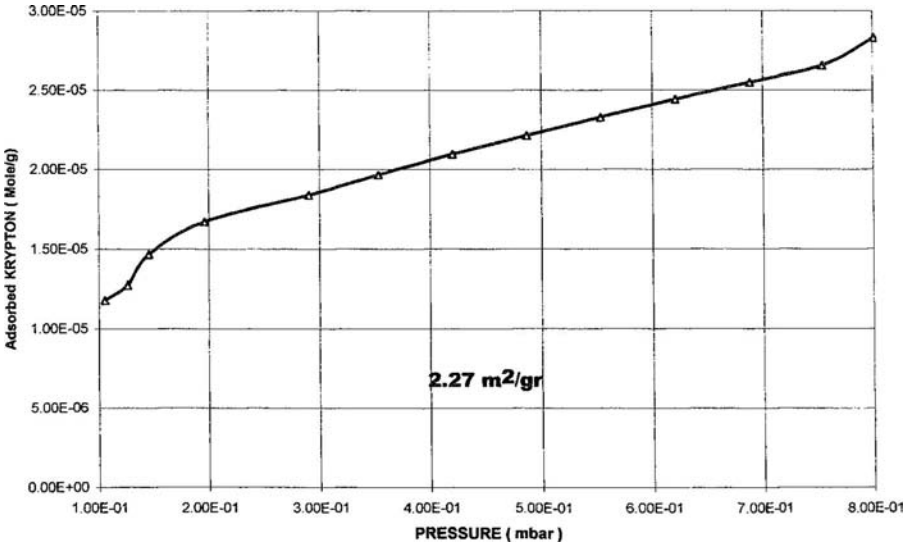

FIGURE 14 Determination of the specific area of freeze-dried Serono Gonal F75 UI by BET (sample weight 0.0325 g).

possible determination is that of the specific area since, with krypton being solid at liquid N_2 temperature, it is not feasible to perform a complete adsorption-desorption cycle for the evaluation of pore distribution and sizes. For obvious reasons, krypton measurement is bound to become the routine one for most freeze-dried pharmaceuticals.

Figure 14, for instance, represents the krypton adsorption curve for a sample of Gonal F75 UI from Serono, and we can see that it gives a pretty accurate reading despite the fact that the absolute surface measured is only 0.07 m^2.

It is beyond the scope of this chapter to indulge in more details about this technique, but it might be of interest to note that it allows the evaluation of the influence, on the product structure, of different factors such as the initial concentration of the starting fluid, the rate of freezing (macro or microcrystalline structures), the pertinence of the drying cycle, and of the final conditioning.

Since many functional properties of the dry cake derive from its internal surface and porosity such as solubility, oxygen, and water sensitivity, these measurements might be of great interest, especially for the assessment of reliability of a new process in view of its potential validation.

Some people will ask why we did not use penetration by mercury for the measurement of pores. Our answer is that for delicate, flexible products that can be easily crushed or simply distorted in their morphology by outside constraints, we found that the application on the cake of pressures ranging to a few thousand bars could be considered irrelevant.

Equilibrium Water Vapor Measurement in a Sealed Vial

For the reasons that we have just described, the measurement of residual moisture within an isolated vial or ampoule is a difficult undertaking. Joan May, in this book, also deals with this topic, and she explains how the FDA developed