Characterization of solid excipients: delving deeper by probing the surface.

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KEY WORDS: Excipients, surface characterization, inverse gas chromatography, surface free energy, excipient signature, grade differentiation, surface charge, surface amorphicity

Performance differences in different lots of solid excipients often cannot be detected by bulk physicochemical methods. This is because some of these (performance) differences originate at the *surface* of individual excipient particles, accounting for attributes that comprise a disproportionately large part of the surface but a very small fraction of the total *amount* of the material. Because surface interactions play a significant role in the formulation and stability of solid dosage forms, it should not be surprising that excipients that may be indistinguishable at the compendial, and/or bulk level, may yet behave differently due to their different surface characteristics. Surface acidity, surface free energy, surface charge, surface roughness and surface amorphicity (crystallinity) of a bulk excipient powder represent attributes that are not usually measured as part of routine raw material testing by the end user. In addition to the apparent values of these surface characteristics, their intra- and inter-lot heterogeneity can influence functionality, and in some instances, significantly cause it to change.

Measurements of the surface acidity by diffuse reflectance UV-VIS have indicated a variability of as much as 0.4 pH units for starches obtained from different botanical sources, different lots of microcrystalline celluloses and different grades of lactoses. If microenvironment pH is critical to API stability, such variation between excipient lot surfaces must be taken into account during formulation.

When probed by inverse gas chromatography (IGC), different batches of α-lactose monohydrate from the same source, were shown to have very different values for the specific components of the free energy of adsorption, ΔG, for a given polar probe. These batches were found to be indistinguishable by bulk analysis techniques such as FT-Raman Spectroscopy, quantitative X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), anomeric composition and surface area measurement. Because ΔG is related to the ratio of the electron accepting to electron donating propensity of the molecule, inter-lot variation in surface charge and triboelectrification may occur with consequent differences in flowability and mixing uniformity.

Although the glass transition temperature and the water absorption isotherms for a powder

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may not change during storage, the time dependent conversion of the amorphous surface (created by milling) to its crystalline form is readily discernible by IGC which manifests as a change in the relative retention volume for a nonpolar probe as a function of storage time.

The lot to lot variation of surface roughness, as measured by the ratio of the retention volumes of an alkane and its branched isomer by IGC, is often not discernible by measuring either the particle size distribution or the porosity of the material. Yet, surface roughness has been shown to correlate to the angle of repose and flow characteristics.

While characterization of the surface of pharmaceutical solid excipients demands and encourages greater process understanding and control on the part of excipient manufacturers to enable their products to meet this (potentially) expanded set of specifications, it also provides opportunities for further grade differentiation, fine 'tuning' functionality and less batch to batch variation. In addition, if manufacturing processes are discovered that are capable of *independently* imparting certain bulk and surface properties to raw material excipients, then unnatural combinations of these two macrodescriptors could potentially be 'created' so as to lend completely new performance characteristics to existing materials. As an example, it may be possible to impart plasticity to brittle materials (and vice versa) by using different grinding additives to create more basal or lateral surfaces and monitoring the process by measuring the surface energetic heterogeneity by IGC.

The quantitation of surface characteristics brings significant added value in the ongoing saga of excipient variability. It may enable end users and suppliers alike to move toward conformity with an "excipient signature", to drive innovation in performance, as well as, to authenticate supply chains. There is further opportunity for the excipient manufacturers and users to undertake more systematic investigation of excipient variability using newer techniques and thus develop a more comprehensive understanding of excipients that has not been available so far, but will be increasingly necessary going forward into the brave new QbD world. IGC seems to be emerging as a mainstay for many surface characterization applications.

To quote from E.A.Abbott's, *Flatland* - "...You are living on a plane. What you style Flatland is a vast level surface of what I call a fluid, on, or in, the top of which you and your countrymen move about, without rising above it or falling below it...". Surface probing of solid pharmaceutical excipients adds another dimension to this hitherto known 'bulk' flatland.