Journal of Pharmaceutical Sciences xxx (2017) 1-10

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Freeze-Drying From Organic Cosolvent Systems, Part 1: Thermal Analysis of Cosolvent-Based Placebo Formulations in the Frozen State

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ARTICLE INFO

Article history:
Received 14 August 2017
Revised 31 October 2017
Accepted 1 November 2017

Keywords:
freeze-drying/lyophilization
formulation
thermal analysis
calorimetry (DSC)

ABSTRACT

The use of cosolvent systems has been demonstrated to shorten lengthy freeze-drying processes and improve the solubility and stability of certain active pharmaceutical ingredients. The goal of the present study was to evaluate the suitability of 2 thermal characterization techniques, differential scanning calorimetry and freeze-dry microscopy, and to identify an optimal cosolvent system. Binary mixtures of a cosolvent (*tert*-butanol, dimethyl sulfoxide, 1,4-dioxane, acetone, or ethanol) and water were investigated. Ternary mixtures of frequently used excipients (50 mg/g mannitol, sucrose, glycine, or polyvinylpyrrolidone [PVP]) and a solvent-water system were then analyzed for their thermal properties. PVP presented a particularly high glass transition temperature (T_g') in 70% *tert*-butanol at −17.9°C. Large needle-shaped crystals that have been shown to be associated with improved processability were observed with mannitol and PVP in 40% 1,4-dioxane. A heterogeneous sublimation rate of the solvent and water whose impact on product stability remained unclear was observed with PVP in 40% 1,4-dioxane. Freeze-dry microscopy analysis demonstrated a possible extension of the process time for PVP in 99% dimethyl sulfoxide due to a slowly moving sublimation front. Conceivable negative consequences and the need for special treatment for low-melting cosolvents, such as ethanol and acetone, were predicted and discussed.

Introduction

Freeze-drying is a low-temperature drying technology that is frequently used to enhance long-term stability of labile pharmaceuticals.[1] In some cases, the commonly used solvent, water, must be fully or partially replaced by a cosolvent system to make freeze-drying accessible to certain active pharmaceutical ingredients (APIs). The use of a cosolvent system can be required to achieve an acceptable solubility and stability of the active pharmaceutical ingredient (API) in the bulk solution.[2] In this context, an impairment of process characteristics might be tolerable. However, the use of a solvent may also be beneficial in terms of reducing the process time of a lengthy process.[2] The vapor pressure of water-based formulations may limit the drying rate. Cosolvent systems have been routinely used in vacuum drying of APIs.[3] In the past, these systems have also been used to improve dissolution characteristics and drying rates in the field of freeze-drying.[2,4,5] However, comprehensive data to enable a rational selection of the formulation to be freeze dried are, so far, not available in the literature. For a solvent to be applicable for use in freeze-dry formulation design, several characteristics need to be considered, including (1) dissolving properties, (2) stabilizing effects, (3) freezing behavior, (4) drying behavior, and (5) toxicological limits.

In general, solvents can be classified by polarity and their ability to solubilize lipophilic compounds.[6] It has been shown that the use of *tert*-butanol (TBA)-, ethanol-, and 2-propanol-water mixtures may greatly elevate solubility of certain drugs.[4,7,8] Because previous research has mainly focused on freeze-drying from water-based formulations, well-established excipients are predominantly hydrophilic. Therefore, the solubility of excipients commonly used in lyophilized formulations can be limited if an active ingredient requires the use of a very nonpolar cosolvent system. Depending on the route of administration, parenteral administration may require reconstitution with an aqueous system and thus a defined solubility in water.[2] However, in case of intramuscular administration, use of more nonpolar cosolvent systems for very lipophilic drugs and preparation of a suspension may be an option.[9]

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https://doi.org/10.1016/j.xphs.2017.11.003
0022-3549/

In addition to rapid and complete dissolution, chemical stability of an active ingredient in the bulk solution over a defined period is indispensable. Water may accelerate several degradation pathways of pharmaceutical drugs, such as hydrolysis, oxidation, and racemization.[4,10,11] TBA-water mixtures and neat dimethyl sulfoxide (DMSO) have been shown to increase the solution stability of several drugs.[12,13]

In freeze-drying, the first step encompasses conversion of the formulation into a solid state by freezing. Disadvantages to process and product performance arising from incomplete solidification during the freezing phase have been reported for several cases.[2] Cosolvent systems containing low-melting-point solvents (e.g., methanol, ethanol, 2-propanol, or acetone) may not freeze completely during the initial freezing step of the freeze-drying process and may thus remain as liquid residue within the frozen ice lattice. The unfrozen solvent may boil during early primary drying, leading to product defects, long process times, and heterogeneous residual solvent levels in the freeze-dried cakes.[14] Conversely, high-melting-point solvents, such as TBA, appear to nucleate entirely in between the ice crystals. During primary drying, both the solidified solvent and ice can be removed by sublimation.[15] Some cosolvent systems, such as TBA, DMSO, ethanol, or acetone, alter the size and shape of the water ice crystals formed during freezing, thereby potentially accelerating subsequent primary drying by forming larger pores.[15-17] In cases where a eutectic cosolvent system is used, both components nucleate simultaneously upon cooling, thereby forming particular small crystals. Noneutectic mixtures or the formation of hydrates results in gradual component freezing. In this case, phase separation and concentration of formulation components are expected to occur.[18] Precipitation of the API and excipients as well as pH shifts are conceivable negative consequences.[19,20]

The objective of the primary drying phase is to remove the frozen solvent by sublimation under reduced pressure. At product temperatures typically encountered in pharmaceutical freeze-drying, the vapor pressure of frozen water allows sublimation. Nevertheless, numerous organic solvents have much higher vapor pressures.[6,21] It has been reported that the sublimation rate in the primary drying phase rises with increasing proportion of the solvent with higher vapor pressure (e.g., TBA), thereby reducing primary drying time (provided that the cosolvent system completely crystallized upon freezing).[5,22] Despite the relatively low vapor pressure of DMSO (0.61 mmHg at 25°C), freeze-drying of imexon 25 mg/mL from neat DMSO was completed within 57 h (4-mL fill volume, 15-mm fill depth, 32.55 mg/mL solid content).[13] It was reported that the molar ratio of TBA to water remained constant when using 20% TBA (w/w) during 5 h of drying at 0°C and a pressure of 100 mTorr.[15] The impact on process and product characteristics has not yet been investigated. Another important aspect in freeze-drying is the upper product temperature limit during primary drying, which must not be exceeded to obtain an effective product.[23] Cosolvent systems may potentially change this limit, that is, the collapse temperature (T_c) or glass transition temperature of the maximally freeze-concentrated solute (T_g') of a formulation.[1,2] In the case of a lower temperature limit, a lower shelf temperature must be used in order not to jeopardize the final product integrity. However, it has been found that even an unchanged temperature limit of 100-300 mg/mL sucrose in 5% TBA (w/v) was not exceeded at an increased shelf temperature of 30°C due to the large heat consumption of accelerated sublimation.[17] In addition, an increase in the mass flow rate shortens the overall process time.[24]

Residual solvents in pharmaceutical products represent a potential risk to human health due to their toxicity.[25] Toxicological limits of the respective solvent and the dosage of the drug itself determine the acceptable residual solvent level in the final product. The United States Pharmacopeia (chapter <467>) as well as International Conference on Harmonization guideline Q3C(R5) set limits for residual solvents in pharmaceutical products.[26,27] The effects of formulation and process variables of freeze-drying on residual solvent levels have already been investigated for TBA.[28] The physical state of the solute has been described as the most important determinant for residual TBA levels. A crystalline matrix typically relates to lower residual solvent levels compared to amorphous systems. Thus, crystallizing the excipient may be preferred in the case of solvents with high toxicity (e.g., 1,4-dioxane).[27] Furthermore, complete TBA crystallization should be targeted during the freezing phase.[15,29]

The goal of the present study is to build up a sound scientific knowledge based on the use of differential scanning calorimetry (DSC) and freeze-dry microscopy (FDM) analysis to evaluate potential cosolvent systems for freeze-drying. Until now, available information about cosolvents was solely limited to specific case studies on individual drug substances. Moreover, although information on the thermal behavior of TBA-water mixtures is available, transferability of the results is limited because inconsistent methodologies have been applied. These different measurement procedures may lead to different results and ultimately to different interpretations and choosing a different strategy for formulation and process development.

In this study, comprehensive thermal characterization by DSC and FDM of TBA as a cosolvent was conducted to serve as a standard analyzed by a uniform methodology. For this reason, the set of TBA-water–based formulations was therefore extended. Both 1,4-dioxane and DMSO, with similarly high melting points (11.8°C and 18.5°C, compare Table 1), were evaluated as alternatives to TBA while exploring individual advantages and disadvantages. Both 1,4-dioxane- and DMSO-water mixtures have not previously been used

Table 1
Physical Properties of the Cosolvent Systems Included in the Study

Solvent	Relative Polarity (E_T^N)[6]	Dielectric Constant (ε)[6]	Melting Point (T_m)[6]	Vapor Pressure (P)		Permitted Daily Exposure (PDE)[27,a]	United States Pharmacopeia (USP)[b]	European Pharmacopoeia (Ph. Eur.)[b]
			°C	mm Hg at 25°C[30-32]	mm Hg at −23°C[31,33]	mg/d		
Water	1.000	78.36	0.0	23.77	0.5	n/a	X	X
TBA	0.389	12.47	25.6	40.7	0.5	–	–	–
1,4-Dioxane	0.164	2.21	11.8	38.1	n/a	3.8	–	–
DMSO	0.444	46.45	18.5	0.61	n/a	≤50	X	X
Ethanol	0.654	24.55	−114.5	59.3	1.9	≤50	X	X
Acetone	0.355	20.56	−94.7	231	18.1	≤50	X	X

[a] United States Pharmacopeia, USP, chapter <467>.
[b] X, mentioned in USP and Ph. Eur.