CORRESPONDENCE

Vial Breakage during Freeze-Drying: Crystallization of Sodium Chloride in Sodium Chloride-Sucrose Frozen Aqueous Solutions

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ABSTRACT: The purpose of this study was to evaluate sodium chloride-sucrose frozen solutions with regard to sodium chloride crystallization and vial strain. Sodium chloride-sucrose solutions were studied using Differential Scanning Calorimetry (DSC) and a strain gauge instrumented vial. The sodium chloride concentration was varied with a fixed concentration of sucrose to identify a composition where crystallization was observed during heating and this composition was examined using the strain-gauged vials. DSC heating thermograms of a 1:1 (w/w) ratio of sodium chloride–sucrose solution show a sodium chloride crystallization exotherm at approximately −45°C. Examination of this composition in a strain-gauged vial shows an increase in strain, which corresponds to the temperature of the exotherm. Vial breakage is a phenomenon reported for mannitol containing solutions, which is associated with crystallization of mannitol in frozen solution. These data also suggest that vial strain and breakage is associated with the crystallization of solutes and the crystallization of water, which is released from the amorphous phase to form ice, and volume expansion. The results demonstrate the importance of understanding effect of excipient ratios, specifically in systems containing crystallizing and non-crystallizing excipients, and thermal history when developing freeze-dried formulations. J Pharm Sci 96:1848–1853, 2007

Keywords: calorimetry (DSC); crystallization; freeze-drying; excipients; amorphous; sodium chloride–sucrose matrix; vial breakage; strain-gauge; exotherm

INTRODUCTION

When developing freeze-dried formulations it is important to understand the impact of solute concentration and process conditions on the physical state of the solutes. Studies have shown that variables such as pH, excipient concentration, and thermal history can influence the physical state of excipients in frozen solution and dried powders.[1–5]

Mannitol is commonly used in freeze-dried formulations.[5–8] Also, the heating of frozen mannitol solutions is associated with vial breakage.[9,10] These studies show that vial type (molded vs. tubing glass) and fill volume can influence vial breakage. Strain-gauged instrumented vial studies have shown an increase in vial strain when mannitol crystallizes during heating (Craig et al., unpublished results). These studies show that a vial breaks when the strain exerted exceeds the

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mechanical strength of the vial and that vial strain is a precursor to vial breakage.

During the freeze drying of a 1:1 weight ratio of sodium chloride–sucrose mixture vial breakage was observed, where the higher solution volumes and higher fill depths and smaller vial diameters resulted in higher rates of vial breakage. Previous reports have shown that the physical state of sodium chloride in sodium chloride–sucrose frozen solution is influenced by solute concentration and thermal history.[11] However, the potential for sodium chloride crystallization to break vials has not been reported in the literature.

The purpose of this study was to (1) identify a sodium chloride–sucrose mixture where sodium chloride crystallized upon heating of the frozen solution and (2) evaluate the effect of thermal history and crystallization on vial strain, which is a precursor to vial breakage.

EXPERIMENTAL

Materials

Sucrose and sodium chloride used were USP/NF grade. Solutions were prepared from distilled water and filtered through a 0.22 μ filter to remove particulate matter. Eight milliliters (8 mL) of sample solution was filled into strain gauge instrumented 20 mL Type I tubing glass vials with a 20 mm finish (Wheaton Science Products, Millville, NJ). For these experiments a larger diameter vial and lower fill volume was used, compared to the vials that exhibited breakage in the freeze dryer, to minimize the potential for vial breakage and allow the re-use of the instrumented vials. The vials were washed and sterilized prior to applying the strain gauges. A lab freeze dryer (Dura-Stop, FTS System, Stone Ridge, NY) was used to cool and heat samples at a rate of 0.5°C per minute. Table 1 lists the solutions studied:

Table 1. Sodium Chloride–Sucrose Mixtures

Solution Number	Sucrose Concentration (mg/mL)	Sodium Chloride Concentration
1	30	0.25 M (14.6 mg/mL)
2	30	0.35 M (20.5 mg/mL)
3	30	0.50 M (29.2 mg/mL)
4	30	0.65 M (38.0 mg/mL)
5	30	1.00 M (58.4 mg/mL)

Methods

DSC Measurements

DSC measurements were conducted with a TA instruments DSC Q1000 equipped with a refrigerated cooling system. The temperature was calibrated using indium and checked against the NaCl–water eutectic point. About 10–15 mg of solution was weighed in an aluminum pan and hermetically sealed. The formulation was cooled to −55°C at 1°C/min and then warmed to room temperature at 2°C/min. In experiments to determine the effect of annealing, the samples were cooled from room temperature to −55°C at 1°C/min and warmed to the annealing temperature (−25°C). They were held at that temperature for 60 min, cooled back to −55°C, and re-heated to room temperature at 2°C/min.

Strain Gauge Instrumented Vial

Strain-gauged instrumented vials were prepared as previously reported (Craig et al., unpublished results). Strain gauges, data acquisition instrumentation, software, and strain gauge application kit were purchased from Vishay Measurements Group, Instrument Division (Vishay Intertechnology, Inc. 63 Lincoln Highway Malvern, PA 19355-2120). Model 5110 Strain Gauge Card, model 5120 Thermocouple Card, and CardSystem 5000 Model 5101 Scanner S/N 117360 computer card with cable, and StrainSmart software version 1.22 were installed in a lab computer. Model EA-06-250BF-350/P strain gauges with attached lead wires and 30 AWG T-thermocouples were attached along the outside circumference of the glass vials approximately 3 mm from the vial bottom using application kit GAK-2-AE10/15.

The electrical response of the strain-gauged vial is due to: (1) the change in gauge resistance with temperature, (2) strain caused by expansion or contraction of glass due to temperature changes, and (3) strain caused by the expansion or contraction of the vial contents. The temperature-induced changes are unrelated to the mechanical stress and for this study we are interested in the third component, strain caused by the vial contents. A temperature–strain correction curve was calculated to eliminate temperature related factors by cooling the empty strain-gauged vials below the range of interest at 1°C per minute and calculating a third order polynomial correction curve. The coefficients for this curve were then