Poster 19

Empirical Modelling Approaches for expanding the design space of small scale SCT for delivery of higher doses and patient centric dosage form

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Purpose

Swellable Core Technology (SCT) is an innovative solid oral dosage form platform used to control the release of the active pharmaceutical ingredient (API). The controlled release is accomplished through a unique design that includes two tablet layers. One layer contains the API and the other a water-soluble polymer that as dissolved increases the hydrosolic pressure within the tablet core and pushes the API through a laser drilled delivery port at an appropriate rate. It is of interest to understand the impact of several manufacturing and API attributes on the viability of this platform, e.g., drug load, API solubility, API particle size, and required compression forces. It was endeavored to develop robust, empirical models for predicting manufacturability (e.g., tablet friability, functional flow coefficient, and tablet sticking propensity on punches) and performance (dissolution profile prediction) of the SCT tablets.

Methods

Linear, logit and non-linear regression models were built upon data from a pseudo-designed experiment consisting of factor combinations based on compounds that were strategically chosen to provide a range of API attributes such as particle size, solubility, and tensile strength. Manufacturability data was recorded for several compression force profiles to incorporate tabletability factor choices into the models. Each model was built based on API characteristics, desirable drug load and tablet size; and provides the scientist with a range of development target options (e.g, direct compression or dry granulation, target ribbon SF, target compression forces, and dissolution duration). The empirical models built are targeted at predicting friability success (Pass/Fail), Flow Function Coefficient, Sticking propensity, and Dissolution.

Results

The empirical modelling process provided a rigorous pathway for identifying “potential” covariates for predicting the SCT tablet manufacturability and dissolution profile. For example, in the predictive dissolution profile model, time, tablet size, log transformed solubility, type of profile duration (long >8hrs or short <8hrs), granules Solid Fraction, and % drug load are included as predictors of the SCT tablets. The identification of contributing covariates and the best fit non-linear model was achieved in a single modelling step.
Underpinning theoretical issues typically encountered in such models (non-linear models in particular) involve convergence issues and the choice of starting parameter estimates. These issues were successfully averted, via the application of the Levenberg-Marquardt algorithm to facilitate the convergence of the models’ parameter estimates.

Conclusion

Via the development of robust empirical models, the prediction of manufacturability (inclusive of tablet friability, functional flow coefficient, and tablet sticking propensity on punches) and performance (i.e., dissolution profile prediction) of the SCT tablets has been successfully achieved. Convergence issues associated with these models have also been adequately addressed. These present models provide the knowledge of the API material attribute and manufacturing combinations required to ensure a successful SCT tablet manufacture and performance.

Keywords: Swellable Core Technology, Dissolution, Empirical Modelling, Convergence, Manufacturability