**Optimisation of medicine compounding using Quality by Design approach: case studies of two aqueous cream formulations**

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**Background and aims.** Quality-by-Design (QbD) is a proactive, risk-based, regulatory-endorsed approach to the development and manufacture of medicinal products but is rarely applied to medicines compounded by pharmacists. This study aims to apply the QbD approach to optimise the compounding processes for the aqueous cream and cetomacrogol cream formulations listed in the Australian Pharmaceutical Formulary and Handbook (APF).

**Methods.** Thirty-two samples of each cream type were prepared using combinations of processing conditions defined by a three-level factorial design. The viscosity, spreadability and creaming index of samples were assessed as response variables, and results were analysed using Stat-Ease 360© software to determine the optimal processing conditions for the two creams. To validate the predictive model and assess further cream stability, triplicate creams were prepared using the optimised conditions and evaluated for viscosity, spreadability and creaming index.

**Results.** Optimal conditions for aqueous cream involved heating the oil and water phases to 60 °C and 80 °C respectively, followed by stirring the two phases at 250 rpm at 10 °C until the mixture reached 50 °C. For cetomacrogol cream, optimal compounding required heating the oil and water phases to 70 °C and 75 °C respectively, and stirring the two phases at 220 rpm at 25 °C until the mixture reached 40 °C. The models accurately predicted these conditions. Creams compounded under optimal conditions exhibited well-defined oil droplets, with uniform droplet size in aqueous cream and mild size heterogeneity in cetomacrogol cream. Repeated freeze-thaw testing demonstrated stability with no observable phase separation in both optimised creams.

**Conclusion/Discussion.** Systemic quantification and optimisation of compounding parameters for the APF aqueous cream and cetomacrogol cream resulted in high quality, stable, and reproducible products. Formulary guidelines such as the APF could benefit from adopting QbD approaches to improve the standardisation of compounding instructions in pharmacy practice.