

Surface Analytical Techniques in Solid-State Particle Characterization for Predicting Performance in Dry Powder Inhalers[†]

Xiao Wu, Xiaojian Li, and Heidi M. Mansour*
University of Kentucky College of Pharmacy
Department of Pharmaceutical Sciences-Drug Development Division¹

Abstract

The pulmonary route is of interest for both effective local therapy for respiratory and lung diseases, such as asthma, chronic obstructive pulmonary disease and cystic fibrosis, and systemic administration of drugs, such as proteins and peptides. Dry powder inhalers (DPIs) are devices through which a dry powder formulation of drug is delivered via the pulmonary route. The DPIs are highly efficient but complicated systems, the performance of which relies on many aspects, including aerodynamic diameter of the powder formulation, particle density, bulk density, surface morphology and composition, particle shape, interparticulate cohesive forces between drug particles and interparticulate adhesive forces between drug and carrier particles. Among them, surface morphology of both drug particles and carrier particles within the formulation is a very important factor in determining the interparticulate contact area and forces, aerosolization efficiency and subsequent lung deposition. Techniques that have been applied to study surface properties of solid-state particles in DPIs include atomic force microscopy, micro- and nanothermal analysis, inverse gas chromatography and X-ray photoelectron spectroscopy. This paper reviews different aspects of DPIs, with emphasis on their surface properties and influence on aerosol performance, and the techniques that are utilized to examine their surface properties.

Keywords: pulmonary drug delivery, inhalation aerosols, surface chemistry, interparticulate forces, particle engineering, pharmaceutical powders

1. Pharmaceutical Solids

1.1 Overview

The solid-state^{1, 2)} is the most common state in marketed pharmaceutical products. The final solid state dosage form includes the active pharmaceutical ingredient (API) and excipients. One of the main advantages of the solid state relative to the liquid state is higher physical and chemical stability due to slower degradation kinetics. Thereby, a longer pharmaceutical shelf-life can be achieved. Pharmaceutical compounds in the solid-state can exist as crystalline³⁻⁵⁾ and amorphous⁶⁻⁹⁾ forms.

1.2 The Crystalline state & polymorphism

In crystalline materials, structural units are repeated in a regular manner and form a well-defined lattice. In other words, crystalline materials possess both short-range and long-range molecular order. The crystalline forms include polymorphs^{10, 11)} and pseudopolymorphs¹²⁾. Polymorphism^{13, 14)} describes the ability of the crystalline substance to exhibit different lattice structures and/or molecular conformations, without undergoing changes in its chemical composition. The pseudopolymorph refers to crystalline hydrates and solvates^{10, 15, 16)}, which incorporate bound water molecules (hydrates) or bound organic solvent molecules (solvates) in the crystal structure. Depending on the solid phase of an API, properties such as morphology, density, stability, melting point, solubility and color can be different. These differences may, in turn, have significant influence on the API's physical and chemical stability, bioavailability¹⁷⁾ and processability¹⁸⁾, including powder flowability^{19, 20)}

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¹ 789 South Limestone St., Lexington, KY 40536-0596, USA

* Corresponding Author

Telephone: (859) 257-1571

E-mail heidi.mansour@uky.edu

and compressibility²¹). Typically, the thermodynamically stable crystalline form is preferred since the risk of solid-state transformations (ie. solid-state phase transitions) during process and storage is minimized.

Thermodynamically over time, the less stable solid form possesses a higher Gibbs free energy, and hence, will convert to the more stable form which has a lower Gibbs free energy. Hence, solid-state phase transitions are of great importance in pharmaceutical material science. A phase transition can arise through melting, in solution, and solution-mediated, solid-solid transition. Molten transition takes place when a compound is heated and subsequently cooled after melting. A new solid phase can be obtained through solvent evaporation after being suspended or dissolved in a solvent. Solution-mediated phase transition has three steps: 1). dissolution of the metastable form; 2). nucleation as a more stable form; and 3). crystal growth of the stable phase. The solid-solid phase transition circumvents the transient liquid or vapor phase. The solid-solid transition can be categorized into monotropic and enantiotropic systems, in the case of polymorphic pairs. In a monotropic system, one polymorph is stable and the transition is irreversible. However, in an enantiotropic system, the transition is reversible and each polymorph is stable within a certain temperature range. Solid-state phase transformations²²⁻²⁵ include polymorphic interconversions, dehydration or desolvation processes, and order-disorder transformations²⁶. Furthermore, solid-phase transitions can be either thermodynamically or kinetically controlled processes.

In crystalline pharmaceutical powders, a crystalline particle has a number of crystal faces²⁷. Each crystal face possesses unique surface properties. Typical crystal faces and Miller indices are shown in Fig. 1. Various faces of the L-Lysine monohydrochloride dihydrate (LH) crystals have different surface free energies which relates to crystal habit and orientation²⁸. Therefore, understanding the surface energetics²⁹ of a particular crystalline face is of importance in pharmaceutical formulation, processing, and therapeutic delivery. For instance, surfaces energetics of a particular crystal face influences the nature of chemical interactions with excipients in the formulation, as well as with other particles.

1.3 The Amorphous state & other metastable states

Unlike crystalline compounds, which have orientational and positional long-range molecular order in

all three dimensions of space, the amorphous state shows no long-range molecular packing ie. lacks long-range molecular order. Since, the amorphous state is a mesophase/metastable phase (ie. not a thermodynamically stable phase), physicochemical properties such as higher solubility, higher bioavailability, higher molecular mobility (ie. more disordered with higher entropy), higher chemical and physical degradation kinetics, and less stability over pharmaceutically relevant time scales are observed. Pharmaceutical development of amorphous form is being conducted in recent years to gain higher solubility³⁰ because of a higher molecular mobility, although lower physical and chemical stability is associated with it. The strategy of rationally designing the amorphous state into a pharmaceutical product can be utilized to overcome low bioavailability of poorly water-soluble crystalline drug candidates^{6, 9, 31, 32} which is increasingly more common with newer and promising drug candidates. The amorphous form can be generated intentionally or unintentionally by many common pharmaceutical processing methods, including milling³³⁻³⁵, quench-cooling³⁶, spray-drying³⁷⁻⁴², freeze-drying^{9, 43, 44} and compression^{9, 32}.

The amorphous phase often originates on the surfaces of particles during various types of pharmaceutical processing procedures. The oxygen gas and water vapor adsorption on these disordered regions (having a higher molecular mobility) occurs initially on the surface of particles (ie. adsorption) resulting in acceleration in oxidation and hydrolysis reactions

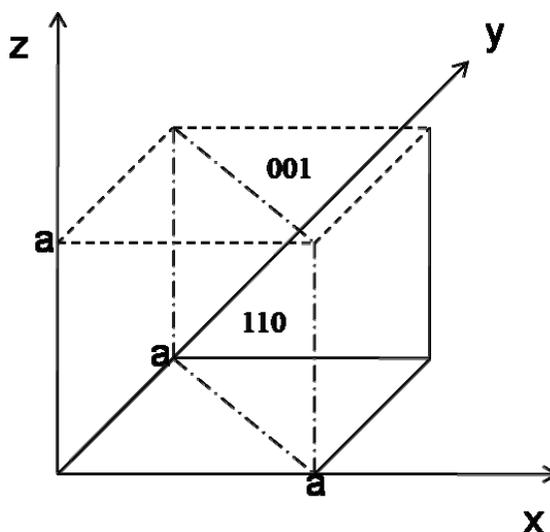


Fig. 1 Illustration of the miller indices of crystal faces of a cubic crystal. The “short dash” (—) plane (001) meets the x, y and z axes at infinity, infinity and a, respectively. The “long dash dotted” (— · —) plane (110) meets the x, y and z axes at a, a and infinity, respectively.

that then propagates below the surface into the bulk region (ie. absorption). Furthermore, the relatively higher molecular mobility of compound is further increased, where absorbed water acts as a plasticizer. Consequently, the physical and chemical stability⁴⁵⁾ over pharmaceutical timescales for the powder becomes compromised.

The thermodynamic tendency for metastable phases existing on the surface of particles in the solid-state to readily take up small amounts of water vapor molecules in the environment is the basis on which quantification of very small amounts (1% or less) of these metastable phases can be carried out using gravimetric water vapor sorption. Gravimetric vapor sorption (GVS), also sometimes called dynamic vapor sorption (DVS), is a powerful and highly quantitative analytical interfacial technique used in pharmaceutical solid-state development, including inhalation aerosols. Moreover, vapor-induced solid-state phase transitions (eg. disorder-to-order phase transition, recrystallization, liquid crystallization, etc.) can be systematically examined and quantified. It is of particular utility in the characterization and performance prediction of particles intended for inhalation aerosol delivery, as often particle size reduction methods (eg. micronization) induce minute but significant amounts of metastable surface phases that can impact aerosol powder dispersion and particle behavior in the high relative humidity of the lungs (> 90%), as well as overall stability of the aerosol formulation product.

In addition to the amorphous form, other mesophases/metastable phases^{46, 47)} are important in the solid-state phase behavior of pharmaceuticals and phase transitions induced by pharmaceutical processing techniques. Based on the type of molecular mobility and directional molecular order along one or two dimensions, a mesophase can be classified into liquid crystal⁴⁸⁾ (with positional and if applicable conformational mobility), plastic crystal (with orientational mobility)⁴⁹⁻⁵¹⁾, and condic crystal (with conformational mobility)⁵²⁾.

Therefore, it is important to be able to determine that the desired form chosen for a pharmaceutical formulation is not contaminated with other solid-state forms that have varying bioavailability and stability. Based on this, it is essential to determine the effects of processing and storage conditions on the API, which may induce solid-state phase transitions and polymorphic transformations caused by mechanical (milling, compression) and thermal stresses or interactions with formulation ingredients. Hence, solid-state transformations have to be closely monitored

and trace amount of contaminating polymorphs or non-crystalline metastable forms (eg. amorphous) should be detected to ensure safety, quality and efficacy of the pharmaceutical product⁵³⁾.

Finally, the presence of partially ordered/disordered phases are influential in affecting performance of particles constituting powders intended for aerosol inhalation, both *in vitro* and *in vivo*^{23, 26, 54, 55)}. These partially ordered/disordered phases may process-induced or rationally designed into the particle for improving aerosol performance⁵⁶⁻⁵⁸⁾ and therapeutic properties (ie. enhanced solubility and bioavailability). These phases include nanocrystals⁵⁹⁻⁶¹⁾ (non-amorphous state lacking long-range order), liquid crystals, plastic crystals, and amorphous phases. There is much interest in dry powder inhaler (DPI) performance prediction based on the static and dynamic properties of the powder, as a manifestation of the solid-state phases described above. Recently, novel insight and predictive correlations between DPI particle surface properties and DPI aerosol performance have been reported⁶²⁻⁶⁵⁾.

2. Dry Powder Inhalers (DPIs)

2.1. Definition of DPIs

In medical therapy, inhaled and aerosolized medications have been used for the treatment respiratory tract diseases, such as asthma and chronic obstructive pulmonary disease, for many decades⁶⁶⁾.

Based on the physical states of dispersed-phase and continuous medium, inhaled drug delivery systems can be divided into three principle categories⁶⁷⁾: pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and nebulizers⁶⁸⁾. Within each class further differentiation is based on metering, means of dispersion, or design⁶⁹⁾. In nebulizers, the drug is dissolved or suspended in a polar liquid, usually water. Because of their large dimensions (including pump, tubing and possibly ventilating air supply), nebulizers are not convenient to use. They are usually used in hospital or ambulatory care settings, and the aerosol is delivered continuously over an extended period of time. pMDIs are bolus drug delivery devices that contain solid drug, suspended or dissolved in a nonpolar volatile propellant. Dry powder inhalers are devices through which a dry powder formulation of drug is delivered for local or systemic effect via the pulmonary route. Lactose carrier-based DPI formulations are comprised of coarse non-respirable carrier particles of α -lactose monohydrate (FDA-approved) physically mixed with jet-milled

drug that is in the respirable size range^{62, 63, 70-72}. Advanced particle engineering design techniques have enabled the formulation of lactose carrier-free DPI formulations⁷³.

2.2. Advantages of a dry powder inhaler

The development of DPIs has been motivated by the desire for alternatives to pMDIs. In 1987, the Montreal protocol called for signatory countries to phase out the production of CFC propellants in medical products, in order to stop depletion of the ozone layer⁷⁴.

In addition to being propellant free, DPIs are very portable, patient friendly, easy to use and do not require spacers⁷³. Because a pMDI is pressurized, it emits the dose at high velocity, probably causing premature deposition in the oropharynx^{75, 76}. Despite use of spacers, incorrect use of pMDIs is still a prevalent problem⁷⁷. Thus, pMDIs require careful coordination of actuation and inhalation. Contrastingly, DPIs with passive devices are activated by the patient's respiratory airflow. They require little or no coordination of actuation and inhalation and can achieve better lung delivery^{78, 79}.

Since DPIs are comprised of particles in the solid-state (ie. powders)⁷³, they possess higher stability relative to the liquid state⁸⁰ and compared with pMDI formulations containing propellant and cosolvents⁸¹. Summary of the advantages and disadvantages of dry powder inhalers is shown in **Table 1**.

2.3. Drugs incorporated in DPIs

There are several factors which should be taken into consideration in the development of a dry powder aerosol delivery system, including drug powder

production, aerosol performance and delivery device.

Among them, the desired site of deposition should be the starting point for every DPI development. When local effects are desired, receptor densities may be indicative for the preferred site of drug deposition, while when systemic absorption is desired, differences in membrane permeability and clearing mechanisms may be decisive. The majority of pulmonary drugs on the market are short-acting and long-acting β agonists, corticosteroids, and anti-cholinergic agents. Bronchodilators (β_2 -agonists) in asthma and COPD, such as salbutamol and formoterol, interact with β_2 -adrenoceptors, which are located on a variety of cells, including smooth muscle and epithelial cells. The concentration of β -receptors throughout the lungs varies. Most of them are located in the alveoli⁸²⁻⁸⁵. Inhalation steroids are the cornerstone in asthma therapy and their molecular action occurs at intracellular glucocorticoid receptors, which are located throughout the airways and alveoli^{86, 87}. Anti-cholinergic agents target muscarinic receptors, which are moderately distributed throughout the airways and periphery^{82, 88}.

2.4. Powder production process

The first step of DPIs manufacture is to produce bulk drug preparations by crystallization from solution, filtration and drying. Subsequently, to create particles in the respirable size range ($< 5 \mu\text{m}$ in diameter), the drug particle size must be reduced. The conventional size-reduction technique is milling⁸⁹⁻⁹², which is simple, cheap and easy to scale up. There are many different mills, three main types of which used in active pharmaceutical ingredient manufacture are fluid-energy mills, high-peripheral-speed

Table 1 Summary of advantages and disadvantages of dry powder inhalers.

Advantages	Disadvantages
Different dose forms (single unit dose, multi-unit dose and multiple dose)	Moderate to high respiratory flow required
Formulation stability	Deposition efficiency dependent on patient's respiratory airflow
No propellant, environmental sustainability	May cause high pharyngeal deposition
Small, portable and quick to use	Not all medications available
Breath-actuated, little or no patient coordination required	
Short treatment time	
Spacers not required and dose counters incorporated in most newer designs	

mills, and the ball mill. The shortcoming of milling is its poor control over the particle crystallinity, shape, size and size distribution.

Other techniques for production of stable micron-sized particles involve spray drying⁹³⁻⁹⁵ and supercritical fluid technology⁹⁶⁻⁹⁸. In spray drying, the feed solution is supplied at room temperature and pumped to the nozzle where it is atomized by the nozzle gas. The atomized solution is then dried by preheated drying gas in a special chamber to remove water moisture from the system, thus forming dry particles. These prepared particles are collected with a cyclone separation device^{99, 100}. Compared with milling, spray-drying offers more flexibility and the possibility of morphology control in addition to size control^{101, 102}; however, spray dried particles are mostly amorphous¹⁰³.

The basic feature of the supercritical fluid process is the controlled crystallization of drugs from dispersion in supercritical fluids, carbon dioxide. This method has demonstrated a wide range of application in producing pulmonary inhalable formulations¹⁰⁴⁻¹⁰⁶. Supercritical fluid technology can be divided into several classes. The most important two are supercritical anti-solvent precipitation (SAS)^{107, 108} and supercritical fluid extraction of emulsions (SFEE)^{109, 110}. The fundamental mechanism of SAS is based on rapid precipitation when a drug solution is brought into contact with a supercritical CO₂. SFEE is based on extraction of the organic phase in oil-in-water or multiple emulsions using supercritical CO₂^{109, 110}. Because most of the drugs (e.g., asthma drugs) are not soluble in CO₂, SAS processes provide an easy and excellent way to produce dry powder inhalation formulations. SFEE can provide uniform crystalline drug particles, composite particles containing polymeric materials and the drugs^{109, 110}. For the formulator, it is important to consider the effect of each technique on the drug when choosing a suitable one to produce the desired results.

2.5. Interparticulate forces and strategies to improve aerosol performance

Micron-sized particle (< 5 μm) produced by high-energy operations such as milling usually have large surface areas and surface energies, which cause poor flow and a high tendency to aggregate¹¹¹. These interparticulate cohesive forces include mechanical interlocking due to surface asperities, capillary forces from the presence of water, electrostatics arising from the insulating nature of the material, and van der Waals forces from the fundamental elec-

tromagnetic nature of matter^{92, 112}. One way to add in particle separation is to agglomerate micron-sized drug particles with larger “carrier” particles of the excipients¹¹³. Excipients can reduce drug cohesiveness by occupying the high-energy sites of the drug particles, consequently improving handling, dispensing, and metering of the drug. According to the FDA guidance for dry powder inhaler drug products, *α*-lactose monohydrate is the only approved sugar that can be used as a larger carrier particle in dry powder inhalation aerosol products to fluidize and disperse the respiratory drug while itself not being delivered to the lung. Lactose is highly crystalline and has the smooth surfaces and satisfactory flow properties desirable for a DPI carrier particle. The disadvantage of lactose is that it is a reducing sugar, which may lead to chemical instability particularly in formulations containing protein and peptides¹¹⁴. Other sugars, such as mannitol and glucose have been shown to be feasible alternatives to lactose¹¹⁵.

Except for blends using fine carriers and ternary components, several other methods can be used to improve the performance of dry powder aerosol delivery systems:

- Low aerodynamic diameters (e.g., small physical size)
- Low particle density (e.g., porous particles)¹¹⁶
- Low bulk density (loose particle packing to reduce particle contacts)¹¹⁷
- Rough surface (to increase air drag force and reduce particle interaction)¹¹⁸⁻¹²⁰
- Surface composition (to reduce surface energy)
- Shape (e.g., elongated particles)

The basic principle of the above methods is to overcome the cohesive forces between drug particles. Moreover, to generate an aerosol containing drug particles in the aerodynamic size range of 1 – 5 μm and deliver the drug particles to the target area for deposition, the drug particles must be detached from the carrier crystals in adhesive mixtures or nucleus agglomerates by shear forces during an adequate inhalation. Coates et al. analyzed computationally and experimentally the influence of airflow rate of a DPI on particle dispersion and throat deposition. An optimal inhaler performance was found at a respiratory airflow rate of 65 liters/min¹²¹.

2.6. Device design of a dry powder inhaler

From the design viewpoint, the primary components of a dry powder inhaler are the same for all types of devices on the market as well as those in development. They consist of a powder formula-

tion, a dose mechanism, a powder de-agglomeration principle, and the inhaler's mouthpiece. The dose mechanism is applied to measure a single drug dose. The powder de-agglomeration principle is used to disperse the powder into the inhaled air stream. In some devices, secondary inhaler parts may be applied for different purposes, such as safety, ease of handling, signaling to the patient and moisture protection of the drug formulation. The de-agglomeration principle is one of the most important parts of the inhaler, as to a large extent it determines the de-agglomeration efficiency and thereby the lung deposition of the drug. The dry powder formulation is also a critical component of a DPI^{122, 123}. Most formulations are sensitive to moisture during manufacturing, storage, and usage, which may affect the ultimate delivery of 1 to 5 micron-sized, stable, and reproducible drug aerosols. Therefore, new packaging technologies, including multidose blister packs, the use of nonirritating excipients, and improved device designs have made DPIs more acceptable¹²⁴.

3. Surface Properties of Powder Formulations and Surface Analytical Techniques

For pharmaceutical solid systems, the surface of the primary active pharmaceutical ingredient and associated excipient particles is crucial during manufacturing, as it affects not only the handling characteristics such as powder flowability and compressibility but also the product performance such as wettability, hardness, and dissolution rates¹²⁵⁻¹²⁷. For dry powder inhalation aerosols, surface morphology (corrugated or smooth surface) of both drug particles and carrier

particles within the formulation directly influence the interparticulate contact area, interparticulate forces, aerosolization efficiency and subsequent lung deposition^{120, 128, 129}. Surface properties of dry powders can be exploited for DPI formulation design by creating or selecting drug particles and carrier particles with specific morphology^{130, 131}. Drug particles, with a higher degree of surface rugosity are reported in lower powder cohesion and consequently increased dispersibility of powder particles¹²⁰. Conversely, high degrees of surface roughness may also promote mechanical interlocking between particles, influencing the powder flow and dispersion¹³². Hence, it is important to choose an optimal value considering both advantages and disadvantages. Surface morphology, together with particle size and shape, determines surface area, which in turn determines the contact area and interparticulate forces between particles. Corrugated particles have more surface area than smooth particles that occupy the same volume. Therefore, ideally, surface properties, including surface morphology, contact area and interparticulate forces, should be adjusted to a level that provides enough adhesion between drug and carrier to obtain a stable formulation, and also allows easy separation upon inhalation. Techniques that have been applied to study surface properties of solid-state particles in dry powder inhalers include atomic force microscopy, micro- and nanothermal analysis, inverse gas chromatography, and X-ray photoelectron spectroscopy. They are summarized in **Table 2** and described in the following sections.

Table 2 Summary of surface analytical techniques as well as parameters accessible by them.

Surface analytical techniques	Applications
Atomic force microscopy (AFM)	Microscopic analytical technique. Characterizes surface structure, morphology, adhesive forces, interparticulate interaction between drug and drug particles, and drug and carrier particles.
Micro- and nanothermal Analysis (MTA/NanoTA)	Highly localized (micrometer or sub-micrometer scale) thermal analytical technique. Measures the composition, morphology, and transition of inhalation powder particles. Distinguishes between the drug substance and excipients in solid dispersion. Evaluates heterogeneity of multicomponent systems and provides three-dimensional information.
Inverse gas chromatography (IGC)	Chromatographic analytical technique. Elucidates a wide range of physicochemical properties of the solid, including surface energy, heats of sorption, adsorption isotherms, glass transition temperatures, solubility parameters, energetic heterogeneity profiles, diffusion coefficients and particular functional groups on the surface of solid materials.
X-ray photoelectron spectroscopy (XPS)	Quantitative spectroscopic technique. Measures surface elemental composition of a dry powder inhalation aerosol, empirical formula, chemical state and electronic state of the elements that exist within a material.

3.1. Atomic force microscopy (AFM)

Atomic force microscopy is a technique employed to analyze and characterize the surface structure, morphology and forces of materials at the nanoscopic and atomic level¹³³⁻¹³⁶.

One of the important components of AFM is a micro-fabricated cantilever whose deflection is usually recorded by laser reflection when it interacts with a moving substrate. Direct measurement of force can be achieved by ramping the tip vertically in z axis direction, towards and away from a sample. When the tip approaches, makes contact with, and is removed from a surface, the relative deflection of the cantilever produces a force-distance curve. The change in hysteresis in cantilever deflection during approach and retraction is related to the magnitude and type of forces acting between the two surfaces^{137, 138}. A schematic representation of principle of AFM is shown in Fig. 2.

Based on its capability to measure morphological properties of materials, AFM is used to predict the aerosolization performance of micron-sized particles for inhalation. As stated above, the force required to aerosolize an adhered drug particle is directly proportional to the sum of the surface energies of the contiguous surfaces, and inversely proportional to the projected contact area. The two most common approaches to improve the aerosolization efficiency in these systems are to reduce the surface free energy of the contacting surfaces or modify the particle shape to limit contact area. Producing drug particles with rough surfaces can reduce surface free energy and particle adhesive forces. Spray drying process has demonstrated the potential to prepare physically stable drug powders with modified surface morphology, presumably due to the differences in initial feed concentration and solvent evaporation rate^{118, 120, 139-141}. To clarify this, in one study, a series of spherical model drug particles of bovine serum albumin (BSA) was prepared with different degrees of surface corrugation by spray drying process¹⁴². The relationship between the morphology of the prepared particles, adhesion and aerosolization efficiency was investigated quantitatively using AFM imaging and colloid probe measurements. The results confirmed that as the degree of corrugation increased, particle adhesion was reduced which, resulted in a concomitant increase in fine particle fraction FPF and better aerosolization performance.

AFM has also been identified as a tool capable of measuring the interactions between individual particulates and substrates at specific environmental

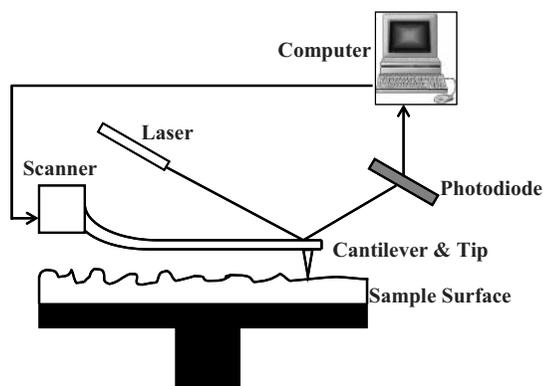


Fig. 2 A schematic representation of general principle of atomic force microscope.

conditions, such as temperature and relative humidity (RH). Capillary interaction due to the water vapor is one of the primary interparticulate forces in dry powder delivery systems. Young et al. investigated into the effect of humidity on drug-drug interactions using the AFM with an attached custom-built perfusion apparatus¹⁴³. Salbutamol sulfate drug particulates were chosen as a model system and mounted on V-shaped AFM cantilevers using a novel micromanipulation technique. Force-distance curves obtained from the measurements between cantilever drug probes and model compacts of salbutamol sulfate were integrated to determine separation energies as a function of RH (15-75%). Significant increases in the median separation energies were observed as humidity was increased, most likely attributed to stronger capillary interaction at higher humidity. This study also shows the potential of AFM as a rapid preformulation tool to quantify the separation energies between micronized drug particles.

In addition to the characterization of the surface morphology and interparticulate interactions between drug and carrier particles, the AFM provides opportunity to assess the interaction between inhaled drug particles and the internal surfaces of the deep lung, that is to say the interaction between micronized drug particles and pulmonary surfactant. In one study, the force of adhesion between micronized budesonide particles and simulated pulmonary surfactant (PS) monolayers (Survanta[®] monolayers) were visualized and quantified by the combination of AFM with a Langmuir-Blodgett (LB) approach¹⁴⁴. The results indicated that budesonide is hydrophobic and Survanta[®] films at increasing surface pressure exhibit a rising hydrophobic character. AFM revealed that PS properties were governed by applied surface pressure and that the degree of interaction of budesonide was greater at higher surface pressure,

where packing of the lipid film was increased; consistent with the point of exhalation. The increasing hydrophobicity of the PS film, on increased pressure, was believed to be the primary reason for increased interaction with the hydrophobic budesonide, which correlates well with the accepted inhaler technique.

Besides, AFM has been used to observe and monitor the crystallization of lactose and the effect of mechanical processing on the powder surface. The cohesive-adhesive balance (CAB) approach to colloid probe AFM has been employed to measure the interfacial force balance between an active pharmaceutical ingredient and substrate surfaces^{145, 146} and determine the influence of micronized budesonide crystal habit on the prediction of dry powder inhalation formulation performance¹⁴⁷. Tapping mode AFM effectively images crystals of various organic compounds, including drugs (cimetidine¹⁴⁸ and felodipine¹⁴⁹), and the adhesional properties of carrier-particle^{130, 145, 150-152}.

3.2. Micro- and nanothermal analysis

Micro- and nanothermal analysis is an emerging localized thermal analysis technique which in essence involves the replacement of the tip of a conventional atomic force microscope with a thermal probe, thereby allowing site-specific characterization¹⁵³⁻¹⁵⁸. It overcomes the disadvantage of conventional bulk thermal measurement techniques, such as differential scanning calorimetry (DSC) and modulated temperature DSC (MTDSC). DSC and MTDSC only provide results representing the sum of all the constituents in the specimen and no information on the size, shape or spatial distribution of constituents within a multicomponent system. The principle of micro- and nanothermal analysis is based on performing highly localized material property characterization on a micrometer to a sub-micrometer scale on a sample subjected to a controlled temperature programme using a heated tip.

Like an AFM, the major component of a micro- and nanothermal system is a cantilever with an integrated tip that is used to scan the surface, its position being controlled in the x, y and z directions by means of a piezoelectric scanner. Laser light is used to measure the bending degree of the cantilever, and thereby the normal force acting between the tip and sample. Instead of standard AFM tips, the instrument uses a thermal probe. Two popular thermal probes are Wollaston wire based probes (platinum/rhodium core surrounded by a silver sheath) and silicon-based nanoprobe. Wollaston wire based probes are approxi-

mately 1 μm , although the use of thinner wires¹⁵⁹ or the addition of diamond tips¹⁶⁰ has achieved a resolution around 100 nm. Silicon-based nanoprobe with a miniature heater has a topographic spatial resolution of around 5 nm and thermal property measurement resolution of up to 20 nm¹⁶¹.

Micro- and nanothermal techniques allow the investigation of the composition, morphology and transition of inhalation powder particles^{162, 163}. It is able to distinguish between the drug substance and excipients in solid dispersions. This technique also allows the study of sample surface as well as analysis of the distribution of materials below the surface of the material by having the probe penetrate the sample surface. Consequently, materials can be characterized in a spatially resolved manner, especially in terms of providing three-dimensional information.

The manufacturing of dry powder inhalers involves the micronization of the drug and mixing with an inert carrier such as lactose in order to facilitate adequate drug penetration into the lungs. The surface properties of both components are crucial to subsequent performance. Since the amorphous material is thermodynamically unstable in terms of recrystallization and may also be more susceptible to chemical degradation, the generation of even small quantities of amorphous material may have a profound effect if the material is located extensively on the powder surface. Therefore, the quantification and mapping of amorphous materials in otherwise crystalline samples has become a major concern. Dai et al. has described a case study using nanothermal analysis for a reliable identification of partially amorphous surface¹⁵³. The authors prepared compressed tablets of amorphous and crystalline lactose and used thermomechanical analysis (L-TMA) performed by using micro- and nanothermal analysis in addition to single point variable temperature pull-off force measurements for mapping amorphous and crystalline lactose at a nano-scale. L-TMA was shown to be able to differentiate the amorphous and crystalline forms of lactose via measurement of the thermal events associated with them. Pull-off force measurement showed that amorphous lactose has higher adhesion than crystalline, even at temperatures below glass transition temperature (T_g), and this kind of adhesion increased on approaching the T_g .

Nanothermal analysis (nano-TA) has also been utilized to characterize nano- and micro-scale heterogeneity in the solid-state properties of drug-polymer formulations¹⁶⁴. Zhang et al. demonstrated that the morphology of a nano-dispersed pharmaceutical sys-

tem containing carbamazepine (CBZ) and hydroxypropyl methyl cellulose (HPMC) at a 50/50 polymer/drug ratio was mapped and determined by using nano-TA probes¹⁶⁴. High resolution image obtained from AFM tapping mode showed a structure with an occluded phase, and the continuous matrix corresponded to HPMC while the bright occluded phase was attributed to the presence of CBZ nano-crystals, approximately 50 nm in size. The phase image contrast observed confirmed the presence of heterogeneity.

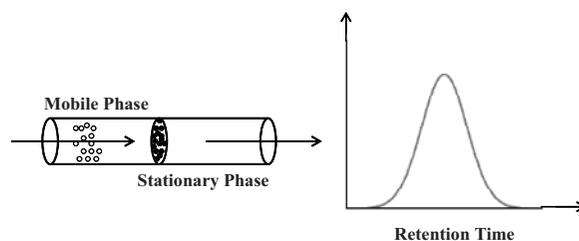
3.3. Inverse gas chromatography (IGC)

IGC is a physical characterization technique that has been used for the measurement of the surface properties of a wide range of solid materials, including pharmaceutical powders, nanomaterials, polymers and coatings.

The concept of IGC is rather simple; taking a standard gas chromatography (GC) experiment and inverting the roles of the stationary (solid) and mobile (gas or vapor) phases. In GC, a standard column is used to separate and characterize several gases and/or vapors. With IGC, the unknown surface is the powder that is packed into a column and the known materials are the vapor probes that are injected into the column (**Fig. 3**). The retention time of the probe molecule is then measured by traditional GC detectors, such as flame ionization detector and thermal conductivity detector. Measuring how the retention time changes as a function of probe molecule chemistry, probe molecule size, probe molecule concentration, column temperature, or carrier gas flow rate can elucidate a wide range of physicochemical properties of the solid.

Parameters accessible by IGC include heats of sorption, adsorption isotherms, glass transition temperatures¹⁶⁵, solubility parameters¹⁶⁶, and particularly surface energy of solids¹⁶⁷⁻¹⁶⁹. Many publications have shown potential for IGC use in batch to batch variability¹⁷⁰, the influence of milling on the surface free energy^{171, 172}, differences of surface free energy for two isomers²⁸, the influence of humidity on surface free energy of different powders and drug-carrier interactions for dry powder formulations^{173, 174}.

The surface energetics of two supercritical CO₂-processed and two commercial reference samples of salmeterol xinafoate (SX), a selective long-acting β_2 -adrenergic bronchodilator used clinically for asthma prophylaxis, have been characterized by IGC at infinite dilution^{175, 176}. The results showed that the metastable SX-II polymorph possessed a higher surface



- Sample powders packed into a column as stationary phase
- Gas probes injected into a column as mobile phase

Fig. 3 Inverse gas chromatography uses injection of a probe gas to analyze the characteristics of solid sample packed into a standard column.

free energy, higher surface entropy, and a more polar surface than the stable SX-I polymorph.

IGC can give information on the relative exposure of particular functional groups on the surface of solid materials, due to electron acceptor and donor properties¹⁷⁷. Grimsey et al. have demonstrated that the acidic and basic parameters of saccharides determined by IGC reflected the concentration of hydroxyl groups exposed on their surface¹⁷⁸. Furthermore, IGC can be used to determine the functional groups on the surface of solid materials at various relative humidities, to explore the extent of the interaction between the surface and water^{179, 180}. Sunkersett et al. have demonstrated that the specific energies of adsorption of polar probes for paracetamol and carbamazepine changed as RH was raised and the particular interaction sites of water molecules on the surface have been identified using a combination of IGC and molecular modeling¹⁷³.

Summarily, IGC appears to be of particular utility for DPI formulation work, as it requires only small samples for analysis, and it is nondestructive, fast and information rich. A more comprehensive review of this technique has been published elsewhere^{169, 181-183}.

3.4. X-ray photoelectron spectroscopy (XPS)

As a quantitative spectroscopic technique, X-ray photoelectron spectroscopy measures the elemental composition, empirical formula, chemical state and electronic state of the elements within a material. Briefly, powder samples are irradiated by an X-ray beam, which induces the ejection of electrons from the atoms. The kinetic energies of the photoelectrons are analyzed and their binding energies are determined. Since the binding energies of electrons in the atom of origin are characteristic for the elements in a certain chemical environment, XPS provides an

elemental analysis and further information on functional groups, including the atomic compositions of a sample, the chemical state of a certain element, the electronic structure and band structure. In many cases, chemical shifts can be used to draw direct conclusions on the local coordination in a system and the electronic change upon adsorption.

One example of the application of this technology in the characterization of surface composition of a dry powder inhalation aerosol is given here. The surface composition of a dry powder aerosols prepared by spray-drying was analyzed by XPS¹⁸⁴. The powder aerosols were made of albumin, dipalmitoylphosphatidylcholine (DPPC) and a protein stabilizer (lactose, trehalose or mannitol). The powders exited a SpinhalerTM inhaler as particle aggregates. XPS results revealed a large surface excess with DPPC relative to albumin under certain spray-drying conditions and self-organized in a gel phase in the particle. Furthermore, no sugar or mannitol crystals were detected by X-ray diffraction and water sorption isotherms showed that albumin/sugar/DPPC combinations were not prone to crystallization upon exposure to moisture. The surface enrichment of DPPC and the avoidance of crystallization offer a physical environment favorable to protein stability.

Conclusion

The fundamental understanding of rational DPI formulation and aerosol dispersion performance is rooted in fundamental principles in the basic science disciplines of solid-state physics, physical chemistry, surface chemistry, micromeritics, powder technology, and aerosol science. This paper describes the important features of DPIs and the techniques used to examine the surface properties of the particles comprising a DPI formulation. Surface analytical techniques such as AFM, MTA/NanoTA, IGC, XPS, and GVS can provide very useful and unique surface parameters, including surface composition, morphology, structure, energetics, phase behavior, and interparticulate forces. The fundamental data acquired from these surface analytical techniques can greatly facilitate an in-depth and rigorous understanding of the powder formulation at the level of particle interfaces (ie. the solid-solid interface, the solid-liquid interface, and/or the solid-air interface) existing in dry powder inhalation aerosol formulations. These interfaces give rise to the interfacial interactions acting between particles and consequently greatly influence the aerosol dispersion performance of particles in the

solid-state. A fundamental understanding, as such, can provide unique predictive insight into rationally designing particles in the solid-state that are intended for use in DPIs having optimal surface properties to provide optimal aerosol dispersion performance for a given DPI formulation. Furthermore, a given DPI formulation can be rationally tailored at the particle surface level to increase its aerosol dispersion performance.

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Author's short biography



Xiao Wu

Dr. Xiao Wu, Ph.D., is currently a Postdoctoral Research Scholar in Pharmaceutical Sciences at University of Kentucky College of Pharmacy. She received her B.S. in Pharmacy from Peking University, China in 2003 and her Ph.D. in Pharmacy and Pharmacology from the University of Bath, United Kingdom in 2008. Her Ph.D. work was in transdermal drug delivery, with an emphasis on various strategies utilizing nano-scaled delivery systems to retard cutaneous absorption of agents that should primarily act on the skin surface or to enhance skin transport of dermal and systemic therapeutics. Her current research in Dr. Heidi Mansour's group at the University of Kentucky College of Pharmacy focuses on the rational design and development of advanced dry powder inhalation aerosols containing multifunctional microparticles and nanoparticles in the solid-state for the treatment and prevention of lung transplant rejection by targeted pulmonary delivery.



Xiaojian Li

Xiaojian Li, M.S. is a graduate student in the Division of Drug Development, Department of Pharmaceutical Sciences at University of Kentucky College of Pharmacy in Lexington, KY, USA. He received his B.S. degree in Pharmaceutical Sciences from Zhejiang University City College, China in 2005 and M.S. degree in Division of Industrial Pharmacy, Department of Pharmaceutical Sciences from University of Toledo in Toledo, Ohio, USA in 2008. His M.S. research focused on physicochemical characterization of amorphous and crystalline pharmaceutical drugs. His Ph.D. thesis project is on the rational design and advanced development of dry powder inhalation microparticulate and nanoparticulate aerosols for the treatment of Cystic Fibrosis by targeted pulmonary delivery.



Heidi M. Mansour

Dr. Heidi M. Mansour, Ph.D., R.Ph. is Assistant Professor of Pharmaceutics and Pharmaceutical Technology in the Drug Development Division at the University of Kentucky College of Pharmacy and Faculty Associate in the University of Kentucky Center for Membrane Sciences,. She currently holds Faculty appointments and Graduate Faculty appointments in the College of Pharmacy at the University of Kentucky and University of North Carolina-Chapel Hill and in the NSF IGERT and NSF REU research training programs joint with the University of Kentucky College of Engineering. Prior to her faculty appointment at the University of Kentucky College of Pharmacy, she was an Instructor (both in the Graduate and Pharm.D. Programs) and a Postdoctoral Fellow and Scholar at the University of North Carolina at Chapel Hill, School of Pharmacy, in the Division of Molecular Pharmaceutics, receiving the 2007 UNC-Chapel Hill Postdoctoral Award for Research Excellence from the Office of the Vice-Chancellor. She earned a B.S. degree in Pharmacy with Honors & High Distinction, PhD in Pharmaceutical Sciences with a PhD Major in Drug Delivery/Pharmaceutics (School of Pharmacy) and a PhD Minor in Advanced Physical & Biophysical Chemistry (Dept of Chemistry), all from the University of Wisconsin-Madison.

More information can be found on her websites:

<http://pharmacy.mc.uky.edu/faculty/HeidiMansour.php>

<http://myprofile.cos.com/surfchemlungmed>