Using NMR Relaxation Measurements for Quality Control of Incoming Materials used in Formulation of Products

Introduction

The preparation of any suspension or slurry comprising a powder material in a liquid, be it for "blue sky" experimental R&D purposes or in the pre-formulation of a commercial product, will always start with a solid and a liquid. Unfortunately raw materials are never 100% pure, and this is true even for National Formulary (pharmaceutical) grade material. Indeed, industrial material can contain as little as 80% of the active component, as a cursory glance at the typical Material Safety Data Sheet and the Technical Data Sheet, always supplied with the material, will attest to! In all cases, the type and level of impurities depends on the source of the material and any subsequent processing.

Supply houses and distributors are not usually the primary manufacturer of raw materials. However, it is critical to verify the technical specification of all materials, as this can directly influence their behavior at every stage in the manufacturing process – from fundamental formulation to final end-use product. Indeed, potential variable chemical and physical characteristics can have profound effects on formulations (see Mageleka Technical Note #3: NMR Relaxation as an Aid in Formulation). Thus, an exact specification is needed for all materials used in formulations because, without these, comparisons (e.g., between batches, lots, or just concentrations) can often be meaningless.

This Application Note will explore nuclear magnetic resonance (NMR) relaxation measurements as a fast and easy method to determine how the quality of raw materials can vary depending on the source and differences in processing. The case studies presented here demonstrate just two potential applications of NMR relaxation measurements in a formulation setting. More information as to how such measurements can be of use is available at www.mageleka.com.

About NMR Relaxation

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

NMR relaxation time is a fundamental intrinsic property of solids and liquids. What the *M*agno*M*eter measures is the extent of molecular motion as protons react when perturbed by a magnetic field. 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

> *"Variable chemical and physical characteristics of raw materials can have profound effects on formulations."*

MAGELEKA, Inc.
1319 N. New York Avenue
Winter Park, FL 32789 USA

Worldwide: +1 617 331 1130
Europe: +44 (0)1744 325005

www.mageleka.com

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 the dynamic exchange between the liquid associated with the particle surface and the bulk liquid is very rapid (i.e., a "fast exchange"). Thus, the measurement of relaxation time provides direct information about the extent and nature of any particle-liquid interface (see Mageleka Technical Note 1: Physical Characterization of Suspensions and Slurries using NMR Relaxation), and it is this basic technique that is used in the *M*agno*M*eter.

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:

$$R_{no} = (R_{av} - R_b)/R_b$$

Where, R_{av} and R_b are the relaxation rates of the suspension and its (bulk) dispersion fluid, respectively. Note that the relaxation rate is the reciprocal of the measured relaxation time. The relaxation number can be used to follow kinetic processes such as adsorption and desorption, settling, and even competitive adsorption.

What does the *M*agno*M*eter do?

The *M*agno*M*eter provides complementary information and intelligence to traditional particle characterization devices. The actual relaxation number obtained from NMR is an average 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.

Importantly, the *M*agno*M*eter's measurement technique is both non-invasive and non-destructive so samples can be stored, if required, for re-analysis at some future time. Hence, the *M*agno*M*eter can be used to measure properties such as accelerated aging or shelf storage. Further, the instrument will work with suspensions at any industrially-relevant concentration and opacity, and the inherently simple measurements technique takes only minutes (see Mageleka Technical Note 2: The Mageleka *M*agno*M*eter XRS Relaxometer).

Comparing the Quality of Basic Raw Materials Using NMR Relaxation Measurements

Here we show data for two widely used chemicals – alumina and lime – that demonstrate how nominally identical raw materials can vary when sourced from different locations or subsequently processed.

Alumina is produced from bauxite ore that is mined in different parts of the world. The four samples measured were raw material sourced from Australia, Brazil, West Africa, and Russia (Fig. 1). High solids slurries were prepared at 37.5 wt% in ethanol and the relaxation time measured directly. The reproducibility of the relaxation times was no more than 1% and the results are displayed as a relaxation number. The difference between the four samples is small but statistically greater than experimental error.

The alumina from Sources 1 and 3 are similar, as are the materials from Sources 2 and 4. The difference between the four materials is likely a consequence of real variations in the geometric surface area (because of both the size and surface roughness of the slurry material particles) as well as, potentially, the surface chemistry (see Mageleka White Paper #2: Wetted Surface Area as a Critical Metric in the Characterization of Suspensions of Materials). Determining which would require additional physical characterization using, for example, traditional particle sizing and zeta potential instrumentation.

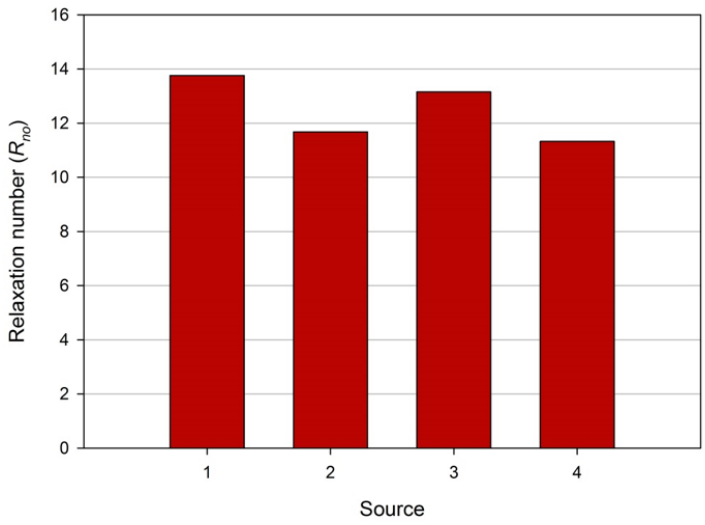

FIGURE 1: Variation in relaxation number of slurries of alumina sourced from different countries. All slurries were prepared at 37.5 wt% in ethanol.

Crude, mined limestone is converted to slaked lime by heating and hydration, but variation in this process can influence the quality of the final product. The samples shown in Figure 2 were created using different processing conditions and were compared by measuring the relaxation time of 11 wt% suspensions in methanol (to minimize dissolution). The reproducibility of the relaxation times was, again, no more than 1%, and the results are displayed as a relaxation number. Here, there is a significant difference between the two materials. It is clear that the differences in physical and chemical processing methods had a major impact on the final material.

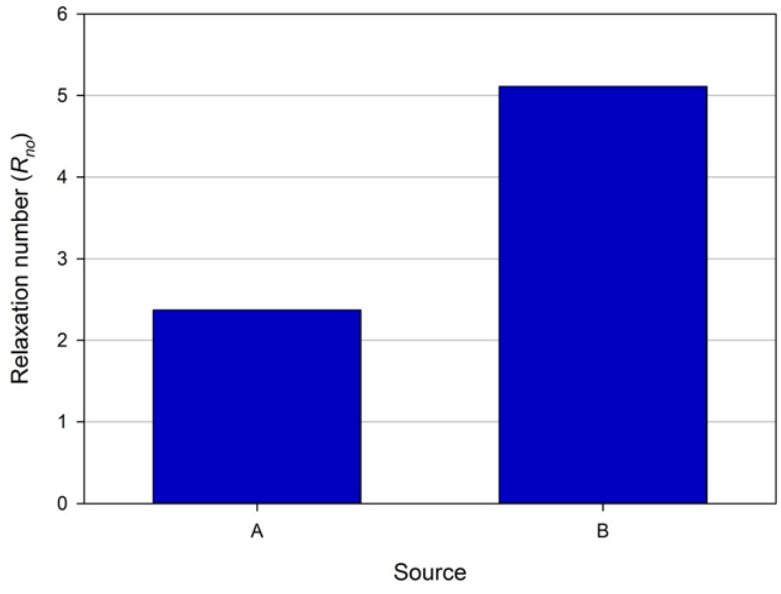

FIGURE 2: Variation in relaxation number of suspensions of lime prepared at 11 wt% in methanol. Lime from the two sources differed in how they were physically and chemically processed.

MAGELEKA, Inc.
1319 N. New York Avenue
Winter Park, FL 32789 USA

Worldwide: +1 617 331 1130
Europe: +44 (0)1744 325005

www.mageleka.com

In Conclusion

The NMR relaxation data presented above shows that, for both types of chemicals investigated, nominally identical materials were clearly not the same. In addition to influencing performance of any subsequent procedures that use them, the potential economic impact of variation in these raw materials must also be considered. Furthermore, these two case studies demonstrate how the Mageleka *M*agno*M*eter XRS™ can be a fast, simple tool for easy comparison of raw materials obtained from different sources and after any physical or chemical processing. NMR relaxation measurements made by the *M*agno*M*eter are well-suited to any context where solid-liquid or liquid-liquid dispersions need to be monitored routinely.

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

MAGELEKA, Inc.
1319 N. New York Avenue
Winter Park, FL 32789 USA

Worldwide: +1 617 331 1130
Europe: +44 (0)1744 325005

www.mageleka.com