PARTICLES IN LIQUIDS: Wetted Surface Area as a Critical Metric in the Characterization of Suspensions of Materials

The Dispersed State and Wetted Particle Surface Area of Suspensions

The overwhelming majority of manufactured commercial products – from industrial automotive paint to health-care formulations – involves, either in the final state or at some stage of their production, suspensions of particulate materials, or emulsion droplets, dispersed often at high volume fraction. One only has to look at the vast array of cosmetics, personal care, and pharmaceuticals to recognize the importance of adequate dispersion. For example, in decorative cosmetics, the dispersion of colored organic/inorganic pigments and dyes affects brightness and gloss. In sunscreens, the quality of the dispersion not only affects the formulation aesthetics but also the performance (e.g., the "SPF factor")[1]. Further, with the advent of active pharmaceutical ingredients (APIs) possessing poor overall aqueous solubility – for example, Biopharmaceutical Classification System Class II molecules such as levonorgestrel, (a hormonal birth control agent) and paclitaxel (a chemotherapy medication) – optimal dispersion is necessary for maximizing bioavailability and uniformity of dose.

The *state* of dispersion of any solid material directly affects suspension properties. For example, as particulate material is added to any liquid medium the suspension's flow becomes increasingly non-Newtonian and, with high particle concentrations, can become thixotropic or rheopectic. These rheological characteristics determine suspension functionality[2,3], such as film forming, lubricity, and efficacy. The importance of the process of dispersion and its profound effect on product economics and quality has long been recognized[4,5]. A detailed discussion of the factors affecting the dispersion process can be found in *Mageleka White Paper 3: Factors Affecting the Preparation of Suspensions: Wetting, Dispersing and Stabilizing.*

Dispersing solid particles in liquids can present problems. Many dry powders start as massive solid phases and require size reduction even prior to dispersion of the powder in a liquid (see *Mageleka White Paper 5: Milling of Solids*). Conversely, agglomerates are formed when fine particles are handled, shaken, rolled, or stored in a single position. Indeed, de-agglomeration and stabilization are necessary to obtain optimal dispersion[6].

All suspensions of solid materials are inherently thermodynamically unstable. They will, through random motion (such as settling and shear-induced flocculation) of the particles over time, aggregate because of the natural and dominant tendency to decrease the large specific surface area and excess surface energy[7]. This tendency becomes increasingly important with smaller initial particle size and is significant for colloidal-sized particles (<1 μm). However, nanoparticles (<<100 nm) can be kinetically stable. In practice, the stability of suspensions is a complex process because it involves the role of interparticle forces of attraction and repulsion and whether any ensuing aggregation that occurs is due to the mechanics of coagulation or flocculation (see Mageleka White Paper 3).

Hence, the *state* of dispersion critically affects the particle surface area and, to be useful, it is essential that a technique be used that is appropriate to the specific application in question. Importantly, it is the *wetted particle surface area* of any suspension (and especially for nanoparticulates) that is the vital metric in quantifying the performance of such materials.

Further, as will be explained below, it is essential that this wetted particle surface area be measured *directly* on these materials as obtained.

In practical terms, the total particle surface area of a given suspension is a consequence of three important factors: the size, the shape, and the concentration of the particles in the final dispersed state. To gain a better understanding of not only the behavior of dispersions, but ultimately the quality of the final products that are based on them, it is worth exploring each of these factors in detail.

Particle Size and the Surface Area of Particulate Materials

Particle size is known to be important to an extraordinarily wide variety of manufacturing and processing contexts. For example, particle size determines characteristics as diverse as the color intensity of paint and the sintering shrinkage of ceramic materials. It is also clear that, as the size of any material is reduced (indirectly via milling/ comminution or prepared directly by nucleation/ precipitation), the particle surface area will increase (as $1/d^2$, for spheres; where d is the diameter), so the actual total area depends on the number of particles. But, what is less obvious is the exceptionally large surface area-to-volume ratio per given mass for the particles involved. This is an essential characteristic common to all colloidal dispersions and of critical import to nanoparticulate systems.

To illustrate this, take the example of what happens when a particle (say, a cube) with sides that measure 1 cm (10^{-2} m) – about the size of a sugar cube – is broken down into many smaller cubes having a side of only 10^{-6} cm (or, 10 nm), which is a size typical of many new nanoparticulate materials being developed (Figure 1). The *total* particle surface area increases from 6 cm^2 to 6×10^6 cm^2, or, 600 m^2 – because 10^{18} new particles have been created from that single particle[8]. To put this figure into perspective, that is enough to cover about half the area of an Olympic-size swimming pool, or approximately two tennis courts! Thus, for nanoparticulate systems, the particle surface area becomes orders of magnitude larger than it is for particles of even only a few micrometers in size[9].

The Influence of Particle Shape on Particle Surface Area

Particle asymmetry is a factor of considerable importance in determining the overall properties of colloidal systems, and especially those of a physico-mechanical nature. For example, while metallic nanoparticles make powerful catalysts because of their surface-to-volume ratio, their activity is also affected by the particle shape because different crystal facets result in different selectivity[10].

Shape is a function of the history of the formation of the particles (e.g., crystallization)[11], and it can be visualized using complex analytical techniques such as electron diffraction[12] and small-angle neutron scattering[13]. Although the exact shape may be much more complex, colloidal and nanosize particles can be roughly classified, in particular for modeling and theoretical purposes, as *corpuscular* (spherical and ellipsoid), *laminar* (disc- or plate-like), or *linear* (cylindrical, rod- or needle-like). Thus, it is obvious that, for a given mass, the particle surface area will differ depending upon the shape of a material.

Polymorphism

An important characteristic of some materials is that they exist in more than one shape or structure. This is called *polymorphism* and can potentially be found in any crystalline material. Polymorphs have different stabilities and may spontaneously convert from a metastable form to the stable shape/structure at a particular temperature. For example, particles of zinc oxide (a common active in sunscreens) can be spherical or linear, but the latter form absorbs UVA/ UVB radiation more poorly. Polymorphism is very important in the development of APIs because it can affect, via the resulting particle surface area, drug solubility. This, in turn, impacts the drug's dissolution rate and, consequently, its bioavailability in the body. Many drugs receive regulatory approval for only a single crystal form or polymorph. Despite the potential implications, polymorphism is not always well understood but should be considered when creating formulations with materials that are prone to it.

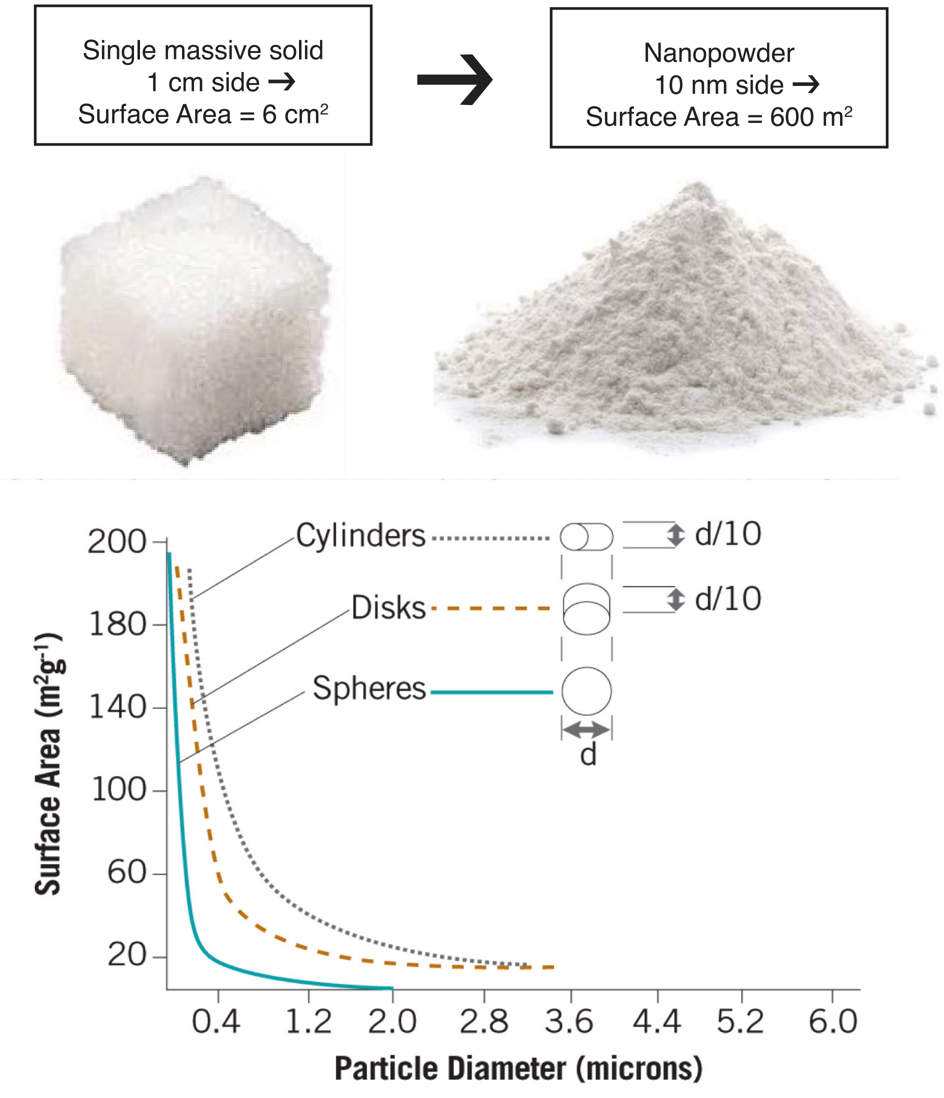

FIGURE 1: A comparison of particle size relative to surface area per gram. Note the dramatic increase in surface area – for particles of any shape – in the colloidal domain (<1 *μ*m).

The Practical Consequences for Particle Surface Area of Solids Concentration

The greater the concentration of colloidal particles, the greater is the total particle surface area of the system and, hence, the ability to interact (and react) with the immediate surrounding environment. Further, as material is broken down, surfaces that were previously internal become exposed and, with this, a change in the number and/or type of surface chemical sites and groups. Referring again to our particle (cube) of 1 cm, only two or three molecules in 10 million are "surface" molecules. However, when divided into 10 nm-size particles, more molecules/atoms (that comprise the molecular structure) become *surface moieties* and the ratio rises to over 1:3 (see Fig. 2). With a 1 nm particle size, this ratio rises considerably so that 80% of the atoms are at the surface. To put this into perspective, a typical micellar solution containing 0.1 mol dm^{-3} of amphiphile has ~40,000 m^2 of micellar-water interfacial area per liter of solution – enough to cover almost 10 acres of surface as a monolayer!

A practical consequence of such large numbers of interfaces between the disperse phase and the dispersion medium is the increased relevance of electrical (surface charge) effects: what are normally negligible effects for massive solids become dominant in the description of colloidal behavior. Thus, with increasing surface area, surface electrical (charge) effects play an increasing part in determining the physico-chemical properties, such as surface chemistry/activity and catalysis, of the system as a whole. This matter has been addressed in the Deryaguin-Landau-Verwey-Overbeek (DLVO) theory of electrostatic interactions between particles[14].

In the case of catalysts, it is not just the particle surface area of the material but also, importantly, the concomitant increase in *surface energy* as the material is finely divided. Taking again our example particle (1 cm cube), the increase in surface energy per gram of material gained by subdivision down to 10 nm-size particles is ~10 million Joules. This is equivalent to about 3 kW hours of energy. For comparison, an air conditioning unit in an average large house runs at 1.5 kWh. One high-profile example of the importance of this effect is that of batteries used in laptop computers and automobiles. The energy storage capacity and charge/discharge rate of batteries are directly controlled by the particle surface area of the (nanoparticulate) suspension used as the electrolyte.

Hence, when characterizing suspensions of particles, both the *extent* (surface area) and the *nature* (surface chemistry) must be considered. Moreover, it is important to note that these two fundamental parameters do not act independently – and nuclear magnetic resonance relaxation measurements (see below) are sensitive to both.

Milling

The practical significance of overgrinding massive solid material or the use of excessive mechanical attrition during formulation that results in “fines” cannot be emphasized enough. Fines are typically defined as the portion of particles smaller than some arbitrarily determined size. This latter value varies from industry to industry; for example, in soil science the limit would be a No. 200 sieve (75 μm). The effect of this on product performance and the economics of manufacture can be considerable. Milling is an expensive, labor-intensive process. As an example of product performance, consider the “microfine” grade of titanium dioxide (TiO_2) used to attenuate UV radiation in sunscreen formulations. Microfine TiO_2 can appear transparent in films on the skin. Unfortunately, the presence of fines (e.g., that can arise from overgrinding) can impart a bluish hue to the film but also reduces its ability to attenuate the UVA (and, to a lesser extent, UVB) radiation. Thus, overmilling – in addition to adding to production costs – ultimately reduces the aesthetics and the efficacy of the sunscreen product. One way to optimize this process, and thus improve product economics, is to measure the particle surface area directly (e.g., using nuclear magnetic resonance relaxation; see below) throughout the milling process.

In addition, a huge increase in particle surface area dramatically affects not just adsorption of chemicals and other moieties onto the particle surface, but also the interaction between particles and system properties such as suspension rheology, coating, and adhesion. It also allows for much faster dissolution of drugs/APIs and, thereby, increases bioavailability, regardless of the route of administration[15]. Low drug active bioavailability can lead to inefficient treatment, higher cost, and risk of toxic side effects. Any increase in efficacy can reduce the potential toxicity because less drug substance is needed, which also has obvious consequences for the economics of pharmaceutical and biomedical products. There is also a growing body of evidence that, specifically with nanoparticulate materials, it is the particle surface area (and not particle size) that is the defining metric that controls toxicological interaction[16-18]. This has led to the recent drive to develop reformulations based on nanotechnology.

Particle Surface Area Measurement

Thus, it is clear that the particle surface area is a critical metric in the characterization of suspensions, especially colloidal dispersions and nanoparticulate systems. But what is the best means of measuring particle surface area? A detailed discussion of the most common methods for determining surface

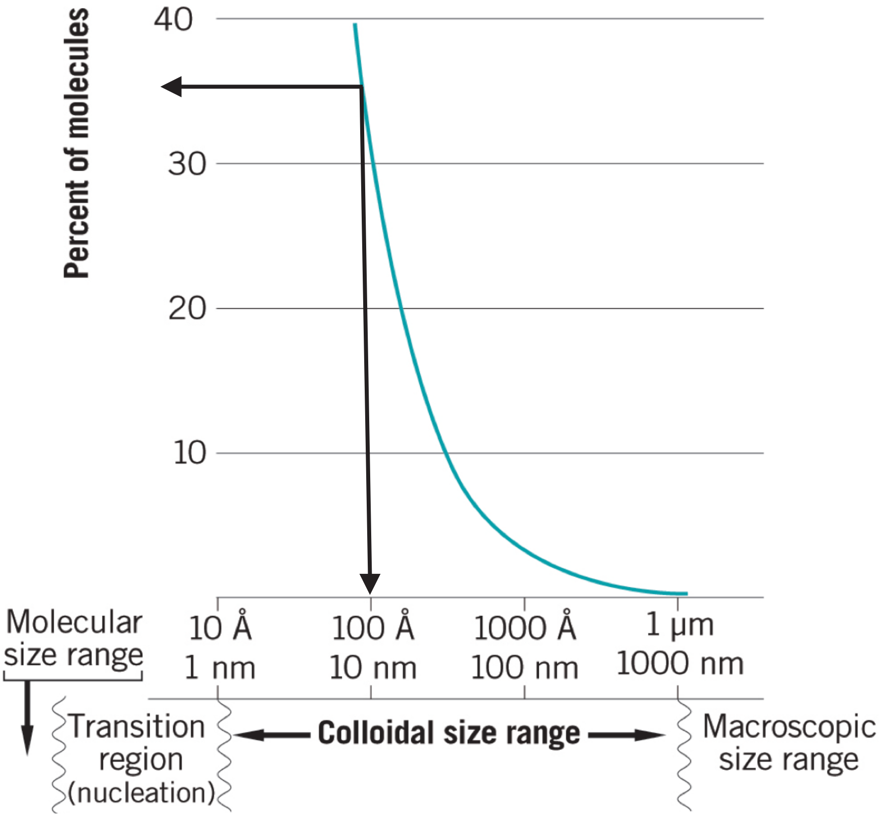

FIGURE 2: The relationship between particle size and the percentage of molecules at the surface of the particle.

area is given in the *Mageleka White Paper 1: NMR Relaxation and its Relevance to the Measurement of the Surface Area of Suspensions*.

The most common method for determining particle surface area is nitrogen (N_2) gas adsorption[19,20]. In this method, N_2 is adsorbed on a sample kept at liquid N_2 temperature across a series of different pressures. This technique requires that the sample be initially degassed to drive off any adsorbed material (sample conditioning), and so it further requires a source of liquid N_2 to maintain the proper sample temperature, which is also a critical experimental requirement[21]. Additionally, this technique requires the material being tested 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, the preparation of which are required in the production of literally millions of products, it is therefore essential that the surface area be measured *directly*.

It is possible to calculate the particle surface area from measurements of the particle “size” but this approach assumes that the particles are spherical and of a monodisperse size distribution – two conditions clearly not met by the majority of real-world suspensions. Any surface area calculated for such materials is, at best, only a crude approximation and it is well-recognized that particle shape, surface irregularities, and porosity will inevitably lead to estimated values significantly lower than the true value[22].

NMR Relaxation Measurements and the Mageleka *M*agno*M*eter XRS™ Relaxometer

Nuclear magnetic resonance (NMR) spectroscopy provides a means of measuring particle surface area directly, without making assumptions about particle size or shape, and without the need for dilution. High-resolution NMR spectroscopy is one of the most powerful analytical tools used to probe details of molecular structure and dynamics. However, such high resolution instrumentation requires very high magnetic fields and thus uses extremely large, powerful, high-field (ca. 100MHz – 400MHz) magnets. These instruments are typically located in universities and analytical departments of large companies and are very costly.

The need for portable, economic, and routine laboratory NMR has been evident for the past decade, and research has demonstrated[23] that low-field devices can often provide better relaxation time resolution, and are more easily accessible, compared with traditional high-field analytical NMR spectrometers. With the advent of small, powerful permanent magnets, the *M*agno*M*eter XRS™, which uses low-field (ca. 13 MHz) NMR, is now available to measure the wetted particle surface area of any suspension. Importantly, NMR relaxation works with particles in virtually all liquids and at any industrially-relevant concentration (see *Mageleka Technical Note 1*).

The technique is based on the fact that liquid in contact with, or "bound" to, the particle surface behaves differently than the free or "bulk" liquid. The NMR relaxation rates of bound and bulk liquids are markedly different: the relaxation rate of the latter is much shorter. There are no assumptions made about the particle size (distribution) or shape in the determination of the particle surface area by NMR measurements. As mentioned previously, measurement of virtually any particle in any fluid is possible, and the technique does not require dilution of the sample.

Finally, it is feasible to use NMR relaxation to measure other characteristics of dispersions. For example, diffusion can be measured (only emulsions or nanoparticles < 30 nm), from which particle size can be estimated. Further, it is possible to directly measure volume fraction and, potentially, the molecular weight of polymers. One important practical application is the ability to determine competitive adsorption and/or displacement of polyelectrolytes, macromolecules, and surfactants at interfaces. Adsorption of surfactants and dispersants onto particles is often a key step in the preparation of stable suspensions, and multiple additives are often employed (e.g., in paint formulation)[24]; the order of their addition is critical to obtaining stable dispersion conditions. NMR relaxation measurements can be used to study the effect of these complex processes directly.

In Conclusion

The small size and ease of use of the Mageleka *M*agno*M*eter XRS™ Relaxometer make it ideal for routine analysis in R&D, QC/QA and process laboratories. But it is the *M*agno*M*eter's NMR technology that makes it indispensable to anyone working with suspensions. In addition to measuring the wetted surface area of any solid-liquid dispersion directly without making assumptions of particle size, shape, or concentration, the *M*agno*M*eter can also provide more information in the characterization of suspensions of materials than just that critical metric. For additional information on the *M*agno*M*eter XRS™ and the utility of NMR relaxation measurements for characterizing dispersions, see *Mageleka Technical Notes 1 & 2*.

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