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Rationale

Many different types of co-solvents are already widely being used during freeze-drying Examples of these solvents are acetone, isopropyl alcohol, ethanol, methanol, cyclohexane, and tertiary butyl alcohol (1). The reason these co-solvents are used is that they could offer advantages such as an increased sublimation rate and the improved wetting of lipophilic compounds. The increased sublimation rate results in shorter drying times and therefore a cheaper process, while the improved wetting gives the possibility to freeze-dry concentrated solutions of lipophilic compounds.

For most applications the co-solvent of choice should have specific physico-chemical properties. In order to get an homogeneous solution, the co-solvent should be fully miscible with water. Secondly the vapor pressure should be sufficiently high to facilitate rapid sublimation. Thirdly, the freezing point should be high enough, to be able to freeze the solution at typical shelf temperatures. Finally, the solvent should have a low toxicity. An example of such a solvent is tertiary butyl alcohol (TBA). TBA is fully miscible with water; it has a relatively high vapor pressure of 5.49 kPa, a freezing point of 24 ºC, and a low toxicity.

Opportunities

The use of co-solvents during freeze-drying offers several advantages. The first advantage that will be discussed here is the opportunity to optimize the length of the freeze-drying cycle. Freeze-drying consists of a freezing step, a primary drying step, and a secondary drying step. One strategy to decrease the process length is to decrease the total drying time. This can be achieved by increasing the sublimation rate of the used solvents. The sublimation rate is dependent on the vapor pressure of the used solvent and the product resistance. This means that if a co-solvent with a higher vapor pressure is used, sublimation will be faster resulting in a higher drying rate. Furthermore, the use of a co-solvent can result in differently shaped ice crystals, resulting in a lower product resistance and consequently higher sublimation rate (2).

The second advantage that the use of co-solvents offers is the opportunity to freeze-dry lipophilic compounds. Due to the hydrophobic nature of the compound, large volumes of solvent are necessary when these products are freeze-dried from water. However, when organic solvents are added as co-solvent, the solubility of the lipophilic compound in the medium is increased and it can therefore be dried from smaller volumes.

Applications

When lipophilic compounds are being freeze-dried from co-solvent systems, one might want either an amorphous product or a crystalline product. For example, to increase the dissolution rate of a drug with a high glass transition temperature (T_g) an amorphous drug product might be advantageous. However, for a drug product with a low T_g, a nanocrystalline product might be better. Both types of products can be obtained after freeze-drying. To obtain an amorphous drug product, freeze-drying should be performed at a relatively low temperature [below the glass transition temperature of the maximally freeze-concentrated fraction (T_g')], while a crystalline drug product could be obtained by

freeze-drying at a relatively high temperature (above the T_g' but below the eutectic temperature) (3). In this webinar, it will be explained how small changes in the process conditions will result in either an amorphous or a crystalline product. This will be illustrated by examples of different drugs.

Conclusions

This webinar shows why co-solvents are used during freeze-drying, which advantages they offer, and what the requirements are for a solvent to be used during freeze-drying. Based on a lot of examples, opportunities offered by co-solvents and applications of co-solvents are being discussed. The webinar will end by describing how the freeze-drying process can be adjusted in such a way that different types of products can be obtained.

References

1. Teagarden DL, Baker DS. Practical aspects of lyophilization using non-aqueous co-solvent systems. Eur J Pharm Sci. 2002;15:115-33.
2. Kasraian K, DeLuca PP. Thermal analysis of the tertiary butyl alcohol-water system and its implications on freeze-drying. Pharm Res. 1995;12:484-90.
3. de Waard H, Hinrichs WLJ, Frijlink HW. A novel bottom-up process to produce drug nanocrystals: controlled crystallization during freeze drying. J Control Release. 2008;128:179-83.

Additional papers of interest on this topic include:

Practical aspects of lyophilization using non-aqueous co-solvent systems.
Teagarden DL, Baker DS. Department of Sterile Products Development, Pharmacia Corporation, 7000 Portage Road, 49001-0199, Kalamazoo, MI 49001-0199, USA. dirk.l.teagarden@pharmacia.com
http://www.ncbi.nlm.nih.gov/pubmed/11849908

Thermal Analysis of the Tertiary Butyl Alcohol-Water System and Its Implications on Freeze-Drying
Kasra Kasraian and Patrick P. DeLuca
http://www.springerlink.com/content/0b3hucea66e7f6y9/?p=bc0e5d626f064ae6a35e401f16c40e19&pi=1

A novel bottom-up process to produce drug nanocrystals: controlled crystallization during freeze-drying.
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http://www.ncbi.nlm.nih.gov/pubmed/18423767