Design, Development and Optimization of a Pilot Scale Multi-Source Clobetasol 17-Propionate (CP) Cream

Roderick B. Walker, Ayeshah F. B. Fauzee
Faculty of Pharmacy, Rhodes University, Grahamstown 6140, South Africa
R.B.Walker@ru.ac.za

ABSTRACT SUMMARY
The formulation and optimization of a pilot scale manufacturing process for a multi-source interchangeable CP cream was achieved using experimental design techniques and evaluation of product and equipment performance.

INTRODUCTION
During the course of product development studies, progressive refinements of a manufacturing procedure and the formulation are made. Research and Development groups put a considerable amount of effort into developing successful pharmaceutical dosage forms from laboratory scale through the scale-up process to industrial scale. Pilot scale manufacture is crucial since many process limitations that are not apparent on a laboratory scale often become significant at a larger scale, therefore it is essential to manufacture intermediate-size batches. The manufacture of topical formulations from a small scale to large production batches can give rise to stability issues. Intermediate scale batch manufacture tends to correspond to the lowest level of each factor, +2 to the highest level and -1, +1, 0 to the mid-level. The viscosity formulation consisted of CP, propylene glycol, water, chlorocresol, sodium citrate, citric acid, glyceryl monostearate, cetostearyl alcohol, Gelot®, white beeswax and chlorocresol. The mixture was stirred with an anchor at different speeds for two hours at 70°C until all the excipients had melted and were well mixed. The homogenizer speed and time were then set for emulsification purposes and to ensure thorough mixing. Following homogenization the anchor was used to continue stirring at a set speed and cold water was allowed to pass through the heating jacket during cooling. Anchor agitation was continued until the temperature in the bowl reached between 30°C-35°C. The finished bulk product was packed into 5 Kg opaque containers and stored at 22°C until required for testing. A Central Composite Design was chosen to determine the manufacturing parameters and used as a 2⁴ full factorial design with 16 factorial points, 8 axial points and 6 centre points. Based on preliminary studies, the processing variables selected for evaluation were homogenizing speed (X₁), anchor speed (X₂), homogenizing time (X₃) and cooling time (X₄). In this experimental design, there were 5 coded factor levels: -2, -1, 0, +1, +2 in which -2 corresponds to the lowest level of each factor, +2 to the highest level and -1, +1, 0 to the mid-level. The viscosity (Yᵢ), spreadability (Yⱼ) and in vitro release of CP (Y₃) were assessed. The optimal conditions for the manufacture of the multi-source interchangeable CP cream formulation were predicted using the optimisation function of Design-Expert® software. The target was to achieve a viscosity, spreadability and a cumulative % CP released over 72 hours of a test formulation that was similar to that of the reference formulation, Dermovate®.

RESULTS AND DISCUSSION
All pilot scale creams were assessed a week after manufacture. The creams were white, smooth and homogeneous with no bleeding and phase separation apparent. The creams were free from any gritty particles. The predicted values for each parameter were generated by a model fitting technique using Design Expert Version 6.06 software and were found to correlate with the experimentally observed values. Fitting of the data to a quadratic polynomial model and subsequent ANOVA shows that correlation between the responses of the
mathematical data generated during data analysis facilitated this decision. A comparison of the results revealed that the optimized process variables were a homogenization speed of 1900 rpm, anchor speed of 35 rpm, homogenisation time of 100 minutes and cooling time of 100 minutes. Difference and similarity factors were used to characterize the in vitro release of CP from pilot scale formulations and revealed that the optimized product exhibited similar physical characteristics and in vitro release for CP to that observed for Dermovate®.

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REFERENCES