Surface science and particle interactions in dry powders for inhalation

Understanding the forces that affect cohesiveness of dry powder mixes

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The delivery of fine particles adhered to a carrier in a binary powder blend is at the core of pharmaceutical dry powder inhaler (DPI) development. In fact, the majority of commercially available pharmaceutical powders for inhalation consist of a cohesive micronized drug mixed with coarse α-lactose monohydrate as a carrier to form adhesive mixes [1, 2]. For such drug-α-lactose monohydrate systems to be therapeutically effective, a significant number of drug particles must detach from the carrier particles upon the application of a removal force; however, the adhesion forces must also be strong enough to prevent disruption under processing conditions, storage, and transport. A thorough understanding the interactive forces responsible for adhesion between drug and carrier particles could lead to optimization of both product and process. Although significant progress has been achieved in this area, the relationship of drug physicochemical properties that affect interactions with α-lactose monohydrate in powders for inhalation has been only sparingly evaluated. This review addresses the importance of focusing on the surface free energy of powders to understand the forces binding drug/carrier mixtures and will discuss some novel surface analytical techniques currently in use for characterizing the relationship between interfacial forces and aerosol behavior.

The overall performance of a dry powder inhaler, as far as device filling, emptying, and powder lung penetration is concerned, relies on a formulation's characteristics and its interactions with the device, which in turn depend on a significant number of variables. Dispersion of micronized drug particles in inspired air depends on the energy required to overcome the strength of the cohesive forces between drug particles and the adhesion of fine drug particles onto the surface of larger particle substrates [3, 4]. In addition, physical adsorption and adhesion phenomena are also known to influence physical and mechanical properties of powders including blend stability, flowability, dispersibility, and dissolution characteristics. The physicochemical characteristics of the individual components, including moisture content, morphology, particle size, drug/carrier mass ratio, and crystallinity all affect the interactive forces among particles. Environmental and processing conditions such as the time and scale of mixing and the inclusion of ternary components also influence those interactions [5-10].

Interparticle forces acting in dry powder mixes

The interparticle forces acting between small drug particles and large carrier particles in an ordered mix include London van der Waals, electrostatic forces, and surface tensional or capillary forces [11]. The total adhesion force (F) consists of the sum of component forces present in a given system [12]:

$$F = F_{vdW} + F_e + F_{im} + F_s$$

where F_{vdW} are van der Waals forces, F_e are the contact potential forces, F_{im} are the Coulombic interactions and F_s are the surface tensional forces. The relative contribution of these forces to the overall adhesion in a particular system depends on the material properties and environmental and processing factors. Because of the small particle sizes typically found in drug-carrier systems, van der Waals interactions represent the major factor in particle-particle adhesion, strength of solids, surface tension, wetting and physical adsorption. Van der Waals forces are present in all molecules when two particles are in contact [13] and have bond energies typically in the range of 1-10 Kcal/mol.

In general, for powders that are not artificially charged by a high voltage field, the electrical interactive force due to contact (F_e) is much greater than the Coulombic image force (F_{im}). Contact forces are the result of a shell of oppositely charged electronic layers located at the interface of the par-

ticles, while Coulombic interactions result from the contact of charged particles with uncharged surfaces. Pharmaceutical powders, generally organic materials that behave as electrical insulators under ambient conditions, can acquire a surface electrical charge through a variety of mechanisms: contact and frictional electrification (triboelectrification) during mixing or transport, mechanical fracture, corona charging, spray drying, induction charging of sprayed liquids, ion and electron beam charging, photoelectric charging, thermionic and field emissions [14]. Particle surfaces often remain charged even after separation [15, 16], but increasing the humidity can reduce those surface charges.

While van der Waals and electrostatic forces predominate in low humidity environments, surface tension effects become increasingly important at humidities greater than 65%, which can be an issue in dry powder inhaler formulations since micronized drugs are usually highly charged and sensitive to humidity, and the presence of even a small amount of amorphous lactose in the carrier may lead to moisture adsorption. Although surface energy can represent a critical variable in dry powder formulations, it is very difficult to measure, much more so than for liquids, because the surface of a solid is usually heterogeneous. A few methods can provide indirect estimates of surface tension: calorimetry to determine heats of adsorption, gas adsorption studies, contact angle measurements, and fractal surfaces analysis for the determination of surface area [17]. For example, powder characteristics such as the batch uniformity have been used to estimate the surface energies of well characterised materials such as griseofulvin [18], and some studies have addressed interactions between gases and solid materials [19]. Contact angle measurements have been used to characterize α-lactose monohydrate [20], and the contact angle technique has been the most widely used, although the necessary compression of a powder results in uncertainty about which faces are creating the interface at the time of measurement. As a result of this uncertainty, several alternatives or complements to contact angle measurement have been explored recently.

Thermodynamic approaches to determining surface energy for the evaluation of particle interactions

Sorption isotherms are especially useful for studying the surface integrity of powders in terms of crystallinity/amorphous content for stability purposes. The most recent techniques for the study of water sorption on solid pharmaceutical systems are gravimetric or microbalance, inverse gas chromatography, and isothermal microcalorimetry. The interfacial free energy at a solid-vapor interface can also be obtained by gas adsorption studies [21]. Adsorption experiments are usually conducted at constant temperature, and the amount adsorbed is represented as a function of the equilibrium gas pressure, followed by a thermodynamic treatment, providing some indication of the energy of adsorbate-adsorbent interaction.

The thermodynamic aspects of surface phenomena can be related to forces between particles and to the imbalance of forces at an interface [22]. The solid-vapor interface offers a system well suited for the experimental assessment of surface energetics, allowing some direct energy measurements and, for solids, thermodynamic functions can provide theoretical interpretations of the physical phenomena occurring in powder surfaces. One study observed that the face of a crystal has a greater tendency to wet than does bulk powder due to the differences in energetics of crystal defects and edges compared to the energetics of flat surfaces, and small changes in surface energetics of materials, including α-lactose monohydrate, have been detected using a vacuum microbalance [23, 24] and active pharmaceutical ingredient (API) [25].

Inverse gas chromatography (IGC) is another high-resolution technique that has been used successfully to determine surface properties of drugs and excipients [26-28] by investigating their thermodynamic properties. IGC involves packing the powder of interest into a standard glass GC column and injecting small amounts of non-polar alkanes and polar volatile organic solvents as probes. The selection of different organic probes is based on the molecular reactivity [29], and the column retention of a given probe reflects the difference in surface energetics between the solid materials used for packing the column. From the retention data, the observed capacity factors are used to estimate thermodynamic parameters, including heats of sorption, Gibbs free energy, entropy and enthalpy of sorption. Examination of the structural and thermodynamic solid state properties of a powder by IGC allows the estimation of solid properties for pharmaceutical systems [25, 30-32], and studies have demonstrated that this technique is suitable for surface analysis of powders before and after a processing operation. For example, IGC analysis has shown that a high-energy mechanical treatment like milling increases cohesive energy of the materials processed [27, 31, 33, 34].

Microcalorimetry, which measures the heat of adsorption of solvent vapors flowing through powder samples in a flow cell and which has the sensitivity to measure very small heat changes of the order of μJ/s on the surface of a sample, has a number of applications in physical pharmacy [35].

Extensive studies of surface thermodynamic properties of powders relevant to pharmaceutical systems have been completed using a Thermal Activity Monitor (TAM) microcalorimeter. Because the microcalorimeter contains sample and reference cells held at constant temperature by a large heat sink, the technique provides a direct measurement of energy changes in a process by monitoring heat change in an isothermal system. The recorded heat flux can be related to the reaction rate and reaction enthalpy of the process under study [36, 37]. A gas pressure controller device allows very accurate control of solvent vapor pressure of the continuously flowing gas phase to which the sample is exposed [38] in order to cover the entire range of relative humidity or vapor pressure change at ambient temperature. When two polymorphic forms of an API have differing levels of cohesiveness, isothermal microcalorimetry can help to explain the difference through determination of the two different adsorption characteristics [25].

New and promising techniques

Over the past 20 years, Atomic Force Microscopy's ability to characterize force curves containing information about adhesion forces [39], van der Waals forces [40], and electrostatic forces [41] has been documented. In AFM, an atomically sharp tip scans a surface, measuring both the roughness of a surface and the interfacial forces by sensing the deflection of a cantilever. When a particle is affixed to the cantilever, the interaction forces between the particle and another particle or between the particle and a substrate can be measured as a function of variables such as particle diameter, particle-particle or particle-substrate separation distances, or environmental conditions such as relative humidity [42]. The major drawback to using this technique is that it requires extreme experimental care and consumes a great deal of time, which, along with the elusiveness of reliable computational interaction parameters required with these techniques, has limited its use. Nonetheless, AFM has been used in pharmaceutical systems as complements to IGC [28, 33], and TAM [25]. In recent years, more emphasis has been focused on using AFM [9], and a colloidal probe AFM technique has been used to characterize powders used in some inhalation systems [28, 43, 44].

Another technique being explored for measuring the surface characteristics of inhalable powders involves the Surface Enhanced Raman Scattering (SERS) method, designed to examine monolayer films [45, 46] and potential for microstructure of powders at the surface [47]. SERS measurements can be carried out in a conventional Raman system and a system based on an atomic force microscope (AFM) controller with a cantilevered fiber optics probe. The SERS operation can, in principle, detect variations in interactions across an area in the order of 1 μm with 10000 times greater sensitivity than that of a standard Raman microscope and spatial resolution in the order of tens of nanometers. Although SERS is used now only as a complement to more established methods, it looks like a promising method for the future and is currently gaining in popularity.

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