ABSTRACT SUMMARY

The development and optimization of a sustained release formulation of nevirapine (NVP) was achieved using a Box-Behnken experimental design approach, product evaluation and manufacture.

INTRODUCTION

The use of Response Surface Methodology (RSM) has become common in the development and optimization of drug delivery systems [1]. RSM is based on the principles of Design of Experiments (DOE) and involves the application of one of different types of experimental design, generating polynomial mathematical relationships and subsequently mapping the observed responses over the experimental domain to select the optimum formulation composition [2]. RSM has an advantage of significantly reducing the number of experiments that need to be performed to find a solution and therefore reduced quantities of reagents and considerably a lower amount of experimental work are required. Furthermore, RSM enables the development of mathematical models that can be used to assess the relevance, in addition to the statistical significance of formulation composition or process variables under investigation. Furthermore this approach permits an investigation of any interactive effects of composition and process variables on responses [3].

Highly active antiretroviral therapy (HAART) has helped reduce the number of deaths from HIV/AIDS in low and middle income countries. However, many challenges still exist with current treatment regimens as most ARV drugs have a short half-life, necessitating frequent administration, causing undesirable adverse effects and exhibiting unpredictable bioavailability. These factors may result to reduced adherence to medication and ultimately, treatment failure. The use of sustained release (SR) drug delivery systems for the management of HIV/AIDS has received much attention as there is the potential to overcome the challenges faced when using most commercially available ARV dosage forms [4].

The focus of this work was to design, develop, optimize and manufacture a SR formulation of NVP using DOE and to evaluate the quality attributes of the tablets.

EXPERIMENTAL METHODS

All batches of tablets were manufactured by direct compression. A preliminary formulation was developed and a composition that was found to produce a similar in vitro release profile to the commercially available Viramune® XR tablets was selected for further development and optimization. The formulation composition included hydroxypropyl methylcellulose (HPMC), spray dried lactose (SDL), microcrystalline cellulose (MCC), magnesium stearate, talc and colloidal silicon dioxide. NVP and the excipients except the anti-frictional agents were accurately weighed and screened through a #20 mesh sieve and then blended in cube blender for 30 minutes at 27 rpm. The anti-frictional agents were weighed, screened through a #44 mesh sieve and added to the blend and the mixture was blended for a further 3 minutes. The powder blends were compressed to a target hardness of 80-100 N using a Manesty® B3B Rotary Press tooled with 4 sets of punches at a speed of 27 rpm. A Box-Behnken design (BBD) approach was used to generate an optimal formulation composition to produce tablets that met the desired specifications. The independent variables studied were polymer, X1, diluent, X2, and filler, X3. The % NVP released at 2hr, Y1, 8hr, Y2, 14hr, Y3, and 24hr, Y4, similarity factor f2, Y5 and NVP diffusion exponent n, Y6, were the target responses that were monitored and were restricted to 8-12%, 40-50%, 60-75%, 85-100%, 50-100 and 0.5-1.0, respectively. The dissolution data were fitted to selected kinetic models to establish the kinetics of NVP release. The optimal conditions for the manufacture of the SR formulation of NVP were predicted using the optimisation function of Design-Expert® software Version 7.0.0 and the standard physical characteristics of tablets were monitored.

RESULTS AND DISCUSSION

Tablets from 17 batches produced according the BBD passed Pharmacopeial tests [5] for content uniformity, assay, weight uniformity and friability thereby indicating that the manufacturing process was suitable to produce a product with appropriate quality attributes. The responses that were observed for the BBD were fed into the Design Expert® software and fitted to different quadratic models. The quadratic models were evaluated for adequacy to describe the relationship between input variables and output responses using p-values, predicted residual sum of squares (PRESS), residuals, lack of fit and correlation coefficient (R²) values. ANOVA was used to identify significant factors that had an impact on the responses. Evaluation of model adequacy revealed that responses Y1 and Y4 were best described by a quadratic model, Y2 and Y6 by a linear model and Y3 and Y5 by a 2-factor interaction (2FI) model. These models were used to predict the values for each response which were compared to the actual responses obtained following testing of tablets manufactured using the input variables suggested by the optimization process. Predicted values for each parameter under investigation were found to correlate to the values observed through experimentation.
The polynomial equations for the responses were:

\[ Y_1 = 10.52 - 3.79X_1 + 0.20X_2 - 0.18X_3 + 0.23X_1X_2 - 0.014X_1X_3 + 0.80X_2X_3 - 1.48X_1^2 + 0.40X_2^2 + 0.34X_3^2 \]
\[ Y_2 = 45.38 - 10.08X_1 + 1.99X_2 - 0.40X_3 \]
\[ Y_3 = 64.08 - 8.51X_1 + 0.001875X_2 - 0.43X_3 + 4.50X_1X_2 - 1.78X_1X_3 + 2.61X_2X_3 \]
\[ Y_4 = 85.77 - 0.34X_1 + 0.12X_2 + 0.97X_3 + 2.71X_1X_2 - 1.09X_1X_3 + 0.86X_2X_3 \]
\[ Y_5 = 62.62 + 2.53X_1 + 6.11X_2 + 1.51X_3 + 0.47X_1X_2 - 1.98X_1X_3 + 2.35X_2X_3 - 13.29X_1^2 + 6.09X_2^2 + 0.44X_3^2 \]
\[ Y_6 = 0.89 + 0.087X_1 + 0.016X_2 + 0.008288X_3 \]

The results of ANOVA for the regression models indicate that the response surface model developed for \( Y_1 \), \( Y_2 \), \( Y_3 \) and \( Y_6 \) were significant and adequate since the p-value was < 0.05. Further, the results of the model summary statistics for responses \( Y_1 \), \( Y_2 \), \( Y_3 \) and \( Y_4 \) show an R^2 value > 0.9 indicating a good correlation between the observed and predicted responses exists. In addition, the predicted R^2 value is in reasonable agreement with the adjusted R^2 value and the lack of fit analysis produce p-values > 0.05 indicating that the models are reliable. Although the models selected for responses \( Y_2 \) and \( Y_5 \) were not significant they were used as they best described the relationship between the input variables and responses when compared to the other models tested. ANOVA of the responses revealed that a significant factor affecting response \( Y_1 \) was an antagonistic effect of the linear contributions of HPMC (\( X_1 \)). Response \( Y_2 \) was affected significantly by an antagonistic linear interaction of HPMC(\( X_1 \)) and the diluent used (\( X_2 \)) while response \( Y_3 \) was significantly affected by an antagonistic linear contribution of HPMC (\( X_1 \)) and the combination of HPMC and filler (\( X_1X_2 \)) and the synergistic interaction effects of \( X_1X_2 \) and \( X_1X_3 \). Response \( Y_4 \) was significantly affected by an antagonistic quadratic interaction of \( X_1^2 \) and a synergistic quadratic interaction of \( X_2^2 \). No significant interaction effects were observed for responses \( Y_4 \) and \( Y_6 \).

The optimized formulation was comprised of 33.12% w/w HPMC, 25% w/w SDL, 15.32% w/w MCC, 1.1% w/w magnesium stearate, 1.1% w/w talc and 1% w/w colloidal silicon dioxide. The results generated using a BBD in addition to evaluation of the statistical and mathematical data generated during data analysis facilitated this decision.

The optimized formulation released 10.41%, 34.01%, 61.65% and 88.81% NVP at 2hr, 8hr, 14hr and 24hr, respectively. NVP release from the formulations followed the Korsmeyer-Peppas and Higuchi models and the diffusion exponent, \( n \), was 0.9753 indicating an anomalous mechanism of release for NVP. A comparison of the dissolution profiles from the optimized formulation to that of Viramune® XR yielded a similarity factor of 69.7, indicating that the two profiles were similar.

**Figure 1.** Dissolution of NVP from the optimized batch and Viramune® XR

**CONCLUSION**

NVP SR tablets that have a dissolution profile similar to commercially available Viramune® XR tablets have been successfully developed, optimized and manufactured using RSM. The experimental model that was developed was considered precise as the predicted values of responses were close to those of the observed responses. NVP release in the initial stages of dissolution testing was predominantly affected by the amount of HPMC in the matrix formulation. Lactose had an effect on NVP release at 8 hours and although MCC had an effect on NVP release this was not as pronounced as the effects of HPMC and lactose. NVP release occurs by an anomalous process implying that diffusion, polymer relaxation, swelling and erosion impact NVP liberation from the matrix formulation.

**REFERENCES**


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