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A lidocaine dry powder inhaler to modulate cough: particle engineering and human proof-of-concept

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ABSTRACT

Chronic cough remains a major unmet clinical need, particularly in patients with refractory or unexplained disease. This study aimed to develop a spray-dried dry powder inhaler formulation of lidocaine hydrochloride capable of targeting deposition to the upper and central airways, where cough receptors are mainly located, while minimizing deep lung delivery and systemic exposure. Lidocaine was incorporated into sodium hyaluronate, selected as a mucoadhesive and release-modifying excipient. The effects of polymer molecular weight, drug-to-polymer ratio, and spray-drying parameters on the key quality attributes of the formulation were investigated. Low-molecular-weight sodium hyaluronate at a 20:80 lidocaine-to-polymer ratio produced amorphous microparticles with appropriate solid-state characteristics and controlled dissolution behaviour. Optimization identified a lead formulation with a median particle size of 8.9 μm and a non-respirable fraction of about 85%, supporting preferential deposition in the tracheobronchial region. Aerodynamic performance, assessed using a Next Generation Impactor and an anatomically realistic mouth-throat model, confirmed efficient delivery with limited fine particle deposition. Compared with raw lidocaine, the optimized formulation showed slower in vitro release, consistent with drug incorporation within the polymer matrix. In a randomized, single-blind, crossover proof-of-concept study in healthy volunteers, inhalation of 8 mg of lidocaine powder significantly increased the cough threshold at 15 and 30 min versus placebo, without clinically relevant safety concerns, bronchoconstriction, or impairment of the gag reflex. These findings show that particle engineering can enable regional airway targeting of lidocaine by dry powder inhalation and support the potential of this approach as a rapid, on-demand antitussive strategy.

1. Introduction

Cough plays a fundamental protective role in maintaining airways and lung integrity; however, under certain conditions it can become excessive and non-productive, leading to discomfort and potential damage to the airway mucosa (Polverino et al., 2012).

The cough reflex is initiated by the stimulation of cough receptors located principally in the larynx, trachea and carina. Chemical, mechanical, and thermal stimuli activate specific ion channels, leading to membrane depolarization. When this depolarization reaches the threshold, it triggers the opening of voltage-gated sodium (NaV) channels and the subsequent activation of sensory nerves (The American Journal of Managed Care, 2026).

Chronic cough (CC), defined as a cough lasting more than 8 weeks, is a major global health concern, affecting approximately 10% of the adult population and significantly impairing quality of life (National Library of Medicine, 2021). In some cases, cough persists despite treatment of the underlying causes, giving rise to the so-called “refractory chronic cough” (RCC), whereas in other cases no underlying cause can be found leading to the “unexplained chronic cough” (UCC). Safe and effective antitussive treatments remain a major unmet clinical need. Current therapeutic strategies include suppression of central cough pathways (e.

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g. with GABA derivatives or opioids), blockade of specific receptors activated by stimuli (e.g. P2X3 receptor antagonists), or inhibition of signal conduction along afferent nerves via NaV channel blockers. In this context, international guidelines (American College of Chest Physicians and European Respiratory Society) recommend off-label options such as gabapentin and low-dose slow-release morphine when approved alternatives are lacking. Although agents such as the oral P2X3 antagonist gefapixant are now available in some settings, their efficacy remains modest and adverse effects may limit their clinical use (National Library of Medicine, 2021; National Library of Medicine, 2024). Currently, the administration of hypertonic divalent salts (HDS) via a soft mist inhaler (droplet size ~ 13 μm) is under clinical evaluation and has shown efficacy in reducing daily cough frequency in RCC patients (Abubakar-Waziri et al., 2024; Yahoo Finance, 2024).

Inhalation therapy represents one of the most effective and safe approaches for the treatment of respiratory diseases, as it enables direct drug delivery to the lungs, rapid onset of action, high local concentrations, and reduced systemic exposure (Borghardt et al., 2018). In the treatment of cough, however, deep lung deposition should be avoided to limit systemic absorption and the associated risk of side effects (Covino1, 1981). Instead, the optimal aerodynamic particle size for deposition in the airway regions where cough receptors are mainly located is estimated to range between 6 and 12 μm. This target range was selected to favour deposition in the upper and central conducting airways rather than in the peripheral lung. Particles with aerodynamic diameters below approximately 5 μm are conventionally considered respirable and are more likely to reach the lower airways, whereas larger particles are preferentially retained in the mouth-throat and central airway regions. Therefore, a formulation enriched in particles above the conventional respirable range was considered appropriate for targeting cough-relevant airway regions while limiting deep-lung exposure.

Local anaesthetics are non-selective inhibitors of voltage-gated sodium (NaV) channels and may exert antitussive effects (National Library of Medicine, 2023). Interest in lidocaine as an antitussive dates back several decades, with studies from the late 1970 s and early 1980 s showing that nebulised lidocaine can reduce cough frequency and intensity in respiratory patients (National Library of Medicine, 2025; Buttini et al., 2012; Lim et al., 2013). In a retrospective study of off-label nebulised lidocaine, symptomatic control was reported in 49% of patients; no serious adverse events occurred, although many patients were dissatisfied because of oropharyngeal anaesthesia and dysphagia (Lavorini et al., 2019). A randomised placebo-controlled trial in RCC found that lidocaine throat spray significantly reduced cough frequency over 10 h—particularly during the first hour—whereas nebulised lidocaine was not superior to placebo. These findings emphasise the importance of formulation and delivery method in determining deposition site and clinical efficacy (Sonvico et al., 2021).

In this context, a NaV blocker-containing dry powder inhaler (DPI) is under clinical development (Taplucainium NOC-110/NTX-1175; Nocion Therapeutics) (National Library of Medicine, 2023; National Library of Medicine, 2025). This product selectively inhibits sodium channels in activated sensory neurons expressing large-pore channels, without affecting non-nociceptors or passively diffusing into surrounding tissues. This example supports the rationale that DPI may represent an effective approach for the CC localized treatment.

Spray drying with specific particle-forming excipients enables the engineering of particle properties in terms of shape, size, and morphology, thereby optimising the aerodynamic performance of inhalable formulations (Buttini et al., 2012) as well as to control and sustain the drug release. This is particularly important for freely soluble drugs, such as lidocaine hydrochloride, which dissolve rapidly and could be quickly cleared by the mucociliary clearance system.

To our knowledge, no inhalable lidocaine formulation is currently under clinical investigation for this indication. Nevertheless, off-label nebulization of injectable solutions is well documented in literature with doses typically ranging from 300 to 600 mg (Abubakar-Waziri et al., 2024; Lim et al., 2013). In this respect it is worth underscoring the significant drug loss associated with nebulization, owing to device retention and environmental dispersion. In addition, the typical respirable fraction obtained with such devices ranges from 40 to 70% (Lavorini et al., 2019). Because conventional nebulizers generate a substantial respirable fraction and are not designed to maximize deposition in cough-relevant upper and central airway regions, only a limited and poorly controlled fraction of the nominal dose is expected to deposit at the intended target site. Moreover, a liquid formulation developed for injection is certainly not optimized to produce a targeted size distribution in the region of interest and it does not contain excipients that allow retention on the mucosa, slowing mucociliary clearance. Although the addition of mucoadhesive hydrophilic polymers could address this limitation, it would markedly increase solution viscosity, thereby making nebulisation more difficult.

The present work therefore explores a non-conventional DPI design strategy in which particle engineering is used not to maximize deep-lung deposition, as in most inhaled therapies, but to promote preferential deposition in cough-relevant upper and central airway regions while limiting peripheral lung exposure.

On this basis, the aim of the present study was to design and develop an engineered spray-dried powder formulation of lidocaine hydrochloride (Lido), specifically intended to target deposition in the upper airways (larynx, trachea and carina) and thus, be suitable for administration via DPI for the treatment of CC.

The powder formulation consisted of Lido embedded into a hydrophilic, biocompatible polymer, namely sodium hyaluronate (HA), used to enhance mucoadhesion and slow drug release from the engineered polymeric particles. The study investigated the impact of HA molecular weight and the Lido-to-HA ratio on the key quality attributes of the medicinal product. Powder optimization was carried out through *in vitro* characterisation and testing of aerodynamic properties and dissolution rate. The optimized powder was then assessed for antitussive efficacy in a validated model of induced cough in healthy volunteers.

2. Materials and methods

2.1. Materials

Lidocaine hydrochloride Ph. Eur. (batch number 18303001) was purchased from ACEF (Fiorenzuola d'Arda, Italy). Sodium hyaluronate Ph. Eur. grade 50–250 kDa (average 92 kDa) (batch number 1000014109) was purchased from Altergon (Avellino, Italy) whereas sodium hyaluronate technical grade 750–1000 kDa (batch number 215–11154) was purchased from Contipro Biotech (Dolní Dobrouč, Czech Republic).

HPMC extra-dry capsules for DPIs (Quali-V®-I size #3) were provided by Qualicaps (Madrid, Spain), and a single-dose, high-resistance (0.031 $kPa^{0.5}$ $min\ L^{-1}$) DPI RS01 was kindly provided by Amcor (Zurich, Switzerland).

All other chemicals used were obtained from commercial suppliers and were of analytical grade. Whatman glass fibre filter type 934-AH with diameter of 70.0 and 82.6 mm were purchased by Sigma Aldrich (St. Louis, Missouri, US).

2.2. Quantification of lidocaine by HPLC

Lidocaine was quantified using an HPLC Agilent Technologies Series 1200 equipped with a UV detector set at 230 nm. Test and reference solutions were prepared using a methanol/water (75:25 v/v) mixture. The stationary phase was an Eclipse XDB-C18 column, 4,6 x 150 mm, 5 μm (Agilent, Santa Clara, California, US).

The quantification method was linear over the concentration range of 40-400 μg/mL ($R^2 = 0.999$) and the precision was 0.62%.

2.3. Production of lidocaine spray-dried powders

Spray drying was performed using aBüchi mini-spray dryer B-191 (Büchi, Labortechnik, Flawil, Switzerland). Powders were produced with an inlet temperature of 120 °C, the spray gas flow was 600 L/h, and the aspiration rate was 35 m^3/h; the feed rate varied between 2 and 4 mL/min, the nozzle diameter between 0.7 and 1.4 mm and the solute content in the feed solution between 1 and 5% w/v.

Spray-drying feed solutions were prepared using purified water as solvent. Process yield was calculated as the percentage ratio between the mass of powder collected at the end of the process and the dry mass of solutes initially dissolved in the feed solution.

2.3.1. Lidocaine spray drying powder production

Preliminary tests were carried out to select the most suitable HA molecular weight, and the Lido-excipient w/w ratio in the formulation. Briefly, lidocaine and HA were dissolved in water at different ratios: 50:50 and 20:80 Lido:low molecular weight (LMW) HA; 50:50 and 20:80 Lido:high molecular weight (HMW) HA. Spray-dried powders had a solute concentration of 1% w/v. Spray-dried powders were produced with the following process parameters: inlet temperature of 120 °C, feed rate of 3.0 mL/min, nozzle diameter of 0.7 mm, spray gas flow of 600 L/h and aspiration rate of 35 m^3/h.

For formulation optimization, a LMW HA in a 20:80 Lido:HA weight ratio was selected. A full-factorial design of experiments (DoE) with three input variables at two levels each was adopted, using Minitab® 17 software. A total of 8 experiments (2^3) were carried out.

The optimization included three critical process parameters (CPPs): feed rate (2.0 or 4.0 mL/min), solute concentration (3 or 5% w/v) and nozzle diameter (1.4 and 2.0 mm). Table 1 illustrates the details of the eight powders and the relative process conditions. To minimize the influence of potential systematic errors and time-dependent process variability, the experimental runs were performed in a randomized order. The powders reported in Table 1 are listed not according to the randomized run order in which the experiments were carried out, but according to their formulation and process conditions. The output parameters of the DoE, which represented the critical quality attributes (CQAs) of the powders, were drug content, particle size (dv50) and amount of aerosolised powder with aerodynamic size > 5 μm.

The eight spray-dried powders were produced at an inlet temperature of 130 °C, while the spray gas flow and aspiration rate were kept fixed at the values used in the preliminary tests.

2.4. Evaluation of the CQAs of Lido-HA LMW spray-dried powders

2.4.1. Dv50 by laser diffraction

The particle size distribution of Lido-HA LMW spray-dried powders was evaluated by laser diffraction using a Spraytec instrument (Malvern, Worcestershire, UK).

Ten mg of each powder was dispersed in 10 mL of 0.1% w/v SPAN 80 in cyclohexane and sonicated for 5 min. The particle size was expressed as a volume-equivalent sphere diameter, namely as dv10, dv50 and dv90. The dv50 represents the median particle diameter, below which 50% of the particle population is found. The dv10 and dv90 values correspond to the diameter below which 10 and 90% of the particle population are found, respectively.

Three runs were performed for each sample.

Table 1
2^3 full factorial DoE to produce Lido-HA LMW_80 spray-dried powders.

Powder	Solute concentration (% w/v)	Feed rate (mL/min)	Nozzle diameter (mm)
#1	5	2.0	2.0
#2	3	2.0	2.0
#3	5	4.0	2.0
#4	3	4.0	2.0
#5	5	4.0	1.4
#6	5	2.0	1.4
#7	3	2.0	1.4
#8	3	4.0	1.4

2.4.2. Non-respirable fraction of Lido-HA LMW spray-dried powders

The Non-Respirable Fraction (NRF), defined as the amount of aerosolised powder with aerodynamic diameter >5 μm, of Lido-HA formulation was assessed *in vitro* using a Fast-Screening Impactor (FSI, Copley Scientific, Nottingham, UK). The FSI is composed of an Induction Port (IP), a Coarse Fraction Collector (CFC), collecting particles with an aerodynamic diameter >5 μm, and a Fine Fraction Collector (FFC), fitted with a glass fibre filter, collecting particles with an aerodynamic diameter <5 μm.

The analysis was performed using an RS01 DPI (Amcor, Zurich, Switzerland). Capsules were manually filled with 40 mg of powder, corresponding to a nominal lidocaine dose of 8 mg for the selected 20:80 Lido:HA formulation. The same capsule type and fill weight were used for FSI, NGI and the healthy-volunteer proof-of-concept study. The inhaler was activated at a pressure drop of 4 kPa corresponding to a flow rate of 65 L/min, for a duration of time sufficient to sample an air volume of 4.0 L. After deposition, the amount of drug retained in the capsule, device and impactor was collected using a methanol/water mixture (75:25 v/v) and the samples were analysed by HPLC. In all tests, the mass balance exceeded 85%.

The NRF was calculated as the percentage ratio between the mass of drug recovered in the IP and CFC, and the amount of drug emitted from the inhaler.

Three runs were performed for each sample.

2.5. Aerodynamic particle size distribution by Next Generation Impactor of Lido-HA LMW spray-dried powders

In vitro aerodynamic assessment of the two best-performing powders was also carried out using a Next Generation Impactor (NGI, Copley Scientific, Nottingham, UK), according to USP–NF 2026. Two throat geometries were employed: a USP standard throat (Induction Port, IP), and an adult realistic mouth-throat developed and validated by Virginia Commonwealth University (VCU throat) to provide clinically relevant *in-vitro* testing and improved drug deposition prediction. Forty mg of powder were manually loaded in HPMC size #3 capsule and aerosolized with an RS01 inhaler activated at a pressure drop of 4 kPa corresponding to a flow rate of 65 L/min, for a duration of time sufficient to sample an air volume of 4.0 L. The cups of the impactor were coated with a solution of Tween 20 in ethanol (2% w/v) to prevent particle bouncing.

The NGI was connected to the vacuum pump (Model SCP5, Copley Scientific Limited, Nottingham, UK) and the airflow was set using a flowmeter (Model DFM 2000, Copley Scientific Limited, Nottingham, UK). The analysis was performed under critical flow control conditions (Critical Flow Controller Model TPK-R, Copley Scientific Limited, Nottingham, UK). The device was connected to the NGI through a rubber adaptor, and one single dose of powder was discharged and collected into the apparatus. At the end of the deposition experiment, the NGI was disassembled and the amount of drug remaining in capsule and device, as well as the drug deposited in the different portions of the impactor was recovered using a methanol/water mixture (75:25 v/v) and quantified using HPLC.

The Metered Dose (MD) was defined as the total mass of drug recovered from the inhaler and the impactor (capsule, device, IP, stages 1–7 and micro-orifice collector, MOC). The Emitted Dose (ED) was defined as the amount of drug leaving the device and entering the impactor. The Median Mass Aerodynamic Diameter (MMAD) was determined as the mid-point of the line obtained by plotting the cumulative percentage of mass less than the stated aerodynamic diameter for each NGI stage on a probability scale versus the aerodynamic diameter of the stage on a logarithmic scale. The Fine Particle Mass

(FPM) is the mass of drug below 5 μm (calculated from the log-probability plot equation) and the Fine Particle Fraction (FPF) is the ratio between FPM and ED in percent.

Three runs were performed for each sample.

2.6. Optical and scanning electron microscopy of lidocaine spray-dried powders

For the preliminary investigation, samples of about 1 mg were placed with a spatula on a microscope slide and observed under polarised light using an optical microscope (Labophot Nikon, Tokyo, Japan) at 20 and 40× magnification.

Lido-HA spray-dried powders morphology was also investigated by Scanning Electron Microscopy (SEM) using a SUPRA 40 SEM (Carl Zeiss, Oberkochen, Germany).

Each powder sample (10 mg) was placed on a conductive sample holder previously covered with a double-sided conductive carbon tape to allow the dispersion of the charge. Particles in excess were removed by a gentle flow of nitrogen.

The samples were analysed under high-vacuum conditions (1.89-2.75 × 10^{-6} Torr), and the images were collected at 5.00k× magnification using an accelerating voltage of 1.0 kV.

2.7. Differential Scanning Calorimetry (DSC) and X- ray powder diffraction (XRPD) analysis of Lido-HA powders

The DSC analysis of the Lido-HA LMW powders of the preliminary tests, containing 50, 65, 80, or 90% w/w of polymer, was carried out using the DSC instrument TGA/DSC 1 STARe System (Mettler Toledo, Columbus, OH, USA). Approximately 5 mg of sample was accurately weighed and placed into hermetically sealed aluminium pans, while an empty sealed pan was used as reference. Samples were heated from 25 °C to 130 °C at a heating rate of 5 °C/min under a nitrogen purge (flow rate: 100 mL/min). Thermograms were recorded and analysed to determine thermal transitions, including glass transition temperature (Tg), melting point (Tm), and possible crystallization events.

X-ray powder diffraction (XRPD) analysis of the eight spray-dried Lido–HA LMW_80 of the DoE was performed using the instrument XRD- S6000 (Shimadzu Corporation, Japan), with Cu Kα radiation (λ = 1.5418 Å) at 30 kV, a scanning speed of 0.05°/min and a scanning range (2θ) between 5°- 35°. Diffraction patterns were collected and analysed to evaluate the crystalline or amorphous nature of the samples. The presence or absence of characteristic diffraction peaks was used to assess changes in crystallinity following processing.

2.8. Dissolution of lidocaine raw material and Lido-HA LMW spray-dried powder

In vitro dissolution tests were carried out using RespiCell™ (Sonvico et al., 2021) a vertical diffusion cell apparatus composed of an upper part, the donor chamber (6.8 cm diameter), and a lower part, the receptor chamber (170 mL with a side arm of 10 cm length), linked together by a clamp and separated by a glass microfiber filter (type 934-AH diameter 76.0 mm, Whatman, Kent, UK), used as diffusion membrane in contact with the dissolution medium.

The receptor chamber was filled with phosphate-buffered saline (PBS) as dissolution medium (pH 7.4) and kept under stirring. The apparatus was connected to a heating thermostat set at 37 ± 0.5 °C.

Eight mg of lidocaine raw material or 40 mg of Lido-HA LMW_80 spray-dried powder or 13.3 mg of Lido-HA LMW_40 were manually spread with a spatula. The suffixes “80” and “40” indicate the polymer content of the formulations, corresponding to 80% and 40% w/w HA, respectively. Then the filter was wet with 1 mL of PBS and at fixed intervals (5, 10, 15, 20, 25, 30, 40, 50, 60, 80, 100, 120 min), 1 mL of the receiving solution was collected from the receptor chamber and replaced with 1 mL of fresh buffer to maintain a constant volume. The amount of drug in the samples and the one remained on the filter were assessed by HPLC.

Three runs were performed for each sample.

2.9. Antitussive efficacy of lidocaine powder formulation

Antitussive efficacy against ultrasonically nebulized distilled water (“fog”) was assessed in nine (four females) non-smoking healthy subjects, aged 25–60 years. The methodology of the fog cough challenge has been fully described elsewhere (Lavorini et al., 2007). In brief, cough was induced by inhalation of fog generated by a Mist-O_2-Gen EN143A ultrasonic nebulizer (Allied Healthcare Products, St. Louis, USA). The nebulizer output, controlled by a potentiometer and monitored as a direct current (DC) signal, produced progressively increasing fog outputs—hereafter referred to as “scalar fog concentrations”—ranging from 0.08 mL/min (at 30% DC signal) to 4.45 mL/min (at 100% DC signal). Cough occurrence was detected through the electromyographic (EMG) activity of abdominal muscles, recorded via surface Ag–AgCl electrodes (Lavorini et al., 2007). The EMG signal was amplified, full-wave rectified, and processed through a custom-made, leaky integrator (low-pass RC filter, time constant 50 ms) to obtain a moving average, or integrated EMG (IEMG) signal, which was analysed qualitatively. Participants were connected to the nebuliser via a mouthpiece and a two-way non-rebreathing valve and tidally inhaled each fog concentration for one minute, with rest intervals of 2–3 min between exposures. When a cough occurred, the test was interrupted, and subjects rested for 30 min. The challenge was then resumed with the fog concentration immediately below the previous one. If cough was elicited again at the same output, that level was defined as the subject’s cough threshold. If no cough occurred, the sequence continued until a cough was reproducibly induced twice at the same fog concentration in two consecutive challenges separated by 30 min. Hence, the cough threshold corresponded to the lowest fog output capable of evoking at least one cough effort in both runs (Lavorini et al., 2007). This procedure ensures that recorded cough response was evoked by fog inhalation and not a random event.

Once cough threshold had been determined, participants entered a randomized, single-blind, crossover study and received either placebo (InhaLac 150, Meggle, Wasserburg am Inn, DE) or lidocaine powder (Powder #3 of Table 1) via the RS01 capsule-based dry powder inhaler in two separate sessions at least 48 h apart.

InhaLac 150 was selected as an inhalation-grade placebo excipient because it was considered pharmacologically inert and was not expected to exert local anaesthetic or antitussive effects. Sodium hyaluronate was not used as a placebo because its physicochemical and mucoadhesive properties could influence powder deposition, airway residence time and local sensory perception, thereby potentially confounding the pharmacodynamic assessment. During preliminary sessions, the inhalation technique was carefully demonstrated and practiced under the supervision of trained physicians. The cough threshold was then reassessed at 15, 30, and 60 min after administration of Powder #3 or placebo. Values of forced expiratory volume at 1 s (FEV_1), ECG parameters (i.e. R–R and Q–T intervals, T wave amplitude), blood pressure and heart rate were measured at baseline and 15–20 min after Powder #3 administration. In all subjects, any adverse events were recorded throughout the study. In addition, the gag or retching reflex was assessed before and after lidocaine inhalation using a sterile tongue blade or cotton swab to gently touch the posterior pharyngeal wall (back of the throat) on each side. The clinical study was approved by the local Institutional Review Board (#14131–2022), and an informed written consent of participants was obtained after detailed explanation of the study aims.

2.10. Statistical analysis

The output parameters of the DoE, representing the critical quality

attributes (CQAs) of the powders, were drug content, particle size (dv50), and the Non-Respirable Fraction (NRF%). The results obtained for the eight spray-dried powders with respect to these CQAs were statistically analysed and compared using the ANOVA in Minitab® 17 software.

Regarding the human cough test, baseline cough threshold values measured within each subject on the two study days, before placebo or lidocaine administration, did not significantly differ according to a paired t-test and were therefore pooled for subsequent analysis. Cough threshold values obtained after Powder #3 and placebo administration were compared using the Friedman test for non-parametric repeated measures, followed by Dunn's test for multiple comparisons. A $p < 0.05$ was taken as significant.

3. Results and discussion

The main pharmaceutical contribution of this study is the integration of particle-size engineering, sodium hyaluronate-based matrix formation, controlled dissolution, and regional aerodynamic targeting into a lidocaine DPI designed for cough modulation. This distinguishes the formulation from conventional carrier-based DPI systems and from nebulized lidocaine solutions, which are not optimized for controlled deposition or mucosal residence at cough-relevant airway sites.

A common formulation approach for pulmonary DPI products is based on adhesive mixtures consisting of micronized drug particles blended with a coarse carrier. However, for low-melting compounds such as lidocaine base (melting point 68–70 °C) and lidocaine hydrochloride (melting point 79–80 °C) (Gallo et al., 2017), micronization by jet milling represents an unsuitable strategy as the high energy transferred to the particle surface may generate metastable, transient solid phases resulting in poorly reproducible and unreliable final dosage forms (Della Bella et al., 2016). Micronization also increases surface area and, consequently, dissolution rate; in addition, it may hinder the downstream processing of active pharmaceutical ingredients by decreasing bulk powder flowability and promoting lump formation after milling (Bultereys et al., 2025).

By contrast, spray drying represents a more suitable alternative. This technique converts a liquid solution into a dry powder through nebulization, followed by rapid drying with heated gas, typically air or nitrogen. However, processing compounds such as lidocaine presents challenges related to particle formation and melting during processing. Indeed, spray drying of lidocaine raw material alone did not yield a stable powder, owing its low melting point which prevented recovery of a dry powder.

The use of appropriate excipients is, therefore, critical to improve powder properties, enhance process yield, and modulate the release profile of the drug. When combined with polymeric excipients, this method enables the formation of stable, engineered particles with controlled properties.

The formulation strategy adopted in the present work differs substantially from the conventional design principles of dry powder inhalers. Most inhalation formulations are engineered to maximize deposition in the bronchi and peripheral lung through the generation of fine particles (<5 μm), since these regions represent the therapeutic target for diseases such as asthma and COPD. Although regional airway deposition has previously been investigated, it has mainly relied on aerodynamic particle engineering combined with controlled inhalation manoeuvres rather than on formulation design. In particular, human scintigraphic studies demonstrated that aerosols with an MMAD of approximately 9.5 μm, inhaled at a very low inspiratory flow rate (0.080 L s^{-1}), maximized deposition within the conducting airways (≈35%) while reducing oropharyngeal losses compared with conventional 5-μm aerosols (Zeman et al., 2010). This study provided the rationale for selecting large particles and a slow inhalation manoeuvre to target the conducting airways, although it did not involve the development of a spray-dried mucoadhesive formulation. Other approaches, including hygroscopic excipient-enhanced growth and CFD-guided aerosol design, have similarly aimed to modulate regional deposition but remain primarily aerosol engineering strategies rather than formulation-based solutions (Tian et al., 2013; Longest et al., 2016; Tian et al., 2015).

Likewise, mucoadhesive excipients such as hyaluronic acid, carboxymethylcellulose, alginate, chitosan and Carbopol have been widely investigated to prolong the pulmonary residence of inhaled drugs through interactions with airway mucus (Li et al., 2017; Gallo et al., 2017). However, these systems were developed to increase the residence time of bronchodilators, corticosteroids and other therapies intended for deposition in the distal lung. In contrast, the present work intentionally combines large-particle engineering with a mucoadhesive carrier to favour deposition and prolonged residence within the upper and central airways, particularly the tracheal region where cough sensory receptors are predominantly located. To the best of our knowledge, this represents the first spray-dried mucoadhesive dry powder specifically designed to prolong the local residence and antitussive activity of lidocaine at the site of cough generation.

3.1. Preliminary formulation screening

As a polymeric excipient approved for inhalation, hyaluronic acid sodium salt (HA) was selected as particle forming agent because of its potential to modulate drug release and provide mucoadhesion to the lung surface. Both low-molecular weight (LMW, 80–100 kDa) and high-molecular weight (HMW, 750–1000 kDa) HA were investigated. The results of preliminary tests in terms of process yield and solid-state characteristics of the obtained powders are reported in Table 2 and Fig. 1.

The addition of HA to the lidocaine solution led to the formation of solid particles with a process yield that in all the cases was >60%; nevertheless, the powders presented important differences in solid-state characteristic. Indeed, the optical microscope analysis under polarised light revealed that HA molecular weight was critical for the solid-state characteristics of Lido-HA spray-dried powders. With HMW HA, the obtained microparticles exhibited a partially crystalline structure at both polymer percentages (Fig. 1 A and B). In contrast, when LMW HA was employed, the particles assumed predominantly amorphous characteristics: possible drug crystals were still visible when the polymer was added at 50% (Fig. 1 C) but disappeared when the polymer was increased to 80% (Fig. 1 D). Under these conditions, the polymer chains of LMW HA were less likely entangled in the aqueous solution compared to HMW HA, thereby facilitating a more effective drug–polymer interactions and drug entrapment during the droplet drying process which eventually led to the formation of a lidocaine molecular dispersion in a HA micromatrix.

These data indicate that, in addition to the polymer's molecular weight, also its concentration in the powder proved to be a key factor affecting the amorphous nature of the microparticles. To further investigate this aspect, various aqueous Lido-HA LMW solutions were prepared with polymer contents ranging from 50% to 90% (w/w) and

Table 2
Preliminary spray-drying tests with Lidocaine and HA formulation, yield of the process and qualitative observation about the solid-state of particles.

Formulation	Lido:Excipient (w/w %)	Yield (%)	Solid-state observation
Lido-HA HMW_50	50:50	60%	Apparent lidocaine crystalline particle within HA structure
Lido-HA HMW_80	20:80	60%	Possible lidocaine crystals
Lido-HA LMW_50	50:50	85%	Main amorphous structure, few potential crystals of drug
Lido-HA LMW_80	20:80	85%	Potentially amorphous structureNo crystals

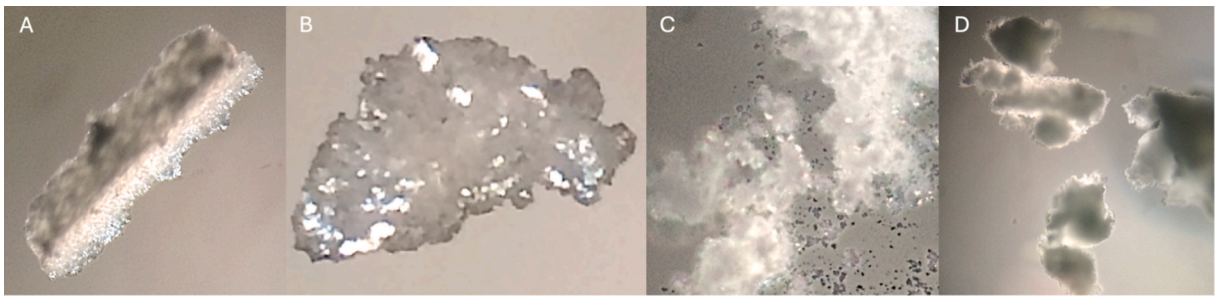

Fig. 1. Optical microscope images at 20X (C-D) and 40X (A-B) magnification of spray-dried powders: Lido-HA HMW_50 (A), Lido-HA HMW_80 (B), Lido-HA LMW_50 (C), Lido-HA LMW_80 (D).

subsequently dried in an oven for 48 h and the powder samples analysed. DSC analysis was performed to support the microscopy-based observations and to evaluate the solid-state behaviour of Lido–HA LMW powders with different polymer contents (supplementary materials). The thermal event observed in the powders was attributed to crystalline lidocaine, as the raw material exhibited a characteristic melting endotherm at approximately 74 °C. To further confirm this assignment, the DSC thermograms of raw lidocaine and a Lido:HA LMW 50:50 (w/w) physical mixture were included for comparison. As expected, the physical mixture displayed a melting endotherm at the same temperature as raw lidocaine. The corresponding 50:50 Lido–HA LMW powder exhibited a clearly detectable thermal event corresponding to that of lidocaine. The peak was only weakly discernible in the 35:65 Lido:HA formulation and was no longer distinguishable in the formulations containing 80% and 90% HA. These findings suggest that increasing HA content promoted a greater dispersion of the drug within the polymeric matrix; however, the absence of a clearly detectable melting endotherm was interpreted with caution and was not considered, by itself, definitive evidence of complete amorphization. Therefore, X-ray diffraction analysis was carried out as a confirmatory technique on all eight spray-dried formulations prepared during the optimization phase described below.

These findings suggest that, below a 20:80 Lido:HA weight ratio, lidocaine may be predominantly dispersed within the polymeric matrix, possibly through hydrogen bonding and/or ionic interactions between the amino groups of the drug and the carboxylate moieties of hyaluronic acid. Such interactions could contribute to the kinetic stabilization of a non-crystalline state and to a more homogeneous distribution of the drug throughout the polymeric network compared with the crystalline phase. This, in turn, may favour a more controlled drug release. These hypotheses were subsequently investigated by X-ray diffraction analysis, which was performed on all eight formulations prepared during the optimization phase.

3.2. Optimization of the selected Lido–HA LMW formulation

Based on the findings of the preliminary tests, a formulation containing 80% (w/w) LMW HA was identified as the best composition for producing spray-dried microparticles targeting cough-relevant airway regions. Beyond the ability of HA to promote mucoadhesion and prolonged residence time, achieving an appropriate particle size was essential to ensure deposition in the tracheobronchial region, where cough receptors are located. Consequently, the development of this inhalation product was unconventional compared with traditional inhalation therapies, as a PSD in the range of 8–15 μm was intentionally targeted and considered optimal. For this reason, both PSD and the non-respirable fraction were defined as CQAs. Statistical models generated through an optimization software were subsequently applied to enable robust optimization and prediction of these CQAs within a defined design space encompassing key formulation and process parameters. The obtained results are reported in Table 3.

Table 3
CQAs of Lido-HA LMW-80 obtained by modulating the spray drying parameters: nozzle diameter, solid concentration and feed rate; NRF = non-respirable fraction. Mean ± standard deviation, n = 3 (replicate measurements of same sample).

Powder	Lidocaine content w/w (%)	Dv_{50}	NRF (%)
#1	20.1 ± 0.4	8.1 ± 0.2	81.3 ± 2.9
#2	19.9 ± 0.4	8.5 ± 0.2	73.0 ± 2.0
#3	20.1 ± 0.1	8.9 ± 0.1	73.0 ± 0.9
#4	20.5 ± 0.3	7.3 ± 0.2	72.8 ± 3.8
#5	19.4 ± 0.3	6.6 ± 0.1	58.2 ± 2.4
#6	19.0 ± 0.1	6.9 ± 0.1	57.9 ± 1.0
#7	18.9 ± 0.3	5.8 ± 0.4	51.2 ± 3.6
#8	19.6 ± 0.3	5.4 ± 0.0	53.3 ± 0.3

Powders produced using 2.0 mm nozzles (#1–4) exhibited a Dv50 of approximately 7–9 μm and a non-respirable fraction (NRF) exceeding 72%. In contrast, the use of the 1.4 mm nozzle resulted in powders with a smaller Dv50 (approximately 5–7 μm) and a lower NRF (<58%).

Linear regression analysis indicated that, as expected, the nozzle diameter significantly affected both the particle size (dv50) ($p = 0.006$) and the NRF% ($p = 0.0003$). As nozzle diameter increased, so did the particle size of the spray-dried powders and, consequently, the NRF% (see Pareto Charts in supplementary materials).

Interestingly, although the sensitivity of X-rays is limited when the drug is diluted in a polymer matrix, this analysis does not reveal peaks attributable to a crystalline structure of lidocaine in any of the eight powders produced regardless of the modulated variable factors (see supplementary materials). The X-ray diffraction data corroborated the DSC findings, confirming the absence of detectable crystalline lidocaine in the selected Lido–HA formulation (20:80, w/w). The lack of characteristic diffraction peaks associated with crystalline lidocaine suggests that the drug is predominantly dispersed within the HA matrix, which may be associated with molecular-level interactions between lidocaine and hyaluronic acid.

Powder #3 was considered the most favourable formulation because was the one where the FSI analysis revealed the lowest fraction deposited in the induction port (38% versus a 43–46% observed for powder #1, #2 and #4, see supplementary material). This distribution is expected to reduce oropharyngeal deposition and favour delivery toward the tracheal region, where cough receptors are primarily located.

Powder #3 was subsequently compared to powder #8 considered the least favourable formulation as, despite having a NRF comparable to that of Powder #7. Although Powder #8 represented one of the least favourable formulations in terms of the target CQAs, it was selected because it exhibited an emitted dose comparable to that of Powder #3. This ensured that the comparison was not biased by differences in the amount of powder delivered from the device, allowing the impact of the different powder quality attributes on aerosol performance to be evaluated under comparable dose emission conditions.

Morphological analysis by SEM revealed that powders #3 and #8

were characterized by rounded particles, primarily with a collapsed surface, though a few exhibited a smooth, inflated appearance. Powder #8 produced with a 1.40 mm nozzle diameter contained a higher number of smaller particles bound to larger particles, compared to the powder #3 produced with the larger nozzle (2.0 mm) composed mainly by large particles, as shown in Fig. 2.

The aerodynamic profile of Powder #3 and #8 was then assessed by NGI (Fig. 3). Moreover, the performance of the lead formulation (powder #3) was assessed using the anatomical VCU mouth throat model. In all tests, the drug was efficiently delivered with emitted doses ranging from 6.6 to 6.9 mg which represents around 90% of the metered dose (Table 4). Notably, powders #3 and #8 exhibited marked differences in throat deposition, which implied distinct drug distribution profiles across the NGI stages. Powder #3, consisting of large microparticles (dv50 of 8.9 μm) resulting in a not respirable dose of 5.9 mg and to NRF of 85%. The MMAD, calculated from the fraction of powder that reached the NGI stages, was 5.6 μm. Although this MMAD suggest the presence of a limited respirable fraction, the high NRF and marked throat deposition indicate preferential deposition in the central airways.

Analysis of Powder #3 deposition in the two different throat models showed that the percentage deposited was similar. However, the analysis of the deposition in the VCU also allowed to identify the fraction of lidocaine (32%) that, by depositing in the oral cavity, potentially associated with swallowing problems and anaesthesia and the fraction of the drug able to reach the larynx and trachea (29%) the target site for antitussive effect.

In contrast, powder #8, composed of small particles (dv50 of 5.4 μm), demonstrated lower IP deposition (39%), higher FPF (66%) and a smaller MMAD (3 μm), indicating a less favourable deposition profile for this specific purpose where a systemic absorption of the drug would be highly undesirable.

Overall, these data highlight that powder #3 offers more advantageous aerodynamic properties for targeting tracheal cough receptors while minimizing deep lung deposition and the potential systemic exposure.

The dissolution of the active ingredient and its release from the formulation represent key elements for antitussive efficacy as they significantly affect not only the onset of action but also the persistence of the effect. The latter depends also on the capability of the formulation to adhere on the mucosa lining the conductive part of the respiratory tree, to counteract as much as possible the mucociliary clearance. While the mucoadhesive properties of hyaluronate are well known, it was also highly relevant to evaluate the dissolution rate and the release of lidocaine from the selected formulation.

Fig. 4 shows the dissolution profile of lidocaine raw material in comparison to that of the lead formulation Powder #3 containing 80% of LMW HA. The lidocaine dissolution from Powder #3 was significantly slower compared to the raw material. While the raw lidocaine was fully dissolved within 15 min as expected, the Powder #3, required approximately 2 h for a complete dissolution. The data demonstrate that the polymer forms a continuous matrix that acts as a diffusion barrier, limiting drug mobility and thereby extending release. Despite exhibiting a larger particle size distribution, the drug raw material dissolved more rapidly than the engineered microparticles, indicating that particle size alone does not govern dissolution behaviour in this system. Although the raw lidocaine showed the expected rapid dissolution profile, the slower release observed for Powder #3 suggests that lidocaine was retained within the HA-rich polymeric matrix, which acted as a diffusion barrier and slowed drug mobility.

For comparison, a spray-dried formulation containing 40% w/w of HA (Lido-HA LMW_40) was also evaluated to demonstrate that both the presence and concentration of HA play a key role in modulating and prolonging lidocaine release. This formulation exhibited a faster dissolution than Powder #3, with complete drug release achieved in about 25 min. Furthermore, this powder contained free lidocaine crystals not embedded in the microparticle matrix, resulting in a dissolution profile more similar to that of the raw material.

3.3. Preliminary data in healthy volunteers

All participants coughed in response to fog inhalation. At baseline, median (interquartile range) cough threshold value was 1.07 (0.66) mL/min (Fig. 5). This value was unaffected by placebo administration at all the time point analysed. The lack of any effect with the placebo further supports the choice of InhaLac 150 as an inert control. A sodium hyaluronate placebo was intentionally avoided because its intrinsic physicochemical and mucoadhesive properties could have influenced airway interactions and sensory responses, thereby complicating the interpretation of the pharmacodynamic findings. Conversely, when subjects were premedicated with Lido–HA LMW spray-dried Powder #3, median cough threshold values significantly ($P < 0.001$ *vs* placebo) rose to 3.38 (1.73) and 4.37 (1.07) mL/min at 15 and 30 min respectively (Fig. 5). In all subjects, cough threshold resumed the control value 60 min after Lido–HA LMW spray-dried Powder #3 administration. The Lido–HA LMW spray-dried Powder #3 caused a slight, transient unpleasant taste and throat irritation but no choking on water nor changes in the gag reflex. In all subjects, Lido–HA LMW spray-dried Powder #3 administration caused only slight and inconsistent changes in heart rate, mean blood pressure, Q–T interval and T wave amplitude. FEV1 values were unaffected by Lido–HA LMW spray-dried Powder #3 inhalation. All participants reported a transient, mild sensation of oral numbness beginning approximately 8–10 min after lidocaine inhalation and resolving spontaneously within a few minutes.

These observations are in line with previous investigations showing that inhaled lidocaine produces a transient inhibition of the cough reflex sensitivity in humans, including healthy volunteers (Hansson et al., 1994) and individuals with heightened airway reflex responsiveness (Hall et al., 1999). Like those reports, the present study confirms that lidocaine acts primarily by blocking voltage-gated sodium channels in airway sensory nerves, thereby reducing the excitability of rapidly

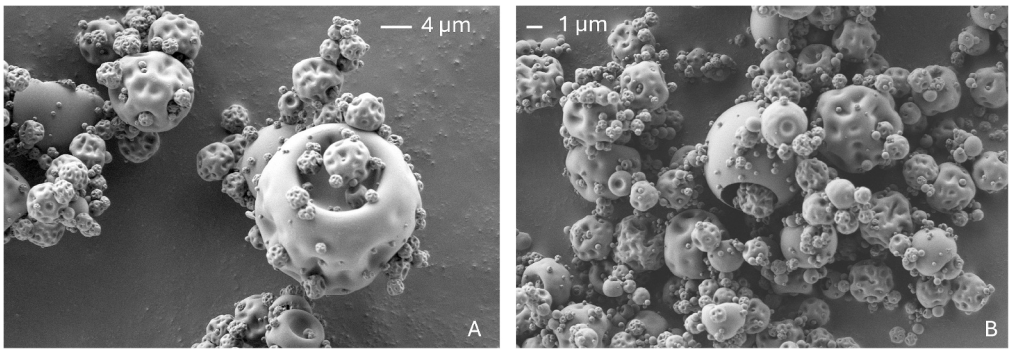

Fig. 2. SEM images of Lido-HA LMW_80 powder #3 prepared with nozzle 2.00 mm (A) and powder #8 prepared with nozzle of 1.40 mm (B).

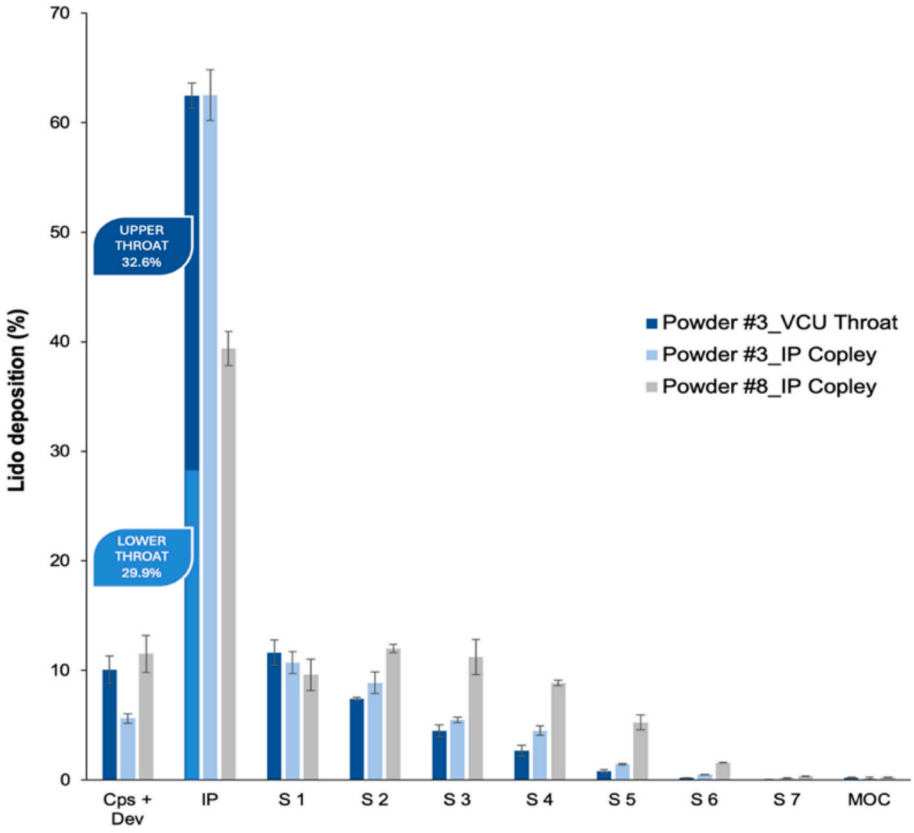

Fig. 3. Comparison between powder #3 (using IP Copley and VCU Throat) and #8 (using IP Copley) of lidocaine deposition after aerosolization in the NGI (n = 3).

Table 4
Metered dose, delivered dose, fine particle mass, fine particle fraction, not respirable mass, not respirable fraction, MMAD, GSD of lidocaine deposition after aerosolization in the NGI of powder #3 (using both IP Copley and VCU Throat) and #8 (using IP Copley); mean value ± standard deviation (n = 3).

Powders	MD(mg)	ED(mg)	MMAD (μm)	GSD	FPM(mg)	FPF(%)	NRM(mg)	NRF(%)
Powder #3_IP Copley	7.36 ± 0.03	6.93 ± 0.01	5.60 ± 0.12	2.54 ± 0.05	1.05 ± 0.09	15.12 ± 1.23	5.89 ± 0.08	84.88 ± 1.23
Powder #3_VCU Throat	7.56 ± 0.15	6.79 ± 0.07	6.88 ± 0.68	1.67 ± 0.07	0.73 ± 0.08	10.72 ± 1.29	6.07 ± 0.14	89.28 ± 1.29
Powder #8_IP Copley	7.46 ± 0.09	6.60 ± 0.05	3.94 ± 0.11	2.36 ± 0.16	2.24 ± 0.08	33.93 ± 1.41	4.36 ± 0.12	66.07 ± 1.41

adapting receptors and C-fibre endings implicated in the cough reflex. The temporal pattern of the effect observed here parallels the pharmacokinetics of topical lidocaine, which reaches peak mucosal concentrations rapidly after inhalation but declines within 30–60 min due to systemic absorption and mucociliary clearance.

Compared with liquid or aerosolized formulations (Lim et al., 2013), the dry-powder delivery employed in the present protocol offers practical advantages, including ease of dosing, rapid administration, and absence of liquid residue in the airways. The reproducibility of the response and the favourable safety profile observed here suggest that dry-powder lidocaine may represent a convenient and well-tolerated model for evaluating the efficacy of candidate antitussive compounds. Moreover, the use of the fog cough challenge provides a sensitive and physiologically relevant method to quantify changes in airway sensory responsiveness.

Despite the sustained-release behaviour observed in vitro, the in vivo antitussive effect was short-lived, likely owing to mucociliary clearance and local drug absorption. Nevertheless, the engineered dry-powder formulation achieved a pharmacological effect at a markedly lower nominal dose than those typically reported for nebulized lidocaine, supporting more efficient targeting of the upper airways. Although the duration of action was limited, the rapid but transient increase in cough threshold observed after lidocaine powder inhalation suggests potential use as an on-demand antitussive strategy. However, the present proof-of-concept study assessed only single-dose administration in healthy volunteers. Therefore, repeated dosing throughout the day cannot be recommended on the basis of these data alone. Future repeat-dose studies in patients with chronic cough will be required to define the optimal dosing interval, cumulative local tolerability, systemic exposure and safety.

4. Conclusions

This study describes the design and development of a spray-dried lidocaine powder for inhalation aimed at the treatment of chronic cough. The formulation consisted of particles with aerodynamic diameters ranging from 6 to 12 μm, optimized for deposition in airway regions containing cough receptors, rather than for conventional deep-lung delivery. The particle size distribution of Lido-HA spray-dried powders was strongly affected by the nozzle diameter employed for the spray drying process. A formulation with higher dv50 and NRF% is essential to prevent drug deposition and absorption in the alveolar region, thereby reducing the risk of serious systemic side effects.

The inclusion of HA in the formulation facilitated the creation of amorphous microparticles and contributed to the sustained release of lidocaine.

The application of particle engineering techniques to produce a lidocaine powder resulted in a formulation with solid-state,

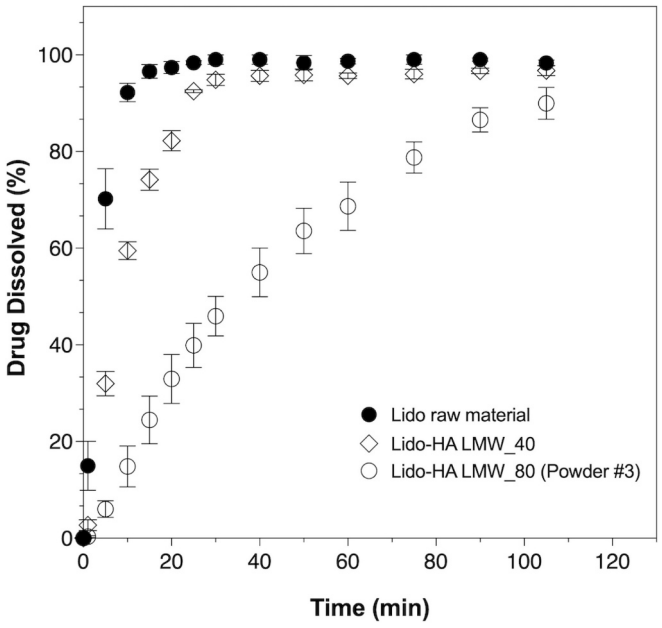

Fig. 4. Dissolution profile of lidocaine raw material and Lido-HA LMW spray-dried powders.

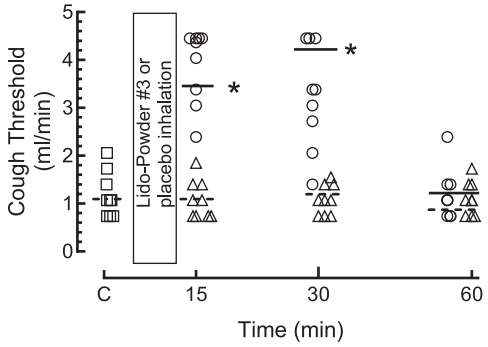

Fig. 5. Individual cough threshold values obtained in control condition (C, squares) and after administration of 8 mg Lido–HA LMW spray-dried Powder #3 (circles) or placebo (triangles) in 9 healthy subjects. Continuous and dotted lines represent median values for Lido-Powder#3 and placebo, respectively. *, $p < 0.01$ comparing Lido–HA LMW spray-dried Powder #3 *vs* placebo.

aerodynamic, and dissolution properties suitable for the intended target and therapeutic goal.

The present findings demonstrate that inhalation of dry-powder lidocaine produces a rapid but short-lived increase in cough threshold in healthy subjects. The prompt onset of action, observed within 15 min, is consistent with the rapid absorption of lidocaine across the airway mucosa and its established ability to attenuate afferent sensory nerve excitability. The transient nature of the effect, with a return toward baseline values within approximately one hour, reflects the limited duration of local anaesthetic activity at the mucosal level. Importantly, the absence of any change in the gag or retching reflex, together with the report of only a mild, short-lasting sensation of oral numbness, indicates that the treatment was well tolerated and its action remained localized to the upper airways. The lack of effect following placebo inhalation further supports the conclusion that the observed antitussive response was pharmacological in origin.

Overall, these results show that inhaled lidocaine exerts a reversible, dose-limited inhibitory action on airway sensory pathways and highlight its potential utility as a pharmacological probe in studies of cough modulation. Further research in patients with chronic cough or heightened cough reflex sensitivity will be necessary to define the translational value of this approach in clinical settings.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the authors used ChatGPT in order to rephrase and revise. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Giada Varacca: Writing – original draft, Investigation, Formal analysis, Data curation. **Diletta Mandrioli:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Fabio Sonvico:** Resources, Methodology. **Federico Lavorini:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Giovanni Fontana:** Supervision, Conceptualization. **Alessandra Sorano:** Investigation, Formal analysis, Data curation. **Giulia Fabietti:** Investigation, Formal analysis, Data curation. **Ruggero Bettini:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Conceptualization. **Francesca Buttini:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Francesca Buttini, Ruggero Bettini, Federico Lavorini, Giovanni Fontana has patent #WO 2023/111930 licensed to Anemos Therapeutics. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2026.127316.

Data availability

Data will be made available on request.

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