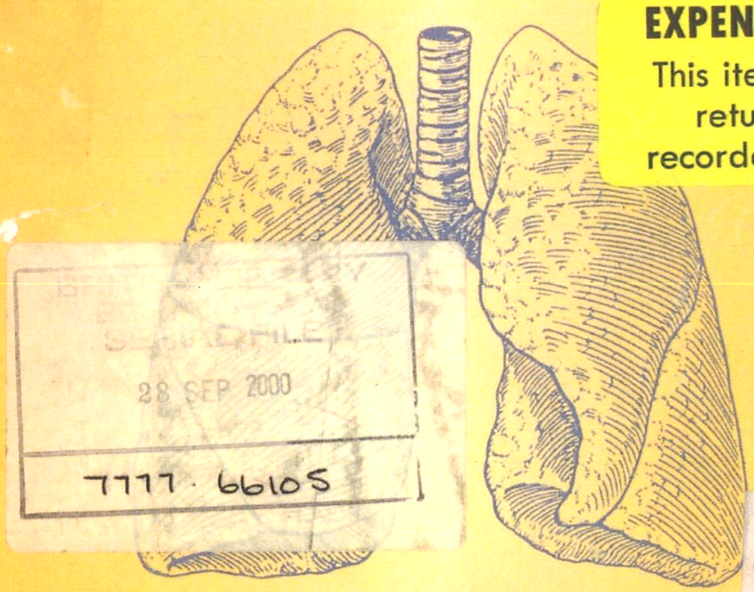
Respiratory Drug Delivery VII

Biological, Pharmaceutical, Clinical and Regulatory Issues Relating to Optimized Drug Delivery by Aerosol



Palm Harbor
at Tarpon Springs, Florida
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The Seventh in a Series of International Symposia Organized by the School of Pharmacy of Virginia Commonwealth University

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Volume I
Conference Papers

Volume II
Suppliers Forum Poster Sessions

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This book belongs to: _____

10 9 8 7 6 5 4 3 2 1

ISBN: Volume I, 1-930114-14-1; Volume II, 1-930114-16-8

Serentec Press, Inc.
612 W. Lane Street
Raleigh, North Carolina 27603
Phone: 919-831-1166
Fax: 919-831-2211

Serentec Press, Inc.
Raleigh, North Carolina
Chichester, England

NANO-THIN COATINGS FOR IMPROVED LUNG TARGETING OF GLUCOCORTICOID DRY POWDERS: *IN-VITRO* AND *IN-VIVO* CHARACTERISTICS

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SUMMARY

A new technique for the preparation of ultra-thin coatings onto inhaled dry powders is presented. The method is based on pulsed laser deposition (PLD) of polymers such as PLGA onto dry powders by directing laser induced high-energy pulses of ultraviolet light onto the polymer. The formed plume of polymer nanoparticles is subsequently deposited onto the dry powder. The coating can be added onto standard dry powder material without the use of wet chemistry. Characterization of the coated particles by SEM and HPLC supported the nanometer-thick nature of the coatings. The deposited material did not affect cell viability in murine alveolar macrophage cell lines over controls and analysis by cascade impaction did not differ from that of uncoated material. Most notable, deposition of PLGA onto dry powders of budesonide and triamcinolone acetonide resulted in a sustained dissolution behavior of approximately 70% of the coated powders from 2 to 24 hours. This resulted in a significant improvement in pulmonary targeting when coated budesonide was compared with uncoated budesonide in a rat animal model for pulmonary targeting.

INTRODUCTION

Inhaled drugs are delivered most commonly via dry powder or metered dose inhalers in order to achieve pulmonary targeting by inducing pronounced local effects with reduced systemic side effects. In addition to drug entity related properties such as oral bioavailability, and clearance, formulation dependent factors, such as pulmonary deposition, and pulmonary mean residence time are recognized as important key features for a successful inhaled anti-asthma drug (1, 2). In particular, computer simulations have shown that, based on receptor occupancies in individual organs, pulmonary targeting can be improved most drastically by optimization of pulmonary dissolution or release rate (1). Recently our group has experimentally shown for liposomal preparations that a slow pulmonary drug release can lead to improved pulmonary selectivity and efficacy (3). It is also likely that pulmonary administration of drugs intended for systemic use will also benefit from a slow pulmonary drug release, e.g., by allowing longer dosing intervals. Unfortunately, the lung represents an organ which is difficult to target because of the enormous blood flow and the resulting pronounced sink conditions, which favor fast pulmonary absorption, especially of small molecules (4-6). The relatively short duration of action in the lungs following inhala-

tion of a drug designed for inducing pulmonary effects and the short systemic effects of a short half-life drug inhaled for inducing systemic effects, therefore, are often the result of their rapid systemic absorption from the airways.

Sustained pulmonary delivery has been achieved with liposomal preparations (for review see [7]), slow dissolving lipophilic drugs (8), microspheres (9), and microparticles (10). The use of porous low density microspheres (11-13) and new pulmonary additives with sustained release producing effects (14) have found recent attention. This paper presents preliminary results on the assessment of an alternative method for the preparation of sustained release delivery forms by the post application of dry-coatings. Over the past few years, the pulsed laser deposition (PLD) technique has emerged as one of the simplest and most versatile methods for the deposition of thin films to a wide variety of flat surfaces (15). Recently, this process has been applied to the coating of fluidized particles, allowing the design of artificially structured, nano-functionalized coatings onto particulate materials with unique physicochemical, optical, cathodoluminescent, or electrical properties (16). This method was applied to the synthesis of pharmaceutically relevant coatings to dry powders (16, 17).

DRY-POWDER COATING TECHNIQUE

This variation of pulsed laser deposition (PLD) uses high-energy pulses of ultraviolet light to deposit solid coating materials onto particles (Figure 1). A laser source is directed in a vacuum chamber towards the polymeric target and induces the plume formation. The generated plume then settles onto the agitated dry powder. Depending on the length of the pulsed laser treatment, either discrete entities or continuous films are deposited onto the surface of the drug particle, which will significantly modulate and enhance the properties of the material (16). Through this coating method, the coating material is generally less than 1% by mass, and coating times are under one hour without the need for drying solvents. Preliminary experiments (16, 17) with biodegradable polymers, faster-degrading poly(lactic-co-glycolic acid) (PLGA) and slower degrading poly(l-lactic acid) (PLA), coated onto micronized budesonide (BUD) and triamcinolone acetonide (TA) are reviewed here, although other coatings on different sized particles have been tested successfully as well.

PHYSICOCHEMICAL CHARACTERIZATION

As indicated in the scheme (Figure 1), discrete clusters form for short exposure times, while longer exposure times result in the formation of a continuous film. Preliminary studies by SEM microscopy of polymer deposited on flat surfaces at different run times suggested that 100 nanometer size or less droplets are deposited (data not shown) and form continuous coatings after several minutes (Figure 2a). Also, coatings onto micronized drug particles (1-5 μm pre-coating, particles not shown) indicate that the size of coated material remains in the size range of smaller than 5 μm (Figure 2b), suggesting that pulsed laser deposition is able to apply ultra-thin coatings without affecting the primary particle size distribution.

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