Investigation of the Impact of Annealing on Global Molecular Mobility in Glasses: Optimization for Stabilization of Amorphous Pharmaceuticals

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ABSTRACT: The purpose of this research was to investigate the effect of annealing on the molecular mobility in lyophilized glasses using differential scanning calorimetry (DSC) and isothermal microcalorimetry (IMC) techniques. A second objective that emerged was a systematic study of the unusual pre-T_g thermal events that were observed during DSC warming scans after annealing. Aspartame lyophilized with three different excipients; sucrose, trehalose and poly vinyl pyrrolidone (PVP) was studied. The aim of this work was to quantify the decrease in mobility in amorphous lyophilized aspartame formulations upon systematic postlyophilization annealing. DSC scans of aspartame:sucrose formulation ($T_g = 73^\circ C$) showed the presence of a pre-T_g endotherm which disappeared upon annealing. Aspartame:trehalose ($T_g = 112^\circ C$) and aspartame:PVP ($T_g = 100^\circ C$) showed a broad exotherm before T_g and annealing caused appearance of endothermic peaks before T_g. This work also employed IMC to measure the global molecular mobility represented by structural relaxation time (τ^β) in both un-annealed and annealed formulations. The effect of annealing on the enthalpy relaxation of lyophilized glasses, as measured by DSC and IMC, was consistent with the behavior predicted using the Tool-Narayanaswamy-Moynihan (TNM) phenomenology (Luthra et al., 2007, in press). The results show that the systems annealed at $T_g - 15^\circ C$ to $T_g - 20^\circ C$ have the lowest molecular mobility. J Pharm Sci 97:3865–3882, 2008

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INTRODUCTION

This research represents part of a program designed to develop a better understanding of the relationship between annealing a glassy pharmaceutical and its stability, and in particular to investigate optimization of the annealing process. The present research describes the investigation of the effect of annealing on the molecular mobility in lyophilized glasses using differential scanning calorimetry (DSC) and isothermal microcalorimetry (IMC) techniques. During the study, unusual pre-T_g thermal events were observed, and an attempt to better understand these features was undertaken.

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To support the increasing interest in developing amorphous pharmaceuticals there is a clear need to better understand the properties of pharmaceutical glasses.[2] Understanding the pharmaceutical significance of molecular mobility in lyophilized glassy systems, and other amorphous solids, continues to present a challenge to pharmaceutical scientists. In spite of considerable research in this field, the relationship between dynamics in the glass and pharmaceutical stability is poorly understood. In many pharmaceutical systems, a correlation has been shown between molecular mobility and chemical stability,[3,4] protein aggregation,[5,6] and crystallization[7,8] in the amorphous state. Not all the systems however, show similar behavior. For example, Yoshioka and Aso,[9] found that in a lyophilized formulation containing Insulin and poly vinyl pyrrolidone (PVP), structural relaxation time estimated using the Adam–Gibbs–Vogel equation did not predict the dimerization rate on Insulin well. Also, Chang et al. reported that sucrose protein colyophilized systems did not always show good correlation of molecular mobility with stability. For reasons unknown, sucrose rich systems (>50% w/w sucrose) showed better chemical stability even though molecular mobility, as indicated by τ^{β} was higher.[10] Based on different effects of structural relaxation time on chemical stability in different amorphous systems, it was argued that the correlation between chemical stability and structural relaxation depends on the premise that chemical reaction of interest requires molecular mobility similar to that involved in structural relaxation, and this premise is not always valid.[4] No relationships based on the structural dynamics of the glassy systems have been developed that would allow reliable prediction of the stability of a formulation. Clearly, current understanding of the relationship between structural relaxation dynamics and pharmaceutical stability is incomplete at best.

Structural relaxation time (τ), which is the time required by a molecule to undergo large scale, or "whole molecule," configurational motion, increases and mobility decreases upon aging at temperatures below T_g. A decrease in mobility would be expected to produce a decrease in degradation rate. Consistent with this expectation, Abdul-Fattah et al.[11] showed a 1.7-fold decrease in decarboxylation rate in moxalactam mannitol systems upon annealing at 70°C ($T_g = 122$°C) for 8 h. The increase in stability on annealing correlated with the increase in structural relaxation time. Recently, Hill et al.[12] compared the extent of Maillard reaction between lysine and glucose in annealed and untreated glasses. In the annealed sample, aging moderately lowered the rate of glucose consumption (~20%). In addition, a marginal increase in chemical stability upon annealing was observed in a lyophilized cefovecin formulation.[13] To the best of our knowledge, these are the only studies in pharmaceutical and food systems which showed that annealing can impact chemical stability. Diffusivities of small molecules in polymer matrices have been known to decrease with aging. Mardaleishvili and Anisimov[14] demonstrated this decrease in their study on polymethyl methacrylate (PMMA) films with an initiator for formation of free radicals via a photochemical reaction. The films which were annealed showed the slow down in rate of free radical formation.

The general aim of our research is to investigate the relationship between annealing and chemical stability in lyophilized aspartame:stabilizer systems by

(1) applying Tool-Narayanaswamy-Moynihan (TNM) phenomenology to calculate optimum annealing conditions for our model system;
(2) quantifying the impact of annealing, based on the above conditions, on global molecular mobility, measured via calorimetry, in the model system;
(3) quantifying the impact of annealing, based on the above conditions, on local molecular mobility, measured via NMR, in the model system;
(4) correlating the global and local molecular mobility data with the chemical stability of aspartame in saccharide matrices.

In a previous study we reported the use of the TNM phenomenology in calculating optimum annealing conditions for our model system.[1] In the current report we focus on quantifying the impact of annealing, under pre-determined conditions, on the global molecular mobility of the aspartame saccharide formulations.

Glasses are thermodynamically unstable systems in a higher energy state relative to both the stable crystalline state and the metastable supercooled liquid state. Thermal annealing causes progress of a glass toward the equilibrium supercooled liquid, leading to formation of a lower energy system.[15,16] Studies of dynamics in pharmaceutical glasses have been conducted using a variety of techniques, for example, mechanical