Mageleka

Technical Note 1

NMR Relaxation Measurements: Their Relevance to the Physical Characterization of Particulate Suspensions and Slurries

Introduction

Suspensions of particulate materials or emulsion droplets are essential components of the overwhelming majority of manufactured industrial products. Dispersions can be involved either in the final state or during some stage of production, but their quality can have profound effects on the characteristics of the final product. For example, many new active pharmaceutical ingredients (APIs) possess poor overall solubility (e.g., paclitaxel, a chemotherapy medication), so optimal dispersion is necessary for maximizing bioavailability and uniformity of dose. Sunscreens use dispersions of microfine zinc oxide and titanium dioxide to absorb UVA/UVB radiation, and the quality of the dispersion affects not only the formulation aesthetics but also the efficacy (e.g., the “SPF factor”). Automotive paints achieve their specific color intensity and gloss characteristics via the dispersion of pigments and dyes.

Given these diverse examples, it should be clear that proper characterization of particulate suspensions is central to consistent product performance and, thus, the economics of production. This Technical Note will discuss a powerful non-invasive technology for characterizing any solid-liquid or liquid-liquid formulation (i.e., suspensions and emulsions), and introduces Mageleka’s *MagnoMeter* XRS™ as a simple and affordable instrument for achieving this. However, to understand how this technology works, we must begin with the basis of the technique – nuclear magnetic resonance (NMR) relaxation – and then discuss how such measurements can be employed to understand the behavior of particulate suspensions and slurries, and how they can be improved.

What is NMR Relaxation?

All solids and liquids possess a fundamental, intrinsic property called the relaxation time and it can be determined directly using a suitable NMR spectrometer. The relaxation time alone can be used to provide direct information about the extent and nature of any particle-liquid interface (i.e., suspensions and emulsions). There are two ways to measure NMR relaxation time – called T_1 and T_2 – and they give complimentary information. An analogy would be using static and dynamic light scattering to determine particle size, or electrophoretic and phase analysis light scattering to determine the zeta potential.

What is actually measured in NMR relaxation is how protons react (through their molecular motion) in a magnetic field. In liquids, where the molecules can move quickly, the relaxation time (both T_1 and T_2) is long and is of the order of seconds. In contrast, the T_2 relaxation time for solids (and adsorbed molecules) is very short – typically <100 µs – whereas the T_1 value, though short, is also variable.

In a dispersion, where the liquid interacts dynamically with the solid surface, an average relaxation time is measured. This depends on the particle surface area in the dispersion, the chemical structure of the interface, and the choice of dispersing liquid. Their importance is discussed in greater depth in Mageleka White Paper 1, Mageleka Technical Note 6, and Mageleka Application Note 4.

The relaxation time of particulate suspensions will, therefore, be intermediate between that

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for the solid and that for the liquid. The actual value is a function of exactly how the liquid interacts with the particle surface (i.e., the wettability and resulting interfacial structure; see Mageleka Application Note 3). It depends also on the material particle size and solids concentration. The smaller the particle size, the greater will be the relaxation time; the greater the solids concentration, the smaller will be the relaxation time. At a simple practical level, a useful dimensionless unit – the “Relaxation Number” – can be defined.

For simple liquids – including liquid mixtures – the T_1 and T_2 times are usually very similar. However, with suspensions, both the T_1 and T_2 values can differ markedly depending upon the particulate surface chemistry (such as concentration of surface functional groups) because this directly impacts wettability.

T_1 and T_2 each respond differently to the translational and rotational motion of liquid molecules and so their magnitude may differ significantly because of the different way in which the two processes are linked to molecular motion. Experimentally, a greater change in T_2 compared with T_1 is typically observed for the same incremental change in concentration and/or wetted surface area.

In general, when reagents such as acids/bases (to change the solution pH) or electrolytes (to increase the solution conductivity) are introduced into the liquid phase it will have little impact on either the T_1 or T_2 relaxation time of the bulk liquid (unless the species are ferro- or para-magnetic ions). The same is true for surfactants, polyelectrolytes, and polymers: unless their concentration is high enough that they create a completely separate phase, the T_1 and T_2 values for solutions of them will be little changed from that of the liquid in which they are dissolved.

However, in contrast to chemicals such as simple electrolytes, some molecules – surfactants, for example – can specifically adsorb at the particle surface and, in so doing, will displace any surface liquid molecules. This will result in a change in both the T_1 and T_2 relaxation time *of the particulate suspension.* This change can be used to study adsorption/desorption phenomena at interfaces.

Both T_1 and T_2 methods are valid and either can be used to understand the behavior of particulate suspensions and slurries. Which method is better will depend upon the specifics of the application for which measurements are being made, as each has its own practical advantage (and limitation). The *M*agno*M*eter instrument provides both T_1 and T_2 measurements (see Mageleka Technical Note 2).

Using NMR Relaxation Measurements

Solids concentration

A simple use of suspension relaxation time would be to provide a fast, direct measure of the percentage of solid and liquid in a system (i.e., solids concentration): the greater the solids concentration, the smaller will be the relaxation time. While the relaxation time can be a useful measure for simple systems, the preparation of a wide variety of industrially-important particulate suspensions often involves the use of polymers, polyelectrolytes, and surfactants. Their presence affects the relaxation time which, in turn, can influence measurement of solids concentration.

Polymer gels

The relaxation time can also be used to quantify the dynamics and structure of, for example, polymer gels – not only with water-soluble polymeric systems but also in non-aqueous fluids, where the presence of water impurity can have a large impact on relaxation time. The relaxation time is also a function of the concentration and molecular weight of the polymer, polyelectrolyte, or surfactant. Further, the presence of any dissolved moiety that changes the bulk viscosity of any liquid will result in a change in relaxation time of that liquid. Another very useful function is to use relaxation time to study mixed polymer/surfactant systems.

Powders and their wettability

The formulation of any suspension involves three distinct steps – wetting, dispersing and stabilizing (see Mageleka White Paper 3) – and measurement of the relaxation time provides direct information at, and about, each of these stages. However, all suspensions initially begin with a dry powder and all dry powders (and, hence, any suspensions prepared from them) will always comprise singlet particles, aggregates of singlet particles, and agglomerates of aggregates. The relaxation time of a suspension is directly related to the "state" of dispersion. So, if you have a poorly wetted suspension – say, if you are using the wrong liquid – you can use the relaxation number (or time) to determine how well a liquid can wet a surface by comparing different liquids or mixtures of liquids. The smaller the relaxation time (or the larger the relaxation number) the better is the wetting. Of course, the efficiency of wetting depends upon the contact angle and interfacial tension of the liquid, as well as the surface area of the material.

Comminution

Just wetting a dry powder does not result in a "good" dispersion. You need to use some mechanical action (such as milling) to improve dispersion. It is possible to follow the comminution process, even at very high solids loading in the mill, by measuring the relaxation time as a function of milling time. As either massive particles or aggregates and agglomerates break apart, this results in smaller particles, which in turn, increases the available wetted area and once again, the relaxation time will decrease (and the relaxation number will increase).

Dispersing agents

Typically, to further improve dispersibility, you then use a suitable dispersing agent. This provides additional chemical action that helps prize apart the aggregates/agglomerates, which means you can use less mechanical energy and thus decrease production costs. The efficiency of dispersants can also be compared because, for a fixed solids concentration, the more efficient the dispersant, the shorter will be the relaxation time (i.e., the greater the relaxation number; see Mageleka Application Note 4). It is important to note that dispersants – especially polymerics – can be expensive, and so determination of the best one, and then optimizing its use concentration, can result in significant savings in production costs.

Measuring NMR Relaxation

As the above examples demonstrate, NMR spectroscopy is one of the most powerful analytical tools used to determine chemical spectra and to probe details of molecular structure and dynamics. However, in practice, NMR spectroscopy has not been easy or accessible for general/routine laboratory use. NMR devices require very high magnetic fields (ca. 100MHz – 400MHz) and, hence, use very large magnets. They are very expensive, complex machines – in some instances requiring liquid nitrogen cooling. Intensive training is need for the sophisticated operation. As such, they are typically located in universities and analytical departments of large companies.

The advent of small, powerful magnets has led to the development of compact, bench-top, low-field (ca. 13 MHz) NMR devices – such as the Mageleka *M*agno*M*eter XRS™ – that are suited to normal, routine use in any laboratory, from exploratory research and development, to quality control/quality assurance (QA/QC) and process monitoring. Despite their small size, low-field devices such as the *M*agno*M*eter have been shown to provide superior relaxation time resolution compared with traditional high-field analytical NMR spectrometers.

Importantly, NMR is a non-invasive technique and so samples can be saved and re-measured at some later date. If the initial "good" dispersion is not stable, then re-aggregation will take place over some time interval – whether it is days, weeks or months. This is especially important with polymeric (steric) stabilization where overdosing can often result in a slowly flocculating dispersion which loses surface area over a long period of time. If (for any reason) the total wetted surface area decreases, then this will result in a subsequent increase in relaxation time. Measurements such as "accelerated aging testing" are critical (and mandated for APIs) for shelf storage, for example. NMR relaxation measurements using the Mageleka *M*agno*M*eter are rapid and can be made automatically over time so that kinetic processes such as sedimentation and coagulation/flocculation can be studied.

Finally, an important practical advantage of NMR relaxation is that measurements can be made directly on samples at industrially-relevant concentrations, without the need for any additional sample preparation such as dilution (see Mageleka Technical Note 2 and Mageleka Technical Note 4).

In each of the above examples you can use the relaxation time alone without the need to calculate an actual value for the wetted surface area. However, in some cases this latter metric might be needed. Unlike the determination of particle size from light scattering intensity data, which involves complex algorithms involving sums of exponentials or sums of Bessel functions, the conversion of the raw relaxation time is a simple calculation (see Mageleka White Paper 1). It necessitates knowing a value for k_A (with units of the $m^2g^{-1}s^{-1}$), which is a calibration constant for the specific solid/liquid dispersion under investigation. The k_A is a simple multiplication factor in the same manner that a zeta potential value is obtained from the measured electrophoretic mobility value (by multiplying it by, for example, the Smoluchowski or Hückel factor). Alternatively, one can think of it as equivalent to a Refractive Index as is needed in dynamic/static light scattering to calculate a correct submicron particle size. The *M*agno*M*eter from Mageleka calculates the wetted surface area automatically via its native *M*agno*S*oft program.

In Conclusion

Given their importance to industrial, cosmetic, and health care products (to name but a few), proper characterization of suspensions and slurries is critical to ensuring consistent product performance and minimizing production costs. NMR relaxation measurements made using the Mageleka *M*agno*M*eter XRS™ provide a fast and easy way to assess key characteristics of any dispersion directly and provide additional information (e.g., wetted surface area) not readily available with other techniques. Moreover, NMR measurements made with the MagnoMeter XRS™ are non-invasive and additional sample preparation is not needed, making it a powerful and flexible tool for any research and development, QA/QC, or production context where suspensions and slurries are routinely tested.

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