Pharma Stability Study

Application Note 132

Measuring concentrated pharma formulations without dilution is one of the biggest advantages of relaxation measurements using the Acorn Area or Drop. In contrast, light based particle size analysis requires extreme dilution, providing little information about the particulate macrostructure of the concentrated formulation. Magnetic resonance results are also uniquely sensitive to the smallest particles because they contribute most to the total surface area of the dispersion.

A non-porous dispersion of non-interacting particles should produce a single relaxation time which can be related to the wetted surface area by appropriate consideration of the particle concentration. These formulations would also exhibit netwonian behavior in a flow curve. When particles aggregate, trapped liquid domains may exist which produce multiple relaxation times. Monitoring the magnitude of these relaxation times and their dependence on time, storage conditions, and batch size provides the user with a mechanism to study the dynamics of structure formation.

The figures below compare the same formulation made using 5, 1.5, & 0.5 kg batch sizes and two different ICH stability temperatures, 25 and 40 Celsius. The figure on the left, T2a, denotes the principal or long relaxation time. The figure on the right, T2b, the shorter relaxation time, related to the aggregates. While we don't see a meaningful difference in T2a, T2b, tells a much more important story. As batch size decreases, we observe a greater reduction in T2b. Varying batch size can alter the shear forces producd during manufacture, reducing the particle size and stability. At 40˚C, we observe a reduction in T2b of approximately 75%.

Sometimes formulators intentionally add components that cause particles to be weakly aggregated, which can then disperse on shaking. It can be challenging to achieve the right balance of aggregation during storage. These phenomena are concentration dependent, hence the need to study formulations at the concentrations used in manufacture to obtain a complete picture of stability. Lastly, the wetted surface area controls bioavailability. Studying how aggreagation influences bioavailability is critical to formulation optimization.