Q&A: Mechanical surface modification

C. C. Huang of Hosokawa Micron answers questions about mechanical methods of modifying dry powder particles

Q *What are some of the modifications you can make to particles using mechanical energy?*

A Our primary focus is on composing small particles in the nano or micro size range, such as an active pharmaceutical ingredient (API), onto a larger particle such as a lactose carrier, creating a mechanical bond between particles without using any binder. We can also sphericalize irregularly shaped particles to make them rounder so that they flow better. In some cases, we can change the surface of a particle from crystalline to amorphous.

Q *How does the composition process differ from mixing?*

A Our composing process creates particle composites with core-shell structure or achieves precision mixing for nano or submicron powders. Normal mixing can only distribute fine or coarse powders uniformly in a macroscopic sense.

To make composites of small particles on larger particles, we place the powder mixture into a rotating chamber with a stator. Centrifugal force pushes the particles onto the inner wall of the chamber, where they eventually get carried into a small gap between the rotating chamber and the stator. Within that gap, compressive, shear, tumbling, friction, and impact forces come into play to disperse small particles and bond them, or embed them, onto the surface of the larger core particles. Depending on the materials, some chemisorption may occur, but generally the bond between particles is purely mechanical.

Q *What are the advantages of mechanofusion vs. other methods of bonding particles?*

A For one thing, we can work with very small particles in the nano to micron size range, such as those used in inhaler formulations, and distribute them evenly among the larger core particles, even with as little as 1% API in 99% carrier. For high potency drugs, you might have a formulation with a very small percentage of drug, and it's very difficult to achieve that kind of distribution with a mixer under those conditions.

The process is completely dry, so no drying is required afterwards; no ingredients must be added to the formulation; and there are no concerns about solution contamination. Temperature control is very good, and batch processing times are very short—less than 5 minutes, for example—so the

process is very suitable for temperature sensitive materials. Mechanical bonding also produces a much stronger bond than an electrostatic bond.

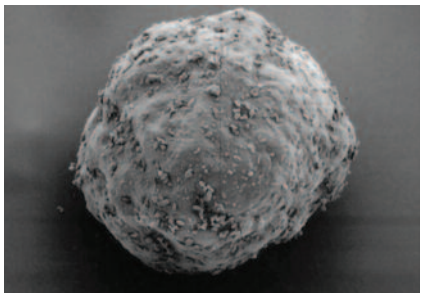
Q *Are there materials that are not suitable for the process?*

A In principle, there are no limitations on the types of materials suitable for mechanical processing. In addition to heat sensitive materials, we can also handle abrasive and adhesive materials. Some large, porous particles may be too fragile to survive the mechanical forces involved in the process and may be crushed. However, almost any particle that is in the respirable size range, under 10 μm, will be strong enough, and we have worked successfully with particles up to several hundred microns.

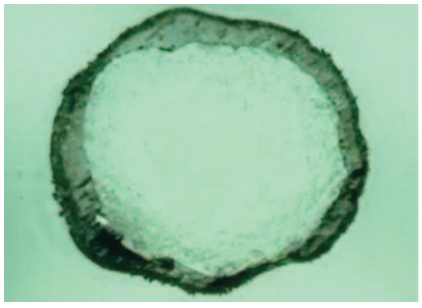
One of the materials in the mixture must be significantly smaller than the other in order to perform the composition. Also, the potential loading of the drug in an API/carrier system may top out at around 25%, depending on the particle sizes, surface properties, etc.

Q *What kinds of applications are there for inhalation powders?*

A Obviously, the primary application is in creating composites of an API and a lactose carrier for dry powder inhaler (DPI) formulations. We have done that in the past with insulin. In fact, first we created a nanosphere composed of insulin and then put the nanospheres on the surface of the lactose particles.



API coated on excipient



Cross section view of the coated particle

Other applications for DPI formulations involve modifying lactose particles in order to improve the formulation's flow characteristics. Small amounts of additives like magnesium stearate can be bonded onto micron size lactose to improve its flowability before mixing it with the API for dry powder formulations.

Q *Isn't the mechanical bond too strong to allow the drug to detach from the carrier during aerosolization as is necessary for inhalation formulations?*

A Actually, we can control the strength of the bond between the API and the lactose by adjusting the process parameters, so we can optimize the amount of force needed for detachment. By varying the loading of the drug, the amount processed, and the amount of energy we put in, we can optimize the fine particle fraction generation during aerosolization.

Q *How widely used is this technique?*

A Commercial mechanofusion equipment was first introduced in 1986, and we introduced our latest design, the Nobilta, in 2004. Since then, we have sold the equipment in a number of industries but have sold only about 10-15 to pharmaceutical companies. In Europe and Japan, there are several GMP machines for commercial pharmaceutical production; in the US, the machines have been used only for research so far.

Q *How much does a laboratory-sized machine cost?*

A A table-top model that can handle samples up to 40 cc in volume costs about $75k.

Q *Do you provide testing services?*

A In New Jersey, we have the ability to test samples in the 500 cc range. Our Japanese facility handles samples below 40 cc.

C. C. Huang is Director, Hosokowa Micron Powder Systems, 10 Chatham Road, Summit, NJ 07901, USA. Tel: +1 908 277-9245. chuang@hmps.hosokawa.com