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Manometric Temperature Measurement (MTM) Lyophilisation of a challenging clinical trial pharmaceutical

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OBJECTIVE

- L-BPA is the premier choice in Boron Neutron Capture Therapy (BNCT) treating selected head and neck tumours.
- L-BPA complexed with fructose has low solubility (30mg/mL). Large administration volumes are required to dose tens of grams of drug. Solutions must be freshly prepared and used within 48 hours [1].
- A new improved formulation lyophilised pH8 L-BPA solution at 100mg/mL in 110mg/mL mannitol [2]. However, the lyophilisation cycle of 6 days was unfavourable.
- **The primary objective was to reduce the L-BPA in mannitol lyophilisation cycle to 3 days or less using MTM technology**

METHODS

- MTM software (SMART®. SP Scientific, Stone Ridge, NY, USA) was operated on an FTS Systems Lyostar II drier (Biopharma, Winchester, UK).
- Hourly pressure rise data are automatically taken at a rate of 10 samples per second. The system calculates the product temperature at the sublimation interface and mass transfer resistance of the product. Adjustments are then automatically made to the shelf temperature and system pressure to achieve a calculated target product temperature. The end of primary drying is determined by comparing the vapour pressure of ice with the system chamber pressure [3].
- Test vials were 21 x L-BPA at 100mg/mL in 110mg/mL mannitol (Sigma-Aldrich, Poole, UK) pH8 filled to 10mL volume in 50mL type 1 clear glass vials (Adelphi Healthcare Packaging, Haywards Heath, UK). Stoppers were 20mm butyl rubber (proved clean) with 20mm tear off aluminium overseals (both Adelphi Healthcare Packaging, Haywards Heath, UK).
- To examine the run performance, a comparator solution of 5% mannitol in water was used.

RESULTS

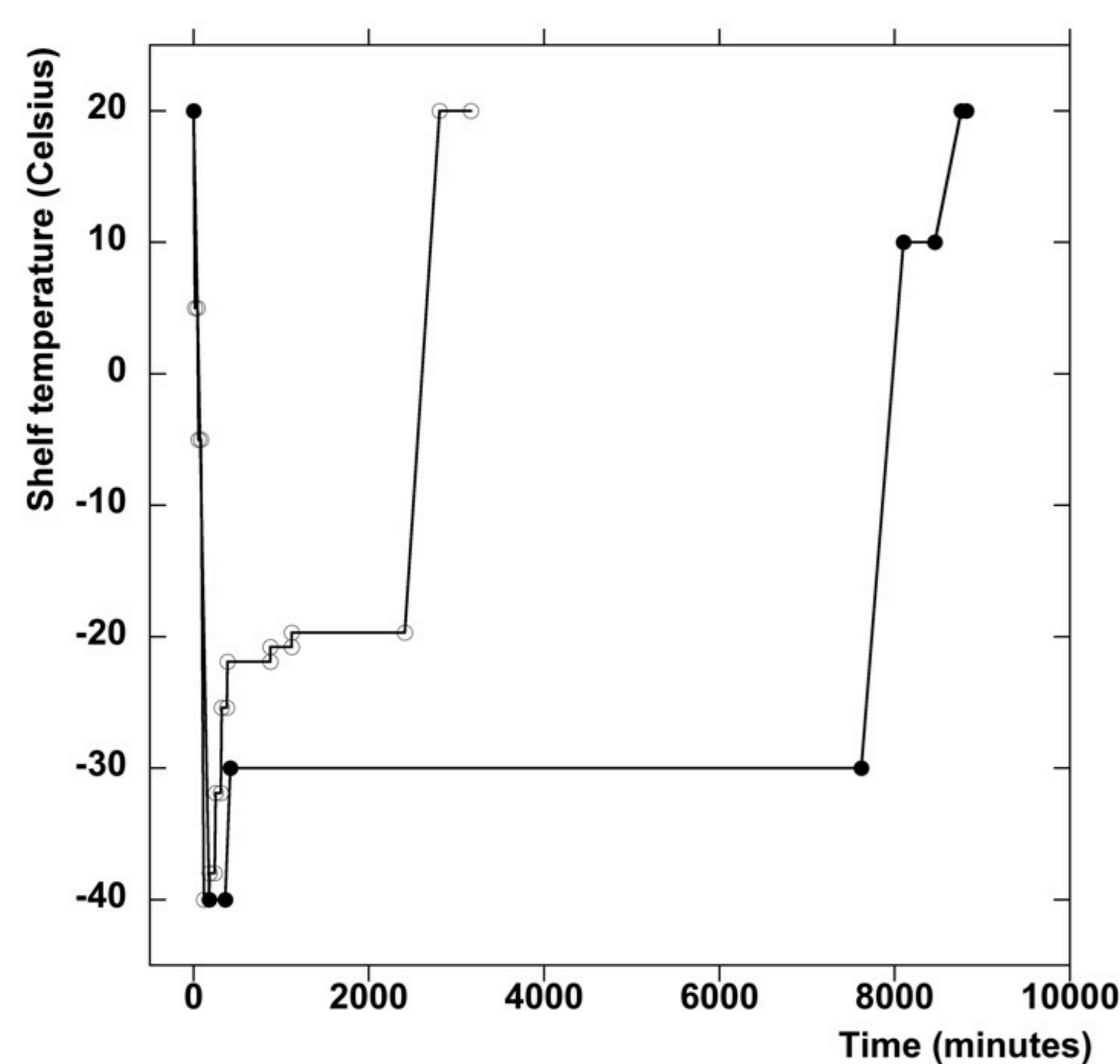


Figure 1. Comparison of drying programs for BPA clinical vials [●] and those dried under SMART® MTM [○].

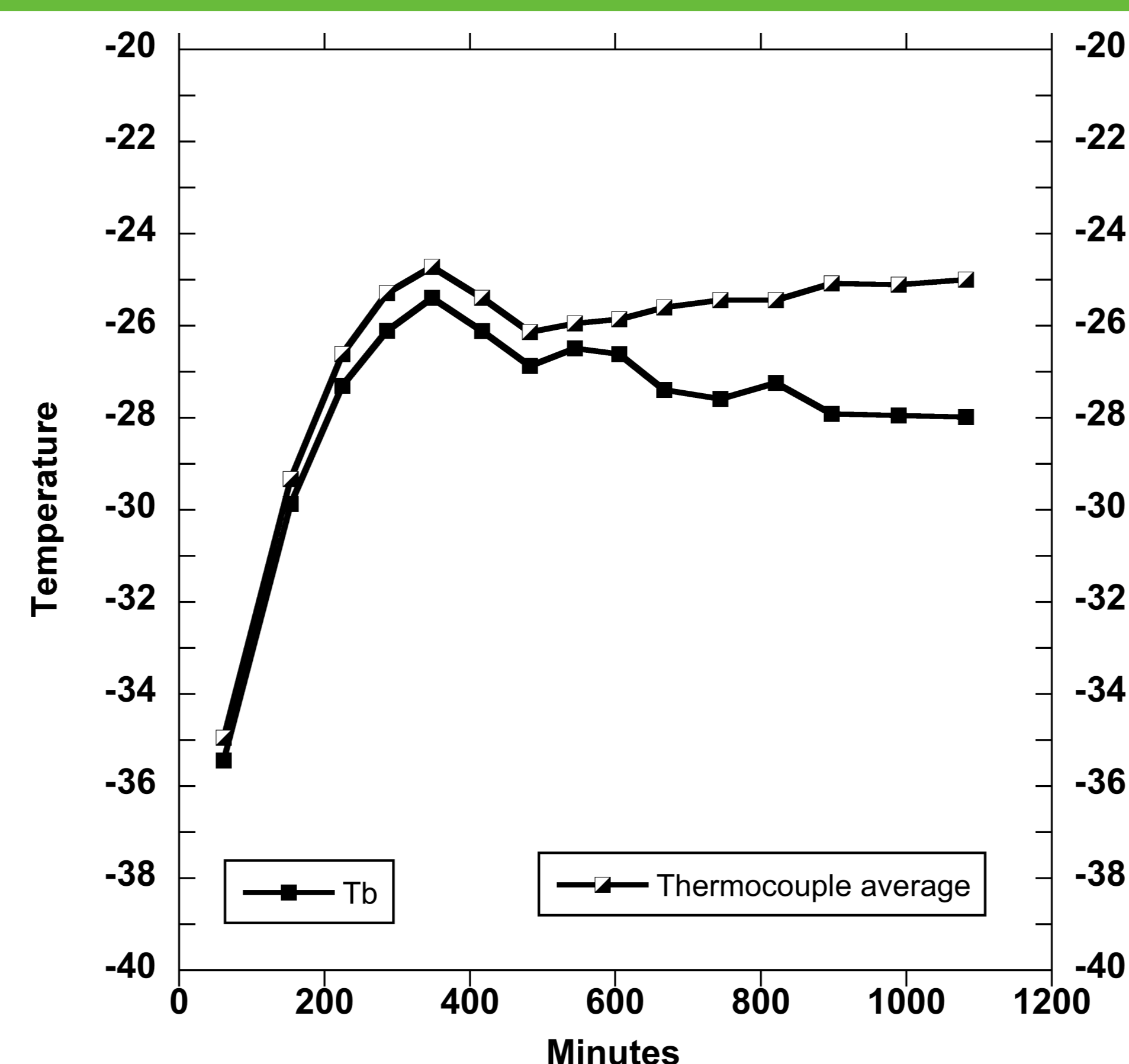


Figure 2. Comparison of thermocouple average and Tb, the MTM calculated base of vial temperature, 5% mannitol test.

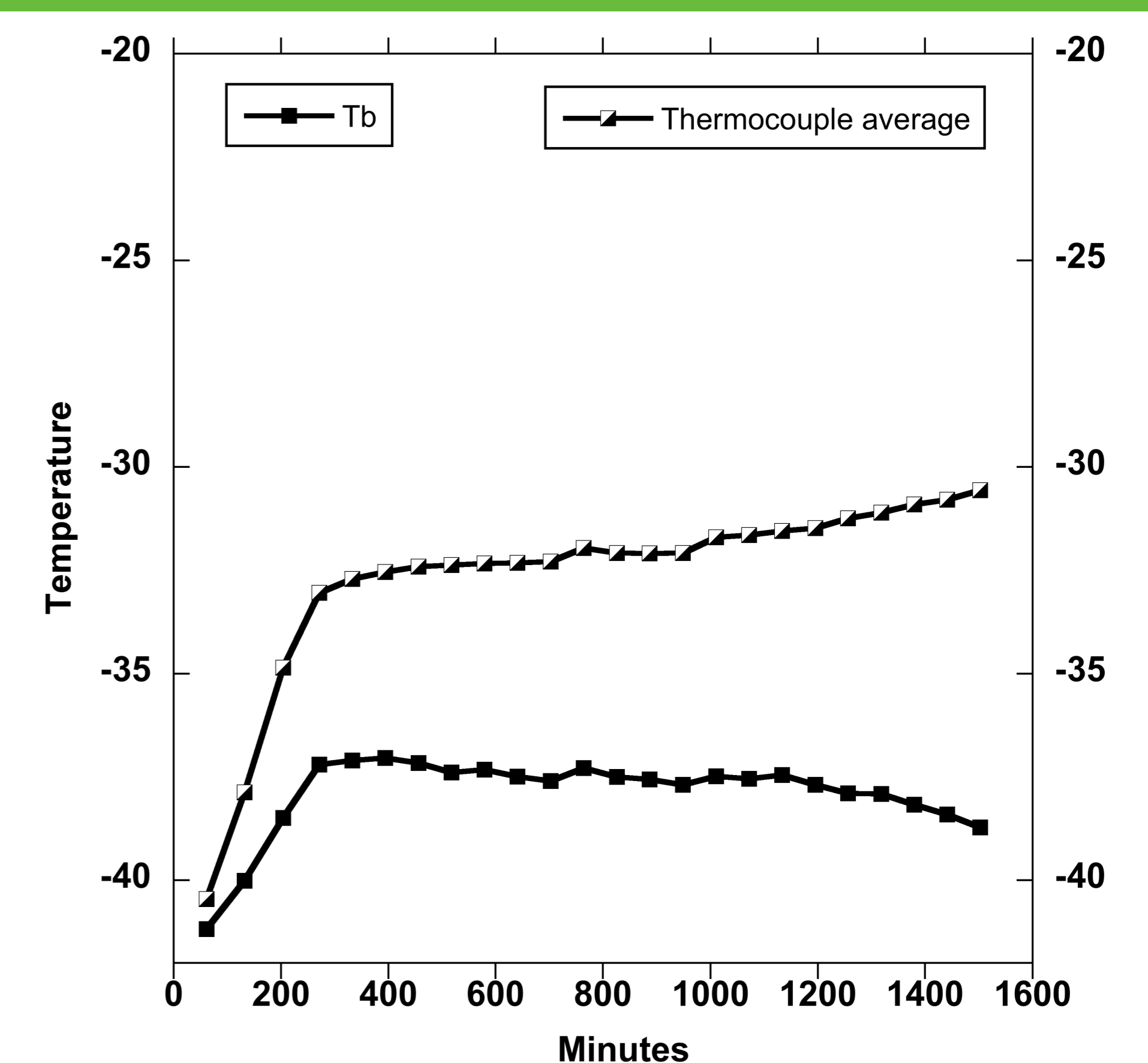


Figure 3. Comparison of thermocouple average and Tb, the MTM calculated base of vial temperature, L-BPA test.

CONCLUSIONS

- Applying MTM lyophilisation reduced an original L-BPA drug product drying cycle from 6 days to 53 hours. The test was challenging using a high solid content, high fill volume solution in which an L-BPA/mannitol complex is also formed.
- The visual appearance of the cake was poor (shrunken appearance).
- Unsurprisingly, the L-BPA test with 21% w/w solids displayed non-ideal drying behaviour. MTM failed to predict drying parameters, e.g., base of vial temperature, that were more closely replicated in the 'ideal' 5% mannitol comparator.
- The Tb / Taverage difference may be explained by drying too close to the critical temperature, risking cycle failure.
- An increased vial number may improve the feedback information for the MTM algorithm. A reduced test vial number will not suit 'non-ideal' formulations.

References

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