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Research paper

Effervescent dry powder for respiratory drug delivery

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Abstract

The objective of this work was to develop a new type of respiratory drug delivery carrier particle that incorporates an active release mechanism. Spray drying was used to manufacture inhalable powders containing polybutylcyanoacrylate nanoparticles and ciprofloxacin as model substances for pulmonary delivery. The carrier particles incorporated effervescent technology, thereby adding an active release mechanism to their pulmonary route of administration. Effervescent activity of the carrier particles was observed when the carrier particles were exposed to humidity. Gas bubbles caused by the effervescent reaction were visualized by confocal laser scanning microscopy. The images showed that nanoparticles were distributed throughout the gas bubble. For the effervescent formulation the average mass median aerodynamic diameter (MMAD) was 2.17 μm ± 0.42, fine particle fraction ($FPF_{<=5.6\ \mu m}$) was 46.7% ± 15% and the GSD was 2.00 ± 0.06. The results also showed that the effervescent carrier particles released 56 ± 8% ciprofloxacin into solution compared with 32 ± 3% when lactose carrier particles were used. The mean nanoparticle size did not significantly change upon release when the nanoparticles were incorporated into an effervescent formulation. However, the mean size significantly increased upon release when only lactose was used as carrier particle matrix. In conclusion, effervescent carrier particles can be synthesized with an adequate particle size for deep lung deposition. This opens the door for future research to explore this technology for delivery of a large range of substances to the lungs with possible improved release compared to conventional carrier particles.

Keywords: Effervescent; Inhalable dry powders; Nanoparticles; Pulmonary delivery; Aerosol; Drug delivery; Ciprofloxacin; Spray drying

1. Introduction

The pulmonary route of administration has been used for many years for the local treatment of lung diseases. More recently, systemic drug absorption has been investigated, e.g., for the treatment of diabetes mellitus and pain relief [1]. In addition, major areas of pulmonary research are aimed at asthma [2], cystic fibrosis [3], lung cancer [4] and tuberculosis [5,6]. Drug delivery to the lungs requires an aerosol vehicle, which consists of either aerosol droplets containing the drug, or powder particles of appropriate size for lung delivery [7]. Dry powder delivery to the lungs remains challenging due to powder aggregation that increases the particle size above the optimal particle diameter, which in general terms for deep lung deposition is between about 1 and 5 μm [8–10]. Spray drying is one technique to manufacture inhalable powders [8,10].

Nanomedicine is an emerging field in the biomedical sciences. Drug delivery systems involving nanoparticles have been investigated for different routes of administration. The first nanoparticle-containing intravenous drug delivery system was recently approved as medicine in the United States under the name Abraxane®. It contains albumin-bound paclitaxel for the treatment of metastatic breast cancer [11]. Nanoparticles have been proposed for pulmonary administration to utilize their advantages in drug delivery to the lungs [12]. Furthermore,

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nanoparticles exhibit certain characteristics that make them ideal for pulmonary drug delivery and for treating lung specific diseases like lung cancer. Research has shown that nanoparticles avoid unwanted mucociliary clearance and in some cases phagocytic clearance [13] by remaining in the lung lining fluid until dissolution [14] or translocation by the epithelium cells [15]. One issue with pulmonary nanoparticle delivery is that their small size limits their lung deposition. Aerosolized nanoparticles have only very limited sedimentation, inertial impaction or diffusion, which causes them to be predominantly exhaled from the lungs after inhalation [7,13,16]. However, Sham et al. have shown that nanoparticles can be incorporated into carrier particles to produce the appropriate size for pulmonary drug delivery [12].

Effervescent preparations have been utilized in oral drug delivery for more than 200 years. Since that time, a large number of preparations utilizing effervescent technology have been produced including stomach distress medications, vitamin supplements, and analgesics [17]. However, effervescent powders have not previously been used for the pulmonary route of administration. In the present study, we investigated and optimized carrier particles for respiratory drug delivery that incorporate effervescent technology. The effervescent reaction adds an active release mechanism to the pulmonary route of administration. In this study, polybutylcyanoacrylate nanoparticles and ciprofloxacin hydrochloride hydrate were used as two different model substances for pulmonary delivery. Ciprofloxacin is a powerful antibiotic that is used orally to treat cystic fibrosis. However, currently there are no commercial dosage forms available for the pulmonary delivery of this antibiotic. Drug release and dispersion of nanoparticles were separately compared using lactose carrier particles that dissolve without effervescent reaction, to the new effervescent carrier particles.

2. Materials and methods

2.1. Chemicals

Butylcyanoacrylate was a gift from Loctite Ltd (Dublin, Ireland). Dextran 70 (~70 kDa), L-Leucine, ammonium hydroxide, Rhodamine G8, citric acid and fluorescein isothiocyanate-dextran (FITC-Dextran) were obtained from Sigma Chemical Co. (St. Louis, MO, USA). Lactose monohydrate was obtained from Wyndale (Kapuni, New Zealand). Sodium carbonate anhydrous was obtained from BDH Inc. (Toronto, ON, Canada). Polyethylene glycol (PEG) 6000 was obtained from Fluka Chemika-Biochemika (Buchs, Switzerland). Polysorbate 80 was from BASF (Ludwigshafen, Germany). 316 Silicone Release Spray was purchased from Dow Corning (Midland, MI, USA). Ciprofloxacin hydrochloride hydrate was obtained from US Biological (Swampscott, MA, USA). Cargille, oil, Type DF, SPI, was obtained from West Chester, PA. All chemicals were of analytical grade and used as received.

2.2. Preparation of poly (Butylcyanoacrylate) nanoparticles (PBCN)

Butylcyanoacrylate nanoparticles were prepared by a standard procedure [18]. In brief, 100 μl of the monomer was slowly added by pipette to an HCl 0.01 N solution, containing 0.0900 g Dextran 70.000 and 0.01 g of fluorescein isothiocyanate-dextran 70,000 (FITC). The polymerization was carried out under stirring (600 rpm) at room temperature for 4 h. The pH of the resulting colloidal suspension was neutralized using sodium hydroxide and did not exceed pH 7. Nanoparticles were protected from light through the polymerization process. The nanoparticles were purified from unbound dye by centrifugation at 20,000*g* (Beckman Model J2-21) for 10 min. The particles were purified by three cycles of centrifugation and redispersion in fresh water. After centrifugation the supernatant was removed and the nanoparticles were resuspended in 1 mL of sterilized water.

2.3. Preparation of empty carrier particles and ciprofloxacin carriers

Seven grams of lactose monohydrate was used to prepare the spray-dried samples. Lactose was added to 100 mL of distilled water. To produce the new carrier particles, different formulations that were used in effervescent tablets were tested. Sodium carbonate and citric acid were tested using different concentrations (see Table 1). Additionally lactose, ammonia water and excipients including L-leucine, PEG 6000 and polysorbate 80 were used. 0.6 mg of methanol solution of Rhodamine G8 was added to the 100 mL of effervescent solution to stain the carrier matrix. The lubricants were chosen from a selection of excipients considered suitable for inhalation [8,16,19] or proven to be safe for human use. Solid ingredients were weighed and added to an aqueous ammonia solution. 10 ml of ammonia was used to increase the pH of the solution to inhibit an effervescent reaction prior to spray drying. The pH was maintained at approximately 8.0. Carrier particles containing ciprofloxacin were prepared using 100 mg of ciprofloxacin hydrochloride hydrate. The drug was first dissolved in HCl 0.01 N and then added to the ammonia–carbonate solution and to the lactose solution. A Büchi 190 Mini–Spray Dryer (Büchi AG, Flawil, Switzerland) was used to produce the carrier

Table 1
Ingredients used for the formulations

	Ingredients used	Concentration tested (%)
Carbonates	Sodium carbonate	0.75–1.5
Acid	Citric acid	1.2
Lubricants	L-Leucine	0.8–1
	Polyethylene glycol 6000	0.8–1
Alcohols	Ethanol	10–30
Surfactants	Polysorbate 80	1
	Sodium lauryl sulfate	1

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particles. The diameter of the nozzle was 0.7 mm. In each experiment, 100 mL of either lactose solution or effervescent solution was spray dried at an inlet temperature 120–160 °C, and an aspirator setting of 15 (out of 20), the air flow in the nozzle was 800 NormL/h and a feed rate of 2 mL/min was used (see Table 2) The spray-dried powders were collected in vials. Immediately after their collection, the powders were stored in a desiccator over silica gel.

2.4. Determination of ciprofloxacin loading efficiency

Fifteen milligrams of the effervescent or lactose powders was dissolved in 100 ml of water. Before the measurements, the samples were filtered (0.22 μm). The dissolved ciprofloxacin content was analyzed using UV spectroscopy at $\lambda = 271$ nm (SPECTRONIC 3000 ARRAY – Milton Ray). A calibration curve was established, the correlation coefficient for the calculated linear regression was 0.9999 and the correlation equation was used to determine the dissolved drug content.

2.5. Incorporation of the nanoparticles into carrier particles and fluorescent labeling

Seven milliliters of a suspension containing polybutylcyanoacrylate nanoparticles was added to either a 7% lactose solution, or to a 7% lactose solution containing PEG 6000 and L-leucine, or to an effervescent formulation solution or to an effervescent formulation solution containing PEG 6000 and L-leucine (5 mL of 2.5% L-leucine and 2.5% PEG). The lactose solution was spray dried at temperatures between 150 and 160 °C and the corresponding outlet temperature was 130 °C. The effervescent formulation was spray dried at temperatures between 125 and 130 °C and the outlet temperature was approximately 110 °C.

2.6. Physico-chemical characterization of the nanoparticles and the carrier particles

2.6.1. Particle size

The particle size was measured using photon correlation spectroscopy (HSA3000, Malvern Instruments, UK). Three milliliters of fresh filtered (0.45 μm) water was filled into a disposable cuvette. An aliquot of approximately 100 μl nanoparticle suspensions was added to the cuvette. Samples were sonicated for 1 min immediately prior to measurement. To measure the size of nanoparticles after spray drying, an adequate amount of both lactose and effervescent powder containing nanoparticles was dissolved in distilled and filtered water and sonicated immediately prior to measurement.

Table 2
Spray drying parameters

Parameters	Effervescent powders	Lactose powders
Inlet temperature	125–130 °C	155–160 °C
Outlet temperature	110 °C	130 °C
Atomizer air flow rate	800 NormL/h	800 NormL/h
Feed rate (pump)	2 mL/min	2 mL/min
Air flow rate (dial setting)	15	15
Heating rate (dial setting)	10	15

2.6.2. Mass median aerodynamic diameter (MMAD)

The MMAD was measured using a Mark II Andersen Cascade Impactor (Thermo Andersen, Smyrna, GA) in combination with a new high efficiency inhaler [20] as shown in Fig. 1. This inhaler deagglomerates powders to a higher percentage compared to conventional inhalers. It utilizes a cyclone action and mechanical impaction to disperse powder particles [20]. The flow rate used was 60 l/min. Calibration of the Andersen at the higher flow rate of 60 l/min has been published by Nichols et al. [21] and this calibration is used here. The MMAD was calculated by a nonlinear regression fit of a log-normal function to the data.

2.6.3. Fine Particle Fraction (FPF), Geometrical Standard Deviation (GSD) and Emitted Dose (ED)

In this study, fine particle fraction (FPF) was defined as the fraction of loaded powder that was collected on plates 1–6 (i.e., aerodynamic diameter $\leqslant 5.6$ μm, at a flow rate of 60 l/min). The Mark II Andersen Cascade Impactor was used to determine the fine particle fraction. Geometric standard deviation is a measure of the variability of the particle diameter within the aerosol [7]. It is defined by the ratio of the diameters of particles from aerosols corresponding to 84% and 50% on the cumulative distribution curve of the weights of particles. To calculate the GSD, a nonlinear least squares analysis with a log-normal function was used. The emitted dose was calculated as the amount of loaded powder minus the amount collected in the Andersen Cascade Impactor.

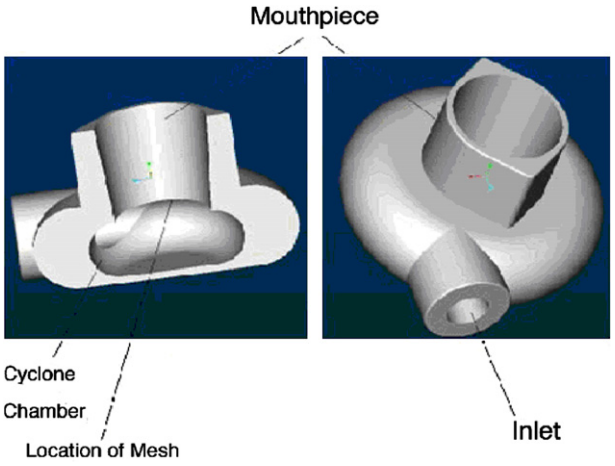

Fig. 1. Dry powder inhaler.

2.6.4. Scanning-electron microscopy (SEM)

The lactose and effervescent powders were sprinkled onto a stub with silicon from a sticky tab. The unbound powders were dusted out by an air gun. The samples were coated with gold sputter using a S150B Sputter Coater (BOC Edwards, Crawley, West Sussex, UK) and examined by scanning electron microscope (S2500 SEM, Hitachi, Tokyo, Japan).

2.6.5. Confocal laser scanning microscopy (CLSM)

The geometric diameter of the spray-dried powders, the distribution of the nanoparticles through the carrier particles and effervescent effect of the carrier particles were investigated using a Zeiss LSM 510 confocal laser-scanning microscope (Oberkochen, Germany). The LSM 510 Software, version 2.0 was used to control the microscope and to analyze the images. The carrier particles were labeled with a red fluorescent label and the nanoparticles with a green fluorescent label. Small amounts of the powders were dispersed in immersion oil on glass slides and visually observed. The samples were observed before and after being exposed to humidity. The oil phase prevented any contact of humidity with the particles during the observation of the images. The particle morphology (porous vs. solid) was investigated by imaging different layers of the carrier particles.

3. Results

Different powder compositions were tested in order to produce carrier particles with an appropriate size. Lactose is the most common type of excipient used for dry powder lung delivery and is well documented in the literature [22,23]. Blank lactose carrier particles were spray dried at inlet temperatures between 140 and 160 °C. The mass median aerodynamic diameter of the carrier particles was analyzed using the Andersen cascade impactor. Ten samples of lactose carrier particles were analyzed and the mean MMAD was found be 10 μm or larger. The fine particle fraction (FPF) was found to be $13.86\% \pm 5.56$ ($n = 8$). Fig. 2 shows a lactose powder that was made without the presence of any other solvent or excipients. The image shows that the majority of the particles in this powder were spherical.

In oral tablet formulations, effervescent formulations use a mixture of acids such as citric acid and carbonates. A typical ratio that generally achieves a fast effervescent reaction and acceptable stability uses a mixture of 50% sodium carbonate and 50% sodium bicarbonate [24]. However, sodium bicarbonate decomposes at temperatures above 50 °C and for this reason it is not recommended to be used for spray-drying procedures which use temperatures that will exceed this value in the powders. The effervescent reaction is pH dependent. Two components react in an aqueous environment as shown in the formula.

$$\mathrm{R{-}COOH} + X\mathrm{HCO_3} \xrightarrow{\mathrm{H_2O}} \mathrm{R{-}COOX} + \mathrm{CO_2} + \mathrm{H_2O}$$

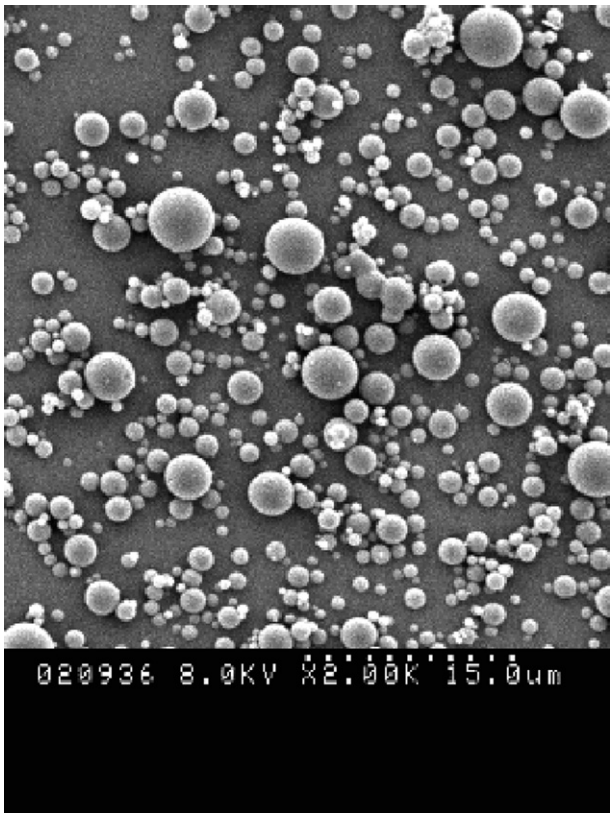

Fig. 2. SEM image of typical lactose particles observed after spray drying of a 7% of lactose solution.

As shown, this reaction releases carbon dioxide. The phase transition from a solid to a gas phase increases the volume and this is used in tablets to increase tablet disintegration and drug dissolution [25].

To produce inhalable effervescent powders, the first step was to establish an effervescent formulation. The basic formulation contained sodium carbonate, citric acid and water. However in order to prevent an effervescent reaction from happening before spray drying, the pH of the solution was increased using ammonia in order to maintain the pH at 8.0. The ammonia evaporates in the spray-drying process and the resulting powders contain citric acid and carbonate in the solid state.

Different ingredients such as ethanol, polysorbate 80, L-leucine and PEG 6000 were added to the basic formulation to improve the particle size and to achieve an appropriate MMAD. In addition, different concentrations of lactose were tested. Different amounts of lactose had a large impact on the size and morphology of the carrier particles. Increasing the amount of lactose led to smaller and denser particles and also produced particles with more spherical shape. These results are in agreement with results reported by Vanbever et al. [19]. Fig. 3 shows a sequence of SEM pictures with increasing concentrations of lactose and consequently increasing the MMAD of the carrier particles. The MMAD of the particles, measured by cascade impaction, were 3.85, 5.22, 8.3, and 10 μm, respectively.

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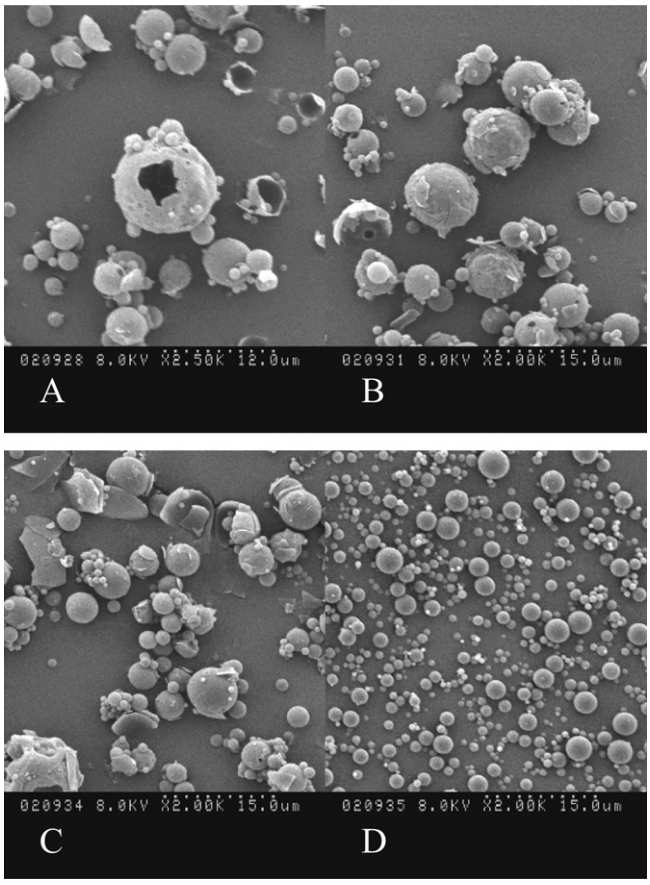

Fig. 3. SEM images of spray-dried effervescent formulations containing (A) 1.2% lactose, (B) 2.4% lactose, (C) 3.5% lactose, and (D) 10% lactose.

Ethanol was added to the formulation with the objective of producing larger porous particles with a lower density. However our results showed that when ethanol was used it did not improve the particle size or the morphology of the carrier particles. The MMAD was still approximately 8.5 μm and not suitable for deep lung deposition. This might be due to the relatively low ethanol concentrations used, which were between 10 and 30% v/v. Other studies have reported using up to 70% of the total volume of ethanol to produce porous particles [16]. Polysorbate 80 also did not show any improvement in particle size when compared to the lactose formulation. A large improvement in particle size and MMAD was observed when 5 mL of both solutions containing 2.5% L-leucine and 2.5% PEG 6000 was added to the formulation. For these effervescent carrier particles the average MMAD were 2.17 ± 0.42 μm, FPF was approximately $46.47 \pm 15\%$ and the GSD was $2.00 \pm 0.06\%$ (see Table 3). The emitted dose for powders made just of lactose was found to be $73.38 \pm 13\%$ and for powders containing the L-leucine/PEG 6000 effervescent formulation was $68.55 \pm 23.90\%$.

Using L-leucine and PEG 6000 (powder 5) in the effervescent formulation, it was possible to obtain inhalable particles as indicated by the SEM pictures in Fig. 4. These particles show a more irregular morphology when compared to the highly spherical lactose carrier particles. For all the following experiments this formulation was used.

3.1. Comparisons of drug release from effervescent and conventional carrier particles

Ciprofloxacin is poorly water soluble at physiological pH. Its drug release from conventional lactose particles was compared with the effervescent formulation. The results show that the effervescent carrier particles released $56 \pm 8\%$ ciprofloxacin into solution compared with $32 \pm 3\%$ when lactose particles were used, which is a significant difference (t-test, $P < 0.05$). The remaining drug was visual as precipitate before filtering the solution.

3.2. Carrier particles containing PBC nanoparticles

Polybutylcyanoacrylate nanoparticles were spray dried in an aqueous solution containing lactose as well as the effervescent preparation. In order to compare the different formulations and the effects of effervescent reaction and excipients, four types of powders were produced. The amount of L-leucine and PEG was kept constant in all formulations. The particle diameter of the nanoparticles was measured before and after spray drying. A t-test was performed to compare the sizes of the samples before and after spray drying. When only lactose was used, the nanoparticles had a size of 126.17 ± 20.20 nm before and 259.00 ± 52.70 nm after spray drying. This is a statistically significant increase in particle size at a P value <0.05. For lactose containing PEG and L-leucine the particle size before was 247.5 ± 13.4 nm and 225 ± 11.17 nm afterwards. For the effervescent particles the results were 244 ± 26.8 nm and 252 ± 29 nm before and afterwards, respectively. Using the effervescent preparations containing L-leucine and PEG 6000, the size before spray drying was 149.9 ± 26.46 nm and the size after spray drying was 176.83 ± 15.45 nm. For the last three formulations a t-test did not indicate a statistical difference between the nanoparticles before and after the spray drying process.

3.3. Effervescent properties of the carrier particles containing nanoparticles

The effervescent properties of the carrier particles were observed when the carrier particles were exposed to water, aqueous surfaces or moist air. Fig. 5 shows a carrier particle, which was under 5 μm in diameter with spherical shape (Fig. 5A–D). The nanoparticles were distributed continuously throughout the carrier particle matrix. Fig. 6 shows the swelling and dissolution of the carrier particles after exposure to humid air (Fig. 6A–C). The matrix of the particles dissolves (red channel) while a green bubble of more than 30 μm is filled with nanoparticles. This indicates that the nanoparticles were actively distributed throughout the gas bubble. If the effervescent powder

Table 3
Particle size measurements are given for a variety of spray-dried powders

Powder	MMAD (μm)	FPF (%)	GSD
Blank lactose (7% lactose)	10	13.86% ± 5.56	–
Ethanol 30%	8.5 ± 1.8	17.87 ± 4	–
Lactose 10%	10	17.60 ± 3.5	–
Polysorbate 80	10	12.50 ± 2	–
Five milliliters of a 2.5% solution of both L-leucine and PEG 6000	2.17 ± 0.42	46.47% ± 15	2.00 ± 0.06

Powder 1 was spray drying only with lactose. Powder formulations from 2 to 5 were all effervescent formulations that included the listed excipients.

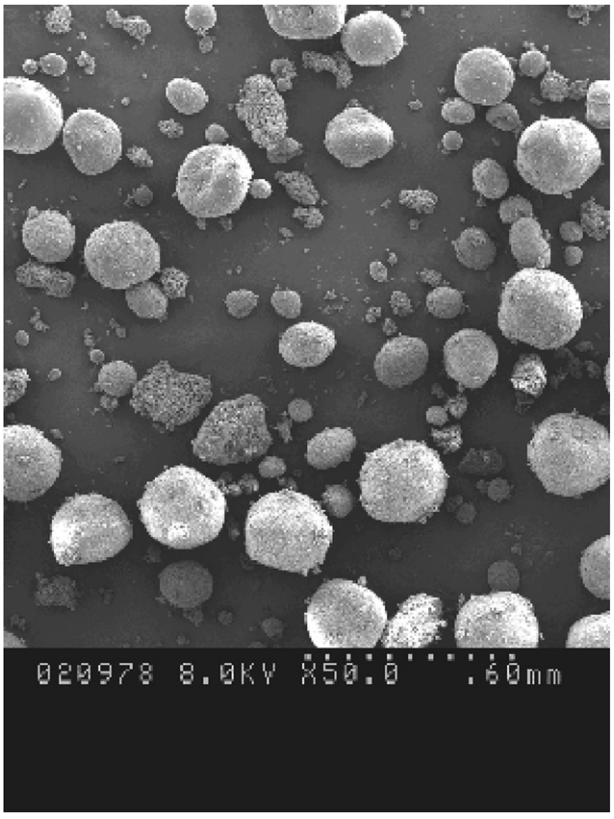

Fig. 4. Scanning electronic micrograph of inhalable effervescent particles containing L-leucine and PEG 6000 as excipients. Some asperities are present on the surface of the carriers due to the presence of PEG 6000.

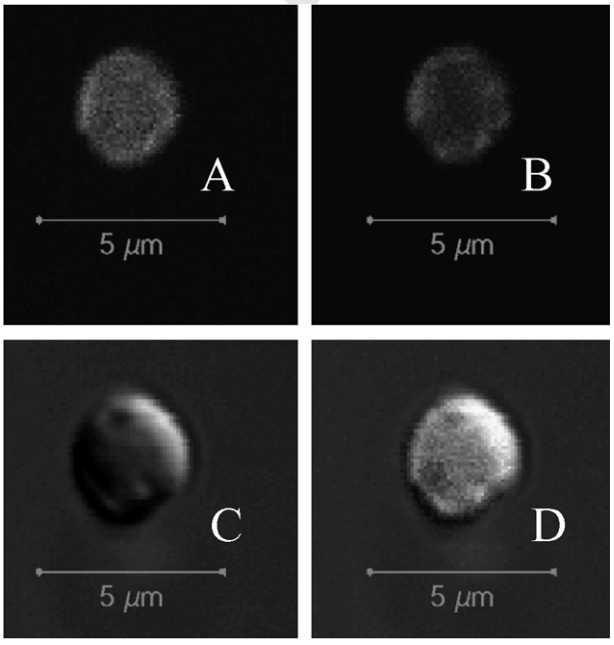

Fig. 5. Confocal microscopy pictures of an effervescent carrier particle. (A) Green channel shows the nanoparticles distributed continuously through out the carrier particle. (B) Red channel shows the matrix of the carrier particle. (C) Particle in normal light. (D) Super imposed picture of the red and green channels.

was dispersed in water, small gas bubbles were visible immediately after dispersion.

4. Discussion

In this paper, different powder compositions were produced in order to develop and partially optimize an effervescent aerosol carrier particle formulation. To improve particle size, the addition of L-leucine, PEG 6000, polysorbate 80 and ethanol was examined. The most pronounced effect on particle size occurred with the addition of L-leucine and PEG 6000, which improved the aerodynamic characteristics of the powder particles. The in vitro results indicated that the particles were suitable for deposition throughout the lungs. These results are also in agreement with other studies [8,26]. Gliński et al. found that when L-leucine was added to a water solution it caused a rapid decrease in the surface tension [26]. In addition, L-leucine allows the preparation of powders with better aerolization properties [27]. Corrigan et al. and Gilane et al. investigated the use of PEG in their formulations [28,29]. They found that polyethylene glycol had a major impact on the size and morphology of carrier particles. In addition, the presence of PEG 6000 changed the surface texture of the carrier particles from a smooth surface to a more aspirated surface. Similar effects were observed in our study using the effervescent formulation. In addition the presence of polyethylene glycol might also influence the crystalline and polymorphic form of spray-dried lactose and presumably of incorporated drugs [28,29].

The results reported for the emitted dose are satisfactory for both the dry powder formulation containing just lactose and the dry powder L-leucine/PEG 6000 formulation containing effervescent carrier particles. However the emitted dose achieved for the lactose carrier particles mostly contained powder particles which were too large

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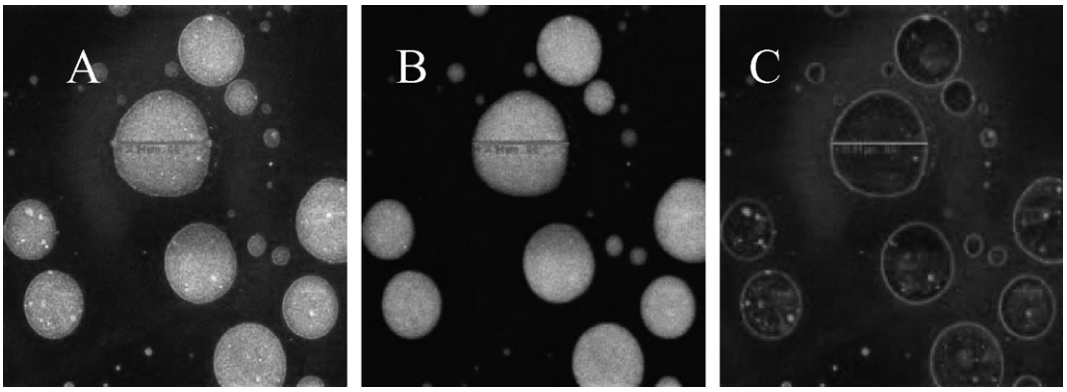

Fig. 6. Confocal microscopy picture of effervescent particles exposed to humidity. (A) Super imposed red and green channel showing gas bubbles of different diameters. (B) Green channel showing the nanoparticles distributed throughout the gas bubble. (C) Red channel showing the dissolved carrier matrix.

for deep lung deposition, since this powder mainly deposited on plate zero of the cascade impactor while most of the effervescent powder was deposited on plates 2, 3, and 4, as shown by the FPF of $13.86 \pm 5.56\%$ for the lactose formulation and $46.46 \pm 15\%$ for the effervescent formulation.

The formulations containing effervescent release mechanisms and the lactose formulations that contained L-leucine and PEG 6000 were able to release nanoparticles with less agglomeration compared to the carrier particles made just of lactose which lack an active release. The results show that both the effervescent formulation and the choice of excipients had a major effect on the release of nanoparticles. The effervescent reaction of the carrier particles generates forces that helped the nanoparticles to disperse more efficiently and avoid particle aggregation. Sham et al. [12] conducted a study using lactose carrier particles containing nanoparticles. In the cited study it was found that some clusters of nanoparticles were observed in the carrier particles, which increased the nanoparticle size after spray-drying. Our results showed a significant increase in the size of the released nanoparticles when lactose alone was used as carrier. However, when effervescent carrier particles were used, no statistically significant difference was observed. These findings indicate that the effervescent reaction appears to improve the dispersion of the nanoparticles from the carrier particle.

Ciprofloxacin was used as a model drug in order to evaluate the effect of active drug release from the carrier particles compared to passive release and dissolution. It was found that the effervescent carrier particles were able to increase the drug dissolution. Rygnestad et al. reported that effervescent paracetamol tablets were absorbed significantly faster compared to conventional tablets [30]. Dosage form disintegration and drug dissolution are typically increased when effervescent formulations are used. However, more studies are needed to evaluate if an effervescent inhalable powder can increase the absorption and bioavailability of drugs in the lungs due to improved drug dissolution properties.

5. Conclusion

A new formulation was established for the use in the pulmonary route of administration. The new formulation contained effervescent and lubricant excipients. The active release mechanism increased drug dissolution and enhanced the dispersion of nanoparticles over the effervescent gas bubble interface. These carrier particles can be synthesized with an adequate particle size for deep lung deposition. Furthermore, effervescent carrier particles can be used to deliver a large range of substances to the lungs with possibly a faster release compared to conventional carrier particles. However further studies are required to evaluate how the effervescent particles will behave at the lung surfactant air interface.

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