Mageleka

**White Paper 1**

# NMR Relaxation: Its Relevance to the Measurement of the Wetted Surface Area of Particulate Suspensions

## INTRODUCTION

The overwhelming majority of manufactured industrial products and increasingly those for health-care purposes involve suspensions of particulate materials dispersed often at high solids concentration. This can occur either in the final state or at some stage of their production. The importance of the process of dispersion and its profound effect on the economics and quality of the subsequent product has long been recognized (1, 2). Thorough characterization of particulate suspensions is, therefore, paramount in obtaining optimum performance features and cost effective benefits from such systems.

A fundamental parameter that controls the nature and behavior of every system in which one phase is dispersed in another phase is the *extent of the interface* of the disperse phase - in other words, the region where one phase interacts with the other. For solid-liquid suspensions, the simplest parameter describing this interface is the *wetted* surface area and, so, it is this metric which must be monitored and controlled. In addition, with the rapid move towards Quality by Design (QbD) (3) methodology in pharmaceuticals, mastery of such techniques is being legislated.

The advent of small, powerful permanent magnets has made possible the design of small, benchtop devices for characterization of particulate suspensions (4, 5). The Mageleka *M*agno*M*eter XRS™, a low field (*ca.* 13 MHz) nuclear magnetic resonance (NMR) spectrometer, is now available to measure the total wetted surface area of any materials suspended in any liquid (containing at least one hydrogen atom or other high-abundance NMR active nucleus). While the determination of surface area from NMR relaxation measurements is well-established (6), the availability of the *M*agno*M*eter now allows such measurements to be made quickly, easily, and for routine analysis in any laboratory (e.g., as an R&D or formulation tool) or plant (e.g., for QC/QA purposes).

## SURFACE AREA TECHNIQUES

### Measurement Using $^1$H NMR Relaxation

What relaxation measures is the extent of molecular motion as protons interact with their environment. In other words, the protons must interact with each other or with a substrate containing another NMR active nucleus. The relaxation process occurs when the system is perturbed by an external event such as placing the sample in a magnetic field. Importantly, liquids and solids behave differently in this regard. The principle of surface particle analysis via NMR relaxation relies on an assumption that the liquid in contact with the particle surface relaxes much more rapidly than does the rest of the liquid, which is free (i.e., "bulk" liquid). For spin-spin relaxation (see below) this is typically of the order of microseconds, compared with the NMR relaxation time for the bulk liquid (i.e., in the absence of particles), which can be of the order of seconds (Fig. 1).

For many dispersions of interest we can assume that the dynamic exchange between the liquid associated with the particle surface and the bulk liquid is very rapid  (i.e., a "fast exchange"). Since it is the *difference* between the bulk and surface liquid relaxation times that determines the amount of available wetted surface area, the shorter the measured surface relaxation time, the more precise will be the estimate of wetted surface area.

For those familiar with NMR, we can utilize either the $T_1$ (spin-lattice) or the $T_2$ (spin-spin) measurement of relaxation time to determine a

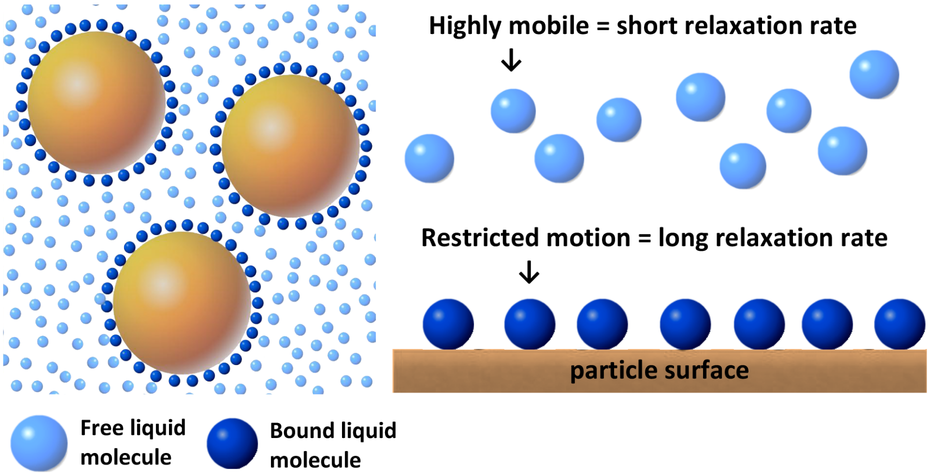


Figure 1: Schematic of bound and free liquid molecules and their relationships with NMR relaxation time. The relaxation rate is the inverse of the relaxation time.

relaxation rate constant, $R$ (defined as $1/T$; i.e., the inverse of the relaxation time), from which the wetted surface area is calculated (see below). In principle, both parameters, $R_1$ and $R_2$ (so-named for being derived from $T_1$ and $T_2$, respectively), demonstrate an increase in relaxation rate with increasing particle surface area. A dispersion of particles in a liquid with a large wetted surface area will have a longer relaxation rate than a dispersion with a small wetted surface area sample because there will be more fluid associated with the particle surface. Although both $R_1$ and $R_2$ depend on the rotation and translation motions of molecules (7), the magnitude of the shift is not necessarily the same.

Experimentally, we typically observe a greater change in $R_2$ compared with $R_1$ for the same incremental change in surface area because of the different way the two processes are linked to molecular motion. In either case, as long as the surface and bulk liquids are in what is termed *fast exchange* (see above), the observed single relaxation rate, $R_{av}$, is computed as an average of the relaxation rates of the surface, $R_s$, and bulk liquid, $R_b$, weighted by their respective volume fractions (equation 1).

$$R_{av} = p_s R_{ns} + p_b R_{nb} \tag{1}$$

Where, $p_s$ is the fraction of liquid at the surface, $p_b$ is the fraction of liquid in the bulk phase, n=1 for spin-lattice relaxation ($T_1$ method), and n=2 for spin-spin (or spin-echo) relaxation ($T_2$ method).

Further, the relaxation rate increases with increasing concentration (Fig. 2). So, in general, the higher the solids loading (i.e., more solids particles in suspension), the greater is the measurement precision. And, since a vast number of industrially useful suspensions are manufactured or used as concentrates, NMR measurements can prove very beneficial because they can be made using suspensions as they are prepared (i.e., no need for dilution).

However, the magnitude of the effect depends very much on the specific material under investigation (8). Figure 3 illustrates the $T_2$ relaxation rate ($R_{2sp}$) behavior of three different aqueous colloidal dispersions. Note that the use of the $T_2$ method is denoted by the subscript “2” of $R_{2sp}$.

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

It can be seen that the relaxation rate for polystyrene is very small (i.e., the relaxation time is long) because it possesses, functionally, the most hydrophobic surface. At the extreme, a completely hydrophobic matrial would not be wetted by liquid and hence,

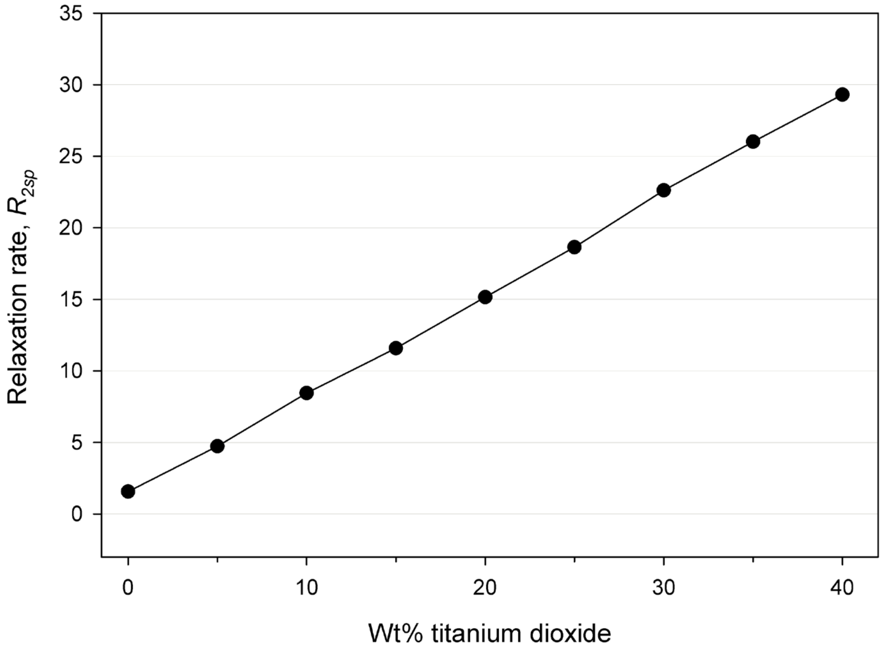


Figure 2: NMR relaxation as a function of suspension concentration of a pigmentary grade of titanium dioxide.

experimentally, there will be a minimal response. For materials like polystyrene, a higher solids concentration would typically be needed (compared to, e.g., silica of the same particle size) to get the same precision and reproducibility of NMR relaxation data.

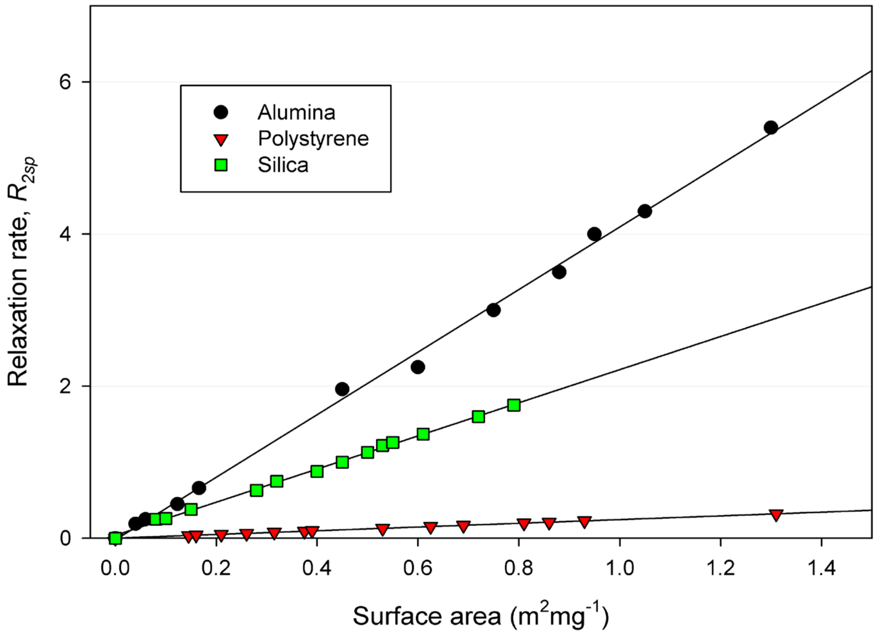


Figure 3: NMR relaxation for different colloidal dispersions.

## Calculation of the Wetted Surface Area from NMR Relaxation Data

In contrast to measurement of particle size, for example, by dynamic light scattering (DLS) or light diffraction (LD), where the raw scattered/diffracted intensity data has to be deconvoluted by means of complex algorithms (9), the NMR relaxation time can be converted into the surface area by means of a straightforward calculation (3):

$$R_{av} = \psi_p \, S \, L \, \rho_p \, (R_s - R_b) + R_b \qquad (2)$$

where $R_{av}$ is the average spin relaxation rate constant, ψp 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, $\rho_p$ is the bulk particle density, $R_s$ is the relaxation rate constant for the bound liquid, and $R_b$ is the relaxation rate constant for the free or bulk liquid.

Using a standard reference material we can define a constant (called the specific surface relaxivity), $k_A$, (= $L \, \rho_p \, [R_s - R_b]$), such that the equation (2) reduces to:

$$R_{av} = k_A \; S \, \psi_p + R_b \qquad (3)$$

Both $R_{av}$ and $R_b$ must be determined experimentally. The $k_A$ parameter is discussed in more detail below.

The wetted surface area, *SA*, can then be calculated from:

$$SA \; = \; R_{sp} \, R_b / \, k_A \, \psi_p \qquad (4)$$

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

Ideally, robust method development should include measurements at a few differing particle concentrations. In other words, plot the relative averaged relaxation rate, $R_{sp}$, as a function of different volume ratios of particle to liquid, $\psi_p$. Using the slope of the plot minimizes errors that might occur with a single point measurement. Further, linearity in the plot would confirm that the assumption regarding fast exchange between the surface and bulk protons applies and, also, that there are no concentration-dependent secondary phenomena that would systematically alter the relaxation data (e.g., particle aggregation/settling and impurities). This is illustrated in Figure 4 for a sample of precipitated calcium carbonate.

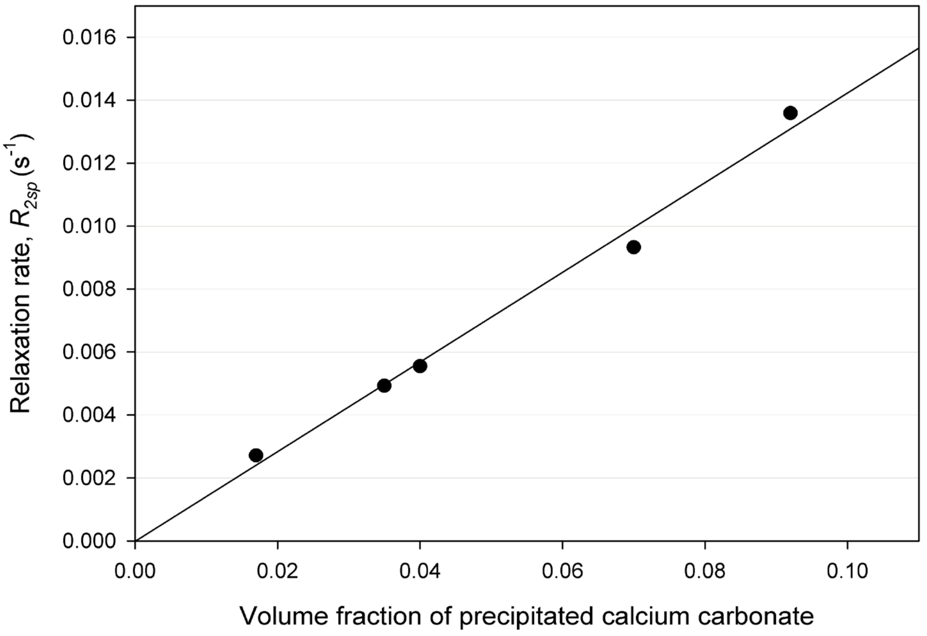


Figure 4: Plot of $R_{2sp}$ vs. volume fraction for a precipitated calcium carbonate.

In the example shown in Figure 4, the initial concentration of the precipitated calcium carbonate was approximately 20 wt%. Dilutions were made using the dispersion liquid (obtained by sedimentation and gentle centrifugation) in order to maintain chemical equilibrium between the solid and solution. The linearity of the response as a function of serial dilution (to ca. 4 wt%) demonstrates the validity of the fast exchange limit. Also using the same liquid to dilute the dispersion ensures that the line in Figure 4 goes through the origin.

In order to calculate a value for the wetted surface area in this case, it is assumed that the particles are non-porous solid materials. Thus, we can use the "planar" assumption, i.e., that the liquid molecules "pack" the surface in a planar sheet as illustrated in Figure 5. This is identical to the same assumption used in the determination of the surface area of dry powders by gas adsorption (e.g., the $N_2$/BET method(9).

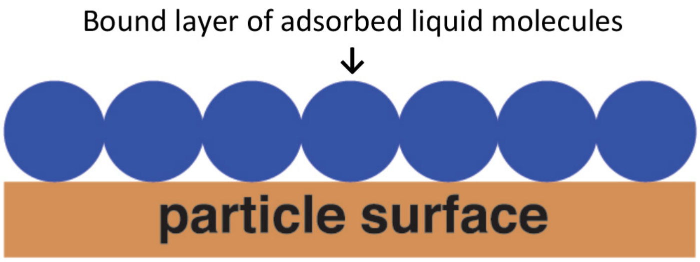


Figure 5: Schematic of adsorbed monolayer of liquid molecules on a solid surface.

**Comparison of Surface Area Values from $N_2$ Gas Adsorption and NMR Relaxation**

The most common method of particle surface area determination is Brunauer-Emmett-Teller (BET) nitrogen ($N_2$) gas adsorption. This technique requires the material under test to be a dry powder (10) and thus wet suspensions must be dried. However, drying wet suspensions inevitably results in unintentional (and unwanted) aggregates and agglomerates. As a consequence, the subsequent surface area results will be skewed. Indeed, it has long been accepted that any procedure which requires a dry sample (such as BET or Knudsen flow of a gas at low pressure) may give a surface area value that, for all its accuracy, has little relation to the effective area in solution (11).

Thus, it is important to recognize that *wetted* surface area values from NMR relaxation measurements can be quite different from those obtained by BET-$N_2$ gas adsorption data. There are three reasons for this.

First, $N_2$ is fairly agnostic in terms of its ability to adsorb at a surface (whether porous or non-porous). The adsorption of water ($H_2O$) vapor onto surfaces is, however, complex (12) and, in the literature, comparisons between BET-$H_2O$ and BET-$N_2$ surface areas present a very confused picture; in many cases the BET-$H_2O$ data shows considerably higher surface area values because of multilayer formation and also, in porous materials, capillary condensation can occur. This is all because there is a high degree of specificity in the interactions of water with solid surfaces (13). Hence, a *wetted* surface area depends critically on not just the morphology of a particle but also its surface chemistry.

Second, a critical experimental requirement of the BET method is that the sample initially has to be degassed to drive off any adsorbed material ("sample conditioning"). This neccesitates proper, constant maintenance of sample temperature (14) under liquid $N_2$ conditions while at the same time maintaining the sample under vacuum. This whole process can take hours. In contrast, the *M*agno*M*eter's NMR approach measures suspensions directly and as they are prepared, requiring no sample pretreatment or extreme temperature control. It is, inherently, a much simpler measurement technique and, further, measurements require as little as 0.1 mL of sample and can be made in a few minutes.

Finally, and importantly, the "total" amount of wetted surface area depends not only on the amount of physical external surface presented but also on the physico-chemical nature of the particle-liquid interface (i.e., surface chemistry).

*Porosity*

It is known that porosity has an impact on relaxation (15). The pore diameter must be large enough such that liquid molecules can penetrate and allow for fast exchange with the bulk. The matter is compounded when pores do not have a uniform cross-section or surface chemistry (16). This matter will not be discussed further but will be the subject of a future White Paper.

**Particle Size and Surface Area**

In principle, a surface area value can be calculated from particle size data. There are a variety of techniques that can give an approximate particle size distribution (PSD) by fitting experimental data to functional forms for the distribution (e.g., log-normal, Gaussian, etc.) (17). Unfortunately, the PSD of many materials are broad and irregular, which raises a number of questions.

The first question is "Which is the most appropriate single value of particle size value to be used to calculate the surface area?" Three common descriptors, when describing the PSD, are the mean, mode and median ($d_{50}$), and values of these can differ markedly as the PSD broadens. The *mean* (also known as the *average*) is the value that most people are familiar with, where you add up a set of numbers and then divide by the number of numbers in the set. The *median* is the "middle" value in the set of numbers. Finally, the *mode* is the value in the set that occurs most frequently. Also, commonly used metrics in particle sizing are the "d" values - $d_{10}$, $d_{50}$ and $d_{90}$ - which are the intercepts for 10%, 50% and 90% of the cumulative mass. For example, the $d_{10}$ is the diameter at which 10% of the sample's mass is comprised of particles with a diameter less than this value. The $d_{50}$ is, therefore the median size of a PSD.

Figure 6 shows the PSD for a sample of an aqueous suspension of a microfine grade of titanium dioxide ($TiO_2$) measured using an X-ray disc centrifugation device (18). It can be seen that the particle size is fairly uniformly distributed about the modal value (70 nm) where the majority of the particles reside, but the suspension contains a "tail" of agglomerates that skews the mean and median sizes. Table 1 lists the surface area values calculated from the three sizes and they are noticeably different.

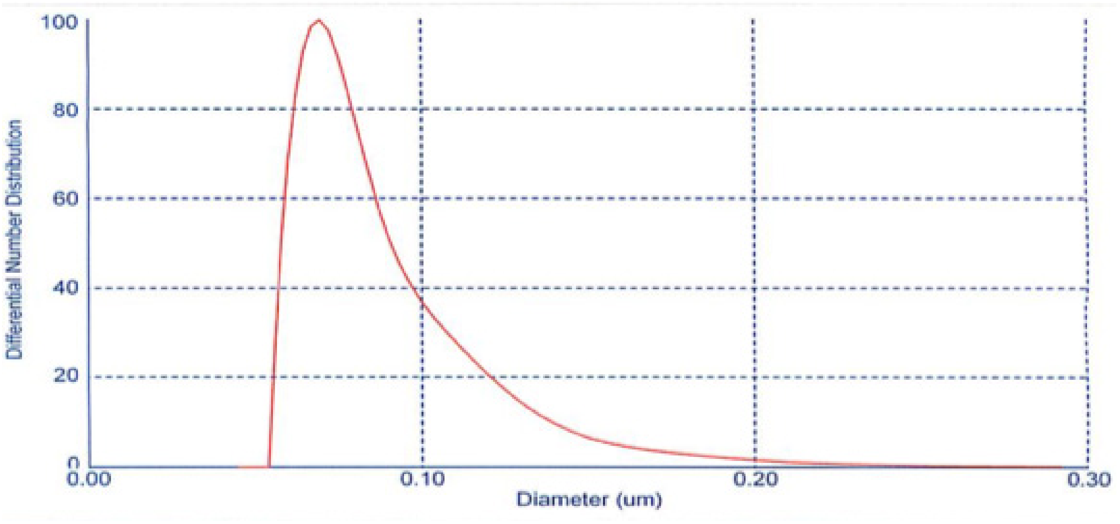


Figure 6: Particle size distribution of a 2 vol% aqueous suspension of a microfine grade of titanium dioxide.

Empirically, we have found for suspensions that a surface area value calculated from the $d_{10}$ of the volume-weighted PSD often gives more reasonable agreement with *wetted* surface area obtained from NMR relaxation. In the $TiO_2$ example, this would result in a calculated value of 29 $m^2/g$ compared with a value of 16 $m^2/g$ based on the mean size – a difference of almost double the surface area. Because surface area is proportional to the square of the particle diameter it is clear that NMR relaxation is much more sensitive to the presence of both primary particles as well as "fines" in any suspension. Fines are typically defined as the portion of particles smaller than some arbitrarily determined size limit, which varies from industry to industry (e.g., in soil science the limit would be a no. 200 sieve).

Table 1: Surface area values derived from particle size distribution data differ based on which measure of particle size is used in the calculations. Values shown are for a microfine grade titanium dioxide (data plotted in Figure 6).

| Measure | Particle size (nm) | Surface area ($m^2/g$) |
|---|---|---|
| Mean | 91 | 16 |
| Median ($d_{50}$) | 82 | 18 |
| Mode | 70 | 21 |
| $d_{10}$ | 55 | 29 |

The PSD in the example above is broad and unimodal. However, consider now a bimodal, volume-weighted, distribution determined using a non-imaging, ensemble averaging device, such as Fraunhofer Diffraction (FD) or DLS (Figure 7a). There is no way to determine if the two modes arise from singlet particles plus a second fraction comprising agglomerates of those particles (Fig. 7b), or a simple mixture of two different fractions of singlet particles each of a different size (Fig. 7c). It is obvious that a suspension of each will have a completely different wetted surface area.

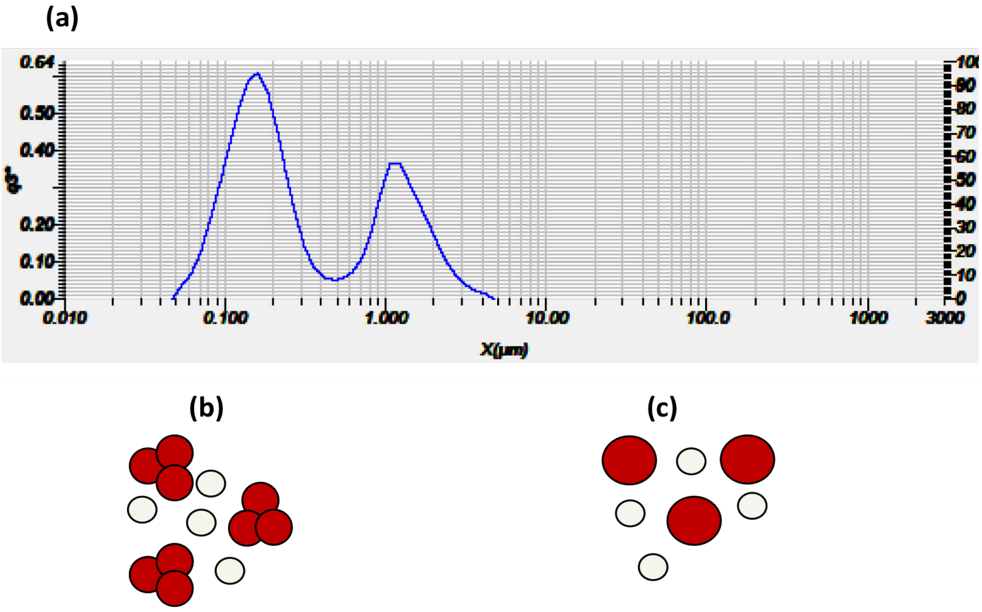
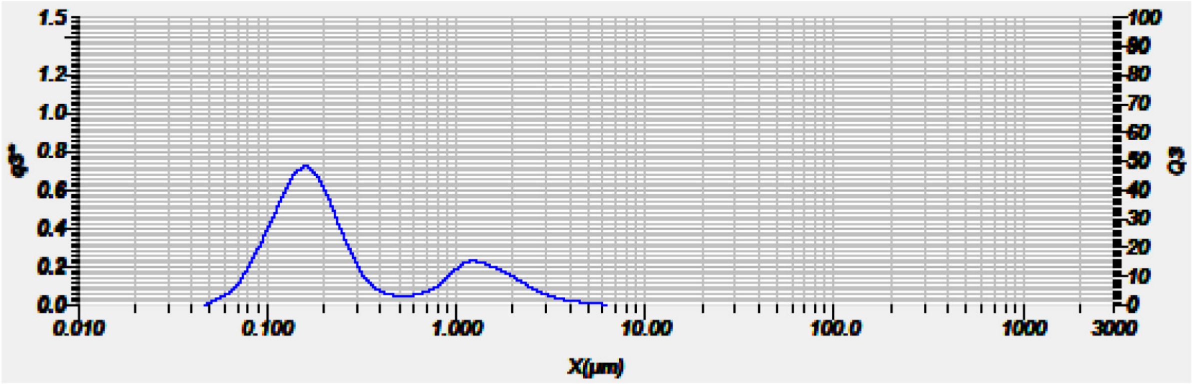


Figure 7: (a) A bi-modal, differential, volume-weighted particle size distribution, and (b and c) illustrations of two possible scenarios that could lead to such a distribution.

Further, a major, often overlooked, complication in light scattering devices is that for materials whose particle size is <1 µm, the Refractive Index (RI) of the material (both the real and imaginary parts) and the RI of the medium are all needed for accurate results when making the necessary (Mie) light scattering corrections (9).

While it should be common practice in light scattering analysis to check if the RIs of the material and medium are accurate, *what happens if those values are not actually correct*? The effect is illustrated in Figures 8a and 8b. With most commercial instruments, the typical default RI settings are for *polystyrene in pure water* because "monodisperse" colloidal suspensions of polystyrene latices are used to validate the device. Figure 8a shows a PSD determined for an aqueous active pharmaceutical ingredient (API) suspension using those assumed values. However, the API in question was colored (yellow) and, moreover, the suspending liquid contained surfactants and polymers. In other words, it was not pure water. Figure 8b, in contrast, shows the PSD using the correct RI values. Note the dramatic shift in shape of the PSD. The differences in the particle size data are summarized in Table 2, together with the wide range of surface area values calculated (using the API density of 1.35 g/cc) from the different sizes.

a) Particle RI: Real 1.59, Imaginary 0.01; Liquid RI: 1.33



(b) Particle RI: Real 1.50, Imaginary 0.10; Liquid RI: 1.38

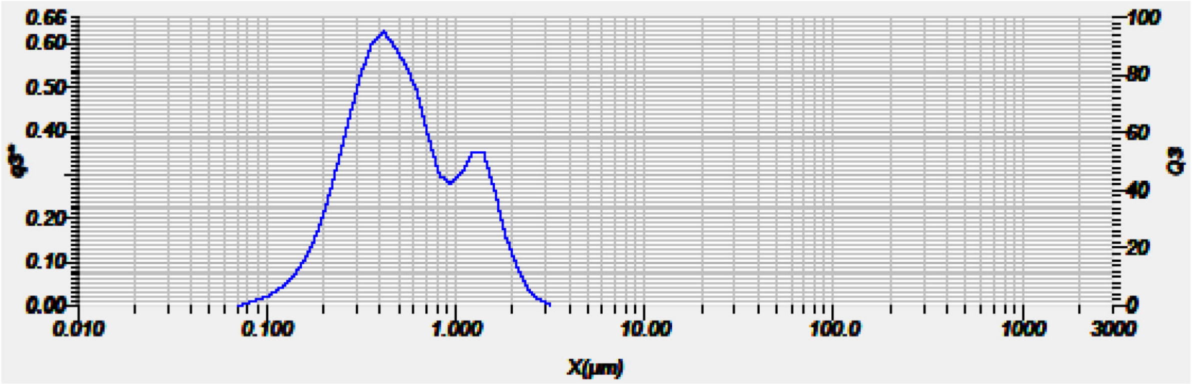


Figure 8a and b: Effect of variation in refractive index (RI) on a particle size distribution from a light scattering device.

Table 2: Summary of particle size data from Figure 8.

| Measure | Particle size (μm) | | Calculated surface areas ($m^2/ g^{-1}$) | |
|---|---|---|---|---|
| Mean | 0.53 | 0.67 | 8.4 | 6.6 |
| Median | 0.16 | 0.50 | 27.8 | 8.9 |
| Mode | 0.19/1.45 | 0.42/1.45 | 23.4/3.1 | 10.6/3.1 |

An additional and critical complication is that many real-world particles (especially crystalline materials) are far from round or uniform. However, all non-imaging techniques (such as light scattering devices) determine an *equivalent spherical diameter* (ESD) – the diameter of a sphere that would give the same result as the actual particle – that may not correlate with any single dimension of the particle. Different techniques can yield very different ESDs for the same particle; the more asymmetric the particle, the bigger can be the difference in ESD (19). Figure 9 is micrograph of an API where it is clear that the particle shapes are random and irregular.

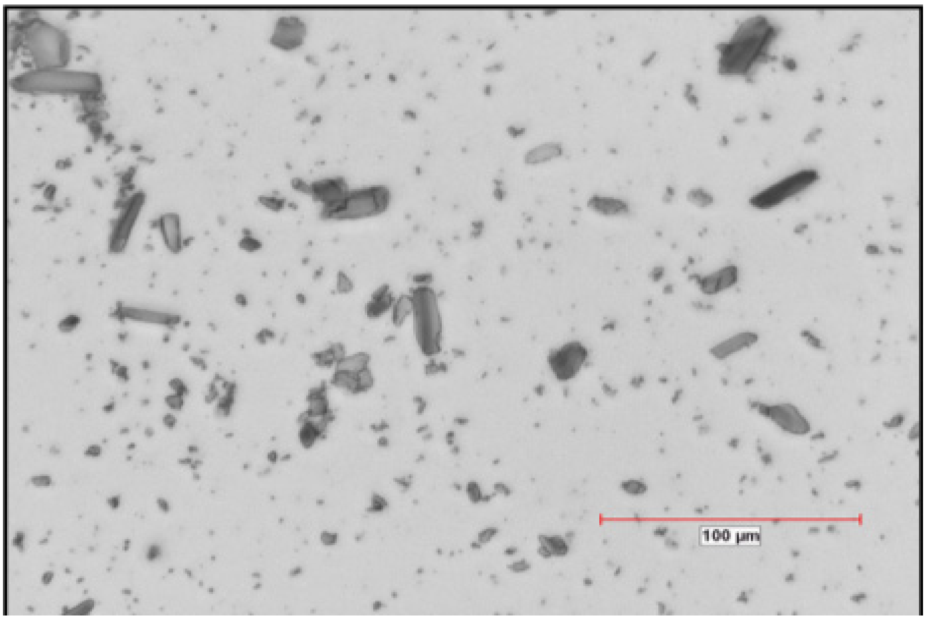


Figure 9: Micrograph of a typical active pharmaceutical ingredient.

Another important consideration is that even spherical particles may not be completely smooth. In the schematic presented in Figure 10, although the diameters are the same for the three particles, the wetted surface area will be completely different. In reality, materials can consist of particles that fall somewhere along a continuum from smooth to porous and, as stated above, will vary from actually spherical to far from it.

Figure 10: Effect of morphology on total wetted surface area of spherical particles.

Determination of a correct value for wetted surface area of, for example, an API is vitally important because it is known that API surface area directly impacts not only bioavailability but also the rate of dissolution, as described by the Noyes-Whitney equation (20). And, critically, there is also a growing body of evidence that, for any type of nanoparticle, it is the surface area and not particle size that is the defining metric that controls toxicological interaction (21-24). For the pharmaceutical and health care industries, details of particle size and morphology have obvious implications for product efficacy, patient outcomes, and the economics of production.

*About Optical Microscopy*

Microscopy is considered a primary technique for particle size analysis, and it is used in conjunction with image analysis for size and shape distributions. However, while normal visual microscopy (and any associated image analysis technique) can easily distinguish between a mixture of two separate modes and agglomerates, unfortunately, it is only applicable to sizes >500 nm. The presence of any smaller sizes will be completely missed because they are not detectable, and so the analyst might erroneously assume 100% of the material's particle sizes have been measured. It is also often overlooked that image analysis requires calibration.

Microscopy also has other limitations. The more irregular a particle, the greater the possibility of surface details being obscured. The orientation of an irregular particle at rest and the resultant projected image can significantly influence the calculated diameter (25). Typically, an estimate of the approximate "size range" is made based on "rod length" or "maximum length". However, because the technique is subjective, preparing the sample by drying the suspension can result in unintentional (and unwanted) aggregation that can skew the data.

Importantly, consider Figure 11, which shows a schematic of what is typically seen in a micrograph of particles. In this simple example, there are some primary particles as well as aggregates and agglomerates of the primary particle. A classic example of this would be for a carbon black. When counting the number of "particles" there are two possible outcomes that are dependent upon the subjective view of the operator: (a) an estimate of PSD based upon all the particles, including aggregates and agglomerates, being counted as "singlets" and (b) a PSD comprising primary particles plus aggregates plus agglomerates. Both estimates are valid unless it is known beforehand that the original suspension was monodisperse. Further, when sizing irregularly shaped particles, automated image analysis software often provides only an *equivalent circular diameter* (26).

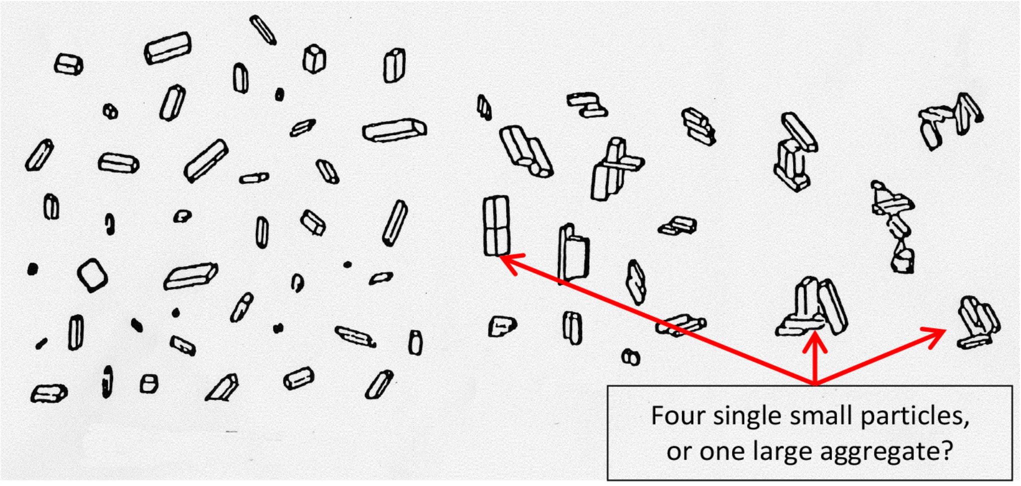


Figure 11: Schematic of a micrograph showing the size nature of particles.

Thus, any surface area value calculated for such materials is, at best, only a crude approximation. Indeed, it is recognized that particle shape, surface irregularities and, further, porosity will inevitably lead to estimated values that vary significantly from the true value (19) and can, therefore lead to misleading or erroneous deductions.

In contrast, when calculating wetted surface area values from NMR relaxation data, there are no assumptions made regarding either particle size or shape. Hence, when reviewing the results of wetted surface area measurements of particulate suspensions, it has to be recognized that the values obtained from NMR relaxation may not necessarily always be consistent (or even trend) with surface area values calculated from simple particle size data – and that data obtained from NMR relaxation may, in fact, be more relevant.

## Titration Methods

In general, (wet) titration methods are non-routine and time consuming; additionally, they may require specific adsorbates. Moreover, it is generally accepted that, in determination of surface area, the results from any secondary method (i.e., one not based on first principles), must be treated with caution (27). This section introduces three such methods and discusses the reasoning behind this conclusion.

### *Surface Area from Colloid Potentiometric Titration*

Potentiometric titration of colloidal dispersions is well established for the determination of the *point-of-zero charge of oxides* (28). However, determination of a *surface area* of a colloidal suspension from such methods is an empirical exercise. The colloid in question is titrated with either acid or base, and the change in pH monitored. This can then be related to the total number of titratable surface hydroxyl (OH) groups. Unfortunately, the pH titration method then requires standardization typically using a BET surface area value - obtained from $N_2$ gas adsorption on a *dried* powder sample – in order to estimate the area occupied by a surface hydroxyl group. Further, and of critical importance in any potentiometric titration, is the assumption that the surface potential is given by the Nernst equation. Unfortunately, the equation is not valid for any colloidal oxide-solution interface (29). It is also assumed there is no specific adsorption of any of the ions present and also no chemical alteration of the solid (no impurities). Thus, while useful in certain contexts, potentiometric titration is far too restrictive (and time consuming) for routine determination of surface area of colloidal dispersions.

### *Sears Number*

The Sears Number (S-number) is often used as a measure of the specific surface area of silica (and, sometimes, other metal oxide) suspensions. It is based on a pH titration method that essentially provides the total concentration of hydroxyl groups (30), from which the material surface area is then deduced.

In contrast with NMR wetted surface area measurement, the S-number methodology results in fairly insensitive data. This should not be surprising given the assumptions used in the determination of, and the number of experimental measurements (and calculations) needed to obtain a value for, the S-number.

First, as mentioned above, the pH titration method requires standardization. Second, the sensitivity of the S-number to surface area depends on the accuracy of measuring the difference between the mass of dry silica (obtained from the dried weight of the dispersion) and the total mass of the silica and bound water. Third, this latter value is obtained from the volume fraction that is, in turn, calculated from a viscosity measurement, typically using the Mooney Equation which is, itself, based on a number of assumptions (31), *viz* (i) the particles have to be non-porous, (ii) the suspension must contain no aggregates and (iii) charge (electro-viscous) effects are minimized. For the titration itself, the pH of the silica suspensions is initially reduced to a pH of 2. This is close to the *iso-electric point* of silicon dioxide (32) meaning that the particles will have little, or no, charge stabilization against possible aggregation.

Fourth, generally, a Brookfield-type device is used to measure viscosity. In spite of their widespread use, with particulate suspensions (and especially concentrates) rotational viscometers provide non-viscometric flow and non-zero shear conditions with, often, no temperature control. Such conditions can render the data obtained virtually unusable. Fifth, conversion of the S-number to a surface area value requires knowing the thickness of the bound water layer, the calculation of which is model dependent, unless some completely independent method (such as neutron scattering!) is available. It has been estimated (33, 34) that there is approximately one bound layer of water at the surface of silica. The calculation assumes that two bound water molecules are present per reacted water molecule (condensed as surface hydroxyls). Since this is an oversimplification, it is usual to use a “calibration” curve.

Clearly, calculating surface area using the S-number methodology is far from ideal.
From a theoretical perspective, the number of assumptions underlying surface area data generated from the S-number make it unreliable for many particulate suspensions and, from a practical perspective, the number of steps required to generate such data makes it overly laborious.

### *Adsorption from Solution*

In theory, solution adsorption seems to offer a versatile method that can be used for the determination of specific surface area of porous and non-porous solids. A variety of adsorbents have been employed, from dye molecules to surfactant ions and polymers. For example, cetyl trimethyl ammonium bromide, a quaternary amine that is cationic (i.e., positively charged) in aqueous solution, has been used to determine the surface area of silica particles (35) and iodine (from potassium iodide solution) has been used with carbon black particles (36).

Although the experimental measurement of adsorption from solution is relatively straightforward, unfortunately a variety of factors often make the interpretation of the experimental data more complicated than with gas adsorption (27). It is assumed that the adsorption of one component (the solvent) is negligible compared to that of the other (the solute), and so the choice of solvent is, therefore, a critical factor. Additionally, the true site area of the adsorbed solute molecule is uncertain, the possibility of solvation of the adsorbed species is usually not taken into account, the reversibility of adsorption is rarely tested, and the exact orientation of the adsorbed molecules is nearly always in some doubt. The result is that repeatability and reliability can be problematic.

### *In Conclusion*

Hence, it is worth reemphasizing that when determining surface area the results from any secondary method (i.e., one not based on first principles), including the titration techniques discussed above, must be treated with caution (27). It is usually necessary to calibrate the method by the determination of the specific surface of a representative sample by means of a more reliable method such as gas adsorption.

### The Specific Surface Relaxivity Parameter, $k_A$

Although the NMR relaxation method is independent of the particle size distribution and shape of a material, the calculation of an absolute value for the wetted surface area requires knowing a value for the specific surface relaxivity, $k_A$. Essentially, this parameter characterizes the relaxation time shift per unit area for a given particle-liquid combination in the following way:

$$SA = R_{sp} R_b / k_A \psi_p$$

and so, $$R_{sp} = SA\, k_A\, \psi_p / R_b$$

Determination of $k_A$ necessitates a *reference material*, which is a particle of known surface area dispersed in the test liquid. The $k_A$ parameter can be considered analogous to the RI required in a laser light scattering device to calculate the correct PSD, in the sense that it depends on the combination of the particle and liquid. So, a $k_A$ for silica in water will be different from the $k_A$ for the same silica in ethanol.

When monitoring changes in particle surface area for a given particle-liquid combination (e.g., in milling), the differences in relaxation rate are absolute and so determination of a specific value for $k_A$ is not necessary. This is somewhat analogous to the situation with the measurement of the *zeta potential*. The zeta potential is a mathematical concept that is related in a non-linear way to particle surface charge. The calculation of an absolute zeta potential value involves a complex algorithm that requires input of the exact composition of suspension liquid as well as the particle size. A single value of the zeta potential has little practical use. However, relative changes in the zeta potential of a suspension as a function of some chemical additive are absolute and, hence, are widely used to monitor any changes in surface chemistry that occur (28).

### *Measuring Nanoparticulates*

When NMR relaxation is used to measure *nanoparticulate* dispersions (<100nm), two effects have to be taken into account that impact the value assumed for $k_A$: (i) the relaxation and translation/rotation of the particles and (ii) the dependence of effective volume of the surface zone upon particle radius. The volume, $V_{curve}$, of a monolayer shell with thickness, $\delta$, on a sphere of radius, $a$, is given by:

$$V_{curve} = 4/3\, \pi\, [(a + \delta)^3 - a^3]$$

Hence the relative volume of the surface film will depend on curvature unless $\delta << a$.

Figure 12 illustrates the effect of curvature (particle size) on the derivative of $R_{2sp}$ with surface area plotted against particle size. The form of the plot is similar for all materials, however, the scale for $k_A$ will vary. As can be seen, the effects become especially important when the particle radius is less than about 80 nm.

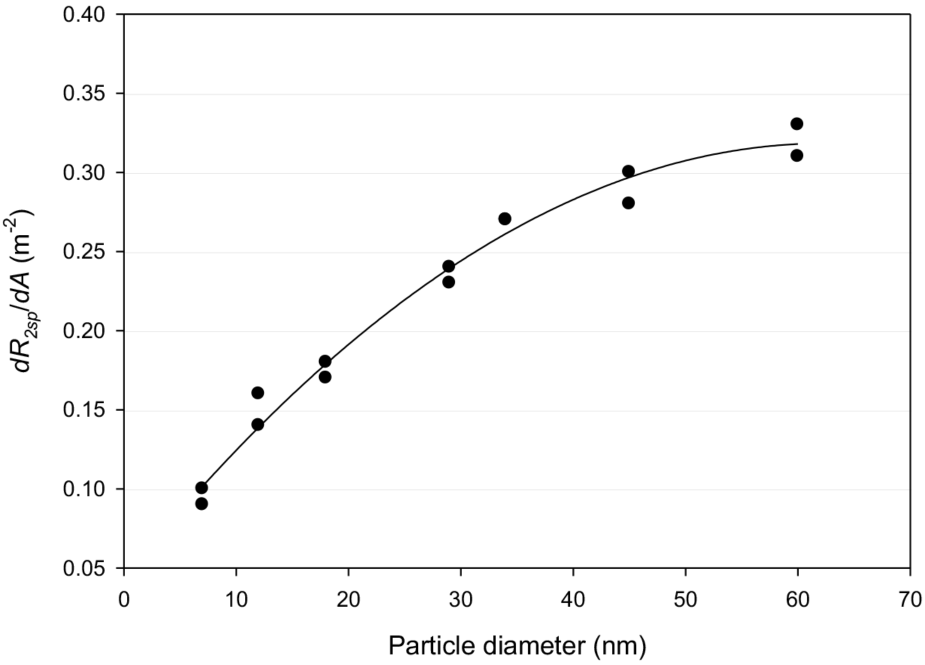


Figure 12: Particle size dependence of the kA factor. The points are experimental data values for a series of colloidal silica, and the solid line is the theoretical plot.

## The Influence of Surface Chemistry

While it is possible to manufacture a material (such as a metal oxide) with a fairly consistent particle size distribution, the resultant surface chemistry may be quite variable. The actual value can be influenced, for example, by the material's source or preparation method, pre-treatment, and presence of trace impurities (37, 38). Thus, it should not be assumed that different lots or batches of the same material will necessarily have the same surface chemistry. Indeed, when comparing "similar" materials from different suppliers, it is more than likely that they will not have equivalent surface chemical behavior (39).

Silicas, for example, are used extensively in a wide variety of applications. The surface chemistry of silica (as with all metal oxides) can be complicated because of anisotrophy (n and p defects in the crystal structure) resulting in amphoteric hydroxyl groups (40). Depending on how it is has been manufactured (synthetic) or processed (natural), the surface properties range from strongly hydrophilic, showing zero contact angle and a thick equilibrium wetted film because of the surface silanol (-SiOH) groups, to strongly hydrophobic, where the surface siloxane groups, -Si-O-Si-, have ether-like properties. In many real-world silica materials, the surface of the particles generally comprises both silanol and siloxane functionalities, and there can additionally be three different types of silanol groups (shown schematically in Figures 13a and b).

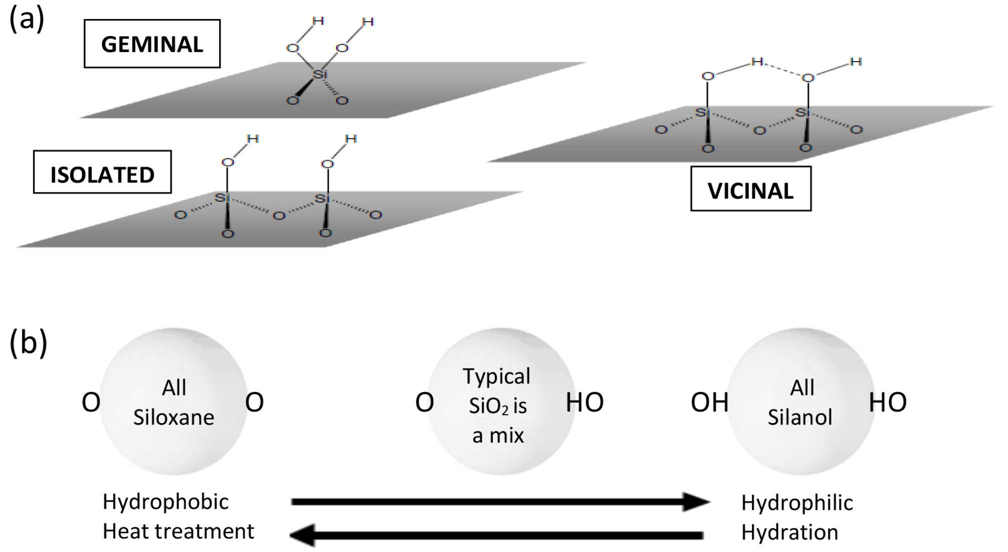


Figure 13: (a) The different types of silanol groups on a silicon dioxide ($SiO_2$) surface, and (b) the possible different types of silica surface chemistry.

Drying, heat treatment, or hydration can alter the surface chemistry of oxides. Thus, in the preparation of dispersions there may be time-dependent effects. And, depending on the nature, type, and distribution of the surface silanol/siloxane groups, water and other liquids will bind differently. It will also impact the adorption of surfactants and polymers.

Because NMR relaxation is known to be a very sensitive probe of liquid mobility in a local environment (41), it can be used to characterize the strength of interaction between water (or other liquids or additives) and particle surface functional groups (42). Hence, NMR relaxation measurements can be very useful in helping understand the *chemical equilibrium* at the particle-liquid interface.

The oxides of most di- and trivalent metals (e.g., MgO and $Al_2O_3$, respectively) are also amphoteric and any dissolution tends to be in the form of the hydroxide. Swings in solution pH must be avoided because it can cause re-precipitation back onto the oxide surface in a different chemical form, thus altering the surface chemistry. If possible with these materials, NMR measurements should be made with solutions at constant pH and between pH 4 and pH 10.

Work on alumina and silica slurries used in chemical mechanical polishing applications (43) suggests that relaxation measurements can be correlated with the number of hydroxyl groups on a metal oxide surface: a sample with a richer content of hydroxyl groups should possess a shorter relaxation time.

The $R_2$ relaxation rate can be more sensitive to the presence of elemental impurities (44), especially ferromagnetic (e.g., Fe) and paramagnetic species (e.g., Al, Co, Cu, Mn). Motion is restricted and this is manifest in a greater increase in the $R_2$ relaxation rate of a suspension compared with $R_1$ (45). Hence, there is a different value of $k_A$ for $R_2$ and $R_1$ measurements. Thus, if materials contain different amounts of impurities (e.g., silicas can contain both Fe and Al as impurities), and if these atoms are at or near the particle surface, this will result in a larger shift in relaxation time resulting in an apparent increase in calculated surface area. Note that this will necessarily then impact the value of $k_A$. Thus, the assumption of a constant $k_A$ value may not always be appropriate, and each class of material may need a unique $k_A$.

Another group of widely-used materials are clays. NMR measurements of alumino-silicate clay materials (e.g. montmorillonite and vermiculite) can be problematic because of the diverse crystal chemistry that gives rise to quite varied morphology and surface chemistry (46). This arises from the difference in valence between the $Al^{3+}$ and the $Si^{4+}$ ions in the alumino-silicate crystal structure, together with isomorphous substitution with varying proportions of minor elements (47). The exact characteristics depend critically on the clay's prehistory and so care must be taken when comparing data on clays from different sources.

Because surface chemical effects can be important, in such cases the total wetted surface area determined by NMR relaxation may be significantly different not only from estimates from particle size data, but also from colloid titration (potentiometric) and solution adsorption methods. That being said, NMR relaxation is the most consistent and versatile of these methods, and is especially preferred when working with concentrated suspensions of irregular-shaped materials. Further, the techniques can be used to study surface effects and changes during, for example, processing.

### Wetting of Particle Surfaces

The affinity of a liquid for a surface is described as *wetting*, and liquids are affected to different extents by the chemical and morphological nature of particle surfaces (e.g., surface chemistry and roughness). The smaller the contact angle of a liquid for a solid surface, the greater the wetting (48). Hence, it is often instructive to measure the relaxation time of particles suspended in an homologous series of liquids (such as alkanols or alkanes) that have different contact angles for a given material surface.

A knowledge of powder wetting is important. It is crucial to understanding dispersibility and it impacts industrial processes/applications – cleaning, coating, printing, paints, textiles, etc. – but there are few reliable measurement techniques. Contact angle measurements are only useful for flat, planar surfaces, and interfacial tension measurements are applicable only to liquids. By contrast, NMR relaxation measurements can provide information about powder wetting for any solid-liquid combination.

Figure 14 illustrates how the choice of wetting liquid affects the relaxation rate for a series of porous silica particles (ranging in surface area up to 300 m²/g and with pore size from 7-35nm). Note that the use of the $T_1$ method in this example is denoted by the subscript "1" of $R_{1sp}$.

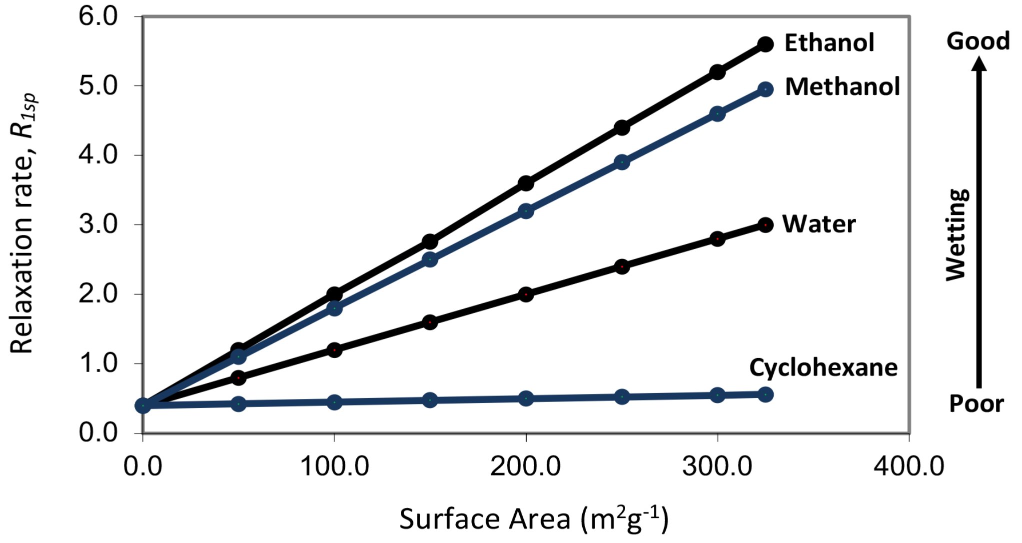


Figure 14: $R_{1sp}$ relaxation rate of a porous silica measured in various pure liquids. Relative wetting ability is provided for reference.

It is clear that the relaxation rate of cyclohexane is affected very little by the presence of silica, whereas the relaxation rate for ethanol is almost twice that of water for the same silica surface. Hence ethanol would be the preferred dispersing liquid when comparing samples of this silica material because of its superior wetting ability.

The wettability is also a function of the interfacial tension between a liquid and a solid. This can be lowered by adding surfactants into the liquid, which is often done when "dispersing" powders in liquids (49). As such, wettability also impacts the measurement of wetted surface area (see below). NMR relaxation can also be used to follow the adsorption of surfactants and polymers onto surfaces and, therefore, potentially can help in optimising industrially relevant formulations (5, 50-52).

Hence, in NMR relaxation, it is important to know, or recognize, if the dispersion liquid is a "pure" liquid, or if it is one that contains additives such as polyelectrolytes or surfactants. This is especially relevant when comparing suspensions from different sources. NMR relaxation can be used not only to monitor the wetting efficiency of pure solvents but also liquid mixtures (see Mageleka Application Note # 11).

*Dispersing*

At this point, it should be clear that the state of dispersion will critically affect the wetted particle surface area and, to be useful, it is essential that a technique appropriate to the application be used. However, it is often difficult to achieve a preparation of wet suspensions having a defined dispersed state with specific properties. In practical terms, the total wetted surface area of a given suspension is a consequence of the concentration and size of particles. The latter derives from the specific dispersion process used, viz the choice/type and concentration of dispersion aids (i.e., wetting agent, de-agglomerating agent, and stabilizing agent) and the type and duration of the mechanical dispersing treatment (53).

The crucial impact of "dispersing" on the total available wetted surface area is illustrated by inspection of the data in Table 3. Both suspensions contained a broad PSD (skewed to the larger size, owing to aggregates and agglomerates). The 90 nm $TiO_2$ is a "microfine" grade used as a sunscreen active; it had a PS ranging from 25 nm to 200 nm. The 270 nm $TiO_2$ is a "pigmentary" grade material used as an opacifying agent; it had a PS from 120 nm to 600 nm. $TiO_2$ is a hydrophilic material that is relatively easily wetted by water but, although an initial aqueous suspension can readily be prepared, the vast majority of the particles will remain aggregated and so the wetted surface area will be small. When a dispersing agent is used the wetted surface area increases dramatically for two reasons. First, because of de-aggregation and de-agglomeration, and second because of the fact that NMR relaxation is sensitive to the smaller end of a PSD (because, as mentioned earlier, surface area trends with $d_2$; the break-up of a single massive particle results in a large number of smaller particles and, hence, much larger total surface area) and is independent of any particle size or shape.

Table 3: Comparison of surface area values from NMR relaxation data of 2 vol% suspensions of two grades of titanium dioxide prepared with and without dispersant.

| **Method** | **Microfine grade**<br>Nominal particle size 90 nm | **Pigmentary grade**<br>Nominal particle size 270 nm |
|---|---|---|
| No dispersant | 5 $m^2g^{-1}$ | 1 $m^2g^{-1}$ |
| Dispersant | 55 $m^2g^{-1}$ | 11 $m^2g^{-1}$ |

## IN CONCLUSION

NMR relaxation is a superior method to gas adsorption and titration techniques for the determination of the wetted surface area of particulate suspensions. Further, it can provide important information about both the *extent* of the particle-liquid interface (and the interplay between internal and external surface) and the *nature* of the particle-liquid interface (surface/interfacial chemistry). It complements results obtained from established techniques such as particle sizing and zeta potential but additionally provides information that cannot be observed simply with those (or other) particle characterization devices. Moreover, it requires fewer assumptions than other techniques, which reduces data bias and, ultimately, the possibility of erroneous conclusions. The relatively small size, ease of operation, and high data fidelity of benchtop NMR spectrometers, such as Mageleka's *Magno**M**eter* XRS™, eliminate the need for large analytical NMR devices in any laboratory that routinely measures wetted surface area of particulate suspensions. Additional advantages of the technique are that measurements are rapid, can be used over a very wide range of solids concentration, and samples can be opaque.

## REFERENCES

1. FK. Daniel, *Natl. Paint, Varn. Lacquer Assoc. Sci. Sect. Circ.,* No.744 (1950)
2. S. Guggenheim, *Off. Dig.*, 30 No.402, 729 (1958)
3. ICH Q8(R1), Pharmaceutical Development, June (2009); ICH Q8(R2), Pharmaceutical Development, November (2009)
4. D. Fairhurst and S. Prescott, *Spectroscopy Europe*, Vol 23, No. 4, 13 (2011)
5. D. Fairhurst, T. Cosgrove and S. Prescott, *Magnetic Resonance in Chemistry*, 54, Issue 6, 521 (2015)
6. GE. Maciel, in *Encyclopedia of Nuclear Magnetic Resonance*, DM.Grant and RK. Harris (Eds), J. Wiley & Sons, New York (1996)
7. RM. Coats, in *Encyclopedia of Nuclear Magnetic Resonance,* DM. Grant and RK. Harris (Eds.), John Wiley & Sons, New York (1996)
8. T. Cosgrove, Colloid Science Inc., private communication
9. M. Kerker, T*he Scattering of Light,* Academic Press, New York (1969)
10. S. Lowell S and JE. Shields, *Powder Surface Area and Porosity,* Chapman Hall, London, (1984)
11. RO. James and GA. Parkes, in *Surface and Colloid Science*, Vol II, E. Matijevic (Ed), John Wiley & Sons, New York (1980)
12. DH. Everett, in *Proceedings of the International Symposium on Surface Area Determination*, DH. Everett and RH. Ottewill (Eds), Butterworths, London (1970)
13. RM. Barrer and PJ. Cram, *Advances in Chemistry Series*, No. 102, American Chemical Society, Washington DC (1971)
14. KSW. Sing, *Colloids and Surfaces*, 38 113 (1989).
15. P. Barrie, *Annual Reports on NMR Spectroscopy*, 30 37 (1995)
16. DH. Everett and JM. Haynes, *Colloid Science*, Specialist Periodical Report, The Chemical Society, London (1973)
17. NG. Stanley-Wood and RW. Lines (Eds), *Particle Size Analysis*, RSC Special Publication No. 102, (1992)
18. P.McFadyen and D. Fairhurst, *Clay Minerals*, 28 531 (1993)
19. T. Allen, *Particle Size Measurement*, Chapman & Hall, 4th Edition, New York (1990)
20. A. Dokoumetzidis and P. Macheras, *International Journal of Pharmaceutics*, 321 1 (2006)
21. DM. Brown et al, *Toxicol. Appl. Pharmacol.*, 175, 191 (2001)
22. G. Oberdörster et al, *Environ. Health Perspect.*, 113 823 (2005)
23. C. Monteiller et al, *Occup. Environ. Med., 64* 609 (2007)
24. K. Van Hoecke et al, *Environ.Toxicology and Chemistry, 27* 1948 (2008)
25. MJ. Rhodes (Ed), *Principles of Powder Technology,* John Wiley & Sons, Chichester (1990)
26. ISO/CD 13322 Particle Size Analysis – Image Analysis Methods (1999)
27. KSW. Sing, in *Characterization of Powder Surfaces,* GD. Parfitt and KSW. Sing (Eds), Academic Press, London (1976)
28. RJ. Hunter, *Zeta Potential in Colloid Science,* Academic Press, London (1981)
29. S. Levine and AL. Smith, *Disc. Faraday Society,* 52 290 (1971)
30. G.W. Sears Jr., *Analytical Chemistry*, 28(12)

1981 (1956)

31. J. Mewis and AJB. Spaull, *Advances in Colloid and Interface Science,* 6(3) 173 (1976)
32. M. Kosmulski, J. *Colloid and Interface Sci.*, 337(2): 439 (2009)
33. RK. Iler, T*he Chemistry of Silica and Silicates*, Cornell University Press, Ithaca, NY (1955)
34. RK. Iler and RL. Dalton, J*ournal of Physical Chemistry*, 60(7) 955 (1956)
35. ASTM Standard Method D6845-12, www.astm.org/Standards
36. ASTM Standard Method D1510-13, www.astm.org/Standards
37. DH. Solomon and DG. Hawthorne DG (Eds), *Chemistry of Pigments and Fillers,* John Wiley and Sons, New York (1983)
38. GD. Parfitt and KSW. Sing (Eds), *Characterization of Powder Surfaces*, Academic Press, London (1976)
39. M. Kosmulski, *Surface Charging and Points of Zero Charge*, CRC Press, Boca Raton, FL (2009)
40. RK. Iler, *Chemistry of Silica.* Weinheim, Germany: Wiley-VCH Verlag (1979)
41. J. Grandjean, in *Encyclopedia of Surface and Colloid Science*, (Ed.) AT. Hubbard, Vol. 3, Marcel Dekker, New York (2002)
42. GP. Van der Beek, MA. Cohen-Stuart and T. Cosgrove, *Langmuir*, 7 327 (1991)
43. R. Mackay, J. Zhang, Q. Wu and Y. Li, *Colloids and Surfaces A: Physicochem. Eng. Aspects*, 250 343 (2004)
44. K. Keating and R. Knight, *Geophysics*, Vol 72, No. 1, E27 (2007)
45. AR Lim, CS Kim and SH Choh, *Bulletin of Magnetic Resonance*, 14(1) 240 (1992)
46. H. van Olphen, I*ntroduction to Clay Colloid Chemistry.* London, England: Interscience Publishers (1963)
47. RS. Carmichael, *Physical Properties of Rocks and Minerals.* Boca Raton, FL, USA: CRC Press Inc. (1989),
48. JC. Berg, *An Introduction to Interface and Colloid Science,* World Science Publishers, New Jersey (2010)
49. GD. Parfitt (Ed), *Dispersion of Powders in Liquids,* Third Edition, Applied Science Publishers, London (1981)
50. A. Nelson, KS. Jack, T. Cosgrove and D. Kozak, *Langmuir*, 18(7) 2750 (2002)
51. SJ. Mears, T. Cosgrove, L. Thompson and I. Howell, *Langmuir*, 14(5) 997 (1998)
52. CL. Cooper *et al*, *Soft Matter*, 9 7211 (2013)
53. D. Fairhurst and MA. Mitchnick, in *Sunscreens: Development, Evaluation and Regulatory Aspects*, 2nd Edition, (Eds.), NJ. Lowe, NA. Shaath and MA. Pathak, Marcel Dekker, NY (1997)

***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***