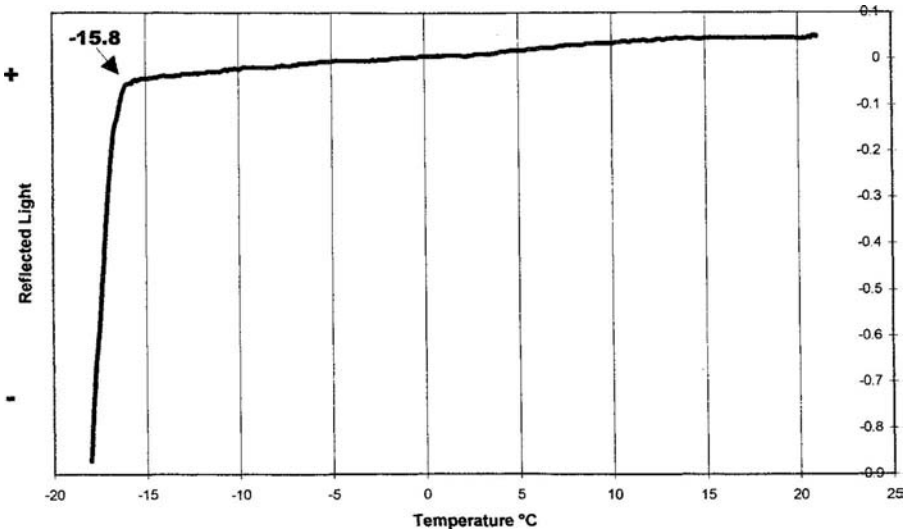

FIGURE 16 Novartis calcitonin dry substance in ampoules.

example of this determination for a sample of Novartis calcitonin dry substance in a sealed ampoule measured at +25°C. At the corresponding temperature of −15.8°C the water vapor pressure inside the ampoule is 1.53 mbar.

The sensitivity of this method is very high since measurements are still possible for condensation temperatures of −60°C, which, in a vial of 10 cm^3, means that less than 0.1 μg of water is present in the overhead space above the pellet.

Over the last 15 years systematic determinations have been done in collaboration with Dr. May from FDA and with several drug companies on a vast number of products. Most of them have been followed during storage (at −20°C, +4°C, or room temperature) for more than two years. Dr May reports on some of her findings later in this book.

Without going into too much detail, let us mention some of the key issues of this particular work.

- In sealed glass ampoules and for the same product we found substantial differences in the equilibrium water vapor pressures according to batches and, within a given batch, according to the position of the ampoule on the shelves of the freeze-dryer. The so-called wall, door, condenser, and corner effects could then be analyzed and amended.
- In sealed glass ampoules we also witnessed an evolution in the course of storage showing that often the remaining water was "restructured" in the course of time going from a rather mobile form to a more firmly bound form, displaying a lower water vapor equilibrium pressure (Fig. 17).
- In stoppered vials we could quite easily follow the transfer of moisture from the stopper toward the plug, which acted as a "getter pump" until a new equilibrium was reached (Fig. 17). We could establish, then, a direct correlation between the water vapor pressure measurements and the Karl Fischer titration (Fig. 18).