Microparticles

Spherical microparticles of a zinc peptide were shown to form during freeze-drying from a *tert*-butanol/water cosolvent system (22). Parameters such as the peptide to zinc ratio, the percentage of *tert*-butanol used, the cooling technique employed, and the use of annealing or not had an impact on whether spherical or irregular-shaped microparticles formed. A unique mechanism for the spherical microparticle formation was proposed that involved the formation of a solid emulsion, which after removal of the solvent generated spherical microparticles.

ULTRALOW TEMPERATURE FREEZE-DRYING

Rey (115) pioneered the use of ultralow temperature freeze-drying by evaluating solvents such as benzene and solid ammonia to lyophilize unstable compounds such as phospholipids. Ammonia is described as an exceptional solvent, on the basis of its remarkable properties, which are somewhat analogous to water. It is easily frozen by liquid nitrogen and can be lyophilized by sublimation between $-130^{\circ}C$ and $-110^{\circ}C$. Liquid ammonia is also a reaction medium that allows the study of new chemical entities and includes the storage of unstable and reactive elements containing free radicals. Liquid ammonia allows the lyophilization of tissues since it completely dissolves the glycerol used to coat and protect the tissue during freezing. Truly freeze-drying low freezing solvents (i.e., those with freezing points ranging from $-50^{\circ}C$ to $-120^{\circ}C$) would require very specialized freeze-dry equipment. A description of the specialized equipment required to achieve these ultralow temperature freeze-drying conditions has been provided by various authors (63,64). Since these solvents, like water, will supercool prior to freezing, a shelf that can reach very low temperatures such as that achieved with liquid nitrogen would be required to enable the solvent to properly freeze. Additionally, external radiation would need to be controlled to achieve uniform drying (63). Rey (115) also describes the use of liquid carbon dioxide to extract organic compounds. Subsequent lyophilization is achieved at low temperature ($-78.8^{\circ}C$) and atmospheric pressure. Solidification of CO_2 is achieved either by using liquid nitrogen or by releasing some CO_2 as a gas with subsequent cooling and freezing of the remaining CO_2. Carbon tetrachloride is also described as a good solvent for lipids, with the use of glycol distearate to modify its solubilizing characteristics. Other solvents used include dioxane and chloroform. Ultralow temperature freeze-drying was found to mimic that of aqueous systems such that with a suitable choice of the drying temperature and pressure, sublimation of the crystallized solvent resulted in preservation of the structure of the frozen interstitial phase (116). Freeze-drying more complex systems was studied by depositing and freezing thin films of two immiscible solvent systems. Two sets of solvents were studied water/dioxane and benzene/chloroform/carbon tetrachloride/cyclohexane. Freeze-drying was described as stepwise if the vapor of one of the solvents is eliminated preferentially and complex if the vapors of both solvents are eliminated together at comparative rates.

TOXICITY ISSUES

As discussed in the previous section, the volatile organic solvent component will be retained to a certain extent by the freeze-dried cake. The amount retained will be governed by the solvent used, the formulation which is lyophilized, and the