Macedonian Pharmaceutical Bulletin, 72 (Suppl 1) 39 - 40 (2026)
Online ISSN: 1857-8969
DOI: 10.33320/maced.pharm.bull.2026.72.03.017
Short communication

Freeze-drying strategies for a stable radiopharmaceutical: Daratumumab immunoconjugate from formulation to quality evaluation

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Introduction

The growing interest in targeted radiopharmaceuticals has increased the need for pharmaceutical technologies of convering complex biomolecules into stable and reproducible ready-to-use kits. Kit-based preparation is a well-established approach, that allows the non-radioactive components to be prepared, quality-controlled and stored separately from the radionuclide, while radiolabeling is performed just before use, a concept that is particularly important for protein-based radiopharmaceuticals, where stability and reproducible labeling are essential (Mukherjee, 2021). Freeze-drying is a key technology for preparing such kits, as it removes water through freezing, primary drying and secondary drying while aiming to preserve the structural and functional properties of the active component. However, freeze-drying may expose proteins to freezing and dehydration stress, potentially affecting their structure, purity and radiolabeling performance.

The quality of freeze-dried protein-based kits should be evaluated through critical quality attribute, including cake appearance, reconstitution time, pH, residual moisture, protein concentration, purity profile, structural integrity, radiolabeling yield and radiochemical purity.

The aim of our work is to present freeze-drying as a pharmaceutical technology for the development of monoclonal antibody-based ready-to-label radiopharmaceutical kits, with emphasis on formulation excipients, process parameters and quality attributes, illustrated using a daratumumab-*p*-

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SCN-Bn-DOTA immunoconjugate as a representative example (Apostolova et al., 2026).

Materials and methods

Daratumumab was conjugated with a 30-fold molar excess of p-SCN-Bn-DOTA and used as a model for immunoconjugate. Formulation development evaluated aqueous and 0.9% NaCl systems, including phosphate-buffered mannitol and buffer-free excipient matrices containing disaccharides as cryo-/lyoprotectants, mannitol as bulking agent, and polysorbate 20 as surfactant; sucrose and trehalose were further assessed for their effect on lyophilized product quality.

Three freeze-drying cycles were investigated, differing mainly in primary and secondary drying conditions. The optimized cycle involved controlled freezing (−40 °C), annealing at −10 °C, primary drying at −15 °C, and secondary drying up to +25 °C. Freeze-dried samples (1 mL in Type I vials) were prepared under controlled shelf temperature ramps and partially stoppered throughout processing.

Results and discussion

Formulation design

During formulation screening, residual moisture was used as the main technological criterion for selecting of freeze-dried formulations. A clear difference was observed between the formulation series: water-based samples retained higher moisture levels, whereas saline-based samples showed more efficient water removal. Among all tested formulations, the saline-based formulation containing sucrose, mannitol and polysorbate 20 showed the lowest residual moisture value of 1.90%, supporting its selection for further quality evaluation.

Freeze-drying cycle and product quality

After freeze-drying, all formulations showed acceptable appearance and rapid reconstitution within 30 s, yielding clear solutions. Although some cakes showed limited mechanical robustness, this did not affect their suitability for further analysis.

Chromatographic purity was the main criteria for formulation selection. Buffer-containing formulations showed increased formation of high-molecular-weight species, while buffer-free disaccharide–mannitol systems better preserved the monomeric form of the immunoconjugate. Based on residual moisture, reconstitution time and purity profile, the saline-based buffer-free formulation containing sucrose, mannitol and polysorbate 20 was identified as the most optimal formulation.

Effect of disaccharide and radiolabeling

The comparison between sucrose and trehalose indicated minor influence on product quality. However, trehalose slightly improved the SE-HPLC purity profile, by reducing low-molecular-weight species to below the detection level. Radiolabeling with lutetium-177 confirmed the applicability of the lyophilized immunoconjugate as a ready-to-label kit. The daratumumab-*p*-SCN-Bn-DOTA formulation achieved high radiochemical purity (up to 99.8%) and replacement of sucrose with trehalose did not adversely affect labeling efficiency, demonstrating compatibility of both excipients with the radiolabeling process.

Conclusion

The freeze-drying process was confirmed as a suitable pharmaceutical technology for the preparation of monoclonal antibody-based ready-to-label radiopharmaceutical kits, with formulation composition, freeze-drying cycle parameters and critical quality attributes are evaluated together. The selected kit formulation, based on daratumumab-*p*-SCN-Bn-DOTA containing a disaccharide, mannitol and polysorbate 20, may serve as a platform for further development of lfreeze-dried antibody-based precursors for 177Lu-radiolabeling.

References

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