Application Note 104

Surface Area of Active Pharmaceutical Ingredients using the Acorn Area™

A cursory glance through the current scientific and patent literature reveals that there are many examples where reducing the particle size of an active pharmaceutical ingredient (API) results in increased bioavailability. In the case of formulations intended for oral administration, poorly water-soluble, highly permeable API's, classified according to the Biopharmaceutical Classification System as Class II (BCS class II), may suffer from an inadequate, or highly variable, rate and/or extent of drug absorption (sometimes as a function of food in the stomach, i.e., fed/fasted variability). Importantly, however, particle size reduction of the API will significantly increase the specific surface area and subsequently the rate of dissolution of the drug in the gut milieu, thereby increasing the efficacy and reducing the potential toxicity (because less drug substance is needed). Thus measuring the surface area of API's can be of critical importance in determining the product performance.

The Acorn Area is a new instrument using a patented technique based on NMR relaxation to determine the wetted surface area of suspensions of particulate materials. The Acorn takes advantage of the fact that liquid that is bound to a particle surface has a much lower relaxation time than the free or bulk liquid. Thus a sample with a high surface area will have a lower total relaxation time than a low surface area sample because there should be more of the fluid bound to the surface. Unlike the measurement of particle size by DLS, where the raw intensity data has to be deconvoluted by means of complex algorithms, here the relaxation time can be converted into the absolute surface area by means of a simple calculation.

The most common method of surface area determination is nitrogen gas adsorption. In this method nitrogen gas is adsorbed on a sample kept at liquid nitrogen temperature at a series of different pressures, This method is useful only for dry powders and requires that the sample be degassed to drive off any adsorbed material and requires a source of liquid nitrogen to maintain the proper sample temperature. Maintaining the sample at the proper temperature is a critical experimental requirement. The Acorn Area measures suspensions and requires no sample pretreatment or temperature control. It is inherently a much simpler measurement technique.

The formula for calculating the surface area from the measured relaxation time is

$$R_{av} = \psi_p S L \rho_p (R_s - R_b) + R_b ,$$

where R_{av} is the average spin relaxation rate constant, ψ_p is the particle volume to liquid volume ratio, S is the total surface area per unit weight, L is the surface

layer thickness of liquid, ρ_b is the bulk particle density, R_s is the relaxation rate constant for the bound solvent and R_b is the relaxation rate constant for the free or bulk solvent.

Using a standard reference material we can define a constant, $K_a = L\ \rho_b\ (R_s - R_b)$ so that $R_{av} = K_a S \psi_b + R_b$.

To demonstrate the wide applicability of the Acorn Area to the measurement of the surface area of API's, we chose three proprietary materials each with a distinct particle size and distribution.

The first API is a synthetic derivative of a naturally occurring steroid hormone, progestorone. The chemical formula is $C_{24}H_{32}0_4$. The API in question is an advanced formulation of magestrol acetate and is prescribed as an appetite enhancer used for AIDS patients. It was supplied as a "nanosuspension" in water at 12.5wt%. The mean particle size, determined by dynamic light scattering (DLS) was 240nm with a fairly narrow size distribution.

The second API is an antiviral. The material was supplied as a dry powder that had been jet-milled to reduce the particle size. We prepared a 10 wt% aqueous suspension using a proprietary (XiGo) surfactant/dispersant mixture. The mean particle size of the dispersed material was determined using Fraunhofer Diffraction (FD) to be 2.4um with a wide, almost bi-modal size distribution. We also used Image Analysis (IA) to confirm that the particle morphology was clearly non-spherical.

The third API is a phosphodiesterase inhibitor and its chemical formula is $C_{22}H_{19}N_3O_4$. It is primarily used to treat erectile dysfunction and was supplied as a dry powder. We again prepared a 10wt% aqueous suspension using the same proprietary (XiGo) surfactant/dispersant mixture. Here, the mean particle size of the dispersed material was determined (using FD) to be 13um with a complex, broad size distribution. Again, IA showed non-spherical particle shape.

Surface Area (m^2g^{-1})

	Estimated Indirectly from Particle Size	Measured Directly by Acorn Area
API **A**	**18**	**19**
API **B**	**2**	**27**
API **C**	**0.5**	**10**

It must be noted that the calculation of surface area assumes spherical particles and a monodisperse size distribution, a condition clearly not met by API's B and C. Thus, the surface areas calculated for those samples are, at best, only a crude approximation. The results also speak to the limitation of using a mean particle size value; the total surface area will be dominated by the smaller size fractions in any particle size distribution.

Clearly and given the increased importance of knowing the surface area of active pharmaceutical ingredients because of its relevance to bioavailability, a direct measurement of the wetted surface area without dilution or other sample preparation is critical. This parameter is now available for the first time with the Acorn Area.