

**2D.1**

**The Effect of Drug Physico-Chemistry on Pulmonary Absorption Pharmacokinetics in Dogs.** KATHLEEN SIMIS, Peter Lloyd, Ron Hale, Alexza Pharmaceuticals.

Dronabinol (THC, delta-9-tetrahydrocannabinol) is the primary active compound in marijuana (*Cannabis sp.*) and has garnered increasing attention in the medical community as a result of its complex and widespread systemic effects. The medical indications that have been reported for THC (and other cannabinoids) are numerous and most notably include appetite stimulation in patients with AIDS, nausea and vomiting associated with chemotherapy, and neuropathic pain and spasticity associated with multiple sclerosis (1). Alexza's Staccato condensation aerosol generation system is an excellent drug delivery platform for THC. The Staccato system is a breath actuated inhaler that generates an aerosol with an appropriate particle size range for deep lung delivery and rapid systemic absorption of the drug.

Dronabinol is a moisture and light sensitive viscous liquid with poor shelf-life stability. A thermally-labile solid prodrug of THC has been identified that meets chemical and physical shelf-life stability requirements. When heated under optimum conditions using Alexza's Staccato system, the prodrug is converted to THC (~90%) and vaporized to form a pharmaceutically active aerosol containing both THC and intact prodrug.

Delivery of the aerosol to dogs via inhalation resulted in rapid systemic absorption and high bioavailability of THC with demonstrable and significant differences (3-fold) in time to maximum plasma concentration (T<sub>max</sub>) between THC and its prodrug. These differences may be attributable to differences in the physicochemical properties of the two molecules.

This study with thermally-labile prodrugs further demonstrated the utility of Alexza's Staccato system in pulmonary delivery of pharmaceutical condensation aerosols and provided insight into the physicochemical mechanisms that govern drug transport from pulmonary to systemic circulation.

1. Janet E. Joy, Stanley J. Watson, Jr., and John A. Benson, Jr., Editors, 1999. *Marijuana and Medicine: Assessing the Science Base*, Washington, D.C.: National Academy Press

**2D.2**

**Development of AERx Essence for Delivery of Novel Inhalation Formulations.** DEBBIE YIM, Eric Johannson, David Cipolla, Aradigm Corporation.

Aradigm has developed a family of devices for use with the AERx strip. The first generation device, currently being used for the delivery of insulin, is a battery-powered, hand-held, electromechanical device designed for extremely precise systemic drug delivery. This device has been used previously to efficiently deliver a variety of solution formulations to the lung. Aradigm has recently developed an all-mechanical, second-generation device platform called Essence. This device is intended for both systemic and precision topical delivery applications. Key advances have enabled Essence to offer very similar aerosol performance in a light, palm-size device.

Preliminary in vitro performance of the AERx Essence platform using a simple cromolyn solution formulation has been shown to be reproducible with emitted aerosol from an individual device averaging 60.0% +/- 2.1% (n=40 strips) and 56.8% +/- 4.6% across fifty devices (n=8-10 strips per device). The fine particle fraction less than 4.95 microns is 90% resulting in a predicted fine particle dose (ED x FPF) of approximately 51-54%. Essence also has the capability to effectively deliver more sophisticated suspension and liposomal formulations. Suspensions of ketoprofen and indomethacin were tested at a concentration of 60 mg/mL using both the electronic AERx with micron-sized nozzles and AERx Essence with sub-micron-sized nozzles. The emitted doses (EDs) were in the range of 49 to 60 % of the loaded dose. Liposomal ciprofloxacin solutions at 50 mg/mL were also aerosolized in Essence with approximately 42% mean emitted dose. Following aerosolization, the liposomes retained >95% encapsulation. This work demonstrates that nano-suspension formulations can be successfully delivered using the AERx Essence all-mechanical system with sub-micron-sized nozzles.

**2D.3****Electromechanical Properties Analysis of Four Pressurized Metered Dose Inhalers Using Laser Doppler Velocimetry.**

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University of Arkansas at Little Rock.

A novel method for analyzing electromechanical properties (e.g., size, electrostatic charge, polarity) of therapeutic aerosols produced by four different commercially available pressurized metered dose inhalers (pMDIs), including Albuterol (TM), Atrovent (TM), Qvar (TM), and, Ventolin (TM) is presented. In recent, influence of electrostatic charge on particle deposition in the respiratory airways has attracted much attention, which requires precise quantification from analytical perspective. Experimental studies using Electrical Low Pressure Impactor (ELPI) reported the net charge ( $q$ ) and aerodynamic diameter ( $d_a$ ) of the pMDIs. However, the ELPI has a limitation of providing the net charge of all particles deposited on its impactor plate, not for each particle in real time. To resolve this issue, we report the application of an Electronic Single Particle Aerodynamic Relaxation Time (ESPART) analyzer, which operates on the principle of Laser Doppler velocimetry to measure simultaneously  $d_a$  and  $q$  (magnitude and polarity) on a single particle basis and in real time. It draws aerosols from an aerosol sampling chamber (ASC). The chamber's inside walls were lined with a grounded wire mesh. The pMDI devices were actuated at the inlet of valve holding chamber, which had the other end connected to the ASC. Prior to each run ASC was cleaned and evacuated (50 mb) to simulate the inhalation of an aerosol bolus @ 30 L/m for 8 s. Aerosol particles from all drug delivery devices were found to not only have different size distributions but also varied in their polarities. The drug aerosols cloud emitted by Albuterol and Ventolin were determined to be electropositive while Atrovent and Qvar were electronegative. Count and mass distributions were reproducible for all pMDIs. These findings can be explained by variation in the drug propellant surfactants, metal surfaces of delivery devices, and drug/carrier homogeneities. In conclusion, the ESPART provided more detailed charge information about the pMDI aerosol particles.

**9B.1****Inhaled Liquid Vaccines: Implications for Devices and Delivery.** JAMES FINK, Nektar Therapeutics.

Liquid vaccines approved for subcutaneous administration have been successfully administered by inhalation. In Mexico, 4 million children were vaccinated by aerosol inhalation using a compressor driven jet nebulizer over a 12 year period, with similar or better protection than subcutaneous injection. The World Health Organization in collaboration with the Gates Foundation, has launched an initiative to license one or more inhaled vaccines for use in the third world during this decade. Several other vaccines have been identified as likely candidates for aerosol administration, in a range of environments. Device design is an integral component of any successful program for liquid aerosol vaccines.

Beyond elimination of needles, aerosol administration of liquid vaccines allows use of proven safe and effective vaccines with a minimum of reformulation, and the potential of providing 2 - 10 fold more vaccinations from the same volume of vaccine. To realize these benefits, liquid aerosol systems must be efficient, portable, inexpensive, and easily used in either the clinic or the field.

The age of subjects vaccinated, the need to reduce second hand exposure greatly impact design requirements for aerosol vaccine delivery. In many cases, vaccines are administered to infants, children and adults. While simple mouthpieces can work for subjects greater than 3 years of age, the infant requires a mask. Reducing second hand exposure is of some importance when aerosolizing live virus vaccines. Masks capable to firmly seal to contain aerosol, and filters to collect exhaled aerosol can add cost and complexity to the device.

In the clinic, vaccination may be limited to a few subjects per day, while in mass campaigns several hundred vaccinations may occur in a few hours. To meet cost targets, liquid aerosol generators may be used to safely administer aerosol for multiple vaccinations. Challenges and examples of device strategies will be discussed.

**9B.2**

**The Staccato System for Thermal Aerosols and its Clinical Evaluation.** DAN MYERS, Pravin Soni, Jim Cassella, Ramesh Damani, Reynaldo Quintana, Martin Wensley, Pete Lloyd, Patrik Munzar, Krishna Sharma, Amy Lu, Ron Hale, Alexza Pharmaceuticals; Josh Rabinowitz, Princeton University.

Pharmaceutical aerosols for systemic delivery via the lung can be generated by rapid, controlled heating of a thin film of pure drug. This method of excipient-free aerosol delivery is applicable to a large number of clinically-relevant pharmaceutical compounds. Alexza incorporates this concept into its proprietary Staccato (R) system for aerosol drug delivery. Alexza is currently developing two versions of the Staccato system. One is a single dose, fully disposable device, which produces aerosols by using an exothermic chemical heating source to vaporize a drug film coated on a stainless steel substrate. The other device is a multi-dose configuration, which uses electrical power to resistively heat thin stainless steel foil substrates. Both Staccato systems are portable, easy to use, and create consistent aerosols of high emitted dose, very low levels of thermal degradants, and ideal particle size for systemic delivery over a broad range of patient use conditions. The Staccato system is breath actuated and delivers the aerosol into the lungs in less than 1 second.

Phase 1 clinical testing of four different pipeline products has been completed, showing good tolerability, rapid absorption into systemic circulation, and high bioavailability of the drugs. Initial Phase 2 trials have also been conducted with two products. Staccato Prochlorperazine showed efficacy in treatment of migraine headache as early as 15 minutes after drug administration, while Staccato Loxapine was effective in treatment of agitation in schizophrenic patients as early as 20 minutes after dosing. Based on these early clinical observations, the simple design and optimal aerosol characteristics of the Staccato system eliminate much of the patient variability inherent in metered dose and dry powder inhalers, and lead to rapid delivery and absorption of the drug into the bloodstream. The fast onset of pharmacological action of the Staccato system could provide great benefit for many therapeutic classes.

**9B.3**

**Development of Inhalable Nanoparticles.** RAIMAR LOEBENBERG, Warren H Finlay, University of Alberta; Wilson H Roa, Cross Cancer Institute; Elmar J Prenner, University of Calgary.

Nano-technology can be considered a new frontier in biomedical sciences. Delivery systems in the nanometer range are very promising drug carriers due to their ability to overcome many limitations associated with conventional drug delivery systems including multi drug resistance in cancer treatment. The presentation will review briefly some historical aspects of nanoparticle based drug delivery technology. Examples of different applications of nanoparticles in drug delivery will be given.

The lungs are getting more and more attention as possible absorption organ for molecules which are difficult to formulate for the oral or intravenous route of administration. Pulmonary drug delivery has the potential to overcome many obstacles of the oral route of administration and to treat lung specific diseases locally or to absorb molecules for systemic delivery. This is especially important for the chemotherapeutic treatment of lung cancers. Advances in dry powder inhalers and the development of suitable carriers for nano-medical drug delivery systems enable the application of nano-medical treatment strategies to the pulmonary route of administration.

The talk will show the strategies which were used for the development of inhalable nanoparticles. One aspect was to add an active drug release mechanism to the carrier particles to improve the dispersion of nanoparticles when the carrier dissolves. Furthermore, nano-medical strategies have to consider nanotoxicological aspects of any nano-based delivery system and the lung surfaces. Any interaction between the nano-medical device and the lungs has to be carefully assessed. Strategies to evaluate nanotoxicological aspects between nanoparticles and the lungs surfactants will be discussed. The cytotoxicity and cellular uptake of doxorubicin loaded nanoparticles using different lung cancer cell lines was investigated and will be discussed. The talk will show preliminary in vivo data of the toxicity of inhalable nanoparticles using an in vivo mouse model.

**9B.4**

**Targeted Delivery of High Aspect Ratio Particles in Small Airway Bifurcations.** ANDREW R. MARTIN, Warren H. Finlay, University of Alberta.

The deposition of elongated, high aspect ratio particles in the respiratory tract has been studied at length owing to the health risk posed by inhaled mineral and synthetic fibers. These particles have smaller aerodynamic diameters than do compact particles of equivalent mass, and as such are better able to penetrate the upper airways and reach the lung. However, in the peripheral regions of the lung, where airway diameters are small, the interception mechanism can enhance deposition efficiencies for elongated particles above those expected for mass-equivalent compact particles. These considerations combine to make elongated particles candidates for broadly targeted aerosol drug delivery to the peripheral lung. More speculatively, the ability to noninvasively control the deposition of elongated particles in order to increase doses received at specific sites within the lung would allow for localized targeting to those sites.

With these goals in mind, we have recently been investigating the deposition of elongated drug particles in small, bifurcating airways. Deposition efficiencies have been measured in physical airway models, and comparison made to mathematical models predicting deposition of such particles due to impaction, sedimentation, diffusion, and interception. In addition, initial *in vitro* experiments demonstrating that noninvasive external control over particle deposition can be achieved in small airway bifurcations will be presented.

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**9B.5**

**Leucine Shells on Spray-dried Medicinal Microparticles.** Christopher I. Grainger; King

Microparticles for pulmonary or nasal delivery must have properties that provide physical and chemical stability of the dosage form and lead to adequate powder and aerosol behavior. Particles must be designed to possess correct aerodynamic diameters and adequate dispersibility to facilitate device emptying and delivery to the intended target.

Leucine has been successfully used as a dispersibility enhancer, both as a particulate additive and as an excipient in a homogeneous powder when manufactured by spray-drying. Microparticles with leucine shells have been developed for therapeutic and vaccination purposes. However, it has not been described how leucine shells form on evaporating droplets and how such particles can be designed.

This Paper presents experimental and theoretical work describing the particle formation process of leucine-containing microparticles made by spray-drying. It presents characteristic times describing the shell formation process in a multi-component droplet. These characteristic times can then be used to select appropriate process and formulation variables to achieve the desired particle morphology.

The experimental tool used in this study was a modified bench-top spray-drier. The atomizer of the dryer was replaced with an aerosol generator to allow drying of monodisperse droplets of known diameter. The aerodynamic diameter of the dry particles was measured *in-situ* using a time-of-flight technique. Particles consisting of immunoglobulin and leucine in various ratios were dried under different conditions that lead to particles with a leucine shell, an immunoglobulin shell, or a shell of mixed composition.

The results are explained in the context of a simplified analytical model based on a steady-state evaporation approximation; and particle engineering guidelines for the design of leucine shells in general are derived.

**9B.6****Drying Behavior of Polymer Solution Droplets during the Production of Microparticles for Sustained Drug Release.**

WILLARD R. FOSS, Amgen, Inc.

Active pharmaceutical ingredients can be encapsulated into microparticles with the biodegradable polymer poly (lactide-co-glycolide) (PLGA) for sustained release delivery by parenteral administration. The microparticles must be small enough to pass through a moderate gauge hypodermic needle but large enough to minimize initial burst release of drug caused by high particle surface area. The microparticles should have a size range between about 10 and 100 microns.

Particles of this size can be effectively produced by spray drying of PLGA solutions with dissolved or suspended drug. High volatility solvents are chosen to speed the evaporation. However, polymer solution droplets form a low permeability skin when dried rapidly, trapping solvent in the particle core and resulting in an undesirable hollow morphology. Subsequent evaporation is limited by the diffusion of solvent through the dry skin.

In this work, we assess the drying kinetics of polymer solution droplets to predict behavior in spray dryers, using PLGA as an example. A combination of experimentation and modeling is used. Dilute polymer solution droplets dry according to the diameter-squared law during the early stages of drying. In this region, drying kinetics are accurately modeled with analytical solutions of pure solvent droplet evaporation and confirmed with measurements in a laminar flow drying column.

At the latter stages of drying, the polymer concentrates near the surface of the droplet due to high Peclet number effects. The development and progression of the skin is modeled with accurate concentration and temperature-dependent polymer diffusion data. Measurement of the polymer-solvent diffusion coefficients is discussed as well as their application to modeling of polymer skin formation within a single droplet. The effects of gas temperature and vapor composition on the skin formation and final particle morphology are reviewed and experimental confirmation of the model is shown.