AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Quantitative Structure-Pharmacokinetic Relationship (QSPkR) Analysis of the Serum Protein Binding Values for Antidiabetic Agents In Humans

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ABSTRACT

An estimate of Serum protein binding (%SPB) is of paramount importance in assessing the efficacy of drugs used to treat diabetes in patients. This study was conducted to develop Quantitative Structure Pharmacokinetic Relationship (QSPkR) for the prediction of %SPB in human for congeneric series of 23 antidiabetic drugs, 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 serum protein binding (%SPB) ($R^2=0.8709$, $F=19.20$, $S^2=93.89$, $Q^2=0.6685$, $p<0.001$). Serum protein binding (%SPB) in the present QSPkR investigations was found to depend upon electrostatic and constitutional parameters. Its positive dependence on such descriptors indicates that hydrogen bonding and vander Waals' interactions play a stellar role in governing protein binding.

Keywords: Quantitative structure pharmacokinetic relationships (QSPkR), Serum protein binding, *In Silico* ADME, antidiabetic drugs

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Received 14 March 2016, Accepted 30 March 2016

Please cite this article as: Sethi R *et al*., Quantitative Structure-Pharmacokinetic Relationship (QSPkR) Analysis of the Serum Protein Binding Values for Antidiabetic Agents In Humans. American Journal of PharmTech Research 2016.

INTRODUCTION

Drug discovery and development is an intense, lengthy and an interdisciplinary endeavor. Drug discovery is mostly portrayed as a linear, consecutive process that starts with target and lead discovery, followed by lead optimization and pre-clinical *in vitro* and *in vivo* studies to determine if such compounds satisfy a number of pre-set criteria for initiating clinical development. For the pharmaceutical industry, the number of years to bring a drug from discovery to market is approximately, 12-14 years and costing up to $1.2 - $1.4 billion dollars. Nearly 45% of the drug candidates fail during the clinical trials owing to their poor pharmacokinetic properties.[1]This is an economic disaster as the failed drugs have been in the pipeline for several years with high expenditure of efforts, time and money invested in their development. More recently *in silico* ADME modelling has been investigated as a tool to optimize selection of the most suitable drug candidate for development. The use of computational models in the prediction of ADME properties has been growing rapidly in drug discovery as they provide immense benefits in throughput and early application of drug design. 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.[2] 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 serum protein binding (%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 antidiabetic drugs for serum protein binding. Antidiabetic drugs were chosen for QSPkR as this category of drugs has extensively been used in the treatment of diabetic diseases. Moreover, Antidiabetic drugs consist of significant number of compounds thoroughly investigated for their pharmacokinetic performance particularly Serum protein binding (%SPB) (n=23) Further, the congeners in this class have many common pharmacokinetic characteristics, mechanism and degree of affinity with body tissues.

APPLICATIONS

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

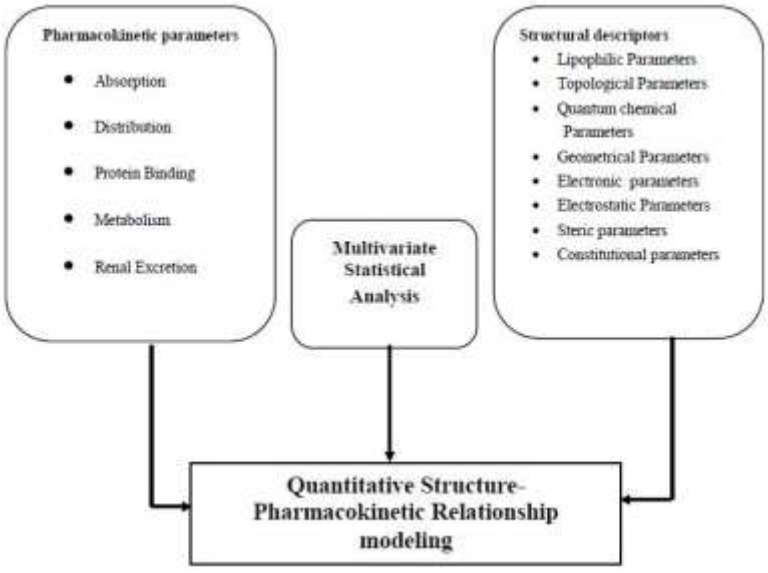
Information on the nature of receptor

Information on the mechanism of fraction

DETECTION OF EXCEPTIONS (OUTLIER)[3]

Methods

QSPkR was conducted amongst antidiabetic 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.



Model 1: Quantitative Structure Pharmacokinetic Relationship (QSPkR) modeling[4]

Dataset Selection

23 Antidiabetic drugs with known human serum protein binding (%SPB) values were selected from literature.[5,6] In order to ensure that experimental variations in determining serum protein

binding (%SPB) do not significantly affect the quality of our datasets. Serum protein binding (%SPB) values obtained from healthy adult males after oral administration of drug were used for constructing the dataset. Serum protein binding (%SPB) value of each of these compounds was also log-transformed (log %SPB) to normalize the data to reduce unequal error variance.

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 DRAGON software, and as many as 4885 diverse descriptors, *viz.* constitutional, geometrical, topological, Whim3D, electronic, electrostatic etc. were calculated. *Molfiles* were also imported in CODESSA 2.0 software (Semichem, Shawnee, USA) for calculation of more molecular descriptors.

Multivariate statistical analyses

Attempts were made to correlate various descriptors with the serum protein binding (%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 Serum protein binding (%SPB) parameter available for 23 Antidiabetic 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 Antidiabetic 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 serum protein binding. 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.

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:

$$Q^2=1-\frac{\sum (ypred-yobs)^2}{\sum (yobs-ymean)^2} \quad (1)$$

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, S1 is variance between samples and S2 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.

RESULTS AND DISCUSSION

Constitutional Serum protein binding was also found Serum protein binding (%SPB) affects the drug to be dependent on electrostatic and geometrical disposition as well as the pharmacodynamic effect of parameters.

Table 1: Significant linear and logarithmic relationship for a series of 23 Antidiabetic drugs using serum protein binding (%SPB) as pharmacokinetic parameter

Equations	M	R^2	F	S^2	Q^2	p<
%SPB= 165.85 - 304.88 Hrel	1	0.3219	12.39	227.86	0.2309	0.005
%SPB= -175.66 + 1067.42 G3p + 0.03016 piPC08	2	0.7018	29.38	89.32	0.6484	0.001
%SPB= -243.65 + 1385.8 G3p + 0.00141 Wap + 9.0720 L2u	3	0.6711	16.35	198.21	0.4233	0.001
%SPB = - 514.32 + 605.24 G3p + 1.1104 piPC03 + 93.347 PJI2 + 1404.3 Gu	4	0.7521	17.45	156.08	0.6153	0.001
%SPB = - 74.787 + 786.18 G3p + 1.1410 piPC03 + 108.01 PJI2 + 1728.2 Gu - 547.28 FDI	5	0.8050	18.14	128.54	0.5863	0.001
%SPB = - 16.259 + 957.13 G3p + 1.2047 piPC03 + 98.908 PJ12 + 1882.8 Gu - 647.82 FDI - 3.4138 DBn	6	0.8281	16.85	118.74	0.5838	0.001
%SPB = - 268.09 + 1168.5 Gm + 0.001421 Wap + 708.65 Orel + 647.61 G3u + 7.4999 AIC0 - 40.406 BIC0 + 544.29 Nrel	7	0.8709	19.20	93.89	0.6685	0.001
Log %SPB= -39012 + 4.7173 Crel	1	0.1924	6.25	0.0710	0.0968	0.005
Log %SPB= -142.44 - 0.3423 AIC2 + 6.2694 MV	2	0.4544	12.56	0.0413	0.3720	0.005
Log %SPB= 1.4632 –0.46712 AIC2 + 1.3248 PJI2 - 0.05167 Es	3	0.5442	11.06	0.0357	0.4301	0.005
Log %SPB= -5.4369 - 7.3118 Crel + 1.2346 PJ12 - 0.1469 RMW + 0.052186 CIC1	4	0.6286	10.56	0.0320	0.4644	0.005

Log %SPB= 2.4516 + 2.2429 Nrel + 25.225 Gu - 0.534 AIC2 + 1.8091PJI2– 0.4326 Es	5	0.6789	11.08	0.0299	0.5006	0.005
Log %SPB= -8.231 - 12.464 Dp + 0.0245 piPC03 - 6.423 Crel – 0.6945 AIC2 + 0.9441 PJ12 - 0.1844 RMW	6	0.7256	11.31	0.0254	0.5466	0.005
Log %SPB = - 8.5039 - 14.722 Dp + 0.0149 piPC03 + 1.8902 PJ13 + 3.4188 L3p + 21.119 Gu + 10.074 SPH - 0.67229 AIC2	7	0.8085	12.09	0.0227	0.6572	0.005
1/%SPB= 0.417 - 0.4225 G3p-0.0157 PJI2	2	0.3936	8.56	0.0016	0.1041	0.005
1/%SPB= 3.6250 + 0.0007471 piPC03 - 0.23505 MSA + 0.00024679 TIE	3	0.4664	9.26	0.0015	0.2829	0.005
1/%SPB= 0.1444 + 0.0003214 TIE + 0.76421 PJI2 - 0.00342 piPC05 – 0.034721 L2u	4	0.5953	9.94	0.0014	0.3126	0.005
1/%SPB= 0.71589 - 1.4909 AIC2 - 0.6532 Es - 1.2303 G3p + 0.1423 Hn + 0.3421 Orel	5	0.6448	10.51	0.0013	0.3936	0.005
1/%SPB = -0.11164 + 0.000631 TIE + 6.4321 Crel + 0.1326 MV – 0.4321 AIC2 + 0.03421 PJI2 + 0.442 Wap	6	0.7251	11.22	0.0013	0.4976	0.005
1/ %SPB = 0.97488 + 0.00032651 TIE - 0.0022819 piPC05 - 1.1538 G3p + 0.00034273 piPC08 + 0.47776 P2s - 0.041872 L2u - 0.073213 AIC1	7	0.8038	11.73	0.0012	0.5942	0.005

Its positive dependence on such descriptors indicates That hydrogen bonding and vander Waals' interactions play a stellar role in governing protein binding. %SPB does not seem to have any dependence on lipophilic parameters indicating that the hydrophobic and ionic bonding of Antidiabetic drugs is negligible. 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=0.8709, Q^2=0.6685).Logarithmic transformations (R^2=0.8085, Q^2= 0.6572) tends to decrease the degree of correlations. Figure. 1 depicts 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 QSPKR studies for a series of 23 Antidiabetic drugs. Figure. 2 shows the corresponding plots for log- transform of %SPB. Figure 1 shows the linear and residual plots between the values of untransformed %SPB, as reported in literature and those predicted using multi parameter QSPkR investigations for a series of 23 Antidiabetic drugs. Figure.3 shows the corresponding plots for inverse- transform of serum protein binding.

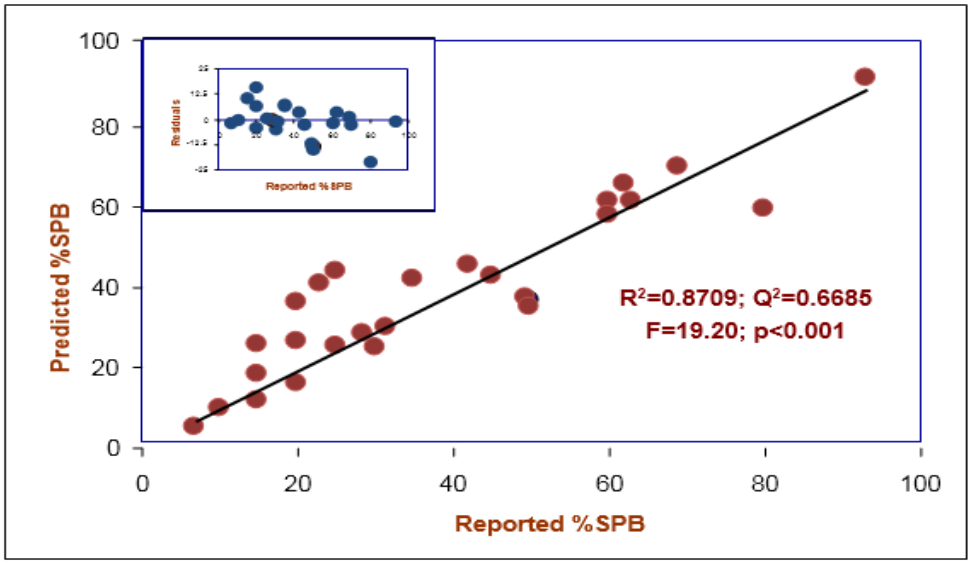


Figure 1: Plot between the predicted and reported values of %SPB for QSPkR of Antidiabetic. The inset shows the corresponding residual plot

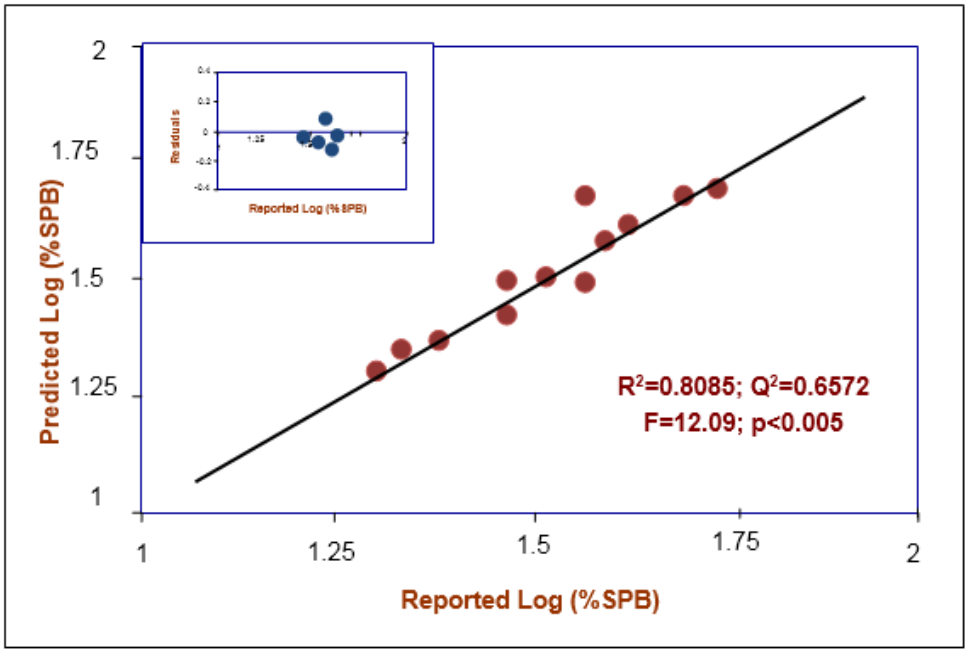


Figure. 2: Plot between the predicted and reported values of Log %SPB for QSPKR of Antidiabetic. The inset shows the corresponding residual plot

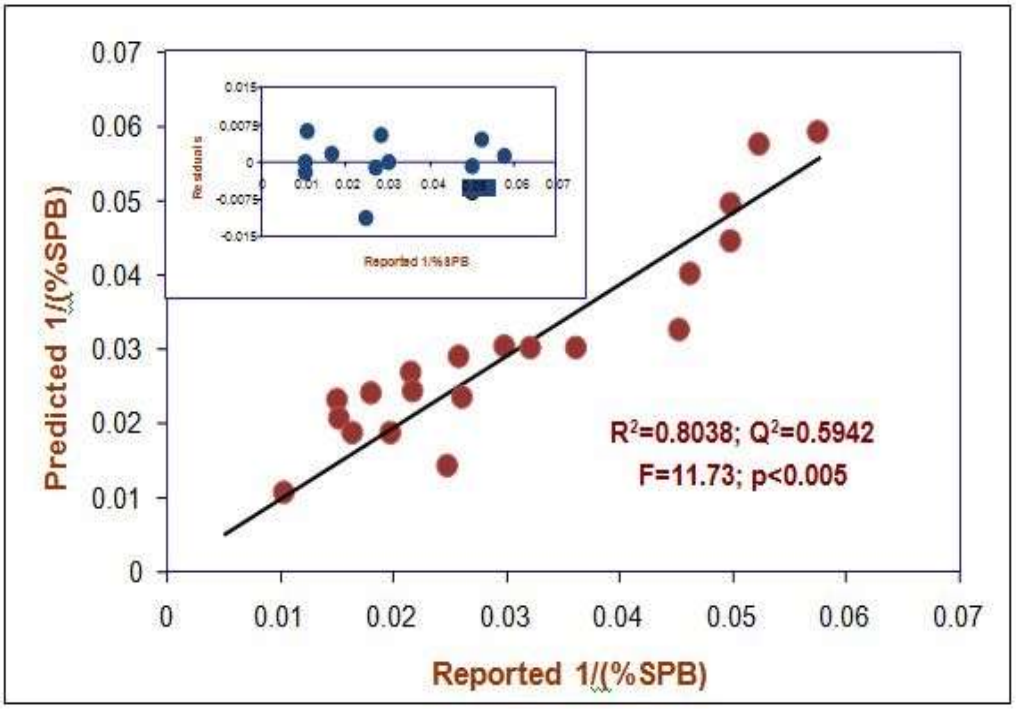


Figure 3: Plot between the predicted and reported values of 1/%SPB for QSPkR of Antidiabetic. The inset shows the corresponding residual plot

CONCLUSION

Highly significant results on *in silico* prognosis of %SPB ($P < 0.001$) attributed major variation to the electronic and topological descriptor, vouching the dependence on the diffusional interactions. Chance correlations, if any, were ruled out in the light of high magnitudes of cross-validated variance, i.e. Q^2, obtained in the current QSPkR studies. Pharmacokinetic performance of a drug is known to be not merely a function of its physicochemical nature but of the biological system(s) too, like somatic, psychological, environmental, nutritional, genetic, hereditary and diurnal status of the human subjects.[7] This causes a great deal of plausible variation in pharmacokinetic profiles among the volunteers/patients undergoing the study. The literature values of the pharmacokinetic parameters taken up in the present investigations pertain to diverse subject populations hailing from different age groups, genders, 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 among the pharmacokinetic parameters, the currently established relationships assume much higher credibility. It seems highly probable that the *in silico* approaches will evolve rapidly, as did the *in vitro* methods during the last decade. Past experience with the latter could be helpful in avoiding repetition of similar errors and in taking the necessary steps to ensure effective implementation of the former.

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