Material Characterization for QbD – excipients and ingredients

Many key ingredients in formulations are in themselves complex mixtures of a large number of individual components differing in molecular weight, substituent pattern, branching, charge density, etc. The exact batch-dependent composition of these complex ingredients directly impacts performance and manufacturability of the products in which they are included. These considerations illustrate the need for careful characterization and in-depth understanding of ingredients, in order to ensure robust manufacturing processes and reproducible product performance.

Choosing green ingredients is a smart and sometimes necessary move. However, the complexity of these materials also brings challenges for formulators and QA staff.

Complexity is the name of the game

Non-ionic surfactants belonging to the polysorbate family are key functional ingredients in both cosmetics and pharmaceutical products. Therefore, we use polysorbate 80 as an example to prove our point. Nominally, polysorbate 80 is the ethoxylated oleate ester of sorbitan, and in many sources of information (for instance, Wikipedia) you will find that it has a molecular weight of 1310 g/mol. The use of an exact molecular weight would seem to indicate that the material is well-defined, and consequently easy to understand. Alas, nothing can be further from the truth. In fact, polysorbate 80 is by no means monodisperse, but rather contains as many components as the resolution of your mass spectrometer allows you to detect (Fig. 1)! A single glance at Fig. 1 should make it blatantly obvious that materials like polysorbate call for analytical methods and specifications that are based on the science of complexity rather than the illusion of simplicity – at least if you want the specifications to be meaningful in the context of process robustness and product performance.

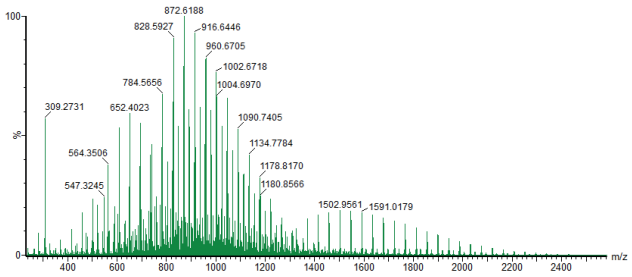

Figure 1. *Positive electrospray mass spectrum of polysorbate 80, illustrating the distribution of species in this complex material. The most prominent peaks stem from doubly-charged species.*

Why generic specifications fail

The generic (e.g. pharmacopoeial) specifications for many complex ingredients are extensive, but quite often obsolete and irrelevant for modern QbD-based formulation and processing. If we continue to use polysorbate 80 as an example, we note that an inherent attribute that is critical in many applications is the cloud point. At the cloud point, key properties are dramatically changed, for instance emulsification efficiency. The cloud point, in turn, depends in a complex way on the exact distribution of species in the material and may vary in the range 75-86 °C in a batch-dependent fashion. Thus, the composition of polysorbate directly impacts the manufacturability of products in which it is used. Nevertheless, the cloud point of a given polysorbate batch is never provided by the suppliers, and only rarely determined by the users.

The same situation holds true for many other complex ingredients. Problems we commonly encounter due to the lack of insight into the critical attributes of ingredients include batch failures (OOS), and variability in product performance and tactile properties.

So which are the critical attributes?

There is no such thing as a generic critical attribute. Therefore, we will sit down with you and together extract the attributes based on the product profile, manufacturing protocol, regulatory framework (post approval flexibility) and other relevant considerations.

How do we approach critical attributes from an analytical perspective?

Since critical attributes of this kind are not covered by pharmacopoeial or other generic specifications, the analytical methods will need to be developed on an individual basis and tailored to the products and processes at hand. In some cases this entails clever use of conventional techniques for instance laser diffraction (Fig. 2), but quite often more advanced techniques are required. Methods we apply in projects like these include:

- C^{13} and H1 NMR (Fig. 3)
- Laser diffraction
- X-ray powder diffraction
- Small angle x-ray scattering
- Dynamic and static light scattering
- Sorption calorimetry
- Differential scanning calorimetry
- Tensiometry
- Vibration spectroscopy (IR and Raman)

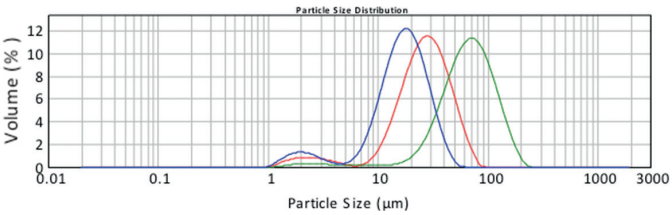

Figure 2. *Laser diffraction data showing the variation in particle size and distribution on three different batches of the same ingredient. The ingredient is of natural origin.*

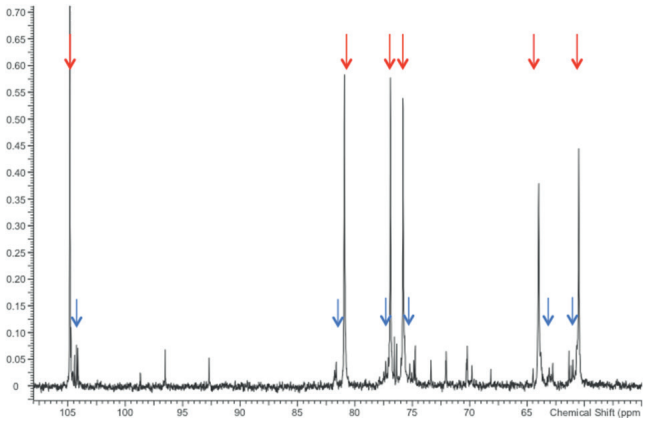

Figure 3. *^{13}C NMR spectrum revealing the occurrence of branching in a complex polysaccharide material.*