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IN SILICO QUANTITATIVE STRUCTURE PHARMACOKINETIC RELATIONSHIP MODELLING ON QUINOLONE DRUGS: TIME OF PEAK PLASMA CONCENTRATION

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ABSTRACT

An estimate of time to reach maximum plasma concentration (t_{max}) is of paramount importance in assessing the efficacy of drugs used to treat acute conditions like pain and insomnia, which can be treated by a single dose. This study was conducted to develop Quantitative Structure Pharmacokinetic Relationship (QSPR) for the prediction of t_{max} in men for congeneric series of 24 quinolone drugs, using computer assisted Hansch approach. The QSPR correlations were duly analyzed using a battery of apt statistical procedures and validated using leave-one-out (LOO) approach. Analysis of several hundreds of QSPR 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 ($R^2 = 0.9147$ $F=33.96$ $S^2=0.0748$, $Q^2=0.8046$ $p<0.001$). Both logarithmic transform and inverse transform of the t_{max} value resulted in decrease in correlation coefficient (for Log t_{max}, $R^2= 0.8636$ and for $1/t_{max}$, $R^2= 0.8701$). Topological and electrostatic parameters were found to primarily ascribe the variation in t_{max}. The results indicate the involvement of dissolution rate limited absorption rather than permeation limited, as hardly any dependence on Log P was observed.

Keywords : Quantitative structure pharmacokinetic relationships (QSPR), Time of peak plasma concentration (t_{max}), *In Silico* ADME, Quinolones.

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INTRODUCTION

Traditionally, drugs were discovered by testing compounds synthesized in time-consuming multistep processes against a battery of *in vivo* biological screens[1]. Promising compounds were then further studied in development, where their pharmacokinetic (ADME) properties and potential toxicity were investigated. Adverse findings were often made at this stage, with the result that the project would be halted or retarded to find another clinical candidate, an unacceptable burden on the research and development budget of any pharmaceutical company[2]. Today, this paradigm has been re-worked in several ways, as the *in vitro* approaches are widely practical to investigate the ADME properties of new chemical entities[3]. More recently, *in silico* modeling has been investigated as a tool to optimize selection of the most suitable drug candidates 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[4].

Time of peak plasma concentration (t_{max}) value of a drug is vital pharmacokinetic parameter because it is directly related to the bioavailability and can be used in assessing the efficacy of drugs used to treat acute conditions like pain and insomnia which can be treated by a single dose. Hence, it is important to predict the t_{max} value of drug leads during drug discovery so that compounds with acceptable rate of absorption can be identified and those with poor bioavailability can be eliminated. Traditinally, the t_{max} value of a drug candidate is obtained via *in vivo* studies, which tends to be quite arduous, time consuming and expensive. Therefore, a computational QSPR modeling method, has recently been explored for predicting the t_{max} value of drug candidates in an effort to eliminate undesirable agents in a fast and cost effective manner[5]. The major aim of *in silico* QSPR is to enable the drug designer to modify the chemical structure of a pharmacodynamically active drug so that its pharmacokinetic properties may be altered without compromising pharmacodynamic potential[6]. The major advantage of QSPR lies in the fact that once such a relationship is ascertained with adequate statistical degree of confidence, it can be a valuable assistance in the prognosis of the behaviour of new molecules, even before they are actually synthesized. An early assessment of ADME properties will help pharmaceutical scientists to select the best drug candidate for development as well as to reject those with a low plausibility of success[7]. Also, these *In Silico* QSPR techniques tend 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, but also the expertise of pharmacokinetists and drug designers[4].

The current study was conducted to investigate in silico QSPR amongst various quinolone drugs for t_{max}. Quinolones were chosen for QSPR as this category of drugs has extensively been used as antimicrobial agents in the treatment of serious infections. Also, quinolones consist of significant number of compounds thoroughly investigated for their pharmacokinetic performance particularly t_{max} (n=24). Further, the congeners in this class have many common pharmacokinetic characteristics, mechanism and degree of affinity with body tissues, etc.

Construction of QSPR

Construction of a typical QSPR model involves pharmacokinetic parameters, structural parameters (descriptors) and statistical techniques (Fig.1).

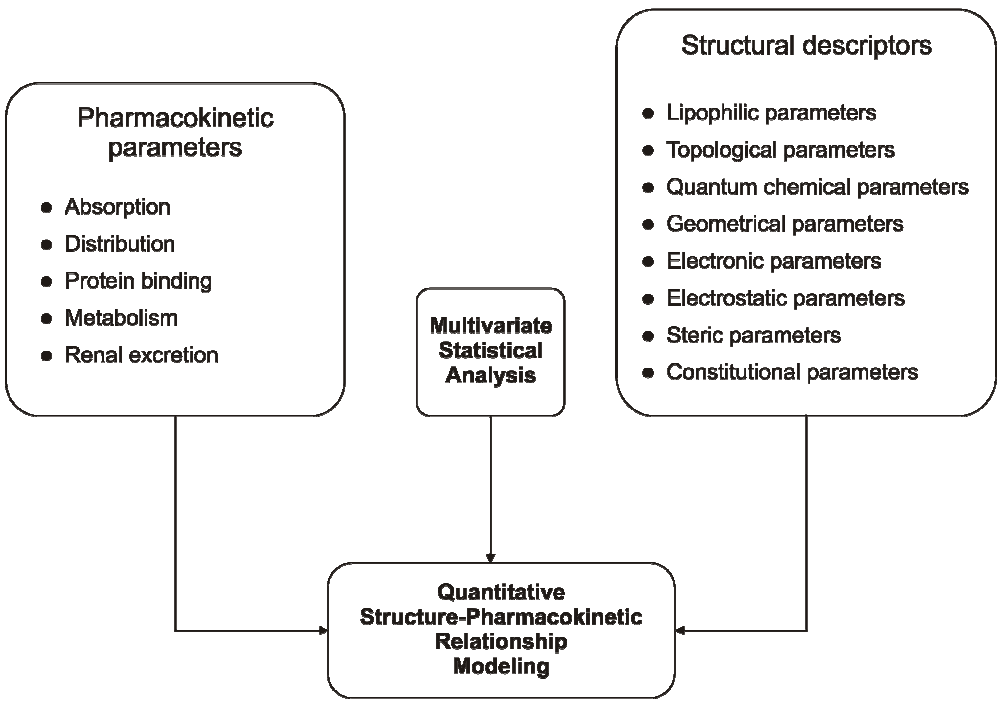

Fig. 1:

Methods

QSPR was conducted amongst quinolone drugs employing extra-thermodynamic Multi Linear Regression Analysis (MLRA or Hansch) approach. The general steps for developing QSPR 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

24 Quinolones with known human t_{max} values were selected from literature [8-13]. In order to ensure that experimental variations in determining t_{max} do not significantly affect the quality of our datasets, only t_{max} values obtained from healthy adult males after oral administration of drug were used for constructing the dataset. The t_{max} value of each of these compounds was also log-transformed (Log t_{max}) and inverse transformed ($1/t_{max}$) to normalize the data to reduce unequal error variance.

Molecular structure and descriptors

Chemical structures were drawn using suitable templates under Chem3D software pro v.3.5. (Cambridge Soft Corporation, Cambridge, MA) and HyperChem 8.05 (hypercube, Inc. USA) software. Energy minimization was carried out using MM2 force field routine(s) and the files were saved as MDL *molfiles*. *Molfiles* generated by Chem3D were exported to DRAGON software, and as many as 1497 diverse descriptors, *viz.* constitutional, geometrical, topological, Whim3D, electronic, electrostatic etc. were calculated. *Molfiles* were also transferred to 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 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 t_{max} parameter available for 24 quinolones were analyzed, limiting the ratio of descriptors: drug to 1:4. 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 quinolones. 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

t_{max}. Regression plots of each correlation thus attempted were examined. Residual plots were also examined 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 rederived 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 (1).

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

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 Equation (2).

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

where, S_1 is variance between samples and S_2 is 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

Variable QSPR results were obtained following application of multivariate statistical analysis on quinolone drugs. Thousands of such correlation and regression analysis were attempted choosing all the possible combination of available descriptors, each yielding an elaborate output. The concise results of only those correlations which were found to be statistically significant, usually at 5% level or less, and/or which have important applications have been taken into consideration. Time to reach maximum plasma concentration is a negative indicator of the rate of absorption of a drug[8]. Good QSPR correlations were obtained for the value of t_{max} for quinolone drugs. Table 1 shows steller

dependence of t_{max} upon various topological parameters, e.g. SPI, Jhetp, PW5 etc. and electrostatic parameters, e.g., FNSA-2, HACA-2, Qhmin etc. Influence of constitutional parameters like Orel & Srel was also noticed during multi-parameter studies. Both logarithmic (Fig. 2) and inverse transform (Fig. 3) of the t_{max} value resulted in decrease in correlation coefficient but the residuals were more evenly distributed around the mean for logarithmic transformation of the t_{max} value.

Table 1 : Significant QSPR polynomial equations along with the statistical parameters for a series of 24 quinolones, using time of peak plasma concentration (t_{max}) as the pharmacokinetic parameter

Equations	m	R^2	F	S^2	Q^2	p<
t_{max} = - 1.1032 + 1.9329 Jhetp	1	0.1323	3.66	0.6026	0.0507	0.1
t_{max} = - 3.4817 - 55.022 Orel+ 80.021 PW5	2	0.3309	5.69	0.4849	0.1645	0.05
t_{max} = 3.9180 + 0.01687 PNSA-2 + 0.00085 SPI + 94.049 Srel	3	0.6767	15.35	0.2449	0.4694	0.001
t_{max} = 31.287 + 0.01834 PNSA-2 + 0.00096 SPI + 101.66 Srel - 291.25 QCmax	4	0.8193	23.80	0.1435	0.6567	0.001
t_{max} = 99.515 + 11.769 FNSA-2 + 0.00084 SPI + 100.24 Srel - 65.521 TI1 + 1.2396 HACA - 2	5	0.8710	27.02	0.1075	0.7954	0.001
t_{max} = 120.67 + 7.7546 FNSA-2 + 0.00072 SPI + 112.15 Srel - 79.458 TI1 + 1.4766 HACA - 2 - 113.18 QHmin	6	0.9147	33.96	0.0748	0.8046	0.001
Log t_{max} = - 0.60293 + 0.54713 Jhetp	1	0.2153	6.59	0.0268	0.1236	0.05
Log t_{max} = 1.4111 - 13.402 Qmax-Qmin + 19.635 PW5	2	0.4417	9.10	0.0199	0.2983	0.01
Log t_{max} = 0.87749 + 22.745 PW5 - 13.515 Orel - 27.003 QCmin + 33.891 SPI + 0.064397 TI2- 49.323 QCmax	6	0.8636	20.05	0.0059	0.7158	0.001

Cont…

Equations	m	R^2	F	S^2	Q^2	p<
$1/t_{max}$ = 0.0796 – 0.00309 PNSA-2	1	0.2708	8.91	0.0526	0.1295	0.01
$1/t_{max}$ = 2.3377 + 0.01045 TI1 - 0.31451 KHI1	2	0.4451	9.23	0.0418	0.2996	0.01
$1/t_{max}$ = - 23.223 + 0.01287 TI1 - 0.29388 KHI1 + 19.925 RCI + 32.405 QCmin - 42.307 SPI- 0.22525 X5sol	6	0.8701	21.21	0.0118	0.7570	0.001

m - No. of descriptors

Jhetp - Balaban-type index from electronegativity weighted distance matrix

Orel - Relative no. of O atoms

PW5 - path/walk5-Randic Shape Index

PNSA-2 - PNSA-2 Total charge weighted PNSA [Zefirov's PC]

SPI - Superpendentic Index

Srel - Relative no. of S-atoms

Qcmax - Max partial charge for C atom [Zefirov's PC]

FNSA-2 - FNSA-2 Fractional PNSA (PNSA-2/TMSA) [Zefirov's PC]

TI1 - First Mohar Index TI1

HACA-2 - H-Acceptors charged Surface Area HACA-2 [Zefirov's PC]

QHmin - Min partial charge for H atom [Zefirov's PC]

Qmax-Qmin - Polarity parameter (Qmax-Qmin)

QCmin - Min. partial charge for C atom [Zefirov's PC]

TI2 - Second mohar index TI2

KHI1 - Kier and Hall index (order 1)

X5sol - Solvation connectivity index chi-5

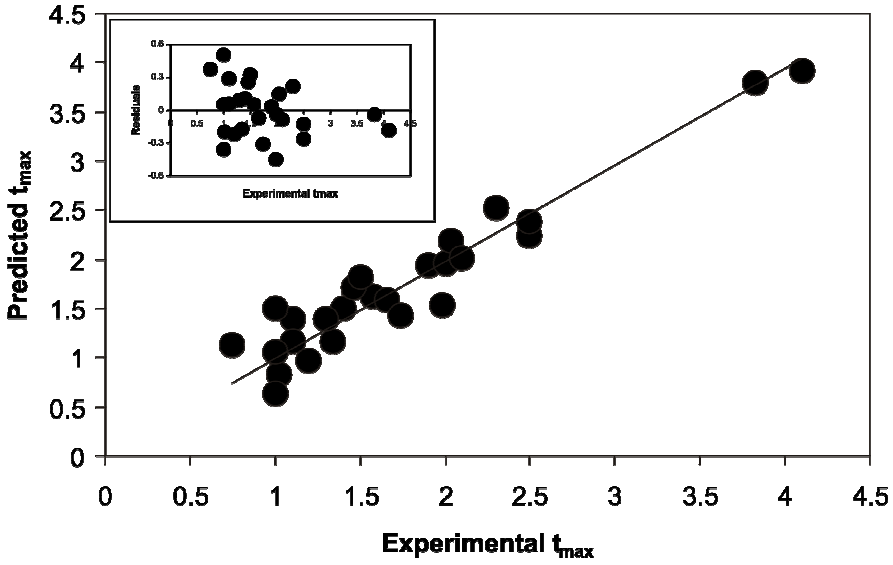

Fig. 1 : Linear correlation plot between the values of t_{max} as reported in literature and those predicted using multi-parameter QSPR for a series of 24 quinolones. The inset shows the corresponding residual plot.

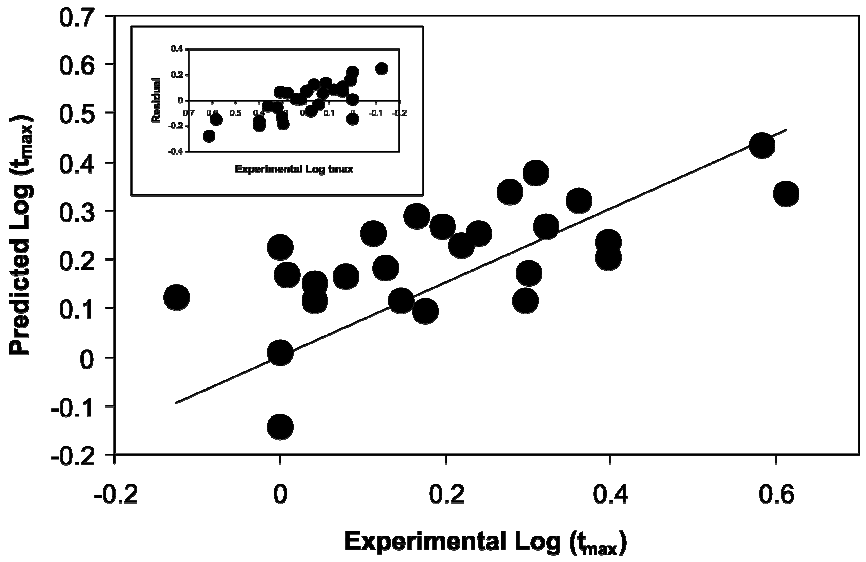

Fig. 2 : Linear correlation plot between the values of log transform of t_{max} as reported in literature and those predicted using multi-parameter QSPR for a series of 24 quinolones. The inset shows the corresponding residual plot.

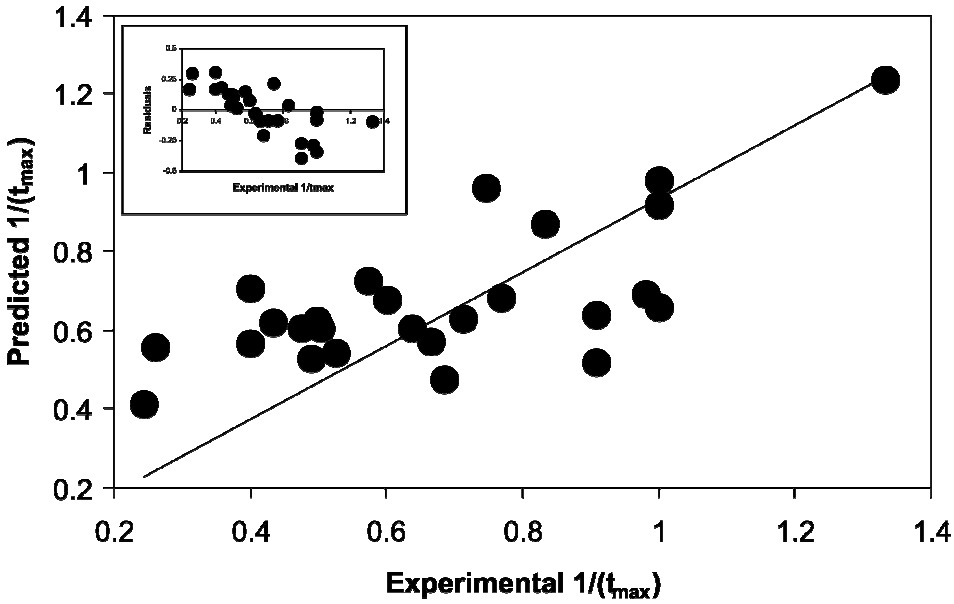

Fig. 3 : Linear correlation plot between the values of inverse transform of t_{max} as reported in literature and those predicted using multi-parameter QSPR for a series of 24 quinolones. The inset shows the corresponding residual plot

CONCLUSIONS

In case of quinolones, the joint dependence of t_{max} values on topological and electrostatic parameters signifies the importance of diffusion and ionization of quinolone drugs *in vivo.* The involvement of constitutional parameters like Orel further confirms the diffusional contribution in ascribing intra-class variation in t_{max} values. As hardly any dependence upon lipophilic parameters was observed, it signifies that absorption is dissolution rate limited rather than permeation limited. 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 QSPR 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, pathological environmental, nutritional, genetic, hereditary and diurnal status of the human subjects. This causes a great deal of plausible variation in pharmacokinetic profiles amongst the volunteers/ patients 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, 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 amongst the pharmacokinetic parameters, the currently established relationships assume much higher credibility.

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