

FHAL-P9 HEMOMETRIJSKO ISPITIVANJE RETENCIONIH KARAKTERISTIKA RISPERIDONA I NJEGOVIH NEČISTOĆA

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Hemometrijska analiza je obuhvatala ispitivanje kvantitativnog odnosa strukture i retencije (QSRR) antipsihotika risperidona, njegovih nečistoća A, B, C, D, E, K, L, M i korelacionu analizu. Cilj rada je bio da se formira model koji može da predvidi retenciono ponašanje drugih strukturno sličnih jedinjenja koja nisu oficinalna u monografiji Evropske farmakopeje (EP12.2-01/2011:1559) kako bi se ubrzao postupak ispitivanja novih nečistoća/metabolita koje mogu da budu od toksikološkog značaja.

Za QSRR modelovanje i izračunavanje molekulskih parametara korišćen je *ChemMaster software 1.3. basic* program primenom metode parcijalnih najmanjih kvadrata (PLS). Retenciono ponašanje analizirano je u hromatografskim uslovima propisanim za ispitivanje srodnih supstanci u monografiji risperidone (EP12.2-01/2011:1559). QSRR modelom je uspostavljena korelacija između izračunatih molekulskih parametara ispitivanog seta jedinjenja i vrednosti relativnog retencionog vremena (RRT) u RP-HPLC sistemu. RRT vrednosti su izračunate na osnovu preuzetih retencionih vremena iz oficinalne metode.

PLS-QSRR model sa dve značajne komponente, regresionim parametrom za trening i test set ($R^2=0,969$, $R^2=0,807$), niskom srednjom kvadratnom greškom procene za trening i test set ($RMSE=0,034$, $RMSE=0,100$) je odabran za dalja ispitivanja. Ispitivana je vrsta i intezitet korelacije molekulskih deskriptora sa retencijom ispitivanih jedinjenja. Utvrđeno je da su skoro svi fizičko-hemijski molekulski deksriptori u modelu sa značajnom pozitivnom korelacijom ($r>0,76$): molekulska masa, tačna molekulska masa, molekulska masa teških atoma, *hydrogen bond acceptors* (HBA), od kojih LogP ($r=0,8520$) sa najznačajnijom.

QSRR modelom je uspešno predviđeno retenciono ponašanje dodatnih nečistoća H, I, F, J i risperidon-N-oksida u hromatografskim uslovima za srodne supstance (EP12.2-01/2011:1559) koje nisu korišćene za formiranje modela, čime je potvrđen značajan doprinos ovog modela.

FHAL-P9 CHEMOMETRIC EVALUATION OF THE RETENTION BEHAVIOR OF RISPERIDONE AND ITS RELATED COMPOUNDS

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Chemometric evaluation of the Quantitative Structure–Retention Relationship (QSRR) of antipsychotic drug risperidone and its impurities A, B, C, D, E, K, L, and M, has been performed, together with correlation analysis. The aim of the study was to develop a model capable of predicting the retention behavior of structurally related compounds not included in the European Pharmacopoeia monograph (EP12.2-01/2011:1559), thereby facilitating rapid evaluation of new impurities/metabolites of potential toxicological concern.

QSRR modeling and molecular descriptor calculations were performed using ChemMaster Software 1.3 Basic and the Partial Least Squares (PLS) method. The developed model established a relationship between the calculated molecular descriptors and relative retention time (RRT) obtained under the chromatographic conditions prescribed by the official Ph. Eur. method.

Among the evaluated models, the PLS-QSRR model with two significant components showed the best predictive performance and was selected for further analysis. The model achieved R^2 values of 0.969 and 0.807 and RMSE values of 0.034 and 0.100 for the training and test sets, respectively. Correlation analysis revealed strong positive relationships between RRT and most physicochemical descriptors ($r>0.76$), including molecular weight, exact molecular weight, heavy atom molecular weight, and *Hydrogen bond acceptors* (HBA). LogP exhibited the strongest positive correlation with RRT ($r=0.852$).

The QSRR model successfully predicted retention behavior of additional impurities H, I, F, J and risperidone-N-oxide under the chromatographic conditions specified for related substances (EP12.2-01/2011:1559). Since these compounds were not used for model development, the results confirmed its applicability for retention behavior prediction of structurally related compounds.