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Influence of formulation excipients and physical characteristics of inhalation dry powders on their aerosolization performance

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Abstract

The objective of this study was to determine the effects of formulation excipients and physical characteristics of inhalation particles on their in vitro aerosolization performance, and thereby to maximize their respirable fraction. Dry powders were produced by spray-drying using excipients that are FDA-approved for inhalation as lactose, materials that are endogenous to the lungs as albumin and dipalmitoylphosphatidylcholine (DPPC); and/or protein stabilizers as trehalose or mannitol. Dry powders suitable for deep lung deposition, i.e. with an aerodynamic diameter of individual particles <3 μm, were prepared. They presented 0.04–0.25 g/cm^3 bulk tap densities, 3–5 μm geometric particle sizes, up to 90% emitted doses and 50% respirable fractions in the Andersen cascade impactor using a Spinhaler™ inhaler device. The incorporation of lactose, albumin and DPPC in the formulation all improved the aerosolization properties, in contrast to trehalose and the mannitol which decreased powder flowability. The relative proportion of the excipients affected aerosol performance as well. The lower the bulk powder tap density, the higher the respirable fraction. Optimization of in vitro aerosolization properties of inhalation dry powders can be achieved by appropriately selecting composition and physical characteristics of the particles.

Keywords: Inhalation dry powders; Respirable fraction; Andersen cascade impactor; Excipient; Bulk tap density

1. Introduction

Inhalation aerosols offer the potential for needle-free, systemic delivery of small molecule drugs as well as therapeutic peptides and proteins. The lungs have in fact been demonstrated an efficient port of entry to the bloodstream due to: (i) the tremendous surface area of the alveoli (100 m^2), immediately accessible to drug; (ii) a relatively low metabolic activity locally, as well as a lack of first-pass hepatic metabolism; and (iii) the elevated blood flow (5 l/min) which rapidly distributes molecules throughout the body [1,2]. In order to promote the systemic absorption of the drug, aerosol particles need to reach the alveolar region of the lungs and therefore need to present an adequate aerodynamic particle size following dispersion, i.e. between 1 and 5 μm [3].

Among aerosol generation systems, dry powder inhalers present several advantages. They are propellant-free, portable, easy to operate and low-cost devices with improved stability of the formulation as

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a result of the dry state [4–6]. The challenge of any inhalation delivery system is however to generate particles with an adequate range of particle sizes. In case of dry powders, this is greatly impeded by particle aggregation which lowers the fraction that is respirable, i.e. the fraction of particles (and particle aggregates) with an aerodynamic diameter ≤ 5 μm [1,3,7,8]. Different strategies have been developed to improve the flowability of dry powders and attempt to make them behave as individual particles. These include the mixing of the drug particles with coarse lactose carrier [1,9,10], the use of compressed air to deaggregate the drug particles in a spacer chamber [11], the preparation of large and porous particles presenting low inter-particle cohesiveness [12].

In this article, we studied the parameters that governed the aerosolization performance of inhalation powder drug particles. Dry powders were prepared by spray-drying using GRAS (generally recognized as safe) excipients, i.e. (i) excipients that are FDA-approved for inhalation as lactose; (ii) materials that are endogenous to the lungs and locally present in large quantities (in order to avoid altering the normal concentrations by the external input) as albumin and dipalmitoylphosphatidylcholine (DPPC)–albumin can be considered as a model drug in the case of the delivery of therapeutic proteins as well; and/or (iii) a sugar, trehalose, or a polyol, mannitol, as alternatives to lactose [13]. Sugars and polyols possess protein stabilization properties and, in contrast to lactose, trehalose and mannitol do not exhibit a reducing character [5]. The dependence of the in vitro deposition of the aerosol on excipient type and proportion as well as on the physical characteristics of the particles, i.e. particle size, bulk tap density and aerodynamic diameter of individual particles, was evaluated in the Andersen cascade impactor.

2. Materials and methods

2.1. Chemicals

Human serum albumin (fraction V, 96–99% albumin), D-mannitol, D-trehalose dihydrate and 96% ethanol were obtained from Sigma; α-lactose monohydrate from Acros Organics (New Jersey, USA). DPPC was purchased from Lipoid (Lipoid GMBH, Ludwigshafen, Germany) and coumarin from ICN (ICN Biomedicals Inc, Ohio, USA).

2.2. Formulation of the dry powders

Dry powders were made with DPPC, albumin and a sugar (lactose or trehalose) or a polyol (mannitol) by spray-drying [13]. Albumin and the sugar or polyol were dissolved in ultrapure water. The pH was then adjusted to 7 by addition of a few droplets of NaOH 0.01N (Vel, Leuven, Belgium). DPPC and coumarin were dissolved in 96% ethanol. Coumarin, a fluorescent marker, was incorporated in all the formulations at a low load (0.1% w/w) in order to allow the quantification of the powder deposited in the Andersen cascade impactor as it is requested by pharmacopoeias [7,8]. The two solutions were then combined to form a 70, 80, 87 or 90% ethanolic solution of 0.1% or 0.5% w/v total powder concentration.

The powders were produced using a LabPlant laboratory-scale spray-dryer (LabPlant Limited, Huddersfield, UK). Solutions were pumped into the drying chamber at a rate of 10 or 20 ml/min and pneumatically atomized through a two fluids external mixing 0.5 mm nozzle using compressed air at 0.5 or 1.5 bar. The inlet temperature was established at 100 or 110°C; the outlet temperature depended on the inlet temperature and the liquid and gas flow rates, and varied between 50 and 65°C. The powders were collected and stored in a dessicator (i.e. at ambient temperature and 25% relative humidity) and analyzed within 1 week of production. Yields ranged between 10 and 30%, with the highest yields achieved with the densest powders.

In order to evaluate the reproducibility of the powder preparation, six different samples with the same composition, i.e. albumin/lactose/DPPC 20/20/60 w/w/w, were prepared under identical spray-drying and formulation parameters, i.e. an inlet temperature of 100°C, an atomization pressure of 0.5 bar, a 10 ml/min feed rate, a 70% ethanol concentration and a total excipients concentration of 0.1% w/v. The powders were then characterized. They presented bulk tap densities ranging from 0.04 to 0.08 g/cm^3 (coefficient of variation, CV, of 17%), 4.0 to 4.6 μm geometric diameters (CV=5%) and

0.9 to 1.2 μm aerodynamic diameters of individual particles (see below for definition; CV=12%).

2.3. Particle size, density and morphology

The particle diameter (*d*, mode) was determined by electrical zone sensing (Coulter Multisizer II™, Coulter Electronics, Luton, UK). The powders were suspended in saline (Isotone II, Analis, Belgium) and the suspensions vortexed for 1 min before sizing. The mode of the mass size distribution was used instead of the median, because it was shown to closely near optical and electron microscopy mass median sizes and to remain unaffected by the particle aggregates that appeared at large sizes in the Multisizer mass size distribution in case of moderately cohesive powders (e.g., powders prepared without albumin) [14]. Because the mannitol/DPPC powder was excessively cohesive, the mode from the Multisizer was indistinguishable and the particle size (mass median) was measured in this case by optical microscopy.

The powder density (ρ) was evaluated by tap density measurements [15,16]. Assuming a perfect packing, the tap density of monodisperse spheres is approximately a 21% underestimate of the particle density due to the void spaces between particles. In case of polydisperse particles, the void spaces are reduced but this is probably counterbalanced by incomplete packing [13].

The theoretical aerodynamic diameter of individual particles, d_{aer}, was calculated based on the following definition [17]:

$$d_{aer} = \sqrt{\frac{\rho}{\rho_1}} d$$

with $\rho_1 = 1$ g/cm^3.

The powder particles were viewed using a conventional scanning electron microscope (Phillips CM12/STEM, Eindhoven, Netherlands). The dry powder samples were mounted on metal plates and a 10-nm-thick gold film was sputter coated on the samples with a Balzers SCA 020 (Balzers Union, Liechtenstein) before visualization.

2.4. In vitro aerosol deposition

The pulmonary deposition of the dry powders was investigated in vitro using an Andersen cascade impactor (1 ACFM Eight Stage Non-Viable Cascade Impactor, Graseby Andersen, Atlanta, GA). The trays of the impactor were coated with an hydroxypropylmethylcellulose gel (22.5% w/v in water). A hard gelatin capsule (size 2, Capsugel) previously stored in a dessicator for at least two days, was filled to approximately 50% of its volume with the powder and placed in a Spinhaler™ inhaler (Fisons, Bedford, MA). The capsule was then pierced and the liberated powder drawn through the impactor operated at 28.3 l/min (the flow rate at which the Andersen impactor is calibrated) for a period of 10 s which allowed the aspiration of approximately 4 l of air in the apparatus, as recommended by pharmacopoeias [7,8]. The powder deposited on the different levels was recovered by immersing each tray and the stage below in 80% ethanol. The powder deposited in the throat and pre-separator was also collected. After dissolution of the particles, the fluorescence of each solution due to coumarin was determined using a Perkin Elmer Luminescence Spectrometer LS50B ($\lambda_{excitation} = 458$ nm, $\lambda_{emission} = 545$ nm).

The emitted dose (ED) was determined as the percent of total powder mass exiting the capsule. The cumulative mass of powder less than the stated size of each stage of the Andersen impactor was calculated and plotted on a log probability scale, as percent of total mass recovered in the impactor against the effective cut-off diameter. The experimental mass median aerodynamic diameter (MMAD) of the particles is defined from this graph as the particle size at which the line crosses the 50% mark and the geometric standard deviation (GSD) as $\text{GSD} = \sqrt{\frac{\text{Size } X}{\text{Size } Y}}$, where size *X* is the particle size for which the line crosses the 84% mark and size *Y* the 16% mark. The respirable fraction (RF) was calculated from the same plot as the fraction of powder emitted from the inhaler with a particle size ≤ 5 μm [7,8].

The inter-day reproducibility of the Andersen cascade impactor technique was estimated by performing five measurements on the same powder. ED equalled 75±7% (CV=9%), RF 36±6% (CV=17%), MMAD 6.3±0.7 μm (CV=11%) and GSD 1.9±0.1 (CV=5%). The reproducibility of the preparation of the dry powders in terms of aerosolization

performance was assessed with the six powders previously described for their reproducibility in density, size and d_{aer} (see above). ED was 76±4% (CV=5%), RF 35±4% (CV=11%), MMAD 6.6±0.5 μm (CV=8%) and GSD 2.1±0.4 (CV=19%).

2.5. Data analysis

Each spray-drying run was reproduced three to six times in the study of the effect of particle composition and spray-drying parameters on particle diameter, tap density and shape. Particle geometric diameters and tap densities are presented as average values (±S.D.) of the different runs in Fig. 4. Electron micrographs of representative particles are shown in Fig. 1. Emitted doses, respirable fractions, MMAD, geometric sizes and tap densities are average values of two successive measurements (Figs. 2–3 and 5–6). The particle diameters, tap densities and respirable fractions were compared by the ANOVA test ($P<0.05$; Figs. 2–4). The data shown in Figs. 5 and 6 were analyzed by Pearson correlation. All the data were validated by the Dixon test.

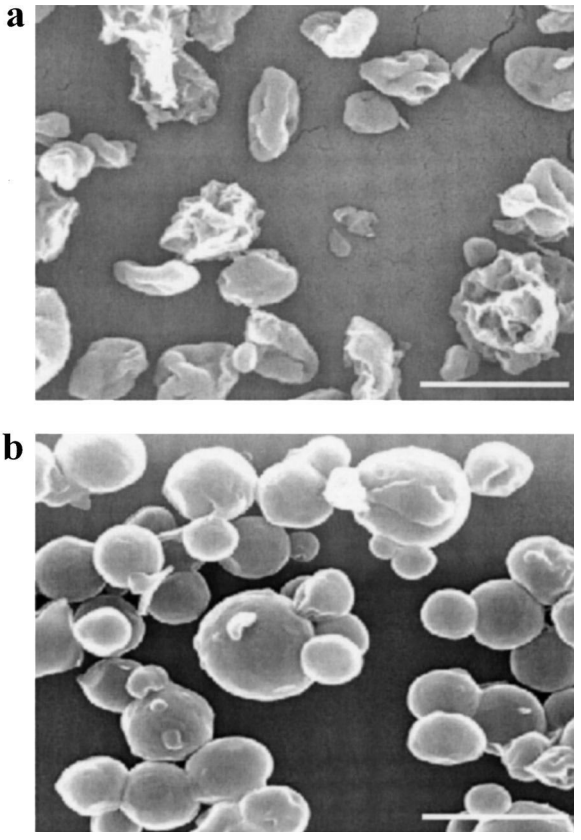


Fig. 1. Scanning electron microscope images of particles made with (a) or without (b) albumin. The powders were prepared with albumin/trehalose/DPPC (20/20/60, w/w/w; a), or lactose/DPPC (40/60, w/w; b). Scale bars=5 μm.

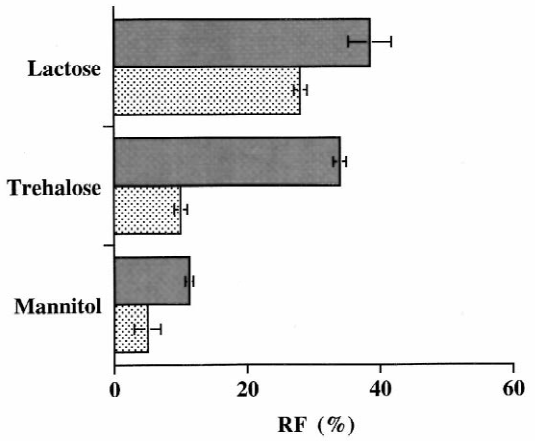
3. Results

3.1. Preparation of the dry powders

In a first step, the dependence of the dry powder physical characteristics, i.e. particle size, tap density and morphology, on the formulation and spray-drying parameters was explored. As reported previously, the powder composition and solution properties most greatly affected particle characteristics [13,18,19].

The addition of albumin to the dry powders changed particle morphology as visualized by electron microscopy from smooth and spherical to extremely porous and sponge-like shape (Fig. 1). The type of sugar or polyol incorporated did not affect the particle size, density and overall morphology of the powders ($P>0.05$; Fig. 2, data not shown). Varying DPPC proportion from 80 to 50% by weight in albumin/lactose/DPPC powders did not affect particle size and density ($P>0.05$; Fig. 3a), but removing it from the formulation led to denser and smaller size particles ($P<0.05$; data not shown). Varying albumin load from 10 to 40% in powders made of 60% DPPC had little impact on size and density ($P>0.05$; Fig. 3b), but removing the protein from the formulation led to heavier powders ($P<0.05$; Fig. 2).

Increasing the concentration of the excipients in the solution to be spray-dried as well as increasing its ethanol content greatly increased bulk powder density ($P<0.05$), but did not affect particle size ($P>0.05$; Fig. 4). The spray-drying parameters, feed rate, pressure of the compressed air, had little impact on powder properties; but the inlet temperature, for which an increase tended to make the powders heavier ($P>0.05$; data not shown). Overall, in the experimental conditions tested, the powders could be designed with the desired bulk tap density by



ED (%)	d (μm)	ρ (g/cm^3)	d_{aer} (μm)
81	4.2	0.08	1.2
72	4.0	0.12	1.4
79	4.8	0.05	1.1
55	4.0	0.10	1.3
74	4.6	0.11	1.5
64	4.5	0.18	1.9

Fig. 2. Influence of the sugar, polyol and albumin on dry powders respirable fraction (RF). The powders were made with 60% DPPC, 20% albumin and 20% lactose, trehalose or polyol (■); or with 60% DPPC, 40% lactose, trehalose or polyol and no albumin (▨). Spray-drying was carried out with a 70% ethanolic solution of 0.1% total powder concentration, an inlet temperature of 100°C, a feed rate of 10 ml/min and a pressure of 0.5 bar. ED, dose emitted from the Spinhaler™ device; *d*, particle diameter; *ρ*, bulk powder tap density; d_{aer}, aerodynamic diameter of individual particles.

properly selecting the formulation and spray-drying parameters, i.e. with a density that could be chosen between 0.03 and 0.60 g/cm^3. In contrast, the experimental conditions had little impact on geometric particle diameters and the powders presented a size between 2.5 and 6.0 μm according to preparation, showing that less adjustment could be made on this physical property.

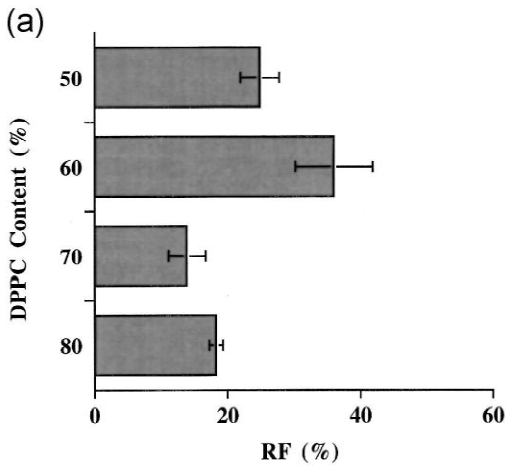
3.2. Influence of the powder composition on aerosolization properties

Based on the rules outlined in the previous paragraph, dry powders with aerodynamic diameters of individual particles, d_{aer}, smaller than 3 μm were produced. The effect of the type of excipients on the aerosolization performance of those powders was then investigated. In Fig. 2, we compared in terms of respirable fraction, powders prepared with DPPC, albumin, and two different sugars (lactose or trehalose) or a polyol (mannitol). Presenting similar densities, geometric sizes and d_{aer}, powders made with either sugar demonstrated elevated respirable fractions (RF), but the powder prepared with mannitol was less respirable ($P<0.05$). Removing albumin from the formulations led to denser powders as well as to a important decrease in RF and emitted doses ($P<0.05$); however, lactose and mannitol still presented the best to poorest aerosolization properties (Fig. 2). The particular cohesiveness of the mannitol/DPPC particles was also evident in Coulter Multisizing, which was rendered impossible due to aggregates (data not shown).

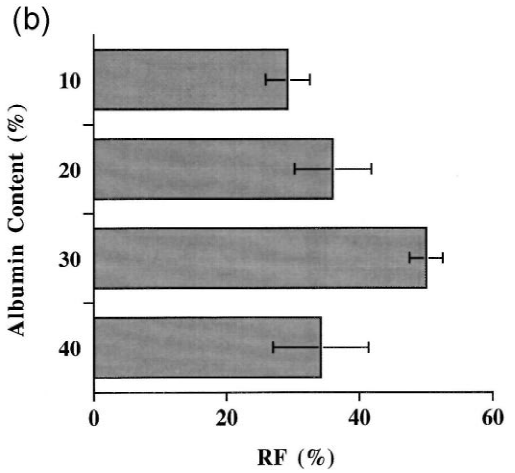
Excipients proportion greatly affected in vitro deposition as well. Powders presenting similar density, geometric size and d_{aer} were prepared with varying DPPC content. DPPC proportion influenced RF, with powders made of 60% DPPC demonstrating the best aerosolization performance ($P<0.05$; Fig. 3a). Albumin content was then varied in the dry powders keeping DPPC proportion at 60%. The amount of albumin had also an effect on in vitro deposition ($P<0.05$) and respirable fractions as high as 50±3% were reached with the formulation albumin/lactose/DPPC 30/10/60 w/w/w (Fig. 3b).

3.3. Influence of the powder tap density and particle size on aerosolization properties

The effect of the physical characteristics of the powders on their RF was studied with powders of the same composition, i.e. albumin/lactose/DPPC, 20/



ED (%)	d (μm)	ρ (g/cm^3)	d_{aer} (μm)
72	4.0	0.08	1.1
75	4.0	0.06	1.0
62	3.9	0.12	1.4
60	4.8	0.08	1.3



ED (%)	d (μm)	ρ (g/cm^3)	d_{aer} (μm)
87	4.0	0.08	1.2
75	4.0	0.06	1.0
75	4.2	0.07	1.1
59	4.8	0.04	1.0

Fig. 3. Influence of DPPC (a) and albumin (b) proportion on dry powders respirable fraction (RF). DPPC was incorporated in variable content, and albumin and lactose in equivalent amounts in (a). DPPC was maintained at a proportion of 60% and albumin was in variable amount in (b). See Fig. 2 for the spray-drying parameters and acronyms of the table.

20/60, w/w/w, prepared with varying formulation and spray-drying parameters. Decreasing the density of the powders increased their respirable fraction ($P<0.01$; Fig. 5a). The geometric diameter had no effect in the range of sizes considered ($P>0.05$; Fig. 5b). All the powders exhibited an aerodynamic diameter of individual particles suitable for deep lung deposition, i.e. <3 μm. The smaller the d_{aer}, the higher the RF ($P<0.01$; Fig. 5c).

In Fig. 6, we pooled the powders of varying proportion of excipients presented in Fig. 3 and plotted their RFs as a function of density, geometric size and d_{aer}. As in the previous case, decreasing the density greatly increased the in vitro deposition of the powders ($P<0.01$; Fig. 6a), which meant that differences in respirable fraction obtained with those powders were partly due to alterations in density. No influence of the size and d_{aer} was observed in the range of sizes studied ($P>0.05$; Fig. 6b, c).

Although the powders presented in Figs. 5 and 6 exhibited aerodynamic diameters of individual particles, d_{aer}, below 3 μm, the experimental mass median aerodynamic diameters (MMADs) measured in the Andersen cascade impactor were larger and

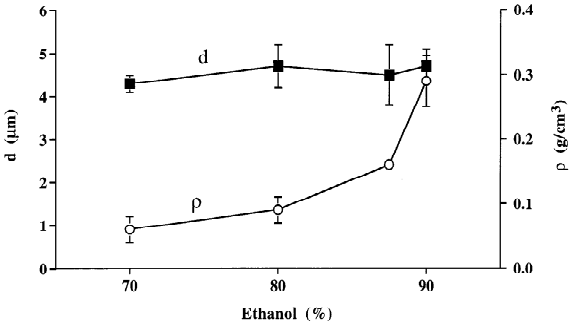


Fig. 4. Influence of ethanol concentration on geometric diameter (d, ■) and tap density (ρ, ○) of powders made of albumin/lactose/DPPC (20/20/60, w/w/w). See Fig. 2 for the other spray-drying parameters.

ranged between 4 and 11 μm, probably due to the formation of particle aggregates (Figs. 5d and 6d). The dispersion of the powders in the impactor was variable, with GSD values ranging between 1.3 and 2.8. No obvious correlation appeared between degree of dispersion and powder composition or physical characteristics.

4. Discussion

In this study, we wanted to determine the effects of formulation excipients and physical characteristics of inhalation drug particles on their aerosolization properties in order to optimize their respirable fractions. Dry powders were produced by spray-drying using GRAS excipients [13]. When formulated with an appropriate composition and adequate physical characteristics, the powders exhibited excellent aerosolization properties in the Andersen cascade impactor with emitted doses reaching 90% and

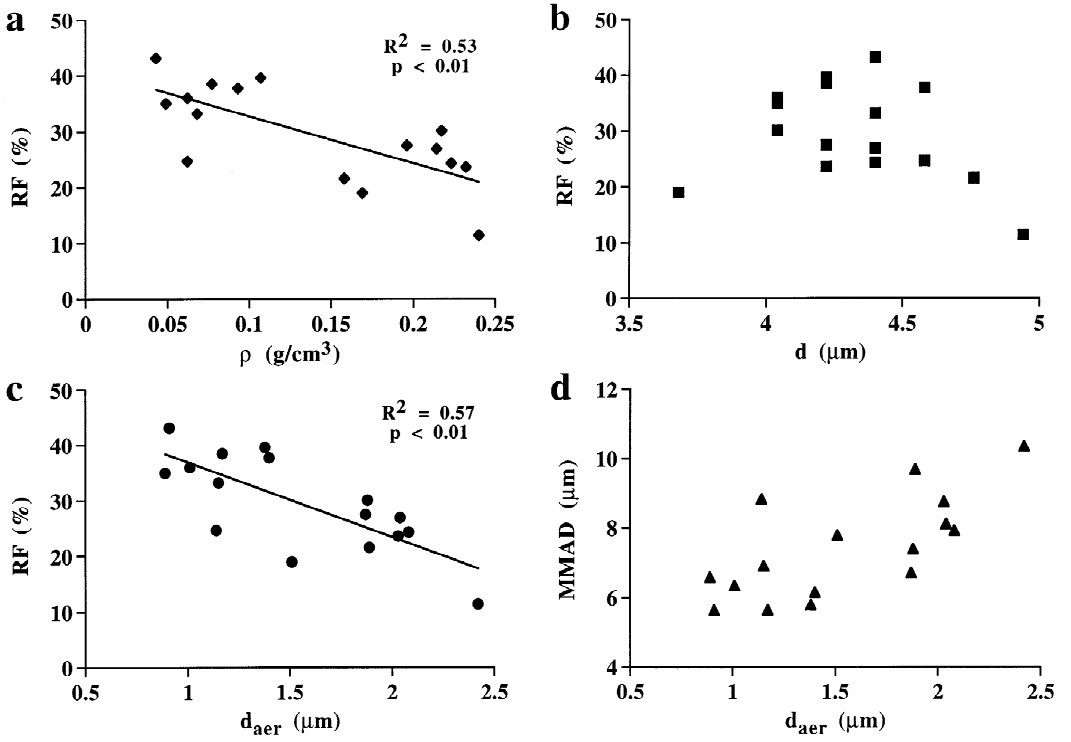


Fig. 5. Influence of tap density (ρ; a), geometric diameter (d; b) and aerodynamic diameter of individual particles (d_{aer}; c) on the respirable fraction (RF) of powders made of identical composition (albumin/lactose/DPPC, 20/20/60, w/w/w). The powders were prepared with varying spray-drying and formulation parameters. When the correlation between RF and the different parameters was significant, the regression line and the correlation coefficient are shown. In (d), the experimental mass median aerodynamic diameter (MMAD) of the powders measured in the Andersen cascade impactor is plotted versus d_{aer}.

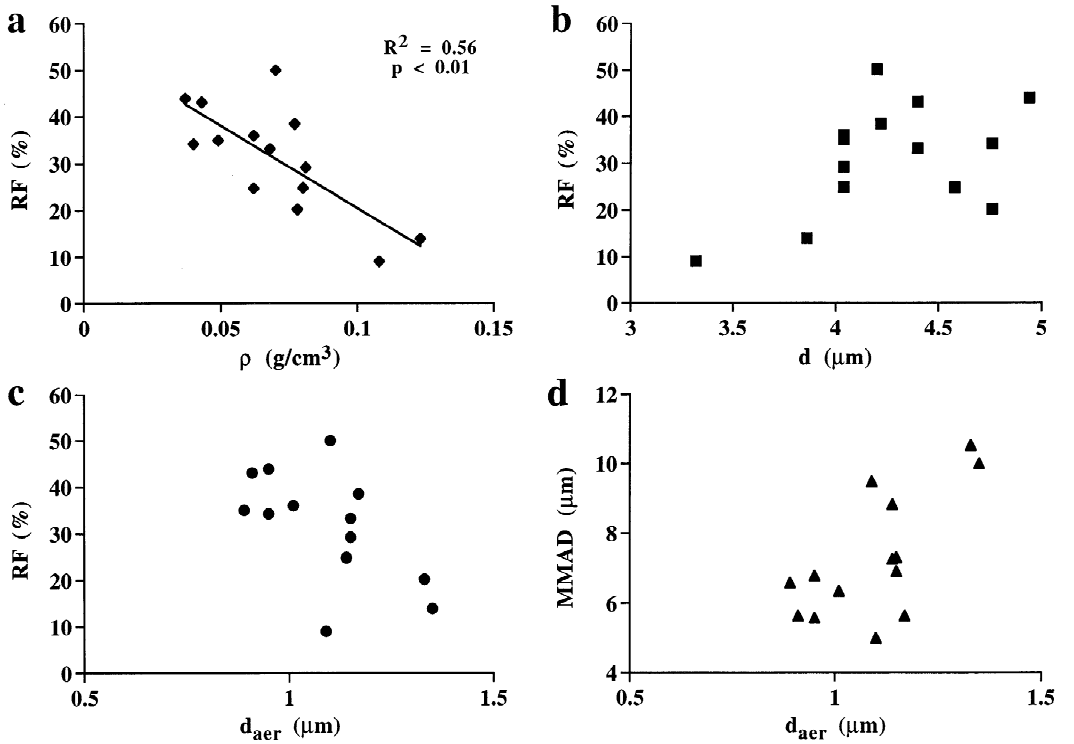


Fig. 6. Influence of tap density (ρ; a), geometric diameter (d; b) and aerodynamic diameter of individual particles (d_{aer}; c) on the respirable fraction (RF) of the powders made of variable composition presented in Fig. 3. When the correlation between RF and the different parameters was significant, the regression line and the correlation coefficient are shown. In (d), the experimental mass median aerodynamic diameter (MMAD) of the powders measured in the Andersen cascade impactor is plotted versus d_{aer}.

respirable fractions up to 50% using the Spinhaler™ device, a first-generation inhaler device (Figs. 2, 3, 5, 6). Those powders can incorporate conventional drugs as well as drugs from biotechnology origin, i.e. peptides, proteins and DNA, and be tested for drug delivery to the lungs for a local action or systemic delivery [13,20].

The excipient type and their relative proportion greatly affected the in vitro deposition of the dry powders and the albumin/lactose/DPPC (30/10/60, w/w/w) powder particularly demonstrated efficient aerosolization performance (Fig. 3b). Each excipient in the formulation appeared necessary for the achievement of optimal aerosolization properties. DPPC, the most abundant component of lung surfactant, might facilitate droplets formation in the atomization step of spray-drying, as well as likely decreased particle surface energy [21,22], and thereby powder cohesiveness [13,23]. Lactose and albumin might offer the skeletal structure necessary for the formation of solid particles by spray-drying, which could not be provided by DPPC alone (Fig. 3a).

The type of sugars/polyol greatly influenced the in vitro deposition of the powders, with lactose, trehalose and mannitol presenting the best to poorest behavior in the Andersen impactor (Fig. 2). The physical characteristics of those powders, particle size, density and overall morphology, as visualized by electron microscopy, were relatively similar, suggesting that the differences in respirable fractions rather resulted from differences in powder cohesiveness with the type of excipient. The Hamaker constants — a material property that represents the strength of the van der Waals attraction — of the sugars and polyol must be in the same range of magnitude as made of identical atoms [24]. Differences in hygroscopicity of the materials and thereby alteration of capillary forces and/or differences in

surface properties may explain those results. Andya et al. [25] have similarly studied the effect of lactose, trehalose and mannitol on the aerosol performance of spray-dried powders of an anti-IgE antibody. The best aerosolization performance was achieved with lactose as well, while trehalose and mannitol exhibited increased cohesiveness with increasing quantities incorporated in the powders.

Removing albumin from the formulation dramatically decreased respirable fractions (Fig. 2). This effect could be partly explained by an increase in density and therefore d_{aer} and MMAD. However, albumin likely reduces inter-particle adhesion forces as well, since proteins decrease the value of the Hamaker constant [24], possess surfactant properties, and may limit point-to-point contacts due to highly indented surface geometries (Fig. 1a). This was similarly proposed by French et al. who compared human granulocyte-colony stimulating factor/mannitol powders to less flowable pure mannitol particles [9].

Decreasing the tap density of the dry powders as well as the aerodynamic diameter of individual particles significantly increased the respirable fraction (Fig. 5). The geometric size had no effect on RF in the range of sizes studied. A low density increased RF probably because of the reduced d_{aer}, which makes the cumulative mass of particles or particle aggregates respirable statistically higher. In order to evaluate the influence of density on cohesiveness, the powders from Fig. 5 with tap density <0.1 g/cm^3 and >0.2 g/cm^3 were separately pooled. The first and second groups of powders presented in average 0.06 and 0.23 g/cm^3 density, 4.3 and 4.4 μm geometric size, 1.0 and 2.1 μm d_{aer}, and 7 and 9 μm MMAD, respectively. As an estimate of aggregation, the ratios of the experimental MMAD on the computed d_{aer} were calculated for each group; they were worth 7 and 4 for the light and dense powders, respectively. This suggests that a decrease in density may result in greater aggregation, a fact that must be related to weaker separation forces due to gravity [26].

The effect of particle size on respirable fraction was little explored in our experimental study because of the limited range of particle sizes that laboratory-scale spray-dryers are capable to produce. Comparison between the aerosolization properties of our powders and those of powders of identical composition prepared previously by Vanbever et al. [13] can however bring insights into the effect of size on flowability for this type of aerosols. The particles produced in this previous article presented similar tap densities, respirable fractions and MMADs, but their geometric sizes and d_{aer} were twice greater. The differences between d_{aer} and MMAD were therefore reduced in this previous study, which indicates a decreased state of aggregation for larger size particles. The aerosolization efficiency of large porous particles can be related to their smaller surface-to-volume ratio and thereby surface energy, as well as their easier deaggregation under shear forces [9,12,20,26].

The proportion of the excipients in the powder had great impact on in vitro deposition as well (Fig. 3). This effect could be partly explained by changes in density (Fig. 6). However, similarly to the effect of excipient type, other factors as alterations in surface properties are likely involved [24].

The experimental MMADs of our powders were three to eight times larger than the aerodynamic diameters of individual particles, d_{aer}, probably due to incomplete powder deaggregation by the Spinhaler™ device in the Andersen cascade impactor at 28.3 l/min, a sub-optimal air flow rate (Figs. 5 and 6). In order to demonstrate particle aggregation in the Andersen impactor, the powder fractions deposited on each tray of the impactor (in this case, uncoated but covered with filters [13]) were collected and measured for particle size. No difference in particle size was evident among the different stages of the impactor and as compared to the particle size of the bulk powder before delivery, suggesting that particles separated in the impactor based on the size distribution of aggregates and not on the size distribution of individual particles. This underlies that particles, which are theoretically suited for deposition on the small size (≤ 5 μm) stages of the impactor (representing the deep lungs), are impeded to do so by the phenomenon of aggregation.

5. Conclusion

The objective of this research was to evaluate the influence of formulation composition and the phys-

ical characteristics of inhalation drug particles, tap density, geometric and aerodynamic sizes, on in vitro aerosolization properties. The composition of the particles, i.e. excipient type and proportion, significantly influenced aerosol performance and powders prepared with lactose behaved best in the Andersen cascade impactor, as compared to trehalose or mannitol. The incorporation of albumin improved in vitro deposition as well. The lower the powder tap density, the greater the respirable fraction. Among the combinations tested, the albumin/lactose/DPPC (30/10/60, w/w/w) formulation was particularly optimal and exhibited respirable fractions as high as 50% of doses emitted from the Spinhaler™ device. Further understanding of the origin of the excellent performance of those powders will be sought through the analysis of particle nature and surface by adsorption isotherms and microcalorimetry, X-ray powder diffractometry, X-ray photoelectron spectroscopy and atomic force microscopy.

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