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Scott D. Barnhart, MS
The Future of Dissolvable Films

Andrew Loxley, PhD
Nebulizable Nanoparticle Dispersions: A Novel Inhalable Dosage Form

Ms. Cindy H. Dubin
Hand-Held Injection Systems Boast Safety & Efficiency

IN THIS ISSUE

INTERVIEW WITH PENWEST'S PRESIDENT & CEO
MS. JENNIFER L. GOOD

FEATURING

SPECIALTY PHARMA
Strategies For Business Development

Nebulizable Nanoparticle Dispersions: A Novel Inhalable Dosage Form

By: Andrew Loxley, PhD, and Ismar Dizdarevic

INTRODUCTION

The inhalation route, employed primarily for drugs acting in the respiratory tract, is now being expanded for use in systemic drug delivery. A properly designed drug delivery system utilizing the inhalation route can help overcome many of the hurdles associated with conventional therapies: difficult formulation, poor bioavailability, poor patient compliance, and of course, first pass issues. For example, most protein drugs are difficult to deliver through conventional delivery systems because they degrade, either partially or completely, before they reach their therapeutic target. Avoiding the digestive tract not only increases the deliverable therapeutic dose, but also lowers the risk of unintended adverse events such as irritation of the GI tract. Furthermore, by delivering drugs via nanoparticles, one is able to increase the surface-area-to-volume ratio, effectively augmenting the drug's bioavailability through faster dissolution and release rates.

AQUEOUS AEROSOL DELIVERY

In the past, systemic delivery of drugs via the lungs has been achieved by aerosolizing a solution or suspension of the active. Examples of such devices include nebulizers, metered dose inhalers, and nasal spray devices. The aerosol formed by a nebulizer consists of droplets with diameters between approximately 1 to 10 microns, an ideal size range for delivery to the lungs via inhalation. Smaller particles tend to be exhaled immediately, while larger particles tend to adhere to the back of the throat when inhaled, and do not reach the lungs.

Such targeted delivery to the lungs is not a new development by any means; a number of drugs in today's markets employ this mechanism. In hospitals, for example, Ribavirin (virazole) is delivered via nebulizer for treatment of respiratory syncytial virus and other viral diseases. However, this drug crystallizes wherever the nebulized mist lands, including equipment, bedding, and the patient, thus creating a hazard to health workers. Of course, delivery of dry powders of actives and non-aqueous dispersions of microcrystalline drugs have been in use since the 1950s in metered-dose and dry powder inhalers, though doses are typically low and the metered dose inhalers require organic propellants.

More recently, a joint venture between Pfizer and Aventis has led to the development of Exubera, an inhalable dosage form of insulin. The common thread between Ribavirin and Exubera is that both drugs are

FIGURE 1

Encapsulation of Model API 0.1% w/w Loading

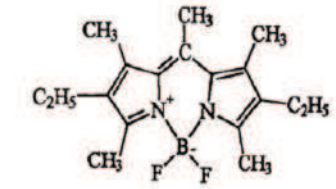
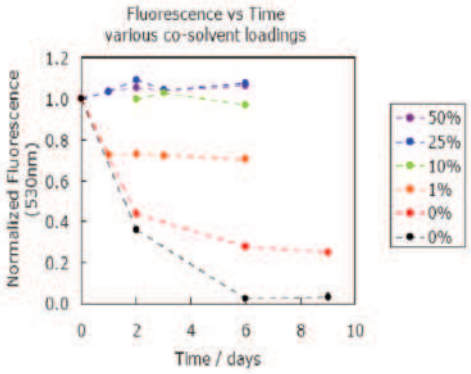


Figure 1. Structure of PM-567.



relatively water-soluble. Delivery of drugs in higher doses from aqueous vehicles is an attractive approach; Ribavirin's solubility of 142 mg/ml enables nebulized delivery in an aqueous system, while the insulin protein can be delivered as a dry powder that is bioavailable owing to the protein's inherent hydrophilic properties.

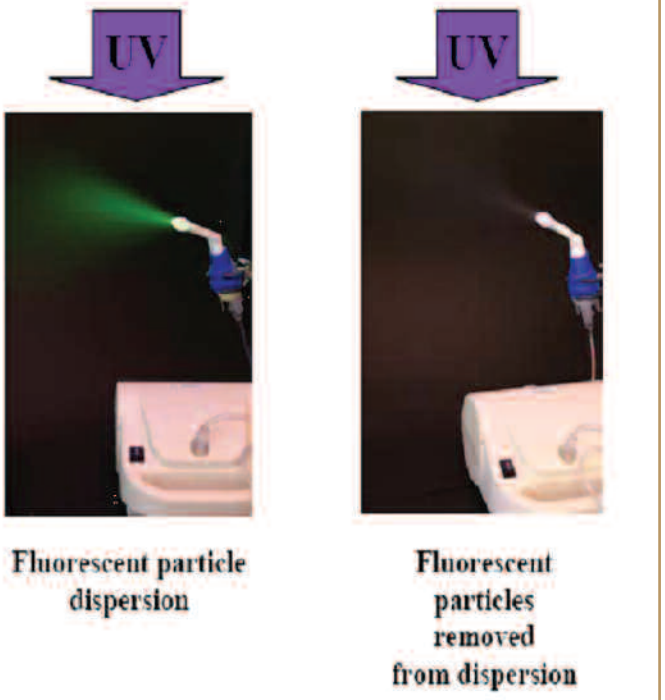
CHALLENGES & POTENTIAL SOLUTIONS FOR HYDROPHOBIC DRUGS

On the other hand, delivery of poorly water-soluble drugs presents a bigger problem for aqueous aerosol delivery to the lungs, for example larger drug particles in a dispersion of the active can, and do, block the nebulizer orifice, and can settle in the dispersion over time, causing dosage consistency issues. Thus there is a need for aqueous inhalation formulations of hydrophobic drugs that have the following characteristics: controlled particle size, improved deposition efficiency, targeting, trafficking through the mucus membrane, bioavailability, sustained release and stability (particularly for higher solids formulations).

Recently, researchers at Particle Sciences developed a technology by which hydrophobic APIs can be encapsulated in wax nanoparticles in aqueous dispersion that can be effectively nebulized via an over-the-counter nebulizer. For nebulization studies, nanoparticle dispersions were prepared in which the nanoparticles contain either a hydrophobic fluorescent dye for particle tracking studies, or a hydrophobic non-nucleoside reverse-transcriptase inhibitor HIV microbicide as proof of concept for hydrophobic drug encapsulation. A proprietary melt-chill process was used to prepare the active-loaded nanoparticles, using only biodegradable, non-toxic, Generally Regarded As Safe (GRAS) excipients, such as natural carnauba wax. Figure 1 shows the molecular structure of the pyrromethene 567A fluorescent dye, and the fluorescence stability of the nanoparticle dispersion in which it was encapsulated. A 10% co-solvent is required in the nanoparticles to maintain fluorescence for longer than 1 week. Below this concentration, aggregation of dye molecules within the particle appears to lead to fluorescence auto-quenching. This suggests that a small amount of co-solvent should always be used when encapsulating the API to maintain stability.

FIGURE 2

UV Analysis of Nebulized Plume



The nanoparticle dispersions containing dye were readily prepared with a Z-average particle diameter of 480 nm and when nebulized, the plume glowed to a brilliant green under black light illumination, indicating the presence of fluorescent particles in the aerosol droplets (Figure 2). To confirm the fluorophore was encapsulated within the wax nanoparticles and not simply dispersed in the water phase, the nebulized dispersion was collected,

FIGURE 3

Droplet Size Distribution of Nebulized Aerosol

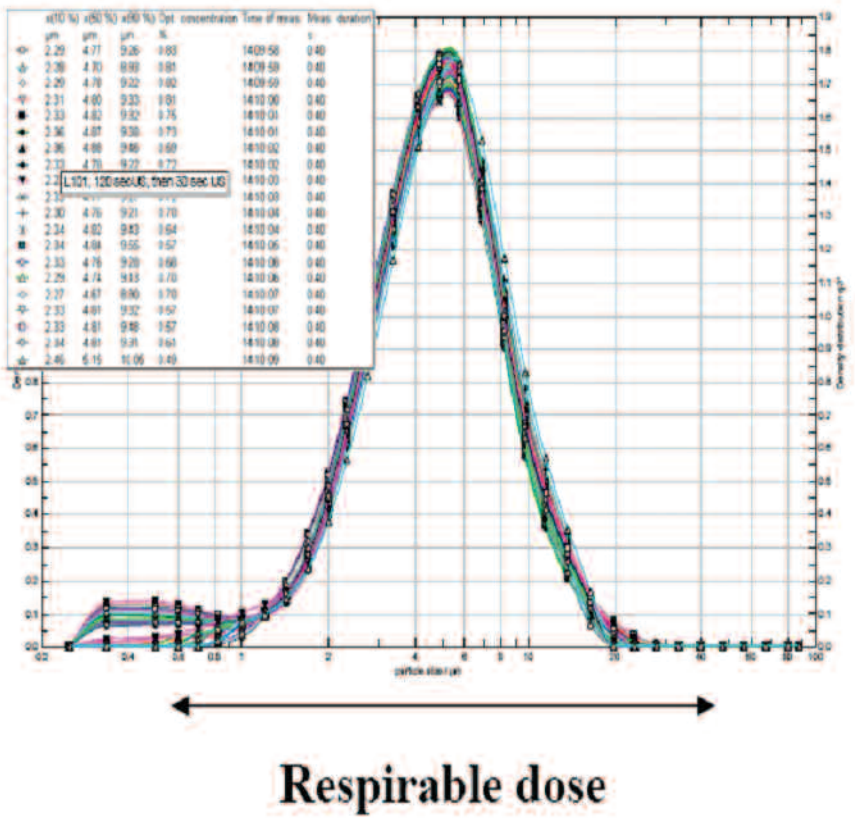


FIGURE 4

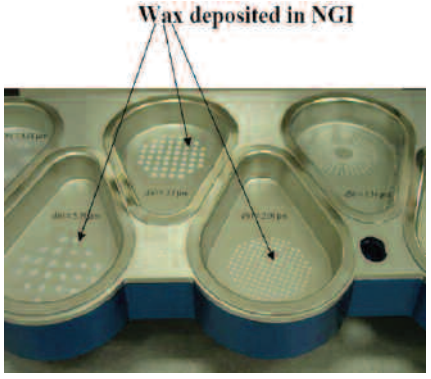
NGI Used at MSP

NGI with Induction Port and Pre-Separator

NGI - Showing Nozzles and Cup Tray

FIGURE 5

Wax Deposited Efficiently in NGI



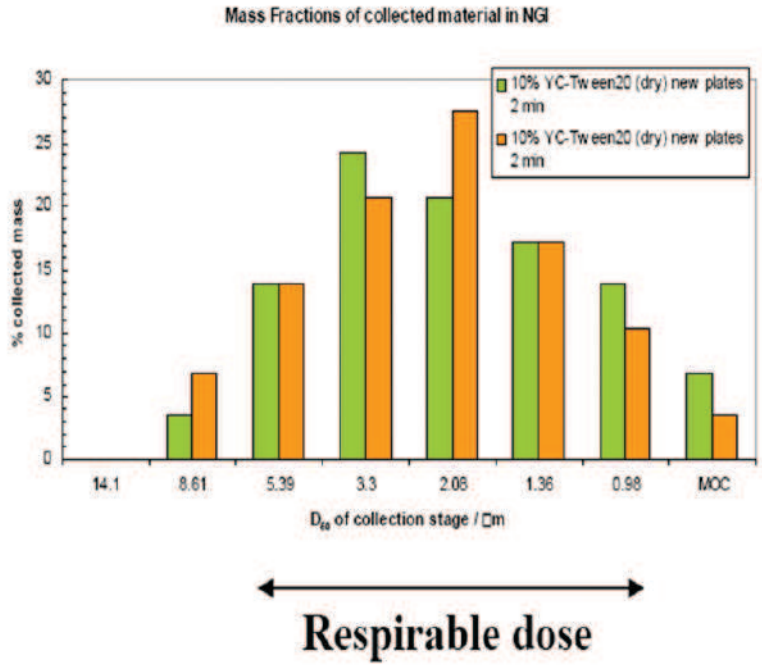
centrifuged to remove particles, and the supernatant examined for traces of dye. As expected, the supernatant showed zero fluorescence. Conversely, the plume formed by nebulizing the fluid after removing the particles by filtration does not fluoresce. The nanoparticles were the same size after nebulizing the dispersion as before, indicating good dispersion stability upon nebulization.

To guarantee that the formulated wax particles formed aerosol droplets of a respirable dose, real-time particle sizing of the nebulized mist was required. Collaborators at Sympatec Corp. in Lawrenceville, New Jersey, determined the size of the aerosol droplets containing the 480-nm wax particles using a HELOS Laser Diffraction Particle Size Analyzer. Figure 3 illustrates that the majority of nebulized droplets have diameters that fall well within the ideal range for maximizing respirable dose, with a D50 diameter of 4.8 microns, and D90 diameter of 9.5 microns.

With a reliable method to encapsulate drugs in wax nanoparticles stable enough for nebulization, forming aerosol droplets of the appropriate size for pulmonary delivery, all that remained was to determine if the droplets had the ability to target even the deepest lung cavities. For the final phase of the project, Particle Sciences' researchers collaborated with MSP Corp. in Minneapolis/St. Paul, the manufacturer of the Next Generation Cascade Impactor or NGI (Figure 4). This device is used to simulate deposition of particles into the lung. The deposition distribution of the nanoparticles in the NGI was

FIGURE 6

Fractional Deposition Distribution - The Wax Nanoparticles are Deposited Ideally for Pulmonary Delivery



determined. The photograph in Figure 5 shows that the majority of nanoparticles (27%) were recovered from the stage of the NGI in which 2-micron aerosol droplets containing them were collected. All of the nanoparticles were deposited in stages corresponding to 0.96- to 8.6-micron aerosol droplets, as shown by the fractional deposition histogram in Figure 6. This demonstrates that the nanoparticles should be readily delivered to the lungs when delivered via nebulizer.

PARTNERSHIP OPPORTUNITIES

Having successfully produced stable nanoparticulate dispersions of encapsulated poorly water-soluble dyes and drugs, and demonstrating that these nebulized dispersions are ideal for pulmonary delivery, Particle Sciences filed for patent coverage of the technology and is now in talks with potential partners interested in applying the technology to their pulmonary delivery projects in areas such as cystic fibrosis and asthma treatment.

BIOGRAPHY

Dr. Andrew Loxley, is Manager of Special Projects at Particles Sciences Inc., a contract research organization in Bethlehem, PA, specializing in pharmaceutical formulation development. He leads a variety of projects, many based on novel and proprietary nanotechnologies, in fields from HIV vaccine and microbicide development to gene-silencing SiRNA delivery. Prior to joining Particles Sciences, he worked as a researcher in the nanotechnology space. British-born, he earned his BSc in Chemistry from the University of Sussex and his PhD in Physical Chemistry focusing on Microencapsulation from the University of Bristol.

Mr. Ismar Dizdarevic, born in Bosnia and Herzegovina, raised in New Jersey, earned his BS from Lehigh University. He is currently pursuing a degree in Medicine at Jefferson Medical College.