Freeze Drying of Nanosuspensions, 2: the Role of the Critical Formulation Temperature on Stability of Drug Nanosuspensions and Its Practical Implication on Process Design

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ABSTRACT: The present study investigates whether controlling the product temperature below the critical formulation temperature (CFT) during primary drying in a freeze drying cycle is a prerequisite for the stabilization of drug nanoparticles. For that purpose, the CFT of four drug nanosuspensions stabilized with different types (amorphous and crystalline) and concentrations of steric stabilizers and either of the disaccharides, trehalose and sucrose, was determined by differential scanning calorimetry and freeze-dry microscopy. Freeze-drying experiments were performed such that product temperatures during primary drying remained either below or well above the CFT of individual mixtures. It was found that glass formation did not influence the stability of the nanoparticles, suggesting that an adequate type of steric stabilizer and lyoprotectant concentration is present. Freeze drying could also be performed above the eutectic temperature without compromising on the final product quality profile, such as nanoparticle size and structural preservation of the lyophilized cake. The high concentration of solid drug nanoparticles provided additional cake stability. The results of this study confirm for the first time that primary drying for drug nanosuspensions can be greatly shortened because induced viscous flow or even meltback is not a limitation for nanoparticle stability and cake elegancy. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:4471–4481, 2011

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INTRODUCTION

It is well known that the underlying concept for the stabilization of proteins during freeze drying is glass formation by excipients. Such excipients are denoted as "cryoprotectants" in the event that they stabilize a protein structure primarily during freezing, and "lyoprotectants" in the event that stabilization can be achieved during the dehydration step.[1–4] It has been reported that many excipients can serve as both cryo- and lyoprotectants. The term "vitrification" is defined as the transformation of an aqueous solution into a rigid, solid glass. Vitrification would be assumed when the product temperature of a formulation is lower than the glass transition temperature of the freeze-concentrated solute, T'_g.[2] Numerous studies have been presented addressing protein stability as a function of vitrification, and the validity of this rule has initially also been proposed for the stabilization of nanoparticulate formulations.[5,6] Agglomeration of suspended nanoparticles is prevented by formation of a solid amorphous glass, where the colloidal particles are arrested in an infinite high viscous environment and are isolated from each other.[7] However, even if glass formation of a stabilizer is the preferred mechanism to preserve the original particle size distribution (PSD), some questions still need to be addressed. Allison et al.[8] suggested that the separation of individual particles within the unfrozen fraction prevents aggregation during the freezing step, and this idea was called the particle isolation hypothesis. In this hypothesis, the relatively low surface tension of mono- and disaccharides plays an integral role

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that, in turn, allows phase-separated particles to remain dispersed within the unfrozen solute. In addition, Armstrong and Anchordoquy[9] modeled diffusion of particulate nonviral vectors in the frozen matrix and argued that these formulations could be dried above T'_g as long as aggregation was avoided. Drug nanoparticles are also referred to as particulate colloids, but they are clearly different in their structure than, for example, liposomal systems. It seems, therefore, of great interest to study whether drying of such systems above T'_g without negative impact on product stability attributes would be possible as well.

Drug nanoparticles are commonly stabilized using a steric stabilizing mechanism. The relevance of this class of stabilizers in combination with the frequently used disaccharides sucrose and trehalose (both are known to serve as lyoprotectants during primary drying) is the goal of the present study. Importantly, it is not clear until today how crystalline steric stabilizers and amorphous lyoprotectants will affect each other in terms of stabilization capacity during freeze drying because principally, glass formation is considered to provide stabilization for amorphous structures.[10] In the event that T'_g does not directly limit the product temperature profile during primary drying, a subsequent question would target the maximum allowable product temperature that still assures final product stability. Freeze-dry microscopy (FDM) has been used in the course of the present investigations to determine the (onset) collapse temperature (T_{oc}) of the mixtures. It is well known that T'_g and T_{oc} are not identical for many drug formulations due to the different measurement principle.[11] As a rule of thumb, T_{oc} is found about 2°C–5°C higher than the corresponding T'_g. It has already been demonstrated that T_{oc} is more indicative for the critical formulation temperature (CFT) than the corresponding glass transition.[11] Maintaining the product temperature above T_{oc} induces changes in the inner cake morphology due to viscous flow, which is denoted as either "microcollapse," "shrinkage," or "collapse". Such structural changes are demonstrated to affect the target quality aspects of the final product (e.g., appearance, reconstitution time, etc.).[12] However, although recent FDM reports illustrated that T_{oc} is, among other things, a function of total solid content of the formulation,[11] it is also of great interest to address the question that at which solid nanoparticle concentration level additional cake stability is provided.

Another aspect that deserves consideration in the present discussion is the introduction of crystallizing materials (i.e., steric stabilizers). Assuming that nanoparticle stability is not a function of immobilization in the excipient matrix, freeze drying at or above the eutectic temperature (T_{eut}) might be feasible as well. As mentioned above, high concentrations of solid drug nanoparticles might also compensate for meltback. PSD is not automatically expected to be influenced because the steric barrier surrounding the particles can avoid physical instabilities in a highly mobile environment. It has already been pointed out in the literature that the key role of the steric stabilizer is to impart the initial stability in the liquid phase right after milling.[13,14] The concept of steric stabilization is possible for those materials that can be attached or adsorbed onto the nanoparticle surface and provide a large and dense steric barrier, which is mandatory to overcome the attractive van der Waals forces (e.g., polyethylene glycol, cellulosics, pluronics, polysorbates, etc.).[13–15] In addition, previous studies have already depicted that the selection of an adequate steric stabilizer is important to preserve the original PSD. This observation might then mitigate the relevance of vitrification.[16–18] An elevated mobility in the excipient matrix must not inevitably lead to aggregation or particle fusion during lyophilization.

Besides the science-related aspect of this study, another practical consideration is grounded in process economics. The possibility to process drug nanosuspensions well above their CFT allows rather unconventional, aggressive cycle conditions, which could significantly decrease freeze-drying process times and therefore, turnover.[19] Using drug nanoparticles as a model system might offer an opportunity to learn whether other nanopartiulate formulations, for example, nanospheres or nanocapsules, can be processed above T'_g as well. To get down to the essence of the matter experimentally, four drug nanosuspensions stabilized with two different steric stabilizers were freeze dried conservatively, moderately, or aggressively in the presence of two different commonly used lyoprotectants, namely, sucrose and trehalose. The original suspension of the nanoparticles right after milling was found unstable in terms of complete preservation of the original PSD during freeze thawing experiments. To investigate the influence of the steric stabilizer and disaccharide concentration, both excipients were added in varying concentrations.

MATERIAL

A poorly water-soluble, crystalline active pharmaceutical ingredient (API) and 0.3-mm yttrium-stabilized zirconia beads were kindly provided by Johnson & Johnson Pharmaceutical Research & Development (Beerse, Belgium). Lutrol F108 Prill (Poloxamer 338) and Cremophor EL were donated by BASF (Ludwigshafen, Germany). Trehalose and sucrose were of analytical grade and were purchased from Sigma (Sigma Chemical Company, Munich, Germany). All excipients were used as received. Either water for injection (B.Braun Melsungen AG, Melsungen, Germany) or water distilled from an all-glass apparatus was used throughout this study. As