Heterogeneity of Protein Environments in Frozen Solutions and in the Dried State

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Introduction

Typical solutions for freeze-drying contain 80–95 wt.% of water and several solutes, including an active ingredient and excipients, such as buffer components, lyoprotector or/and bulking agent, and a stabilizer such as surfactant. Behavior of such systems during freezing and freeze-drying is commonly described with the aid of supplemented phase diagrams, also known as solid–liquid state diagrams and extended phase diagrams. Use of the state diagrams for cryobiology and freeze-drying was pioneered by Luyet, Rasmussen, MacKenzie, and Franks, based on the evaluation of binary water–sucrose system and similar systems in which solutes do not crystallize [1–3]. Solid–liquid state diagrams of aqueous systems containing both crystalline and amorphous solutes were introduced for cryobiology [4] and freeze-drying applications [5]. In particular, the state diagrams allowed a generalized description of the phase behavior of typical aqueous solutions used in freeze-drying [6, 7], as follows. When an aqueous solution is cooled below its equilibrium melting point, a fraction of water molecules is isolated in a separate phase as hexagonal ice, leaving behind amorphous freeze-concentrated solution

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