

Scientists in product development in the pharmaceutical industry seek to optimize drug product characteristics such as pharmacokinetics, chemical and physical stability at the same time using the most cost effective manufacturing strategy for a given dosage form. A complete understanding of the nature and the extent of the wetted particle surface provides the pharmaceutical industry with a valuable tool to optimize product performance in each of these categories in development, and later, during manufacturing, to monitor product quality.

Until the advent of the Acorn Area, particle size analyzers were the most popular particle analyzer used to study particles dispersed in drug product. Size measurements were constrained to very dilute conditions, are agnostic to the chemistry of the particle surface, reported only an equivalent spherical diameter, and are not very sensitive to the smallest fraction in a particle size distribution. Reducing the particle size of drug product has been correlated with increased bioavailability. Importantly, however, reducing the particle size will significantly increase the specific surface area-to-volume ratio. This dramatically affects not just adsorption of chemicals and other moieties onto the particle surface but also the interaction between particles and system properties such as suspension rheology, coating and adhesion. Despite the importance of the particle surface on product performance, until the Acorn Area, particle surface area measurements required that the particles first were separated from the liquid drug product and were very tedious to perform. These results have very little relevance to the behavior of API particles suspended in a liquid drug product.

Drug Product Storage Stability

Formulation stability includes both chemical stability and physical stability. Flocculation and sedimentation processes are two physical processes that influence formulation physical stability. When particles sediment, a concentration gradient develops in a vertical NMR tube. Since the NMR signal observed is proportional to the quantity of fluid in the measurement zone of the tube, the magnitude and the relaxation time of the sample changes as sedimentation progresses. The benefit in comparison with light based sedimentation methods is that this can be done with high solids loaded dispersions, and monitors the behavior of the dispersion throughout the sample, as opposed to a small portion of the sample as in backscatter measurements. NMR measurements are quite sensitive, and can detect sedimentation long before any settling can be perceived by eye.

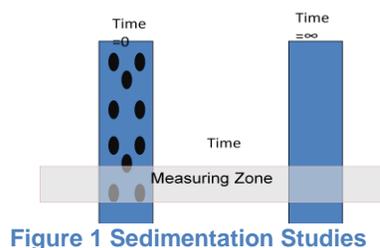


Figure 1 Sedimentation Studies

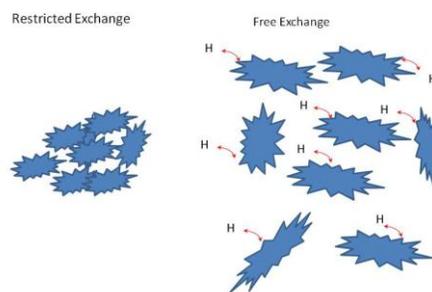


Figure 2 Flocculation and Restricted versus Free Exchange

As particles flocculate, as shown in Figure 2, the liquid protons inside the floc have limited ability to exchange with protons in the bulk liquid as shown at left. Any change in the dispersion structure which alters proton exchange between the particle and surface can be observed with NMR. Thus flocculated dispersions demonstrate a relaxation time shorter than that of an identical stable dispersion.

One of the benefits of NMR is that the measurements are non-invasive- measurements can be made repeatedly on the same sample, which minimizes the amount of clinical trial material required for a stability study, and reduces variations in sample results associated with sampling, especially in early development manufacturing processes. Thermal studies can be performed with drug product in NMR tubes, both elevated temperature studies as well as freeze thaw thermal cycling. Scientists use rheology to monitor physical stability in concentrated dispersions, however, that measurement typically requires a great deal of sample and is destructive, while NMR measurements can be made on the same sample throughout the entire stability study.

Pharmacokinetics

Increasing API particle surface area allows for much faster dissolution of drug API in the gut milieu; the Noyes-Whitney equation illustrates how drug API dissolution rate is directly related to surface area. Low drug active bioavailability can lead to inefficient treatment, higher cost and risk of toxic side effects. There is also a growing body of evidence that, specifically with nanoparticulate materials, it is the surface area and not particle size that is the defining metric that controls toxicological interaction. Thus, the dispersed (or wetted) surface area can be a critical metric of drug product performance.

It is well-known that particle shape, surface irregularities and porosity will inevitably lead to estimated values of surface area from particle size measurements that differ significantly from the true value. Quantitative estimation is possible for spherical, monodisperse particles such as silica but not for irregular particles such as API. Thus, indirect estimate of surface area from particle size measurement can result in misleading, if not erroneous, assumptions about bioavailability, etc. Clearly, the directly measured surface area will be the more relevant value.

Drug Product Formulation Development

Poorly water-soluble APIs need to be correctly dispersed and stabilized or the subsequent suspensions may suffer from an inadequate, or highly variable, rate and/or extent of drug adsorption. Further, new approaches especially in the design of “nanoparticulate” API formulations and drug delivery platforms necessitate elaborate stabilization as they proceed from manufacture to patient; obtaining optimum stability of each of these multi-component systems poses significant problems. Very frequently hydrosoluble neutral polymers are used in conjunction with surfactants and their adsorption onto particles is key to the preparation of stable homo- and hetero-dispersions.

Acorn Area measurements can be used to answer the type of challenges described above. For example, the molecular motions of the species adsorbed onto the particle surface can be used as a very sensitive probe of the particle surface. NMR relaxation measurements are sensitive to the extent of available surface and so can be used to directly measure the surface area of particles dispersed in a liquid, independent of particle size (distribution) or shape. Suspensions can be measured non-invasively and in their native state without further preparation or dilution; suspensions can be monitored over time. Thus, drug product formulations can be studied under, for example, ICH guidelines to measure the effects of accelerated aging.

Further, if a moiety adsorbs at an interface it will result in a change in the relaxation time. One important consequence of this is that competitive adsorption and/or displacement of polyelectrolytes, macromolecules and surfactants at interfaces can be studied. It is straightforward, especially using the flow-through option of the Acorn Area, to determine “optimum coverage” of an adsorbed species and to correlate it with, for example, change in solids concentration.

There are two basic procedures used for the preparation of suspensions: dispersive and condensation methods. In the former, often referred to as a “top-down” method, one phase is “dispersed” in another by comminution and attrition using mills of various types; although the average particle size can be made quite small the PSD is usually broad. The effect of overgrinding of massive solid material, or the use of excessive mechanical attrition during formulation, results in “fines” and the consequence of this to product performance can be significant. NMR relaxation measurements, using the Acorn Area, are rapid and so API milling processes can be studied virtually in real-time.

In the case of condensation, called a “bottom-up” method, conditions are created (starting from molecular solutions) in which individual molecules combine to form aggregates. Here the resulting PSD is much narrower and can approach exceptionally low polydispersity but, unless well stabilized, these dispersions are subject to Ostwald ripening. Such changes in the state of dispersion can be monitored using the “time-mode” function of the Acorn Area.

There is currently much effort underway in producing nanoparticulate suspensions of drug materials and to develop reformulations based on nanotechnology because the creation of API's that are “nano-size” offers additional advantages that are not attainable with even typical micronized drug products. The reason for the commercial success of nanotechnology-based drug delivery approaches can be attributable to the improved biological performance and compliance, which in turn may give rise to patentable technologies, which is a key metric for investors.

Pharma and the Acorn Area



Characterization of nanoparticles is often difficult due not only to their active nature but also because of limitations and requirements of available techniques (such as particle sizing). The advent of the XiGo Acorn Area provides a unique opportunity to study not only the extent of the API particle-liquid interface but also the chemical equilibrium at that interface.