

READY-TO-USE NESTED VIALS – A HIGH-VALUE SOLUTION FOR LYOPHILISED DRUG PRODUCTS

READY-TO-USE NESTED VIALS ARE EXPERIENCING GROWING DEMAND

The biologics market is growing at a compound annual growth rate (CAGR) of over 15% and, furthermore, 24% of biologic drugs newly approved by the FDA between 2017 and 2021 were in lyophilised form.¹

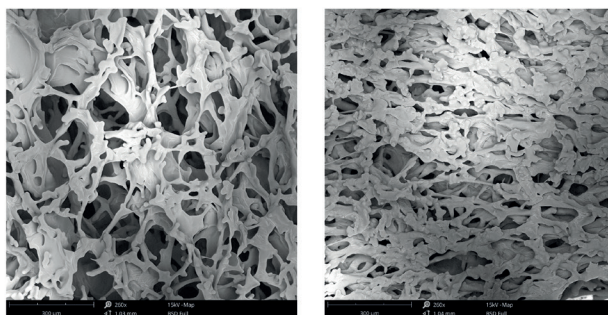
These figures confirm the growing need for sterile filling in small batches. In addition, drug stability remains a major concern and ultra-low temperature storage cannot be the only answer from a handling and especially supply chain cost perspective, and it is often impractical. Ready-to-fill containers, such as EZ-fill vials from Stevanato Group, have proven to be an excellent solution for small batch filling, but can nested vials also be used effectively for lyophilised products?

Stevanato Group, in collaboration with the Politecnico di Torino University (POLITO), has conducted a series of tests on freeze-drying pharmaceuticals in nested vials, the results of which are described in this article.^{2,3}

INTRODUCING RTU NESTED VIAL – A HIGH-VALUE SOLUTION FOR LYOPHILISED DRUG PRODUCTS

Nested vials are in a suspension frame “nest”, contrary to conventional loading where the vials are in direct contact with the freeze-dryer shelf. The suspended configuration according to ISO 21882 avoids glass-to-glass contact during the filling phase and reduces mechanical stress which could lead to vial breakage.

The nested configuration may raise doubts about the heat transfer mechanism from the shelf to the vials.



ABOVE: SEM micrographs at the dried cake centre in the case of (left) vials nested in a rack system and (right) in direct contact with the shelf.

TESTING CONDUCTED BY STEVANATO GROUP AND POLITO

The overall study results, performed on a 3ml ISO vial, not only confirmed the usability of nested vials for lyophilisation but, above all, demonstrated their potential as a high-value solution for freeze-dried pharmaceutical products.

The test series included primarily the following:

- **Influence** of the loading configuration on the **temperature distribution of ice nucleation** and **on the morphology** of the lyophilised product
- **Influence** on the **residual biological activity**

Nested vials tended to nucleate at higher temperature compared with vials resting on the shelf. It is known from the literature that the higher the nucleation temperature (i.e. the lower the degree of supercooling) and therefore the higher the sublimation rate, the larger the ice crystals and pores during the sublimation phase.

The average pore size of the sample in the nested vials was 170 µm compared with 75 µm for vials placed directly on the shelf.

A freeze-drying cycle of a 5% Mannitol solution was performed to compare the thermal behavior of the product during primary drying. Overall, the differences in temperature and time were very minimal.

The biological activity of the enzyme LDH (lactate dehydrogenase) was almost 30% higher in the nested vials after freeze-thawing and after lyophilisation. Nested vials exhibited bigger crystals and, consequently, a smaller interfacial area between the ice and the cryo-concentrated solution. This is the trigger for the denaturation of LDH, and the recovery of LDH bioactivity was always higher in nested vials.

BELOW: EZ-fill® Nested Vials



CONCLUSIONS

Main advantages of the EZ-fill nest configuration:

- Easier cycle scale-up and transfer to the final industrial site
- No significant impact on freeze-drying cycle time
- Reduction in interfacial stresses a biopharmaceutical product is exposed to during the freezing and drying phases
- Better recovery of LDH bioactivity
- Reduced intra- and inter-batch variability

These results confirm the advantages of EZ-Fill vials for lyophilisation. Find more information at: <https://www.stevanatogroup.com/en/offering/drug-containment-solutions/vial-systems/>

REFERENCES

1. Source: IQVIA and Stevanato Group internal analysis
2. Pisano R, Artusio F, Adami M, Barresi AA, Fissore D, Frare MC, Zanetti F, Zunino G. Freeze-Drying of Pharmaceuticals in Vials Nested in a Rack System-Part I: Freezing Behaviour. *Pharmaceutics*. 2023 Feb 14;15(2):635. doi: 10.3390/pharmaceutics15020635. PMID: 36839958; PMCID: PMC9960346.
3. Artusio F, Adami M, Barresi AA, Fissore D, Frare MC, Udrescu CI, Pisano R. The Freeze-Drying of Pharmaceuticals in Vials Nested in a Rack System-Part II: Primary Drying Behaviour. *Pharmaceutics*. 2023 Nov 2;15(11):2570. doi: 10.3390/pharmaceutics15112570. PMID: 38004549; PMCID: PMC10674193.