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Review

Characterisation of dry powder inhaler formulations using atomic force microscopy

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ABSTRACT

Inhalation formulations are a popular way of treating the symptoms of respiratory diseases. The active pharmaceutical ingredient (API) is delivered directly to the site of action within the deep lung using an inhalation device such as the dry powder inhaler (DPI).

The performance of the formulation and the efficiency of the treatment depend on a number of factors including the forces acting between the components. In DPI formulations these forces are dominated by interparticulate interactions. Research has shown that adhesive and cohesive forces depend on a number of particulate properties such as size, surface roughness, crystallinity, surface energetics and combinations of these. With traditional methods the impact of particulate properties on interparticulate forces could be evaluated by examining the bulk properties. Atomic force microscopy (AFM), however, enables the determination of local surface characteristics and the direct measurement of interparticulate forces using the colloidal probe technique. AFM is considered extremely useful for evaluating the surface topography of a substrate (an API or carrier particle) and even allows the identification of crystal faces, defects and polymorphs from high-resolution images. Additionally, information is given about local mechanical properties of the particles and changes in surface composition and energetics. The assessment of attractive forces between two bodies is possible by using colloidal probe AFM.

This review article summarises the application of AFM in DPI formulations while specifically focussing on the colloidal probe technique and the evaluation of interparticulate forces.

Contents

Abbreviations: AFM, atomic force microscopy; API, active pharmaceutical ingredient; CA, contact angle; CAB, adhesive–cohesive balance; COPD, chronic obstructive pulmonary disease; DMT, Derjaguin–Muller–Toporov; DPI, dry powder inhaler; FPF, fine particle fraction; JKR, Johnson–Kendall–Roberts; MDI, metered dose inhaler; MYD, Muller–Yushchenko–Derjaguin; RH, relative humidity; RMS, root mean square; SCA, surface component approach; SEM, scanning electron microscopy; Si, silicon; Si_3N_4, silicon nitride; SMI, soft-mist inhaler; STM, scanning tunnelling microscopy; vdW, van der Waals; XRD, X-ray diffraction.

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1. Introduction

In recent years, atomic force microscopy (AFM) has become one of the most significant tools in surface chemistry with applications ranging from simple topographical imaging to force measurements, including tailor-made colloidal probe measurements, and also meeting specific requirements such as the evaluation of electric forces or magnetic fields.

AFM based research has been found to be particularly beneficial in the field of pharmaceutics, especially in the area of inhalation formulations. Relevant applications will be discussed in this article while focussing on dry powder inhaler (DPI) formulations. Issues regarding such experiments are discussed and an overview of common approaches is given. Additionally, a brief summary of adhesion theories provides a better understanding of the forces dominating DPI formulations and the challenges AFM users have to overcome.

2. Pulmonary drug delivery

Respiratory disorders such as asthma and chronic obstructive pulmonary disease (COPD) are usually treated by direct pulmonary delivery of drug formulations via inhalation (Global Initiative for Asthma, 2014). Owing to the rapid onset of action, the circumvention of the first pass metabolism and a generally lower risk of side effects, inhalation formulations are generally considered superior to conventional oral dose alternatives (Hoppentocht et al., 2014; Patton and Byron, 2007; Sung et al., 2007; Wang et al., 2014). Delivery relies on nebulisers, soft-mist inhalers (SMI), metered dose inhalers (MDI) or dry powder inhalers (DPI), with the latter providing a convenient way of delivering the drug with unique advantages such as easy handling and relatively high patient compliance (Dalby et al., 2004; Hoppentocht et al., 2014; Labiris and Dolovich, 2003a,b; Patton and Byron, 2007; Sung et al., 2007; Wang et al., 2014). In terms of shelf life and drug stability, DPI formulations also benefit from being stored in the solid state which makes the active pharmaceutical ingredient (API) less susceptible to degradation and therefore superior to MDI suspensions (Zeng et al., 2000).

Efficient drug delivery is controlled, first and foremost, by the properties of the formulation. In order to reach the targeted sites in the respiratory tract, the API needs to penetrate the deep lung (Cui et al., 2014). Upon inhalation, the drug particles are subject to different deposition mechanisms—impaction, sedimentation and diffusion—depending on their size (Heyder, 2004; Zeng et al., 2000). Impaction leads to particles with aerodynamic diameters above 5 μm remaining in the oropharynx. APIs with aerodynamic diameters below 5 μm deposit in the smaller airways, including bronchi and bronchioles, where sedimentation by gravitational forces is the main deposition mechanism. A particle's settling velocity correlates directly with the square of the particle diameter (Frijlink and De Boer, 2004), assuming an ideally spherical shape. Therefore, sedimentation depends critically on particle size. Frijlink and De Boer (2004) found particles below 1 μm to be unsuitable for sedimentation. Most particles below this diameter are exhaled while small percentages are drawn into the deepest regions of the lung, the alveoli, where the particles deposit due to diffusion.

The key factor for drug deposition is the aerodynamic diameter of the drug particles (Eq. (1)). The aerodynamic diameter, D_{ae}, depends on the particulate density, ρ_p, the geometric diameter of the particle, D_g, and its geometry, expressed by the dynamic shape factor, χ, which is 1.00 for an ideal sphere but increases with irregularities. D_{ae} represents the diameter of a sphere with a standard density, ρ_o, of 1000 kg m^{-3} and the same terminal velocity as the irregular particle (Wang et al., 2014) (Eq. (1)):

$$D_{as} = D_g \sqrt{\frac{\rho_p}{\rho_o \chi}} \quad (1)$$

For optimum efficacy, the particles' aerodynamic diameters should be between 1 μm and 5 μm (Cui et al., 2014). However, other particle and formulation characteristics are critical too. Moisture uptake needs to be known precisely on account of its impact on the effective aerodynamic particle diameters as the particles migrate through the respiratory tract (Heyder, 2004). Dispersion and flow related properties are also crucial for the success of inhalation therapy. For example, flowability affects the mixing and capsule filling performance (Neumann, 1967; Tan and Newton, 1990), and the detachment of the API from the carrier during inhalation (Zeng et al., 2000).

Successful API delivery is influenced by particle shape, size and size distribution, and also by surface morphology (De Boer et al., 2005; Neumann, 1967). If excipients are included in the formulation, carrier particle size and texture also have to be considered. The forces acting both between drug particles and between drug and excipient particles are of high importance: they have to be strong enough to allow for easy formulation preparation and to prevent segregation during transport and storage (Cui et al., 2014). At the same time, they need to be low enough to ensure dispersion and disaggregation during inhalation (Cui et al., 2014), as only small particles and agglomerates (<5 μm) can penetrate the deep lung and be therapeutically active (Cui et al., 2014; Zeng et al., 2000). The drug load itself also affects formulation performance along with the choice of inhaler device (De Boer et al., 2005) and the patient's individual breathing pattern (Chrystyn and Price, 2009; Heyder, 2004). The relationship between particulate characteristics and their respective effects on formulation performance have been studied and reviewed widely over the years (Adi et al., 2013; Chan, 2008; Chow et al., 2007; Donovan and Smyth, 2010; Guenette et al., 2009; Healy et al., 2014; Zellnitz et al., 2014; Zeng et al., 2000; Zhang et al., 2011).

3. Atomic force microscopy (AFM)

To assess the particulate characteristics of a dry powder formulation, specifically adapted methods are often necessary. This is particularly true for surface analyses, e.g. the evaluation of surface morphology, surface rugosity or surface energetics (Wu et al., 2010) and for determining the interparticulate forces between the API and/or carrier particles (Tsukada et al., 2004). For a number of decades, one technique in particular has proven to be extremely valuable for measuring such forces: atomic force microscopy (AFM). The range of AFM-based applications is summarised in Table 1.

AFM is an advanced technique for surface characterisation studies (Wu et al., 2010). In contrast to conventional optical or