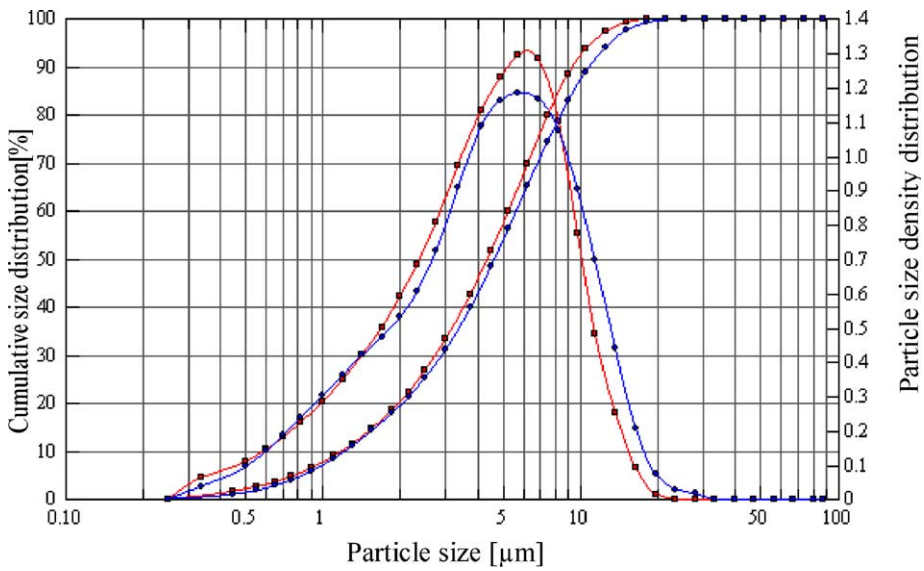

Fig. 2. Volume particle size distribution of batch HPCD-20-$MeCl_2$-30-Pol-1.

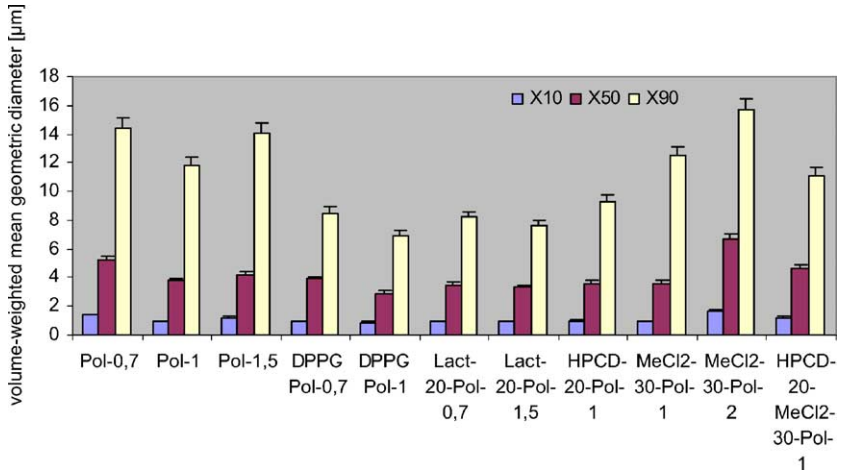

Fig. 3. Particle size distribution of the powders produced with the modified spraying technique (error bars = S.D.).

$MeCl_2$-30-Pol-1). The network-like structure of the particles also results in a high specific surface area (Fig. 5).

The lower the bulk density is, the higher is the specific surface area. Especially those particles prepared by lowering the vapour–pressure of the propellant during the spray-drying process (with the help of dichloromethane) show a very low bulk density and a high specific surface area (Fig. 5, $MeCl_2$-30-Pol-1, $MeCl_2$-30-Pol-2), followed by the particles designated as Pol-1 and HPCD-20-$MeCl_2$-30-Pol-1 (Fig. 5). Pol-1-particles were prepared like the $MeCl_2$-30-Pol-1-particles, but without adding dichloromethane to the hydrophobic phase of the emulsion. The positive effect of dichloromethane in combination with Solkane® 227 on the bulk density and specific surface area has to be seen in the changed morphology of the particles. Another approach to modify the particle properties was the addition of filling agents like HPCD that might influence the morphology of the particles in the way of getting an even more network-like appearance of the particles. The powders named as HPCD-20-Pol-1 and HPCD-20-Pol-1.5 (Fig. 5) contain HPCD but were prepared without dichloromethane. The resulting particles show a higher bulk density and a lower specific surface area. The use of dichloromethane in this solid-composition led to the particles HPCD-20-$MeCl_2$-30-Pol-1. The increase in the bulk density and the reduction of the specific surface area resulting from the addition of HPCD in the HPCD-20-Pol-1- and HPCD-20-Pol-1.5-formulations could be compensated by lowering the vapour–pressure of the propellant by dichloromethane as it was found for the HPCD-20-$MeCl_2$-30-Pol-1-formulations (Fig. 5).

3.2. Aerodynamic behaviour

Besides the particle size of a drug powder, the deagglomeration behaviour in an air stream as well as the flowability are important to get an idea, how the powder deposits in the lungs and how the drug delivery to the lungs might occur. The relationship of the geometric diameter and the aerodynamical diameter of large porous particles with a low bulk density are well documented in the literature (Edwards et al., 1998). Accordingly, it is possible to enhance the aerosol efficiency by reducing the particle density, thereby tolerating an increase of the average particle size. The aerodynamic behaviour analyzed in a multi-stage liquid impinger (MSLI) for several formulations is shown in Table 2.

The formulations including bulking excipients like lactose and HPCD (Lact-20-Pol-0.7, HPCD-20-Pol-1) only show a small fine particle fraction (FPF). By increasing the amount of poloxamer 188 within these formulations, a higher FPF was observed (Lact-20-Pol-1.5, HPCD-20-Pol-1.5). Comparing different formulations that contain the same amount of poloxamer 188 (1%), the following aerodynamic behaviour was found: without adding any further excipients

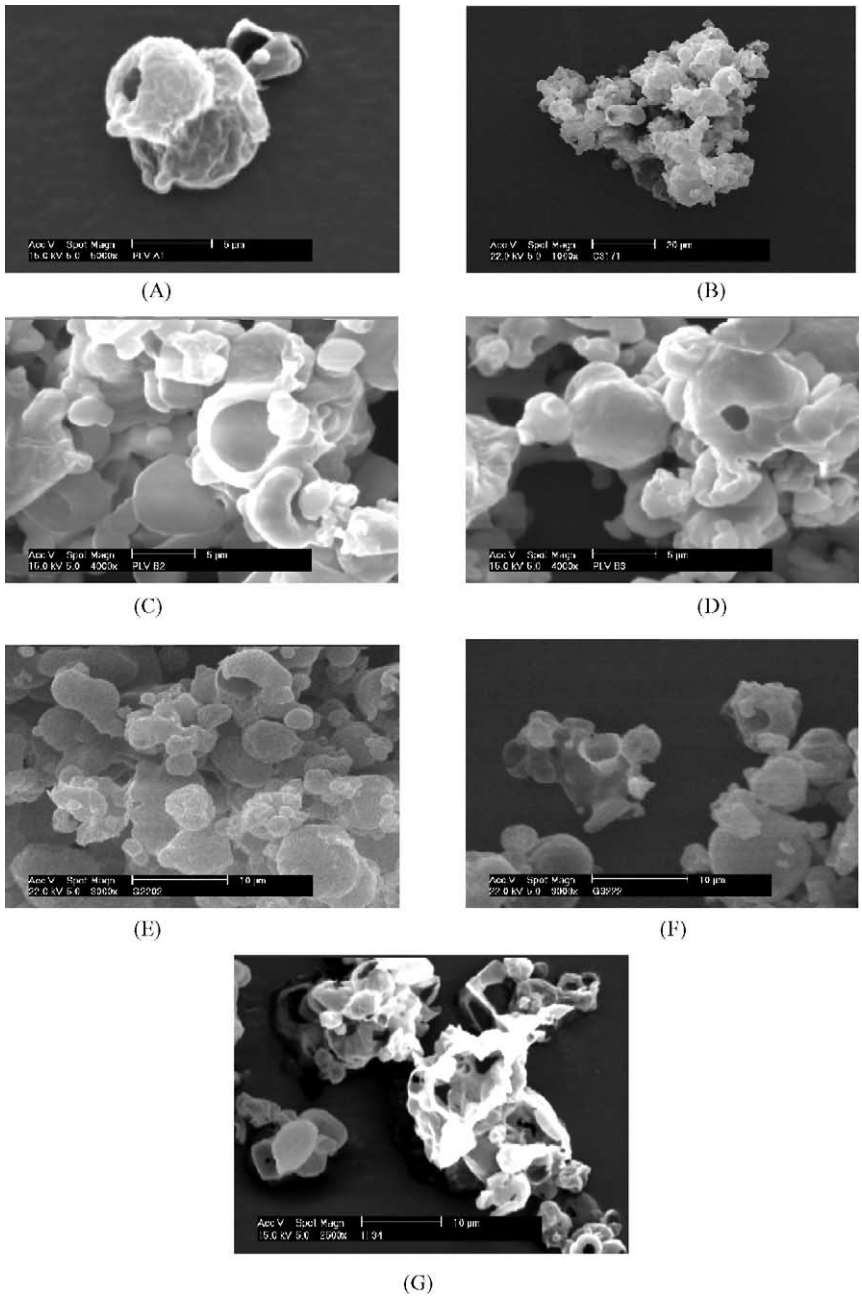

Fig. 4. SEM photographs of different spray-dried powders: (A) Pol-0.7; (B) Pol-1.5; (C) DPPC-Pol-1; (D) DPPC-Pol-1.5; (E) HPCD-20-Pol-1; (F) HPCD-20-Pol-1.5; (G) $MeCl_2$-30-Pol-1.

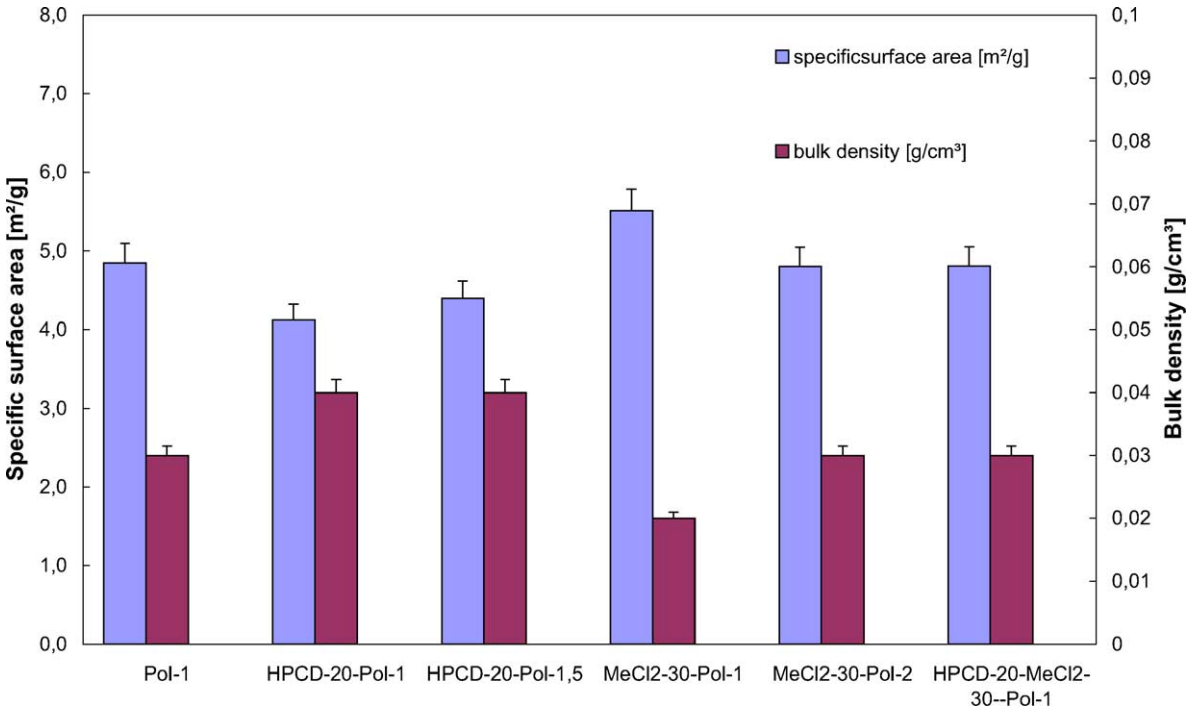

Fig. 5. Specific surface area and bulk density of the prepared powders (error bars = S.D.).

a FPF about 40.7% was received (Pol-1) whereas the particles including HPCD exhibit a much lower FPF of 20.1% (HPCD-20-Pol-1). These two particle formulations were also prepared with the help of dichloromethane leading to the powders $MeCl_2$-30-Pol-1 and HPCD-20-$MeCl_2$-30-Pol-1. Both show a high FPF but HPCD in the HPCD-20-$MeCl_2$-30-Pol-1-powder seems to lower the FPF in comparison with the HPCD-free formulation ($MeCl_2$-30-Pol-1). It was possible to elevate the high FPF value of the powder batch $MeCl_2$-30-Pol-1 by increasing the amount of poloxamer 188 up to 2% ($MeCl_2$-30-Pol-2) resulting in a FPF of 59%. Higher concentrations of poloxamer 188 (>2%) led to highly charged particles limiting the use of poloxamer 188 to a concentration of 2%.

Table 2
Fine particle fraction of the spray-dried drug powders

Powder batches	Fraction $< 5\,\mu m$ (%)
Pol-1	40.7
DPPC-Pol-0,7	30.8
Lact-20-Pol-0,7	23.2
Lact-20-Pol-1.5	38.9
HPCD-20-Pol-1	20.1
HPCD-20-Pol-1.5	44.4
$MeCl_2$-30-Pol-1	43.3
$MeCl_2$-30-Pol-2	59.0
HPCD-20-$MeCl_2$-30-Pol-1	41.9

It was observed that increasing the amount of poloxamer 188 affects the flowability and dispersibility of the powders as higher fine particle fractions were achieved. Also, it was possible to improve the aerodynamic properties of the powders by lowering the vapour–pressure of the propellant during the spray-drying process with dichloromethane.

The use of poloxamer 188 and dichloromethane provides large particles with a low bulk density, resulting in a reduced agglomeration tendency and in high FPF values.

4. Conclusions

In this study, a modified spray-drying technique for particle engineering is presented. An emulsion

consisting of a propellant and an aqueous phase was spray-dried from a pressurized canister. The resulting powders exhibit a large surface area and a low bulk density. The main excipient utilized for the particle formation is hydrated phosphatidylcholine which is endogenous to the lung. The propellant used for the spray-drying process led to a special network-like structure of the produced particles and a low bulk density of 0.02 g/cm^3. Due to the particle properties, good powder flowability was observed, making the powders ideally suitable for use in carrier-free dry powder inhalers.

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