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Research paper

Investigating factors leading to fogging of glass vials in lyophilized drug products

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ABSTRACT

Vial "Fogging" is a phenomenon observed after lyophilization due to drug product creeping upwards along the inner vial surface. After the freeze-drying process, a haze of dried powder is visible inside the drug product vial, making it barely acceptable for commercial distribution from a cosmetic point of view. Development studies were performed to identify the root cause for fogging during manufacturing of a lyophilized monoclonal antibody drug product. The results of the studies indicate that drug product creeping occurs during the filling process, leading to vial fogging after lyophilization. Glass quality/inner surface, glass conversion/vial processing (vial "history") and formulation excipients, e.g., surfactants (three different surfactants were tested), all affect glass fogging to a certain degree. Results showed that the main factor to control fogging is primarily the inner vial surface hydrophilicity/hydrophobicity. While Duran vials were not capable of reliably improving the level of fogging, hydrophobic containers provided reliable means to improve the cosmetic appearance due to reduction in fogging. Varying vial depyrogenation treatment conditions did not lead to satisfying results in removal of the fogging effect. Processing conditions of the vial after filling with drug product had a strong impact on reducing but not eliminating fogging.

1. Introduction

Cosmetic defects in lyophilizates have recently gained increased attention. A phenomenon that has been referred to as "fogging" of glass vials [1] can be described as a white haze or cloud of different patterns and forms after freeze drying, e.g., in the form of finger-like protrusions, branching, or uniform haze. Fogging of glass vials has been observed for some time now in the pharmaceutical industry, but it had not gained much scrutiny because it has been viewed as a non-critical cosmetic defect. However, given that fogging may also be observed in the vial neck region, there may be considerations on whether this may have an impact on container closure integrity (CCI), though there is no direct data or evidence of such concern. High incidents of glass vial fogging may lead to significant reject rates for lyophilized drug product (DP) during inspection (manual, semi-automatic, or automatic), by virtue of just being a cosmetic defect and/or fogging reaching all the way up to the vial shoulder. Furthermore, appearance can be of specific interest and focus for specific markets and may become costly to the company – as is in the case of fogging – if the problem cannot be solved or controlled.

Root causes of fogging are complex and not well researched. It is believed that it starts with solution wetting of glass vial walls and adsorption of solution components onto the glass inner surface, followed by solution creeping up vial inner walls due to gradients in surface tension driven by thermal and/or compositional factors. The solution remains on the inner walls of the vials until loaded into the freeze dryer and is dried in such state. Interestingly, the phenomenon of solution creeping up an inner container surface during filling can also be observed in daily life: when filling coffee into a clean coffee mug, the quick rise of a film of coffee on container surface can be observed. The rise of wine along the walls of a glass cup is another example that has been brought forward for creeping (Tears of Wine). When the wine is placed in a glass cup, it climbs along the walls to wet the walls in the same manner capillary rise does [2], although the "Schlieren" phenomena in wine can also be attributed to alcohol content or other parameters.

Studies are available in the literature that investigated the mechanism of creeping and film transfer through observing creeping behavior of charged nanoparticles in aqueous solutions to the interior glass surface of vials or containers [3–5]. It was suggested that Marangoni flow [2–6] was a possible mechanism for film

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transfer to a glass solid surface. In aqueous formulations, especially when containing a surfactant, and possibly even with a hydration film alongside the walls of a vial (i.e., pre-wetting of the interior surface, e.g., by a thin layer of condensed water vapor from the surrounding) [3], a difference in the surface tension ($\delta\gamma$) between two points on the solution surface (i.e., surface tension gradient) triggers a driving force for fluid flow toward the region of high γ value [2,3,7]. As described by Levich [7], surfactant molecules adsorb along fluid interfaces, where they lower the interfacial tension. Convection in solution tends to increase (or decrease) the surface concentration of adsorbed surfactant near zones where the flow converges (or diverges). However, both adsorptive/desorptive and bulk diffusive fluxes tend to reduce gradients in surface concentration. If either of these fluxes is slow, a non-uniform distribution of adsorbed surfactant is established, causing a gradient in the interfacial tension [7]. At the end, the driving force for fluid to flow toward the region of high γ must be strong enough to overcome the resistance of the fluid to flow (viscosity, η) and fast enough to avoid equilibration of all gradients by diffusion [8]. The resulting transfer of adsorbed surfactant molecules from the regions of lower surface tension toward the regions of higher surface tension constitutes the Marangoni effect or Marangoni convection (Fig. 1). Due to mass conservation, the fluid recirculates in the bulk, which creates the typical pattern for Marangoni convection. The difference $\delta\gamma$ can be due to temperature gradients at the interface (the thermocapillary effect) or concentration gradients (the destillocapillary effect) [9]. Marangoni convection can manifest as macro-convection, where convection originates from concentration or temperature differences due to an asymmetry in the system, or micro-convection, where the convection is initiated by small (random) temperature or concentration disturbances that grow with time [8–11].

Previous studies suggest that Marangoni flow/convection is influenced by the interaction between formulation and primary packaging container. The extent of this interaction will influence solution creeping behavior and ultimately influence the degree of fogging after lyophilization. The degree of interaction between formulation and primary packaging container is a function of formulation composition (e.g., pH, composition, ionic strength, viscosity), as well as surface properties of glass. The current study was done in the context of researching glass fogging of a commercial product (labeled as mAb1 in this study). During the investigation to solve the problem, different variables were systematically evaluated:

1. *Formulation composition*: Surface activity is known to impact Marangoni effect and subsequent potentially creeping, but it is not clear to what extent it will impact fogging, especially with ingredients known to adsorb onto glass. To our knowledge, there is no study that systematically correlates fogging with formulation properties/composition. We investigated what formulation ingredients contribute to fogging (while keeping pH and ionic strength in all test solutions relatively the same) using commonly used vials for lyophilization.
2. *Surface properties of glass*: Glass surface properties are known to differ between different glass types/vendors, as well as within one single lot of glass vials [12]. The inner surface properties of glass vials are influenced by the glass composition, the glass forming process [12,13] as well as storage conditions of the primary packaging containers. The resulting differences in surface properties between different glass vials are expected to result in varying degree of interaction with formulation ingredients and hence influence creeping and ultimately fogging. To our knowledge, there is no study that investigates fogging as a function of glass surface. In this study, we investigated the impact of vial glass quality/inside coating on fogging. Vials with inner surface coated with baked-on silicone versus "unsiliconized" surfaces were used.
3. *Process conditions*: The extent of formulation-container closure interaction can be influenced, in theory, by altering process conditions. Processing conditions that "favor" this interaction are expected to worsen the fogging problem post-lyophilization, and vice versa. For example, it was shown that changes in topological structure and chemical composition of the inner surface of unsiliconized glass vials occur after washing and depyrogenation, depending on the process and related controls [12]. Because glass vials are to be used for parenterals, they need to be washed, depyrogenated, and sterilized according to the prescribed methods (e.g., EU and US Good Manufacturing Practice) before the pharmaceutical solutions are filled [1]. The impact of washing, depyrogenation, and sterilization on glass vial inner surface is a subject of research. To our knowledge, there is no study that investigates fogging as a function of process or cold temperature exposure. In our studies, we investigated if there is an impact of the vial washing and depyrogenation step on fogging post-lyophilization (using unsiliconized and siliconized glass vials). Furthermore, we looked into the impact of modifying pre-lyophilization conditions (exposing vials containing solution of drug product to cold/refrigerated temperatures prior to freeze drying) on fogging.

Through our studies, we will discuss possible process improvements and solutions to control the fogging problem in development and at production scale.

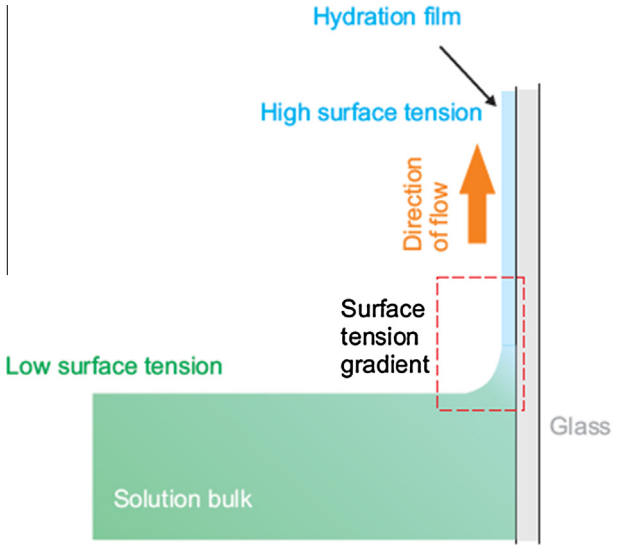

Fig. 1. A simplistic illustration of the interaction between surface active solutions and hydrophilic glass vials. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2. Materials and methods

2.1. Materials

2.1.1. Chemicals

Pharmaceutical quality recombinant humanized monoclonal antibody 1 (mAb1) was produced and purified (>99%) at Roche, Penzberg. The antibody formulation used was 0.01% w/v Polysorbate 20, 60 mM Trehalose, 5 mM Histidine/Histidine HCl all at pH 6.0, at 25 mg/mL of mAb1.

Similarly, a pharmaceutical quality recombinant humanized monoclonal antibody 2 (mAb2) was produced and purified