Optimization of a commercial peptide-based lyophilized formulation: What to have in mind for a robust and effective drug product

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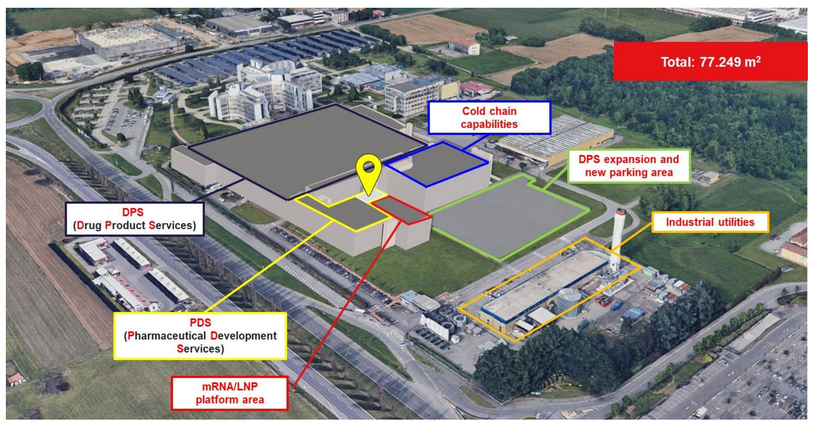
Monza Campus | Layout overview



TFS Monza PDS Formulation & Analytical Development Laboratory Services and Tailor-Made Solutions

Early Stage

- Pre-formulation studies & prototype
- Familiarization Study & Compounding Design
- Purification/Filtration Design
- Lyophilization Cycle Development & Scale-up
- Fill Volume Determination
- Spiking Study (oxidant)
- Terminal Sterilization Study
- Vials to PFS Transition Study

Middle Stage

- Product Contact Part Compatibility & In-Use Studies
- Lyophilization Cycle Robustness (DoE)
- Formulation Robustness (DoE)
- Holding Time Studies
- Freeze-thaw Studies
- Pumping Recirculation Studies
- Mixing Study

PDS FD Lab Capabilities

INTRODUCTION

Formulation development is a crucial step in creating an effective drug product (DP) in a specific dosage form, ensuring its stability, usability, and patient safety. This process depends on the drug substance (DS) and the target product profile (TPP), with excipient selection being of utmost importance.

In this case study, we examine the activities carried out in the Formulation & Analytical Development Laboratory at Thermo Fisher Monza to optimize a peptide-based therapeutic lyophilized formulation (DP) and increase its potential for commercial success. The objective was to develop a stable and effective formulation that meets the desired TPP criteria.

Excipient selection played a critical role in the formulation development. Excipients are inactive ingredients that can influence the stability, efficacy, and manufacturability of the DP. For this peptide-based formulation, mannitol was chosen as the bulking agent due to its favorable properties in lyophilized formulations. However, during stability studies of the DP, a degradation peak was observed to increase over time. This unexpected result prompted further investigation to identify the root cause of the degradation.

It was hypothesized that the degradation peak could be attributed to either the lyophilization process itself or interactions between the peptide and mannitol in the solid state after lyophilization.

To test these hypotheses, a series of experiments were designed and conducted. These included:

1. Lyophilization Process Optimization: The lyophilization cycle parameters, such as introduction of annealing during the freezing step, was investigated to determine their impact on the stability of the peptide.
2. Excipient Compatibility Studies: Bulking agent was evaluated at different concentrations to assess their compatibility with the peptide. This involved preparing formulations with different bulking agent brand and concentration and subjecting them to accelerated stability testing.

The results from these studies provided valuable insights into the factors contributing to the degradation of the peptide. It was found that selecting a bulking agent at appropriate concentration that did not interact with the peptide in the solid state improved the stability of the DP. Through meticulous formulation development and optimization, a stable and effective peptide-based lyophilized formulation was achieved. This not only enhanced the potential for commercial success but also ensured patient safety and efficacy of the therapeutic product.

INVESTIGATION #1

To identify the root cause of degradation, two formulations with different mannitol concentrations were prepared. Both formulations underwent lyophilization following two distinct protocols: the GMP manufacturing lyophilization recipe (target lyo recipe) and a modified lyophilization recipe that included an annealing step, which is commonly used in mannitol-based formulations. The goal was to understand the impact of mannitol concentration and the lyophilization process on the stability of the drug product (DP).

Importance of Mannitol Crystallization:

Complete crystallization of mannitol during the freeze-drying process is essential for the stability of lyophilized formulations. Partial crystallization can lead to the subsequent crystallization of the amorphous fraction during storage, which can compromise drug stability.

Formulation Preparation:

Two formulations were prepared with different concentrations of mannitol.

Formulation A: Higher concentration of mannitol.

Formulation B: Lower concentration of mannitol.

Lyophilization Protocol:

Target Lyo Recipe: The standard GMP manufacturing lyophilization recipe.

Modified Lyo Recipe: Included an annealing step intended to promote complete crystallization of mannitol.

Stability Studies:

After lyophilization, samples from both lyophilization cycles were subjected to stability testing. They were stored under stress conditions of 40°C and 75% relative humidity (RH) for 1 and 2 months. The stability of the formulations was analyzed using High-Performance Liquid Chromatography (HPLC) upon reconstitution.

Stability Testing Outcomes:

Target Lyo Recipe: As shown in Figure 1, Formulation B (lower mannitol concentration) exhibited increased stability compared to Formulation A (higher mannitol concentration). Lower mannitol concentration reduced impurity generation, enhancing the drug product's stability and enabling the achievement of a DP that meets the desired TPP criteria (Acceptance Criteria for impurity levels: ≤1 %).

Modified Lyo Recipe: As shown in Figure 2, neither formulation showed improved stability with the annealing step as impurity levels are non-compliant (greater than 1 %).

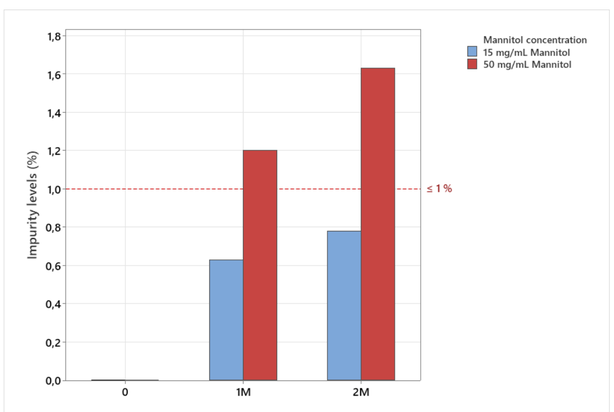


Figure 1: Impurities at different bulking agent concentration after 1- and 2- month storage condition at 40°C.

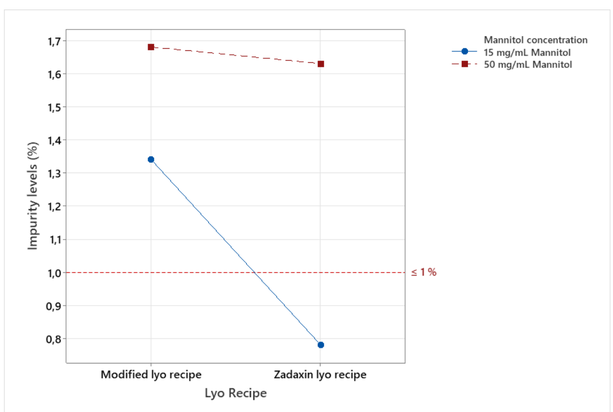


Figure 2: Impact of lyophilization recipe after 2-month storage condition at 40°C.

INVESTIGATION #2

A second investigation was conducted to test five different brands of mannitol at various concentrations to determine if the impurity levels in each brand could be linked to the degradation of the drug product. The formulations were lyophilized using only the target lyophilization recipe.

Formulation Preparation:

Five different brands of mannitol were selected for testing.

Each brand of mannitol was used to prepare formulations at various concentrations.

Lyophilization protocol:

All formulations were lyophilized using the target lyophilization recipe, which is in the GMP manufacturing protocol.

Stability Studies:

After lyophilization, samples from both lyophilization cycles were subjected to stability testing. They were stored under stress conditions of 40°C and 75% relative humidity (RH) for 1 and 2 months. The stability of the formulations was analyzed using High-Performance Liquid Chromatography (HPLC) upon reconstitution.

Stability Testing Outcomes:

The investigation revealed that the brand of mannitol used in the formulations significantly impacted the degradation rate.

As shown in Figure 3, formulations using mannitol from brands #3 and #5 exhibited the highest stability, particularly when mannitol was used at low concentrations, enabling the achievement of a DP that meets the desired TPP criteria (impurity levels:≤1 %).

Mechanism of Degradation:

While the exact mechanism by which the mannitol brand affects stability is unclear, it is hypothesized that differences in the manufacturing processes of the mannitol brands may play a key role.

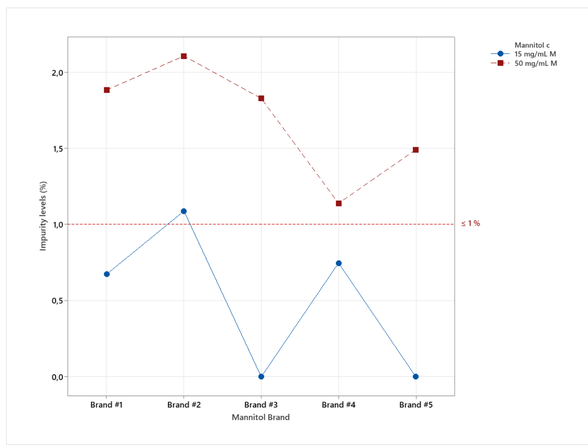


Figure 3: Impurities for each bulking agent brand and concentration after 2-month storage condition at 40°C.

CONCLUSIONS

Investigations aimed at improving the stability of the lyophilized drug product (DP) revealed that, contrary to the literature, reducing the concentration of mannitol enhances the formulation's stability, making it suitable for the GMP manufacturing for commercial purposes. Additionally, selecting the appropriate brand of mannitol can further increase the formulation's stability, a mechanism that requires further investigation. These findings are crucial in defining the final formulation to be used for the upcoming clinical batches manufacturing, ensuring product quality and patient safety.

In conclusion, these investigations highlight the importance of a detailed and methodical approach to formulation development. By challenging conventional wisdom and exploring alternative strategies, it is possible to achieve significant improvements in drug product stability. This not only enhances the potential for commercial success but also ensures that patients receive a safe and effective therapeutic product.

REFERENCES

García, M. C., & Koster, K. L. (2019). "Impact of formulation and process conditions on the structure of lyophilized cakes: A review." Journal of Pharmaceutical Sciences, 108(4), 1425-1438.

Harma, A., & Bansal, A. K. (2018). "Mechanistic understanding and formulation approaches for the stabilization of proteins during freeze-drying: A review." *Journal of Pharmaceutical Sciences, 107*(5), 1230-1245.