Measuring Solids Concentration of Colloids, Slurries and Suspensions Using NMR Relaxation

Introduction

The ability to rapidly analyze solids loadings – especially at high concentration – in nano-size (colloidal) and macroscopic suspensions is important in many fields and is often a necessary quality control (QC) metric in production. For example, cosmetics, foods, paints, pharmaceuticals, and agrochemicals rely on the quality of solid-liquid dispersions and thus workers in these industries must routinely assess multiple metrics of suspensions.

Until recently, the ability to quickly and accurately measure suspensions has been limited. Optical techniques require transparency of medium, electrical techniques require electrical conductivity, static pressure techniques are not useful when differences in density are small, and ultrasonic techniques require a large amount of information on thermophysical properties of the component phases to interpret ultrasonic spectra.

Further, the number of nanotechnology-based products across all industries has been steadily growing. Unlike the traditional dispersive methods (e.g., milling and comminution) of producing suspensions and slurries of macro-size materials, nano-suspensions are increasingly manufactured using *in situ* condensation methods (i.e., starting from molecular solutions) because the particle size distribution is much narrower and can approach exceptionally low polydispersity. Here, there is a need for a direct measurement of the final solids concentration.

Irrespective of the application, a methodology that is quantifiable, fast and non-invasive – without the need to dilute, re-suspend or wash particles – offers practical advantages to any industry working with suspensions.

Nuclear magnetic resonance (NMR) relaxation is a technique that is easy to employ, produces rapid results, and requires limited input data. Importantly, and as we will explore in this Application Note, it is an ideal technique for measuring suspensions at high solids loadings because it does not make any assumptions about the size, shape, or concentration of particles, or the liquid in which they are suspended. The NMR relaxation technique is particularly useful in the pharmaceutical field where sample volumes may be limited, and so may be beneficial not only for characterizing final product attributes but also for large-scale processing and quality control to monitor good mixing and accurate dosing.

About NMR Relaxation

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

> *"When producing nano-suspensions, there is a need for a direct measurement of the final solids concentration."*

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

What the *M*agno*M*eter measures is the extent of molecular motion as protons interact when perturbed by local magnetic fields. The liquid in contact with a particle surface relaxes much more rapidly than does the rest of the liquid, which is free (i.e., "bulk" liquid). This surface relaxation 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. For many dispersions of interest we can assume that there is a fast dynamic exchange between the liquid associated with the particle surface and the bulk liquid. We measure a dynamic average which reflects the properties of the interface.

What does the MagnoMeter do?

The *M*agno*M*eter provides complementary information to traditional particle characterization devices. But it also provides additional interfacial insight not possible with those devices. The actual relaxation value obtained by NMR for the bulk liquid is an average that is dependent upon the exact composition of the suspension. This is somewhat analogous to the zeta potential of a material where the value depends critically upon the exact composition of the dispersion fluid.

The *M*agno*M*eter's measurement technique is non-invasive and non-destructive and it can work with suspensions at any industrially-relevant concentration. This is especially important with industrial slurries that can be highly concentrated. Of practical utility, the *M*agno*M*eter eliminates the dilution issues inherent in making measurements using, for example, traditional light scattering techniques. Moreover, the simple measurement technique takes only minutes (see Mageleka Technical Note 2: The Mageleka *M*agno*M*eter: What is it, and Why use it?).

Using NMR relaxation to determine the solids concentration in a slurry

In this case study, the NMR T_2 relaxation time was measured for a series of five proprietary suspensions containing micron-sized particles of a proteinaceous drug material dispersed at different known concentrations in a non-aqueous fluid, together with a test sample of a similar suspension at a masked (unknown) solids concentration and a sample of the solvent (suspension fluid). Proteinaceous drugs are used to boost a patient's immunity against disease, and they can bind many kinds of pathogens such as viruses, bacteria, and fungi.

Prior to measurement, the bulk suspension was dispersed using an ultrasonic bath for 30 seconds, vigorously shaken for 10 seconds and the procedure repeated four times to ensure complete homogeneity. Enough sample had been prepared such that it was possible to obtain four separate aliquots from each bulk suspension to ensure reproducible sampling. The actual amount of sample required for relaxation analysis is immaterial – here we used only 0.1 mL. Each of the four aliquots was run a minimum of five times and the entire data averaged. No issues were experienced and the total measurement time per sample was less than 10 minutes. Table 1 summarizes the results of the relaxation measurements.

Table 1: Summary of relaxation time data for suspensions of micron-sized particles of a proteinaceous active pharmaceutical ingredient (API) dispersed in a non-aqueous fluid. The concentration of the TEST sample was unknown.

API Concentration (mg/ml)	Average T_2 Relaxation Time (ms)
--------	456.0
107.11	402.1
132.99	390.7
156.98	381.2
197.33	360.1
198.56	360.0
246.05	340.2
315.36	307.1
TEST	334.4

The reproducibility was typically 1.25% or better; the results are, therefore, statistically robust and the differences found are reliable.

Next, a calibration plot was constructed by plotting the Relaxation Number, R_{no}, as a function of the Volume Ratio (of solid-to-liquid), ϕ. To calculate a volume ratio (which is dimensionless) from concentration, the protein material density was assumed to be 1.3 g/cc and that for the solvent (ethyl oleate), taken from the literature, was 0.87 g/cc.

The Relaxation Number

Although the fundamental measurement from the *M*agno*M*eter is a relaxation time, a very useful practical metric, in any application, is the relaxation number, R_{no}, which is a dimensionless parameter defined as:

$$R_{no} = [R_{susp} / R_{sol}] - 1$$

where,

R_{susp} and R_{sol} are the relaxation rates of the (API) suspension and its (bulk) dispersion fluid (ethyl oleate), respectively.

Note that the relaxation rate is the reciprocal of the measured relaxation time (i.e., R=1/T). The relaxation number, which is essentially a relative relaxation rate, can be used to follow kinetic processes such as adsorption and desorption, settling, and even competitive adsorption.

Table 2 shows the calculated values for the relaxation number and volume ratio for the same samples in Table 1, and the data are graphically presented in Figure 1.

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Table: Calculated values for relaxation number and volume ratio for suspensions of micron-sized particles of a proteinaceous drug dispersed in a non-aqueous fluid. Data are the same as in Table 1.

Volume Ratio, ϕ	Relaxation Number, R_{no}
0.080	0.132
0.103	0.164
0.125	0.191
0.164	0.264
0.166	0.273
0.218	0.336
0.308	0.480
-------	0.359

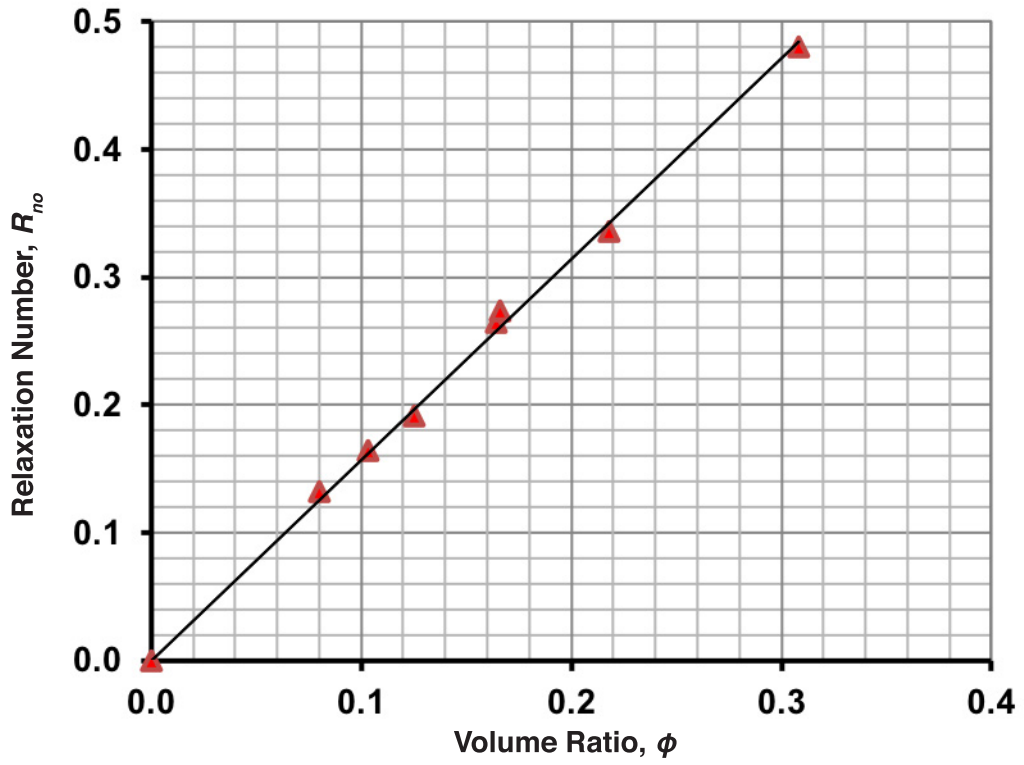

Figure 1. Calibration plot of relaxation number as a function of volume ratio for suspensions of micron-sized particles of a proteinaceous drug dispersed in a non-aqueous fluid.

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The calibration plot is linear, which confirms the validity of the fast exchange assumption. And, from this plot, it was concluded that the TEST sample (T_2 relaxation time = 334.4 ms) had a solids concentration of 260 mg/mL. Comparing this value to the sample concentration based on gravimetric analysis (265 mg/mL), it can be seen that the two measurements differed by <2%.

In Conclusion

This Application Note presents data obtained on samples of protein microparticles dispersed in a suitable suspension liquid that illustrates both the utility and simplicity of the NMR relaxation technique. Although the typical total analysis time for a single sample (20 repeat measurements) was <10 min, a single run could take as little as 5 sec, which could prove useful if the sample was settling or changing with time. From a calibration plot of the relaxation number vs. volume ratio, the solids concentration of an unknown test sample was found to be within 2% of a known value, demonstrating the accuracy of the *M*agno*M*eter's NMR technology.

Considering that the concentrations analyzed in the present study reached 31.5%, these data also demonstrate that NMR relaxation offers a quantifiable, fast and non-invasive method for determining the solids concentration of a suspension or slurry, even at high solids loadings. Importantly, measurements with the *M*agno*M*eter were made directly on the suspensions without any further sample preparation other than ensuring suspension homogeneity.

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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