POTENTIAL DEEP LUNG DELIVERY OF WATER-INSOLUBLE DRUG NANOCRYSTALS™ VIA THE AMICI SWIRLER™ NEBULIZER SYSTEM.

Kevin D. Ostrander*[1], H. William Bosch[1] and Michael Bono[2]

[1]NanoSystems (Division of Elan Pharmaceutical Technologies)

3000 Horizon Drive, King of Prussia, PA 19406

[2]AMICI Inc., 518 Vincent Street, Spring City, PA 19475

Abstract:

Purpose: To assess the ability of the Amici Swirler® jet-nebulizer to aerosolize a water-insoluble NanoCrystal™ colloidal drug dispersion for deposition within the peripheral airways. ***Methods:*** Through wet-milling techniques, a 5 %w/w colloidal dispersion of a corticosteroid was prepared with a mean particle size of 82 nm and 90 percent of the particles below 130 nm (volumetric distribution). The dispersion was then filtered through a 0.2 μm Gelman Supor® capsule filter and further diluted with distilled water to yield a drug concentration of 0.50 %w/w. The dispersion was aerosolized in triplicate to an Andersen 8-stage cascade impactor to determine the aerodynamic droplet size distribution for the emitted dose. ***Results:*** The study indicated that 96 percent of the emitted dose for a 0.50 %w/w drug dispersion was within the respirable region (<4.8 μm) and 86 percent was below 1.1 μm. The mass-median-aerodynamic-diameter (MMAD) observed was approximately 550 nm from the nebulizer tested. Furthermore, the peripheral-to-central airway deposition ratio was 75 to 1 respectively. ***Conclusions:*** The results indicate that the Amici Swirler® system can efficiently generate high respirable fractions of aqueous drug dispersions containing sub-100 nm drug particles. In addition, approximately 95 percent of the emitted dose correlates to peripheral lung deposition (<2.1 μm). Lastly, both NanoCrystal™ drug product technology and Swirler®device technology utilized in this experiment demonstrate the feasibility for deep lung delivery of water-insoluble drugs in the treatment of cystic fibrosis, respiratory infection and various forms of cancer.

Introduction:

Pulmonary drug delivery through jet-nebulization is commonplace for the administration of solution-based products (albuterol, ipratropium, cromolyn sodium, etc.). The selection of nebulizer will dictate the size of droplets formed during the aerosolization process, subsequently determining the primary deposition region within the lung. Generally, jet-nebulizers produce droplets with mass-median-aerodynamic-diameters (MMAD) within the range of 2.0 - 6.0 μm. The aforementioned drugs, targeted for the conductive airways, perform well in these nebulizer systems. Yet, the delivery of water-insoluble drugs via jet-nebulization has not been fully explored. With the exception of budesonide suspension marketed in Europe/Canada, there are no commercially available water-based suspensions available for nebulization of poorly water-soluble drug compounds.

The concept of NanoCrystal™ technology allows for successful formulating of water-insoluble drug substances, which can then be further processed into inhalation products of nasal sprays, dry powder inhalers and dispersions for nebulization. For these liquid dosage forms, the product is a water-based vehicle of sterically stabilized nanometer-size drug crystals. Thus, these formulations do not require solubilization of the drug through pH manipulation, cosolvent addition (ethanol) or liposome formation. Therefore, the NanoCrystal™ colloidal dispersions do not possess irritating excipients which have been shown to cause bronchospasm in certain instances. Additionally, since the mean diameter (volumetric) of the drug crystals are ca. 100 - 200 nm, they can be completely contained within the droplet formed by the nebulizer. This unique property makes feasible the ability for deep lung delivery of water-insoluble drug NanoCrystals™ in conjunction with nebulizers which possess MMAD's below 1.0 μm, a task not possible for micronised drugs.

Purpose:

The intent of this experiment was thus two-fold. Firstly, it was necessary to generate a NanoCrystal™ colloidal drug dispersion of a poorly water-soluble compound through wet milling techniques. The corticosteroid agent budesonide was selected for its poor water solubility (<0.2 mg/mL). The size reduction of the drug was to be such that the volumetric mean diameter would be approximately 100 nm, thus amenable to sterile filtration techniques. The dispersion could then be loaded into the selected nebulizer and the emitted aerosol assessed via cascade impaction. This experiment would afford an increased understanding of the potential human lung deposition patterns expected from the drug delivery system.

Secondly, the study was designed to demonstrate the feasibility of peripheral lung delivery (regions of gas exchange and a high degree of vasculature) with a water-insoluble drug. Therefore, the selection of a suitable nebulizer system was critical, specifically a device capable of producing an MMAD of <1.0 μm while maintaining a relatively high aerosolization rate. Since most commercially available devices are engineered to deliver drug solutions to the conducting airways (3.0 - 6.0 μm), a device from the nuclear medicine field was selected. The Amici Swirler® nebulizer was thus employed in this experiment. Designed for rapid generation of fine droplets (MMAD ca. 550 nm), the Swirler® also utilizes both one-way valves and a product trap to control the dose administered to the patient and minimize the exposure of drug to the respiratory therapist. Thus, the nanocrystalline budesonide will be small enough to remain in the fine aerosol droplets formed by the device and reach the deep airways of the lung.

Materials and Methods:

NanoCrystal™ Budesonide: A 5.0 %w/w budesonide (Sicor, Lot# 6353/M1) and 0.50 % w/w tyloxapol (Nycomed, Lot#N047NN) aqueous-based formulation was high-energy milled for a period of 27 hours in the presence of 50 μm polymeric media. The milled concentrate was filtered through a 0.2 μm Gelman Supor® capsule filter. The filtered concentrate was further diluted to 0.50 % w/w with deionized water.

Jet-Nebulizer: An Amici Swirler® (Amici, Lot#980715L) jet-nebulizer was utilized without the mouthpiece affixed. The unit was operated with medical grade nitrogen operating at a flow rate of 8 liters/minute. A 1 mL sample of NanoCrystal™ budesonide colloidal dispersion was injected into the product port.

Cascade Impactor: An Andersen 1 ACFM 8-stage cascade impactor fitted with the USP defined induction port as supplied by Graseby-Andersen was used. The vacuum pump was calibrated with a Gilmont Instruments flowmeter (#51801-51900) to achieve an inspiration rate of 28.3 liters/minute through the unit.

HPLC Analysis: A Hewlett-Packard series 1050 HPLC with a 240 nm UV detector was utilized for the budesonide analyses. A mobile phase of 65 %v/v Phosphate buffer and 35 %v/v Acetonitrile was run at a flow rate of 1.5 mL/minute; an injection volume of 20 μL was employed. A Waters Bondapak® C-18 column of 5 μm packing was used for separation.

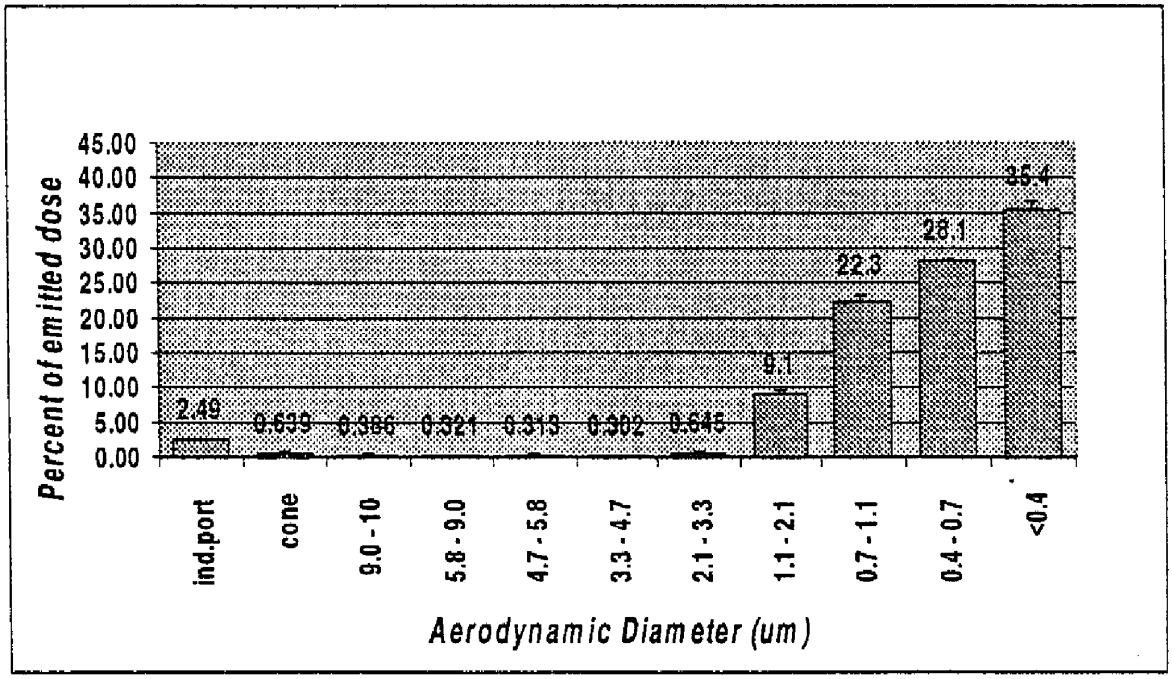
Results:

Cascade Impactor Data

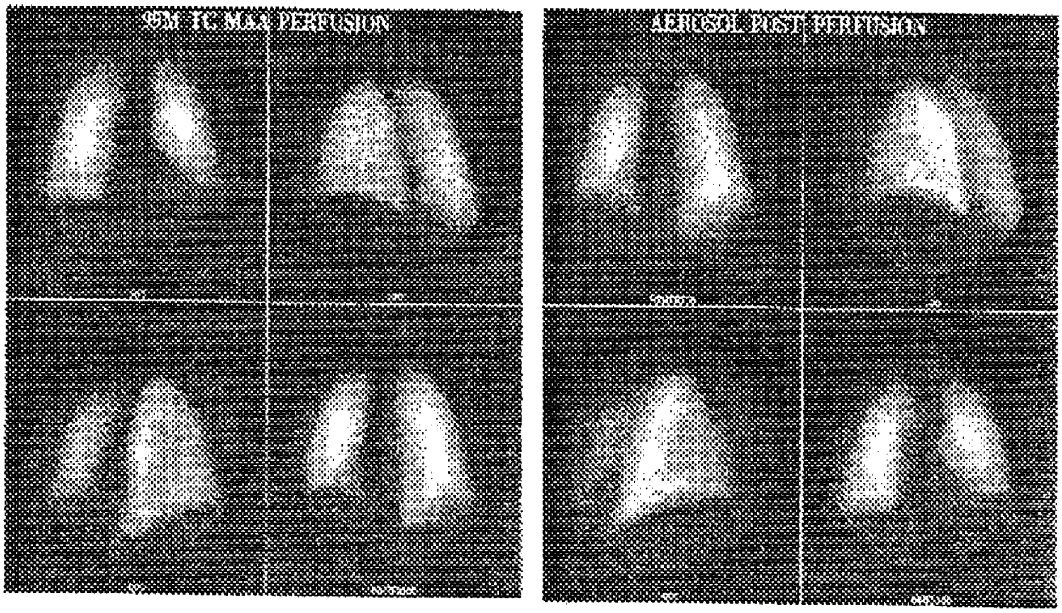
Impactor Region	Aerodynamic P. Size Range	Run #1 (µg drug)	Run #2 (µg drug)	Run #3 (µg drug)	Ave. % of emitted dose
Induction Port	NA	11.1	12.0	11.1	2.49 (0.12)
Cone	NA	2.94	3.12	2.70	0.64 (0.05)
Stage 0	9.0–10 µm	2.71	1.47	1.08	0.39 (0.19)
Stage 1	5.8–9.0 µm	1.64	1.55	1.20	0.32 (0.06)
Stage 2	4.7–5.8 µm	1.57	1.69	1.03	0.31 (0.08)
Stage 3	3.3–4.7 µm	1.59	1.30	1.24	0.30 (0.05)
Stage 4	2.1–3.3 µm	3.22	2.91	2.71	0.65 (0.07)
Stage 5	1.1–2.1 µm	42.3	40.0	43.0	9.10 (0.36)
Stage 6	0.7–1.1 µm	100	98.2	108	22.3 (0.90)
Stage 7	0.4–0.7 µm	127	127	132	28.1 (0.38)
After Filter	<0.4 µm	155	169	161	35.4 (1.33)
Total (µg)		449	458	465	
Resp. Fraction		95.6 %	96.1 %	96.6%	96.1% (0.50)

Note: Standard Deviation in parentheses.

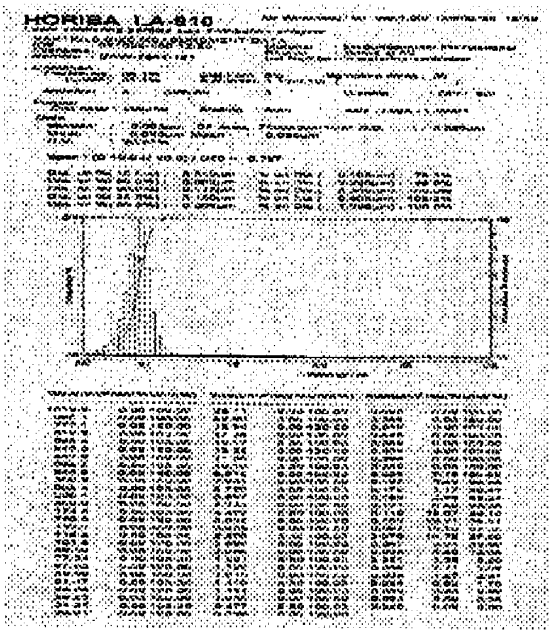
Deposition Profile as Percent of Emitted Dose



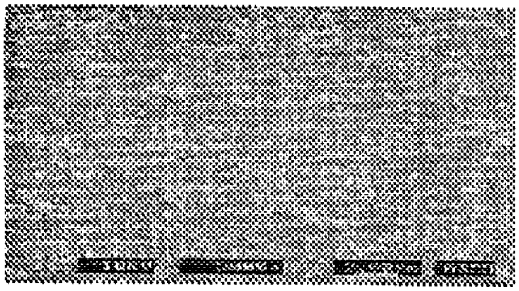
Perfusion vs. Aerosol:



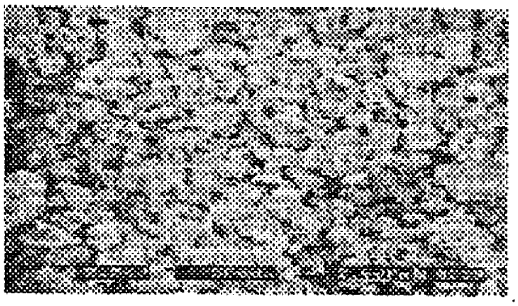
Particle Size Distribution- NanoCrystal™ Budesonide



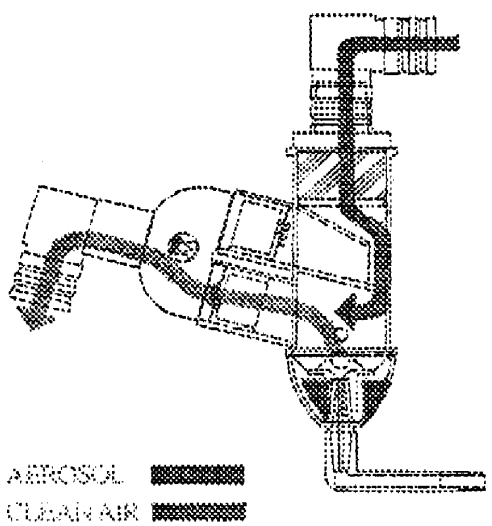
SEM- NanoCrystal™ Budesonide

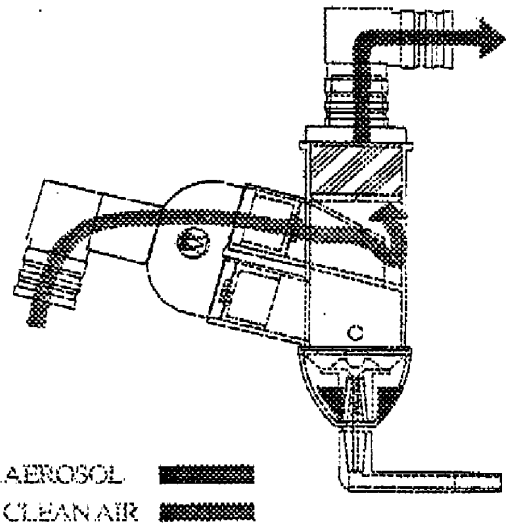


SEM- Micronized Budesonide



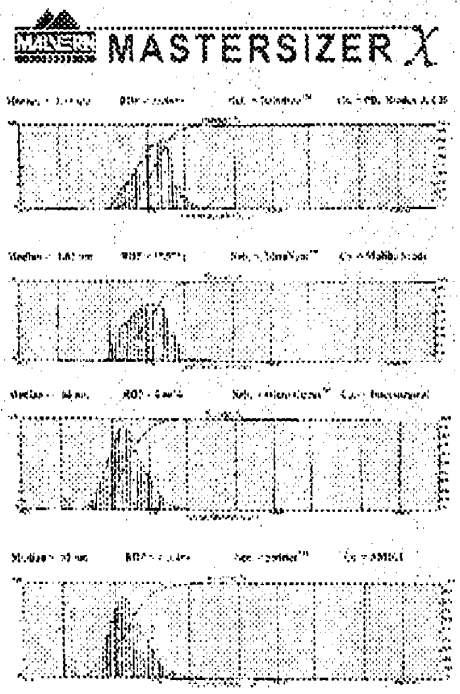
Device Flow:

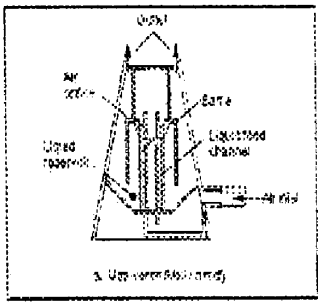


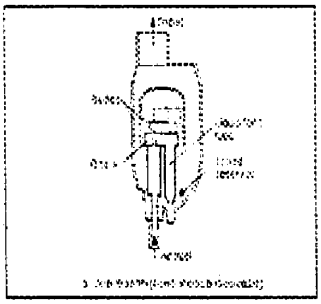


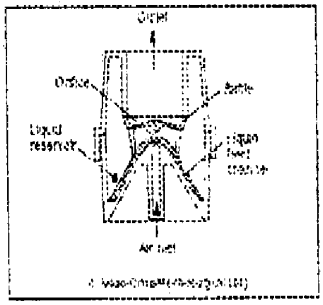
INHALATION CYCLE *EXHALATION CYCLE*

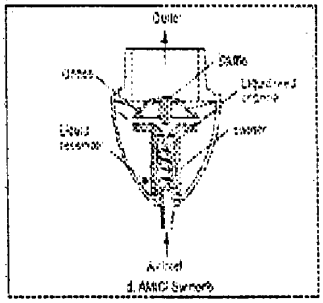
Nebulizer Comparison: Droplet Size Distribution and Design











Conclusions:

- An aqueous-based colloidal dispersion with a volumetric mean particle size of ca. 82 nm was developed.
- The NanoCrystal™ budesonide was amenable to sterile filtration through a 0.2μm filter, thus affording product development of a sterile suspension.
- The fine particle size of the dispersion allows for drug incorporation within a mean aerodynamic droplet size of <1.0 μm (in this case 550 nm).
- The dispersion contains only drug, water and a nonionic stabilizer (Tyloxapol, USP).

- The Amici Swirler® is effective at generating fine aerosol droplets for deep lung administration (MMAD ca. 550 nm), 86 percent less than 1.1 μm.
- The nebulizer has a high throughput or rate of delivery as compared with other fine aerosol nebulizer systems.
- The Swirler® is available with one-way valves and a product trap as part of a containment system to minimize drug exposure to the respiratory therapist (ideal for potent drug compounds).
- Both NanoCrystal™ drug technology and the Swirler® delivery system can successfully deliver water-insoluble drugs to the deep airways (alveoli) of the lung, thus presenting opportunities for drug substances of poor water solubility.