Effect of processing conditions on the physical state of excipients in lyophilized formulation

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Lyophilization is a commonly used drying technique for thermolabile pharmaceuticals. Crystallization of formulation components may occur during various stages of the freeze-drying process. While crystallization of bulking agents is desirable, both from processing and product-elegance perspectives, buffer salt crystallization can cause a significant pH shift. Lyoprotectants (compounds that protect macromolecules, both during freeze-drying and subsequent storage) are effective only when remained amorphous. In this study, crystallization of pharmaceutically relevant buffer systems and the phase behavior of lyoprotectant in frozen solution were investigated.

When the succinate solution buffered to pH < pKa_2 at 25 °C, was cooled, the freeze-concentrate pH first increased and then decreased. Based on X-ray diffractometry (synchrotron source), the 'pH swing' was attributed to the sequential crystallization of succinic acid, monosodium succinate and disodium succinate. A similar swing, but in the opposite direction, was seen when the solution buffered to pH > pKa_2, was cooled. Other pharmaceutically relevant buffers were rank ordered based on their pH shift in the frozen solution, due to selective crystallization. Malate buffer showed lowest crystallization tendency, followed by citrate buffer, but only when buffered to pH > pKa_2.

Crystallization of trehalose dihydrate was observed in frozen solutions. The dehydration of the trehalose dihydrate to a substantially amorphous anhydrate occurred during drying. Mannitol, by readily crystallizing as a hemihydrate, accelerated trehalose dihydrate crystallization in frozen solutions. Lyoprotectants, such as sucrose and trehalose, only when retained amorphous in a frozen solution, effectively inhibited the crystallization of succinate buffer components and prevented pH shifts. In addition to stabilizing the active pharmaceutical ingredient, lyoprotectants may prevent pH shift by inhibiting buffer salt crystallization.