RSM Analysis on in Silico in Vitro Binding of Apixaban to Factor Xa

Reza Mamizadeh Arkhazlo

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Authors' Affiliations:
Student Research Committee, School of Pharmacy, Ardabil University of Medical Sciences, Ardabil, Iran

Abstract Presenter:
Reza Mamizadeh Arkhazlo

****Correspondance:***
Reza Mamizadeh Arkhazlo

Coauthors:
Nima Razzaghi-Asl

Introduction:

Apixaban is an orally bioavailable anticoagulant drug, used for the treatment of venous thromboembolic events, recurring deep vein thrombosis. Response surface method (RSM) is an efficient computational technique for simultaneous estimation of factor effects on response, the issue not covered in traditional one-factor-at-each-time approaches. In the present project Apixaban, a factor Xa inhibitor, was subjected to analysis of variance (ANOVA) incorporated into RSM statistical package. The aim was to estimate the interactive effectiveness of selected factors for in silico target binding accuracies with regard to validated experimental binding affinities towards factor Xa and interpretation of data.

Methods:

RSM was applied to model the influence of six independent factors on docking accuracies of Apixaban with regard to validated experimental binding affinities. Three distinctive levels (-1, 0, and +1) were dedicated for each factor under study and ANOVA was performed for each endpoint (response) on the basis of Box-Behnken matrix, including 62 independent runs. Responses were defined as the differences between in silico and in vitro data in terms of binding to factor Xa. All statistical analyses were performed via Box-Behnken method, incorporated into Design-Expert (DOE) software-v.7. Docking simulations were done by AutoDock4.2.

Results:

ANOVA results exhibited that quadratic model was significant and could best describe the relationship among dependent variables (ΔnH: difference of hydrogen bonds within in silico and in vitro modes & ΔnHyd: difference of hydrophobic contacts within in silico and in vitro modes) and independent ones (A: Translation distance for drug, B: initial drug conformation, C: quaternion degrees for drug, D: torsion degrees for drug, E: grid box size, F: target conformation and G: grid spacing) with R2 values of 0.9282 and 0.8202, respectively. Model F-values were found to be 24.90 and 3.47, which indicated that in both cases the models were significant. The obtained models for ΔnH and ΔnHyd in terms of significant factors and their coded levels were as follows:

$$\Delta n\_H=1.96+0.042B+1.17C+0.12D-0.46F+0.13G-0.25CD-0.25CG-0.25DG$$

$$\Delta n\_Hyd=7.37-0.17B+0.12D+0.12E-0.54F+0.58G+0.75BE-0.25CD-0.75DG+0.75EG+1.75FG$$

As can be understood from the model terms, the most significant terms for predicting hydrogen bonds was quaternion for degrees for drug, whereas in the case of hydrophobic bonds, grid spacing (distance between autogrid adjacent points) was most determinant in predicting hydrophobic contacts. Moreover, factor F (target conformation) and factor G (grid spacing) indicated significant interaction in the second model. The most significant interactive terms for first model were found to be C×D, C×D, and D×G. Moreover, desirable solutions to achieve minimized responses (minimum differences between in silico and in vitro results) were offered.

Conclusions:

The optimized docking technique provided a convenient and efficient method toward comparative qualitative/quantitative exploration of Apixaban binding to its target. The outputs of this study provide optimization of effective factors for the development of in silico-in vitro correlation.

Keywords: Response Surface Method, Docking, Factor Xa, Apixaban