also be difficult to acquire,for example, it would be difficult to find an excipient with both a large mean particle diameter (a high setting in an imaginary design) and high density (also a high setting in such a design). These factors, together with factors for example LOD and particle shape, can clearly make the task of finding excipients representing extreme settings difficult or impossible. Use of a D-optimal selection from a candidate set described in a few variables could be a feasible option. This alternative has not been investigated by the author or reported in the literature. Another alternative is to use qualitative variables. The drawback of this approach is that only a few excipients, that is, levels in the design, can be included before the number of experiments becomes unfeasibly high. Using PPs and multivariate design instead of qualitative factors is a viable alternative if many excipients are to be included in a screening study. In many cases, of course, the resulting model will be less detailed compared to a model derived from a set of experiments where physical properties of one or a few excipients are studied. Nevertheless, it should at least give a good indication of areas in the multivariate domain that should be further explored, which may be sufficient in some cases.

LIII. PARTICLE SIZE STUDIES

The particle size of new drug substance is a critical parameter as it affects every phase of formulation and its effectiveness. Appropriate particle size is required to achieve optimal dissolution rate in solid dosage forms, control sedimentation and flocculation in suspensions, small particle size (2−5 μm) is required for inhalation therapy, content uniformity, and compressibility is governed by particle size. As a result, the preformulation studies must develop a specification of particle size as early as possible in the course of studies and develop specifications that need to be adhered to throughout the studies.

Conventional methods of grinding in mortar or ball milling (where sample quantity is sufficient; generally it is not and limited to about 25–100 mg) or micronization techniques are used to reduce the particle size. The method used can have significant effect on the crystallinity, polymorphic structures (often to amorphous forms) and drug substance stability that can range from discoloration to significant chemical degradation. Changes in polymorphic forms can be determined by performing XRPD before and after milling.

Micronization where possible allows increase in the surface area to the maximum which can impact on the solubility, dissolution and as a result, bioavailability. Since the aim of most preformulation studies is to determine if a solid dosage form can be administered, knowing that reduction of particle size where it changes dissolution rates can be pivotal in decision making for the selection of dosage forms. In the process of micronization, the drug substance is fed into a confined circular chamber where it is suspended in a high velocity stream of air. Interparticulate collisions result in a size reduction. Smaller particles are removed from the chamber by the escaping air stream towards the center of the mill where they are discharged and collected. Larger particles recirculate until their particle size is reduced. Micronized particles are typically less than 10 μm in diameter. In some instances, micronization can prove counterproductive, where it results in increased aggregation (leading to reduced surface area) or alteration of crystallinity, which must be studied using such methods as microcalorimetry, dynamic vapor sorption or inverse gas chromatography.

The introduction of dynamic vapor sorption (DVS) in 1994 revolutionized the world of gravimetric moisture sorption measurement, bringing outdated, time, and labor intensive desiccator use into the modern world of cutting-edge instrumentation and overnight vapor sorption isotherms. With a resolution down to 0.1 μg, a 1% change in mass of a 10 mg sample on exposure to the humidity controlled gas flow is both easily discernable and reproducible. DVS is a valued tool for studies related to polymorphism, compound stability, bulk and surface adsorption effects of water and organic vapors. The dynamic vapor sorption studies would typically show percent mass increases but often a hysterisis loop relationship is observed where there is crystallization of compound that results in the expelling of excess moisture. This effect can be important in some formulations, such as dry powder inhaler devices, since it can cause agglomeration of the powders and variable flow properties. The DVS is useful study when amorphous forms are involved upon size reduction; in many cases, a low level of amorphous character cannot be detected by techniques such as XRPD; microcalorimetry can detect <10% amorphous content (the limit of detection is 1% or less). The amorphous content of a micronized drug can be determined by measuring the heat output caused by the water vapor inducing crystallization of the amorphous regions.

Excellent instrumentation support and advice is available through Surface Measurement Systems, http://www.smsuk.co.uk/index.php, manufacturer of DVS-Advantage and DVS-1000 and 2000 series of equipment for dynamic vapor interaction studies. The DVS-HT represents the first new generation in gravimetric vapor sorption analyzers for more than a decade by Surface Measurement Systems (5 Wharfside, Rosemont Road, Alperton, Middlesex. HA0 4PE United Kingdom).

A. Particle Size Distribution

Particle size reduction particularly mandates study of particle size distribution studies using such techniques as sieving, optical microscopy in conjunction with image analysis, electron microscopy, the coulter counter and laser diffractometers depending on the anticipated size of the particles. Whereas the size characterization is simple for spherical particles, study of irregular particles required specialized methods. The Malvern Mastersizer Series (http://www.malvern.co.uk/home/index.htm) is an example of an instrument that measures particle size by laser diffraction. The use of this technique is based on light scattered through various angles, which is directly related to the diameter of the particle. Thus, by measuring the angles and intensity of scattered light from the particles, a particle size distribution can be deduced. It should be noted that the particle diameters reported are the same as those that spherical particles would produce under similar conditions. In the former, each particle is treated as spherical and essentially opaque to the impinging laser light.

Two different light scattering methodologies can be used to characterize particles. The classical, also known as "static" or "Rayleigh" scattering or MALLS provides a direct measure of mass.

The dynamic light scattering (DLS), which is also known as "photon correlation spectroscopy" (PCS) or "quasi-elastic light scattering" (QELS), uses the scattered light to measure the rate of diffusion of the particles. This