The Use of Colloid Probe Microscopy to Predict Aerosolization Performance in Dry Powder Inhalers: AFM and *In Vitro* Correlation

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ABSTRACT: The atomic force microscope (AFM) colloid probe technique was utilized to measure cohesion forces (separation energy) between three drug systems as a function of relative humidity (RH). The subsequent data was correlated with *in vitro* aerosolization data collected over the same RH range. Three drug-only systems were chosen for study; salbutamol sulphate (SS), triamcinolone acetonide (TAA), and di-sodium cromoglycate (DSCG). Analysis of the AFM and *in vitro* data suggested good correlations, with the separation energy being related inversely to the aerosolization performance (measured as fine particle fraction, FPF_{LD}). In addition, the relationship between, cohesion, RH, and aerosolization performance was drug specific. For example, an increase in RH between 15% and 75% resulted in increased cohesion and decreased FPF_{LD} for SS and DSCG. In comparison, for TAA, a decrease in cohesion and increased FPF_{LD} was observed when RH was increased (15–75%). Linear regression analysis comparing AFM with *in vitro* data indicated R^2 values > 0.80, for all data sets, suggesting the AFM could be used to indicate *in vitro* aerosolization performance. © 2006 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 95:1800–1809, 2006

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INTRODUCTION

The atomic force microscope (AFM) colloid probe technique has become a useful pharmaceutical tool for investigating particulate interactions relative to pharmaceutical aerosols.[1–14] The technique involves attaching a single drug or excipient particle to the end of a microfabricated AFM cantilever. The colloid 'drug probe' can then be brought into contact and pulled away from a material under investigation, and the relative deflection can be converted into a force of interaction or separation energy. Such a technique is a powerful tool and has been used extensively to investigate drug and/or excipient interactions *in situ* (model propellants) for pressurized metered dose inhalers (pMDI)[1–3] and in air for dry powder inhalers (DPI).[4–13] However, it is interesting to note, that with a few exceptions,[12–14] little work has been done to correlate observed AFM measurements with formulation performance.

By modifying the AFM to operate under different environmental conditions, it becomes possible to investigate the influence of, for instance, relative humidity (RH) on particle-substrate adhesion.[6–11] For example, Berard et al.[6] reported increased adhesion between individual drug crystals of zanamivir and lactose (commonly used as a carrier in DPI formulations) as humidity was

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increased from 0% RH to 85% RH, attributing this to both capillary forces and morphological change on the surface of the particles. In another study, Price et al.[9] correlated the surface adsorption of water at specific humidities to adhesion between two micronized drugs and atomically smooth crystals of lactose monohydrate. Young et al.[7,8] measured drug-drug interactions (cohesion) as a function of humidity, suggesting that the cohesion profile for a particular drug will be related to its physico-chemical properties. Young et al.[7] went on to report both increased and decreased cohesion with respect to humidity. Such variation was dependent on drug type and was related to the materials propensity for water, variation in capillary force, and the existence of long-range electrostatic forces which could be dissipated at higher humidity. More recently, Tsukada et al.[10] reported variations of lactose adhesion with respect to humidity and substrate roughness, suggesting that lactose cohesion reversibly increased with increased humidity, while Hooton et al.[11] described both increased and decreased adhesion as humidity was increased, relating this to the distribution of adsorbed water onto surfaces with varying geometry.

A limited amount of work has been carried out on the influence of humidity on materials used in DPIs. This focus is most likely due to an awareness of the potential issues facing DPI formulators. In order to penetrate the respiratory tract, drug particulates used in DPIs must have an aerodynamic diameter of <5 μm to avoid impaction and sedimentation in the upper airways.[15] Since particles in this size range have a high surface area to mass ratio they tend to be highly cohesive, with the relative input force required to successfully aerosolize them being high. Although DPI formulations are routinely prepared it is important to understand the influence of RH on performance since any alteration in the cohesive and adhesive forces within a device may result in a deviation from optimal performance.

The need for experimental observation of formulation components under specific temperature and humidity conditions is clear. Historically, the understanding of the influence of humidity on formulation performance was achieved through *in vitro* testing,[16–21] however, such procedures tend to be time consuming and require both testing and analytical expertise.

Since it is likely that variation in performance with respect to humidity will most likely be related to variations in particle cohesion/adhesion within a formulation, the AFM colloid probe technique may be used to directly predict *in vitro* aerosolization performance. Here the authors directly compare AFM inter-particulate cohesion measurements, as a function of humidity, with an *in vitro* performance study reported by the authors previously.[21] Three drugs were chosen as model systems; salbutamol sulphate (SS), triamcinolone acetonide (TAA), and di-sodium cromoglycate (DSCG), due to their different physico-chemical properties. Previous data, investigating the influence of humidity on the cohesion of SS using AFM was utilized and is reported alongside data for TAA and DSCG for completion.[8]

MATERIALS AND METHODS

Materials

Micronized SS (median diameter ($d_{0.5}$) 4.79 μm), TAA ($d_{0.5} = 4.39$ μm), and DSCG ($d_{0.5} = 5.44$ μm) were supplied by Sanofi-Aventis (Holmes Chapel, UK) (for all materials 100% undersize <11 μm). Water was purified by reverse osmosis (Millipore, Molsheim, France).

Preparation of Model Drug Compacts

Atomic force microscope colloid probe measurements were conducted between individual drug particles and model compacts of the said material. This was to allow collection of a large interaction data set over a relatively large measurement area (10×10 μm). As in the previous study, model surfaces from the micronized material were prepared by direct compression.[8] Micronized material (250 mg) was weighed into a 10 mm stainless steel die and compacted at a compression rate of 0.5 mm/s (500 kg, dwell time 180 s) using a TA HDi Texture analyzer (Stable Micro Systems, Surrey, UK).

Atomic Force Microscopy

Individual micronized drug particles were mounted onto tipless AFM cantilevers (nominal spring constant 0.58 N/m) using a micromanipulation technique described elsewhere.[8] As in the previous study the tipless cantilevers were sourced from a single wafer where thermal calibration indicated a coefficient of variance less than 14%.[8] A Multimode AFM with Nanoscope IIIa controller

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