LYOPHILISATION VIALS: QUICK AND EFFECTIVE SOLUTIONS TO REDUCE FOGGING

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Diane McCormick and **Clément Condouret** of **NIPRO** discuss lyophilisation fogging, explaining its negative downstream effects and presenting NIPRO's thermal treatment, VIALEX™, to minimise this issue.

Today, around half of all biopharmaceuticals and about 40% of all parenteral medications rely on freeze drying as a critical part of their manufacturing process (Figure 1). With this widespread use comes a major challenge – the freeze-drying process must accommodate an ever increasing diversity of complex formulations. New excipients, new drug modalities and higher product sensitivities all add layers of complexity.

VIAL FOGGING: A CONTINUOUS CHALLENGE DURING THE LYOPHILISATION PROCESS

One of the most persistent and challenging phenomena encountered during the lyophilisation process is vial fogging, also referred to as lyophilisation fogging (Figure 2). This phenomenon not only affects aesthetics, it can directly impact

> "ONE OF THE MOST PERSISTENT AND CHALLENGING PHENOMENA ENCOUNTERED IN LYOPHILISATION IS VIAL FOGGING, ALSO REFERRED TO AS LYOPHILISATION FOGGING."

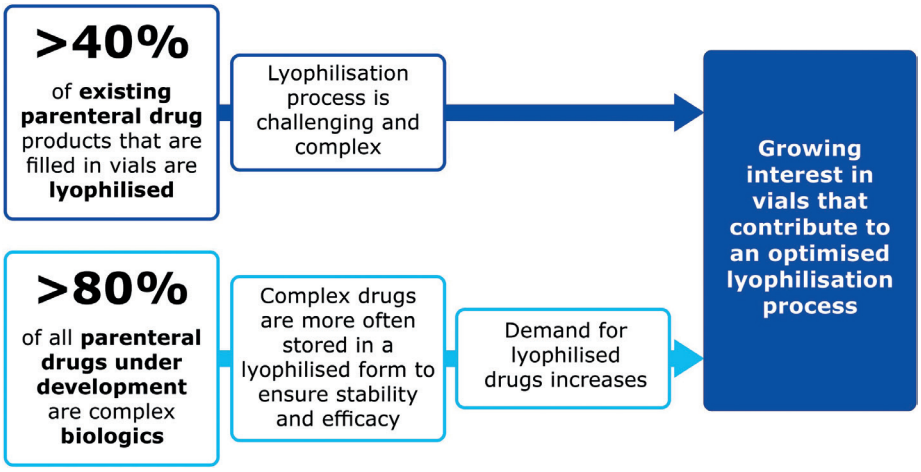

Figure 1: A growing need for lyophilisation.

manufacturing performance and quality control. Vial fogging increases reject rates during final camera-based inspection, reducing overall equipment efficiency and, in critical cases, compromising container closure integrity.

Occurrence of Lyophilisation Fogging During the Freeze-Drying Process

A closer look at the lyophilisation process helps to understand where and how vial fogging occurs (Figure 3).

Step 1: Filling

The vial is filled with the drug product in liquid formulation. This formulation typically contains several excipients in addition to the API. Many of these components reduce the surface tension of the liquid, which plays a crucial role later in the process.

Step 2: Water Evaporation

Immediately after filling, a small amount of water from the formulation begins to evaporate. This evaporated water condenses and deposits on the inner walls of the vial, forming a thin film.

Step 3: Marangoni Flow Setup

At this stage, two liquids co-exist: the drug formulation with lower surface tension and the condensed water with higher surface tension. This contrast creates ideal conditions for Marangoni flow, causing the drug product to begin moving up the inner wall of the vial.

Step 4: Freeze Drying

During freeze drying, the temperature at the vial wall differs from the temperature at the centre of the vial. This temperature gradient then further increases the surface tension gradient, intensifying the Marangoni

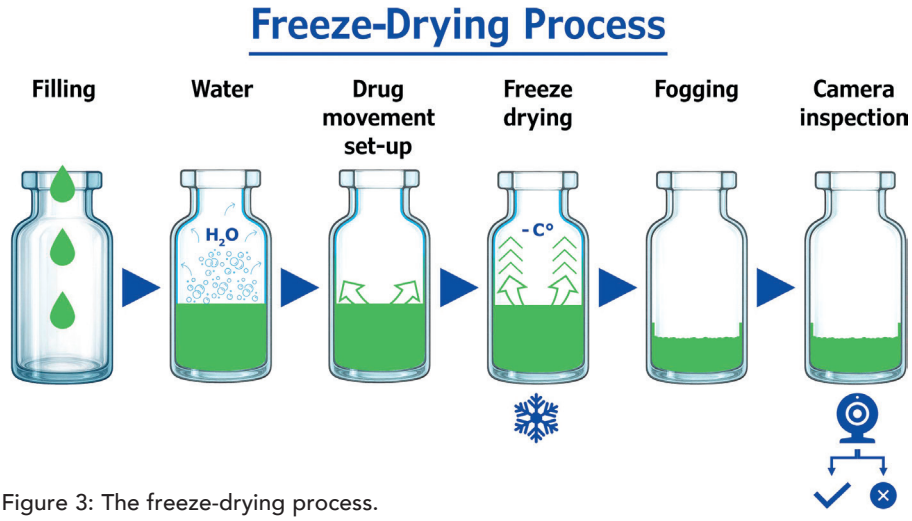

Figure 3: The freeze-drying process.

Figure 2: Vial/lyophilisation fogging.

effect, so the drug product continues to travel up the wall. At this stage, the product on the wall remains invisible because it has not yet dried.

Step 5: Vial Fogging

Once the freeze-drying cycle is complete, the product deposited on the wall dries. Only then does it become visible, appearing as a cloudy, fog-like residue – vial fogging.

Step 6: Impact on Visual Inspection

Once fogging appears, automated visual inspection systems struggle to distinguish it from true defects. As a result, acceptable vials may be rejected, leading to increased scrap rates and unnecessary loss of valuable API.

PRIMARY APPROACHES TO MITIGATE LYOPHILISATION FOGGING

Approach One: The Formulation

This approach focuses on reducing the difference in surface tension between the condensed water and drug formulation. This can be achieved by removing or reducing surfactants or by modifying the formulation, such as by selecting different lyoprotectants or excipient combinations.

However, this approach has a major limitation: vial fogging is often identified late in the drug development phase, when the formulation is nearly finalised. At this stage, changes are difficult to implement and may require further costly stability studies and regulatory assessments. For this reason, formulation changes are rarely the preferred solution.

Approach Two: The Vial

This approach aims to prevent the formation of the water layer during the filling process. One method is applying a coating to the inner surface of the vial to ensure that the surface is hydrophobic. However, coated vials typically require additional regulatory documentation and validation, lengthening project timelines and increasing complexity.

A more straightforward option is the NIPRO thermal treatment (Figure 4). This treatment creates a hydrophobic inner surface without adding any external material. It is a fast, simple and effective solution that avoids regulatory complications while strongly mitigating vial fogging.

NIPRO'S PROPRIETARY SOLUTION FOR REDUCING VIAL FOGGING

NIPRO applies a proprietary thermal treatment (VIALEX™) to the inner surface of the glass vial without using additional materials such as a coating. This requires no change to the glass chemistry – manufacturers can continue using standard Type I borosilicate glass. A 100% inline thermal inspection process confirms that the treatment has been conducted properly and the resulting inner surface is comparable with that of glass tubing or moulded vials.

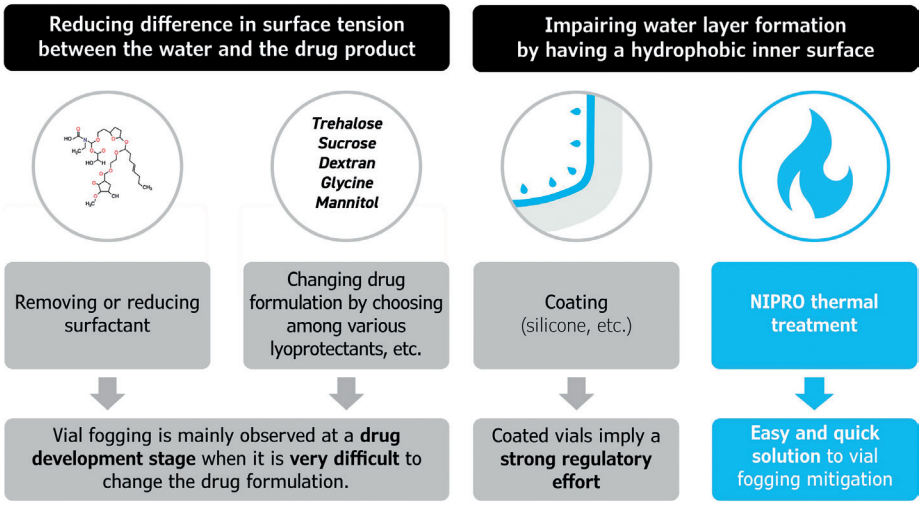

Figure 4: NIPRO's thermal treatment solution to mitigate vial fogging.

As a result, the vials feature:

- Low levels of extractables and leachables
- Reduced surface alkalinity
- Enhanced chemical durability
- A more hydrophobic inner surface.

This can lead to:

- Significantly less lyophilisation fogging
- Reduced container-drug product interactions
- Lower pH shift
- Reduced risk of glass delamination.

To explain further, vial fogging is typically considered a cosmetic defect of the lyophilisation cake. In severe instances, when fogging extends into the neck region of the vial, it may compromise seal integrity and thus drug properties. This phenomenon is related to interfacial energy between the glass, liquid and gas interfaces. A hydrophobic vial surface has been shown to reduce these interactions and mitigate fogging.

> "NIPRO APPLIES A PROPRIETARY THERMAL TREATMENT (VIALEX™) TO THE INNER SURFACE OF THE GLASS VIAL WITHOUT USING ADDITIONAL MATERIALS SUCH AS A COATING. THIS REQUIRES NO CHANGE TO THE GLASS CHEMISTRY – MANUFACTURERS CAN CONTINUE USING STANDARD TYPE I BOROSILICATE GLASS."

Vial	Type
Vial 1	Standard
Vial 2	Altered geometry
Vial 3	Altered geometry with thermal treatment

Table 1: Vial selection for fogging study.

NIPRO LYOPHILISATION VIALS: TESTED BY AN EXTERNAL LABORATORY

The benefits of NIPRO lyophilisation vials were demonstrated in a 2025 case study, conducted at LyoHub, a research facility at Purdue University (West Lafayette, IN, US).[1] This study aimed to reproduce a typical vial fogging situation using demanding freeze-drying conditions with typical test solutions.

Three sets of vials were selected to evaluate the effect of inner surface hydrophobicity on fogging during the lyophilisation process (Table 1). All vials were 10R/10 mL Type I borosilicate glass with a thermal expansion coefficient of 51×10^{-7} K^{-1}.

Each vial was washed according to USP <660> and filled at room temperature with 3 mL of a model formulation:[2]

- 4% (w/v) mannitol
- 2% (w/v) sucrose
- 1.55 mg/mL histidine
- 0.1 mg/mL polysorbate 80 (PS80)
- 5 mg/mL pyranine (fluorescent tracer).

This was followed by a regular freeze-drying cycle, performed in a MicroFD system (Table 2).

Surface Free Energy

Droplets were measured using a DSA25 Basic Device (KRÜSS, Hamburg, Germany). The surface energy of each material was determined using Owens-Wendt-Rabel-Kaelble method:[3]

$$2\sqrt{r_{sv}^{d}r_{sl}^{d}} + 2\sqrt{r_{sv}^{p}r_{sl}^{p}} = r_{lv}(1+\cos\theta)$$

Using this model, the surface energy of a material can be calculated by measuring the contact angles of two liquids, a polar liquid (water) and a non-polar liquid (diiodomethane), as shown in Figure 5.

Surface energy depends on both vial geometry and inner surface condition, so a smaller contact angle means stronger attraction to liquids and hydrophilic behaviour and a larger contact angle means lower attraction and hydrophobic behaviour. Vials 2 and 3 showed reduced surface energy, confirming the effect of surface treatment and geometry (Figure 6).

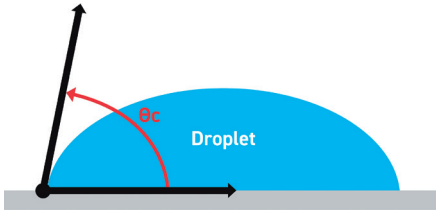

Figure 5: Measuring the contact angle of two liquids to calculate surface energy.

Freezing Phase	• Hold at 20°C • 20°C to -40°C • Hold at -40°C	• 10 min • 1°C per min • 120 min
Primary Phase	• -40°C to 10°C • Until (PVG/CM) < 7 mTorr	• 0.5°C per min • 100 mTorr
Secondary Drying	• 10°C to 40°C • Hold at 40°C	• 0.5°C per min • 6 hrs at 100 mTorr
Post-Drying Hold and Stoppering	• Hold at 25°C • Stoppering	• Shelf temp • Under vacuum

Table 2: Freeze-drying outline as part of vial fogging study.

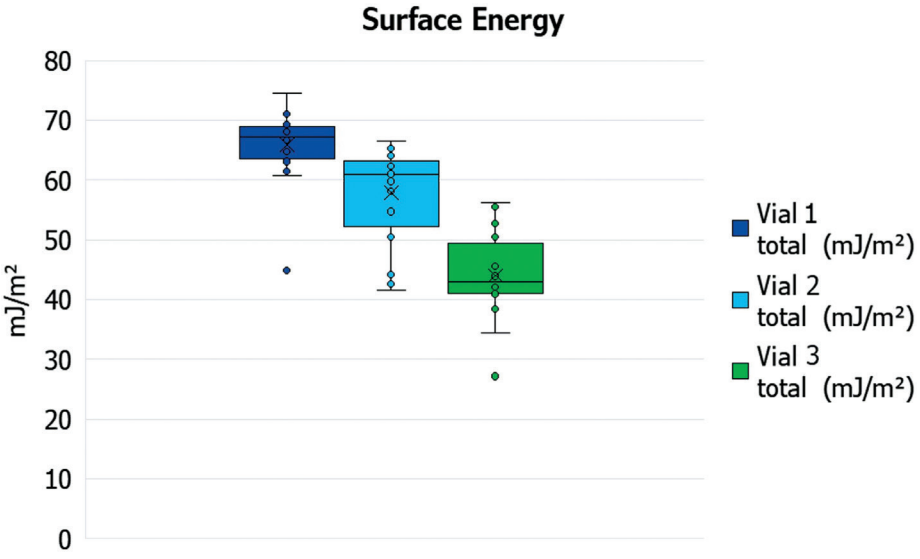

Figure 6: Surface energy calculated for each vial.

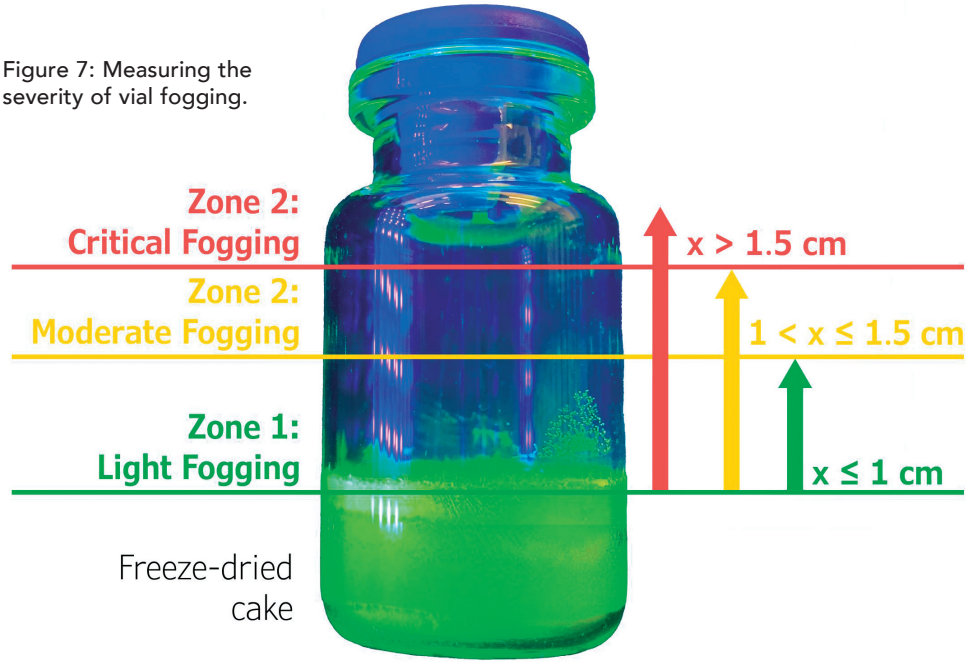

Figure 7: Measuring the severity of vial fogging.

Fogging Data

Fogging was assessed using a scoring system (Figure 7 & Table 3):

- No fogging: 0 points
- Light fogging: 1 point
- Moderate fogging: 2 points
- Critical fogging: 3 points.

Vial 3 showed an approximately 70% reduction in its overall fogging score compared with a standard vial. These data demonstrate that applying this surface thermal treatment to NIPRO's lyophilisation vials lowers their surface energy, thereby reducing fluid creep and inherent fogging during the lyophilisation process.

Vial	No Fogging	Light Fogging	Moderate Fogging	Critical Fogging	Fogging Score
Vial 1	0	0	3	50	**156**
Vial 2	0	6	26	18	**112**
Vial 3	16	22	11	1	**47**

Table 3: Fogging score for tested vials.

Diane McCormick

Diane McCormick is a Product Development & Laboratory Engineer at NIPRO PharmaPackaging, with a degree in Chemical Engineering and a specialisation in pharmaceutical packaging and lyophilisation technologies. Based in Millville (NJ, US), Ms McCormick leads R&D efforts focused on optimising glass container performance under extreme processing conditions. Her work integrates material science and drug delivery, with a particular emphasis on improving inner glass surface integrity to enhance product stability. Ms McCormick collaborates across multidisciplinary teams to translate laboratory insights into scalable solutions for the biotechnology and injectable pharmaceutical sectors.

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Clément Condouret

Clément Condouret is a Product Portfolio Manager at NIPRO PharmaPackaging, where he has led the vials, cartridges and ampoules portfolios for the past five years. He notably contributed to the development of NIPRO's lyophilisation vial range. Mr Condouret holds a Master's degree in Packaging Sciences from ESIReims (Reims, France). Prior to joining NIPRO, he gained experience in moulded glass packaging for the cosmetics and luxury sectors at Gerresheimer in Belgium. His expertise spans pharmaceutical packaging development, product innovation and glass container technologies.

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"APPLYING THIS SURFACE THERMAL TREATMENT TO NIPRO'S LYOPHILISATION VIALS LOWERS THEIR SURFACE ENERGY, THEREBY REDUCING FLUID CREEP AND INHERENT FOGGING DURING THE LYOPHILISATION PROCESS."

NIPRO LYOPHILISATION VIALS: LESS FOGGING FOR AN EFFECTIVE LYOPHILISATION PROCESS

Existing lyophilisation vials feature a specific bottom geometry that supports heat transfer. NIPRO Type I borosilicate vials are further enhanced through a proprietary thermal treatment that requires no additional materials. This treatment reduces the sodium concentration at the glass surface and improves surface quality. As a result:

- The inner surface is restored and becomes more hydrophobic
- Marangoni flow is reduced
- Lyophilisation fogging is significantly decreased.

Performance improvements include:

- Up to 70% overall reduction in fogging
- Up to 98% reduction in critical fogging (previous studies have demonstrated an 85% reduction)
- Optimised bottom geometry that supports consistent and efficient heat transfer
- Improved overall equipment efficiency through reduced reject rates
- Easy implementation with no changes required to existing processes or materials.

With this treatment, NIPRO can improve the reliability of lyophilisation at a time where its demand continues to grow, de-risking the production of lyophilised drugs and permitting their smoother entry onto the market.

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1. *"Fogging Study: NIPRO-PURDUE Collaboration". Research Summary Report, Purdue University & NIPRO, Jul 2025.*
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