In diluted solutions, which is a current case in freeze-drying of pharmaceuticals, ice can develop in the course of cooling either as a well-defined front moving upward in the liquid from the cold supporting shelf or as a brusk cloud of individual germs appearing at the same time in the whole mass of a supercooled fluid. In the first case, and especially when the cooling velocity is low, there might be some cryoconcentration of the product, which provokes a solute gradient from bottom to top resulting in an increasing solid concentration in the upper layer. The result is, most often, the occurrence of a thin film, rather compact, at the surface of the dry plug at the end of the process, which might create problems at the reconstitution step and definitely impedes the water vapor (mass) transfer in the course of drying (Fig. 3). In the second case, when nucleation starts up all at once throughout the liquid the structure of the frozen mass is more homogenous, and this may lead to a more finely porous dry cake, but if the degree of supercooling is important and the ice development is pretty fast it may result also in the rupture of the vial. It is thus advisable in that particular case of freezing to measure ahead the crystallization velocity of the solution in function of the degree of supercooling (Fig. 4) to get a better control of the process.

Another concern is that supercooling might not be regular from one shelf to the other one and even all over one single shelf. As a result nucleation may occur at different temperatures and give different structures among the treated vials. Then it becomes advisable to control the structure of all products to equally control the nucleation step and make it simultaneous for the whole batch. The use of acoustic of ultrasound stimulators seems to give an elegant solution to that problem.

Another interesting issue is that if the freezing is delayed, for operational reasons, and the liquid stands for too long a time in contact with the inside surface of the vials, there might be an important interaction between the solution and the glass walls. Active substances might then be adsorbed, often in an irreversible way, or else glass chemicals might leak out into the liquid. These problems will be addressed further in this book but they have to be taken care of when handling solutions in which the active substances are in very small quantity (genetically engineered biochemicals) or as small individual particles (bacteria and virus vaccines).

Finally, the freezing process might be very delicate to carry when the initial liquid is an unstable emulsion and a fast processing, making use of cryogenics, might be then desirable.

An Interesting Development: Soft Ice Technology

Everybody is familiar with the concept of sherbets and soft ice-creams. They are basically frozen plastic pastes, which present a high viscosity and relatively moderate negative temperatures. They are not free flowing but can be stirred and mixed under moderate mechanical strength and can incorporate solid particles like chocolate crumbs, fruit, nuts, and others without losing their structure. Their rheological properties are rather complex and highly dependent on temperature. They are most generally commercialized as such but might be also the first step of a more elaborate process. For instance, in the freeze-drying of coffee, we start with the production of a viscous concentrated coffee extract, which is turned into a plastic icy foam by injection of carbon dioxide under pressure in a rotative scraped surface heat exchanger. There, the liquid is converted into a sherbet-like foamy paste, which is spread over a metallic belt