Active Pharmaceutical Ingredients in AIDS Drugs: Using NMR Relaxation to Determine the Wetted Surface Area of Suspensions

Introduction

Reducing the particle size of materials possessing poor solubility characteristics can be an avenue to substantially increasing the total surface area of the material. This concept can be illustrated when formulating drug products that contain active pharmaceutical ingredients (APIs). A larger surface area allows for much faster dissolution of APIs and, thereby, an increase in bioavailability, regardless of the route of administration. This is of obvious importance in manufacturing because low active bioavailability of drugs can lead to inefficient treatment and risk of toxic side effects. Any increase in efficacy can reduce the potential toxicity because less drug substance is needed, which also serves to reduce costs. There is also a growing body of evidence that, specifically with nanoparticulate API materials, it is the particle surface area and not particle size that is the defining metric that controls toxicological interaction. This explains the recent drive to develop reformulations based on nanotechnology.

The increase in surface area as particles are made smaller also affects adsorption of chemicals and other moieties onto the particle surface, the interaction between particles (i.e., suspension stability), and system properties such as suspension rheology, coating and adhesion. Thus, measuring the surface area of APIs can be of critical importance in determining product performance.

A significant number of products manufactured for pharmaceutical purposes involve, either in the final state or at some stage of their production, suspensions of particulate API materials dispersed into liquid vehicles often at high volume fraction. However, there are both fundamental and practical difficulties associated with measuring the surface area of aqueous and non-aqueous suspensions of API's. The most common technique used to determine surface area is gas adsorption but it works only with dry powders and, importantly, cannot provide any indication of the wetted surface area of the API when it is dispersed in a liquid. Drying a wet suspension 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 API particles it is essential, then, that the surface area be measured directly (see Mageleka White Paper 2).

So, what technique can make fast, reliable, direct measurements of wetted surface area in any suspension and, particularly, nanosize API dispersions? Nuclear magnetic resonance (NMR) relaxation, which is the basis for Mageleka's *M*agno*M*eter XRS™, can directly measure the wetted surface area of any particulate suspension.

"Quick and accurate measurement of the wetted surface area provides major advantages to the pharmaceutical and healthcare industries."

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NMR Relaxation

NMR spectroscopy is one of the most powerful analytical tools used to probe details of molecular structure and dynamics. Devices employing such NMR technology require very high magnetic fields and, hence, very large magnets. However, the advent of small powerful magnets has allowed instruments - such as the Mageleka *M*agno*M*eter XRS™ - to be designed that are suited to normal, routine laboratory analysis.

The basic technique used in the *M*agno*M*eter is NMR relaxation. The relaxation time is a fundamental intrinsic property of solids and liquids and its measurement provides direct information about the extent and nature of any particle-liquid interface (i.e., suspensions and emulsions; see Mageleka Technical Note 1).

Importantly, the *M*agno*M*eter's measurement technique is non-invasive and non-destructive and the *M*agno*M*eter can work with suspensions at any industrially-relevant concentration. The simple measurements technique takes only minutes (see Mageleka Technical Note 2). Thus, the *M*agno*M*eter eliminates many of the problems inherent in making measurements of API dispersions.

What does the *M*agno*M*eter do?

The *M*agno*M*eter provides complementary information and intelligence to traditional particle characterization devices. As mentioned above, the basic measurement is a relaxation time which is directly proportional to the wetted surface area of the suspension or slurry. The calculation of a surface area value is quite straightforward. This is in contrast to the measurement of particle size by light scattering where the raw intensity data has to be deconvoluted by means of complex algorithms.

The actual relaxation value obtained by NMR is an average, and is dependent upon the exact composition of the suspension. This is somewhat analogous to the zeta potential of a material where the value depends critically upon the exact composition of the dispersion fluid.

Case Studies

In the following two case studies, we examine two different API drug materials and show how NMR relaxation measurements from the Mageleka *M*agno*M*eter can be used to achieve optimal bioavailability.

The first API is magestrol acetate, a synthetic derivative of the naturally occurring steroid hormone progesterone. The sample examined is an advanced formulation of the API prescribed as an appetite enhancer used by AIDS patients. It was supplied as a true "nanosuspension" in water at 12.5wt%.

The particle size distribution (PSD) measured using dynamic light scattering was found to be uniform, with a mean equivalent spherical diameter of 240 nm. Assuming that the particles are, indeed spherical, this would compute to a surface area of 18 m^2g^{-1}. However, the wetted surface area, measured directly by the *M*agno*M*eter using NMR relaxation, was found to be 38 m^2g^{-1} (Fig. 1 bottom). The discrepancy in surface area results between the two measurement techniques arises because surface area trends with the square of diameter. NMR relaxation time is more sensitive to the "fines" in any PSD (Fig. 1 top), so, in this application, the *M*agno*M*eter's measurements are superior to dynamic light scattering. And we can see that the NMR result would suggest a magestrol acetate particle size of a little over 100 nm (approximately the D_{10} of the current PSD) will provide superior bioavailability.

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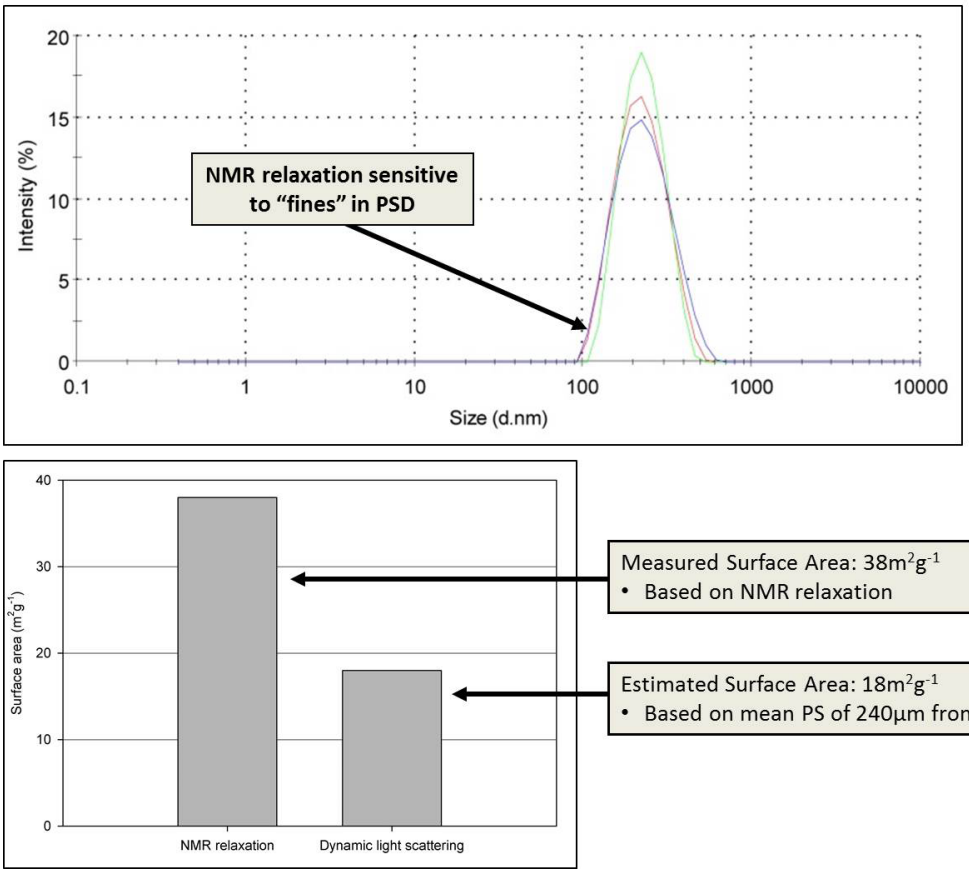

Figure 1. Top: Particle size distribution (PSD) of magestrol acetate. Bottom: Comparison of surface area of magestrol acetate particles measured directly by nuclear magnetic resonance (NMR) relaxation and estimated from mean particle size (PS) data derived from dynamic light scattering (DLS).

The second API is dapivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI) which is an antiretroviral drug originally developed for use in the treatment of AIDS. The material was prepared at 10wt% aqueous suspension. The API was initially produced as a dry powder with a particle size of ~300 μm but the material in question had been jet-milled to reduce the particle size to <10 μm.

The mean particle size measured using a static light scattering device was 2.4 μm and, again, assuming a spherical shape, gave a computed surface area of 2 m^2g^{-1}. However, the surface area measured using NMR relaxation was considerably larger at 24 m^2g^{-1} (Figure 2 bottom). This discrepancy can be easily explained by inspecting the PSD data. First, a micrograph of the particles clearly illustrates that the assumption of sphericity should be rejected (Fig. 2 inset). This highlights the fact that particle size measurements based solely on light scattering techniques can be misleading and lead to erroneous conclusions. Second, we can see that the suspension is, in fact, bimodal (Fig. 2 top) and, if we use the particle size of the smaller fraction, then the surface area values are in agreement. This finding is important because it shows that just 10% of the API accounts for 90% of the surface area and, hence, the bioavailability,

dissolution, and cytotoxicity. This again illustrates the limitation of using light scattering techniques for measurements of surface area in suspensions containing small or very small particles in the presence of large ones.

In both of the above case studies, the results also speak to the limitation of using a mean particle size value to calculate a surface area value. The total surface area of any suspension will always be dominated by the smaller size fractions in any PSD, and both examples show how NMR relaxation measurements, such as those from the *M*agno*M*eter, can provide unbiased surface area measurements in suspensions containing nanoparticles.

Also, if the particles in a suspension are unstable, and so have a tendency to aggregate over time, NMR relaxation measurements can detect this effect quickly because of the ensuing larger loss in surface area. The *M*agno*M*eter has a "Time Mode" specifically for this purpose: it allows for continuous monitoring of a slurry or suspension, providing virtually real-time measurements of surface area.

The speed and simplicity of NMR-based measurements with the *M*agno*M*eter make it an ideal tool for research and development and routine quality control purposes. To obtain meaningful data, traditional light scattering techniques require significant dilution of the sample and so there can be significant issues

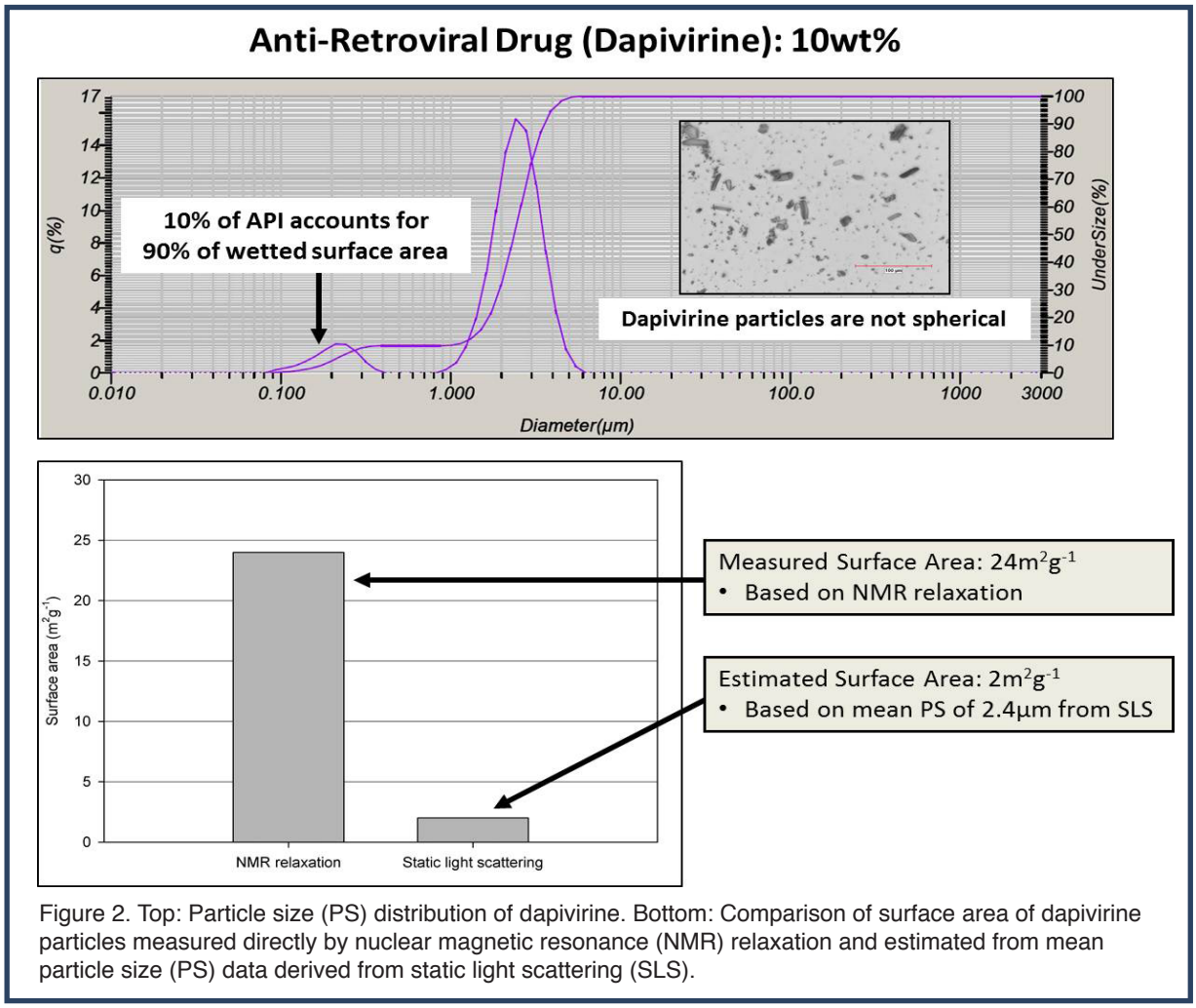

Figure 2. Top: Particle size (PS) distribution of dapivirine. Bottom: Comparison of surface area of dapivirine particles measured directly by nuclear magnetic resonance (NMR) relaxation and estimated from mean particle size (PS) data derived from static light scattering (SLS).

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associated with obtaining representative samples of the bulk material for analysis. The *M*agno*M*eter measures suspensions at any concentration, thus costly errors associated with obtaining representative sampling are eliminated.

Given the relevance of surface area to the bioavailablity of APIs, gaining a direct accurate measurement of the wetted surface area quickly, and without dilution or other sample preparation, provides major advantages to the pharmaceutical and healthcare industries. This metric is now available with the Mageleka *M*agno*M*eter XRS™.

For more information, to send samples, to arrange a demonstration of the MagnoMeter at your facility, or to talk to one of Mageleka's technical applications specialists, please email roger@mageleka.com

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