procedure to introduce it are critical. In that context the structure of the dry cake and the properties of its internal surface constitute a major element.

Another important factor is the level of the residual moisture in the pellet and its evolution, if any, during storage.

Finally, it is definitely of interest to know how this internal water is bound to the structure.

These are three recurrent problems in freeze-drying, among many others. We shall propose some selected experimental means for their investigation.

Internal Surface: BET

Applying the Brunner, Emmett, and Teller (BET) method to pharmaceuticals, whether ingredients or finished products, is of common use in powders for the determination of their specific area and pore sizes. However, generally, the operator has a reasonable amount of substance in hands, and most often this material is relatively resistant to water vapor and can be manipulated without too many risks in the open space of a laboratory or, if needed, within a conventional glove box.

The situation is quite different with sensitive freeze-dried specimens contained in sealed vials or ampoules, which present both a very reduced weight and, of course, a very low density as well as a high hygroscopicity. In that case, the prolonged contact with moist air can provoke a real "collapse" of the internal structure, which cannot be restored to its original state by prolonged pumping. Then a very precise methodology has to be followed to get a reliable measurement. We would like to explain how we proceed to that end.

The sample to be checked (5–100 mg of dry product in a sealed vial or ampoule) is quickly opened with a diamond saw and the bottom part, containing the plug, placed in a special stainless steel BET cell that is immediately capped, weighted, and connected to the manifold of the pumping device. Vacuum is then pulled over the sample at room temperature.

Two to three days later vacuum is broken with dry nitrogen gas and the BET cell connected to an automatic, computerized analyzer (Den-Ar-Mat 1000).

Vacuum is pulled again and repetitively checked until the leak rate (combined with the gas release from the product) falls to the order of $2–3 \times 10^{-4}$ mbar/sec.

The BET cell is then flooded with helium for the determination of the sample volume, which allows the determination of its real density and porosity, since we already know both its weight and its apparent volume.

The BET cell is again pumped and immersed in liquid nitrogen.

When temperature and pressure are stable, known amounts of helium are introduced in the measuring chamber; thanks to special gas-tight microsyringes (7 μL for the smallest one) to perform the calibration of the cavity before adsorption.

The BET cell is pumped again and then the measurement can start. Known amounts of the adsorption gas are then introduced in the specimen chamber and each time we wait for a steady equilibrium. The adsorption isotherm is, thus, constructed progressively throughout the BET range.

When saturation is reached, the BET cell is slowly pumped down, stepwise, to ensure controlled desorption to measure pore size and distribution.

For absolute surfaces ranging from 50 to 5 m^2, the measuring gas to be used is nitrogen. For absolute surfaces of 5 to 0.5 m^2, the measuring gas is argon. For absolute surfaces below this level we use krypton. In the latter case, the only