Measuring particle adhesive ability

Revisiting a centrifugal method that allows for the measurement of adhesive forces between active pharmaceutical ingredient (API) and carrier particles in a dry powder formulation

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Dry powder inhaler (DPI) formulations that include a coarse carrier usually include micronized active ingredient with lactose particles that are too large to be respirable. These formulations require the active drug to detach from the carrier during aerosolization in order for the drug to reach the patient's lung. Developers must ensure that enough energy can be generated to overcome adhesive and cohesive forces between the particles, either by the patient's inspiration alone or with some active component of the delivery device. In most cases, the developers determine the amount of force necessary to generate a sufficient fine particle fraction by an empirical trial-and-error method.

The ability to measure the adhesive forces between the drug particles and the lactose can help to streamline co-development of the formulation and the delivery device. Some pharmaceutical companies turn to academic researchers for fundamental studies of the adhesive properties of particles using inverse gas chromatography (IGC) or atomic force microscopy (AFM). These methods, though sensitive and selective, are expensive and time consuming for measurement of a representative number of particles to probe interaction forces.

A centrifuge method first introduced in the late 1960s allows researchers to get a general idea of the adhesive and cohesive forces present in a representative sample of a drug/carrier mixture under fluidized conditions that more closely mimic aerosolization in an inhaler. Because this technique uses standard lab equipment and requires no special training or sample preparation, the centrifuge method can give fast and inexpensive data about the forces in a dry powder formulation and also provides an indirect method for determining how particle characteristics such as morphology and size affect the formulation performance. A recent study revisited this method to characterize deposition characteristics for drug/lactose mixes prepared with different polymorphs.

The centrifuge method

In order to determine adhesive forces by centrifugation, analysts introduce a known amount of a drug/carrier mixture into the sample compartment of a centrifuge cell under controlled temperature and relative humidity conditions (Fig. 1). Researchers select a spin rate, which will result in the application of a known amount of force to the powder mixture, and select a mesh screen with openings smaller than the lactose particles to separate the sample compartment from the collection compartment.

Figure 1

Sample compartment for use with centrifugal method of particle adhesive ability measurement

After the sample spins for a set period of time, any drug particles that have detached and entered the collection compartment through the screen, along with those caught in the mesh, are weighed (Table 1). Researchers use spectroscopic techniques to differentiate active ingredient that has detached from lactose fines that may also have entered the collection compartment. Depending on the characteristics of the drug, UV spectroscopy may be useful for analysis of all concentrations studied; however, in this case, a more sensitive fluorescence technique was necessary for the 1% mixture.

Repeating the assay at differing spin rates allows analysts to compile data for a profile of the adhesive abilities of the drug in the mixture, which may vary due to particle size, morphology, crystalline form, or other factors. Performing the centrifugation with different formulations containing different ratios of drug and carrier allows for an estimate of the balance between adhesive and cohesive forces.

Determining the detachment force

The forces of separation measured using the centrifuge method correspond to the drug/carrier forces overcome during centrifugation at a particular spin rate. Since each spin rate results in a different detachment force applied to the drug/lactose blend, a series of tests using different spin rates serves as a series of force probes useful for determining a profile of the corresponding attachment forces of the drug particles.

The adhesion force between a fine drug particle and a coarse lactose carrier equals the inverse of the detachment force, F_{det}. The force of adhesion between a fine adherent particle and a carrier substrate surface can be calculated from Newton's second law of gravity:

$$F = m\,(a + g)$$

where F is the force acting on the particle, m is the mass of the particle, a is the centrifugal acceleration and g is the acceleration due to gravity. The centrifugal acceleration (a) equals the square of the angular velocity (ω) times the distance between the center of the particle and the axis of rotation (l). For this study, researchers assumed that the particle would be at the mesh screen when it detaches, so l is the distance from the center of the centrifuge to the screen.

When the centrifugal acceleration greatly exceeds the gravitational acceleration, the gravitational term can be dropped, and the equation can be expressed in terms of centrifugal acceleration only:

$$F_{det} = m\omega^2 l$$

In order to reproduce the experiments using different centrifuges that may vary in size, and which therefore would have different acceleration for a given spin rate, we can express the amount of acceleration applied to the sample independently of l by using relative centrifugal force (RCF):

$$RCF = \frac{F_{det}}{F_g}, \text{ where } F_g = mg \text{ and } g = 980 \text{ cm/sec}^2$$

This equation gives acceleration as "g-force" or "times g", where g is the standard acceleration due to gravity.

To evaluate differences in attachment forces due to differences in median particle size for different drugs or different polymorphs, we can rewrite the formula for F_{det} in terms of density and particle size to determine the detachment force for any single particle:

$$F_{det} = \frac{\rho \pi d^3 \omega^2 l}{6}$$

where d is the API particle diameter, ρ is the API particle density, ω is the angular velocity, and l is the distance between the center of the particle and the axis of rotation. Surface area measurement of poly-

Table 1

Summary of the drug detached from lactose using the centrifuge technique

Powder blend % w/w Drug polymorph	Percentage of drug content found					
	Removed		Adhered		Mesh	
	Mean	s.d.	Mean	s.d.	Mean	s.d.
1% A	1.91	0.48	98.09	2.56	1.43	0.75
1% B	4.88	1.03	95.12	1.33	3.66	2.36
5% A	14.87	2.69	78.89	3.79	6.24	2.04
5% B	18.40	0.42	77.49	5.56	4.11	1.41
25% A	17.48	0.52	72.78	4.18	9.74	3.24
25% B	21.41	1.29	73.54	2.97	5.05	0.84

morphs A and B using the Brunauer, Emmett, and Teller (BET) isotherm have determined that the error produced by assuming spherical shape is a systematic one in this case, allowing meaningful comparisons among data from the two materials.

To determine the detachment force for all particles leaving the substrate, we need to multiply the total particle mass by the RCF. For an experiment conducted using polymorphs with a 50-percentile-diameter size of 2.4 and 2.2 μm for polymorphs A and B, respectively, the RCF increases exponentially from approximately 1 dyne/particle at 1,000 rpm to more than 20 dynes/particle at 5,000 rpm (Table 2).

Comparing two polymorphs

For a series of centrifugal tests of drug X, a beta antagonist with two polymorphs, A and B, the values obtained for the detachment force indicate that the extent of drug detachment for form B exceeds that for form A at all spin rates and drug concentrations (Table 2). The only exception is at the lowest concentration and spin rates, where detachment for both crystal forms is negligible. In other words, polymorph B requires lower force than polymorph A for separation from the carrier, and the percentage of form A still adhered to lactose after the spin time exceeds that of form B at all RCFs studied. In terms of DPI performance, polymorph B would always generate a higher fine particle fraction in a given inhaler.

These results provide developers with the opportunity to optimize a formulation for a particular device by providing data correlating differences in morphology between polymorphs A and B. A difference in the distribution profile could indicate variations in the particle size distribution (PSD), but both polymorphs in this case have similar, though not identical, PSDs (Fig. 2). The A form in this case consists of needle-shaped particles, while the B form has a more rounded shape (Fig. 3). In the event that the A form is more stable, the developers could choose either to formulate with the less stable B form or, more likely,

Table 2

Relative centrifugal force. Centrifuge distance between the center of the particle and the axis of rotation l = 10.8 cm

Centrifuge spin rate RPM 0	ω rad*sec-1	ω2l cm*sec-2	RCF g	F_{det} Dynes/particle A	B
0	0.00	0	1.000	0.00	0.00
1000	104.72	118436	120.853	1.08	0.85
3000	314.16	1065922	1087.676	9.72	7.67
5000	523.60	2960895	3021.322	27.00	21.30

Figure 2

Particle size distribution of forms A and B

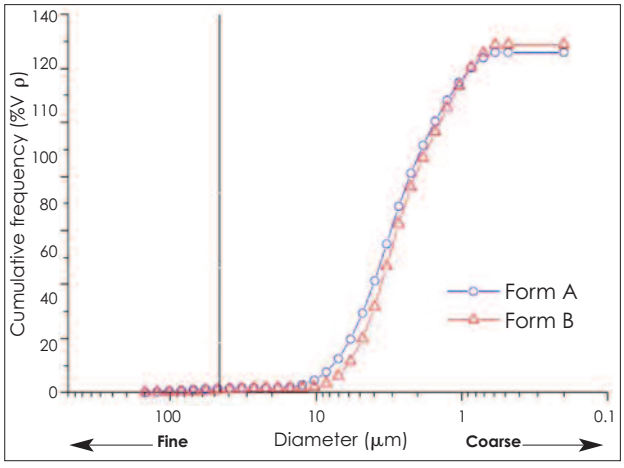
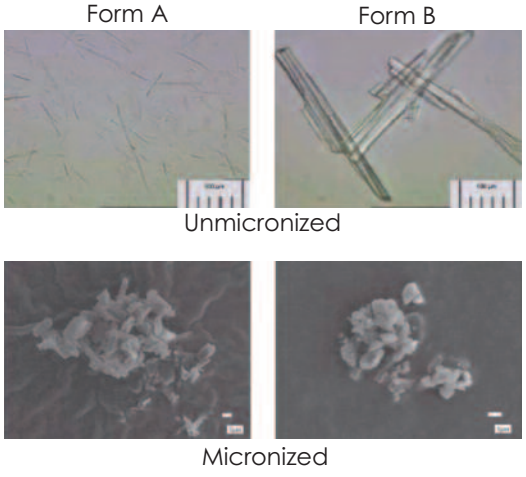


Figure 3

Optical and scanning electron microscope images of form A and form B



to engineer the A particles to detach with less force, possibly by coating them to make them more round.

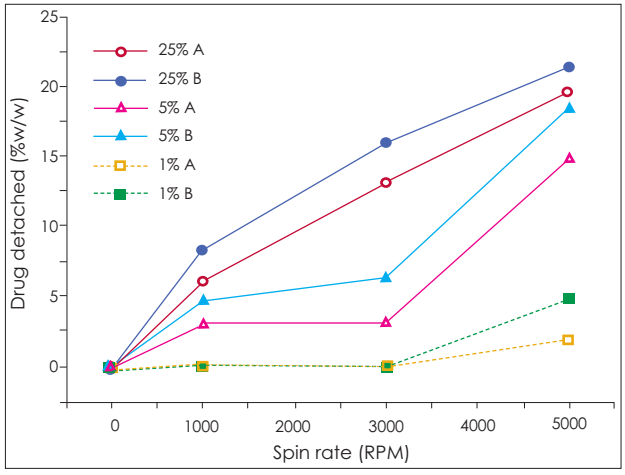
However, plotting the percentage of detached drug against the spin rate for different drug loading concentrations show that drug load in this case has a greater influence on fine particle generation than the crystal form (Fig. 4). Polymorph B detaches more easily than polymorph A at all drug loads, but for a given drug load, the two polymorphs exhibit the same detachment profile. This is a very significant result, indicating that the difference in particle shape between the two polymorphs is not the determining factor in their attachment to lactose particles.

These results suggest that a sufficiently large carrier surface area per drug particle supplies an adequate number of attachment sites on the surface of the lactose particles so that the drug/lactose adhesive interaction is considerably stronger than when the attachment sites on the carrier become scarce. At higher drug loads, drug particles have less chance of adhering to the carrier and more opportunity of cohering to other drug particles. At higher drug loads, therefore, cohesion should play a greater role, with adhesion more influential at lower drug concentrations.

A previous study using a different drug suggested that the minimum force required to detach the drug from the carrier during aerosolization in a DPI corresponded to an RCF of 2,000 g. However, for both polymorphs in this study, the break point, where the RCF is sufficient for complete separation of the API from the carrier, occurs at about 1,000 g, or half that limit, placing it well within the range of removal forces generated within most DPIs (Fig. 4).

Figure 4

Percentage of drug detached vs. centrifugation feed



The difference between the adhesive abilities of polymorphs A and B probably results more from differing physicochemical properties than from different geometries of the two crystal forms. The adhesion ability of a particle is predominantly a surface property, whereas the particle mass primarily determines the counteracting detachment force. Detachment of adhered particles by the centrifuge method takes place by breaking the balance between the force of particle attachment and the gravitational pull imposed by the spin rate, i.e., between a surface and a bulk property.

For this drug, polymorph B, which consistently shows greater detachment than polymorph A, also has a higher absolute density. It follows that for a given particle size, form B particles will experience greater pulling force than form A particles at the same spin rate. If the particle size distributions for the two polymorphs were identical, detachment forces on polymorph B should be consistently greater than on polymorph A by a factor of 1.29/1.26, the ratio of their absolute densities.

Neither the differences in particle geometry between the two polymorphs nor the difference in their density or particle size distributions can account for the difference observed in their detachment behavior. More of polymorph A always remains in the sample chamber of the centrifuge cell than polymorph B. The present analysis cannot conclusively establish whether this effect is attributable solely to a stronger interaction with lactose (adhesion) or also in part to polymorph A's ability to form stronger aggregates (cohesion).

In either case, however, the explanation must reside in a difference between the intrinsic energies of interaction of the two polymorphs. For this drug, centrifugation studies give an estimate of detachment of one powder from another where particle size distribution, crystal habit (shape) and rugosity play a role. However, since the adhesion ability of a particle is predominantly a surface property, hence more specialized techniques such as AFM and IGC could be used.

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