Polycaprolactone Microspheres as Carriers for Dry Powder Inhalers: Effect of Surface Coating on Aerosolization of Salbutamol Sulfate

RINKU A. TULI,[1,2] TIM R. DARGAVILLE,[1,3] GRAEME A. GEORGE,[1,3] NAZRUL ISLAM[1,2]

[1]Institute of Health and Biomedical Innovation, Brisbane, Queensland 4059, Australia

[2]Pharmacy Discipline, Faculty of Science and Technology, Queensland University of Technology, Brisbane, Queensland 4000, Australia

[3]Chemistry Discipline, Faculty of Science and Technology, Queensland University of Technology, Brisbane, Queensland 4000, Australia

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ABSTRACT: This study reports the factors controlling aerosolization of salbutamol sulfate (SS) from mixtures with polycaprolactone (PCL) microspheres fabricated using an emulsion technique with polyvinyl alcohol (PVA) as stabilizer. The fine particle fraction (FPF) of SS from PCL measured by a twin-stage impinger was unexpectedly found to be zero, although scanning electron microscopy showed that the drug coated the entire microsphere. Precoating the microspheres with magnesium stearate (MgSt) excipient solutions (1%–2%) significantly increased ($p < 0.05$, $n = 5$) the FPF of SS (11.4%–15.4%), whereas precoating with leucine had a similar effect (FPF = 11.3 ± 1.1%), but was independent of the solution concentration. The force of adhesion (by atomic force microscopy) between the PCL microspheres and SS was reduced from 301.4 ± 21.7 nN to 110.9 ± 30.5 nN and 121.8 ± 24.6 nN, ($p < 0.05$, $n = 5$) for 1% and 2% MgSt solutions, respectively, and to 148.1 ± 21.0 nN when coated with leucine. The presence of PVA on the PCL microspheres (detected by X-ray photoelectron spectroscopy) affected the detachment of SS due to strong adhesion between the two, presumably due to capillary forces acting between them. Precoating the microspheres with excipients increased the FPF significantly by reducing the drug–carrier adhesion. © 2011 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:733–745, 2012

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INTRODUCTION

Aerosols delivered from dry powder inhaler (DPI) formulations have become a popular pulmonary delivery system for the management of both local and systemic diseases.[1] The most common approach to carrier-based DPI formulations is to mix the active drug particles (<5 μm) with a large carrier to help reduce the high cohesive forces among micron-sized drug particles, improve the flowability of powders, and allow reproducible dose metering.[2,3] Drug delivery from these powder formulations is influenced by interactions and friction forces that occur among the constituent particles in the formulation. Drug dispersion is affected by the physicochemical characteristics of the powder particles in the mixture.[4] Key factors include particle size and distributions, shape and surface properties such as surface roughness, geometry of contact, and adhesional forces.[4–7] Any disparities in the physicochemical or surface properties of the powders in DPI formulations change the adhesion/cohesion and friction forces, affecting drug detachment and subsequent dispersion from the formulation, ultimately affecting the therapeutic performance.[8–10]

Lactose is currently the most commonly employed carrier to which drugs or drug agglomerates are attached by means of adhesional forces. During inhalation, it is patient's inspiratory force that detaches the drug from the carrier surface with the help of mechanical forces by the design of the device. Most

Correspondence to: Nazrul Islam (Telephone: +61-7-3138-1899; Fax: +61-7-3138-1534; E-mail: nazrul.islam@qut.edu.au)

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commercially available carrier-based DPIs deliver only about 20%–30% of the total dose to lungs, whereas the rest of the drug remains adhered on the carrier surface and is subsequently swallowed, resulting in poor performance of DPI devices with respect to drug delivery.[11] The reasons for this inefficient delivery have not been fully elucidated. However it may be attributed to surface morphology, that is, irregular shape and rough surfaces of commercially available inhalation-grade lactose, which affects drug detachment during inspiration. The presence of amorphous regions on the surface of lactose represents a metastable thermodynamic state with high free energy, and if drug particles are adhered onto high-energy sites, a high amount of force is required to detach the drug particles from the carrier surfaces.[12] Aerosolization and dispersion properties of powders in a DPI formulation are dependent on the flow properties of the powder particles, which, in turn, are affected by particle surface morphology, size, surface charge, surface roughness, and forces of interaction among the powders.[4,13,14] Thus, the drug dispersion from lactose carriers is a complex interplay of various variables. The physical characterization of lactose carriers used in DPI formulations has been intensively investigated and the readers are referred to the comprehensive articles demonstrated by Hickey et al.[15,16] for further information.

The difficulty associated with the use of lactose as carriers is controlling the size, shape, and surface roughness of the particle, which, in turn, affects the detachment of drug.[9] Thus, lactose as a carrier has its own limitations. A number of studies have been conducted to improve the delivery of drugs from lactose carriers into lungs. These studies have focused on improving the dispersion of drugs by optimizing the carrier size,[17] smoothing the carrier surface,[8] mixing different grades of carriers,[18,19] and using lactose carriers with smooth and rough surface morphologies.[8,20] Alternatively, modification of the particle surfaces has been reported to improve the dispersibility of the drug from the carrier surface using different technologies. One of the approaches is to coat the surface of coarse lactose by blending it with fine lactose, magnesium stearate (MgSt), or leucine.[21–25] Common techniques for surface modification of carrier particles include spray drying,[26] encapsulation using supercritical carbon dioxide,[27] physical vapor deposition of particles in an aerosol flow reactor,[28,29] and dry coating of active drug particles such as mechanofusion.[7] However, drug dispersion from these powders is still not satisfactory.

Other sugars such as glucose, sorbitol, and xylitol have also been explored as carriers in DPI formulations, but they are hygroscopic and are not able to efficiently generate the desirable fine particle fraction (FPF) of the drug.[30] Solid lipid microparticles (SLMs) have also been investigated as carriers for pulmonary administration. However, these SLMs are preferred for encapsulation of hydrophobic drugs rather than for surface coating and are suitable for sustained release of the drug into lungs.[31,32]

The culmination of the formulation challenges with the use of lactose and its modified counterparts have led to the exploration of new efficient alternative carriers for inhaled therapy. It is well known that a curved surface with small asperities and low surface energy generally reduces the contact area between adjacent surfaces.[33–35] The surface roughness reduces the contact area, increases the distance of separation, and consequently decreases the adhesion between adjacent particles. Hence, such spherical particles may be useful as carriers in DPI formulations. Indeed, spherical spray-dried lactose particles had higher deposition of the drug pranlukast hydrate (FPF 17.8%) as compared with nonspherical lactose with irregular surface morphologies (FPF 3.4%–14.7%).[20]

Biodegradable polymers are an attractive option as alternative materials for use as carriers in DPIs. Controlling the particle size, shape, and surface roughness of polymers is much easier[36] as compared with sugars. Polymers have long been used in various drug delivery technologies and have been investigated widely in pulmonary drug delivery to sustain the release of drugs, but they have not been exploited as carriers in DPIs. Hence, it is of interest to research the use of biodegradable polymers with controlled surface functionality as carriers for the pulmonary delivery of drugs from powder formulations. Polycaprolactone (PCL) has been investigated in drug delivery because it is biodegradable and undergoes hydrolysis by degradation of its ester linkages. PCL nanoparticles, used to encapsulate a variety of drugs by nanoprecipitation, solvent displacement, and solvent evaporation techniques, have been reviewed.[37] Drug-loaded PCL nanoparticles such as anticancer (tamoxifen,[38] Taxol,[39] vinblastine,[40] and docetaxel),[41] peptide (insulin),[42] antiretroviral (saquinavir),[43] and antifungal (amphotericin B)[44] have been studied for drug delivery via other routes, but none of these formulations have been investigated for lung delivery. Recently, Kho et al.[45] reported nanoparticle aggregates (270 nm) of levofloxacin-loaded PCL prepared by spray drying using mannitol, lactose, and leucine as drying adjuvants to maintain the structural integrity of PCL and redispersibility of the agglomerates for lung delivery with prolonged action. The authors demonstrated the development of drug-loaded PCL nanoparticles with desired aerodynamic diameter for direct delivery into lungs. However, the possible degradability or toxicity of PCL in lungs has not been demonstrated. Furthermore, they have not studied the surface properties of PCL particles as large carriers used in DPI formulations.