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Research paper

An in-vitro assessment of a NanoCrystal™ beclomethasone dipropionate colloidal dispersion via ultrasonic nebulization

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Abstract

Short duration ultrasonic nebulization of a concentrated NanoCrystal™ colloidal dispersion of beclomethasone dipropionate demonstrated an increased respirable fraction and decreased throat deposition when evaluated in an Andersen 8-stage cascade impactor in comparison to the commercially available propellant-based product Vanceril®. An aqueous-based 1.25% w/w colloidal dispersion of beclomethasone dipropionate when aerosolized via an Omron NE-U03 ultrasonic nebulizer generated a respirable drug dose from 22.6 to 39.4 μg per 2 s actuation period, compared to 12.8 μg for a single actuation of Vanceril®. When viewed as a percentage of the emitted dose (through the actuator or mouthpiece), the respirable fraction ranged from 56 to 72% for the nanocrystalline formulation versus 36% for the propellant system. In addition, the throat deposition as seen in the induction port was 9–10% of the emitted dose for the novel suspension, as compared to 53% for the commercial product. Thus, when used with the device outlined herein, a nanocrystalline colloidal suspension of beclomethasone dipropionate affords greater potential drug delivery to the conductive airways of the lung in both quantity and as a percent of emitted dose. Additionally, lower potential throat deposition values were observed which may retard the development of undesirable side effects, such as candidiasis, when compared to a propellant based delivery system. Lastly, the ability to atomize aqueous-based nanocrystalline colloidal dispersions represents an environmentally sound alternative to the current chlorofluorocarbon (CFC)-based products and may avoid the technical difficulties of reformulating with chlorine-free propellants.

Keywords: Nanoparticles; Beclomethasone dipropionate; Nebulizer; Colloidal dispersion; Cascade impactor

1. Introduction

Systemic delivery, via gastrointestinal absorption, of glucocorticosteroids (e.g. prednisone, dexamethasone) for severe asthma treatment have historically caused many undesirable side effects, such as edema, osteoporosis, glaucoma and growth retardation [1]. To circumvent these adverse events, low-dose site-specific drug administration via the metered-dose-inhaler (MDI) has been a preferred avenue of therapy. Pulmonary delivery of beclomethasone dipropionate (BDP), one drug in the corticosteroid class, has long been prescribed as an anti-inflammatory agent for treatment in reversible airway diseases, specifically moderate to severe cases of asthma. Drugs of this class enter the smooth muscle cells surrounding conductive airways and cause an anti-inflammatory response through the inhibition of phospholipase A_2, the enzyme responsible for release of arachidonic acid from membrane phospholipids [2]. Arachidonic acid is further metabolized into leukotrienes and prostaglandins, both of which impart strong bronchoconstriction reflexes.

The use of nebulization, both ultrasonic and compressed air (jet), has been routinely practiced for the delivery of solution aerosols in the treatment of pulmonary disorders. Examples of drug candidates with significant water solubility include albuterol sulfate, ipratropium bromide and cromolyn sodium. However, the aqueous-based delivery of water insoluble compounds, specifically corticosteroids, has not been commercially practiced outside of Europe or Canada [3]. A cascade impactor study evaluating suspensions containing latex beads with diameters ranging between 1 and 6 μm concluded that efficient aerosolization with an ultrasonic nebulizer was not feasible [4]. A recent experiment conducted using a colloidal dispersion of beclomethasone dipropionate, where the mean particle diameter was less than 400 nm, did demonstrate the feasibility of generating respirable aerosols with a jet-nebulizer [5]. Yet, the compressors for these jet-nebulizers were bulky

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and cumbersome and did not afford the patient with the portability convenience of an MDI. However, recent advances in technology have resulted in the production of smaller battery operated ultrasonic nebulizers, such as the Omron MicroAir® NE-U03 (see Fig. 1). The new generation nebulizers are considerably more portable than their predecessors and allow the user convenience approaching the level of an MDI.

With this information, it was the intent of this study to compare the respirable fraction of beclomethasone dipropionate from a commercially available propellant-based MDI, containing micronized drug suspended in propellants, to an ultrasonically nebulized NanoCrystal™ dispersion of BDP. NanoCrystal™ BDP possesses an approximately 1000-fold increase in crystal number at any given concentration over a micronized drug form (see Section 1.1). It is anticipated that both droplet loading of drug will be improved and that the additional surface area of the NanoCrystal™ material will afford a clinical advantage (i.e. lower dose). The nebulizer was operated as a metering system through timing the aerosol generation for 2 s. By employing a concentrated NanoCrystal™ BDP drug dispersion, an emitted dose equivalent to that attainable from an MDI was possible (c.a. 40–50 μg). An 8-stage cascade impactor was utilized in accordance with USP method < 601 > to assess the respirable fraction of drug delivered [6]. In addition, drug deposition of each dosage form was assessed from the perspective of throat accumulation or oropharyngeal response, as this phenomenon is problematic with pressurized delivery systems.

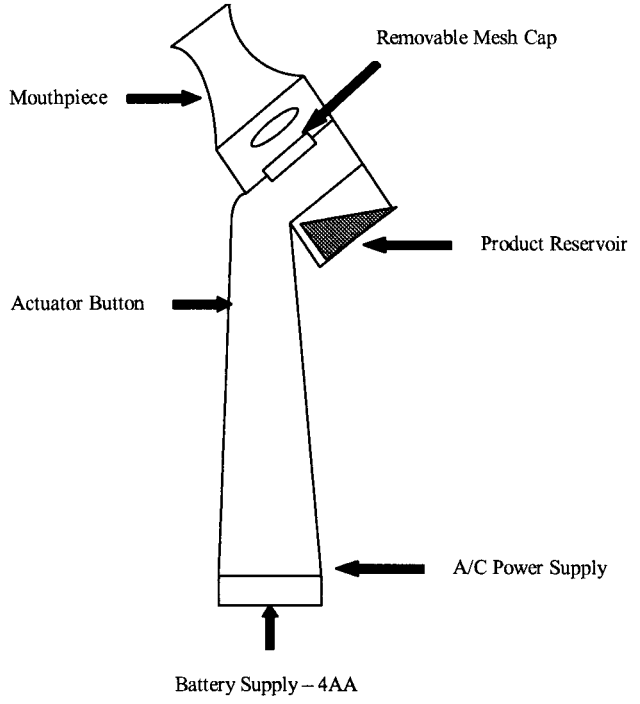

Fig. 1. Drawing of the Omron MicroAir® NE-U03

1.1. Theoretical calculations

Maximum crystal load of a 2 μm diameter droplet as generated by the nebulizer:

Volume of sphere

$$= 4/3\pi r^3 \text{ or } 4/3\pi (d/2)^3;\ r = \text{radius and } d = \text{diameter}$$

$$\text{Volume of 2 } \mu\text{m droplet} = 4/3\pi \left(2 \times 10^{-6} \text{ m}/2\right)^3$$

$$\text{or } 1 \times 10^{-18} \text{ m}^3$$

$$\text{Volume of 2 } \mu\text{m drug crystal} = 4/3\pi \left(2 \times 10^{-6} \text{ m}/2\right)^3$$

$$\text{or } 1 \times 10^{-18} \text{ m}^3$$

Volume of 200 nm drug crystal

$$= 4/3\pi \left(\{2 \times 10^{-7} \text{ m}/2\}\right)^3 \text{or } 1 \times 10^{-21} \text{ m}^3$$

Crystals per 2 μm droplet
= volume of 2 μm droplet/volume of drug crystal

$$\text{Volume of 2 } \mu\text{m drug crystal} = 4/3\pi \left(2 \times 10^{-6} \text{ m}/2\right)^3$$

$$\text{or } 1 \times 10^{-18} \text{ m}^3$$

$$2\ \mu\text{m drug} = 1 \times 10^{-18} \text{ m}^3/\text{l} \times 10^{-18} \text{ m}^3$$

$$= 1 \text{ crystal per droplet}$$

$$200 \text{ nm drug} = 1 \times 10^{-18} \text{ m}^3/\text{l} \times 10^{-21} \text{ m}^3$$

$$= 1000 \text{ crystals per droplet}$$

Thus, based on these calculations, it is possible to theoretically pack as many as 1000 crystals of 200 nm into a 2 μm diameter droplet as opposed to only one 2 μm drug crystal within a 2 μm diameter droplet. This concept is clear based on the fact that there is a 10-fold difference in the crystal diameter and the volumetric manipulation is a cubic relationship. Of course, this situation assumes that the crystals are perfectly spherical in shape and also does not demonstrate the affect of drug concentration in the formulation as outlined below.

Maximum drug crystal load per 2 μm diameter droplet given a 1.25% w/w drug suspension:

In 1 ml of 1.25 %w/w drug suspension the following ratios are assumed along with a density of 1.0 g/cm^3.

$$1.25\% \text{ w/w drug} = 0.0125 \text{ ml} = 0.0125 \text{ cm}^3$$

$$98.75\% \text{ w/w vehicle} = 0.9875 \text{ ml} = 0.9875 \text{ cm}^3$$

To determine the number of drug crystals occupying 0.0125 cm^3, the following equation can be used for each crystal diameter:

Total volume of drug in 1ml/volume of drug crystal

= number of crystals

Number 200 nm crystals = 0.0125 $cm^3/1 \times 10^{-19}$ cm^3

$= 1.25 \times 10^{17}$ crystals

Number 2 μm crystals = 0.0125 $cm^3/1 \times 10^{-16}$ cm^3

$= 1.25 \times 10^{14}$ crystals

To determine the number of 2 μm droplets occupying 0.9875 cm^3, the following equation can be used:

Total volume of vehicle in 1 ml/
volume of 2 μm droplet = number of droplets

Number of vehicle droplets = 0.9875 $cm^3/1 \times 10^{-16}$ cm^3

$= 9.875 \times 10^{15}$ droplets

To further calculate the theoretical crystals per 2 μm droplet of vehicle, the following equation is satisfied:

Crystals per 2 μm =

number of crystals/number of 2μm droplets

For 200 nm drug =

1.25×10^{17} crystals/9.875×10^{15} droplets = 12.5 crystals

For 2 μm drug = 1.25×10^{14} crystals/9.875×10^{15} droplets

= 0.0125 crystals

Therefore, 12.5 drug crystals of 200 nm diameter will reside within each 2 μm diameter vehicle droplet and only 1.25 drug crystals of 2 μm will reside in each 100 2 μm droplets of vehicle. Thus, the use of nanocrystalline material enhances the probability that each droplet will possess a drug population given a perfectly homogeneous suspension.

2. Materials and methods

2.1. NanoCrystal™ beclomethasone preparation

In a 30 ml bottle, a 10% w/w beclomethasone dipropionate (Steraloids, Inc., batch #G315, Wilton, NH) was roller milled in the presence of 2% w/w Tyloxapol (Sigma Lot #65H0905, St. Louis, MO) in distilled water. The milling media utilized was a pre-conditioned yttrium doped zirconium silicate of 0.500 mm diameter as supplied by Performance Ceramics (Peninsula, OH). The suspension was rolled for about 4 days. The concentrate was further diluted with distilled water to provide a drug concentration of 1.25% w/w and 0.25% w/w tyloxapol.

2.2. Nebulizer

An Omron Micro-Air® NEU-03 (Omron Healthcare, Vernon Hills, Il) was utilized for atomization of the NanoCrystal™ budesonide. The unit weighs 148 g and fits within the palm of the hand. The standard dosage cup has a liquid capacity of 5 ml. The aerosol generation is driven by a 65 kHz ultrasonicator with a nebulization rate of 0.25 ml/min. The droplet size is controlled through a ceramic composite mesh cap that contains a series of pores with final diameters within a range of 1–7 μm [7].

2.3. Differential scanning calorimetry

A TA Instruments DSC 2920 (New Castle, DE) was used to investigate the crystallinity of the BDP before and after milling. The NanoCrystal™ dispersion was centrifuged in 1 ml tubes at 80 000 rev./min for a period of about 7 min. The supernatant was removed and several successive washings were made with deionized water following the aforementioned procedure. The final material was dried at RT overnight. The BDP materials were scanned in crimped aluminum pans at a rate of 10°C/min.

2.4. Cascade impaction

The following evaluations were conducted on an Andersen 1 ACFM 8-stage cascade impactor fitted with the USP defined induction port as supplied from Graseby-Andersen (Smyrna, GA). The vacuum pump was calibrated with a Gilmont Instruments flowmeter (serial #51801–51900) to achieve a flow of 28.3 l/min through the cascade impactor. The nebulizer mouthpiece was affixed to the induction port using an approximately 2.0″ length of Tygon® tubing with 1.25″ internal diameter.

2.4.1. Vanceril®

An 80 dose (42 μg/actuation) Vanceril® inhaler (Lot #4-AMA-316, Key Pharmaceuticals, Kenilworth, NJ) was thoroughly shaken and two doses were delivered to waste. The actuator was removed and it and the valve stem were rinsed with methanol and dried. The weight of the unit was recorded and 10 actuations were delivered to the cascade impactor, allowing a 30 s pause between subsequent actuations. Shaking was applied to the unit prior to each delivery in the impactor. Upon completion, methanol rinses of the valve stem, mouthpiece and impactor components were taken and analyzed via HPLC in accordance with the USP monograph. The dry MDI was again weighed to determine the delivery weight of the actuation series. This procedure was performed in duplicate. The material balance for each run was within 90–110%.

Table 1
Particle size distributions of BDP[a]

Product	Mean (nm)	90% < (nm)	10% < (nm)
Micronized	1960	4060	600
NanoCrystal™	164	228	103

[a] Note: distributions are volumetric.

2.4.2. NanoCrystal™ BDP

Approximately 1.5 g of mildly hand-shaken suspension was dispensed into the 5 ml medication cup. The unit was attached to the nebulizer and the mesh cap screwed in place. A 2-s actuation (controlled by a GraLab #451 timer/foot switch, Centerville, OH) was delivered into a 250 ml separatory funnel fitted with a folded glass fiber filter and connected to a vacuum source. After priming, the mouthpiece was positioned on the unit and the device was attached to the cascade impactor. A timed 2-s actuation was delivered into the impactor. All nebulizer components and impactor pieces were rinsed with methanol and quantitated via HPLC as for Vanceril above. In addition, to ensure drug accountability, the medication cup containing the remaining unaerosolized suspension was also assayed. This procedure was conducted in duplicate for two different screens and the material balance for each run was within 90–110%.

2.5. HPLC analysis

A Hewlett-Packard (Rockville, MD) series 1050 HPLC unit was utilized for all drug analyses. Samples were diluted in HPLC grade methanol and a mobile phase of 60% acetonitrile and 40% water (v/v) was used. A flow rate of 2.0 ml/min and an injection volume of 10–25 μl was employed. Detection was handled at a wavelength of 254 nm. A 30 cm Waters Bondapak C-18 column of 5 μm packing (Waters Inc., Milford, MA) was utilized for separation. Standards of beclomethasone dipropionate, at concentrations ranging from 0.10 to 50 μg/ml, were assessed for linearity and a correlation (r^2) of 0.99998 was observed.

2.6. Particle size distribution analysis

A volumetric particle size distribution of the nanocrystalline suspension was performed with a Microtrac UPA (Leeds and Northrup, St. Petersburg, FL) dynamic light scattering instrument. The UPA system possesses a detection range from 0.003 to 6.54 μm [8]. Diluted samples were measured in water after mild hand agitation. The volumetric particle size of the micronized suspension was measured via a Microtrac FRA after mild hand agitation. The FRA has an instrument range from 0.12 to 704 μm [8]. The flow-through design cell was employed to prevent the settling effects of a static cell when analyzing particles in the micrometer size range. Distilled water was utilized as the dispersing medium.

2.7. Scanning electron microscopy

Aluminum specimen mounts (Table diameter = 15 mm, height = 15 mm) and glass coverslips (12 mm diameter circles) were cleaned thoroughly with alcohol. Once cleaned, a coverslip was glued to the top of each specimen mount. The sample suspensions were prepared by diluting the sample 1:20 with distilled water and vortexing for approximately 15 s. A 5 μl aliquot was placed onto the coverslip surface of the specimen mount and left to dry in a dust-free environment. The dried sample preparation was then sputtered-coated with gold-palladium and viewed with a Topcon SM 510 scanning electron microscope (Topcon Technologies Inc., Paramus, New Jersey).

3. Results and discussion

Table 1 displays the particle size distribution of micronized drug as received from the manufacturer and the NanoCrystal™ drug which is the same material subjected to roller milling. Milling decreased the mean particle size from 1960 to 164 nm over the course of approximately 4 days. In addition, the 90% value dropped from 4060 to 228 nm and the 10% value from 600 to 103 nm. Tyloxapol proved to be an excellent stabilizer for this system, as the mean size has not increased at room temperature conditions for the 6 weeks of the study. Furthermore, tyloxapol is currently approved for pulmonary use within the United States as a neonatal lung surfactant in Exosurf [9].

Scanning electron micrographs of the starting (micronized) and NanoCrystal™ material can be viewed in Figs. 2 and 3, respectively. The 1000-fold volumetric size differential between the two products, as discussed in Section 1.1, can be visually distinguished. Thus, it is evident why the NanoCrystal™ BDP can transcend the 1–7 μm pores of the Omron nebulizer and why the delivery of micronized BDP (mean sizes of 2–3 μm) is questionable with this style device. Furthermore, the crystallinity for the milled/unmilled BDP was assessed via DSC. A pronounced endothermic melt was found for both materials within the 205–215°C melting point range determined by the manufacturer (see Fig. 4). In conclusion, the milling process maintained the crystalline form of the drug substance.

Table 2 contains the deposition values for beclomethasone dipropionate quantitated from each region of the cascade impactor for the three specimens tested. The emitted dose is that quantity of material exiting the device (through-the-mouthpiece) and is used in subsequent respirable fraction calculations. The respirable fraction is defined as the percentage of the emitted dose that deposits within the region of therapeutic benefit. Although not contained within the table, the collar and any necessary mouthpiece adapters were analyzed for drug content and used accordingly within the respirable fraction calculations. For this experiment, impactor stages 3 through the after filter (4.7 μm and

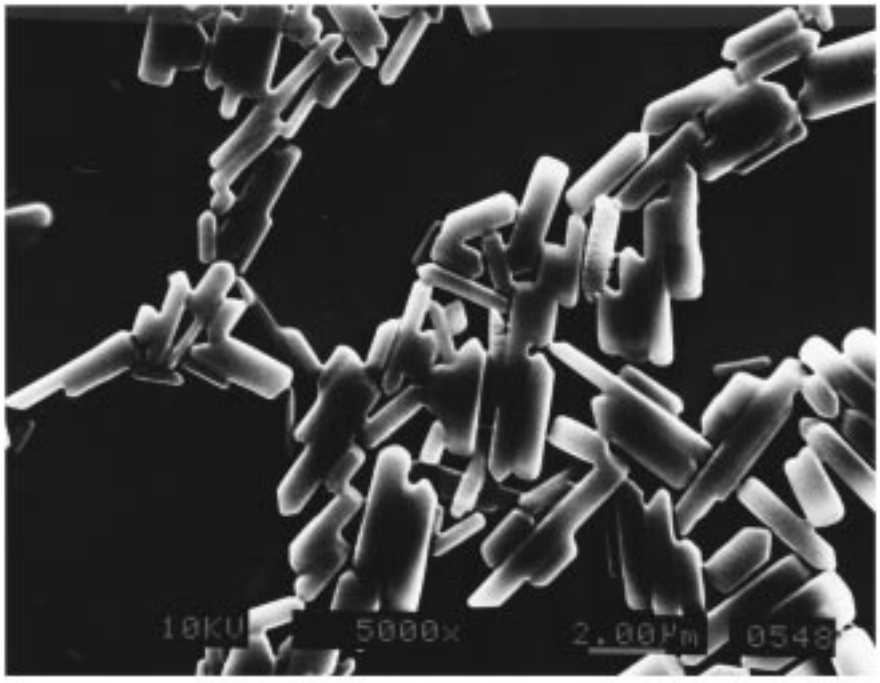

Fig. 2. SEM of micronized BDP.

below) were considered respirable regions. The respirable dose can be defined as the quantity of drug (in μg) found within the respirable regions; stages 3 through the after filter. Throat deposition was defined as the material quantitated in the induction port of the cascade impactor (simulates the human throat). Lastly, average accountability (material balance) for the experiments was determined by assaying all components of the collection apparatus and dividing by the drug load to the nebulizer and total delivery from the MDI.

Upon review of Table 2, it is clear that the droplet size range atomized by the nebulizer is indeed, sufficient for drug delivery within the aerodynamic size range corresponding to the conducting airways of the lung. The experiment demonstrated that all emitted doses of BDP were within 12.8–39.4 μg per actuation. The NanoCrystal™ formulation

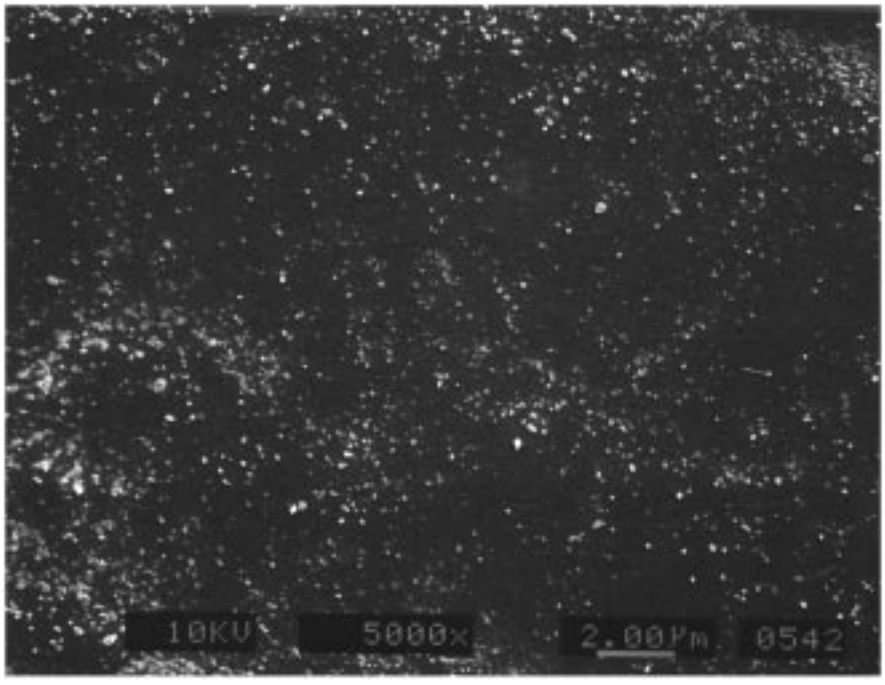

Fig. 3. SEM of NanoCrystal™ BDP.

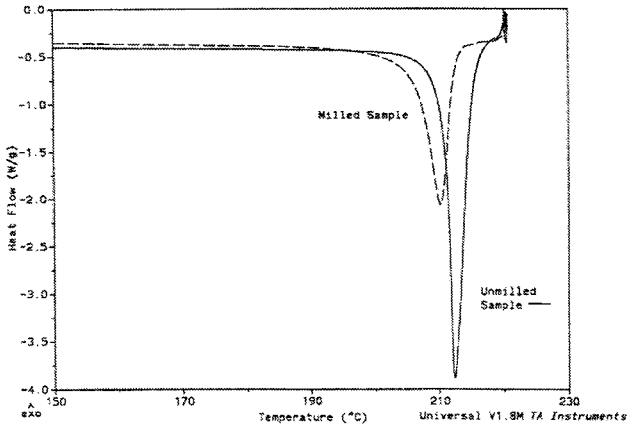

Fig. 4. DSC results of milled/unmilled BDP.

with screen #1 demonstrated a respirable dose (22.6 μg) nearly twice as high as the MDI (12.8 μg), while delivering an emitted dose of 5 μg less. The NanoCrystal™ formulation delivered with screen #2 yielded a respirable dose of 39.4 μg or nearly twice that of screen #1, while exhibiting an emitted dose of 67.4 μg, also nearly twice that of screen #1. The throat deposition observed was 2.85–11.4 μg/actuation for the nebulized BDP versus a 19.2 μg/actaution deposition for the MDI. Thus, in both cases the NanoCrystal™ BDP respirable dose was higher than that of the MDI and the throat deposition was lower than that seen with the MDI.

Table 3 further tabulates the deposition data in terms of percent of emitted dose. This can also be viewed in graphical form by Fig. 5. While viewing the data in this normalized fashion, it is possible to eliminate the differences in screen variability of the nebulizer and the emitted dose differences seen with all the samples. Therefore, classification of the aerosol can be better understood as it relates to regional deposition for each system tested herein. Thus, it was determined that the nebulized NanoCrystal™ dispersion generated respirable fractions of approximately 56–72% as related to the emitted aerosol dose. These values were nearly 160–206% of the 35% respirable fraction observed for Vanceril® (see Fig. 6). Another significant finding from the study was the ability for potential deep lung delivery with the ultrasonic nebulizer. The Omron nebulizer generated a greater population of droplets below 2.1 μm than the particle distribution observed with the MDI. Specifically, the percent of emitted dose for the NanoCrystal™ formulation found within stage 5 through stage 6 was between 27.9 and 30.1%, versus only 3.99% for the MDI. This is noteworthy, as a recently developed BDP MDI product has shown that a decreased drug dose is efficacious due to the smaller MMAD (c.a. 1.1 μm) of the product [10–12]. This leads one to believe that inflammation may exist deeper in the lung than initially presumed.

A word about the variability of the experimental data is in order. Specifically, the emitted dose for the NanoCrystal™ dispersions for screen #1 and #2 varied by approximately 36 μg BDP per actuation. Stereoscopic evaluation of the mesh caps as supplied by the manufacturer did show incompleteness in regard to both pattern (number of pores) and bore (pore flow through). This most probably explains the output variability observed between the two screens assessed within this experiment. The current use of this device, as for all nebulizers, dictates aerosolization and subsequent inhalation over the course of several minutes or until the nebulizer is dry. This administration technique though creates for uncertain dosing, as it is unclear how much emitted drug the patient is actually inhaling. Within the course of our study, however, we focused on metering the dose over a defined or timed 2-s actuation period. It was observed that a 2-s inhalation period is similar to the inspiration time for an MDI actuation. If this application progresses, it will be imperative to regulate the mesh cap construction and establish tight specifications as to maintain consistent emitted dose levels.

Table 2
BDP deposition per actuation[a]

Impactor region	Aerodynamic size range (μm)	Vanceril® μg/act. (range)	NanoCrystal™ screen #1 μg/act. (range)	NanoCrystal™ screen #2 μg/act. (range)
Stage 0	9.0–10.0	0.48 (0.08)	3.05 (3.42)	10.7 (3.96)
Stage 1	5.8–9.0	1.28 (0.28)	1.90 (0.12)	5.24 (2.04)
Stage 2	4.7–5.8	2.38 (0.04)	0.85 (0.20)	1.44 (0.24)
Stage 3	3.3–4.7	7.07 (0.88)	2.58 (1.70)	3.08 (1.34)
Stage 4	2.1–3.3	4.25 (0.78)	6.93 (1.92)	10.8 (2.66)
Stage 5	1.1–2.1	1.45 (0.06)	7.65 (2.34)	15.5 (4.50)
Stage 6	0.7–1.1	<0.50 (N/A)	1.90 (0.38)	3.74 (1.76)
Stage 7	0.4–0.7	<0.50 (N/A)	0.71 (0.22)	1.23 (0.36)
After filter	<0.4	<0.50 (N/A)	2.78 (1.06)	3.39 (1.52)
Throat deposition		19.2 (0.50)	2.85 (2.50)	11.4 (11.4)
Emitted dose (TTMP)		36.1 (2.50)	31.7 (4.37)	67.4 (1.97)
Respirable dose		12.8 (1.70)	22.6 (1.74)	39.4 (3.42)
Average accountability %		92.6	97.2	98.9

[a] TTMP, through-the-mouthpiece. Experimental range in parentheses.

Table 3
BDP Deposition as a percentage of emitted dose[a]

Impactor region	Aerodynamic particle size (μm)	Vanceril® % dose	NanoCrystal™ screen #1 (% dose)	NanoCrystal™ screen #2 (% dose)
Stage 0	9.0–10.0	1.32 (0.32)	9.27 (9.46)	15.6 (6.31)
Stage 1	5.8–9.0	3.53 (0.50)	5.99 (0.48)	7.62 (3.24)
Stage 2	4.7–5.8	6.56 (0.35)	2.67 (0.72)	2.09 (0.42)
Stage 3	3.3–4.7	19.5 (2.20)	8.14 (6.48)	4.48 (1.85)
Stage 4	2.1–3.3	11.7 (1.30)	21.9 (9.10)	15.7 (3.50)
Stage 5	1.1–2.1	3.99 (0.11)	24.1 (4.05)	22.5 (7.30)
Stage 6	0.7–1.1	0.00 (N/A)	5.99 (0.37)	5.44 (2.77)
Stage 7	0.4–0.7	0.00 (N/A)	2.24 (0.39)	1.79 (0.47)
After filter	<0.4	0.00 (N/A)	8.77 (4.57)	4.93 (2.39)
Throat		53.2 (2.30)	8.99 (6.67)	10.4 (8.19)
Respirable fraction		34.8 (3.40)	71.6 (15.3)	55.9 (6.60)

[a] Experimental range in parentheses.

The data do indicate that the dose uniformity for the MDI was tighter as evidenced by the data range of drug deposition per actuation. For instance, the observed range for any impactor region varied by no greater than 0.88 μg/actuation. This is notably less than that observed with the nebulizer system. NanoCrystal™ BDP delivered with screen #1 showed a range as great as 3.42 μg/actuation and screen #2 as high as 4.50 μg/actuation. This is not surprising, as the delivery force from the MDI propellant is consistent with each subsequent actuation. There is a constant internal pressure maintained, due to the equilibrium between the liquid and vapor contained therein. The Omron MicroAir® nebulizer on the other hand atomizes through a mesh cap of varied pore size. Therefore, the resultant effluent is more varied, especially over short duration delivery.

Further discussion on MDI therapy is warranted beyond the scope of the experimental results. Aside from good dose uniformity, the propellant-based MDI offers a patient convenience, in that it is easily portable, contains up to 300 doses and is fairly rapid to clean. Yet, with these advantages, the MDI also possesses some disadvantages that are worthy of mention. Primarily, the dose administration usually results in significant oropharyngeal deposition from the rapid evaporation of the propellants, leading to increased occurrences of candidiasis and voice hoarseness in the case of steroidal compounds [13]. In addition, much

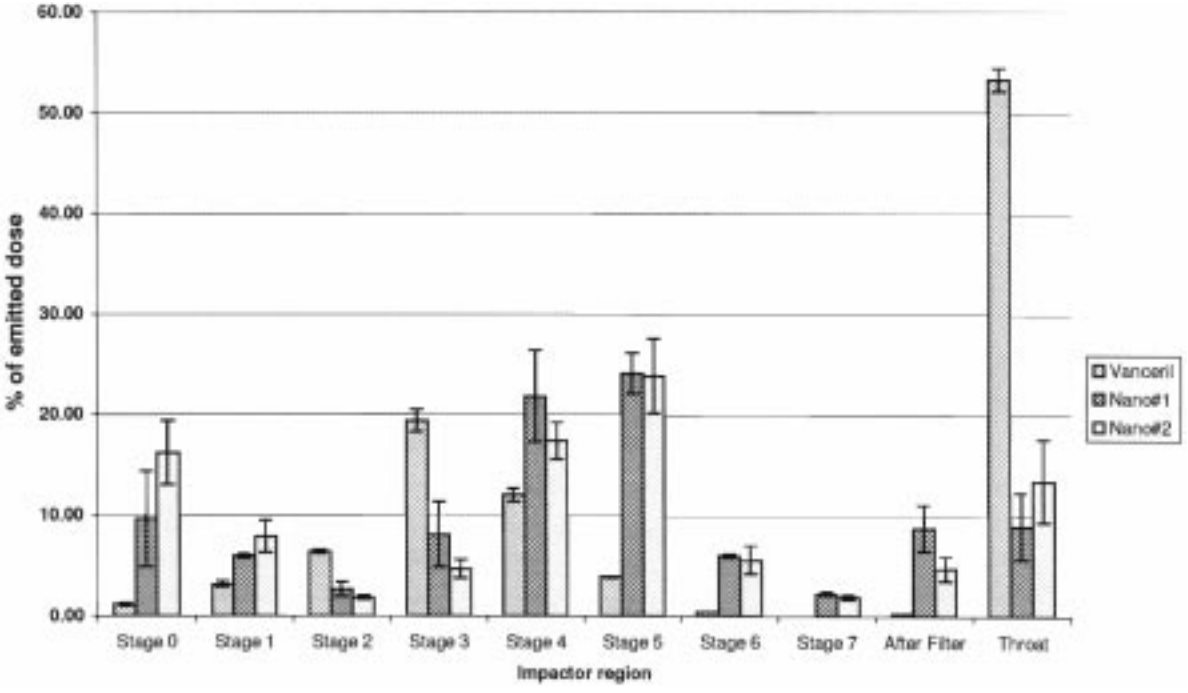

Fig. 5. BDP deposition as a percentage of emitted dose.

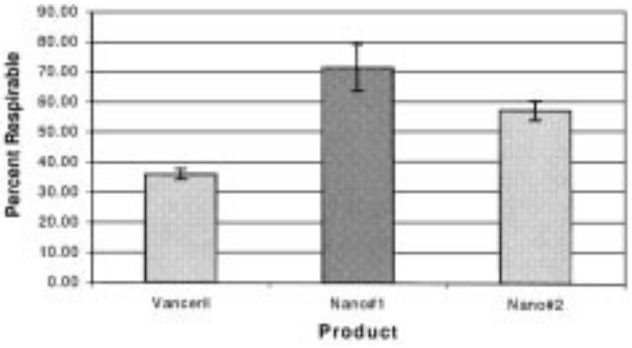

Fig. 6. Respirable fraction of emitted dose for BDP products.

of the dose is therefore swallowed, allowing for gastrointestinal absorption and side effect generation. Another significant finding is that many users have difficulty coordinating drug inhalation with actuation of the valve mechanism [14]. Thus, little to no drug may be reaching the target sites and therapeutic relief is compromised.

Lastly, drug deposition within the throat represented another focal point for this study. The physiological problems of hoarseness and candidiasis have been attributed to oropharyngeal deposition of steroids. The lack of volatility in the plume travel of the nebulized aerosol as opposed to the propellant formulation was clearly seen in the induction port (throat) deposition. The NanoCrystal™ formulation demonstrated a drug deposition of 9–10% of the emitted dose, while Vanceril® showed deposition of 53% (Table 3 and Fig. 5). Although, a spacer may appear to provide an optimal solution to this dilemma for an MDI, the use of a spacer reduces the respirable dose of drug [15]. The nebulizer used within this study eliminates the need for such devices and therefore does not compromise the delivered dose.

Regardless of the potential delivery advantages of the nebulizer-based NanoCrystal™ BDP, the use of metered-dose-inhalers (MDIs) are currently the most popular means of administration for corticosteroids due to both their limited systemic absorption and low incidence of side effects. Yet, with the phase out of CFCs looming with compliance to the Montreal Protocol of 1987, many pharmaceutical companies are pursuing reformulation of propellant-based MDIs with ozone friendly hydrofluorocarbons (HFCs). The two most actively researched compounds of this class are 134a and 227. Both replacement propellants lack chlorine in their structure, the atom responsible for atmospheric ozone degradation. Replacement with HFCs, however, is not a simple substitution process, as package elastomer compatibility, surfactant/valve lubricant solubility and vapor pressure differences need to be carefully handled [16]. Additionally, non-member access to the new propellants' toxicity data must be purchased through the International Pharmaceutical Aerosol Consortium for Toxicity Testing (IPACT), a consortium of companies organized to fund and conduct the necessary regulatory toxicity testing to ensure human safety with the propellants. Considering these issues, the concept of pulmonary delivery with aqueous-based corticosteroid suspensions poses some interesting advantages over the current propellant MDI commonly used.

4. Conclusions

This study demonstrated several important aspects of ultrasonic nebulization with NanoCrystal™ beclomethasone dipropionate. Primarily, nanometer-size aqueous suspensions can be aerosolized through a mesh style nebulizer and deliver a superior respirable fraction, as compared to an MDI. Additionally, a higher respirable dose could be delivered in a 2-s actuation period when atomizing the concentrated NanoCrystal™ BDP, when compared to a metered actuation of Vanceril®. Within the scope of this experiment, the nebulized respirable fraction was 21–37% higher and throat deposition was 42–43% lower than the Vanceril® product, when viewed as a function of emitted dose. Therefore, more drug substance is being delivered to the conductive regions of the lung, resulting in potentially greater therapeutic relief. Secondly, the use of this technology avoids the technical concerns associated with HFC propellant formulations and the pitfalls of a volatile delivery system in general.

Overall, given the current environmental consciousness of today's patient, non-propellant delivery devices may be more openly accepted. It is therefore anticipated that the use of ambulatory nebulizers, as an aerosol generation technique, will grow due to the new portable designs and ease of operation. Given their suitability for delivery of nanocrystalline aqueous dispersions, the ability to deliver water-insoluble corticosteroids or other pulmonary therapies via ultrasonic nebulization should be further explored. Through modifications of the device's mesh cap and the addition of a multi-dose cartridge system, the Omron MicroAir® could be a well accepted device for the delivery of water insoluble asthma therapies. Also, the ability for the device to readily aerosolize a nanometer-sized colloidal dispersion has shown that water-based delivery of insoluble compounds represent an alternative to both propellant and dry powder systems.

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