motion data is conventionally processed to derive a size distribution for the sample, where the size is given by the "Stokes radius" or "hydrodynamic radius" of the protein particle. This hydrodynamic size depends on both mass and shape (conformation). Dynamic scattering is particularly good at sensing the presence of very small amounts of aggregated particles and studying samples containing a very large range of masses. It can be quite valuable for comparing stability of different formulations, including real-time monitoring of changes at elevated temperatures. For submicron materials, particularly colloidal particles, quasi-elastic light scattering is the preferred technique. Two theories dominate the theory of light scattering; the Fraunhofer and Mie. According to Fraunhofer theory, the particles are spherical, nonporous, and opaque; diameter greater than wavelength, particles are distant enough from each other, random motion, and all the particles diffract the light with the same efficiency, regardless of size and shape. The Mie theory takes into account the differences in refractive indices between the particles and the suspending medium. If the diameter of the particles is above 10 μm, then the size produced by utilizing each theory is essentially the same. However, discrepancies may occur when the diameter of the particles approaches that of the wavelength of the laser source.

Although laser light diffraction is a rapid and highly repeatable method in determining the particle size distributions of pharmaceutical powders, the results obtained can be affected by particle shape. The laser light scattering generally reports broader size distribution compared to image analysis. In addition, the refractive index of the particles can introduce an error of 10% under most circumstances and should be accounted for. Another laser-based instrument, relying on light scattering, is the Aerosizer (http://www.erc.ufl.edu/facility/equipment.asp?n=20). Aerosizer measures particles one at a time in the range of 0.20 to 700 microns. The particles may be in the form of a dry powder or may be sprayed from a liquid suspension as an aerosol. The particles are blown through the system and dispersed in air to a preset count rate. The Aerosizer operates on the principle of aerodynamic time of flight. The particles are accelerated by a constant, known force due to airflow and are forced through a nozzle at nearly sonic velocity. Smaller particles are accelerated at a greater rate than large particles due to a greater force-to-mass ratio. Two laser beams measure the time of flight through the measurement region by detecting the light scattered by the particles. Statistical methods are used to correlate the start and stop times of each particle in a particular size range (channel) through the measurement zone. The time of flight is used in conjunction with the density of the particles and calibration curves established to determine the size distribution of the sample.

LIV. SURFACE AREA

Since the surface area exposed to the site of administration determines how fast a particle dissolves in accordance with the Noyes–Whitney equation, these determinations are important. Also in those instances where the particle size is difficult to measure, a gross estimation of surface area is the second best parameter to have to characterize the drug. The most common methods of surface area measurement including gas adsorption (nitrogen or krypton) based on what is most commonly described as the Braunauer, Emmet and Teller, or BET, method applied either as a multipoint or single point determination.

Adsorption is defined as the concentration of gas molecules near the surface of a solid material. The adsorbed gas is called *adsorbate* and the solid where adsorption takes place is known as the *adsorbent*. Adsorption is a physical phenomenon (usually called physisorption) that occurs at any environmental condition (pressure and temperature) but only at very low temperature, it becomes measurable. Thus physisorption experiments are performed at very low temperature, usually at the boiling temperature of liquid nitrogen at atmospheric pressure. Adsorption takes place because of the presence of an intrinsic surface energy. When a material is exposed to a gas, an attractive force acts between the exposed surface of the solid and the gas molecules. The result of these forces is characterized as physical (or Van der Waals) adsorption, in contrast to the stronger chemical attractions associated with chemisorption. The surface area of a solid includes both the external surface and the internal surface of the pores.

Because of the weak bonds involved between gas molecules and the surface (less than 15 KJ/mole), adsorption is a reversible phenomenon. Gas physisorption is considered nonselective, thus filling the surface step-by-step (or layer by layer) depending on the available solid surface and the relative pressure. Filling the first layer enables the measurement of the surface area of the material, because the amount of gas adsorbed when the monolayer is saturated is proportional to the entire surface area of the sample. The complete adsorption/desorption analysis is called an adsorption isotherm.

Once the isotherm is obtained, a number of calculation models can be applied to different regions of the adsorption isotherm to evaluate the specific surface area (i.e., BET, Dubinin, Langmuir, etc.) or the micro- and mesopore volume and size distributions (i.e., BJH, DH, H&K, S&F, etc.).

The surface area of a solid material is the total surface of the sample that is in contact with the external environment. It is expressed as square meters per gram of dry sample. This parameter is strongly related to the pore size and the pore volume that is, the larger the pore volume, the larger the surface area and the smaller the pore size, the higher the surface area. The surface area results from the contribution of the internal surface area of the pores plus the external surface area of the solid or the particles (in case of powders). Whenever a significant porosity is present, the fraction of the external surface area to the total surface area is small.

LV. POROSITY

Most solid powders contain a certain void volume of empty space. This is distributed within the solid mass in the form of pores, cavities, and cracks of various shapes and sizes. The total sum of the void volume is called the porosity. Porosity strongly determines important physical properties of materials such as durability, mechanical strength, permeability, adsorption properties, etc. The knowledge of pore structure is an important step in characterizing materials, predicting their behavior.

There are two main and important typologies of pores: closed and open pores. Closed pores are completely isolated from the external surface, not allowing the access of external fluids in neither liquid nor gaseous phase. Closed pores influence parameters like density, mechanical and thermal