International Journal of Pharmaceutical Science and Research
ISSN: 2455-4685, Impact Factor: RJIF 5.28
www.pharmacyjournal.net
Volume 2; Issue 3; May 2017; Page No. 20-23

In silico quantitative structure pharmacokinetic relationship modeling on cardiovascular Drugs: Serum protein binding

***[1] Chouhan Jagtar Singh, [2] Jat Rakesh Kumar, [3] Paul Yash**

[1,] Research Scholar, Shri Jagdish Prasad Jhabarmal Tibrewala University, Jhunjhunu, Rajasthan, India

[2] Shri Jagdish Prasad Jhabarmal Tibrewala University, Jhunjhunu, Rajasthan, India

[3] Lord Shiva College of Pharmacy, Sirsa, Haryana, India

Abstract

An estimate of serum protein binding (%SPB) is of paramount importance in assessing the efficacy of drugs used to treat acute conditions like hypertension, arrhythmias. This study was conducted to develop Quantitative Structure Pharmacokinetic Relationship (QSPKR) for the prediction of %SPB in men for congeneric series of eighteen cardiovascular derivatives, using computer assisted Hansch approach. The QSPKR correlations were duly analyzed using a battery of apt statistical procedures and validated using leave-one-out (LOO) approach. Analysis of several hundreds of QSPKR correlations developed in this study revealed high degree of cross-validated coefficients (Q^2) using LOO method ($p<0.001$). The overall predictability was found to be high % SPB (R^2=0.9673 F=226.38.31 S^2=2.25, Q^2=0.9274 $p<0.001$). %SPB in the present QSPKR investigations was found to depend upon electrostatic, constitutional and topological etc. Its positive dependence on such parameters indicates that hydrogen bonding and van der Waals' interactions play a stellar role in governing protein binding. %SPB does not seem to have any dependence on lipophilic and electronic parameters indicating that the hydrophobic and ionic bonding of cardiovascular is negligible.

Keywords: quantitative structure pharmacokinetic relationships (QSPKR), serum protein binding, *In silico* ADME, cardiovascular

1. Introduction

Quantitative structure pharmacokinetic relationships (QSPR) have increasingly been used for the prediction of pharmacokinetic properties of the drug leads. The primary aim of QSPR studies is to enable the drug designer to modify the chemical structure of a pharmacodynamically active drug in such a manner as to alter its pharmacokinetic properties without compromising its pharmacodynamic potential. For more rational drug design, the derivation of QSPR is thus a necessary pre-condition2. In the current QSPR investigation, cardiovascular drugs were chosen due to the availability of % serum protein binding (% SPB) values for a large number of congeners (n = 21). Binding to plasma proteins is of fundamental importance in pharmacokinetics, since it affects volume of distribution, degree of metabolism and rate of elimination.

Traditionally, the % SPB value of a drug candidate is obtained via *in vivo* studies, which tends to be time-consuming and expensive. Therefore, a computational QSPR modeling has been explored to predict % SPB value of drug candidates, as this modeling not only saves considerable amount of time, money, animal life and involvement of normally, healthy human volunteers required for conducting experimental pharmacokinetic studies, but also the expertise of pharmacokinetists and drug designers.

The major aim of *in silico* QSPKR is to enable the drug designer to modify the chemical structure of a pharmacodynamically active drug so that its pharmacokinetic property may be altered without compromising pharmacodynamic potential. An early assessment of ADME properties will help pharmaceutical scientist to select the best drug candidate for development and as well as to reject those with a low plausibility of success. *In silico* QSPKR technique tends to save considerable amount of time, money, animal life and involvement of "normal, healthy and drug –free volunteers" required for conducting the experimental pharmacokinetic studies.

Serum protein binding (%SPB) is a vital pharmacokinetic parameter because it is directly related to the bioavailability and can be used in assessing the efficacy of drug. Hence it is important to predict the values of %SPB during drug discovery, so that compounds with acceptable rate of absorption can be identified and those with poor bioavailability can be eliminated. The current study was conducted to investigate *in silico* QSPKR amongst cardiovascular for % serum protein binding. Cardiovascular drugs were chosen for QSPKR as this category of drugs has extensively been used in cardiovascular disorders in the treatment of hypertension, arrythmias and angina pectories etc. Moreover, Cardiovascular drugs consist of significant number of compounds thoroughly investigated for their pharmacokinetic performance particularly %SPB (n=21) Further, the congeners in this class have many common pharmacokinetic characteristics, mechanism and degree of affinity with body tissues.

2. Application

1. As an instrument for prediction

Estimation of physicochemical properties using subsistent constants Reduction of the number of compounds to be synthesized Faster detection of the most promising compounds Avoidance of synthesis of compounds with same activity

2. As a diagnostic instrument

Information on possible types of interaction forces
Information on the nature of receptor
Information on the mechanism of fraction

3. **Detection of exceptions (outlier)**

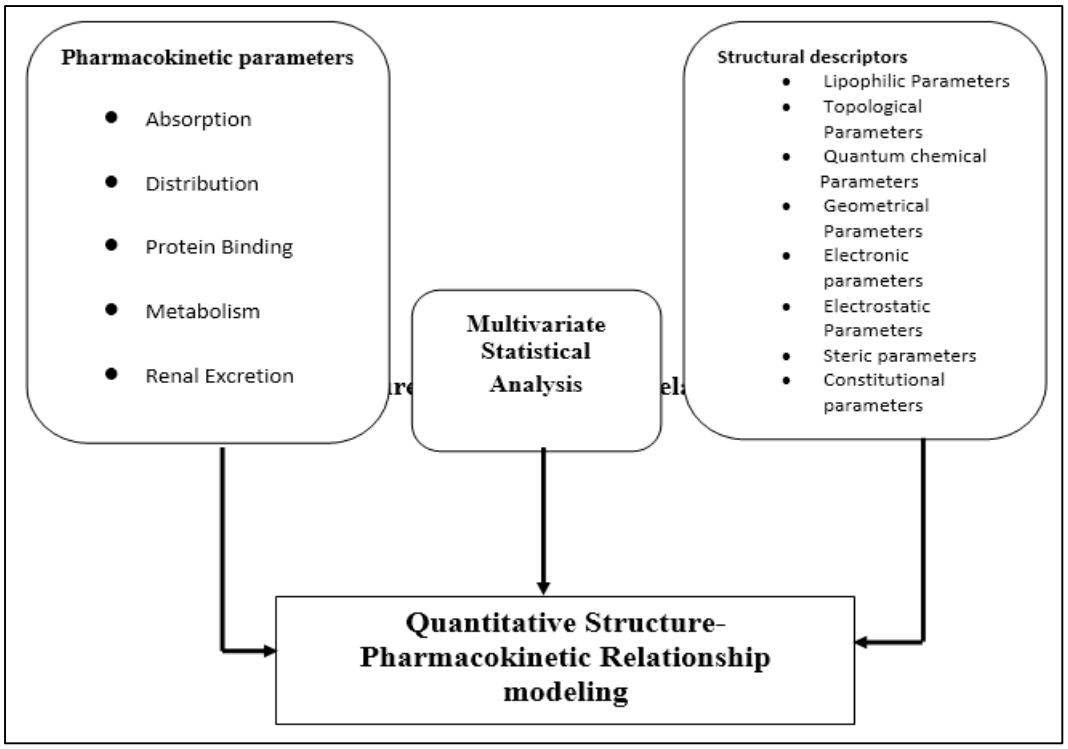

Fig 1: Quantitative Structure Pharmacokinetic Relationship (QSPKR) modeling

3. Methods

QSPKR was conducted amongst cardiovascular drugs employing extra-thermodynamic Multi Linear Regression Analysis (MLRA or Hansch) approach. The general steps for developing QSPKR model include data set selection, chemical structure entry, 3D structure generation and descriptor calculation, model construction that involves selection of descriptors and validation of testing set using a Pentium dual core (Intel, USA), Desktop (IBM, USA) with 1GB RAM and 160 GB Hard Disk.

3.1. Dataset Selection

Eighteen cardiovascular drugs with known human %SPB values were selected from literature. In order to ensure that experimental variations in determining %SPB do not significantly affect the quality of our datasets %SPB values obtained from healthy adult males after oral administration of drug were used for constructing the dataset. %SPB value of each of these compounds was also log-transformed (Log V_d) to normalize the data to reduce unequal error variance.

3.2. Molecular structure and descriptors

Chemical structures were drawn using suitable templates under Chem draw 7.0 software (Cambridge Soft Corporation, Cambridge, MA) and energy minimization was carried out using Chem3D pro 3.5 software and the files were saved as MDL *molfiles*. *Molfiles* generated by Chem3D were exported to CODESSA 2.0 software (Semichem, Shawnee, USA) for calculation of molecular descriptors.

3.3. Multivariate statistical analyses

Attempts were made to correlate various descriptors with the %SPB values. The initial regression analysis was carried out using heuristic analysis followed by best MLRA (RGMS) options of CODESSA software. All the descriptors were checked to ensure that value of each descriptor was available for each structure and there is a significant variation in these values. Descriptors for which values were not available for every structure in the data in question were discarded. Thereafter, the one and multiple parameter correlation equations for each descriptor were calculated.

Pharmacokinetic data of %SPB parameter available for twenty one cardiovascular drugs was analyzed, limiting the ratio of descriptors: drug to 4:1. As a final result, the heuristic method yields a list of the best ten correlations each with the highest r^2 and F-values. Many such attempts were carried out to obtain significant correlations for cardiovascular drugs. A set of important descriptors found to significantly ascribe the variation of %SPB, was constructed. Further, a search for the multi-parameter regression with the maximum predicting ability was performed. A number of sets of descriptors were thus made and MLRA performed with %SPB. Regression plots of each correlation thus attempted were examined. Residual plots were also studied for absence of randomization and distinct patterns to eliminate chance correlations.

3.4. Validation of Testing Set

The predictability of the final models was tested by LOO method. Briefly, the descriptors of one compound are removed, the model is redefined and the target properties of the removed compound are predicted. This process is repeated until all target properties have been predicted once for each drug. A value of cross-validated R^2, commonly called Q^2, is then computed analogous to the conventional R^2 according to equation no.1:

$$Q^2 = 1 - \frac{\sum (y_{pred} - y_{obs})^2}{\sum (y_{obs} - y_{mean})^2} \quad (1)$$

A model with good predictive performance has a Q^2 value close to 1, models that do not predict better than merely chance alone can have negative values.

The F-values were computed according to Equation no.2:

$$F = \frac{S_1^2}{S_2^2} \quad (2)$$

Where, S_1 is variance between samples and S_2 variance within samples.

The values of computed F-ratio were compared with the critical values tabulated in statistical texts and levels of significance discerned. The correlations found to be statistically significant were compiled from CODESSA software.

4. Results and Discussion

Serum protein binding (%SPB) affects the drug disposition as well as the pharmacodynamic effect of the drugs. % SPB in the present QSPR investigations was found to depend upon various electrostatic parameters like FNSA-2, PNSA-1, TMSA, RNCS etc. The quantitative prognosis was further fortified by encompassing its dependence on constitutional parameters like NoDB, RnAB, MW/XYZ and topological parameters KFI, KSI, WI, etc. Its positive dependence on such descriptors indicates that hydrogen bonding and van der Waals' interactions play a stellar role in governing protein binding. %SPB does not seem to have any dependence on lipophilic and electronic parameters indicating that the hydrophobic and ionic bonding of calcium channel blockers is negligible.

Table 1: Significant linear, logarithmic relationships for a series of 21 cardiovascular drugs using %SPB as pharmacokinetic parameter

Eqns. s	m	R^2	Q^2	SSE	F	P<
%SPB = 3.859 – 15.909 (FNSA-2) – 7.5038 (TMSA) – 5.56 (KSI) + 4.57 (MW) – 3.269 (WI)	5	0.9453	0.9323	3.2091	273.550	0.001
%SPB = 5.075 – 18.064 (PNSA2) – 8.022 (RNCS) + 5.82(NoDB) – 3.637 (KFI) – 2.69 (RnAB)	5	0.9530	0.9199	3.5707	255.681	0.001
%SPB = 3.4173 – 20.043 (MoICA) – 7.8445 (PNSA-2) + 6.2244 (ABIC2) + 4.139(RNCS-1) – 3.469 (KFI)	5	0.9673	0.9274	2.2480	266.382	0.001
Log %SPB= 1.4440 – 22.7659(MoIA) – 10.035(KFI) + 7.4504(ABIC2) - 4.1918(MPCCA) + 3.4487(PNSA-3)	5	0.9558	0.8618	3.7865	314.340	0.001
Log %SPB= 3.0292 – 19.7742(FNSA2) – 5.491(TMSA) + 5.7811(ABIC2) + 4.8540(HDCA-1) + 4.3163(NOAB)	5	0.9657	0.9178	3.4163	307.113	0.01
Log %SPB =2.1122 – 18.3191(MoIA) – 9.4672(TMSA) + 7.5197(ABIC2) + 3.1460(PNSA-3) – 3.2116(MPCCA)	5	0.9756	0.8856	3.2276	302.990	0.001

Logarithmic transformations (R^2=0.9756, Q2=0.8886) tends to improve the degree of correlations.

Figure 2 depict the linear plots (governing the line through the origin) and the residual plots between the values of %SPB as reported in literature and those predicted using multi-parameter QSPR studies for a series of 18 cardiovascular. Figure 3 show the corresponding plots for log- transform of %SPB

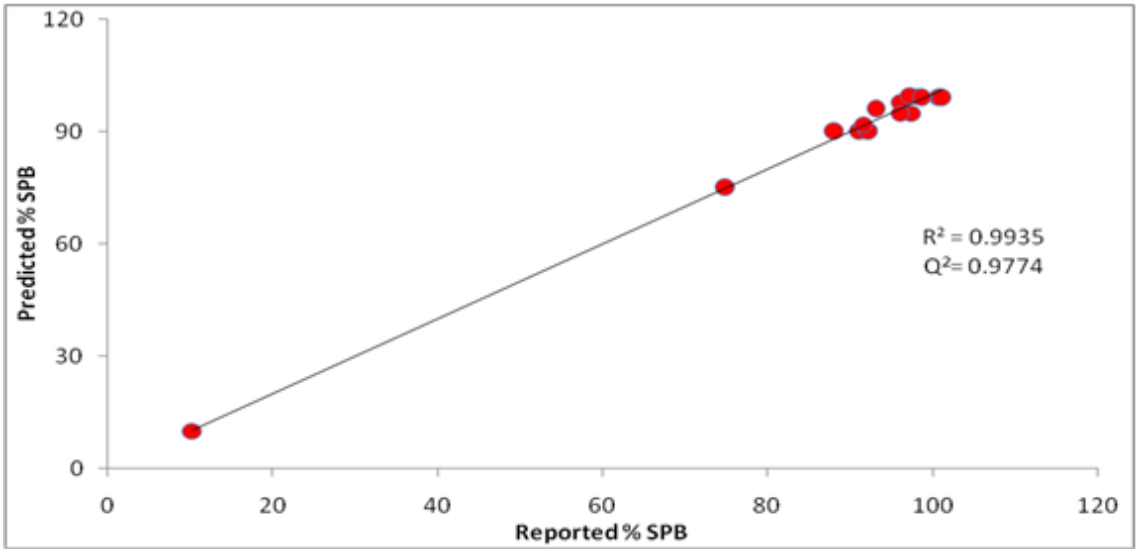

Fig 2: Plot between the predicted and reported values of %SPB for QSPKR of cardiovascular. The inset shows the corresponding residual plot

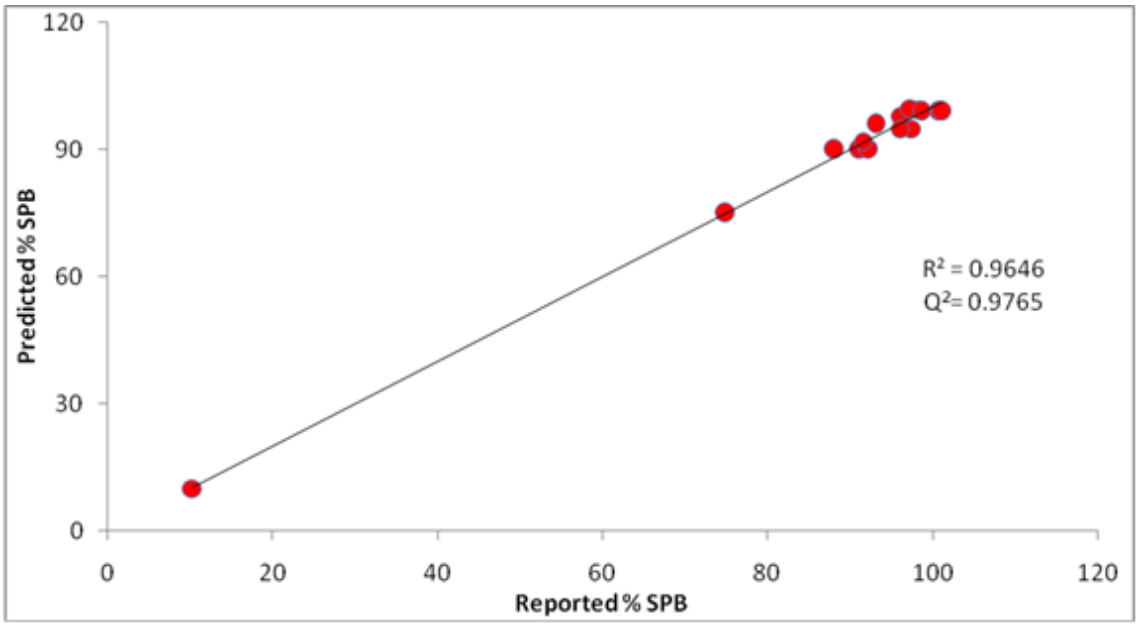

Fig 3: Plot between the predicted and reported values of Log %SPB for QSPR of cardiovascular. The inset shows the corresponding residual plot

As portrayed from these plots (Fig.2-3), the residuals were comparatively more regulated around the zero-axis for untransformed % SPB Vis a-vis Log transformed %SPB.

5. Conclusions

Analysis of several hundreds of QSPKR correlations and consequent profiles in the current investigations on cardiovascular revealed that:

The quantitative relationships for various pharmacokinetic parameters were highly predictable in most cases ($p<0.001$).

The study of the results as shown in Table 1, indicated that correlations of %SPB with various descriptors were statistically significant ($p<0.001$) with good prediction power of ($R^2=0.9673$, $Q^2=0.9274$). Logarithmic transformations ($R^2=0.9765$, $Q^2=0.9586$) tends to improve the degree of correlations.

It is a duly accepted fact that the pharmacokinetic performance of a drug is not merely a function of its physicochemical nature, but of the complexities of biological system(s). The list of biological variants embodies the somatic (age, sex, weight, etc.) psychological, pathological (nature and degree of disease), environmental, nutritional, genetic, hereditary and diurnal (chronopharmacokinetic) status of the human subjects. This causes a great deal of variation in pharmacokinetic profiles amongst the patients/volunteers undergoing study. The literature values of the pharmacokinetic parameters taken up in the present investigations, pertain to diverse subject populations, hailing from different age groups, gender, races, nutritional and physical attributes, etc., studied in different geographical regions under different weather conditions. Considering these potentially high inter-subject and intra-subject variations amongst pharmacokinetic parameters, the correlations in QSPKR studies even with moderate statistical significance ($p < 0.05$) cannot even be overlooked. Accordingly, the QSPKR results ($p<0.001$) should be taken up very high level of credence and confidence. It is expedient to render deeper insight for future studies on such *in silico* ADME predictive relationships of very high statistical significance.

6. Acknowledgements

The author highly acknowledges the efforts of Lord Shiva College of Pharmacy for technical and Software Support.

7. References

1. Singh B, Dhake AS, Sethi D, Paul Y. Part I: Fundamental Aspects. The Pharma Review. 2007; 29(5):93-100.
2. Singh B, Parle M, Paul Y, Khurana L. Part II: Descriptors. The Pharma Review. 2007; 30(5):63-68.
3. Paul Y, Dhake AS, Singh B. Asian J. Chem. 2009; 21:4728.
4. Van de Waterbeemed H, Gifford E, Drug Discov, 2003; 2:192.
5. Beresford AP, Segall M, Tabit MH. Curr. Opin. Drug Discov. Dev. 2004; 7:36.
6. Grover M, Singh B, Bakshi M, Singh S. Pharm. Sci. Tech. Today, 2000; 3:28.
7. Paul Y, Dhake AS, Parle M, Singh B. Res. J. Pharm. Tech. 2008; 1:106.
8. Shargel L, Wu-Pong S, Andrew YU. Applied Biopharmaceutics and Pharmacokinetics, McGraw Hill Companies Inc, New York, edn. 2005; 5:259, 864-866.
9. Hooper DC, Wolfson JS. Quinolone Antimicrobial Agents, American Society for Microbiology, Washington, edn. 1993; 2:195-223.
10. Maryadele J, Neil O. The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals, Merck Research Laboratories Division of Merck and Co. Inc., USA, edn. 2006, 14.