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International Journal of Pharmaceutics 269 (2004) 457–467
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Formulation and characterization of spray-dried powders containing nanoparticles for aerosol delivery to the lung

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Received 24 June 2003; received in revised form 15 September 2003; accepted 24 September 2003

Abstract

Spray-drying is a common practice of powder preparation for a wide range of drugs. Spray-dried powders can be used to deliver particles to the lungs via a dry powder inhaler (DPI). The present study investigated the feasibility of developing a platform for aerosol delivery of nanoparticles. Lactose was used as the excipient and spray-dried with two different types of nanoparticles: gelatin and polybutylcyanoacrylate nanoparticles. Results showed that some carrier particles were hollow while others had a continuous matrix. Gelatin nanoparticles were incorporated throughout the matrix and sometimes accumulated at one end of the lactose. Polycyanoacrylate nanoparticles mostly clustered in different spots within the lactose carriers. The mean sizes of both nanoparticle types were characterized at two different times: before they were spray-dried and after they were redissolved from the spray-dried powders. Both nanoparticle types remained in the nano-range size after spray-drying. The mean nanoparticle sizes were increased by approximately 30% after spray-drying, though this increase was statistically significant only for the gelatin nanoparticles. Dispersion of the powder with an in-house passive dry powder inhaler and subsequent cascade impaction measurements showed that incorporation of the nanoparticles did not affect the fine particle fraction (FPF) or mass median aerodynamic diameter (MMAD) of the powders. FPF was approximately 40% while MMAD was $3.0 \pm 0.2\,\mu$m, indicating the present formulations yield aerosols of a suitable particle size for efficient lung delivery of nanoparticles.

The present work demonstrates that nanoparticles can be delivered to the lungs via carrier particles that dissolve after coming in contact with the aqueous environment of the lung epithelium. This opens the way for new drug-targeting strategies using nanoparticles for pulmonary delivery of drugs and diagnostics.

Keywords: Nanoparticle; Pulmonary delivery; Powder inhalation; Spray-drying

1. Introduction

Aerosols are an effective method to deliver therapeutic agents to the respiratory tract. Nebulizers, metered dose inhalers, or dry powder inhalers are commonly used for this purpose (Finlay, 2001). Local delivery of medication to the lung is highly desirable,

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doi:10.1016/j.ijpharm.2003.09.041

especially in patients with specific pulmonary diseases like cystic fibrosis (Mallol et al., 1997), asthma (Georgitis, 1999), chronic pulmonary infections (Touw et al., 1995), or lung cancer (Newhouse and Corkery, 2001). The principal advantages of local delivery include reduced systemic side effects and higher dose levels of the applicable medication at the site of drug action (Bennett et al., 2002; Dhand, 2001; Herbst, 2002; Parthasarathy et al., 1999; Sharma et al., 2001). Unlike the oral route of drug administration, pulmonary inhalation is not subject to first pass metabolism. Therefore, expensive biotechnology drugs like recombinant human deoxyribonuclease (rhDNase) for the treatment of cystic fibrosis (Fiel et al., 1995) or toxic chemotherapeutics are ideal drug candidates for local pulmonary administration (Sharma et al., 2001). Indeed, aerosol delivery has long been viewed as a promising approach for lung cancer (Koshkina et al., 2001). Given the advantages of pulmonary delivery for certain diseases, it is foreseeable that specialized inhalation treatment for diseases such as lung cancer or gene therapy will be developed further (Bennett et al., 2002; Dhand, 2001; Herbst, 2002).

Carbohydrates and especially mannitol and lactose are widely used as the excipients for dry powder inhalers since they are approved by the Food and Drug Administration (FDA) and other regulatory bodies as excipients for inhalation purposes (Bosquillon et al., 2001). This is due to their non-toxic, readily degradable properties after administration. To prepare inhalable powders, spray-drying is a commonly practiced method (Bosquillon et al., 2001; Mackin et al., 1997; Vanbever et al., 1999). In fact, spray-drying has been applied to a variety of substances, such as peptides (Millqvist-Fureby et al., 1999), antibiotics (Kim and Kim, 2001), vaccines (Maa et al., 2003), and carrier particles (Elversson et al., 2003). One of the principal purposes of aerosolizing spray-dried powders is to achieve powder particle diameters of several micrometers with a narrow particle distribution (Elversson et al., 2003). This ensures, assuming an appropriate mass median aerodynamic diameter (MMAD), a maximum deposition of the embedded drugs in the tracheo-bronchial and deep alveoli regions for normal inhalation rates (Finlay, 2001).

Independent of the method used to produce an inhalation aerosol, delivery by inhalation must overcome certain obstacles before reaching the site of drug action. This is particularly important when the particle deposition takes place in the upper bronchial area. In this area of the tracheo-bronchial region the epithelium is protected by a mucus layer (Courrier et al., 2002). Any particle or drug is transported away from the lung by mucociliary clearance (Gehr et al., 1996). However, the cellular uptake of small molecular weight drugs by epithelium cells or the permeation of such drugs into the systemic circulation is generally expected if the drug can reach the alveolar epithelium, or diffuse through the mucus and reach the epithelium cells. This might not be the case for large biotechnology molecules like oligonucleotides. Such large molecules might not be able to cross the epithelium or the cytoplasm membrane (Wall, 1995). Consequently they will not be able to reach their site of drug action. This is a general drug delivery problem for large molecules and applies to other routes of administration as well (Tamura et al., 1996).

Nanoparticles are solid colloidal particles ranging in size from 10 to 1000 nm (Kreuter, 1994). They can be made from biodegradable and biocompatible biomaterials. Active principles like drugs of oligonucleotides can be adsorbed, encapsulated or covalently attached to their surface or into their matrix (Kreuter, 1994). In vitro and in vivo studies have demonstrated that nanoparticles are promising carrier systems for drug targeting strategies (Couvreur and Vauthier, 1991; Kreuter, 1991, 1996; Löbenberg et al., 1997; Löbenberg and Kreuter, 1996).

Studies using inhaled nanoparticles dispersed in aqueous droplets suggest that the mucus clearance can be overcome by nanoparticles, possibly due to rapid displacement of particles to the airway epithelium via surface energetics (Schurch et al., 1990). Therefore, nanoparticles may be possible vehicles of transporting drugs efficiently to the epithelium, while avoiding unwanted mucociliary clearance.

Cellular uptake studies have demonstrated that besides macrophages, other cells like cancer cells and epithelium cells are also able to take up nanoparticles (Ghirardelli et al., 1999; Huang et al., 2002; Russell-Jones et al., 1999). Body distribution studies using intravenous injections of nanoparticle preparations have revealed that the surface characteristics of colloidal carriers are one of the most important

parameters in avoiding macrophage uptake (Araujo et al., 1999). Furthermore, in vivo studies have observed an accumulation of nanoparticles in tumor sites (Brigger et al., 2002). This was attributed to the leaky blood vessel structure of tumors. Such properties make nanoparticles a very attractive delivery vehicle for lung cancer treatment. However, the disadvantage of using nano-sized delivery systems for pulmonary application is that their MMAD is not suitable for inhalation purposes (Finlay and Gehmlich, 2000; Finlay et al., 1997). Many nanoparticles are of a size that places them in a transition region where neither diffusion nor sedimentation or impaction is effective deposition mechanisms. Consequently, it is expected that a large fraction of the inhaled dose will be exhaled and little particle deposition will take place in the lungs. However, if nanoparticles can be delivered to the lungs, then their unique properties in avoiding mucociliary clearance and delivering drugs directly to the target tissue or target cells might be utilized for therapeutic treatments of lung-specific diseases like lung cancer.

In the present study, we investigated the feasibility of developing carrier particles to deliver nanoparticles to the lung. The objective was to incorporate nanoparticles into the matrix of carrier micro particles. The MMAD of such carriers can be adjusted to give sufficient lung deposition in the desired upper or lower generations of the lung (e.g. either the bronchial region or the alveolar region). After deposition in the lung, the carrier matrix dissolves and releases the nanoparticles. Gelatin was chosen as a model for protein-based nanoparticles. It possesses abundant functional groups, such as carboxyl and amino groups, on the particle surface which enables easy modification and the covalent binding of drugs (Weber et al., 2000). Polybutylcyanoacrylate nanoparticles were chosen as a model for synthetic particles. They are well characterized in the literature and are considered as potent drug carriers (Couvreur and Vauthier, 1991; Kreuter, 1991, 1996; Löbenberg et al., 1997; Löbenberg and Kreuter, 1996). This study describes the development of dry powder formulations loaded with synthetic or protein-based nanoparticles. The nanoparticles were spray-dried together with the carrier matrix. The physicochemical properties of the carrier particles and nanoparticles were investigated.

2. Materials and methods

2.1. Chemicals

Lactose monohydrate was obtained from FMC (Philadelphia, USA); gelatin B from bovine skin (225 Bloom), glutaraldehyde grade I 25% aqueous solution, sulforhodamine 101 acid chloride (Texas Red), fluorescein isothiocyanate-dextran (FITC-Dextran) and cyanoacrylate were obtained from Sigma Chemical Co. (St. Louis, MO, USA); acetone and acetonitrile were purchased from Caleda (Georgetown, Canada). All chemicals were of analytical grade and used as received.

2.2. Preparation of gelatin nanoparticles

A two-step desolvation method was used to prepare gelatin nanoparticles according to the method described by Coester et al. (2000). In brief: 1.25 g of gelatin B was dissolved in 25 ml of distilled water and stirred at 600 rpm and under constant heating of 40 °C. Twenty-five milliliters of acetone were added to the gelatin solution. The high molecular weight (HMW) gelatin precipitated from the solution. The supernatant containing low molecular size gelatin which is still soluble in the aqueous/organic solvent mixture was discarded. The HMW gelatin was redissolved in 25 ml of distilled water and stirred at 600 rpm and under constant heating of 40 °C; the pH of the solution was adjusted to 2.5 by adding 1N HCl; 75 ml of acetone were added to the acidic gelatin solution drop-wise and the nanoparticles precipitated from the solution. One hundred and twenty-five microliters of 1 mg/ml of solution of Texas Red in acetonitrile was added and stirred for 1 h. The particles were stabilized using 400 μl of 25% glutaraldehyde as cross-linking agent and the suspension was left stirring for 12 h without heating. The remaining solvent was evaporated using a Rotavapor (IKA, Model RV 05, Staufen, Germany). The nanoparticles were purified by centrifugation at 100,000 × g (Beckman Model J2-21) for 30 min and were washed three times with distilled water. The resulting particles were re-dispersed in 25 ml of distilled water. The fluorescent-labeled nanoparticles were stored at 4 °C and protected from light.

2.3. Gravimetric determination of the gelatin nanoparticles

The nanoparticles were freeze-dried using a Labconco (Kansas City) Freeze Dryer model 3 over 24 h. The particles were completely removed from the bottle and weighed on an analytical balance.

2.4. Preparation of polybutylcyanoacrylate particles (PBCA)

Polybutylcyanoacrylate nanoparticles were prepared by an emulsion polymerization process described by Scherer et al. (1993). Fifty milligrams of FITC-Dextran was added to 10 ml of 0.01N HCl. The solution was stirred at 600 rpm; 100 μl of the monomer were slowly added by pipette to the solution; the solution was stirred for 4 h and was protected from light; the pH was subsequently adjusted using 1N NaOH to pH 5.0. The particles were purified from unbound dye and polymerization residuals as described for the gelatin particles.

Nanoparticles were suspended to 25 ml of distilled water after centrifugation, yielding 2 mg/ml of polycyanoacrylate nanoparticles.

2.5. Particle size analysis

The particle size of the gelatin and the polycyanoacrylate nanoparticles was determined by photon correlation spectroscopy (Zetasizer model HSA 3000). One hundred microliters of the nanoparticle suspension were diluted with 4 ml of fresh filtered de-ionized water. The measurements were carried out at room temperature. The particle size was determined before and after spray-drying. A 50 mg aliquot of the nano-particle lactose powder was dissolved in 4 ml of distilled water and the particle size was determined directly without any further dilution.

2.6. Spray-drying of nanoparticles

A Mini-Spray Dryer produced by Büchi Laboratoriums-Technik (Flawil, Switzerland) was used. The Mini-Spray Dryer operates on the principle of a nozzle spraying in a parallel-flow (the sprayed product and the drying air flow are in the same direction). The adjustable parameters include inlet and outlet temperature, solution pump flow rate, and the aspirator partial vacuum. In the present experiments, the inlet air temperatures ranged from 170 to 180 °C, the pump flow rate was 2 ml/min, the aspirator was set to 40 m^3/h, and the atomizing air flow rate was 700 l/h (80 psi). The solution was pumped into the feeding system of the spray-dryer. The resultant powder was blown through the cyclone separator and collected in a container. Exhaust air was extracted out of the cyclone by a vacuum pump and filtered by a fiber filter.

Five grams of lactose were dissolved in 75 ml of distilled water and heated up to 40 °C to increase the lactose solubility. Then, the solution was mixed with 25 ml of either gelatin nanoparticles or polybutylcyanoacrylate nanoparticles. The glass chambers of the spray dryer were shielded from light. The powders were removed from the collector vessel and stored at room temperature under light protection.

2.7. Fluorescent-labeling of lactose

The carrier particles were stained with a florescent label to increase their visibility for the confocal microscopy. The dyes were added to the lactose solution prior to spray-drying. The lactose was stained using 500 μl of 1 mg/ml solution of Texas Red in acetonitrile if butylcyanoacrylate particles were used or 500 μl of 1 mg/ml solution containing 5(6)-carboxyfluorescein if gelatin nanoparticles were used.

2.8. Powder characterization using confocal laser scanning microscopy

The morphology of the powders was examined using a Zeiss LSM 510 confocal microscope. The microscope is equipped with the capability to collect 12-bit images using four different detectors for fluorescent signals from fluorophores excited by four lasers with multiple laser lines (Argon, HeNe1, HeNe2, UV) and a transmission detector for bright field images (DIC). Small aliquots of the spray-dried powders were dispersed in immersion oil on glass slides. The powder particle sizes from all samples were manually measured using the software Metamorph (v. 5.0, Universal Imaging Corporation). At least 25 particles were measured for each powder sample. The mean powder size was calculated based on all measurements.

2.9. Powder dispersion and sizing by cascade impaction

The dispersibility of each powder was assessed using a Mark II Andersen impactor (Thermo Andersen, Smyrna, GA) with the powder aerosolized using a proprietary, low-resistance dry powder inhaler developed by Finlay and Wang (2002). The powder was dispersed at a steady flow rate of 60 l/min. This flow rate was higher than the standard flow rate of 28.3 l/min (1 SCFM) normally used in the Andersen impactor, but was more representative of human inspiratory flow rates in typical dry powder inhalers (DPIs). The Andersen impactor was recalibrated at 60 l/min using different cut points (Nichols et al., 1998). Using this calibration, the size range of the powder impacted on each plate is known. An inhaler was attached to the inlet of the Andersen impactor and the impactor was fixed on the testing stand horizontally. It is known that using the impactor in a horizontal position does not alter its particle size selection (Willeke and Baron, 1993). The flow rate was maintained by a vacuum pump (Emerson Electric Co., USA) and monitored by a pneumotachometer (PT) (4719, Hans Rudolph Inc., 0–100 l/min).

For all of the deagglomeration experiments, the test powder was used in its original state collected from the spray dryer. No post-treatment was applied to the powder. The sample powder was weighed using an analytical balance (Sartorius 1207MP2, Germany). Ten powder doses (5 mg each) were loaded individually into the inlet of the DPI. The eight metal plates within the impactor were coated with a thin layer of 316 silicone grease (Dow Corning, MI) to prevent fine particles from bouncing on the plates and becoming re-entranced in the air stream, which could give an incorrect size distribution (Esmen and Lee, 1980; Vanghan, 1989). Indeed, tests done with lower and higher dose loadings did not yield significant differences in the measured total fine particle fraction ($FPF_{ED<5.6\,\mu m}$), indicating an absence of plate overloading. A pre-separator was attached to the top of the impactor to prevent large particles aggregating or from reaching rear stages. Before assembling the apparatus, the inhaler, the pre-separator and all impactor plates were weighed on an analytical balance. After dispersion of the powder into the impactor was completed, the inhaler, the pre-separator, and all the impactor plates were weighed again by the same balance. The fine particle fraction ($FPF_{ED<5.6\,\mu m}$), or equivalently the respirable fraction, was determined by the weight increase of each part. For accuracy, each test was repeated three times. The method was validated using a colorimetric assay with rhodamine 6G-labeled lactose.

2.10. Statistical analysis

A paired *t*-test was performed to compare the sizes of nanoparticles before spray-drying into powders and after release from dissolved powders, and another to compare the size of powders with and without nanoparticles at the statistical *P*-value of 0.05.

2.11. MMAD

Mass Median Aerodynamics Diameter (MMAD) was calculated by linear interpolation of the cumulative mass distribution to obtain the particle size for which the cumulative mass under this size was 50%.

3. Results

The mean particle size of the nanoparticles was 242 ± 14 nm for gelatin and 173 ± 63 nm for polybutylcyanoacrylate. The gravimetric determination of the gelatin nanoparticles after freeze drying revealed that $69 \pm 5.3\%$ of the initial amount of gelatin formed nanoparticles. The spray-dried lactose produced spherical powders (see Fig. 1). CLSM cross-sections through the powders showed that some particles were hollow while other powder particles had a continuous matrix. Figs. 1 and 2 are typical examples for such particles. Both Texas Red and 5(6)-carboxyfluorescein-stained the lactose very well. The mean particle size determined by CLMS measurements of pure lactose powders, powders with gelatin nanoparticles and powders with polycyanoacrylate nanoparticles were 2.50, 2.59, and 2.60 μm, respectively. A *t*-test was performed to compare the size of these different powder types and showed that the incorporation of nanoparticles into lactose by spray-drying did not affect the size of the powders formed.

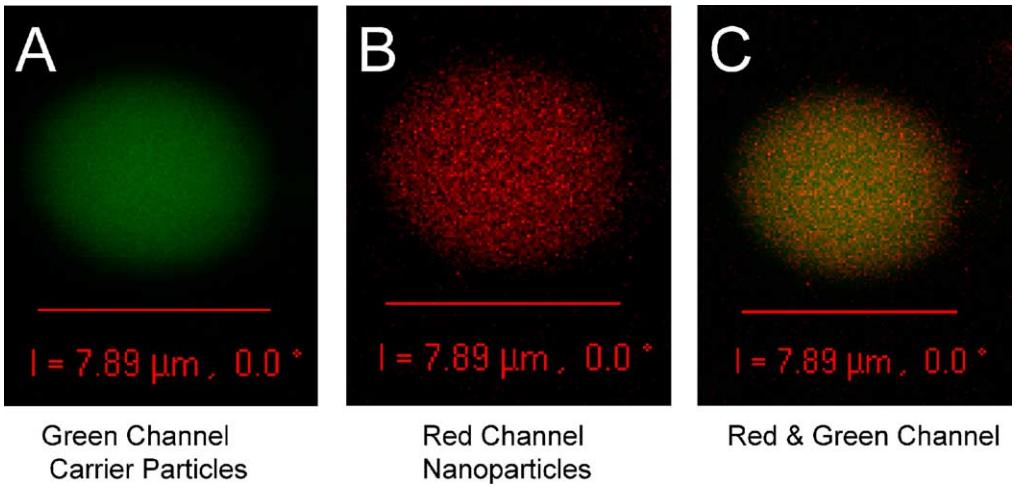

Fig. 1. Picture of a green-stained carrier particle (A) containing red-stained nanoparticles (B) and both pictures superimposed (C).

3.1. Gelatin nano-particle lactose powders

Gelatin nanoparticles stained with Texas Red were incorporated into lactose powders by spray-drying (see Fig. 1). As seen, the distribution of gelatin nanoparticles was even throughout the carrier particle. CLSM cross-section images through the carrier particle were taken to further examine the distribution. It was observed that gelatin nanoparticles do embed in the body of the carrier. In some instances clusters of gelatin nanoparticles were observed as bigger red spots within the particles or they appeared as polarized red staining on one side of the particles.

3.2. Polycyanoacrylate nanoparticles loaded lactose powders

Fig. 2 shows the distribution of FITC-Dextran-stained polycyanoacrylate nanoparticles in a hollow carrier particle. The figure shows two different

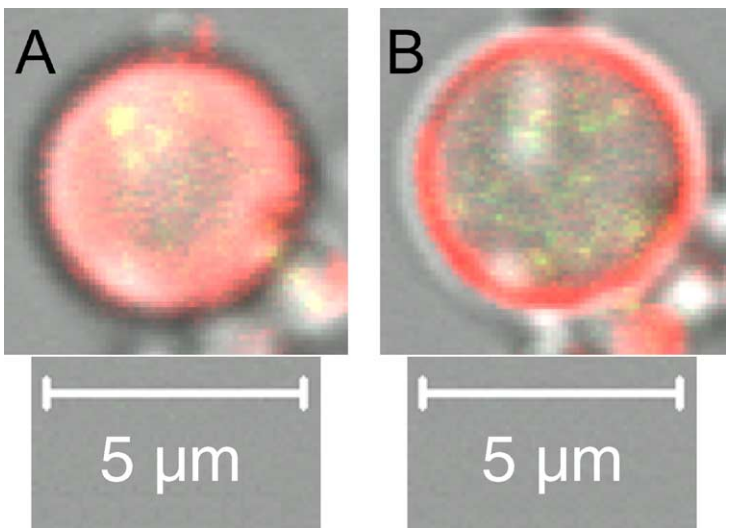

Fig. 2. Cross-section through a red-stained hollow nanoparticle powder carrier. The yellow and green spots are nanoparticles. The sections are 1.8 µm apart from each other. A particle core; B particle cross section.

layers of the carrier particle separated by 1.8 μm. The cross-section images show that the polybutylcyanoacrylate particles tend to accumulate more as clusters within the carrier particle (yellow spots; Fig. 2A) compared to the gelatin nanoparticles. Larger lactose particles tend to contain more clusters of the polycyanoacrylate nanoparticles than smaller ones. Visual observation showed a continuous distribution of the nanoparticles between different particle sizes.

3.3. Powder dispersion using a dry powder inhaler

The powder recovery efficiency from the cascade impaction test was >90%. The fraction of all particles smaller than 5.6 μm represents the inhalable fine particle fraction ($FPF_{ED<5.6\,\mu m}$). Three batches of typical powder formulations were deagglomerated by the same inhaler. The results indicate that the $FPF_{ED<5.6\,\mu m}$ varied within a narrow range of 38–42%. The results showed the presence of the nanoparticles had no significant effect on the fine particle fraction of the powders.

Fig. 3 shows the weight fraction according to the size distribution of the aerosolized particles. Each bar represents the powder of certain sizes collected on a defined stage of the Andersen cascade impactor. The average MMAD of the powders was 3.0 ± 0.2 μm. The comparison of the data indicates that no statistically significant differences occurred on the aerodynamic diameter distribution among the different powder types (*t*-test; $P = 0.05$).

3.4. Effect of spray-drying on the size of polycyanoacrylate nanoparticles and gelatin nanoparticles

The mean particle sizes of the gelatin and polybutylcyanoacrylate nanoparticles were measured before spray-drying and after re-dissolving of the spray-dried powders. The mean particle size of gelatin nanoparticles increased from 242.2 ± 17 nm to 319.9 ± 58 nm. The average size of the polybutylcyanoacrylate particles was 173.0 ± 59 nm before spray-drying and 231.7 ± 33 nm after spray-drying. A *t*-test was performed to compare the size of individual nanoparticle type before and after spray-drying at $P = 0.05$. Although after spray-drying the gelatin nanoparticles were still in the nano-range, they differ significantly

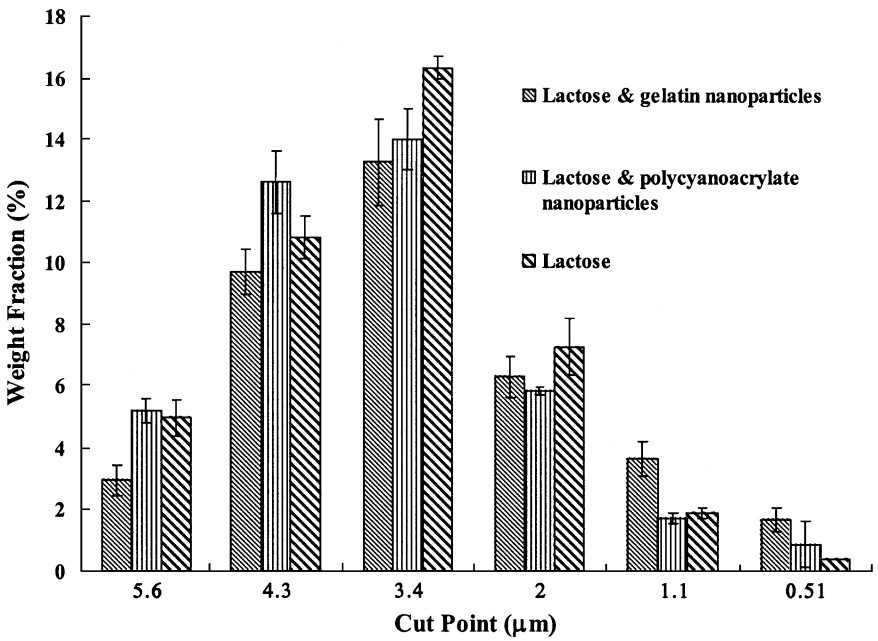

Fig. 3. Comparison of the powder dispersion among different spray-dried powders by an Andersen impactor. Each bar represents the average of three repeats and error bars refer to standard deviation.

in size from the original; whereas the difference between polybutylcyanoacrylate nanoparticles before and after spray-drying was statistically insignificant.

4. Discussion

The present study investigated a new concept for nanoparticle delivery to the lower respiratory regions of the lung using micrometer-sized carrier particles. Other routes of administration have shown that nanoparticles are potent drug carriers (Couvreur and Vauthier, 1991; Kreuter, 1991, 1996; Löbenberg et al., 1997; Löbenberg and Kreuter, 1996). The data presented in this study show that a nanoparticle delivery to the lung is a feasible concept if the carrier particles have an appropriate MMAD (Finlay, 2001). This delivery system can be used to develop a new platform for pulmonary drug targeting strategies.

The present study describes nanoparticle-loaded carrier particles which are different compared to the study of Tsapis et al. (2002). The cited study used large porous particles for potential pulmonary nanoparticle delivery and found that the concentration and the nature of the nanoparticles determined the shape and the size of the resulting aerosol particles. In contrast, the shape and size distribution of the carrier particles described here are independent of the presence of the nanoparticles.

Figs. 1 and 2 show CLMS pictures of the incorporation of nanoparticles into the carrier particles. Fig. 1 shows the distribution of gelatin nanoparticles throughout the carrier particles visualized using a green and red staining. Fig. 1A shows the green-stained lactose carrier while Fig. 1B shows the red nanoparticles and Fig. 1C shows both pictures combined. Visualizing different layers of the carrier particle using CLMS has shown that the nanoparticles are homogenously distributed throughout the matrix of the particle. The larger size of the gelatin nanoparticles after spray-drying may be a result of a change in conformation under the thermal condition of spray-drying. This might be overcome by a lower thermal exposure of the spray-drying process or using spray freeze dying. The latter process is preferable if heat-sensitive drugs are attached to the gelatin nanoparticles. However, studies have shown that suitable spray-drying conditions expose biological molecules only for a few milliseconds to seconds in the spray dryer chamber and it has been argued that this might not cause extensive damage given that the powder temperature is in the order of 40–45 °C (Linders et al., 1996; Masters, 1991).

In some carrier particles clusters of gelatin nanoparticles were observed. Such clusters, if not deaggregated after the carrier particle dissolves, may also cause an increase in the particle size. The tendency of proteins and peptides to accumulate on the surface of spray-dried powders as clusters was described in various studies (Adler et al., 2000; Millqvist-Fureby et al., 1999). During atomization, the liquid/air interface of the spray solution greatly and suddenly expands (Maa et al., 1998; Paulsson and Dejmek, 1992; Tripp et al., 1995). This is a distinct interface in which proteins or peptides tend to adsorb to each other and the gelatin nanoparticles in this study are no exception. However, Maa et al. found that adding polysorbate 20 to the spray-drying process reduced surface aggregation of recombinant human growth hormone by 15 to $<2\%$ (Maa et al., 1998). In another study using bovine serum albumin (BSA), Adler et al. reported similar results in which increasing concentrations of polysorbate 80 or sodium dodecyl sulfate reduced the surface accumulation of BSA in a concentration-dependent manner (Adler et al., 2000).

Fig. 2 shows two layers of a hollow carrier particle (Fig. 2A, the particle shell and Fig. 2B, through the equator of the particle). The red staining represents the lactose carrier while the yellow dots are aggregates of polybutylcyanoacrylate nanoparticles. The formation of nanoparticle clusters may be due to the adhesive nature of cyanoacrylate nanoparticles or their free surface energy. However, dissolving the particles in water revealed that the clusters do not stick together. The particle size analysis shows that the spray-drying process has no significant effect on the average size of the nanoparticles. This might be due to the dissolution process of the carrier particles which contributes to the deagglomeration of the nanoparticle clusters.

Aerosol powders ranging from 1 to 5 μm are considered the optimum size for deposition beyond the increasingly narrow airways into the alveoli. However, such particles often also stick together which lowers the fine particle fraction (French et al., 1996; Li et al., 1996; Timsina et al., 1994). One approach to overcome this is the use of large porous particles (>5 μm)

with a low mass density ($<0.4\,g/cm^3$) (Edwards et al., 1997). It has been shown that larger particles aggregate less and deaggregate more easily (Vanbever et al., 1999). Another approach is the use of high efficiency dry powder inhalers. Such powder inhalers are able to deagglomerate powders more ably than conventional powder inhalers (Finlay and Wang, 2002). The results of our cascade impactor tests clearly show that the spray-died powders can be aerosolized and a high percentage is in the fine particle range appropriate for inhalation. Further optimization of the carrier particles and incorporation of protein-based nanoparticles would allow perhaps even higher fine particle fractions.

The described delivery technology can be used for lung-specific applications such as lung cancer, cystic fibrosis or asthma. However, patients with systemic diseases may also benefit from such delivery technology if nanoparticles facilitate the entry of drugs and proteins through the lung epithelium into the systemic circulation.

5. Conclusion

The present study demonstrates that incorporation of nanoparticles into respirable carrier particles is possible. The described carrier particles can deliver nanoparticles into the lung. The size and shape of the spray-dried powders is suitable for respiratory deposition of the carrier particles. The carrier is expected to dissolve quickly after landing on the aqueous covered epithelium of the lung. In vitro results show that the delivered nanoparticles are released immediately. Nanoparticles can be loaded with active principles like drugs, peptides, oligonucleotides or diagnostics for local or systemic delivery of the active principles. This delivery platform opens up a wide range of treatment applications of pulmonary and possibly systemic diseases using targeted delivery strategies via nanoparticles.

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