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Amorphous powders for inhalation drug delivery☆

Lan Chen [a], Tomoyuki Okuda [b,c], Xiang-Yun Lu [a], Hak-Kim Chan [c,*]

[a] School of Medical Instrument and Food Engineering; University of Shanghai for Science and Technology; Shanghai 200093; China
[b] Faculty of Pharmacy; Meijo University; 150 Yagotoyama, Tempaku-ku, Nagoya 468-8503; Japan
[c] Advanced Drug Delivery Group; Faculty of Pharmacy; The University of Sydney; Sydney; 2006, NSW, Australia

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ABSTRACT

For inhalation drug delivery, amorphous powder formulations offer the benefits of increased bioavailability for poorly soluble drugs, improved biochemical stability for biologics, and expanded options of using various drugs and their combinations. However, amorphous formulations usually have poor physicochemical stability. This review focuses on inhalable amorphous powders, including the production methods, the active pharmaceutical ingredients and the excipients with a highlight on stabilization of the particles.

Contents

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* Corresponding author.

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1. Introduction

Inhaled aerosol therapy has gained wide acceptance as an effective non-invasive method for local and systemic therapeutic delivery of active pharmaceutical ingredients (APIs). This is due to the unique features of the lung [1,2], including large and highly vascularized surface area (80–100 m^2/adult and blood flow of 5 L/min), thin alveolar-capillary membrane (0.1–0.5 μm), low enzymatic activity and avoidance of hepatic first pass metabolism [3–5]. In particular, inhaled drug delivery is anticipated to realize the clinical application of biopharmaceutical drug candidates including peptides, proteins and nucleic acids, which are rapidly eliminated from body by enzymatic degradation when administered orally or parenterally. Among inhaled aerosol formulations and devices, those for dry powder inhalations (DPIs) have attracted more attention because of their advantages including easy handling, superior portability, no need of propellant, high storage stability and greater hurdle for competitors for generic market entry.

For successful inhalation therapy with DPIs, there are several key issues for consideration. Firstly, the water solubility of APIs determines their local activity or systemic bioavailability. However, about 40% of marketed drug products and 70–90% of drug candidates in development are poorly soluble in water [6,7]. In addition, poorly water-soluble API particles if persist long-term on the surface of lung epithelium might cause unwanted inflammatory response. The application of amorphous form, which present higher water solubility and higher dissolution rate than the crystalline form in DPI formulations is considered as a potential strategy to overcome the problems caused by poor water solubility. For protein and polypeptide therapeutics, moreover, a glassy state is required to maintain the conformational and biological stability of the macromolecules. Amorphous powders for inhalation can thus contribute to the achievement of innovative and effective aerosol therapy. However, physical instability of amorphous particles which will affect the powder dispersibility is always a major issue to be addressed [8]. Hence, a fine balance is necessary between stability and aerosol performance of amorphous powders [9]. A formulation excipient which improves the powder dispersibility does not necessarily also improve the powder physical stability (e.g. to moisture), and vice versa, and the situation is complicated by the presence of additional excipients. Aerodynamic performance determines aerosol deposition in the lungs and consequently the therapeutic outcomes. The aerodynamic diameter of a particle governed by the formula below [10]

$$d_{ae} = d_{geo}\sqrt{\left(\frac{\rho_p}{\rho_0 \chi}\right)} \quad (1)$$

where d_{ae} is the aerodynamic diameter, d_{geo} the geometric diameter, ρ_p and ρ_0 are the particle and unit density, respectively, and χ the dynamic shape factor. It is obvious that the size, density and shape of particles will all affect d_{ae} [11]. Non-spherical morphology, small d_{geo} and low density or high porosity will contribute to achieving smaller d_{ae} which usually should be between 1 to 5 μm for DPIs [12].

In this review, amorphous powders for inhalation drug delivery are discussed focusing on the methods for powder production, amorphous inhalable drugs and functional excipients for DPI formulations. Suitable devices for amorphous DPI formulations and the approaches for promoting the stability of amorphous powders are also highlighted.

2. Methods for amorphous drug powder formation

Inhalable fine powders are usually obtained by conventional methods such as high-energy milling. However, most industrially adopted milling processes would render crystalline materials partially amorphous by introducing mechanical stress with very limited control [8,13]. Thus, milling alone is difficult to fulfill the needs for more complex engineered structures, such as porous/hollow particles, nanoaggregates, and surface-modified, coated or encapsulated particles [10]. Other existing methods using melt quenching or thin-film evaporation are not suitable due to the heat involved or inability to produce respirable particles. Alternative techniques for production of amorphous powders for inhalation include spray drying, spray-freeze drying and supercritical antisolvent precipitation [1,14–15].

2.1. Milling

Cryomilling has been used to prepare amorphous solids of pure drugs and drug mixture with amino acids to form co-amorphous solids [16]. The process was performed using a ball mill (e.g. 30 Hz and 60 min) in liquid nitrogen. However, the method is yet to apply to production of inhalable particles. Although milling may have limitations for controlling important particle characteristics such as size, shape, surface properties, and electrostatic charge [17], it can also offer the advantages of simple procedure, cost effectiveness, and easy scale-up [18].

Zijlstra et al. investigated the inhalation characteristics of amorphous dry powder particles of cetrorelix, a synthetic decapeptide with gonadotropin-releasing hormone (GnRH) antagonistic activity, prepared by milling [19]. Cetrorelix as a peptide drug was micronized by a specific pearl milling system using heptafluoropropane as a dispersion medium for low-temperature operation [20]. The milling system achieved limited degradation of cetrorelix (<1.17%) and minimal metal contamination. In the milled particles, submicron-sized primary particles formed agglomerates with the mean diameter of approximately 1.3 μm. In a formulation physically mixed with lactose carrier particles (Pharmatose® 110 M), the milled particles showed approximately 28% and 39% of fine particle fractions (FPFs) when dispersed with the ISF inhaler® (airflow rate; 90 L/min, pressure drop; 2.8 kPa) and Novolizer® (airflow rate; 71 L/min, pressure drop; 4 kPa), respectively.

Onoue et al. reported an effective application of solid dispersion to inhaled amorphous dry powder particles of cyclosporine A (CsA), a cyclic undecapeptide with immunosuppressive activity, prepared by milling [21]. Solid dispersion of amorphous CsA to methylcellulose was formed by wet-bead milling, followed by freeze drying to obtain the powder form. Interestingly, the solid dispersion formulation had a much higher water solubility of CsA than amorphous CsA alone or its physical mixture with methylcellulose. Using Fourier transform infrared (FT-IR) spectral analysis, the authors also found molecular interactions between CsA and polymer in the solid dispersion formulation which might contribute to increasing water solubility of CsA [22]. To achieve respirable powder formulations, the solid dispersion powders were micronized by jet milling after mixing with erythritol. The particles after jet milling had a mean diameter of 2.4 μm and, after physically mixed with lactose carrier particles (Respitose® SV-003), showed approximately 96% of output efficiency and 54% of fine particle fraction using the Jethaler (airflow rate; 28.3 L/min). Furthermore, histochemical examination and inflammatory cell counts in ovalbumin-sensitized rats (asthma/chronic obstructive pulmonary disease model) demonstrated that the respirable powder formulations containing the solid dispersion exhibited higher in vivo anti-inflammatory effects than the physical