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Study of ageing of dry powder inhaler and metered dose inhaler by atomic force microscopy

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ABSTRACT

Investigation by atomic force microscopy (AFM) is necessary for the analysis of the interaction between grains of powder used in dry powder inhalers (DPIs) in controlled atmosphere and metered dose inhalers (MDIs) in liquid phase. Measurements of nanonewton forces leading the powder cohesion resulting between active substances were performed. We have developed a protocol based on standard analysis: Scanning Electron Microscopy (SEM) and nano-analysis. This paper deals with the direct analysis of morphology evolution performed over three months in controlled atmosphere at various relative humidities (RH) and temperatures for DPIs and in a mimetic HFA134a liquid for MDIs in order to understand the behaviour of a binary mixing. Atomic force microscopy was also employed to characterize the interactions between particles.

In this study, colloid probe AFM has been used to measure adhesive forces between drug particles in a controlled atmosphere for DPIs and in a liquid medium for MDIs. A link connecting the colloidal powder quality and particle–particle interactions is extracted from this study.

1. Introduction

One of the most efficient ways to administrate a drug synthesised to treat respiratory diseases is the oral way. Those drugs are usually made of many compounds that play different roles (excipients, drug, and carriers). Several systems have been developed in order to administrate the drug to the lungs. Among these systems, the most used are the pMDIs (pressurized Metered Dose Inhalers) and the DPIs (Dry Powder Inhalers). The first one usually contain therapeutic active ingredients dissolved or suspended in a propellant (flocculation), a mixture of propellants, solvents and/or excipients in compact pressurized aerosol dispensers. In that case, the displacement vector of the drug is a pressurized gas in a liquid form. The first pMDI used CFC's as aerosols but now, proper vectors are used, like the HFA 134a (1, 1, 1, 2-Tetrafluoroethane). When the patient actuates the cartridge, the gas compressed in a liquid phase expends into gas and releases the drug to the lungs.

Although similar in many features to other drug products, MDIs have unique differences with respect to formulation, container, in-process and final controls, closure, manufacturing, and stability. These differences need to be considered during the development program because they can affect the ability of delivering reproducible doses to patients over the life of the product as well as the product's efficacy.

DPIs are an alternative to the aerosol based inhalers (MDIs). It consists in a capsule containing a mixture of dried powders composing the drug. This capsule is loaded inside an inhaler device. Patients put the mouthpiece of the inhaler into their mouth and take a deep inspiration. Air is the vector of the drug displacement. Lactose, known for good lung tolerance, is usually used as a carrier to bring drugs to the target. In order to be efficient and to achieve the lungs (particularly the pulmonary alveolus), those powders must have a micrometric size [1,2].

DPIs are complex drug products that differ in many aspects from more conventional drug products as well as from MDIs. The unique characteristics of DPIs should be considered during development, particularly with respect to formulation, manufacturing, container and closure system or device, and both in-process and final controls. Regardless of the DPI design, the most crucial attributes are the reproducibility of the dose and particle size distributions. In DPIs, complex and subtle interactions may occur between the drug substance, carrier(s) [3], components of the container and closure system that significantly affect the safety and effectiveness of the drug. For example, gravitational, fluid dynamic, and other interactive forces, such as electrostatic, van der Waals, and capillary forces, are responsible for different fluidization behaviours exhibited by different powders in an inhaler. Electrostatic charge interactions influence the overall efficiency of DPIs, since such forces are considered to be

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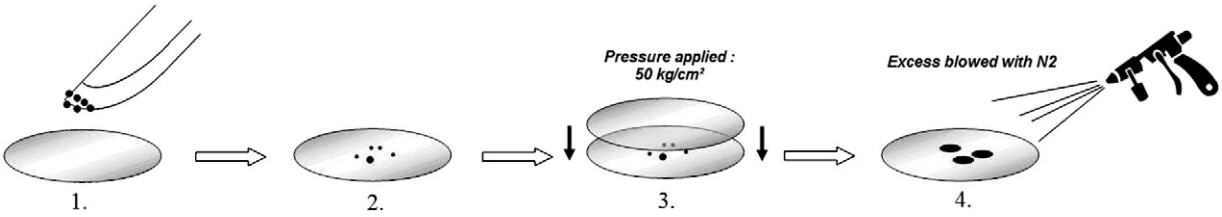

Fig. 1. Sample preparation.

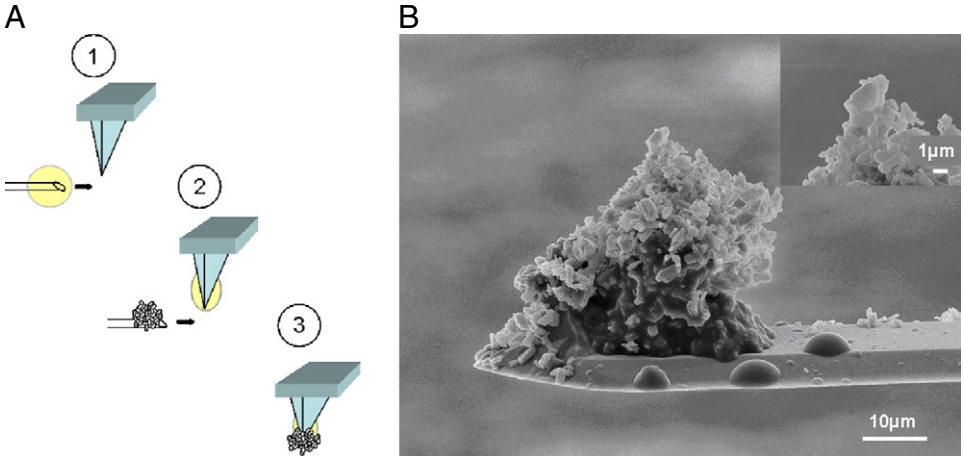

Fig. 2. A: Tip functionalisation. 1) A microdroplet of epoxy resin is deposited at the extremity of the tip. 2) A small amount of powder is glued. 3) 24 h is necessary to obtain a good fixation. B: SEM micrograph of a functionalised tip.

significant for attraction and adhesion between the drug substance particles, excipient particles, and device surface. Additionally, those interactions depend on many parameters like the intrinsic properties of the powders (coating, surface energy, and reactive chemical groups), particle properties (size distribution [4], shape, roughness, porosity, and morphology), and environmental conditions (mechanical processing [5], temperature and relative humidity (RH)) [6–8]. These can greatly influence the bulk properties of the formulation and the product performance.

For now, the drug studied could be administrated with both of the two systems presented. In this way, the evolution of the powders in different storage conditions has to be known. Some researches focus on other drugs where the impact of temperature and RH in the air have already been studied, but the behaviour of the drug in a liquid [9–11] and its evolution in time are still not completely understood.

Many techniques could bring some useful information in the field of the characterization of pharmaceutical powders including scanning electron microscopy (SEM) for imaging samples, X-Ray Diffraction (XRD) for the determination of crystalline or amorphous structures, and Zeta potential measurements for the behaviour of emulsions or dispersions. It has long been recognized that surface charge is an important physical property of colloidal particles. However, the measurement of this property is not always straightforward. The standard method of measuring Zeta potential gives only an average

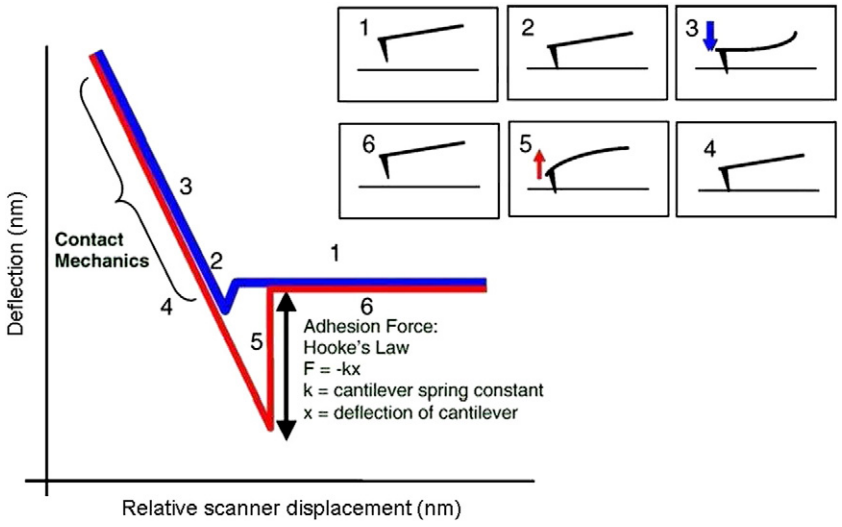

Fig. 3. Typical force curve.