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IN SILICO QUANTITATIVE STRUCTURE PHARMACOKINETIC RELATIONSHIP MODELING ON ANTIDIABETIC DRUGS: HALF-LIFE

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ABSTRACT

An estimate of half-life ($t_{1/2}$) 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 $t_{1/2}$ in human for congeneric series of twenty 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 was found to be high half-life ($t_{1/2}$) ($R^2 = 0.9354$ $F = 31.35$, $S^2 = 46.9583$, $Q^2 = 0.7860$, $p<0.005$). Half-life ($t_{1/2}$) in the present QSPkR investigations was found to depend upon geometrical and constitutional parameters. As lipophilic and electronic parameters were observed to be considerably significant, the biological half-life tends to be diffusional rate limited for antidiabetic drugs.

Key words: Quantitative structure pharmacokinetic relationships (QSPkR), Half-life, *In Silico* ADME, Antidiabetic drugs.

INTRODUCTION

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

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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 QSPR investigations as, this category of drugs consist of significant number of compounds thoroughly investigated for their pharmacokinetic performance (n = 20). 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 1 GB RAM and 160 GB Hard Disk.

Dataset selection

20 Antidiabetic drugs with known human half-life ($t_{1/2}$) values were selected from literature[4,5]. In order to ensure that experimental variations in determining half-life ($t_{1/2}$) do not significantly affect the quality of our datasets. Half-life ($t_{1/2}$) values obtained from healthy adult males after oral administration of drug were used for constructing the dataset. Half-life ($t_{½}$) value of each of these compounds was also log-transformed (log $t_{1/2}$) to normalize the data to reduce unequal error variance.

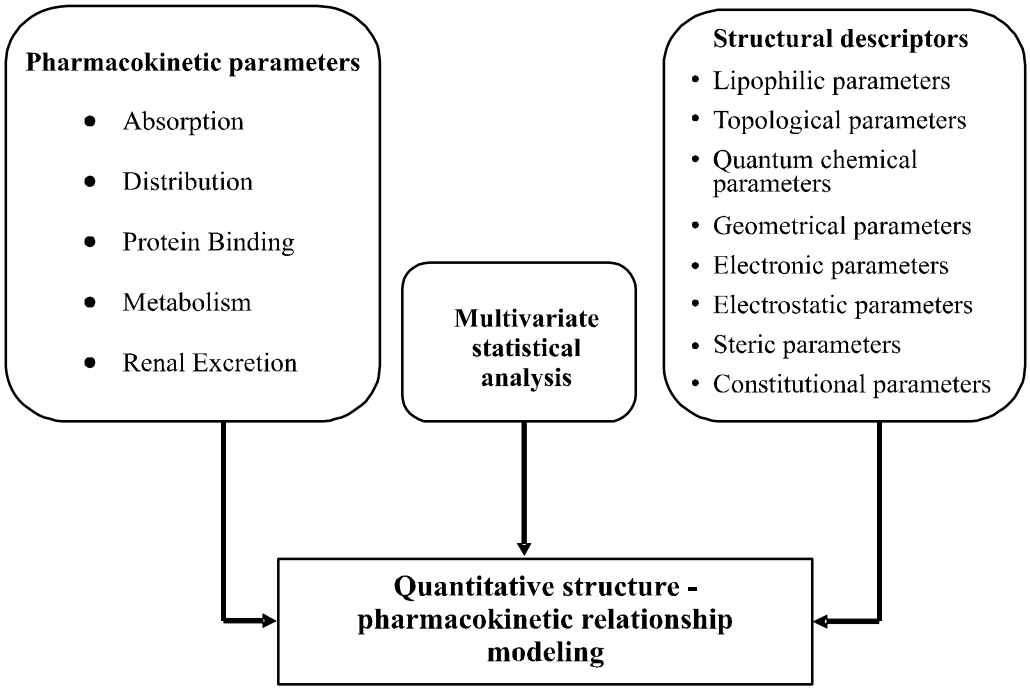

Fig. 1: Quantitative structure pharmacokinetic relationship (QSPkR) modeling[6]

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 half-life ($t_{1/2}$) 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 half-life ($t_{1/2}$) parameter available for 20 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 ($t_{1/2}$), 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 Eq. 1:

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

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 Eqn. 2:

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

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.

RESULTS AND DISCUSSION

Biological half-life ($t_{1/2}$) expresses the period of time required for the amount or concentration of a drug in body fluids to get reduced by one-half of its original[4]. The half-life ($t_{1/2}$) values were available for 20 antidiabetic drugs.

Table 1: Significant linear and logarithmic relationship for a series of 20 antidiabetic drugs using half-life ($t_{1/2}$) as pharmacokinetic parameter

Equation(s)	M	R^2	Q^2	S^2	F	p <
$t_{1/2}$ = 4.6378-8.1121MPCHA + 5.97 61–MAXDP-3.5078NTB-2.8840RNR -2.2218 XYS/ XYR	5	0.8707	0.5504	87.2464	18.85	0.005
$t_{1/2}$ = 4.8007+8.1314NTB+6.8693 Eta_F _-5.1956SpMAD_AEA (bo) -3.4064 YZS/ YZR+2.8749MPCNA	5	0.8886	0.6438	75.1156	22.35	0.005
$t_{1/2}$ = -4.8515+8.6756NTB+5.25 47 Eta_F_ A-5.3154NOR+2.9671C-006+2.4328–SP19	5	0.8902	0.6090	74.0533	22.71	0.005
$t_{1/2}$ = 0.8379-0.2205P_VSA_ MR_7 + 6.24 54 NTB + 4.6489P_VSA_LogP_6-4.6177 NOR + 3.8443–nBM	5	0.8946	0.6697	71.0719	23.78	0.005

Cont…

Equation(s)	M	R^2	Q^2	S^2	F	p <
$t_{1/2}$ = -3.8370 + 6.0352Eta_F_A-6.1340 X 4 sol + 3.9563SP19 + 4.4039C-006-3.43 67 Eta_FL _A	5	0.9354	0.7860	46.9583	31.35	0.005
Log $t_{1/2}$ = - 0.0725-5.8812MPCHA + 3.35 61 - SpDiam_AEA (ed) + 2.5431P_VSA _s_5 -2.2745NDB + 1.3549SP19	5	0.8094	0.5886	0.0639	11.89	0.005
Log $t_{1/2}$ = -1.1082-6.7812MPCHA + 5.00 69 -SpDiam_AEA (ed)-2.8920-SRW09 + 2.4267 - SP19 -1.9870Eta_F_A	5	0.8132	0.6086	0.0626	12.19	0.005
Log $t_{1/2}$ = 2.7196 -6.5111MPCHA + 3.5434-SpMax_EA + 3.2940P_ VSA_s_5-2.6376 NDB-2.2511ZXS/ZXR	5	0.8331	0.6702	0.0560	13.98	0.005
Log $t_{1/2}$ = 1.5279-6.5185MPCHA + 3.6095-SpDiam_AEA (ed) + 3.5189P_VSA_s_5-2.5417NDB-2.0981ZXS/ZXR	5	0.8360	0.6716	0.0550	14.27	0.005
Log $t_{1/2}$ = -3.1510MPCHA + 5.6638 SpDiam _AEA (ed)-2.7834 –SRW09 + 2.8422SP19 + 2.6784RNHA	5	0.8417	0.6960	0.0531	14.89	0.005

NTB = No. of triple bonds, NDB = No. of double bonds, NOR = No. of rings,
RNR = Relative number of rings, nBM = No. of multiple bonds, YZS/YZR= YZ Shadow/ YZ Rectangle, ZXS/ZXY = ZX shadow/ZX rectangle, RNHA= Relative no. of H atoms,
MPCHA = Maximum partial charge for a H atom [Zefirov's PC],
MPCNA= Maximum partial charge for a N atom [Zefirov's PC]

The values of half-life ($t_{1/2}$) of all antidiabetic drugs were found to depend upon various topological, constitutional, electrostatic and geometrical parameters. As seen from Table 1, the correlations are highly significant ($p<0.005$) with high values of R^2 (0.9998) and Q^2 (0.9981) values.

The study of the results as shown in Table 1, indicated that the correlations of $t_{1/2}$ with various descriptors were statistically significant ($p < 0.005$) with very good prediction power of the best correlation R^2 (0.9354-08707) and Q^2 (0.7860-0.5504). Logarithmic transformations R^2 (0.8417-0.8094) and Q2 (0.6960-0.5886) 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. As lipophilic and electronic

parameters were observed to be considerably significant, the biological half-life tends to be diffusion rate limited[3].

Figure 1 shows the linear and residual plots between the values of untransformed $t_{1/2}$, as reported in literature and those predicted using multi parameter QSPkR investigations for a series of 20 antidiabetic drugs. Figure 2 shows the corresponding plots for log- transform of half-life.

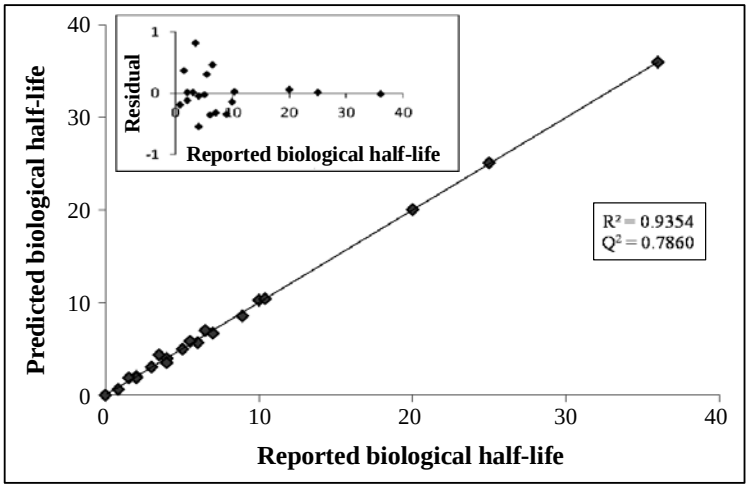

Fig. 1: Plot between the predicted and reported values of Half-life ($t_{1/2}$) for QSPkR of antidiabetic drugs. The inset shows the corresponding residual plot.

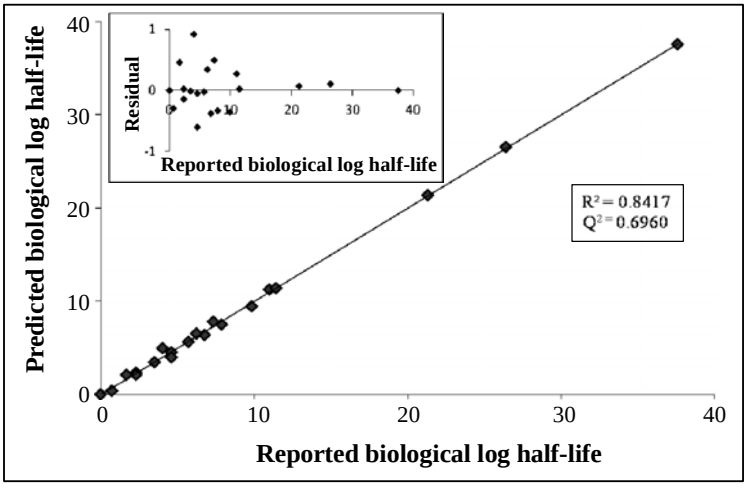

Fig. 2: Plot between the predicted and reported values of Log Half-life ($t_{1/2}$) for QSPkR of antidiabetic drugs. The inset shows the corresponding residual plot.

CONCLUSION

Analysis of several hundreds of QSPkR correlations and consequent profiles in the current investigations on antidiabetic drugs revealed that:

The quantitative relationships for various pharmacokinetic parameters were highly predictable in most cases ($p < 0.005$).

Half-life ($t_{1/2}$) in the present QSPkR investigations was found to depend upon various constitutional parameters *viz.* NTB, RNHA, NOR, RNR. nBM, NDB, etc. The vital geometrical parameters *viz.* XYS/XYR, YZS/YZR, ZXS/ZXY, etc. However, influence of lopophilic parameters *viz.* P_VSA_Log P_6 and electrostatic parameters *viz.* MPCHA, MPCNA and topological parameter *viz.* SP-19, etc. were also noticed during multi-parameter studies.

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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