Thermal Analysis of the Tertiary Butyl Alcohol-Water System and Its Implications on Freeze-Drying

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Utilizing differential scanning calorimetry (DSC) for tertiary butyl alcohol (TBA) solutions a phase diagram was constructed for the TBA-water system. By utilizing thermal treatment during the DSC measurements the metastable states were eliminated. The phase diagram fit for a congruently melting compound in which compound formation occurred with a maximum at 70% TBA representing pure TBA hydrate. Two eutectics occurred at 20% (Eutectic A) and 90% (Eutectic B). A freeze-drying microscope revealed that TBA altered the crystal habit of ice. A concentration of 3% TBA was required before large needle-shaped ice crystals became evident. The addition of 10% TBA to the system resulted in even finer needle-shaped ice crystals. At the eutectic compositions (20% and 90% TBA), the frozen eutectic mixture could not be resolved with the microscope because eutectic crystals are very small. The 70% TBA solution, which corresponds to the melting of pure TBA hydrate, formed very large hydrate crystals. The rate of sublimation of the TBA and water molecules was found to be concentration dependent. At concentrations below 20% TBA (water rich portion of the phase diagram) water molecules sublimed faster while at concentrations above 20% TBA (TBA rich portion of the phase diagram) TBA molecules sublimed faster. At the eutectic A composition, both TBA and water molecules sublimed at the same rate. This may be because all of the TBA molecules are strongly associated with each other in the form of a clathrate hydrate.

KEY WORDS: lyophilization; tertiary butyl alcohol; freeze-drying microscope; phase diagram; crystal habit.

INTRODUCTION

Drug solutions may contain various concentrations of organic solvents which are often added to reduce the degradation rate of the drug in water or to increase solubility (1,2). The presence of these organic solvents has been shown to affect the freezing characteristics of the solution intended for freeze-drying, a phenomenon which subsequently affects the rate of drying and the physical appearance of the freeze-dried product (2).

The solvent of interest in this study was tertiary butyl alcohol (TBA), an organic substance which has been shown to increase the efficiency of the freeze-drying process (3). Because of the growing interest in using TBA in freeze-drying, both as a mass-transfer accelerator and solubilizing agent, a thorough thermal analysis was undertaken using Differential Scanning Calorimetry (DSC). The thermal analysis was done to identify and eliminate the metastable states so that a phase diagram which would be applicable to freeze-drying could be constructed. The metastable states do not occur consistently as has been implied in previous studies of the TBA-water system (4,5). The thermal transitions in the various regions of the phase diagram were then assessed using a freeze-drying microscope. Finally, the sublimation rates in these regions were determined using a freeze-dryer equipped with a sample thief.

MATERIALS AND METHODS

Materials

Tertiary butyl alcohol (Fisher Scientific, Fairlawn, NJ); freeze-drying microscope (specially made freeze-drying stage with a Zeiss microscope, Eli Lilly & Company); freeze-dryer (Hull Model 10FXS12C, Hartboro, PA) equipped with a sample thief; toluene (Fisher Scientific, Fairlawn, NJ); n-butanol (Fisher Scientific, Fairlawn, NJ); gas chromatograph (Varian 3500, Walnut Creek, CA).

Thermal Analysis of the TBA-Water System

Distilled TBA and filtered deionized water were used in this study. A differential scanning calorimeter (DSC) (Perkin-Elmer TAS-7) series equipped with a 5000 series computer) was used for the analysis. Solutions of various concentrations of TBA and water were prepared by weight. About 10–15 mg of the sample solution were pipetted into an aluminum pan and the pan was capped with a hand press to prevent evaporation of the solution. The pan was placed in the sample compartment and an empty pan was similarly capped and placed in the reference compartment. The solution was frozen at a rate of 5°C/min to −40°C and held at this temperature for 5 minutes to allow for complete solidification. The solution was heated at a rate of 2.5°C/min to 25°C.

![Fig. 1. Standard Curve and typical chromatogram for TBA analysis. Retention times are TBA, 1.378 min; n-butanol, 1.781 min; toluene, 3.185 min.](image-url)
Fig. 2. DSC warming thermograms for TBA-water mixtures. a) 15% w/w TBA; b) 20% TBA; c) 50% TBA solution, Endotherm A: melting of metastable eutectic; Exotherm B: recrystallization of metastable eutectic to from stable form; Endotherm C: melting of eutectic, Endotherm D: melting TBA hydrate; d) thermal treatment of 50% solution at −7°C to eliminate metastable states.

Triplicate scans were performed. The temperature at which a thermal event occurred for a given concentration was plotted against the TBA concentration to construct the phase diagram. Metastable thermal events were identified and excluded in the phase diagram. For example, at high concentrations (>20% w/w) of TBA, two metastable thermal events occurred. The first event was endothermic and the second exothermic. When the frozen solution was warmed to −7°C, held at this temperature for 20 minutes, then cooled to −25°C and rewarmed, these events were no longer present.

Crystal Structure of TBA-Water Mixtures

A freeze-drying microscope was created by interfacing a high vacuum cold stage with an optical microscope (specially made freeze-drying stage with a Zeiss microscope, Eli Lilly & Company). This system was used to examine the crystal structure of frozen TBA-water mixtures. A drop of the sample solution was placed on a 24 × 24 mm coverslip and spread evenly by covering it with an 18 × 18 mm coverslip. Silicone stopcock grease was applied to the bottom of the coverslip and the temperature controlled plate. A temperature probe was also glued to the coverslip with silicone grease. The temperature of the cold stage was controlled by passing cold nitrogen gas through the channels in the plate. The sample solution was cooled to −40°C and a polaroid camera was used to photograph the changes.

Freeze-Drying of Aqueous TBA Solutions

Aqueous solutions containing 10%, 20%, 44%, and 80% by weight of TBA were prepared and filtered. Preweighed 10