COVER STORY:
Surface Area: The Most Underutilized Particle Property in Pharma

What’s Inside:
- Surface Area: The Most Underutilized Particle Property in Pharma
- PSG Job Fair Exceeds Expectations
- New USP Quality Standards Limiting Elemental Impurities in Medicines Announced
- Regulatory Intelligence Update
- Processes for Quality & Organizations - Part 3 - “Managing Quality”
- 12 Communication Blunders that can trip up Supervisors and Managers
- President’s Message
Surface Area: The Most Underutilized Particle Property in Pharma?

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Hopefully it’s no surprise that the surface of a solid is different from the bulk. Therefore it should be self evident that as particle size becomes smaller the more different the material behaves. If the surface were not involved, what one would have at the end of milling or grinding would be simply a greater number of particles but no change in properties. Certainly an increased number of particles make it easier to disperse API further so as to improve content uniformity - notwithstanding the difficulties of maintaining that dispersion of API amongst excipients in a blend. But the surface area must increase with a decrease in particle size and with it the surface free energy. That is, the work put into breaking particles down is at least in part stored in the surface! As the particle size distribution is moved to smaller sizes so then the energy of the system must increase. Physical chemistry aside, even every-day experience tells us that finer powders do behave differently than their coarser cousins.

Let’s consider some reasons why, recognizing that surface area is a quantitative, albeit the geometric component, expression of the total surface free energy of the system. The surface is where contaminants tend to congregate because of the thermodynamic need for the surface to reduce its free energy (think of surface free energy as potential energy for adsorption). Probably the single most important contaminant, certainly the most prevalent, is adventitious moisture - that adsorbed from the atmosphere. All other parameters being equal, a powder having greater surface area will adsorb a greater mass of moisture. Such moisture can, for example, cause caking by enhancing particle-particle adhesion, and can hasten crystallization of an amorphous compound by its lowering of the glass transition point.

So, surface area is “unstable” because it represents an undesirable thermodynamic state; any system always seeks the minimum energy state. It is driven not only to adsorb but also, for example, to sinter and to cause Ostwald ripening (Ostwald ripening is the phenomena...
in which smaller particles in solution dissolve and deposit on larger particles in order to reach a more thermodynamically stable state wherein the surface to area ratio is minimized). If molecules in a solid have sufficient mobility, this loss of surface area can be observed in a matter of days even at room temperature! Small differences in surface area including such temporal changes played their part in Nifedipine patent litigation. [1]

Dwell for a moment on the idea of tableting. When particles are brought together in a recognizable compact aggregate or agglomerate then the notion of particle size is obsolete, at least in terms of the original powder particles that no longer exist as discrete entities. But surface area remains as a measurable parameter. In fact the decrease in accessible surface area as particles are pressed further together represents the increase in particle-particle bonding. This is well understood by ceramists and other materials scientists who regularly follow the loss of porosity and surface area as green compacts are heat-sintered. There’s no reason why similar knowledge shouldn’t be part of understanding and engineering granulation and tableting processes.

A greater surface area presents more species to the surrounding fluid at any given point in time. That’s why dissolution rates are enhanced by reduction in particle size. There’s an additional effect related to greater ‘curvature’ of the surface of a small particle compared to a larger one. Either way we know surface area is involved and important, but just how often do we take the time to measure it? Not usually, unless you’re a magnesium stearate manufacturer, or are producing one of the very few actives whose USP monograph requires it.

Lack of familiarity? Perhaps because it’s not a “comfortable” spectroscopic technique, or because it’s not an “instant” measurement. True, it’s much slower than a particle size analysis (think tens of minutes rather than two or three), but as the material gets finer a surface area analysis actually gets easier because there’s more of it to measure! How then is surface area measured? It simply involves quantitatively adsorbing an inert gas to the surface of the sample around the (sub-ambient) pressure required to form what’s called a monomolecular layer, or monolayer for short. That pressure is usually in the range 0.05 to 0.3 P/Po where Po is the saturated vapor pressure of the analysis gas at the temperature of the measurement. P/Po is called “relative pressure”. We most often employ nitrogen gas at its own boiling point, i.e. liquid nitrogen temperature (77.36 K / -195.79 °C).

Don’t worry about the exact details, modern instruments take care of that, everything from evacuating the sample cell, dosing gas into the sample cell, monitoring the pressure changes

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Surface Area......
due to adsorption etc and making the final calculation. But the calculation is historically significant. In the early days of gas sorption measurements, the surface area of a sample was estimated graphically from the isotherm data (that’s what we call a plot of amount adsorbed as a function of P/Po). But in 1938 a theoretical treatment of multilayer adsorption was developed and published by Stephen Brunauer, Paul Emmett and Edward Teller [2] (yes, the same Teller of the Jahn-Teller effect, and of the hydrogen bomb). We have been using the B.E.T. “method” ever since. Usually it requires three or more data points of volume adsorbed (V, as a function of P/Po) to be recorded and a plot of the transformed isotherm, P/V(Vo-P) against P/Po, constructed. From the slope and y intercept of the resulting straight line, the quantity Vm or monolayer volume is found.

Remembering that Vm is the volume of gas which is adsorbed in the monolayer usually expressed at STP (standard temperature and pressure), simple math and Avogadro’s constant is used to calculate the number of molecules. Assuming we know the area occupied by each adsorbed molecule, 0.162 square nanometers in the case of nitrogen at 77.36 K / -195.79 °C, also known as the ‘cross-sectional area’ calculating the total surface area of the sample is trivial. It is usual then to divide the total area by the dry mass of the sample to give the specific surface area, expressed in square meters.

It’s the B.E.T. method that is called out in USP <846> [3] together with some generic experimental considerations. While a straight B.E.T plot is appealing evidence that the 1938 multimolecular adsorption theory is obeyed (linearity is demanded by <846>), its correctness is not proven. As Brunauer himself wrote in 1945 [4], it is also necessary that the evaluated constants (from slope and intercept) Vm and c have reasonable values. What is c? It is a number related to the heat of adsorption. What is reasonable? The value of c depends both on the gas and the surface. But in general we expect a low value for a weakly adsorbing surface, like a metal or polymer and organics, and higher values for more strongly adsorbing surfaces like zeolites and other microporous materials. We should expect therefore rather low values when analyzing API’s (organic and of little or no porosity). As for excipients, the USP magnesium stearate monograph [5] requires (where there is a functionality-related concern) that a BET surface area value be reported, and we know that a reasonable c value for it is in the teens - so a surface area result that yields a value say in the hundreds can be called into question (but not considered by the USP Monograph). Magnesium stearate presents a number of issues and isn’t the easiest of materials to analyze for newcomers to
the challenge, but success usually boils down to making the analysis as quickly as possible (to avoid thermally induced changes at 77.36 K / -195.79 °C while still ensuring mostly equilibrated conditions (that is equilibrium between gaseous and adsorbed phases of the analysis gas).

So surface area measurements, specifically according to the B.E.T. method, are part of the pharmaceutical industry but have been adopted sparsely. Yet surface area can quite easily reveal an excess of fines that might be challenging for a particle size analysis, surface area can distinguish between different morphologies of similar particle size, surface area can be used to follow the generation of particle-particle bonds under pressure, be part of tighter control on specifications of raw materials so as to avoid surprises during later processing, and explain unexpected dissolution behavior. Perhaps surface area measurements could be utilized more than they are right now.

References
1. 212 F.3d 1241 (Fed. Cir. 2000) United States Court of Appeals for the Federal Circuit
3. “Specific Surface Area, General Chapter <846>” U.S. Pharmacopeial Convention

Bibliography

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Dr. Thomas has more than twenty-eight years of industrial experience in the characterization of powders and porous materials. He obtained a Masters degree in Analytical Chemistry and a Doctorate in Inorganic/Physical Chemistry at the School of Chemistry, University of Birmingham (UK). In 1985, he joined ICI’s Catalyst Research Centre (now a Johnson-Matthey facility) as a Principal Research Officer in charge of the porous materials characterization lab. Dr. Thomas joined Quantachrome in 1991 as Technical Manager and provided expert technical assistance to all clients. Dr. Thomas is currently Director of Business Development and regularly lectures for the Center for Professional Advancement on powder properties and processing. He presents courses and seminars in the field of porous materials and catalyst characterization techniques. Dr Thomas co-authored the popular handbook “Characterization of Porous Solids and Powders: Surface Area, Porosity and Density” published by Springer, and his name appears on four US patents and two European patents.

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