OPTIMISATION USING RESPONSE SURFACE METHODOLOGY APPLIED TO A PHARMACEUTICAL PLANT

Kathleen O'Sullivan[1], Sinead O'Neill[1], John O'Mullane[2], Martin Rea[3], David Cadogan[3]

[1]Statistical Consultancy Unit, University College Cork, Ireland
[2]Department of Computer Science, University College Cork, Ireland
[3]Wexport Ltd, Cork, Ireland

Heparin and Tinzaparin are drugs used to prevent the formation of blood clots. These drugs are often used in the treatment of deep vein thrombosis, pulmonary embolism and in post surgery care. They work by interfering with the body's natural blood clotting mechanism by inactivating thrombin, a key clot promoter. Tinzaparin, a low molecular weight Heparin, has many advantages over normal Heparin. It is a more effective anticoagulant resulting in a reduced risk of bleeding and a longer duration of action. Tinzaparin is derived from Heparin by enzymatic depolymerisation using Heparinase. Two factors, process factors A and B, of this system were assessed. The aim of this study was to determine the combination of these two factors that optimises an outcome variable in the manufacture of Tinzaparin while satisfying the required manufacturing specifications.

Response surface methodologies (RSM) are experimental procedures employed to identify factor settings that optimise a response [1]. We employed a rotatable central composite design in which five levels of each factor were chosen with 22 experimental runs executed. We used a second-order model to evaluate the linear, quadratic and interaction effects of the factors on the outcome variable. The manufacturing specifications of the additional parameters were assessed by examining the relationship between the process factors A and B, and each of the parameters. Each model was evaluated in terms of the optimal factor settings and the required specifications.

The analysis of the second-order model indicated that a linear-model provided a good fit to the data. We derived three-dimensional response surface and contour plots from the linear model. These plots indicate that optimal values of the outcome variable were produced for low levels of process factor A, while process factor B had a negligible effect. However, the manufacturing specifications necessitated that these factors had to be constrained. Subsequent analysis revealed that one constraint (K) dominated and that reducing process factor A must occur with an increase in process factor B so as to meet required specifications.

This experimentation and analysis demonstrated that it was not possible to reduce process factor A without increasing process factor B in order to maintain manufacturing specifications, in which constraint K had the greatest impact on process factor settings. We have begun transferring the results of this analysis from laboratory to the production process.

References

[1] Myers, R. and Montgomery, D. (2002). Response Surface Methodology. Wiley & Sons Inc., USA.