Quality Control of an Active Pharmaceutical Ingredient

Introduction

Delivering products that meet or exceed customers' expectations is essential to building a successful business. Quality control (QC) is a process through which a business seeks to ensure that product quality is maintained or improved. It involves testing of units and determining if they are within the specifications for the expected final product. It is a well-recognized that high quality products are much more efficient and effective, so strict QC benefits both the manufacturer and the consumer.

QC is an essential function in the pharmaceutical industry, where drug manufacturers must thoroughly test materials, processes, equipment, and techniques to ensure their final products are consistent, safe, effective, and predictable. Compromising the quality of active pharmaceutical ingredients (APIs) – and, indeed, in pharmaceutical products in general – risks compromising the overall health of those who use drug formulations.

A major function in QC is to verify the product quality against some predefined standard(s), to ensure the quality of all the batches of drug products manufactured at every stage of the production. The production of the overwhelming majority of APIs involves, at some point in their production, the formulation of suspensions. Thus, a methodology that is quantifiable, fast, and non-invasive – *without the need to dilute suspensions* – offers practical and economic advantages as a QC tool in the pharmaceutical industry. However, the test must be objective, easy to run, and be predictive – that is, a test that measures *fundamental* characteristics and is neither a function of the instrument nor of the operator. NMR spectroscopy provides such a test.

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 to be designed that have small footprints and are suited to normal, routine laboratory analysis.

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; see Mageleka Technical Note 1 at www.mageleka.com).

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

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liquid. We measure a dynamic average which reflects the properties of the interface.

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

Many particle characterization and analysis instruments used in R&D studies are, often, not well-suited for use in a quality control (QC) environment, where rapid assessments are key. In addition to its speed (measurements can be made in a few minutes), the *R*elaxo*M*eter provides complementary information to traditional characterization devices and additional interfacial insight not possible with those devices. Moreover, the *R*elaxo*M*eter's measurement technique is noninvasive and non-destructive and it can work with suspensions at any industrially relevant concentration. This latter feature is especially important for slurries – which can be highly concentrated.

Of practical utility, the *R*elaxo*M*eter eliminates the dilution issues inherent in making measurements using, for example, traditional light scattering techniques. Since dilution is never an innocuous process, wherever possible suspensions or slurries should be analyzed as they are prepared (see Mageleka Technical Note 5). Moreover, the simple measurement technique takes only minutes (see Mageleka Technical Note 2). Thus, it is ideal technique for measuring suspensions at high solids loadings; it does not make any assumptions about the size, shape, or concentration of particles, or the liquid in which they are suspended.

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. Thus, for a suspension of known composition, prepared by a fixed process, the average relaxation time should – within experimental error – be the same (see Mageleka Application Note 12). This makes the *R*elaxo*M*eter's measurement technique ideally suited to QC because the relaxation time of ingredients, components, or products from different batches or lots can be used to assess quality.

In this Application Note, we will explore how NMR relaxation measurement from Mageleka's *R*elaxo*M*eter can reveal differences in what should be identical APIs – differences that can affect, for example, the rate of absorption or metabolism.

Using NMR relaxation for fast Quality Control of Active Pharmaceutical Ingredients

In this case study, two sets of different API materials were supplied by a major generic manufacturer. The first set comprised six different lots of an API pre-dispersed at approximately 20 wt% in IsoparG – a synthetic C_{10}-C_{11} isoparaffinic fluid. All batches had passed normal quality control testing based on the measurement of the mean particle size on a *diluted* sample of the suspension made using a device based on laser light scattering.

The relaxation time was measured directly on the suspensions as received without dilution. The repeatability was good (a coefficient of variation <1%) and so we can conclude that the results are statistically robust. A value for the wetted surface area was calculated (see Mageleka White Paper 1) from the average relaxation time and the results are shown in Table 1.

Note that for a given (fixed) solids concentration), a larger relaxation time is typically indicative of a smaller available wetted surface area (larger particles). This latter metric directly impacts drug performance because, as dictated by the Noyes-Whitney equation, the rate of dissolution of an API is driven by concentration and surface area.

As can be seen in Table 1, lot #1 had a significantly smaller surface area (4.4 m^2g^{-1}) and lot #3 had a somewhat larger surface area (5.6 m^2g^{-1}) than lots 2,4,5 and 6. If sufficient data were available, it would be possible to define precise upper and lower control limits for QC purposes.

Given the importance of knowing the surface area of APIs because of its relevance to bioavailability, a

Table 1: Wetted surface area of non-aqueous suspensions of six lots of an active pharmaceutical ingredient calculated from NMR relaxation times

Lot	1	2	3	4	5	6
Solids %	20.05	19.91	19.89	19.95	20.00	20.07
Surface Area (m^2g^{-1})	4.4	5.3	5.6	5.4	5.2	5.3

direct measurement of the wetted surface area without dilution, or other sample preparation, is critical. This parameter is now accessible quickly and easily using the *R*elaxo*M*eter.

Since the total surface area is dominated by the fine end of any particle size distribution (PSD) – because, in the simplest case, surface area trends with the square of particle diameter – this suggests that lot #1 would have fewer small particles and lot #3 would have more, respectively. A limitation of laser light scattering is that the technique is not sensitive to small fractions of small particles within a PSD. Hence, it is not surprising that the measured mean particle sizes for the six lots, provided by the manufacturer as normal QC, was less precise. Thus, the results presented here highlight that reliance on measurements based solely on light scattering techniques can be misleading and lead to erroneous conclusions (see Mageleka Application Note 10).

The second set comprised five batches of aqueous suspensions of an API dispersed at approximately 13 wt%. The samples had apparently been selected at random from different milled batches. Here, the QC standard was *in-vitro* release testing (IVRT) using a Franz cell.

As in the previous study, a value for the wetted surface area was calculated from the average relaxation time measured on directly on the suspensions as received without dilution. Again, the repeatability of the NMR relaxation measurements was good (coefficient of variation <2%) and so we can conclude that the results are statistically robust. The results are shown in Table 2.

Table 2: Wetted surface area of Aqueous suspensions of an API calculated from NMR relaxation times

Batch	2	4	3	1	5
Solids %	13.30	13.30	13.31	13.25	13.29
Surface Area (m^2g^{-1})	4.7	4.9	5.8	8.5	12.8

The results shown in Table 2 are in order of increasing wetted surface area, the values for which were found to trend directly with IVRT data (i.e., the greater the API surface area, the faster the release). Given the range of surface area values found, the data suggests that the APIs in the suspensions must have been milled either using different shear rates, or for different times.

IVRT is expensive and can take considerable time. By contrast, the speed and simplicity of NMR-based measurements made with the RelaxoMeter make it an ideal tool for routine QC selection.

In Conclusion

The NMR relaxation data in the examples above demonstrates how the Mageleka *R*elaxo*M*eter can be a fast, simple tool for quality control of batch-to-batch and lot-to lot variations of API suspensions. The *R*elaxo*M*eter's NMR-based technique revealed fundamental differences in APIs that traditional QC techniques, such as laser light scattering was not able to detect and is easier, cheaper and faster than IVRT. Furthermore, the ability to interrogate API suspensions without dilution provides a major practical advantage for NMR relaxation over other particle characterization techniques (especially particle sizing by light scattering methods).

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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