

Table 10-4 Advantages and Limitations in Using Co-Solvents in Lyophilization (59)

Advantages	Limitations ^a
Increased drug solubility	Safe handling of flammable solvents
Increased sublimation rates	Special facilities and/or equipment
Increased predried solution stability	Determination and control of residual solvent levels
Increase dry product stability	Toxicity of remaining solvent
Decreased reconstitution time	Qualification of appropriate GMP purity
Possible enhancement of sterility assurance	Qualification of supplier
	Overall cost benefit
	Possible adverse environmental impact
	Potential increased regulatory scrutiny

^aAnother possible limitation not mentioned in Ref. 59 is the loss of product during sublimation of solvent.

Two other common problems with rubber closures and lyophilized products during manufacturing are (i) the closure not being completely inserted into the vial opening after the lyophilization cycle is completed, and (ii) the closure sticking to the shelf after the shelves have been lowered to enable full insertion of the closure into the vial.

The West Company has developed a special stopper for lyophilized products (LyoTec™) where the top surface of the stopper is treated with Flurotec® that prevents the stopper from sticking to the top pressure plates of the freeze-dryer shelves, that otherwise would require manual intervention to remove vials from the freeze-dryer. The stopper segment that makes contact with the opening of the glass vial is uncoated to allow for maximum container-closure integrity (see Fig. 7-10).

CO-SOLVENTS

Tertiary butyl alcohol (TBA) offers advantages when used as a co-solvent with water (57). TBA was used to enable the freeze-dried cake of the antibiotic, tobramycin, to be readily loosened as a free-flowing powder so that the contents could be poured from the vial in orthopedic surgery (58). Applying a slow rate of freezing allowed the crystallization of the TBA solvent prior to drying, with annealing after freezing, significantly reducing the level of residual TBA in the final cake.

Teagarden published an excellent review paper on the use of nonaqueous co-solvents in freeze-drying (59). While co-solvent usage in freeze-dried preparations has been used in at least 20 products (Table 1 in Teagarden's paper), few are commercially available. One product that is currently marketed, Caverject® Sterile Powder, is prepared using a co-solvent solution (20% v/v tert-butanol/water) that is freeze-dried.

Co-solvent use in freeze-dry formulations offers some advantages, but significant limitations must be considered as reviewed by Teagarden and summarized here and in Table 10-4. Residual solvent levels in the finished product can be a problem, but steps can be taken to control the amounts. While residual tert-butanol levels in a crystalline matrix are generally in the 0.01% to 0.03% range, amorphous systems can contain 3% residuals or more. These levels can be decreased in amorphous formulations by (i) humidifying the dried solid to decrease the glass transition temperature, allowing crystallization of the matrix and subsequent rapid release of the residual tert-butanol; (ii) adding an annealing step to enable any remaining unfrozen tert-butanol hydrate to crystallize and produce a more uniform product; or (iii) actually increasing the amount of tert-butanol in the formulation to a level above the threshold concentration required for eutectic crystallization of the solvent. These steps have been shown to decrease the amount of residual tert-butanol to levels of 1% or lower.

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