Mageleka

Technical Note 3

A Next-Generation Low-Field NMR Device: Overcoming Practical Challenges in Characterizing Suspensions and Slurries

Introduction

The vast majority of products manufactured for use in a wide variety of industrial applications involve suspensions of particulate materials dispersed into a liquid often at high volume fraction. Industries such as personal care, agrochemicals, pharmaceuticals and, increasingly, the growing field of nanomedicine regularly utilize dispersions, either in the final state or at some stage of their production.

The state of dispersion of any solid material directly affects suspension properties. A common example of the importance of adequate dispersion can be found in the vast array of decorative cosmetics. The dispersion of colored organic/inorganic pigments and dyes affects the product's brightness and gloss, two aesthetic characteristics of great consequence to the cosmetics industry. In sunscreens, the quality of the dispersion not only affects the formulation aesthetics but also the performance (i.e., SPF factor). Optimal dispersion is also necessary for maximizing bioavailability and uniformity of dose of drugs, which is increasingly relevant for novel Active Pharmaceutical Ingredients (APIs) possessing poor aqueous solubility.

In addition to being central to product performance, the profound effect of the dispersion process on the economics of the product has long been recognized. As a practical example, cellulose nanomaterials (CNM) are an attractive alternative to other high-aspect-ratio nanoparticles, such as carbon nanotubes and silica nanowhiskers, because of their renewable, sustainable origins and low toxicity. To be effective, CNM must be manufactured reproducibly with consistent particle geometry, surface properties, and molecular-scale morphology. Thus, the ability to characterize these key CNM metrics quickly, reliably, and routinely is critical to manufacturing CNM as an economically-feasible product.

Nuclear magnetic resonance (NMR) liquid relaxation measurements provide a means of monitoring a variety of characteristics of dispersions. However, this requires an NMR device that is suited to routine laboratory analysis – and one that is adaptable enough to handle the diversity of challenges faced when formulating dispersions.

This Technical Note will introduce a powerful and flexible next-generation, benchtop, low-field NMR instrument, the Mageleka *M*agno*M*eter XRS™ Relaxometer, that has been designed specifically to overcome a variety of limitations inherent in making such NMR measurements in industrial, production, and specialized research contexts. The focus here will be on how the technical specifications of the *M*agno*M*eter XRS™, including its state-of-the-art software defined radio – the heart of the radio frequency (RF) pulse generation – provide practical advantages over first-generation low-field NMR devices.

> *"Measurements need to be made on suspensions as they are formulated or manufactured in order to relate the results to the application."*

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NMR Spectroscopy

NMR spectroscopy is one of the most powerful analytical tools used to probe details of molecular structure and dynamics techniques. NMR relaxation works by measuring the extent of molecular motion as protons are subtly perturbed by local and external magnetic interactions, and this provides significant advantages over other particle characterization methods, such as light scattering techniques (see Mageleka White Paper 1). However, traditional high resolution NMR requires very high magnetic fields and, hence, generally uses extremely large and powerful magnets. The size, complexity of operation, and expense of such high-field instruments make them overly impractical and/or expensive for users with small labs, minimal resources, or no access to industrial or academic analytical departments, where such devices are typically housed.

The development of portable low-field NMR dispersion analyzers makes the measurement of physical properties of dispersions available to a much wider range of labs. These compact devices are particularly well-suited to contexts where fast, routine, measurements are needed, and in space-limited environments. Despite these benefits, the design of first-generation devices has limited their ability to adequately address many practical issues in dispersion technology.

The *M*agno*M*eter XRS™ Relaxometer from Mageleka is a notable advancement in particle characterization and surface analysis of dispersions. The design of the *M*agno*M*eter XRS™ improves upon existing technology found in other low-field devices to overcome problems inherent in making measurements of dispersions. The four issues discussed below are frequently faced by formulators in a diversity of contexts such as research, development, quality control (QC), and process monitoring. The *M*agno*M*eter XRS™ was designed with these difficulties in mind and makes NMR relaxation measurements easier, more practical and, thus, more accessible to users in any context where routine analysis of complex solid-liquid and liquid-liquid formulations is needed.

Working remotely, in specialized and hazardous environments, or in multiple locations

Working in specialized environments poses a unique set of constraints for making NMR measurements. For example, in production contexts, flow-through measurements are needed in ceramic slurries used in a variety of chemical mechanical planarization applications for integrated circuit manufacture. Some research labs and industrial facilities contain hazardous or controlled environments, as is common when working with radioactive substances or infectious diseases. Additionally, regardless of the environment, sampling may need to be conducted in multiple locations.

The above constraints greatly limit the use of first-generation low-field NMR instruments because their sample probe/magnet and electronics are integrated into one unit. This requires the whole device to be situated within an area which may not be practically possible or safe. Even in cases where extensions/adapters can be attached to a first-generation instrument (e.g., for flow-through sampling), these still must be placed near the electronics of the instrument and, again, this may not be practical or safe. Similarly, for safety, users may not wish to situate their instrument in areas certified for hazardous substances, or such areas may be space-limited and thus not able to accommodate a workstation. Moreover, in manufacturing where multiple sampling locations or production lines are required, operating multiple instruments (one for each location or line) is neither efficient nor cost effective.

Mageleka's next-generation low-field NMR device – the *M*agno*M*eter XRS™ – possesses superior practicality because the sample probe/magnet assembly – called a MagnoPod™ – is an entirely separate unit from the electronic control box. This unique design feature has several advantages. The *M*agno*P*od™ is small, lightweight, and can be sited remotely from the control box, meaning that the sample can be measured in a production line or controlled environment but operated remotely from another location. Conversion of a *M*agno*P*od™ for flow-through use in manufacturing process operation is simple, exchanging *M*agno*P*ods™

is easy, and multiple probe nuclei are available (e.g., ^{7}Li, ^{19}F, ^{31}P). This useful feature is advantageous in, for example, the manufacture of lithium ferrophosphate materials utilized in the fabrication of cathodes for rechargeable batteries. Importantly, multiple *M*agno*P*ods™ can be connected and driven by one controller, eliminating the need to purchase multiple instruments. Thus, the *M*agno*M*eter XRS™ provides cost-effective flexibility for a variety of specialized environments.

Temperature control

It is well known that characterizations of dispersion properties need to be made at constant temperature. Variations in temperature can affect the quality of the dispersion making, for example, QC comparisons among samples (batch-to batch, different sites, etc.) virtually meaningless. Additionally, the storage stability of any suspension is directly impacted by excessive temperature change; hence the requirement for accelerated aging studies at elevated temperature (typically at 40°C) for drug formulations.

As with all particle characterization devices, temperature fluctuations can add unwanted variation to NMR relaxation measurements. The data in Figure 1 was obtained from relaxation measurements made on a 6 wt% suspension of a microfine grade of a silica-coated zinc oxide dispersed in N-methyl-2-pyrollidone. The results show a decrease in relaxation time of *ca.* 1 %/°C, over the temperature range measured – in agreement with literature.

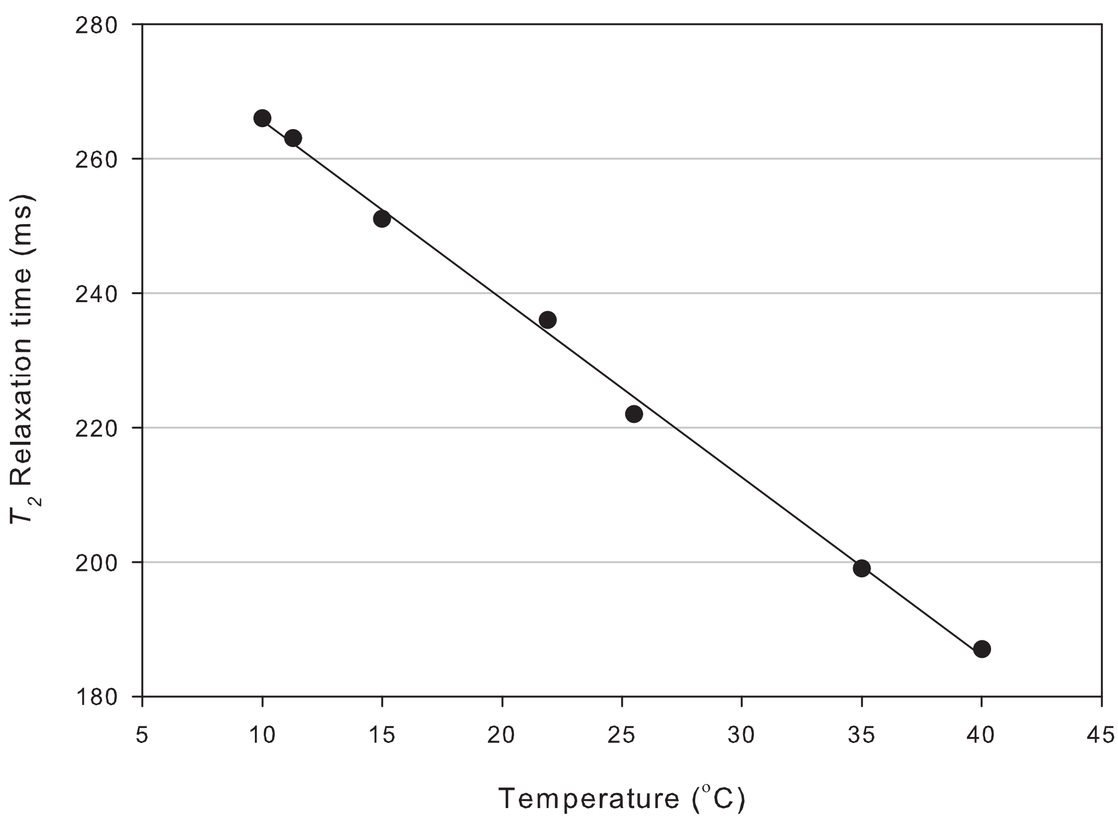

Figure 1. NMR relaxation time as a function of temperature for a non-aqueous suspension of zinc oxide.

From a practical perspective, when an NMR instrument's magnet assembly and electronics are integrated as a single unit, as is the case with first-generation devices, the heat generated by the power supply can easily result in the instrument's temperature rising by more than 5 °C above ambient, which is obviously problematic. Moreover, and importantly, any change in temperature results in a shift in the resonant frequency which must be constantly manually re-set. Thus, a lack of temperature control on low-field NMR devices limits their utility to controlled environment labs and precludes their use in many production plants.

Next-generation devices such as the *M*agno*M*eter XRS™ overcome the temperature issue in three ways. First, the *M*agno*P*od™ has a programmable temperature control allowing temperatures of up to 80 °C. Second, as mentioned above, the *M*agno*P*od™ and the control box can be sited separately (up to 10 meters apart). Third, the resonant frequency is continuously monitored and automatically re-set before every measurement.

These design features give the *M*agno*M*eter XRS™ important practical advantages. The separate pod assembly positions the sample away from the heat of the electronics and it allows for remote operation. Monitoring and rapid automatic adjustment of the resonance frequency saves time and frustration because temperature changes do not result in additional work for the user.

NMR Tubes

Bench-top NMR devices measure samples that are contained in glass tubes, and NMR tubes come in a variety of diameters (typically an outside diameter of 2 to 10 mm). It is challenging to fill a narrow NMR tube with a highly viscous fluid, so larger-diameter tubes (e.g., 10 mm) are needed; conversely, when sample volume is very low, or higher resolution is needed, a narrow-diameter tube (e.g., 2 mm) is ideal. First-generation low-field NMR devices accept only a single diameter NMR tube, and this "one-size-fits-all" approach limits the usefulness of such devices. Next-generation NMR devices, such as the Mageleka *M*agno*M*eter XRS™, provide much more flexibility because they can accept a range of diameters (2 – 10 mm). This practical advantage gives users greater control, both in terms of the range of type and volume of samples that can be measured, but also the measurement sensitivity and averaging of sampling inconsistencies.

Another practical consideration of using NMR tubes is that they can be delicate, especially at narrow diameters. Breakage can occur when a tube is inserted into, or removed from, a benchtop device, and so users occasionally need to clean-up broken sample tubes. While often just an inconvenience, clean-up can be a serious issue when samples contain hazardous materials. First-generation NMR devices that are a single unit are particularly problematic in this regard because the whole instrument must be opened to properly remove any sample and broken glass. In contrast, the design of the *M*agno*M*eter XRS™ greatly reduces the frustration and hazard of removing a broken NMR tube: the "cassette" that includes the RF coil is a simple push-fit connection, so it can be removed easily; from there, the user simply removes a PTFE screw and pushes out the broken NMR tube. Moreover, because the MagnoPod™ is a separate unit, the user does not have to open the whole instrument, so there is no risk of damaging the electronics of the instrument.

Digital vs. Analogue Electronics

The layout of first generation NMR devices is based on conventional, traditional, electronics. This typically includes many analogue components involved in generating and detecting the NMR signal but analogue electronics are inflexible.

In contrast, the electronic design in the *M*agno*M*eter XRS™ is based on the new technique of Direct Digital Synthesis (DDS), which incorporates a software defined radio (SDR) device. Using total digital synthesis and detection of NMR measurements in real time means that complex pulse sequences can be easily programmed with precise phase, amplitude and length. Data sampling at 14 bits and 125 MHz is possible, this has real advantages for characterizing dispersions because of optimized signal to noise and data processing. Not only is this design simpler, but it is much more efficient because it has a lower operating power demand. RF generation and detection is done digitally. Additionally, all filtering and phase detection at the Larmor frequency is done digitally.

Measurement of sedimentation provides a good example of the superiority of digital electronics in NMR instruments. Sedimentation is an essential process in the removal of debris of technological and biological origin from industrial wastewater and domestic sewage, respectively. Conversely, it is problematic in long-term storage of suspensions of dense materials such as ceramics and refractories.

Accurate measurement of sedimentation rates can often be problematic because of instrumental delays since, when particles settle too quickly (through the RF detection zone), precise and repeatable detection of relaxation time is difficult. The sedimentation rate of a suspension depends on a number of factors. In the simple case of a spherical particle it is directly proportional to the density difference between the particle and the fluid and the square of the particle radius and inversely proportional to the fluid viscosity. Table 1 compares the calculated settling rates for different nanosize particles of polystyrene (ρ ≈ 1.04 g/cc) and barium titanate (ρ ≈ 6.02 g/cc) in water.

Table 1: Settling rates (cm per second/10^{-6}) for low- (polystyrene) and high-density (barium titanate) materials at various particle sizes.

	Particle size			
	100 nm	**250 nm**	**500 nm**	**1000 nm**
Polystyrene	0.03	0.20	0.81	3.24
Barium Titanate	3.1	19.2	76.9	307

The data in Table 1 show that the settling rate for the refractory is approximately 100 times that for the polymer. Thus, for dense materials, the speed of measurement over the first few minutes is critical because particles in a suspension will rapidly pass through the RF detection zone before the measurement of relaxation time is completed.

The cutting-edge DDS technology used in the *M*agno*M*eter XRS™ significantly enhances the speed of data processing, which drastically reduces relaxation measurement time. For example, a single scan measurement of T_2 relaxation time can be made on the *M*agno*M*eter XRS™ in a few seconds. Figure 2 shows a graph of relaxation time measured as a function of time for a dilute (< 0.01%) aqueous suspension of magnetic iron oxide particles (ρ ≈ 5.2 g/cc). Note the initial rapid increase in relaxation time over the first minute as the particles quickly settle; the number of data points obtained in the first 20 seconds demonstrates the speed with which measurements can be made. Also, by using multiple pulse sequences even this time can be reduced substantially.

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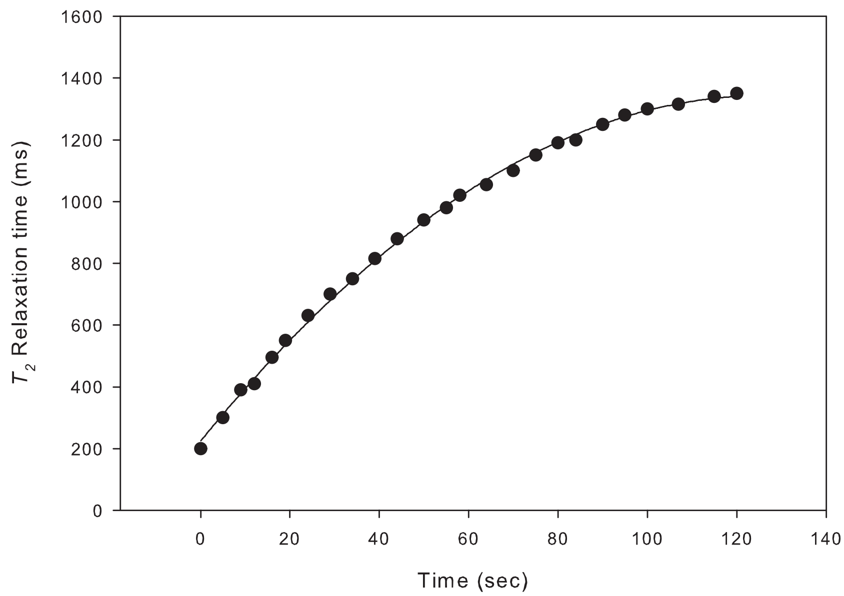

Figure 3: NMR relaxation time as a function of time for a dilute (< 0.01%) aqueous suspension of magnetic iron oxide particles.

Hence, the *M*agno*M*eter XRS™ can be used to study not just sedimentation and settling but also kinetic processes, such as coagulation and flocculation (see Mageleka Application Note 16).

The *M*agno*M*eter XRS™ also incorporates two 14-bit, 8 ns analog-to-digital convertors, giving superior time resolution. RF pulses of up to 1 ms at 8 ns resolution are possible, with any phase shift from 0°-360° as well as dual frequency generation. Note (in Fig. 2) the short initial relaxation time for the suspension (ca. 200 ms). Further, the SDR device provides better control of RF generation (using composite pulses), and a very large pulse sequence library is possible.

The digital technology of the *M*agno*M*eter XRS™ adds up to considerable savings in time and money for analysts. For example, the MagnoMeter XRS™ typically can provide statistically reliable and repeatable results in only minutes. As such, its sample turnover rate makes it feasible for QC as well as in-process applications. In any QC laboratory, throughput is a dominant factor since multiple samples need to be measured or analyzed on a daily basis. Even for research and development applications, it is vital that more than just the measurement duration is considered. The actual total time per sample includes sampling, sample preparation, measurement, calculation, printing, and clean-up. Thus, the time taken to collect data may be only a small fraction of the actual time per sample. Next-generation devices, such as the *M*agno*M*eter XRS™, have been designed with sample-cycle time in mind to provide maximum throughput to the user.

Conclusions

There is great potential for low-field NMR measurements to be applied broadly in the specialized environments of industrial, production, and research labs. However, practical challenges inherent in these environments can greatly limit the utility of first-generation devices. In contrast, next-generation low-field NMR instruments, such as the *M*agno*M*eter XRS™ from Mageleka, have been designed specifically to overcome these challenges and can help formulators in any industry that utilizes suspensions or emulsions, and especially in contexts that pose challenges to other NMR instruments. The flexibility of a separate, temperature-controlled, probe assembly, combined with superior digital electronics and faster signal processing speeds, makes next-generation devices, such as the *M*agno*M*eter XRS™ from Mageleka, the future of low-field bench-top NMR spectroscopy.

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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