Original Article

In silico Quantitative Structure Pharmacokinetic Relationship Modeling on Antidiabetic Drugs: Time to Reach Peak Plasma Concentration

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ABSTRACT

An estimate of time to reach peak plasma concentration (t_{max}) is of paramount importance in estimating thr rate of absorption and efficacy of drugs to treat acute conditions viz. polyphasia, polydispia and fatigue to treat diabetes in patients. This study was conducted to develop Quantitative Structure Pharmacokinetic Relationship (QSPkR) for the prediction of tmax in human for congeneric series of seventeen 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 ($p<0.005$). The overall predictability for time to reach peak plasma concentration was found to be high ($R^2=0.9325$, $F=30.41$, $S^2=0.1253$, $Q^2=0.8502$, $p<0.005$). The value of t_{max} of all drugs was found to depend upon various constitutional, topological and electrostatic parameters. Logarithmic transformation of the t_{max} value resulted in increase in correlation coefficient ($R^2=0.9751$, $F=65.19$, $S^2=0.0016$, $Q^2=0.9411$, $p<0.005$).

Keywords: Quantitative structure pharmacokinetic relationships (QSPkR), Time to reach peak plasma concentration, In Silico ADME, antidiabetic drugs.

INTRODUCTION

Of late, it has been recognized by the pharmaceutical industry that undesirable absorption, distribution, metabolism and excretion (ADME) of new drug candidates are the major cause(s) of many clinical phase trial failures. Accordingly, it has been an endeavor of the pharmaceutical scientists to design new drug molecules realistically

predicting their pharmacokinetic and pharmacodynamic characteristics prior to their synthesis. Drug discovery and development using the traditional approaches of random screening, in this regard, have proved to be quite time consuming and expensive. This has resulted in a paradigm shift to identify such problems early during the drug discovery process. Apart from the scientific interest, there are economic considerations as well, as out of numerous compounds synthesized; only a few eventually reach the market as a new drug. A sizable proportion of drug candidates fail during clinical trials because of poor pharmacokinetic (i.e., ADME) properties. This is an economic disaster, as the failed drugs have been in pipeline for several years, with the large amounts of effort and money invested in their development. Hence, the focus of drug development has widely expanded to include procedures aimed at identifying potential failures as well as successes[1].

The *in vitro* approaches are widely practiced to investigate the ADME properties of new chemical entities. More recently, *in silico* Quantitative Structure Pharmacokinetic Relationships (QSPR) modelling has been investigated as a tool to optimize selection of the most suitable drug candidates for development. Being able to predict ADME properties quickly using computational means is of great importance, as experimental ADME testing is both expensive and arduous yielding low productivity. 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[2].

Antidiabetics are oral hypoglycaemic agents effective in the treatment of diabetic diseases. For the present study antidiabetics were selected for QSPkR investigations as, this category of drugs consist of significant number of compounds thoroughly investigated for their pharmacokinetic performance (n=17). Moreover, congeners of this class have many common pharmacokinetic characteristics, mechanism and degree of affinity with body tissues, etc. Also, important descriptors like experimental log P, melting point, molecular weight etc. of these drugs are known and are available in standard texts or journals.

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
3. **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.

Dataset Selection

17 Antidiabetic drugs with known human time to reach peak plasma concentration (t_{max}) values were selected from literature[4]. In order to ensure that experimental variations in determining time to reach peak plasma concentration (t_{max}) do not significantly affect the quality of our datasets. Time to reach peak plasma concentration (t_{max}) values obtained from healthy adult males after oral administration of drug was used for constructing the dataset. Time to reach peak plasma concentration (t_{max}) value of each of these compounds was also log-transformed (log t_{max}) 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 time to reach peak plasma concentration (t_{max}) 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 time to reach peak plasma concentration (t_{max}) parameter available for 17 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 t_{max}, 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 half-life. 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

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

$$\dots (1)$$

A model with good predictive performance has a Q2 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

$$F = \frac{S_1^2}{S_2^2}$$

… (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

The point of maximum concentration of drug in plasma is called as the peak and the concentration of drug at peak is known as peak plasma concentration[6]. t_{max} is a negative indicator of the rate of absorption of a drug.[7] The Time to reach peak plasma concentration (t_{max}) values were available for 17 antidiabetic drugs. Therefore, correlations were attempted keeping the number of maximum descriptors to 5 thereby limiting the drug: descriptor ratio to 4:1, as per the topless rule[8].

The values of time to reach peak plasma concentration (t_{max}) of all antidiabetic drugs were found to depend upon various topological, constitutional, and electrostatic parameters. As seen from Table 1, the correlations are highly significant ($p < 0.005$) with high values of R^2 (0.9325) and Q^2 (0.8502) values.

The study of the results as shown in Table 1, indicated that the correlations of t_{max} with various descriptors were statistically significant ($p < 0.005$) with very good prediction power of the best correlation R^2 (0.9325-0.9099) and Q^2 (0.8502-0.7970). Logarithmic transformations R^2 (0.9751-0.9354) and Q^2 (0.9411=0.8181) tends to rather reduce the degree of correlations. There was quite significant reduction is S^2 values, attributable to reduction in the magnitude of the property values. The values were found to be highly predictable ($p < 0.005$) during the QSPkR studies above.

Figure 2 shows the linear and residual plots between the values of untransformed t_{max}, as reported in literature and those predicted using multi parameter QSPkR investigations for a series of 17 antidiabetic drugs. Figure3 shows the corresponding plots for log- transform of half-life.

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.

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Table 1. Significant linear and logarithmic relationship for a series of 17 antidiabetic drugs using time to reach peak plasma concentration (t_{max}) as pharmacokinetic parameter

Equation (s)	M	R^2	Q^2	S^2	F	P^o
t_{max} = 6.3162 -3.7465 - HASA-1 +0.4007 – nO - 4.1986 - T(N..N) -3.3593 – XYS/XYR -2.7367 - Psychotic-80	5	0.9099	0.7970	0.1674	22.21	0.005
t_{max} = 5.8793 -4.0261 HASA-1+ 0.4989 NOA-4.1837 - T(N..N) - 3.0722 – XYS/XYR -2.8142 P-80	5	0.9106	0.8107	0.1661	22.41	0.005
t_{max} = 7.3257 -3.7804 HASA-1 + 0.0938 NOA -3.7257 C-005 - 4.5386 XYS/XYR -3.6622 T(N..N)	5	0.9320	0.8358	0.1263	30.16	0.005
t_{max} = 7.9887-3.1106 - HASA-1 -0.2979 - P_VSA_m_3 -3.8417 - T(N..N) -4.9443 - XYS / XYR-3.7526 - C-005	5	0.9325	0.7713	0.1254	30.39	0.005
t_{max} = 7.8112-3.8892 - HASA-1 + 0.3058–nO - 3.7008 -C-005 - 4.8125 - XYS/XYR- 3.5960 - T(N..N)	5	0.9325	0.8502	0.1253	30.41	0.005
Log t_{max} = 8.1180 -7.2315 HASA-1 - 4.7691 C-005 - 5.05 02 XYS/ XYR -4.1654 – CATS 2D_03_AA + 2.3962 nR06	5	0.9354	0.8181	0.0038	31.87	0.005
Log t_{max} = 7.6380 -5.8953 HASA-1 -4.8884 C-005 -5.03 71 XYS/XYR - 4.2485 – CATS 2D _03_AA +2.4971 NTB	5	0.9373	0.8107	0.0037	32.88	0.005
Log t_{max} = 7.2215 -6.8816 HASA-1 -2.7340 C-005 -3.7844 XYS/XYR -4.1594 CATS2D _03_AA -2.6564 - Psychotic-80	5	0.9401	0.8242	0.0035	34.55	0.005
Log t_{max} = 2.0969 -11.6585 HASA-2 -9.6262 NTB +9.4033 IVDE -7.2300 X1Av +4.6056 SpDiam_EA(bo)	5	0.9634	0.9134	0.0022	57.89	0.005
Log t_{max} = 1.4547 -13.4434 HASA-2 -10.6023 NTB 10.9191 IVDE -8.5949 X1Av -2.1646 nDB	5	0.9751	0.9411	0.0016	65.19	0.005

NDB = No. of double bonds, NTB = No. of triple bonds, NOA = No. of atoms, HASA-1 = Hydrogen acceptor dependent HASA-1 [Zefirov's PC], HASA-2 = Hydrogen acceptor dependent HASA-2 [Zefirov's PC], T (N…N) = Sum of topological distances between N..N, XYS/XYR = XY Shadow/ XY Rectangle, nR = Number of rings, nO = No. of oxygen atoms.
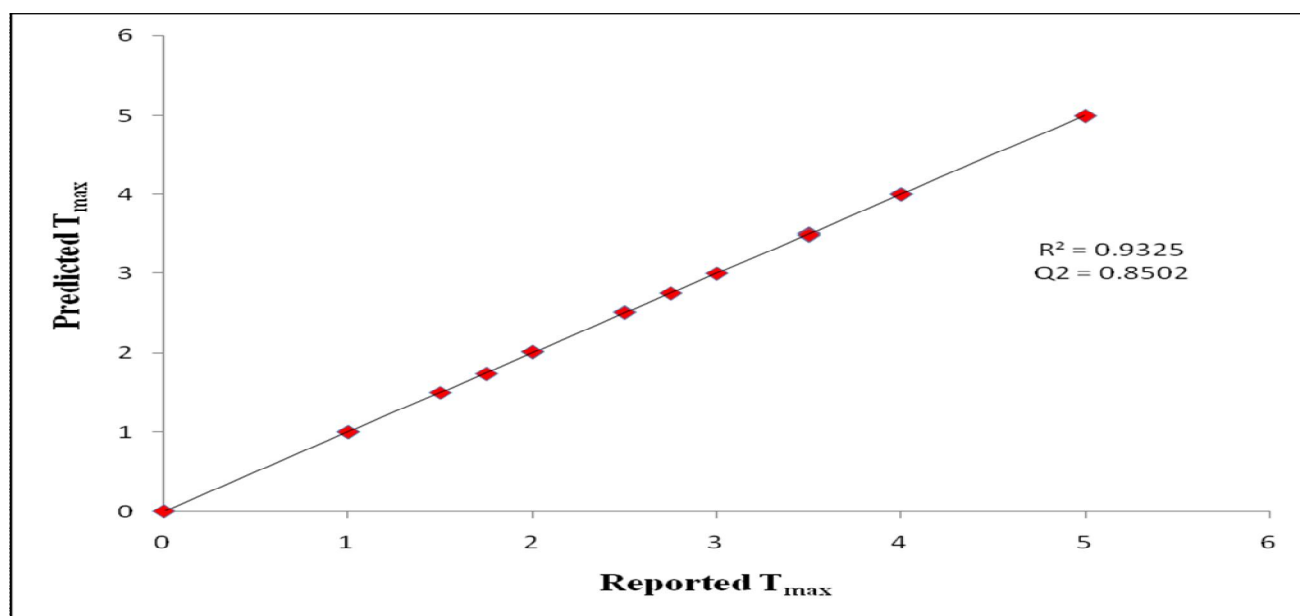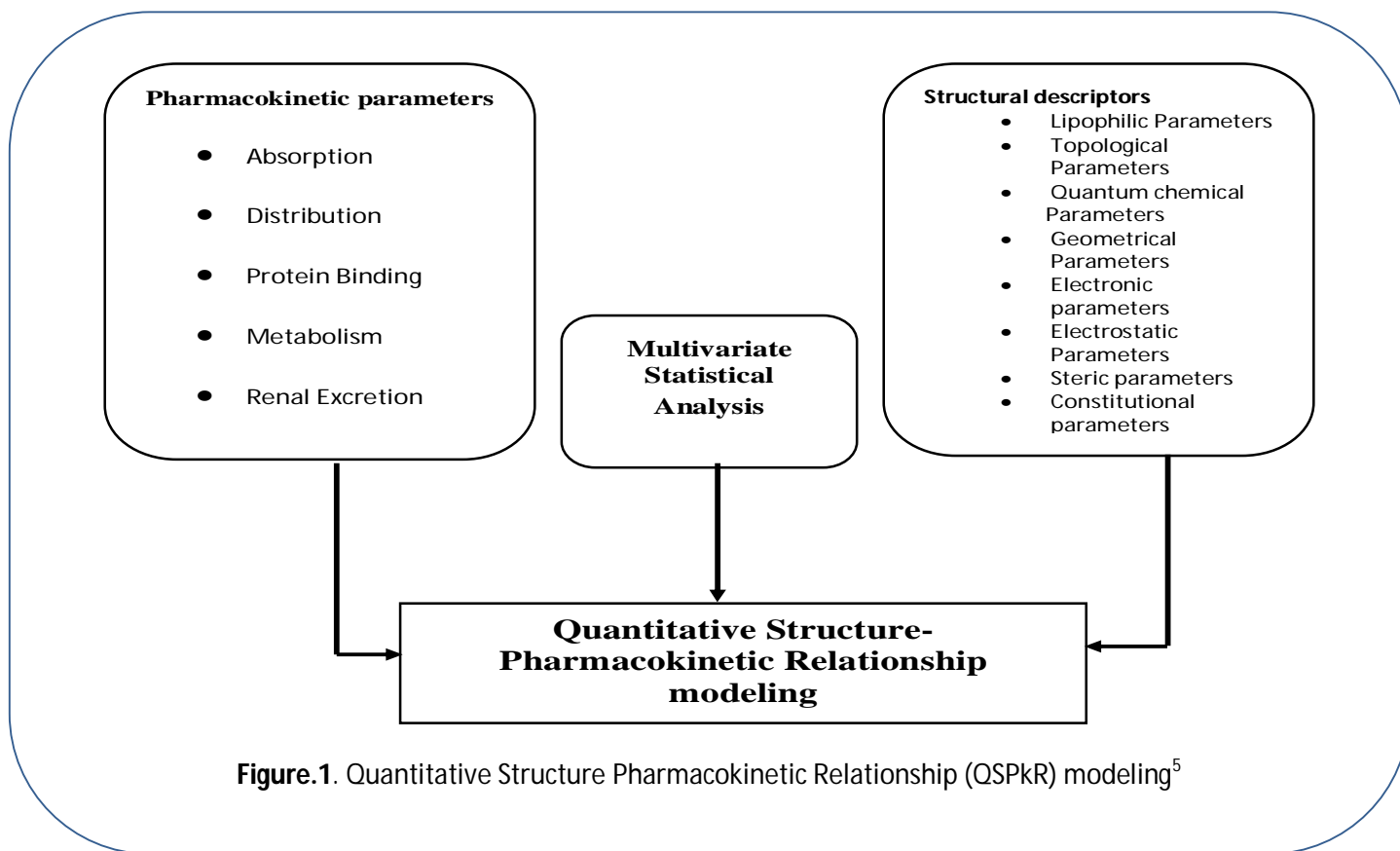
Figure.1. Quantitative Structure Pharmacokinetic Relationship (QSPkR) modeling[5]

Figure.2. Plot between the predicted and reported values of time to reach peak plasma concentration (t_{max}) for QSPkR of antidiabetic drugs. The inset shows the corresponding residual plot.
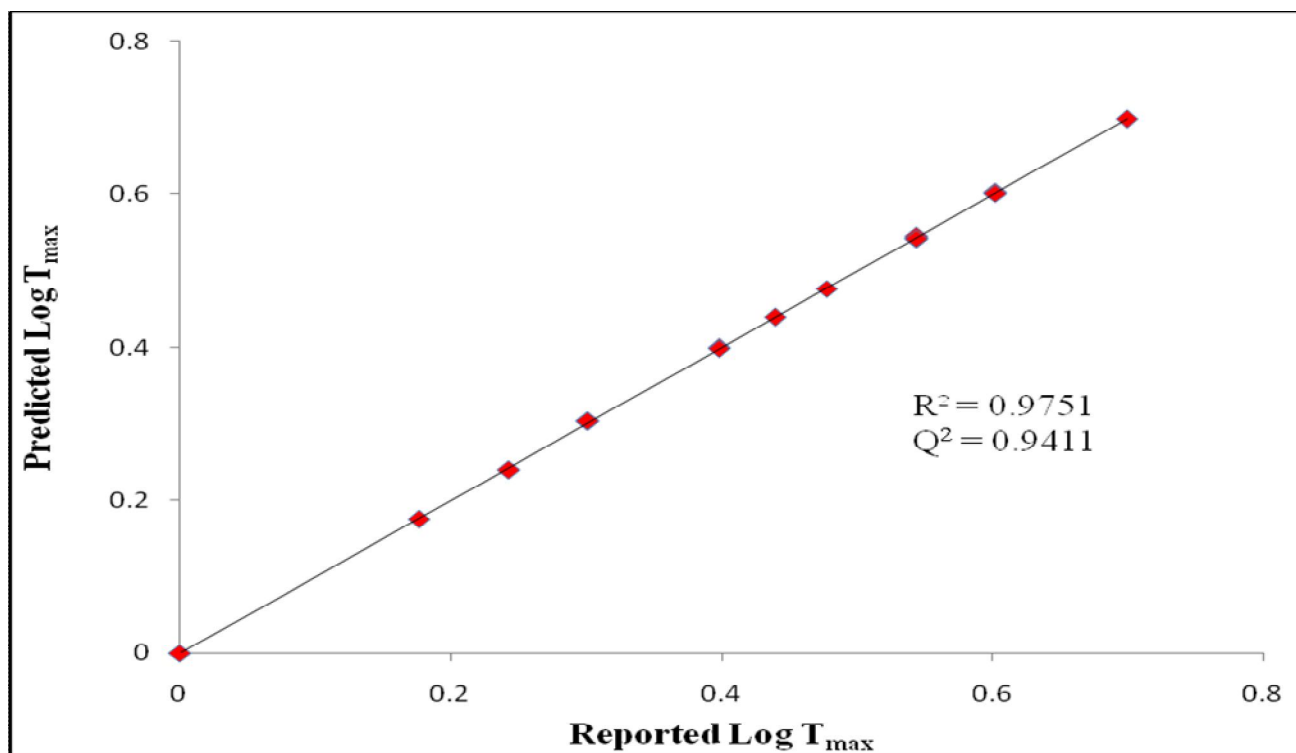
Figure.3. Plot between the predicted and reported values of Log time to reach peak plasma concentration (t$_{max}$) for QSPkR of antidiabetic drugs. The inset shows the corresponding residual plot.