The Relationship between Pharmaceutical API Milling and NMR Relaxation time

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Application Note 108

Many pharmaceutical active ingredients (API) are wet milled to manipulate particle size. Increasing API wetted surface area provides pharmaceutical companies with a mechanism to regulate dissolution and correspondingly, bioavailability. This discussed in more detail in XiGo Note 104. Milling operations are typically performed using high concentration dispersions. The results below we obtained from a pharmaceutical API wet milled in a pin mill at a concentration of 20% by volume. These data illustrate how radically the relaxation time changes as a function of milling time. Although these results were obtained by removing aliquots of dispersion, alternatively, sample could be circulated from the mill, then tested and circulated back to the mill automatically using the flow through option of the Acorn Area. These measurements take about a minute to perform and are clearly very sensitive to changes in particle size distribution, highlighting their utility as a means to monitor changes in particle size distribution during milling.

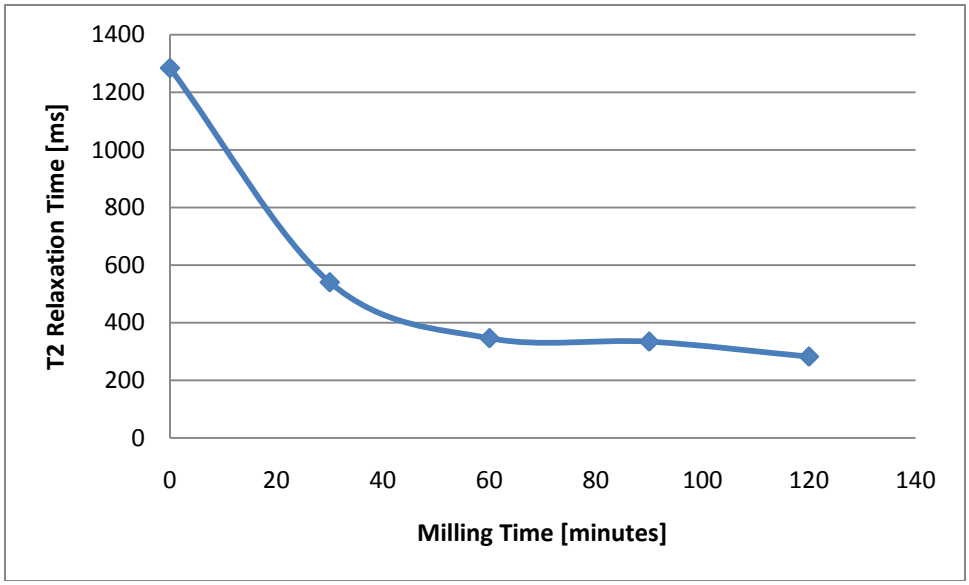

Figure 1 Relaxation Time as a Function of Milling

Surface area measurements are exquisitely sensitive to the presence of fines. As the particle size of a material is reduced, the surface area increases in proportion to the particle diameter^2. Consequently, the surface area-to-volume ratio of the particles increases dramatically. For example reducing the particle diameter from 10 microns to 1 micron increases the surface area/gram by a factor of 100. This is an essential characteristic common to all particulate suspensions. It matters little what the particle shape is - the surface area per mass of any colloid is orders of magnitude larger than it is for particles of even

only a few micrometers in size[1]. Measurement of the surface area is commonly determined using BET (N_2) gas adsorption but requires the material under test to be a dry powder. However, drying wet suspensions inevitably results in aggregates and agglomerates and, as a consequence, the subsequent surface area measured by gas adsorption will be seriously underestimated. For wet suspensions of particles it is essential, then, that the surface area is measured directly.

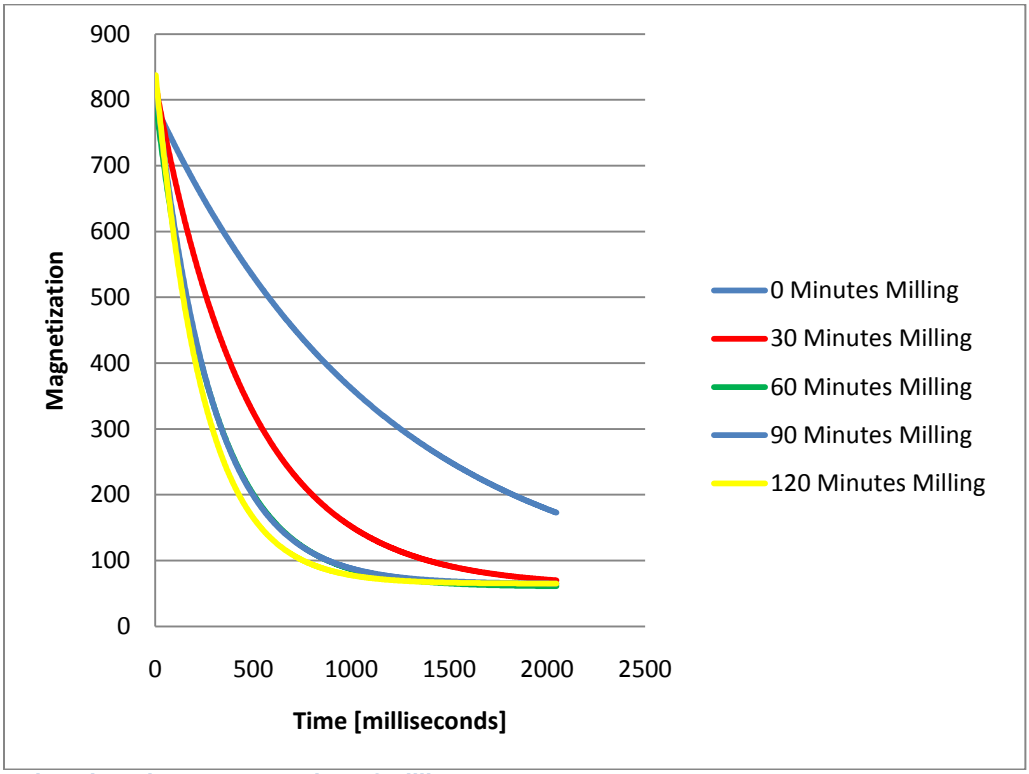

Figure 2 Relaxation Time as a Function of Milling

The Acorn Area™

The Acorn Area uses a patented technique based on NMR relaxation to determine the wetted surface area of suspensions of particulate materials[2]. The Acorn Area takes advantage of the fact that liquid that is bound to a particle surface has a much smaller relaxation time than the free or bulk liquid. Thus a sample with a high surface area will have a smaller total relaxation time than a low surface area sample because there should be more of the fluid bound to the surface. In contrast to measurement of particle size by dynamic light scattering, where the raw intensity data has to be deconvoluted by means of complex algorithms, the NMR relaxation time can be converted into the absolute surface

[1] D.H. Everett, "Basic Principles of Colloid Science", *RSC Publications*, London (1988)

[2] US Patent, 7,417,426, August 26, 2008.

area by means of a straightforward calculation. As in the BET gas adsorption method, monolayer coverage of fluid onto the particle surface is assumed.

The most common method of surface area determination is nitrogen (N_2) gas adsorption[3,4]. In this method, N_2 is adsorbed on a sample kept at liquid N_2 temperature at a series of different pressures. It is useful only for dry powders and requires that the sample be degassed to drive off any adsorbed material (sample conditioning); this requires a source of liquid N_2 to maintain the proper sample temperature; and this is also a critical experimental requirement[5].

It is possible to calculate the surface area from measurements of the particle size but it assumes spherical particles and a monodisperse size distribution, a condition clearly not met by many materials. Any surface area calculated for such materials is, at best, only a crude approximation; it is well-recognized that particle shape, surface irregularities and porosity will inevitably lead to estimated values significantly less than the true value[6].

In contrast, the Acorn Area measures suspensions directly and requires no sample pretreatment or temperature control. There are no assumptions about the sample particle size (distribution) or shape used in the determination of surface area; it is measured directly. Thus, it is, inherently, a much simpler measurement technique; and as little as 0.5 ml of sample is needed.

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

$$R_{av} = \psi_p \mathbf{S} L \rho_p (R_s - R_b) + R_b \qquad (1)$$

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 the equation (1) reduces to:

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[3] SJ. Gregg and KSW. Sing, "Adsorption, Surface Area and Porosity", 2nd Edition, Academic Press, London, 1982.
[4] S. Lowell and J E. Shields, "Powder Surface Area and Porosity", Chapman Hall, London, 1984.
[5] KSW. Sing, "The Use of Gas Adsorption for the Characterization of Porous Solids", *Colloids and Surfaces*, 38 113 (1989).

[6] T. Allen, "Particle Size Measurement", Chapman & Hall, 4th Edition, New York, 1990.

$$R_{av} = K_a \mathbf{S} \psi_p + R_b \quad (2)$$

The surface area can then be calculated from:

$$\mathbf{S} = R_{sp} R_b / K_a \psi_p$$

where, $R_{sp} = R_{av}/R_b - 1$

A more precise method is to use the slope of a plot R_{sp} as a function of different volume ratios, ψ_p (i.e. concentrations).