IMPACT ON DISSOLUTION RATE FOR NONSTERILE PRODUCTS

Studies have also been completed that demonstrated that freeze-drying from cosolvents such as *tert*-butanol can improve the dissolution behavior of lipophilic drugs such as fenofibrate (24). This work illustrated how to produce nanocrystalline particles via controlled crystallization during freeze-drying. Crystallization could occur during either the freezing or the drying phase. When crystallization occurred during freezing, faster freezing or use of solution with lower water/*tert*-butanol ratios produced smaller crystals. However, when crystallization occurred during drying, faster freezing or use of higher water/*tert*-butanol ratios resulted in the formation of smaller crystals. Other workers demonstrated that cryogenic spray freezing of danazol/hydroxypropyl β-cyclodextrin complex in tetrahydrofuran/water followed by lyophilization produced high surface area powders with improved dissolution characteristics (38). Other investigators freeze-dried hydrophobic drugs such as budesonide or salmeterol xinafoate with either β- or hydroxyl propyl β-cyclodextrins from *tert*-butanol/water cosolvent systems (17). The resulting complex exhibited an enhanced dissolution rate. Model drugs, ketoprofen and nitrendipine, and their hydroxyl propyl β-cyclodextrin complexes were prepared by freeze-drying from *tert*-butanol. The resulting dried complex exhibited markedly enhanced dissolution rate in simulated gastric and intestinal fluids (84,85). Drug cyclodextrin complexes prepared by this method can be further manufactured into injection powders, tablets, or capsules that exhibit improved in vivo absorption (86). The lipophilic drug diazepam, when freeze-dried with sugars from *tert*-butanol/water systems and later tabletted, produced anomalous dissolution behavior, which was governed by how it crystallized (21). The latter study noted that the fastest dissolution occurred for low drug loads or when using slow dissolving sugars. Others found that freeze-drying from a *tert*-butanol/water mixture is an excellent method to produce solid dispersions of lipophilic drugs in sugar glasses (87). The dispersions prepared by this method were usually amorphous and had improved dissolution rates. The residual *tert*-butanol trapped after freeze-drying could be reduced by the exposure to moist air. Spray freeze-drying using *tert*-butanol/water as a solvent was used to produce solid dispersions of Δ^9-tetrahydrocannabinol in inulin (82). The dispersions produced fine particles with improved dissolution characteristics that were suitable for inhalation therapy.

ENHANCEMENT OF STERILITY ASSURANCE

Since many freeze-dried products tend to be injectable formulations, they are required to be manufactured under sterile conditions. The growth-promotive properties of the bulk solution prior to freeze-drying can impact the facilities and processes required to manufacture the sterile freeze-dried product (e.g., conventional aseptic manufacturing vs. advanced aseptic manufacturing such as barrier-type suites). Many of the potential organic cosolvents proposed for lyophilization possess some form of microbicidal properties (88). Ethanol and isopropanol at concentrations of greater than 20% exhibit excellent antimicrobial activity against both gram-positive and gram-negative bacteria, fungi, yeasts, and molds (89). However, neat ethanol is less bactericidal than mixtures with water because the combination of alcohol plus water promotes the loss of cell