Nested Vials for Improved Lyophilisation Efficiency

PEER REVIEWED

Lyophilisation vials are normally washed and sterilised prior to processing and filling, which requires the use of cleanrooms, washing machines and sterilisation tunnels — depending on the level of containment needed — to perform these tasks. However, to improve efficiency and to reduce both time and costs, prewashed and sterilised ready-to-use packaging materials may offer a solution and improve the overall process.

Owing to newly developed products, increasingly smaller batches, more highly potent products and the need for flexible and efficient vial- and syringe-filling solutions, there are constant demands by the pharmaceutical and biotechnology industry to make the freeze-drying process faster, safer and more cost-effective, particularly regarding changeovers.

The advantage of such nested vial systems is that they can be used with existing nest-filling systems and allow pharmaceutical companies to freeze-dry and handle filled vials inside the nest. In collaboration with GEA, one of these systems - SCHOTT adaptiQ - has been tested to ascertain its suitability for the freeze-drying process in both a standard pilot plant and a production-scale lyophiliser, specifically to assess its handling capabilities with a standard loading and unloading system.

Johannes Selch, Product Manager, ALUS™, at GEA, was available to discuss the results. "Our focus," he says, "together with SCHOTT, was to find out how the nested vial product influences the freeze-drying process, particularly in terms of handling (loading and unloading), in a production environment. The obvious advantage is that there's no need to use a washing machine or a sterile tunnel in front of the filling line. The vials are supplied clean, sterile and ready-to-use in a sealed, nest/ tub configuration. The user can then bring the nest/tub into their containment area — be it an open/closed RABS system or an isolator — where it can be manually or automatically opened." In essence, all process steps are possible within the nest, handling is smooth and reliable, and there's no glass-to-glass contact. Container production, depyrogenation and washing are done prior to nesting, after which the package is sterilised by gaseous ethylene oxide (ETO). Vial/ tub transport, filling, stopper setting, lyophilisation and closure with press-fit caps can all be done with the vials in the nest. For in-process-control and crimping, the vials have to be removed from the nest and reinserted for further processing.

He added: "Normally when you operate a freeze-drying process, the user has to wash and sterilise the vial frames or trays. And, after the process, the washing/sterilisation step has to be repeated. With nested vials, this is no longer the case; it's a single-use, disposable technology and the post-lyophilisation washing step is not required."

Other key points are

Flexibility: existing nested filling equipment can be used; machinery for the optimised filling of small batches is available.

Product quality: the vials are supplied clean, sterile and ready-to-fill in a nest/ tub; there's no glass-to-glass contact during transport, fill and finish; and the system offers increased safety benefits for highly potent products.

Cost of ownership: Lower capital employed and reduced running costs, minimised defects during filling and reduction of cleanroom space required.

Configuration and Structure of the Nest

The nest uses a rigid honeycomb structure that both provides stability and separates the individual vials from each other. Each vial is resting on three clips that vertically support it by the collar. The bottom of the vial is freely accessible. This allows the vials to remain nested during most processing steps including lyophilisation. If the vial has to be removed (e.g. for traditional crimping) it can be pushed out of the nest from below for so-called denesting. Using the same principle, the vials can be re-inserted (renested) by placing them on a piston that spreads the clips from below and receives the vial to be securely lowered back into the nest.

Thanks to this design, the vials are

unable to come into contact with other vials, to prevent scratches and breakage and consequently lower the reject rate. The nests also have walls for freeze-dryer handling, finger cut-outs for manual removal and an alignment guide for precise positioning. Individual nests can be linked together and a wide variety of sizes are available, from 2/4R (100 vials) and 6/8/10/15R (48 vials) to 20/25/30R (25 vials) in an industry-standard tub format (Figure 1). And, as it has been designed for existing nest-fillers and novel flexible filling equipment, the system is scalable from research and development (R&D) to commercial production.

Under Test Conditions

"Having tested the nested vials using a standard tray-loading system, they performed perfectly well," notes Johannes, "irrespective of whether the nests were fixed together or left unattached (Figure 2). Unloading using a standard system was also problem-free." He commented that the interconnectivity most likely plays a greater role in manual handling; but, for automated systems, the nests can be used as individual units. "In development and when processing very expensive product in small batches, the connectivity would also be an advantage, as it facilitates manual loading and unloading," he noted, adding: "Key advantages here are simplified and stable loading/unloading, and less downtime as a result of higher loading/ unloading speeds."

Nesting/de-nesting can also be automated quite easily, providing

- reliable removal of vials (individually or in batches)
- stable reinsertion of vials after checkweighing/closure.

Further research is ongoing with machine vendors to further advance nested processing. Containment issues can also be avoided with the use of nested vials, which are suitable for both open and closed RABS, isolators and GEA's Automatic Loading and Unloading System (ALUSTM).

Capacity Restriction

Regarding capacity, Johannes said: "We have calculated how many vials can be processed, with and without nesting, using a standard loading/unloading procedure without frames or trays. Using a freeze-dryer with standard shelf dimensions, a process capacity reduction of up to 40% was recorded using nested vials compared with non-nested ones (hexagonal format)."

Commenting on the results, Johannes said: "We can process 200–300 nested vials a minute to improve the overall efficiency (100 vials/nest means 2–3 nests/min), but the 40% capacity loss is significant. To fully utilise nested vials and to compensate for this loss in the future, it will be necessary to address the issue at the design stage and produce tailor-made freeze-dryers."

It is presumed that nested vials will, initially, be used to process very expensive products. It's apparent that the increased stability inherent in the system is a clear benefit for high-value or highly potent compounds. And, being able to guarantee that no vials fall or become damaged is a key consideration. Even an average non-nested fall rate of 0.02% when working in a high containment facility or with a limited supply of a toxic product would be problematical and time-consuming to remediate.

Johannes adds: "The current trend would suggest that nested vials will not be used for high-volume, low-value product processing, only for small batches of high-value products. This does not preclude the use of an automatic loading and unloading system, though; more and more often, automatic loading/unloading systems are used to prevent operator intervention, reduce contamination risks and protect both the product and the user, particularly when potent products are involved (Figure 3)."

Processing Tests

In a comparative drying test at pilot-plant scale, a 3% mannitol solution was processed in a standard freeze-dryer. Nested and non-nested (hexagonal format) vials were used. The test showed that placing the vials in nests resulted in a 10% faster drying cycle. It could be concluded that the surrounding plastic had no detrimental insulating effect, and that the less dense arrangement of the vials in the nest led to a positive influence on the total drying time.

Scaling up to a production-level freeze-dryer, a comparable test was done with 3% mannitol. Once again, a similar result was obtained.

In addition, stoppering was also examined and the result was nearly identical for both sets of vials. It was remarkable, though, that fixing the vials in the nest prevented the stoppers from sticking to the freeze-dryer shelves, and that no nested vials fell over during the procedure.

When looking at residual moisture values, it was noted that the nested vial results were slightly better than the non-nested vials at the edges of the containers. The additional space between the vials enhances the sublimation flow and reduces the total level of residual moisture. "Overall," notes Johannes, "apart from the tiny variation in residual moisture levels, there is absolutely no difference between the results obtained from the nested and non-nested vials in a production-scale freeze-drying process. The data are extremely comparable."

"For the pharmaceutical market, however, it is important to demonstrate that nested vials can effectively be used in both a pilot and full-scale freeze-dryer, and with a standard loading/unloading system, without risk, and that the same results can be achieved compared with using a regular hexagonal vial format (Figure 4). And, as far as we know, there is also no disadvantage associated with nested vials when it comes to resolving lyophilised end-products," he added.

To summarise, SCHOTT adaptiQ® vials allows nested freeze-drying and it is demonstrably possible to use the nests in existing automatic loading and unloading systems. They meet the pharmaceutical industry's requirements that the nest is made from a proven material and that the bottoms of the vials are freely accessible to enable the freeze-drying of sensitive formulations without having to remove the vials from the nest. The nest-and-tub configuration, as used for pre-fillable syringes, offers a lower packaging density that allows for equivalent or faster drying cycles.

The higher price for ready-to-fill sterile vials compared with conventional vials will be more than compensated at a total cost of ownership (TCO) level. Investment, energy use and utility consumption can all be reduced by eliminating washing machines, water for injection (WFI) systems and sterilisation tunnels. And, despite big pharma being a very conservative industry, there are clear applications for this technology in both R&D and full-scale production. A system is already in operation, at start-up phase, in Asia. Comprising a GEA freeze-dryer with a back-pusher unloading system, full-scale production is expected to commence in 2015.

Conclusion

It is unlikely that nested vials will replace non-nested ones in standard freeze-drying and vial-handling production cycles. However, this innovative development does open up new possibilities for future production. Nested vial-handling can easily be implemented into existing and proven lyophilisation equipment and, as such, both the nests and the technology are "ready to use."

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