

Introduction to the Acorn Area

Exploring Surfaces

SLIDE 1: Exploring Surfaces with the Acorn Area

Welcome to the first in a series of short, instructional videos from XiGo Nanotools, where we will describe a range of instruments that we offer for particle characterization and analysis, how they work and the applications where they can be utilized. The title of this first talk is Exploring Surfaces with the Acorn Area,

SLIDE 2: Agenda

Our agenda will cover “Why should we use nuclear magnetic resonance?”; “What are the practical advantages of the technique?”; “Why is it important to work with concentrated suspensions and the consequences of diluting suspensions?”; How does NMR work?”; “The relaxation method and measurement techniques”; “The utility of the measurement” and, finally, we will briefly describe the Acorn Area device and the various options that are available for the instrument.

SLIDE 3: Why characterize Suspensions using NMR Relaxation

So, let’s start by discussing why characterize suspensions using NMR relaxation. Most particulate materials are made, or used, as suspensions in liquids; and, the majority of suspensions are concentrates. Further, it is the particle-liquid interface - no matter what the particle, no matter what the liquid – that controls product performance. And, product performance is defined as what the suspension is designed to do, or be used for.

Nuclear magnetic resonance is uniquely sensitive to two very important features of any particle-liquid interface. The first is the extent of wetted surface in a given suspension. Here we can include size, shape, morphology and, indeed, porosity. Second, NMR is also sensitive to the chemical nature of a particle surface. This would include the fundamental surface charge and, thereby, the type and number of functional groups – both of which will impact the wettability of a surface by a given liquid. This is encapsulated in the small schematic at the bottom right-hand side. NMR is unique in this because, typically, traditional characterization instruments are only sensitive to one of the features – for example, particle size or zeta potential but not both simultaneously.

SLIDE 4: Practical Advantages of NMR Relaxation Measurements

What, then, are the practical advantages?

First, any particle, of any size or shape can be studied. It does not matter whether it is an active pharmaceutical ingredient. It does not matter if the “particle” is even a liquid. So, you can work with emulsions and solid materials from alumina to zircon.

Second, you can work with any liquid as long as it contains at least one hydrogen atom. So, for example, we can make measurements in hexane but not carbon tetrachloride. Even mixtures of miscible liquids such as ethanol/toluene can be used. This is a very useful benefit, particularly in non-aqueous media, when investigating the wettability of surfaces.

Third, the solids concentration can be very high indeed – the limit is simply dictated by whether you can get the sample into an NMR tube.

No dilution is necessary. Samples can be measured as they prepared, or used – an industrially important benefit. The overall measurement time can be very fast. Of course, it depends upon the sample under investigation and the precision required but is typically less than 5 minutes.

Only a small amount of sample is necessary (ca 0.1mL) and, importantly, the technique is non-invasive and non-destructive. This means that samples can be stored in the NMR tube and re-analyzed at any later date.

NMR is a very versatile technique, indeed.

SLIDE 5: Why Concentrates?

Now, let's discuss why you need to measure suspensions as they are prepared and without dilution. What is so important?

In the schematic on the left-hand side of this Slide, the “header” is labelled “Initial Contact”. What this refers to is any suspension as it is made or formulated. And, what is shown is a representation of the particles in that suspension. The particles themselves are red and the blue “dots” symbolize the “surface chemical nature”. In practice this could be the fundamental functional groups, or something adsorbed, on the surface.

On the right-hand side is that same suspension in which a defined chemical equilibrium has been established between the particles and the liquid. What it means is that any species that can potentially desorb, or dissolve, or dissociate does so to the limit or capacity of the available liquid phase. The greater the particle concentration, the less will be the volume of free liquid available. Which means that the solubility

limit for surface species will be exceeded inhibiting any further desorption, dissolution, etc. So, in concentrated suspensions, the equilibrium is always shifted towards the surface and the little icon represents the surface “probed” by any characterization technique.

SLIDE 6: Dilution Affects surfaces

As we see in the schematic on the left-hand side of this next slide, the initial contact in a dilute suspension looks much like that seen in the previous slide except, now, there are fewer particles. However, once this system reaches its equilibrium state it is completely different because the total volume of liquid is much larger; this then allows more surface species to desorb, dissociate, etc. The equilibrium is now shifted towards the solution. And, the more dilute the suspension the greater the shift.

At the extreme you can end up with a suspension where the surface “probed” is now represented by the little icon - a surface that has no blue “dots”. This is completely different from that existing in the concentrated suspension.

The important point to take away is that dilution is never an innocuous process and the consequence is that you will get a value from whatever characterization technique used that is not representative of the concentrated suspension and so may not translate into a useful performance metric.

However, I do not mean to imply that you cannot dilute any suspension – there are ways to minimize the shift in chemical equilibrium but is beyond the subject of this webinar.

SLIDE 7: How it works...

So, how does the methodology work?

Hydrogen atoms in liquids behave a bit like little “magnets” and so, in this schematic we show each liquid molecule (the blue ellipses) with a “North” and a “South”. In the *absence* of an applied magnetic field the orientation of these proton “magnets” are random and so the net magnetic field is, of course, zero.

SLIDE 8: How it works...

When we place a sample, contained in an NMR tube, into the cassette assembly of the Acorn Area, it is concentric within an RF coil that is located between two permanent magnets - shown by the green discs in the Schematic at left (and the red discs in the Schematic on the right) - that provide a static magnetic field (B_0). All the

liquid proton “magnets” (the blue ellipses) align in the direction of this static magnetic field - a process that occurs rapidly (in a few seconds).

SLIDE 9: How it works...

If we apply an RF pulse (at an appropriate frequency and duration) to the RF coil, a temporary magnetic field, $B_{\text{sub-1}}$, is produced and this is superimposed over the original magnetic field. The proton “magnets” now rotate and realign with this new field that, in the Acorn Area, is 90 degrees to the original static field – a process that takes a few micro seconds. When the RF pulse is switched off, $B_{\text{sub-1}}$ is removed and, so, the proton “magnets” “relax” and rotate back to their original orientation within $B_{\text{sub-0}}$.

A moving magnet in an RF coil produces a decaying voltage, which has an exponential shape, as shown in the graph (at bottom right) where the blue line is the fit to the experimental data points (red dots). From this exponential decay we can obtain a characteristic “relaxation time” for the liquid.

SLIDE 10: Proton NMR relaxation

We can define two liquid domains - liquid on the surface of a particle (bound liquid) and liquid far away from the particle surface (bulk liquid). When a liquid molecule adsorbs to a particle surface (in other words, wets the surface) its rotational and translational motion is restricted and so bound liquid molecules (darker blue) relax much more quickly - on the order of only 0.5-2 milliseconds) than free liquid molecules far away from the particle (light blue) - on the order of 2-3 seconds. In reality, of course, it is a dynamic equilibrium where liquid molecules rapidly switch between the surface and bulk domains (called fast exchange) and this is faster than the timescale of a single NMR experiment. That is why we observe a single relaxation time.

So, any changes in the extent (and nature) of the surface, or the rate of exchange, can be measured with NMR.

A suspension of particles in a liquid with a large wetted surface area (for example, a nanoparticulate pigment) will have a smaller relaxation time than a suspension with a small wetted surface area (for example, micron-sized active pharmaceutical materials) because, in the former, there is more liquid molecules fluid associated with the particle surface.

SLIDE 11: NMR Relaxation: Surface, Liquid and Suspension

So, now let's look at practical situation. There are three separate relaxation phenomena occurring simultaneously as shown in the graph on the left. The first is that for a bulk liquid and, ideally, we need to measure this independently. The next is that for the solid surface. Here the relaxation time is so fast that we can ignore it using our low-field Acorn Area instrument. Third, there is the relaxation time of a suspension. Since the solid surface relaxation rate is so fast, it does not take much surface-associated liquid to produce a significant shift in the relaxation time of a suspension (compared with that for the bulk liquid).

The upper graph on the right shows how the relaxation time decreases as the particle concentration (and, hence, total wetted surface area) in a suspension increases. The example given here is for an aqueous dispersion of 100 nm titanium dioxide. The biggest change (shorter relaxation time) occurs for high concentration suspensions. For repeatable measurements it is important to know the concentration fairly precisely, especially the more dilute a suspension.

Although what is measured is a relaxation "time", we can define a new term, the relaxation "rate", as the reciprocal of the relaxation time. This change in parameter linearizes the data (lower graph on the right) and so provides a much more convenient means to express the data.

SLIDE 12: Utility of NMR Relaxation

Finally, NMR relaxation is an exceptionally informative technique.

As I have mentioned earlier it can be used to probe the extent (wetted surface area) and nature (surface chemistry) of a particle surface and look at effects of morphology and porosity. Each of these will be discussed in more detail in future short webinars.

NMR relaxation is also very useful in optimizing formulation development. Any species that can displace the bound liquid of a wetted surface - such as a dispersant, or surfactant or polymer, will change the relaxation rate. Hence, we can use NMR relaxation to study adsorption and desorption processes – comparing and contrasting the efficiency of wetting agents, dispersants and stabilizers – as well as sedimentation rates. It is particularly useful to study aggregation phenomena such as flocculation and coagulation. Because NMR measurements can be made at any concentration, the technique is very convenient to monitor milling and grinding, almost in real-time. Again, each of these applications will be covered in future webinars.

At a practical level, NMR relaxation measurements will find use from blue-sky, exploratory research and development, through quality control/quality assurance to process monitoring in almost any industry.

SLIDE 13: The Acorn Area

In conclusion, let's look at the Acorn Area instrument.

It is a low-field, 13Mhz device that is small, portable (weighing only about 7 kilogram/14, or so, pounds). Patents have been issued in the US, China, Japan and the EU. Interestingly, a paper by Claves demonstrates that low-field devices provide superior relaxation time resolution compared with traditional expensive, high-field analytical NMR instruments.

The Acorn Area is controlled using proprietary AreaQuant software that simple to operate and requires minimum training. It measures relaxation time and calculates the wetted surface area of suspensions.

Measurements are typically made in Batch Mode. A Time Mode allows time-dependent process to be monitored.

Two separate Temperature Control Options are available. The first provides control from approximately 10 degrees Celcius to 40 degrees Celcius. The second allows control from ambient up to in excess of 60 degrees Celcius.

There is also variant called the Acorn Flow. This modification allows for stop-flow measurement of any suspension that can be pumped. No alignment is necessary because the Acorn Area has no moving parts and so, upgrade in the field is straightforward. The Acorn Flow is particularly useful for continuous sampling of heterogeneous and asymmetric particle systems to obtain better reproducibility. It also permits measurements to be made of the addition of reagents and additives.

SLIDE 14: Thank You

Thank you very much for joining me on this introductory webinar. Please access the XiGo website for upcoming follow-up presentations.