Quality by Design (Qbd) Approach for Formulation Development and Optimization of Controlled Release, Swellable Tablet Matrices of Diltiazem Hydrochloride

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Purpose
Controlled release formulations are designed to deliver drug at a pre-determined rate over a prolonged period of time. Controlled release formulations are often recommended for the treatment of chronic diseases, thereby reducing the frequency of administration and bypassing the peak drug blood levels as opposed to conventional formulations. However, formulation development of controlled release formulations is often a major challenge due to the impact of various formulation and process variables. In the past decades, FDA has emphasized the use of quality by design (QbD) approach to develop pharmaceutical products with minimum variations. The quality by design (QbD) is a systematic approach that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science and quality risk management. Therefore, the objective of the present study was to develop controlled release, swellable tablet matrices for a water-soluble drug, diltiazem hydrochloride, using a combination of a hydrophobic and a hydrophilic polymer by application of QbD approach.

Methods
To identify and investigate critical material attributes and process parameters affecting critical quality attributes of tablet matrices, risk assessment was carried out using Plackett-Burman design. For risk assessment analysis, ratio of ethylcellulose (a non-ionic, hydrophobic polymer) combined with two different grades of hydroxypropyl methylcellulose (a non-ionic, hydrophilic polymer) viz. Methocel® E4M and Methocel® K4M that differ in their hydrophilic characteristics, concentration of dicalcium phosphate (Emcompress®) as matrix diluent and compression pressure, were selected as independent variables. Since dicalcium phosphate did not show a significant impact on response variables during screening studies, in the next phase of the study, it was substituted with microcrystalline cellulose (Avicel® PH 102) in the matrix formulation. Central composite design response-surface methodology was used to optimize the formulation and establish design space. Total polymeric content in the matrix formulation (combination of ethylcellulose and Methocel® K4M) and their ratio (X1), microcrystalline cellulose (X2) and compression pressure (X3) were selected as independent study variables. The influence of these variables on critical quality attributes of tablet matrices, such as tablet crushing strength, water uptake capacity, % matrix erosion and drug release at 2, 6 and 12-hr dissolution time points, was studied. In addition, drug release studies were carried out and dissolution data were subjected to mathematical drug release modeling, and the effect of independent variables on kinetic modeling parameters, i.e. zero-order release rate constant (k0), first-order release rate constant (k1), Higuchi’s constant (b) and release exponent (n), was determined. ANOVA, Pareto charts and lack-of-fit test were used to analyze the effect of independent variables on response variables. Further, optimization of matrix formulation was determined by desirability function.

Results
Risk assessment analysis by Plackett-Burman design revealed that of the two HPMC grades (i.e. Methocel® E4M and Methocel® K4M) investigated, matrix formulations containing Methocel® K4M yielded tablets with higher crushing strength than those containing Methocel® E4M. Also, all selected independent study variables except matrix diluent, i.e. dicalcium phosphate, had significant impact on response variables. Thus risk assessment study aided in the identification and selection of critical material attributes (CMAs) and critical process parameter (CPP) in the formulation development of controlled release, swellable tablet matrices. Drug release modeling demonstrated anomalous drug release mechanism (values of release exponent, n, between 0.45 and 0.89). ANOVA and lack-of-fit for optimization and establishment of design space demonstrated that selected independent study variables had significant impact on response variables except for % matrix erosion at 2-hr dissolution time point, first-order release rate constant and Higuchi’s constant. The optimized formulation by desirability function yielded 78.1% total polymer content in the matrix formulation (combination of ethylcellulose and Methocel® K4M in 9:16 ratio), 20.9% microcrystalline cellulose and 2800 lbs compression pressure as the design space for optimum controlled release formulation of diltiazem hydrochloride; the formulation contained 1% magnesium stearate as lubricant. The observed values of response variables obtained from desirability function test were found to be close to the predicted values thus indicating validity of the selected model.

Conclusion
Controlled release, swellable tablet matrix formulation comprising of hydroxypropyl methylcellulose (a non-ionic, hydrophilic polymer) and ethylcellulose (a non-ionic, hydrophobic polymer) was successfully developed. Critical material attributes and process parameters that significantly affect critical quality attributes of tablet matrices were identified by QbD approach. The selected critical factors demonstrated a significant influence on one or more response variables. The quantitative elucidation by mathematical modeling of the obtained drug dissolution data explained the underlying drug release mechanism. Design space for developing controlled release formulation of diltiazem hydrochloride was successfully established.