



Importance of Lyobeads and Using the MicroPress to Determine Quality Metrics

The development of lyophilised products helps reduce the impact of cold chain management from refrigerated warehouse to point use. These products, typically, benefit from lower shipping costs, simplify product use, and provide a longer shelf life within the diagnostics, biologics, pharmaceuticals and nutraceutical industries.

Recently, we have seen a trend-shift from traditional lyophilised cakes to lyophilised reagent beads, also known as 'lyobeads', which are spheres of customisable, lyophilised material. Unlike traditional lyophilised formats, each individual bead contains a single, accurately measured dose of a precise formulation. These single-dose beads – like all lyophilised material – retain long-term stability at ambient temperature and therefore do not need expensive cold chain shipping or refrigeration during storage.

Lyophilised beads also present further performance and efficiency opportunities,¹ particularly in terms of assay accuracy, speed and ease of process:

- **Accuracy** – lyophilised beads contain a single, precisely measured dose, minimising the potential for variance.
- **Cost savings through improved efficiency** – with less risk of user errors, a longer shelf life, and less exposure to moisture, wastage is significantly reduced, saving time and money.
- **Quick and simple** – lyobeads reconstitute quickly due to their volume to surface area ratio and come pre-packaged, ready for immediate use.

The process of manufacturing lyobeads requires a high level of expertise as it starts with the creation of a custom lyophilised bead which is stable and suitable for large scale manufacture. This is usually achieved by use of a Freeze Drying Microscope (FDM)² to understand the critical temperatures for primary drying phase of the freeze drying cycle. In conjunction with the FDM, the use of a Differential Scanning Calorimetry (DSC) or Lyotherm (DTA & impedance analyser)³ will provide thermal analysis to ensure product stability throughout the and lyophilisation process and future storage conditions. The final process for scale up and manufacturing, is the quality control assessment of lyobeads to meet the required standards for appearance, size and successful drying.

Primary quality control processes for lyobeads include residual moisture content measurement, visual appearance, dissolution rate, assay sensitivity and physical properties. Of these processes, lyobead properties – ultimate tensile strength (maximum strength a bead can withstand before breaking) and friability (how easily the beads can break into smaller parts under duress) – can be best assessed by the MicroPress, a mechanical properties analyser, in a simple non-destructive manner where analysis and quality of the data is independent



Figure 1: Lyobeads stored in vials

of the subjective experience of the operator. The precise dosage measurements within the lyobeads was mentioned earlier as a key differentiator between lyobeads and lyocakes, therefore in the lyophilised format it is paramount to ensure the full product is intact for final use. The lyobeads, during storage, will typically be held within a secondary container and by its nature move within the receptacle, it is therefore imperative that it is manufactured to sustain these movements particularly during shipments.

The MicroPress is an innovative instrument designed and developed by Biopharma Group's instrumentation specialists to quantify in-situ microscopic defects within low density materials and, specifically, in all freeze dried products to provide pivotal data as to whether or not the products produced have the proper physical characteristics. The MicroPress can quantitatively determine the strength and physical robustness of lyobeads and lyocakes in-situ. With set parameters and analysis methods, the MicroPress will be able to analyse the freeze dried product structure. This allows for fast and effective batch screening to be applied to your products, especially when time and resources costs are at a premium; with a standard method the analysis can be completed in less than one minute per freeze dried product.



Figure 2: Lyobeads in well-plates for primary packaging



Figure 3: MicroPress Mechanical Property Analyzer

What does the MicroPress measure?

Stress and strain are two physical quantities commonly used to describe mechanical properties of solid materials.

- **STRESS** is the tensile or compressive loading (force applied)
- **STRAIN** is the amount of deformation at distinct intervals.

The relationship between the stress and strain that a particular material displays, is known as that material's **STRESS-STRAIN CURVE** (see below):

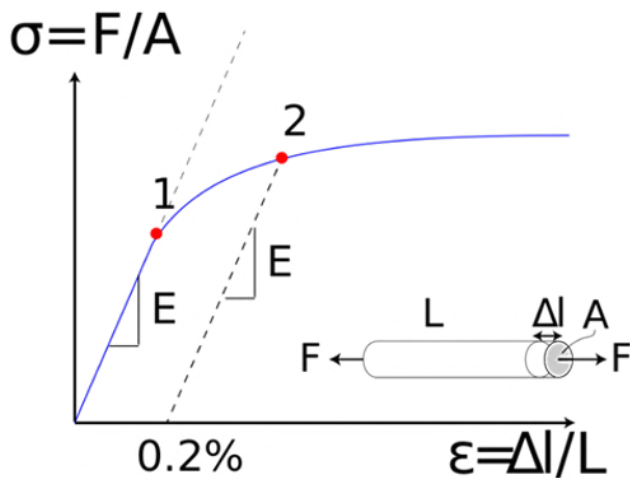


Figure 4: Young's Modulus Equation

In this curve, we can identify a useful term, the "Young's modulus", which is also known as the Modulus of Elasticity (E); this describes the tensile elasticity (or stiffness) of a solid

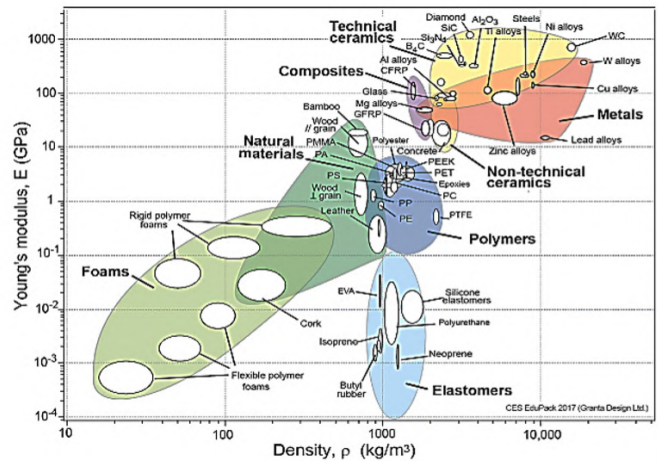


Figure 5: The Young's Modulus Spectrum

material. Compared with most materials that are tested for Young's Modulus (stress-strain), lyophiles, in which lyobeads are included, have results that are VERY light and VERY flexible (see below) and are therefore at the extreme end of the Young's modulus spectrum:

MicroPress and Lyobeads

Use of the MicroPress to assess the elasticity and strength of lyobeads provides quantitative data, which can be diagnostic in nature, to help confirm the best formulation and quality control across batches and for friability testing.

The MicroPress uses an indenter which is lowered down by the use of a programmable actuator (Figure 6) to apply determined pressure onto the sample. The sample is located on a loadcell which will measure the stress being applied to the sample prior to failure. The results are transferred via proprietary software to Excel where the Young's modulus can be obtained for comparison values.

For purposes of example, see below some experimental results looking at the lyobead appearance, storage and strength:

Analysis of Lyobead Strength with Different Exceptions

Through the examples and data shown, before it can be seen that lyobeads add value to the established lyophilisation techniques for storing in bulk prior to packaging, it must be determined that surface area provides better reconstitution rates, each bead is a measured dosage and that the lyobeads are robust enough to withstand handling processes through packaging and shipment procedures. This vial component of the

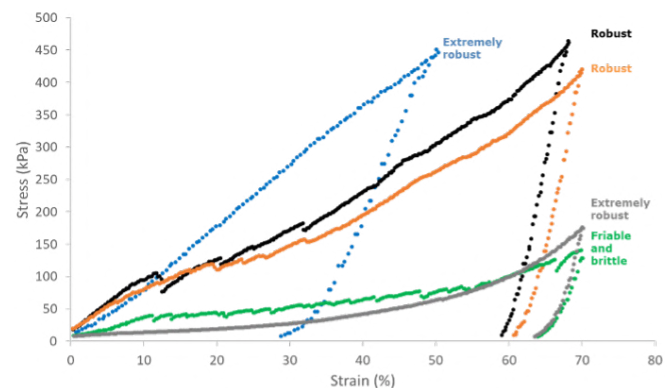


Figure 7: Variations in strength of lyobeads



lyophilised method assessment is of great importance to those utilising the freeze drying processing, especially those with delicate APIs within their products. The MicroPress provides a quantitative assessment for the strength of the product without the use of invasive techniques. With these indicators your production cycles can be increased, leading to larger quantity capabilities with lower batch rejection rates, whilst maintaining lower costs and reduced time.

REFERENCES

1. <https://youtu.be/KT8B0pQANJs>
2. <https://intelligentfreeze-drying.com/analytical-instruments/#lyostat>

3. <https://intelligentfreeze-drying.com/analytical-instruments/#lyostat>
<https://intelligentfreeze-drying.com/analytical-instruments/#lyotherm>



Figure 6: The MicroPress indenter pressing down onto a lyobead



Biopharma Group augments your in-house expertise to achieve successful product results every time. World-renowned for its expertise in field of freeze drying & associated processing technologies, our specialist scientists, R&D and contract production teams can take your product from proof of concept through formulation & cycle development to phase 1 production.

Contact us via www.intelligentfreeze-drying.com to discuss your requirements today.