

Electrostatic Charging of Spray Dried Salbutamol Sulfate Aerosols: Effect of excipient L-leucine

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Summary

Understanding the electrostatic charging of inhalable powders is relevant to dry powder inhalers formulation as particle charges may influence deposition. This study examined the triboelectric charging behaviour of spray-dried salbutamol sulfate formulated with L-leucine at fixed L-leucine concentrations in a range between 5–95% w/w. Electrostatic charge measurements were conducted using an Electrical Low-Pressure Impactor housed in a controlled environment cabinet maintained at 50% relative humidity. The incorporation of L-leucine markedly influenced both the magnitude and polarity of the net charge. A polarity reversal from positive to negative was observed at 5% L-leucine, with the highest charge magnitudes recorded between 5–30% L-leucine. At L-leucine concentrations $\geq 40\%$, a reduction in charge and reversion to positive polarity were observed. The presence of L-leucine was found to suppress charging, likely due to its surface enrichment and affecting charge transfer during dispersion. This finding offers valuable insights into the interplay between formulation composition and particle surface characteristics in governing electrostatic charging during aerosolization of dry powder inhaler formulations.

Key Message

L-leucine reduces electrostatic charge accumulation in salbutamol sulfate powders due to its surface enrichment. However, the charge-suppressing effect was nonlinear: a low concentration of L-leucine (5%) had minimal impact, while concentrations $\geq 20\%$ resulted in a more pronounced charge reduction.

Introduction

Electrostatic charge plays a critical role in dry powder inhaler (DPI) formulations by influencing particle flow, aerosol dispersion, and deposition in the respiratory tract [1]. Charged particles may attract or repel one another, directly impacting drug delivery and dose consistency [2]. Triboelectrification—charge generation through friction between particles or between particles and surfaces—occurs during spray drying and handling of pharmaceutical powders [3]. Charge transfer can involve electrons, ions, or material fragments between contacting surfaces [4]. Electrostatic lung deposition occurs via two main mechanisms: (1) induced charge, where particles polarize airway surfaces that induce opposite charges, and (2) space charge, where like-charged particles repel, affecting dispersion [5].

Despite its significance, the charging behaviour of pharmaceutical powders remains poorly understood, especially regarding the variability in charge magnitude and polarity [6,7]. This knowledge gap extends to interactions between active pharmaceutical ingredients (APIs) and excipients. Salbutamol sulfate (SS), a common bronchodilator, is often used in DPI formulations but suffers from high hygroscopicity, making excipients essential for performance optimization. L-leucine (LL), a naturally occurring amino acid, has shown potential in improving SS aerosolization by modifying surface properties and reducing cohesion [8]. Particle size, shape, and morphology—factors influenced by formulation—can also affect charge behaviour [9].

The objective of this study is to assess the impact of LL on the electrostatic charge characteristics of the spray-dried particles of SS during aerosolization. An ELPI was employed to measure the powder charge magnitude and polarity dispersed at 50% relative humidity (RH).

Materials and Methods

Materials: Raw salbutamol sulfate was provided by NanoMaterials Technology Pte Ltd. (Singapore). L-leucine was purchased from Sigma-Aldrich Co. LLC. (Castle Hill, New South Wales, Australia). Methanol used was of HPLC grade, and all other chemicals were analytical grade. Ultrapure water with resistivity at 18.2 M Ω -cm was obtained from a MilliQ® Direct Water Purification System (Millipore, Bedford, Massachusetts, United States).

Production and characterization of spray-dried powders: Salbutamol sulfate and LL were dissolved in ultrapure water in varied mass ratio of LL (0–95%) at a total solid content of 10 mg/mL. The spray dryer (B-290 mini spray-dryer, Buchi Labortechnik AG, Falwil, Switzerland) was operated under the following

conditions: atomizer 60 mm (742 L/h), inlet temperature 110°C, outlet temperature 68-70°C, feed rate 1.8 ± 1 mL/minute; aspirator 100% (approx. 35 m³/h). The spray-dried powders were stored in a desiccator containing silica gel, molecular sieve, and P₂O₅ at 20±3°C until used.

Characterization of spray dried powders were done as follows: (1) *Particle size distribution* of the powders was analyzed using Mastersizer 3000 equipped with an Aero S dry powder accessory (Malvern Panalytical Ltd., UK) Measurements were conducted in triplicate; (2) *Particle crystallinity* was analyzed via X-ray diffraction (XRD) using Rigaku SmartLab SE (Rigaku Corporation, Tokyo, Japan). Diffraction data were collected using an XSPA-400 ER two-dimensional detector scanning continuously at 5°/min over the 2 θ angle range of 5 to 50°; (3) *X-ray photoelectron spectroscopy* (XPS) was analyzed using Thermo Fisher Scientific K-Alpha with XPS/UPS system (Thermo Fisher Scientific, Waltham, MA, USA). Six sampling points were scanned from each sample powder. Reference data were first obtained from pure compounds to calculate the relative percentages of SS and LL on the surface of the composite particles.

Content uniformity tests were conducted by weighing 5 ± 1 mg of spray-dried powder into a 10 mL volumetric flask, followed by dissolving them in water. The samples were vortexed and left at ambient conditions for at least 15 minutes to ensure complete dissolution. The concentrations of SS and LL were quantified using high performance liquid chromatography (HPLC), as specified below. Ten samples were analysed for each formulation.

Charge measurement and mass quantification: The charge of spray-dried powder was measured by a modified ELPI (Dekati Ltd, Finland). The corona charger was replaced with a stainless-steel straight tube [10]. Silicone grease (DC Products PTY LTD, Australia) was sprayed onto the stages to prevent particle bounce. The grease was allowed to stick onto the stages in the fume hood before reassembling them to the ELPI. The ELPI was operated at a flow rate of 30 L/min and a pressure of 100 mbar. Sample powders (20 ± 1 mg) were loaded in a capsule (size 3 hydroxypropyl methylcellulose transparent capsules, Capsugel, West Ryde, Australia) and dispersed from a HandiHaler® (Boehringer Ingelheim, Pharma GmbH & Co. KG, D-55216 Ingelheim, Germany) in the controlled environment cabinet at 22°C and 50% RH. Immediately after dispersion, all ELPI parts were disassembled, the mass deposited on them was extracted with 5 mL of water for all parts, except the capsule was extracted with 15 mL of water.

The deposited drug and excipient were assayed with HPLC system (Shimadzu CBM-20A controller, LC-20AT pump, SIL-20A HT autosampler, and SPD-20A UV/VIS detector). The mass of LL in the SS and LL formulations was calculated by proportion based on the SS mass measured in the HPLC assay. The chromatographic conditions for SS were as follows: column Nova-Pak C18 (4 μ m, 3.9x150mm, Part No. WAT086344, Waters); injection volume 10 μ L, mobile phase 60% methanol: 40% deionised water: 1.0 g/L sodium lauryl sulfate, flow rate 1 mL/min, oven temperature 30°C, detection wavelength 276 nm. For the pure LL powder, LL was quantified using the same chromatographic conditions as those for SS, except that the mobile phase was phosphate buffer (sodium phosphate dibasic 3.4 g/L, and sodium phosphate monobasic 0.817 g/L), detection wavelength 205 nm.

Results

The production yields for spray-dried SS and LL in various formulations ranged between approximately 52.02% and 72.97%, and the powder recoveries were close to 100% (Table 1). The majority of the particles were smaller than 5 μ m, with pure spray-dried SS (100% SS) showing the lowest D50 (1.43 ± 0.03 μ m), and pure spray-dried LL (100% LL) showing the largest D50 (1.92 ± 0.01 μ m), span values ranging from 1.43 to 1.66. Generally, the more LL added in the feed concentration the larger the D50.

Spray-dried SS was amorphous, while spray-dried LL remained crystalline. Co-spray-dried powders showed increasing crystallinity with $\geq 30\%$ LL. They were amorphous when LL content was $\leq 20\%$ (Figure 1). An increase in LL content generally resulted in a higher LL presence on the particle surface. Theoretically, it should be linear, but experimental results show a sharp increase of LL on the particle surface when LL concentration increased from 5% to 20%. However, after 70SS30LL formulation, the rise of % surface coverage was minimal, less than 5% (Table 1).

Overall, the charge profiles of spray-dried SS and LL were bipolar, characterized by positive and negative charges across different particle sizes (Figure 2). Spray-dried pure SS was positively charged for particle sizes ≥ 1 μ m, with the highest charge of +0.76 nC observed on stage 9 (cut-off diameter 1.6

μm). Spray-dried pure LL showed negative charges with a lower magnitude for particle sizes $> 1 \mu\text{m}$, reaching a minimum of -0.44 nC on the same stage. The charge in the composite powders varied depending on the proportion of SS and LL. The mass profiles for all formulations exhibited similar trends, with a peak on stage 10 (cut-off diameter $2.4 \mu\text{m}$). The charge-to-mass ratios of spray-dried pure SS were mainly positive, whereas those of spray-dried pure LL were mainly negative. The charge-to-mass ratios in the composite powders varied with the LL content (Figure 2).

Table 1. L-leucine surface coverage, content uniformity and particle size distribution of spray-dried powders.

Formulations*	LL surface coverage (%)	Content uniformity (%)
100SS	0.0	102.7 ± 1.4
95SS5LL	4.1	101.5 ± 2.2
80SS20LL	27.7	101.3 ± 3.0
70SS30LL	64.9	102.7 ± 2.9
60SS40LL	68.4	102.5 ± 2.8
40SS60LL	77.9	102.3 ± 2.8
15SS85LL	85.4	103.8 ± 1.4
100LL	100	102.0 ± 3.4

*The labels (e.g., 100SS, 95SS5LL, etc.) represent the compositions of salbutamol sulfate (SS), and L-leucine (LL) in percentages. For example: 100SS is pure salbutamol sulfate; 95SS5LL is a formulation with 95% salbutamol sulfate and 5% L-leucine; 100LL is pure L-leucine.

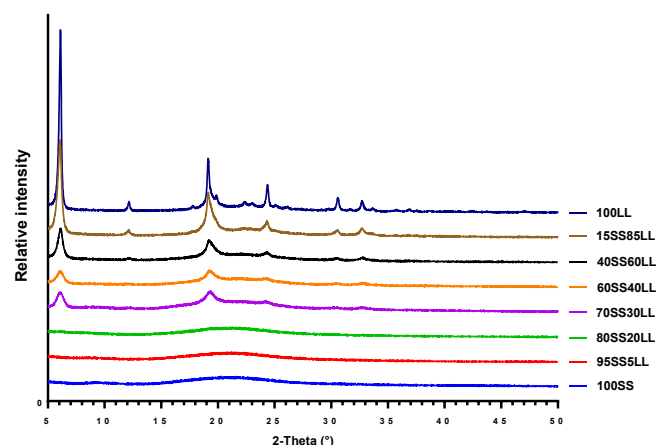


Figure 1 –X-ray powder diffraction patterns of (a) raw materials and (b) spray-dried powders.

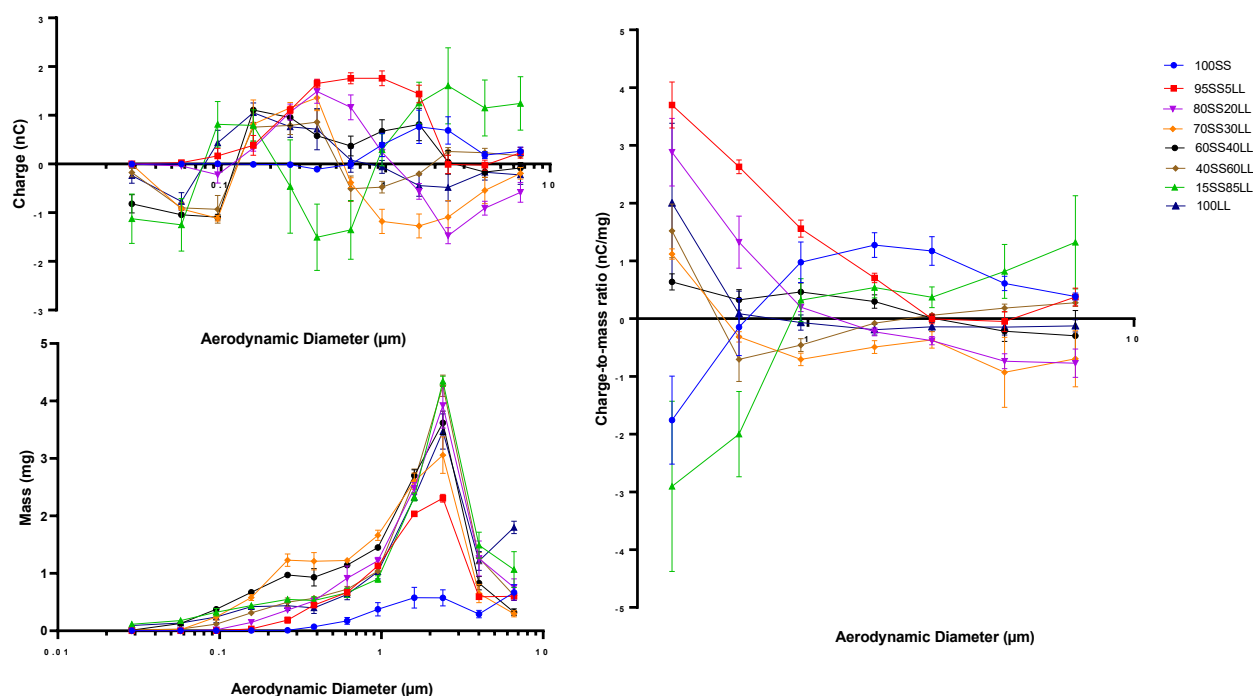


Figure 2 – Charge, mass, and charge-to-mass ratio profiles of the spray-dried powders. Data presented as mean $\pm$ standard deviation ($n = 3$).

Discussion

This study demonstrates that the incorporation of LL significantly altered the electrostatic behaviour of spray-dried SS upon aerosolization. L-leucine's influence was closely tied to its crystallization behaviour, surface localization, and ability to modify particle morphology and charge characteristics. Formulations containing more than 5% LL exhibited marked changes in charge magnitude and polarity. L-leucine

altered net charge polarity in a concentration-dependent manner. Charge polarity shifted from positive (pure SS) to negative at 5% LL, then fluctuated with increasing LL content—peaking between 5–30% LL and eventually declining and reverting to positive polarity above 40% (Figure 2).

These trends closely followed the crystallinity of the powders (Figure 1). The XRD analyses confirmed that spray dried LL was highly crystalline, while spray-dried SS was predominantly amorphous. LL began to crystallize on particle surfaces during spray drying. Crystallinity increased substantially above 30% LL. Amorphous particles—prevalent at low LL content—possessed disordered surfaces rich in defect sites, promoting higher charge accumulation via contact electrification. Crystalline particles, in contrast, exhibited fewer defects and a more uniform surface energy landscape, leading to lower, more consistent charge magnitudes [11].

Data from the XPS results (Table 1) showed that LL has high proportion in the particle surface. Surface morphology changes further corroborated this trend. SEM (Scanning Electron Microscopy) imaging from previous study [8] revealed that LL introduced surface corrugation at low concentrations and progressed to deep invaginations and crack formation at higher levels. These rough features trapped smaller particles and reduced effective contact area, thereby diminishing charge accumulation and potentially reversing charge polarity [12].

Chemical functional groups in SS-LL also played a central role in contact charging. SS contains hydroxyl, amine, and sulfate groups—functionalities that contribute differently to charge polarity. Typically, hydroxyl and amine groups promote positive charging. LL's structure includes amino, carboxyl, and hydrophobic isobutyl groups, which collectively support negative charging and limit moisture interaction. When combined with SS, LL modified surface chemistry through hydrogen bonding, ion pairing, and hydrophobic interactions. XPS confirmed that LL increasingly localized on particle surfaces with higher LL content, forming a hydrophobic coating that not only reduced hygroscopicity but also stabilized electrostatic properties. This surface coating helped insulate particles from ambient moisture and environmental influences, contributing to reduced charge variability.

Taken together, these findings underscore the multifaceted role of LL in modulating the electrostatic behaviour of spray-dried powders. LL influenced charge magnitude and polarity through its crystallinity, surface localization, chemical functionality, and ability to reshape particle morphology. By reducing moisture uptake, stabilizing surface energy, and minimizing charge heterogeneity, LL serves as an effective excipient to enhance aerosolization and electrostatic consistency in DPI formulations.

Conclusion

This study showed that LL significantly modulated electrostatic charging in spray-dried SS powders. Increasing LL shifted surface properties from amorphous to crystalline, altering charge magnitude and polarity. Powders with 5–30% LL charged more, while $\geq 40\%$ LL reduced and stabilized charging via increased crystallinity, roughness, and decreased hygroscopicity. Surface chemistry, including functional groups and hydrophobicity, also influenced charge transfer and retention.

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