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Dry powders for oral inhalation free of lactose carrier particles ☆

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ABSTRACT

Dry powder inhaler (DPI) products have traditionally comprised a simple formulation of micronised drug mixed with a carrier excipient, typically lactose monohydrate. The presence of the carrier is aimed at overcoming issues of poor flowability and dispersibility, associated with the cohesive nature of small, micronised active pharmaceutical ingredient (API) particles. Both the powder blend and the DPI device must be carefully designed so as to ensure detachment of the micronised drug from the carrier excipient on inhalation.

Over the last two decades there has been a significant body of research undertaken on the design of carrier-free formulations for DPI products. Many of these formulations are based on sophisticated particle engineering techniques; a common aim in the formulation design of carrier-free products being to reduce the intrinsic cohesion of the particles, while maximising dispersion and delivery from the inhaler. In tandem with the development of alternative formulations has been the development of devices designed to ensure the efficient delivery and dispersion of carrier-free powder on inhalation. In this review we examine approaches to both the powder formulation and inhaler design for carrier-free DPI products.

Contents

Abbreviations: API, active pharmaceutical ingredient; AUC, area under the curve; BSA, bovine serum albumin; C_{max}, peak concentration; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; DPPC, dipalmitoylphosphatidylcholine; ED, emitted dose; EMA, European Medicines Agency; EMEA, European Medicines Evaluation Agency; FDA, Food and Drug Administration; FDKP, fumaryl diketopiperazine; FPF, fine particle fraction; G-CSF/M, granulocyte-colony stimulating factor/mannitol; HPβCD, hydroxypropyl-beta-cyclodetrin; LPNP, large porous nanoparticulate; LPP, large porous particle; MCT, microstructured carrier tape; MMAD, mass median aerodynamic diameter; NIMs, nano-in-microparticles; NP, nanoparticle; NPMPs, nanoporous/nanoparticulate microparticles; PEG, polyethylene glycol; PLGA, poly(lactic-co-glycolic) acid; SEM, scanning electron microscopy; $scCO_2$, supercritical carbon dioxide; SPION, superparamagnetic iron-oxide nanoparticle; TEM, transmission electron microscopy; t_{max}, peak time; TSI, tobramycin solution for inhalation.

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1 . Introduction

The efficient delivery of an active pharmaceutical ingredient (API) to the respiratory tract from a dry powder inhaler (DPI) depends on four interdependent parameters — the formulation, the metering system (capsule, multi-unit dose and reservoir dose containment elements), the inhaler device and the patient's inhalation technique. In order to achieve good penetration into the pulmonary regions it is generally accepted that particles should have an aerodynamic particle size between 1 and 5 μm. However, particles of this low micron size have a high surface free energy, with a tendency to stick together (*via* cohesive forces) or to any surfaces they encounter (*via* adhesive forces), in an attempt to reduce the surface energy. Such small particles are thus very cohesive or "sticky" and exhibit poor flowability and aerosolisation performance, with a propensity to be retained in the inhaler if used alone. For this reason, in order to improve flowability and dispersion of API particles, the micronised API is usually mixed with an inert carrier or "flow aid" comprising a population of coarse particles (50 to 100 μm in diameter) [1].

Lactose monohydrate is the most commonly used excipient carrier material in DPI formulations. Mixtures of the lactose with API are often called ordered or interactive mixtures, which are easier to handle during the manufacturing processes than micronised API alone. The use of a carrier excipient makes manipulation of small drug doses possible. A typical drug-to-carrier ratio is 1:67.5 [2,3]. The API particles should loosely adhere to the carrrier particles and during inhalation in the turbulent airstream which is created, the API particles detach from the carrier particles and are made available for deposition into the lungs. The larger carrier impacts in the mouth and at the back of the throat and is swallowed. The carrier excipient also provides bulk to the formulation, which improves the handling, dispensing, and metering of the drug, which is of particular importance for low dose formulations such as steroids (typical dose per actuation: 50 μg to 500 μg).

In order to ensure efficient delivery of API, it is critical that adhesive forces between the API and carrier are not so strong that detachment from the carrier is prevented. The balance between adhesive and cohesive forces should be adjusted to ensure sufficient adhesion between drug and carrier so as to provide a stable formulation (homogeneous blend with good content uniformity) but with adequate separation of API from carrier on inhalation. It has been recognised that the efficiency of a powder formulation is highly dependent on the lactose quality, lactose source, particle size and particle size distribution, fine-lactose content, and the inhalation flow rate and dispersion capacity of the respective DPI device [4].

The development of carrier-free dry powder inhaler formulations has the potential to overcome issues associated with lactose (or other carrier) as a critical component of the formulation. Problems of blend uniformity are avoided (for single API formulations) and the aerosolisation properties of the formulation will depend on the characteristics of the API particles or API-containing particles, together with DPI inhaler performance and the patient's inhalation technique.

Additionally, the absence or limited amount of excipient included in carrier-free formulations permits the inhaled powder mass to be limited, and makes the delivery of high dose actives (*e.g.* antibiotics) to the lungs possible. Over the last two decades significant efforts have been invested in the design of carrier-free dry powder inhaler formulations, based on sophisticated particle engineering techniques, together with inhalers suitable for delivering such carrier-free powders efficiently to the patient. A common aim in developing carrier-free products is to reduce the intrinsic cohesion of the particles, while maximising dispersion and delivery from the inhaler.

This review will present the particle technologies on which carrier-free DPI formulations are based, including platform technologies which have resulted in commercial products. Also presented is a short review of marketed dry powder inhalers (DPIs) which have been developed to deliver these formulations, as well as inhaler devices currently in development.

2 . Carrier-free formulations

2.1. Spheroids

Spheroids (soft aggregates) are manufactured by the controlled agglomeration (spheronisation) of micronised particles. Spheroids have large particle sizes (approximately 0.5 mm in diameter) and thus have appropriate flow properties, significantly better than micronised material, and exhibit little static charging during handling and operating [5]. Commercially they are used with the Turbohaler® device (see Section 4 below) and loaded as spheroids into the inhaler, however they break up into individual, primary particles upon inspiration. It has been reported that the main drawback of such systems containing soft pellets is high variability in the emitted dose, as high as 15% in terms of a total relative standard deviation [6].

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