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IN SILICO QUANTITATIVE STRUCTURE PHARMACOKINETIC RELATIONSHIP STUDIES FOR RENAL CLEARANCE OF ANTIDIABETIC DRUGS

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ABSTRACT

Renal clearance (CL_R), a major route of elimination for many drugs and drug-metabolites, represents the net result of glomerular filtration, active secretion and reabsorption, and passive reabsorption. The aim of this study was to develop quantitative structure-pharmacokinetic relationships (QSPkR) to predict CL_R of drugs or drug-like compounds in humans. Human CL_R data for 24 antidiabetic compounds were obtained from the literature. Step-wise multiple linear regression was used to construct QSPkR models for training-sets and their predictive performance was evaluated using internal validation (leave-one-out method). All qualified models were validated externally using test sets. QSPkR models were also constructed for compounds in accordance with their, net elimination pathways, net elimination clearances, ion status and substrate/inhibitor specificity for renal transporters. The overall predictability was found to be renal clearance (CLR) (R^2=0.9337, F=34.96, Q^2=0.8527, $p<0.001$). Moreover, compounds undergoing net reabsorption/extensive net reabsorption predominantly belonged to Biopharmaceutics. In conclusion, constructed parsimonious QSPkR models can be utilized to predict CLR of compounds that, undergo net reabsorption/extensive net reabsorption and are substrates and/or inhibitors of human renal transporters.

KEYWORDS: Quantitative structure pharmacokinetic relationships (QSPkR), Renal clearance, *In Silico* ADME, antidiabetic compounds.

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] Renal clearance (CL_R) 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 renal clearance (CL_R) 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 renal clearance. 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 Renal clearance (CL_R) (n=24) 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

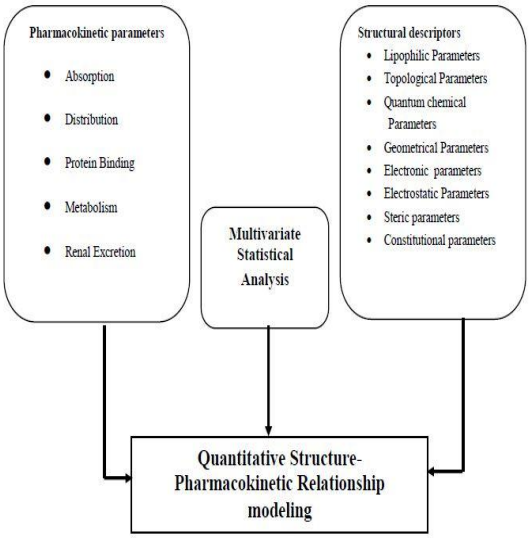
Information on the nature of receptor

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

24 Antidiabetic drugs with known human Renal clearance (CL_R) values were selected from literature.[5,6] In order to ensure that experimental variations in determining renal clearance (CL_R) do not significantly affect the quality of our datasets. Renal clearance (CL_R) values obtained from healthy adult males after oral administration of drug were used for constructing the data set. Renal clearance (CL_R) value of each of these compounds was also log-transformed (log CL_R) 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 Renal clearance (CL_R) 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 Renal clearance (CL_R) parameter available for 24 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 CL_R, 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 Renal clearance. 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 modelswas 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:

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

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:

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

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

Renal clearance (CL_R) affects the drug disposition as well as the pharmacodynamic effect of the drugs. CL_R (Table:1) in the present QSPkR investigations was found to depend upon various electrostatic, constitutional. Renal clearance was also found to be dependent on electrostatic and geometrical parameters.

Table 1: Significant linear, logarithmic and inverse QSPkR equations for a series of 24 Antidiabetic using CL_R as the pharmacokinetic parameter

Equations	m	R^2	F	S^2	Q^2	p<
Clr = 24.474 + 4.6411 WPSA-2	1	0.4155	17.04	14.4341	0.3560	0.001
Clr = -20.106 - 2.8159 LogP + 4.9613 WPSA-2	2	0.6666	24.13	9.0216	0.5192	0.001
Clr = -36.940 - 0.21542 ECC + 6.1506 WPSA-3 + 109.39 ABIC0	3	0.8005	33.01	4.0124	0.7224	0.001
Clr = 58.442 - 3.1447 LogP + 3.7865 WPSA-3 – 6.7318 Hy + 146.87 QNmax	4	0.8591	33.23	3.8739	0.8030	0.001
Clr = 63.891 - 4.503 LogP + 3.9331 WPSA-3 – 6.3842 Hy + 164.75 QNmax – 164.86 Nrel	5	0.8909	31.74	3.1066	0.8250	0.001
Clr = -161.64 - 5.204 LogP + 3.4316 WPSA-3 -4.9704 Hy + 158.75 QNmax + 295.32 Orel + 0.3446 CIC2	6	0.9337	34.96	2.3789	0.8527	0.001
Log Clr = 0.8321 + 134.54 HDCA-2/TMSA	1	0.6157	20.64	0.0347	0.3121	0.001
Log Clr = -2.3468 + 1.3974 HDCA-2 - 0.00504 VRA1	2	0.6469	24.56	0.293	0.3433	0.001
Log Clr = -2.7618 + 159.86 FPSA-3 + 1.793 HDCA-2 + 164.74 HDCA-2/TMSA	3	0.7632	32.96	0.0204	0.4247	0.001
Log Clr = 10.347 + 168.34 FPSA-3 - 0.00819 ECC + 1.414 HDCA-2 + 144.43 HDCA-2/TMSA	4	0.879	59.14	0.0123	0.4339	0.001
Log Clr = 2.917 + 183.15 FPSA-3 - 0.00619 VRA1 + 2.0314 HDCA-2 + 163.71 HDCA-2/TMSA + 24.184 LogP(cdr)	5	0.9336	86.33	0.0096	0.7632	0.001
Log Clr = -19.761 + 169.32 FPSA-3 - 0.0010451 ECC + 191.29 HDCA-2/TMSA – 0.00504 VRA1 + 2.744 HDCA-2 + 25.709 LogP(cdr)	6	0.9826	109.31	0.0064	0.8839	0.001
1/Clr = -2.416 + 47.919 QNmax	1	0.5481	34.96	0.405	0.3153	0.001
1/Clr = 0.34514 + 0.0059221 VRA1 - 0.0043721 WPSA-2	2	0.6852	43.12	0.0262	0.5491	0.001
1/Clr = 1.4571 + 0.0071146 VRA1 - 0.0053142 WPSA-2 + 0.017132 BAC	3	0.7829	61.57	0.0187	0.6324	0.001
1/Clr = 2.3079 + 0.0067603 VRA1 - 0.0061136 WPSA-2 + 33.409 QNmax	4	0.8389	70.23	0.0105	0.6623	0.001
1/Clr = -0.5921 + 0.0063471 VRA1 - 0.1492 WPSA-3 + 0.017113 BAC + 42.903 QNmax –0.26134 PPSA-3	5	0.9372	81.67	0.0091	0.7046	0.001
1/Clr = 2.9321 + 0.0071 VRA1 - 0.14187 WPSA-3 + 0.0026919 BAC + 51.161 QNmax -0.21133 PPSA-3 + 13.981 Qmin	6	0.9904	113.62	0.0052	0.8589	0.001

Its positive dependence on such descriptors indicates That hydrogen bonding and vander Waals' interactions play a stellar role in renal clearance. CL_R 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 CL_R with Various descriptors were statistically significant ($p<0.001$) with good prediction power of (R^2=0.9337, Q^2=0.8527).Logarithmic transformations (R^2=0.9826, Q^2= 0.8839) tends to decrease the degree of correlations. Fig. 1 depicts the linear plots (governing the line through the origin) and the residual plots between the values of CL_R as reported in literature and those predicted using multi- parameter QSPkR studies for a series of 24 Antidiabetic drugs. Figure 2 shows the corresponding plots for log- transform of CL_R. Figure 1 shows the linear and residual plots between the values of untransformed CL_R, as reported in literature and those predicted using multi parameter QSPkR investigations for a series of 24 Antidiabetic drugs. Figure 3 shows the corresponding plots for inverse transform of Renal clearance.

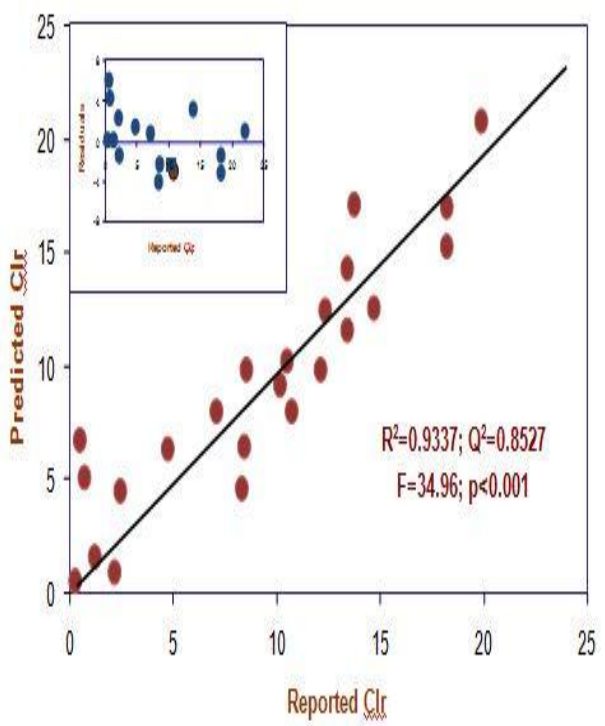


Fig. 1: Plot between the predicted and reported values of CL_R for QSPkR of 24 Antidiabetic compounds. The inset shows the corresponding residual plot.

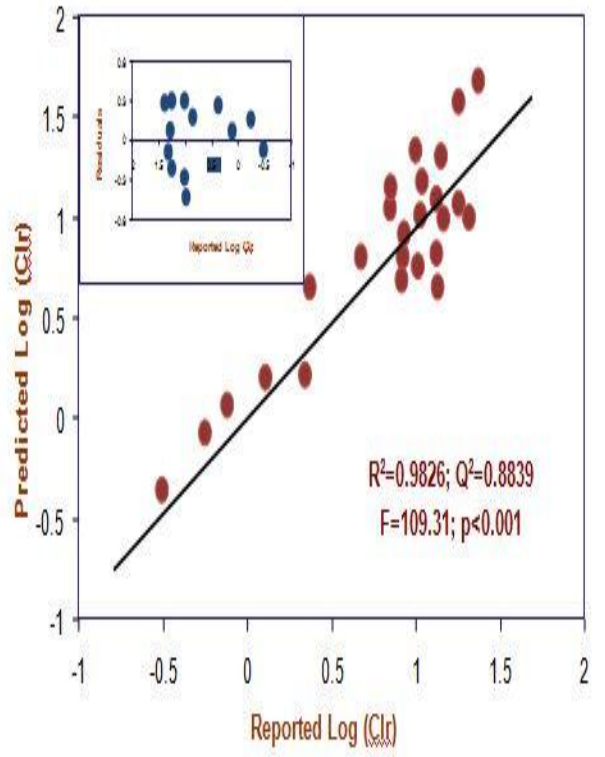


Fig. 2: Plot between the predicted and reported values of Log CL_R for QSPkR of 24 Antidiabetic compounds. The inset shows the corresponding residual plot.

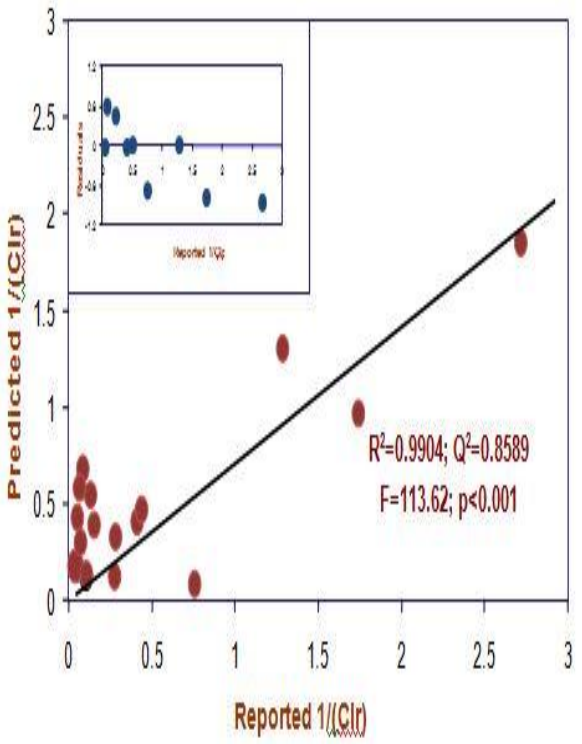


Fig. 3: Plot between the predicted and reported values of $1/CL_R$ for QSPkR of 24 Antidiabetic compounds. The inset shows the corresponding residual plot.

CONCLUSIONS

Highly significant results on *in silico* prognosis of CL_R ($P < 0.001$) 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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