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European Journal of Pharmaceutics and Biopharmaceutics 63 (2006) 51–58
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Preparation and in vitro evaluation of lipidic carriers and fillers for inhalation

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Received 10 October 2005; accepted in revised form 4 November 2005
Available online 27 December 2005

Abstract

The present study relates to compositions of solid lipidic microparticles (SLmP), composed of biocompatible phospholipids and cholesterol, and their use as carriers or as fillers delivering drugs directly to the lungs via a dry powder inhaler (DPI). SLmP were obtained by spray-drying and were formulated as lipidic matrices entrapping budesonide or as physical blends (drug carrier). They were developed in order to improve the delivery of the active drug by the pulmonary route. The SLmP were evaluated for their physical characteristics and in vitro deposition measurements were performed using the Multi-stage Liquid Impinger (MsLI). The Pulmicort Turbuhaler® DPI (AstraZeneca) was used as a comparator product.

The SLmP appeared to be spherical low-density material characterized by a smooth surface. The mass median diameters (D(0,5)), and the volume mean diameters (D[4,3]) were tiny and ranged from 1,7 to 3,1 μm and from 2,0 to 3,9 μm, respectively. The SLmP formulations, delivered by the Cyclohaler® inhaler, were found to emit a fine particle dose (FPD) of 93–113 μg, which is very promising comparing to the FPD (68 μg) delivered by the Pulmicort Turbuhaler®.

Keywords: Inhalation; Lipid particles; Excipients; Dry powder inhaler; Drug deposition

1. Introduction

The pulmonary route presents several advantages in the treatment of respiratory diseases over other administration routes for the same drugs leading to the systemic delivery of such drugs. Drug inhalation enables a rapid and predictable onset of action and induces fewer side effects than administration by other routes [1].

Three main delivery systems have been devised for the inhalation of aerosolised drugs, namely, pressurised metered-dose inhalers (MDIs), nebulizers, and dry powder inhalers (DPIs). The latter are currently the most convenient alternative to MDIs as they are breath-actuated and do not require the use of any propellants [2,3].

The deposition site in the respiratory tract and the efficiency of inhaled aerosols are critically influenced by the aerodynamic diameter, size distribution, shape and density of particles. For an effective inhalation therapy, inhaled particles should have an aerodynamic diameter between 1 and 5 μm to reach the lower airways [2,4]. Since micronized particles are generally very cohesive and characterized by poor flow properties, drug particles in dry powder formulations are usually blended with coarse and fine carrier particles. This improves particle flow into the inhalation device (capsules) during the filling process, ensures accurate dosage of active ingredients and increases the dispersing properties of cohesive dry particles during emission [5–8]. Furthermore, the carrier particles should be chemically and physically stable and inert to the drug substance and should not exhibit harmful effects, especially on the respiratory tract. Carbohydrates, in particular lactose, are widely used as drug carriers in DPI formulations [9].

Over the last decades, attention from various research groups has focused on the use of solid lipid particles (SLP) as a transport system of considerable interest for pharmaceutical applications. Compared to more 'classical' transporters such as liposomes, micelles, or polymeric nanospheres and nanocapsules, SLP posses numerous advantages, including the possibility of increased drug stability, high drug payload, incorporation of lipophilic and hydrophilic drugs, low to non-existent biotoxicity of the carrier and few problems with

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doi:10.1016/j.ejpb.2005.11.003

respect to large scale production [10,11]. Nevertheless, this system has not yet been fully exploited for pulmonary drug delivery. Aqueous SLP dispersions could be nebulized and alternatively, SLP could be used in DPI after being blended with a 'standard' excipient such as lactose [11].

Our aim is to develop new formulations using solid lipid microparticles (SLmP) that are composed of phospholipids and cholesterol, two physiologically well-tolerated components, as a pharmaceutically acceptable filler and/or carrier in order to improve drug-targeting to the lung. Indeed, SLmP may reduce local irritation, offering good tolerance in the pulmonary tract as they are mainly constituted of biocompatible and biodegradable material [12]. SLmP can be formulated either as a lipidic matrix which entraps both water-soluble and water-insoluble drugs and allows prolonged local drug release [11] or as physical blends with the active substance improving drug deposition. Finally, the hydrophobic nature of neutral lipids (cholesterol) reduces the absorption of the ubiquitous vapour leading to a reduction in the aggregation and the adhesion of particles.

The endogenous lung surfactant is a complex mixture of lipids and proteins comprising approximately 85–90% phospholipids (of which 90% are phosphatidylcholine) and 4–7% neutral lipids, (primarily cholesterol) by weight. It is synthesized, processed, packaged, secreted and recycled by type II pneumocytes [13,14]. After performing its physical function, the great majority of the surfactant is reused, directly or indirectly, to augment cellular surfactant stores rather than being lost from the alveolar compartment.

Recycling of phospholipids, proteins, and other components in exogenous surfactants by type II cells is known to occur [15]. Furthermore, clinical studies using Survanta®, a pulmonary surfactant intended for intratracheal use (Abbott/Ross laboratories, USA) in the prevention and treatment of respiratory distress syndrome (RDS, hyaline membrane disease) in premature infants, have shown that the rates of complication were no different in treated and in control infants, and that none of the complications were attributable to Survanta® [16].

In the present paper, micronized particles of budesonide (a non-halogenated glucocorticoid related to triamcinolone hexacetonide) have been chosen as drug model.

2. Materials and methods

2.1. Materials

Budesonide was supplied as a micronized powder (at least 99% by weight of the particles have a size lower than 5 μm) from CHEMO Iberica S.A. (Spain). Cholesterol was purchased from Bufa (The Netherlands) and Phospholipon 90H® (PL90H: hydrogenated Soy-lecithin, with more than 90% of hydrogenated phosphatidylcholine, consisting of approximately 85% distearoyl phosphatidylcholine and 15% dipalmitoyl phosphatidylcholine) was donated by Nattermann Phospholipid GmbH (Koln, Germany). All the other ingredients used were of analytical grade.

2.2. Preparation of solid lipid microparticles

The SLmP were prepared, at laboratory scale, by spray-drying using a modified Büchi mini spray dryer B-191a (Büchi Laboratory-Techniques, Switzerland).

Spray-drying is a one-step process that converts a liquid feed (solution, coarse suspension, colloidal dispersion) to a dried particulate form. The principal advantages of spray-drying with respect to pulmonary drug delivery are the ability to manipulate and control particle size and size distribution, particle shape, and density in addition to macroscopic powder properties such as bulk density, flowability, and dispersibility.

The inlet and outlet air temperatures, in classical spray dryers, are not independently controlled. Typically, the inlet temperature is established at a fixed value and the outlet temperature is determined by such factors as the spraying and drying gas flow rates, chamber dimensions, and feed flow rate [17].

In this study, we brought some modifications to the commercial mini spray-dryer in order to improve the drying efficiency and to avoid partial melting or softening of the lipidic excipients incorporated in the SLmP formulations. The spraying gas (air) was heated, increasing the drying efficiency, and an air cooling system equipped with an air dryer generating cold air in the bottom level of the main drying chamber (as shown in Fig. 1), has permitted a decrease in the outlet temperature (and thus the generated SLmP). Furthermore, a jacketed cyclone with cold water circulation was used to cool the cyclone separator walls and thus to reduce the adhesion and/or agglomeration of the SLmP.

A previous factorial design study permitted the determination of the following optimal conditions of spray-drying for the preparation of SLmP: inlet temperature, 70 °C; outlet temperature, 29 °C; spraying air flow rate, 800 l/h heated to 55 °C; drying air flow rate, 35 m^3/h; solution feed rate, 2.7 g/min; nozzle size, 0.5 mm; cold air temperature, −5 °C, generated at 10 m^3/h; cold water circulation in the jacketed cyclone, 5 °C.

Two different types of formulations, consisting of lipid matrix and physical blends, were produced under these conditions. The matricial formulations (M), consisted of an ethanolic solution, heated to 57 °C, and containing 2.5% w/w of budesonide, cholesterol and phospholipids at different ratios (details are shown in Table 1). The physical-blend formulations (PB) consisted first in the preparation of lipid carrier particles (SLmP not including the drug) by spray-drying an ethanolic solution, heated to 57 °C, and containing 2.5% w/w of cholesterol and phospholipids at different ratios. The obtained lipid carrier particles were further physically blended to homogeneity to the micronized active ingredient in a tumbling blender (Turbula mixer, Switzerland) during 20 min at a high speed (96 rpm). The drug - lipidic excipients ratio in the SLmP formulations was 2:98 (w/w).

It should be noted that a content uniformity test was conducted for both types of SLmP formulations using a conventional invasive sampling method. The assay was carried out by a suitable validated analytical HPLC method

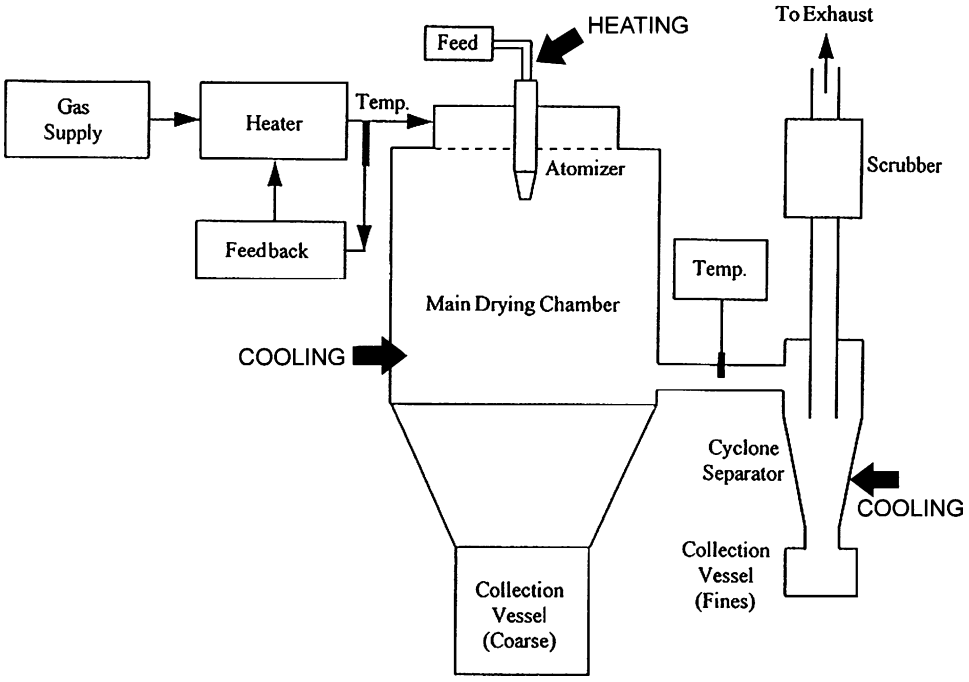

Fig. 1. Schematic representation of the modified Büchi B-191mini spray-dryer (the spraying gas is heated while the bottom level of the drying chamber and the cyclone separator wall are cooled).

(cf. Section 2.7). The mean active drug content ranged between 99 ± 2 and $101 \pm 3\%$ for the M, and between 94 ± 5 and $103 \pm 3\%$ for the different PB formulations.

2.3. Characterization of particle shape by scanning electron microscopy

The morphology of the particles was evaluated by scanning electron microscopy, using a JSM-610 microscope (EDAX CDV 'LEAP' detector, Jeol, Japan). The powders were scattered onto a thin film of a two-component epoxy resin and coated with a platinum layer. Acceleration during observation was 15 kV.

2.4. Particle size measurement by laser diffraction

Particle size distribution was measured with a Mastersizer 2000 laser Diffractometer, using a dry sampling system (Scirocco 2000, Malvern, UK) with a suitable SOP (standard operating procedure). The Mie theory was applied for calculations of the scattering matrix as it provides less biased particle-size distributions for small particles that have a diameter below 50 μm than the Fraunhofer approximation. The refractive index values for the lipidic material (real and imaginary parts for the used wavelength) were 1.6 and 0.1, respectively. The size of the particles was expressed in terms of the mass median diameter (D(0,5)), i.e. the size in microns at which 50% of the sample is smaller and 50% is larger, and the volume mean diameter (D[4,3]). Samples of about 50 mg of powder were measured in triplicate.

2.5. Evaluation of flow characteristics by tapped density tester

Bulk and tapped densities were measured using a tap density tester (Stampfvolumeter, STAV 2003, Jel, Germany). The apparent volume occupied by a mass of powder of about 1 g, carefully placed into a 10 ml graduated cylinder, was determined before and after packing (tapped more than 500 times in order to obtain the closest packed densities). Bulk and tapped density values allow the determination of the Carr's compressibility index by the formula:

$$\text{Carr's Index}(\%) = \frac{\text{Tapped} - \text{Bulk}}{\text{Tapped}} \times 100 \quad (1)$$

2.6. Characterization of crystalline state of SLmP by differential scanning calorimetry and X-ray powder diffraction

Thermal behaviour of SLmP formulations was investigated using a Perkin–Elmer DSC-7 differential scanning

Table 1
Composition of the Matricial (M) and the Physical Blend (PB) SLmP formulations

Formulation	Cholesterol (% w/w)	Phospholipon 90H (% w/w)	Budesonide (% w/w)
M1	97.9	0.1	2
M2	90	8	2
PB1	99.9	0.1	2 in a tumbling blender
PB2	95	5	
PB3	90	10	
PB4	75	25	
PB5	66	34	

calorimeter/TAC-7 thermal analysis controller with an Intracooler-2 cooling system (Perkin–Elmer Instruments, U.S.A.). Samples of about 3 mg were placed in 50 μl perforated aluminium pans and sealed. Heat runs for each sample were set from 10 to 270 °C at 5 °C/min, using nitrogen as the blanket gas. The apparatus was Indium–Cyclohexane calibrated.

X-ray powder diffraction (XRPD) is another powerful and widely-used tool for crystalline state evaluation. Diffraction patterns of lipid excipients and SLmP were determined using a Siemens Diffractometer D5000 (Siemens, Germany), with a Cu line as the source of radiation (WL1 = 1,5406 A, WL2 = 1.54439 A), and standard runs using a 40 kV voltage, a 40 mA current and a scanning rate of 0.02 °/min over a 2θ range of 2–70 °.

2.7. In vitro assessment of aerosol particles

The fine particle dose (FPD) and particle size distribution were determined by the method described in the European Pharmacopoeia 5 for the aerodynamic assessment of fine particles, using Apparatus C—Multi-stage Liquid Impinger (MsLI). A dry powder inhalation device (Cyclohaler®, Novartis, Switzerland) was filled with a No. 3 HPMC capsule (Capsugel, France) loaded with 10 mg of powder (200 μg budesonide). The in vitro deposition test was also performed on a marketed form of budesonide (Pulmicort® Turbuhaler® 200 μg, AstraZeneca, Sweden), used as a comparator. The airflow rate, corresponding to a pressure drop of 4 kPa and drawing 4 L of air through the device, was determined by the test of the uniformity of the delivered dose for each inhaler. The test was conducted at a flow rate of 100 L/min for 2.4 s and at 60 L/min for 4 s for the Cyclohaler® and the Pulmicort® Turbuhaler®, respectively. At least three fine particle determinations were performed on each test substance and analyses were carried out using a suitable validated analytical HPLC method.

The drug quantification system consisted of a high-performance liquid chromatography (HP 1100 series, Agilent Technologies, Belgium), equipped with a quaternary pump, an autosampler, an oven heated to 40 °C and a variable wavelength UV detector set at 240 nm. The separation system, as prescribed in the budesonide monograph, (Eur. Ph., 5th. Ed., 2005), was a 12 cm × 4,6 mm stainless steel (5 μm particle size) reversed-phase C_{18} column (Alltima, Alltech, Belgium). Mobile phase (acetonitrile–phosphate buffer solution adjusted to pH 3.2 with phosphoric acid, 32:68) was run at a flow rate of 1.5 ml/min. The quantity of the test substance deposited on each stage was determined from the HPLC analysis of the recovered solutions. Starting at the filter, a cumulative mass deposition (undersize in percentage) vs. cut-off diameter of the respective stages was derived. The calculation by interpolation of the mass of active ingredient with an aerodynamic diameter of less than 5 μm then gave the fine particle dose (FPD). It is considered to be directly proportional to the amount of drug able to reach the pulmonary tract in vivo: consequently, the higher the value of the FPD, the deeper the estimated lung deposition will be.

3. Results and discussion

3.1. Evaluation of the physical properties of aerosol particles

The characterisation of the physical and the thermal properties of formulations prepared by spray drying is a very important factor in determining the crystalline nature of the product and thus giving an expectation of the long term physical and chemical stability of the preparation. As the drug content of the SLmP formulations evaluated in this study is quite low (2% w/w) and the sensitivity of classical methods used to evaluate the crystallinity of particles is limited, this part of the study was specifically aimed at evaluating the crystalline nature of the lipidic excipients. Nevertheless, it was proved by both DSC and PXRD that the treatment of pure budesonide by spray drying induces its transformation into an amorphous form (data not shown). Indeed, as it is well known that spray-drying gives generally relatively low yields of crystalline products [17,18] because it uses very strong drying conditions that evaporate droplets rapidly, the budesonide particles embedded in the lipidic matrix probably became amorphous due to insufficient time for crystallization. Therefore, the stability of the drug in the SLmP formulations might be critical, more particularly in the matrix formulations, where the drug is homogeneously distributed in the lipidic excipients, probably in an amorphous state. The long-term stability of SLmP formulations will obviously be evaluated using an appropriate analytical method.

A comparison of DSC temperature scans of cholesterol, phospholipon 90H® and different SLmP formulations (Fig. 2) reveals that interactions took place between the lipidic excipients under the experimental conditions. It can be seen from the DSC scans of the physical blend formulations that when the PL90H / cholesterol ratio increases, the endothermic peak of cholesterol shifts to a lower temperature, and a peak is shown at the melting temperature of Phospholipon 90H® in SLmP compositions containing the highest PL90H / cholesterol ratios (PB4 and PB5). For example, the melting peak of cholesterol, detected at 140 °C, shifts to about 139 °C for the 99.9% spray dried cholesterol (PB1), and to about 133 °C for the PB4 formulation. Moreover, a small endothermic peak corresponding to the phase transition temperature of Phospholipon 90H (T_c around 54 °C) is also observed in the SLmP formulations PB3, PB4 and PB5. This also suggested a transformation of phospholipids in an amorphous form under the spray drying process.

On the other hand, the X-ray powder diffraction patterns (Fig. 3) show that the spray-drying process did not completely affect the crystalline form of cholesterol. The peaks that represent the spray dried samples (both M2 and PB2) (Fig. 3a) correspond to those of the original cholesterol (Fig. 3c) but differ in intensity, meaning that the major component (in the formulations) is partly amorphous. After 10 days of storage at 60 °C, the intensity of the peaks (data not shown) was slightly higher. This may signify that the spray-dried powder gradually crystallises after a long period of storage in extreme conditions. Phospholipids also tend to be partially crystalline since the XRPD pattern of PB5 (i.e. the formulation containing the

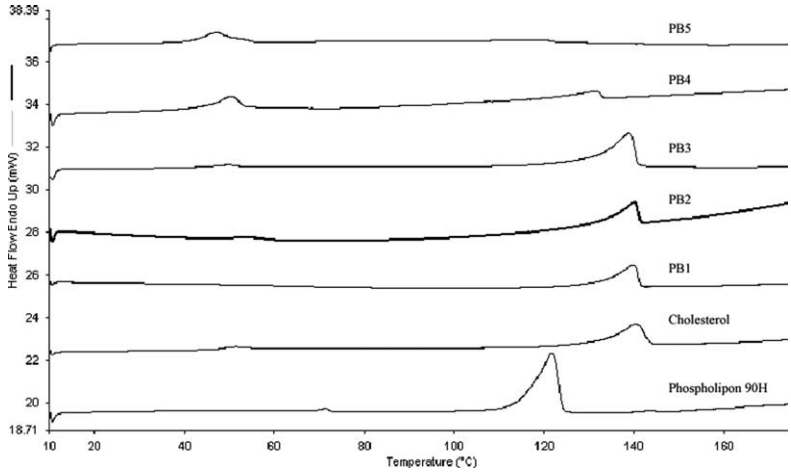

Fig. 2. DSC scans (heating curves) of the lipidic excipients and the PB formulations.

highest amount of PL90H) (Fig. 3b) reveals a peak at 2θ around 21° that could be one of the major peaks of the initial crystalline PL90H (Fig. 3c). The absence of peaks characterising budesonide could again be explained by a lack of sensitivity of the method and consequent non-detection by the X-ray technique.

The morphology of particles of lipid excipients and SLmP was investigated and the SEM micrographs are illustrated in Fig. 4. As can be seen, the bulk Phospholipon 90H® appears as aggregated flat pebbles (Fig. 4a). The original cholesterol is shown as plate-like fine crystals with diameters of approximately 500–1000 μm (Fig. 4b).

Processing the solutions of lipids by spray-drying in order to prepare lipid carrier particles yielded more regular and micron-sized particles, with a substantially different physical appearance. Indeed, spherical structures with a smooth surface consisting of many slightly fused and agglomerated tiny spherical microparticles, approximately 0.25–2 μm in diameter, can be depicted from the SEM micrographs (Fig. 4c). Moreover, the presence of budesonide in the M SLmP formulations does not affect the physical appearance of the particles in comparison to that of the lipid carrier particles (figure not shown). Finally, in the PB SLmP formulations, the irregularly-shaped micronized budesonide particles (Fig. 4d) appear to be homogenously dispersed around the lipidic carrier microspheres, with looser (drug-carrier) interactions in comparison with the bulk budesonide (Fig. 4e left and right inside).

The physical properties of the different SLmP formulations are summarized in Table 2.

The Carr's Index, which is generally considered as an appropriate method of evaluation of the flow properties of solids, was also determined from tapped and bulk density values. Carr's Index values of less than 25 are usually taken to indicate good flow characteristics; values beyond 40 indicate poor powder flowability.

The SLmP formulations prepared by spray drying, especially the M formulations, show relatively low density characteristics with interesting flow properties. The PB formulations show intermediate flow characteristics that are

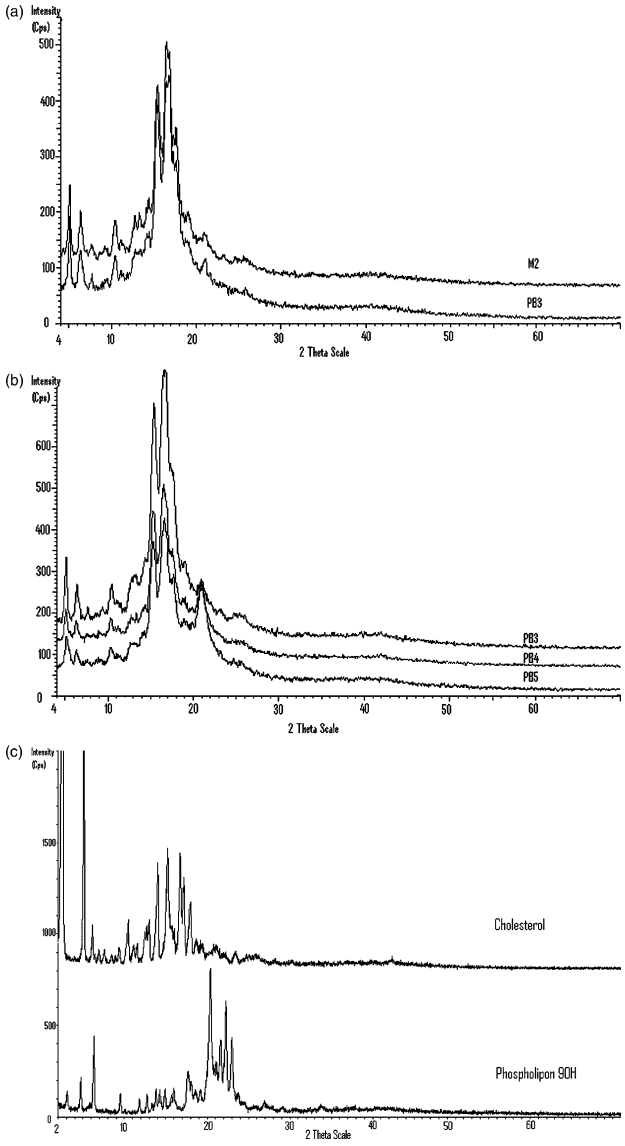

Fig. 3. X-ray powder diffraction patterns of (a) M2 formulation (upper pattern) vs. PB3 formulation (lower pattern), (b) PB products, (c) Cholesterol and phospholipon90H.

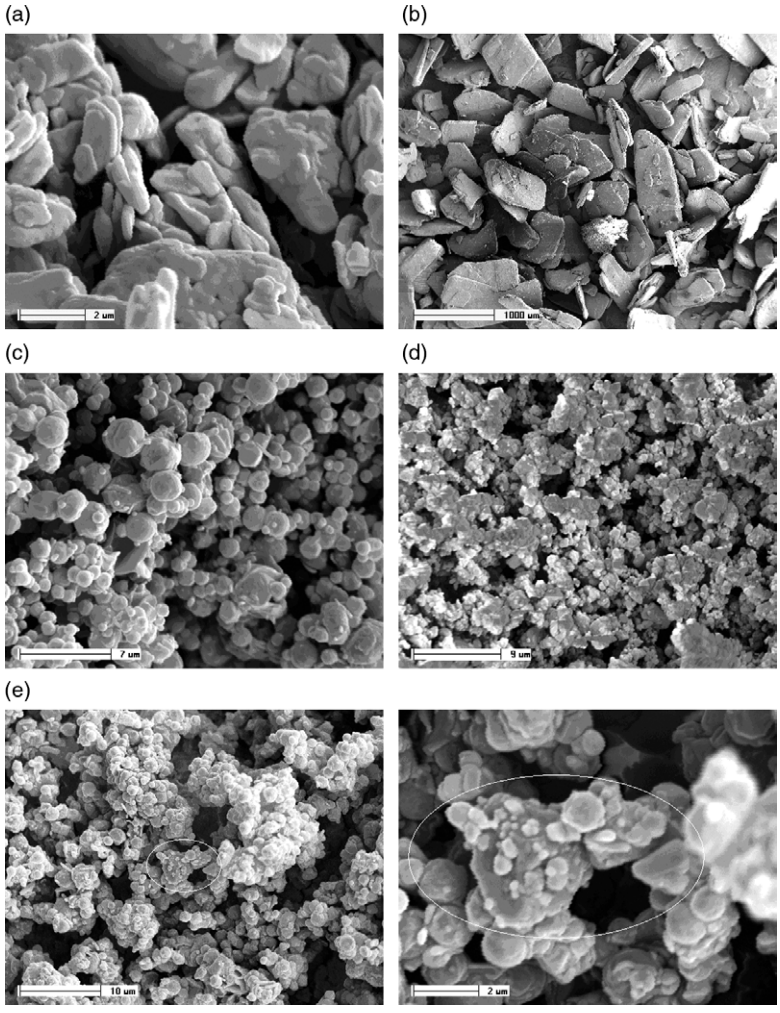

Fig. 4. SEM micrographs of: (a) bulk Phospholipon 90H® powder (magnification 10000X), (b) cholesterol (magnification 25X), (c) the spray-dried lipidic carrier (magnification 4000X), (d) budesonide (raw material) (magnification 3000X), and (e) the PB3 formulation (magnification 2500X (left) and 10000X (right)).

between those of the matrix formulations and the bulk budesonide. Nevertheless, as described in literature, these values might be repeated on higher sample amounts (about 100 g rather than the 1 g in this study) because the reliability of the method used can be influenced by equipment specifications and working protocols [19].

Moreover, the laser diffraction results show that the particle size distributions of SLmP (Fig. 5.) are unimodal, narrow and range from 0.3 to 10 μm, with more than 90% of the particles having a diameter below 5.0 μm, which corresponds to the upper size limit required for an optimal deep lung deposition. The mass median diameters and the volume mean diameters of SLmP formulations are tiny and range from 1.7 to 3.1 μm and from 2.0 to 3.9 μm, respectively (Table 2). These values are slightly higher than those obtained for the micronized budesonide, which is produced by jet milling.

Careful examination of Table 2 shows that the mean particle size results of SLmP are influenced by the lipid composition of

Table 2
Physical properties of M and PB SLmP formulations ($n=3$)

Formulations	Tapped density (g/cm^3)	Bulk density (g/cm^3)	Carr's Index (%)	D (0,5) (μm)	D [4,3] (μm)
Budesonide (raw material)	0.308	0.208	32.5	0.85±0.03	1.05±0.03
M1	0.192	0.150	21.9	2.4±0.1	2.89±0.09
M2	0.204	0.164	19.7	2.38±0.06	2.82±0.06
PB1	0.216	0.158	26.9	2.14±0.03	2.80±0.04
PB2	0.190	0.135	28.9	2.10±0.03	2.50±0.04
PB3	0.214	0.153	28.5	1.70±0.04	2.00±0.06
PB4	0.181	0.133	26.5	1.92±0.03	2.25±0.02
PB5	0.246	0.173	29.7	3.1±0.3	3.9±0.9

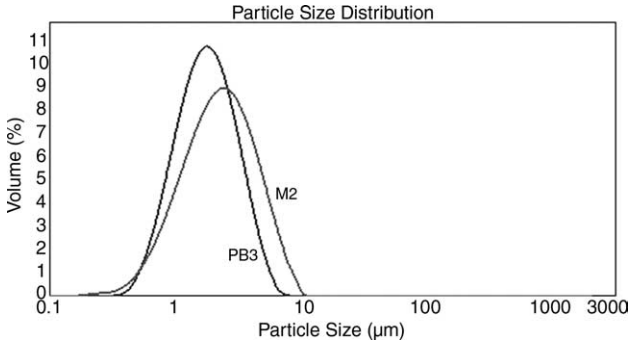

Fig. 5. Laser diffraction particle size distribution curves for M2 (right curve) and PB3 (left curve) formulations.

the formulations. More particularly, in the PB formulations (Table 2) the presence of phospholipids seems to be beneficial at relatively low contents, as the smallest mean particle size values are obtained for a cholesterol/Phospholipon ratio of 90:10. Beyond a cholesterol content of 90% (PB1 and PB2), the particles tend to grow slightly. Increasing the phospholipids content of PB formulations from 10 to 34% (PB3, PB4 and PB5) results in an increase in the mean particle size characteristics of SLmP, whereas formulations containing more than 34% of phospholipids tend to stick strongly to the cyclone separator walls of the spray dryer and thus cannot be produced by this technique. This phenomenon can be explained by the physical state of phospholipids during the spray-drying process. Indeed, the phase transition temperature (T_c) of the phospholipids plays a crucial role in the size characteristics of phospholipids-based powders produced by spray drying. The higher the phase transition temperature of the phospholipids, the lower the mass median aerodynamic diameter (MMAD) of particles [20] will be. In this respect, Phospholipon 90H® is preferred to other commercially available phospholipids, as it shows one of the highest T_c values (around 54 °C). Nevertheless, when relatively high amounts of phospholipids are present in formulations, this is not sufficient to avoid the softening of SLmP during the spray-drying process and consequently does not prevent a certain agglomeration of particles.

3.2. Fine particle dose and particle size distribution

The fine particle assessment results for the M formulations, the PB formulations and the marketed form of budesonide, represented by the FPD, are summarized in Fig. 6. It is interesting to note that the budesonide recoveries from the inhalator and the different parts of the MsLI were very large as they range between 95.1 and 101.2% of the total loaded drug (200 µg nominal dose).

The mean FPD values obtained for the different SLmP formulations were 93±7 and 96±4 µg for M1 and M2, respectively, and 105±3, 95±3, 113±5, 106±1 and 81±3 µg for PB1, PB2, PB3, PB4 and PB5, respectively. These FPD results are especially high and very promising comparing to the FPD value (68±5 µg) of Pulmicort®. The difference is considered to be statistically significant ($p<0.05$) (repeated-measures ANOVA Test).

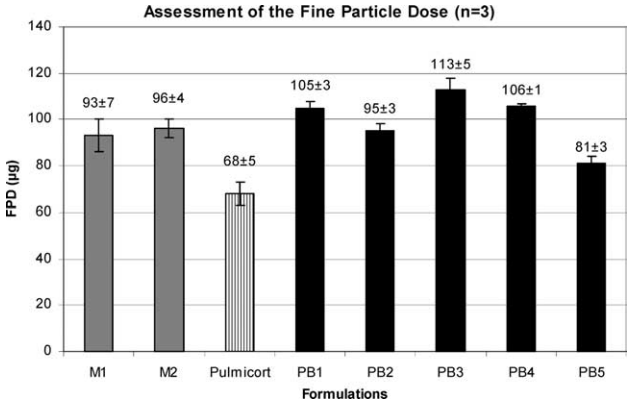

Fig. 6. The FPD (mean±S.D) assessment of the different SLmP formulations loaded with 200 µg of budesonide and Pulmicort Turbuhaler®.

The FPD results are in accordance with the particle size determinations obtained by laser diffraction, since the FPD values increase when the formulation content of Phospholipon 90H® is reduced from 34 to 10% (PB5 to PB3). Indeed, as discussed above, decreasing the Phospholipon content of the SLmP formulations to about 10% tends to reduce the mean particle size and particle agglomeration, and consequently gives a better deep lung deposition.

On the other hand, as it is shown in Fig. 7, the fine particle fraction, which roughly corresponds to the drug deposition at stages 3, 4 and the filter is higher for the PB3 than for the PB4 formulation, which is even higher than for the PB5 formulation. As discussed before, the incorporation of phospholipids in lipid formulations improves the particle size characteristics and the drug deposition (lower mean particle size and higher FPD for PB3 than for PB1). Thus, it seems that a cholesterol/Phospholipon 90H® ratio of 90:10 is the most appropriate one as it reveals the best deposition pattern and gives the highest FPD.

Moreover, examination of the deposition patterns also shows that the FPD values are higher for physical blend formulations in comparison to matrix ones. Indeed, the FPD values were 93±7 µg for M1 (D(0.5)=2.4±0.1 µm, tapped density=0.192 g/cm^3) and 105±3 µg for PB1 (D(0.5)=2.14±0.01 µm, tapped density=0.216 g/cm^3), i.e. for formulations having basically the same composition and quite similar

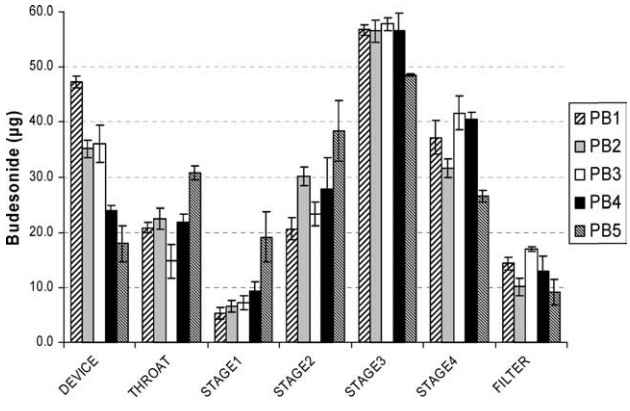

Fig. 7. In vitro deposition patterns of the PB SLmP formulations.

in terms of particle size and density, but differing in the way they are processed.

The difference between the aerodynamic behaviour and FPD values of matrix and physical blend formulations could be explained by the fact that in the first method of production, budesonide is homogeneously entrapped in the matrix and does not separate from the lipidic excipients during inhalation and when reach the lower stages of the MsLI apparatus. In contrast, budesonide particles in the PB formulations, where the drug particles are physically separated from the lipid carrier particles, disperse with the air flow energy generated during inhalation. This is because of the presence of loose interactions between the drug and the carrier particles and because of differences in particle sizes and densities. Thus, with the PB formulations, the smaller drug particles may penetrate deeper in the lung.

4. Conclusions

Given the experimental evidence reported in sections above, the use of SLmP containing cholesterol and phospholipids, offers the opportunity to improve the delivery of drugs to the pulmonary tract. SLmP appear to be a promising new pharmaceutically acceptable filler and/or carrier for dry powder inhalation products. Nevertheless, additional investigations have to be carried out in order to assess the controlled-release properties and the stability of such products, especially if the active drug is found to be amorphous. A randomised clinical trial on volunteers done in order to evaluate the efficiency and the pharmacokinetics of these formulations will be described in a new paper.

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