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Lipid-based carriers for pulmonary products: Preclinical development and case studies in humans☆

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ABSTRACT

A number of lipid-based technologies have been applied to pharmaceuticals to modify their drug release characteristics, and additionally, to improve the drug loading for poorly soluble drugs. These technologies, including solid-state lipid microparticles, many of which are porous in nature, liposomes, solid lipid nanoparticles and nanostructured lipid carriers, are increasingly being developed for inhalation applications. This article provides a review of the rationale for the use of these technologies in the pulmonary delivery of drugs, and summarizes the manufacturing processes and their limitations, the in vitro and in vivo performance of these systems, the safety of these lipid-based systems in the lung, and their promise for commercialization.

Contents

Abbreviations: AE, adverse event; API, active pharmaceutical ingredient; BDP, beclomethasone dipropionate; CF, cystic fibrosis; CFU, colony forming unit; CH, cholesterol; COPD, chronic obstructive pulmonary disease; DLPC, dilauroyl PC; DPI, dry powder inhaler; DPPC, dipalmitoyl PC; DSPG, distearoyl PG; DTPA, diethylene triamine pentaacitic acid; EPC, egg PC; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; hGH, human growth hormone; HRCT, high resolution computed tomography; HSA, human serum albumin; HSPC, hydrogenated SPC; IgG, immunoglobulin G; IM, intramuscular; IT, intratracheal; IV, Intravenous; L-AmB, liposomal amphotericin B; L-CyA, liposomal cyclosporin A; L-PGE2, liposomal prostaglandin E2; L-PTX, liposomal paclitaxel; LOCF, last observation carried forward; LMs, lipid microparticles; MDI, metered dose inhaler; MMAD, mass median aerodynamic diameter; NCFBE, non-CF bronchiectasis; NLCs, nanostructured lipid carriers; O/W, oil in water; O/W/O, oil in water in oil; PC, phosphatidylcholine; PK, pharmacokinetic; PLGA, poly-lactic-co-glycolic acid; PS80, polysorbate 80; PTH, parathyroid hormone; SAE, serious adverse event; SC, subcutaneous; SLNs, solid lipid nanoparticles; SMI, soft mist inhaler; SOD, superoxide dismutase; SPC, soy PC; TIP, tobramycin inhalation powder; 9-NC, 9 nitrocamptothecin.

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1. Introduction

The use of inhaler devices to deliver therapeutics to treat lung diseases like asthma and COPD has become well accepted since the development and marketing approval of the first pressurized metered dose inhaler (pMDI) in 1956, almost sixty years ago [1–3]. There are now four broad classes of inhalation devices including pMDIs, nebulizers, soft-mist inhalers (SMIs) and dry powder inhalers (DPIs). The nebulizer class has been around even longer than pMDIs, with the introduction of the Bennet inhaler in 1654 and the early jet nebulizers in the 1850s [3]. Recent innovations in nebulizers have seen the incorporation of breath control features to increase the efficiency of delivery, or vibrating meshes to produce aerosols with greater concentration of droplets and reduce their administration time; these characteristics can lead to increased patient convenience over the traditional jet nebulizer platform [3]. Soft mist inhalers, of which the Respimat® is an example, emerged in the 1990s and are similar to nebulizers in that they deliver solution formulations. However, rather than the medication being inhaled over many minutes during tidal breathing by the patient, a bolus of aerosol is typically delivered in one or a small number of breaths [4]. This attribute gives the SMI product a convenience benefit comparable to the MDI and DPI formats [4].

The DPI class emerged in the 1970s with a number of passive DPIs that used patient inspiration to disperse the micronized drug powder from the larger lactose carrier particles [1,2]. Over the intervening forty years, device engineering led to DPIs which were easier and more intuitive to use and which provided a higher and more consistent lung dose to the patient [2,3]. Over the past 20 years, the powder formulations that are used in DPIs have garnered more attention, with much of the focus on increasing their dispersibility through reductions in the interparticle adhesive forces [2,3,5]. This has been accomplished via a number of strategies such as by reducing the surface energy through the incorporation of hydrophobic excipients, and by increasing the particle porosity, geometric size, or rugosity [2]. All of these refinements can lead to higher emitted dose performance at lower inspiratory rates and thus reduce oropharyngeal deposition and the variability that it imparts to the dose reaching the lung [2]. One of the most significant advancements in powder technologies was the transition from the micronization of large drug crystals into a respirable size range for use in DPIs, to the use of spray drying to create particles in the respirable size range directly [2]. The incorporation of lipids into these formulations led to the development of porous particles, with transformative properties for the performance of DPIs [2]. While these porous particles have not been incorporated into a new generation of asthma and COPD products, progress has been made in the use of these particles to deliver inhaled antibiotics to treat lung infections and one DPI product has already reached the market, the TOBI Podhaler® [6]. In this review, these solid-state porous particles containing lipids have been termed simply lipid microparticles (LMs).

As recognized in the first published description of large, porous particles for inhalation in 1997 [7], which were actually polymer-based (PLGA) particles rather than lipid-based particles, the motivation to develop porous particles was specifically to create a break-through in the performance of inhalation products for pulmonary applications. There was a subsequent transition from polymer-based porous particles to lipid-based porous particles, presumably due to better acceptability of these excipients. The focus of the use of LMs remains primarily the respiratory field. In contrast, lipids have been utilized broadly in the pharmaceutical field in a variety of formats; e.g., emulsions, liposomes, solid lipid nanoparticles and nanostructured lipid carriers. These formats were not developed specifically with pulmonary applications in mind; the employment of these technologies for respiratory opportunities came after their discoveries, with scientists looking for novel applications in various pharmaceutical fields. A number of pharmaceutical liposome formulations have reached the market, with the majority indicated for oncology conditions following IV administration. However, many liposome formulations have shown promise as inhaled products and two inhaled liposomal antibiotics are in late stages of clinical trials [6,8]. In contrast, SLNs and NLCs are at an earlier stage of evaluation for their potential to provide therapeutic benefit as inhaled products [9]. In this paper we survey the application of LMs, liposomes, SLNs and NLCs for pulmonary delivery. The category of lipid emulsions is still relatively sparsely applied to the pulmonary field; however, the potential for mucosal vaccination using a cationic nanoemulsion as a carrier for DNA was described [10].

2. Lipid microparticles (LMs)

2.1. Background and aerosol requirements

Most solid-state lipid microparticles represent low-density, highly porous particles [11,12]. The practical importance of particles with these characteristics can be established from a brief consideration of their aerodynamic behavior.

The effect of particle density, ρ_p, on the particle aerodynamic diameter, D_a, can be expressed in terms of Stokes' Law, which equates the following terms with respect to the terminal settling velocity, u_T [13]:

$$u_T = \rho_0 {D_a}^2 C(D_a)\, g/(18\eta) = \rho_p {D_g}^2 C\left(D_g\right) g/(\kappa 18\eta) \quad (1)$$

where ρ_0 and ρ_p are the unit density (i.e., 1 g/cm^3) and mean particle density, respectively, D_a and D_g are the aerodynamic and geometric diameter, respectively, $C(D_a)$ and $C(D_g)$ are the slip correction factors

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