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Research article

Quantitative structure pharmacokinetic relationship modeling of Cephalosporins: Elimination half-life

Anu Grover*[1], Manish Grover[2], Komal Sharma[3]

[1]Faculty of Pharmacy, Pacific Academy of Higher Education and Research University, Udaipur.
[2]University Institute of Pharmaceutical sciences, Panjab University, Chandigarh.
[3]Department of pharmacology, B N Institute of Pharmaceutical Sciences, Udaipur.

Abstract

Quantitative structure-property and relationships, often simply known as QSPR, is an analytical application that can be used to interpret the quantitative relationship between the pharmacokinetic property of a particular molecule and its structure. It is considered a major method of chemical researching all over the world today and is frequently used in various fields like agricultural, biological, environmental, and more commonly in pharmaceutical industry. Drug half-life ($t_{1/2}$) is one of the key pharmacokinetic parameters for establishment of dosing regimen. Surprisingly, the relationship between the chemical structure and $t_{1/2}$ is still poorly explored. The aim of the present study was to derive quantitative structure – pharmacokinetic relationships for $t_{1/2}$ of cephalosporins. Molecular descriptors describing molecular size, shape and solubility were calculated from the 3D molecular structure of each cephalosporin. The final predictive models showed significant correlations with literature values of $t_{1/2}$. Electrostatic and constitutional descriptors were shown to play important roles in determining drug $t_{1/2}$. This novel combination of theoretical and experimental data for pharmacokinetic modeling may lead to further progress in drug development.

Key words: Cephalosporins, ADME, QSPR.

***Corresponding Author: Anu Grover,** Faculty of Pharmacy, Pacific Academy of Higher Education and Research University, Udaipur.

Introduction

Drug discovery and development is a cost and time consuming process involving many considerations in molecular design, synthesis, testing and evaluation of drug effects. Only 20% of drug discovery projects are reported to lead to a clinical candidate and only 10% of the compounds that enter clinical development achieve registration. An analysis of the reasons for this apparently low success reveals that poor pharmacokinetics, toxicity and lack of efficacy are the major factors responsible for failures [1]. A cherished goal of chemists has thus been to create molecules with specific properties [2]. Traditionally, a combination of serendipity and empiricism has been the basis of new drug discovery. Trial and error synthesis of

compounds and their random screening for activity have proved to be both time-consuming and uneconomical. Further, therapeutic effects and hazards to health are assessed using a series of experimental and *in vivo* tests. However, usage of animal models is often subject to ethical (and financial) considerations. Therefore, alternative methods have been under development to reduce the requirement of animals in testing [3].

Structure-based design, spurred by significant pitfalls of the traditional methods and rapid advances in molecular structure determination and computational resources, were tested as a means of generating new pharmaceuticals [4, 5] and for predicting their properties prior to synthesis [6]. The structural formula of an organic compound, in principle, contains coded within it all the information which pre-determines the chemical, biological, and physical properties of that compound. If we can understand how a molecular structure brings about a particular effect in a biological system, we have a key to unlocking the relationship and using that information to our advantage. Formal development of these relationships on this premise proved to be the foundation for the development of predictive models. If we take a series of chemicals and attempted to form a quantitative relationship between the pharmacokinetic property and the chemistry (i.e. structure) of each of the chemicals, then it would be possible to form a quantitative structure–property relationship [7, 8].

Quantitative structure-property and relationships, often simply known as QSPR, is an analytical application that can be used to interpret the quantitative relationship between the pharmacokinetic property of a particular molecule and its structure. It is considered a major method of chemical researching all over the world today and is frequently used in various fields like agricultural, biological, environmental, and more commonly in pharmaceutical industry.

Quantitative structure-property and relationships techniques have been used throughout the past century. This has been the endeavor since Crum-Brown and Fraser [9] published the first formulation of a quantitative relationship between "physiological activity" and "chemical structure" in 1868. A few decades later, Richet [10] Meyer [11], and Overton [12] independently found linear relationships between lipophilicity, expressed as solubility or oil-water partition coefficients, and biological effects, like toxicity and narcotic activity. Hammett [13] defined the σ-constant of a substituent in a phenyl ring as the logarithmic ratio of the acidic dissociation constants of the substituted to unsubstituted benzoic acid in aqueous solution. Its applicability was demonstrated for the description of rate and equilibrium constants of various chemical reactions involving substituted benzenes. These linear-free energy relationships were extended by Taft [14] to aliphatic structures by defining σ* constants of substituents as the differences in the logarithmic ratios of the rate constants for acid- and base-catalyzed hydrolysis reactions of substituted and unsubstituted ethyl acetates.

The main objective of QSPR is to observe the pharmacokinetic properties of a set of molecules, measure it, and statistically relate it to some molecular structure on their surface. The product of QSPR will then produce useful equations, images or models in either 2D or 3D form that would relate their properties to their molecular structure. Structure based computational drug design methods mainly focus on the design of molecules for a target site with known three dimensional structure followed by a determination of their affinity for the target, based on which a set of hits are obtained [15-17].

The explosive development of computer technology and methodologies to calculate molecular properties increasingly made it possible to use computer techniques to aid the

drug discovery process. The use of computer techniques in this context is often called computer-aided drug design (CADD), but since the development of drug involves a large number of steps in addition to the development of a high affinity ligand, a more appropriate name computer-aided ligand design (CALD) has also been proposed [18].

Materials and methods

The present study was undertaken with an objective to establish quantitative-structure pharmacokinetic relationships (QSPR) of prognostic relevance in the β-lactam (Cephalosporins) series of drugs. The reason to select β-lactam series of drugs was because such correlations are developed for very few drugs. Further, very few reports on QSPR were available for this series of drugs and that too involving only small sets of drugs and few descriptors. Drug half-life ($t_{1/2}$) is one of the key pharmacokinetic parameters for establishment of dosing regimen. Surprisingly, the relationship between the chemical structure and $t_{1/2}$ is still poorly explored. Thus, quantitative relationships between structural descriptors of cephalosporin molecules and half- life ($T_{1/2}$) were evaluated.

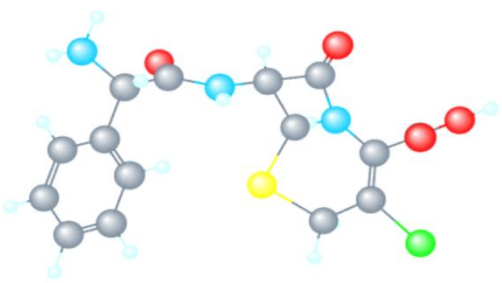
The work was divided into following three phases:

1. Computation of molecular descriptors
2. Compilation of pharmacokinetic data
3. Development of meaningful correlations

Computation of molecular descriptors

It is well known fact that the structure of drug molecules is expressed quantitatively in terms of its physicochemical descriptors, which are lipophilic, electronic and steric in nature. The physicochemical descriptors govern the biological activity of the compounds.

PUBCHEM database contains 2D and 3D minimized structures of large number of drugs and other molecules. Half-life data ($t_{1/2}$) was available for 44 cephalosporins thus 3D structure of selected 44 cephalosporins were downloaded from the database and used as such for correlation studies. Sample 3D structure of one of the cephalosporin, Cefaclor, used in the study is given in **Error! Reference source not found.**. Structures of 44 cephalosporins in molfile format were used as input for computation of descriptors.

S No.	Molecule	3 D Structure
1	Cefaclor	

Here

= Hydrogen	= Carbon	= Oxygen	= Nitrogen
= Sulfur	= Chlorine		

***Source: PubChem Compound**

Figure 1. Sample 3D structure of one cephalosporin used in the study

We used two software, namely, QikProp and CODESSA to calculate the descriptors.

QikProp, an application in Maestro version 10.4.018 which in turn is a part of Schrödinger

Suite release 2015-4, was used for this work. This suite of applications is used to predict physically significant descriptors and pharmaceutically relevant properties of organic molecules, either individually or in batches. In addition to predicting molecular properties, QikProp provides ranges for comparing a particular molecule's properties with those of 95% of known drugs.

CODESSA version 3.2.13 was used in our work. This software integrates all necessary mathematical and computational tools to calculate a large variety of molecular descriptors (up to 400, depending on input files) on the basis of the 3D geometrical and/or quantum-chemical structural input of chemical compounds. Within the framework of the CODESSA program, a variety of statistical techniques are also available for structure-property correlation and for the analysis of the experimental data in combination with the calculated molecular descriptors.

MOL files were used as input to the software by selecting the command Project→Import structures. All the molfiles were selected and imported into QikProp. Descriptors were calculated by using commands Application→QikProp and pressing run. QikProp calculates all the descriptors and creates a project table. The data was imported into CODESSA by using command "Add CODESSA input file", which is a standard CSV format containing all the requisite information like molfiles, descriptor values and property values.

CODESSA calculates additional descriptors for each of cephalosporin. In this case, more than 200 descriptors were calculated using QikProp and CODESSA.

Compilation of pharmacokinetic (half-life) data

The reported values of half-life of cephalosporins in humans were taken from literature [19-21]. Most reviewers, while compiling pharmacokinetic data for a series of drugs, take the mean value as the value for the pharmacokinetic parameter. On similar lines, reported half-lives for all the drugs were compiled and the arithmetic mean was taken for the correlation studies. The mean values of these values for all cephalosporins used in study are compiled in Table 1.

Development of meaningful correlations

Only significant descriptors calculated by QikProp and CODESSA were taken in the correlation studies. Insignificant or intercorrelated descriptors were skipped. Correlation studies were carried out by CODESSA.

Selection criteria and steps used for "Best Multi-linear Regression" in CODESSA is shown as following

- Maximum number of descriptors, started from 1 and then taken up to depending on the number of molecules selected. Drug molecules: Descriptor ratio was taken as 6:1, which implies that not more than one descriptor per 6 molecules in a series was used for developing correlations. For example, if there were 21 molecules for a particular property, maximum number of descriptors used for developing regression equations was kept at 3. Similarly for a series having 44 molecules, maximum number of descriptors was 7.
- Maximum number of correlations per number of descriptor were kept as 5
- Correlation improvement cut-off was kept as 0.01
- Maximum r^2 for orthogonal descriptor was kept as 0.5
- If missing property value, then the selection was made to skip structure

"Best Multilinear Regression" routine tests a large number of correlations as each descriptor type is analyzed for correlations individually for the selected pharmacokinetic property.

Table 1. Half-life values of selected Cephalosporins

#	Drug	$T_{1/2}$ (hrs)	#	Drug	$T_{1/2}$ (hrs)
1.	Cefaclor	0.638	2.	Cefmetazole	1
3.	Cefadroxil	1.382	4.	Cefonicid	4.617
5.	Cefamandole	0.867	6.	Cefoperazone	1.933
7.	Cefamandole nafate	0.8	8.	Ceforanide	2.838
9.	Cefatrizine	1.4	10.	Cefotaxime	1.15
11.	Cefazaflur	0.4	12.	Cefotetan	3.5
13.	Cefazedone	1.9	14.	Cefotiam	0.9
15.	Cefazolin	1.733	16.	Cefoxitin	0.836
17.	Cefbuperazone	1.6	18.	Cefpimizole	1.925
19.	Cefdinir	1.7	20.	Cefpiramide	5
21.	Cefditoren	1.6	22.	Cefpodoxime	2.46
23.	Cefepime	2	24.	Cefprozil	1.35
25.	Cefetamet	2.07	26.	Cefrotil	0.2
27.	Cefixime	3.075	28.	Cefroxadine	0.975
29.	Cefmenoxime	1	30.	Cefsulodin	1.55
31.	Cefuroxime	1.338	32.	Cefsumide	3
33.	Cephacetrile	1.233	34.	Ceftazidime	1.867
35.	Cephalexin	0.842	36.	Ceftezole	0.177
37.	Cephaloglycin	1.5	38.	Ceftibuten	0.136
39.	Cephaloridine	1.2	40.	Ceftizoxime	1.5
41.	Cephalothin	0.567	42.	Ceftriaxone	8.075
43.	Cephapirin	0.683	44.	Cephradine	0.742

Result and Discussion

Half-life value data was available for 44 cephalosporins, thus, correlations were attempted keeping the number of maximum descriptors to 7 thereby limiting the drug: descriptor ratio to 6:1. LOO and y-scramble tests were also performed. The best correlations obtained with half-life ($T_{1/2}$) for selected cepahlosporins are given in Table 2. The table lists equations starting from 1 descriptor equation up to an equation with maximum number of descriptors i.e. 7 in this case.

With the probability of reporting a large number of such correlations for each property, it was considered necessary to change the format of these correlations into an equation format. The validity of the equation and the relative importance of the different parameters used can be judged by four statistical criteria; namely coefficient of determination R^2, Cross validated R^2 (Q^2), Fisher's F value, and R^2 Rand which is the maximum R^2 obtained after randomizing the property values and finding correlations with descriptors again. The larger value of *F* indicates higher probability of QSPR equation being significant. These methods provide correlation coefficient (*r*), standard deviation (*s*), and ratio between variance of calculated and observed activates (*F*). Depending upon the values of these statistical parameters, the significance of each equation was evaluated.

Table 2. Correlations of $t_{1/2}$ in cephalosporins

Equation number				M	N	R^2	Q^2	F-Value	R^2 RAND
1.	$t_{1/2}$	=	0.123*DSASA-3, Zefirov - 3.231	1	44	0.2929	0.1809	17.3945	0.2725
2.	$t_{1/2}$	=	11.79*ZX Shadow / ZX Rectangle - 15.233*YZ Shadow / YZ Rectangle + 3.083	2	44	0.4194	0.2969	14.8109	0.2983
3.	$t_{1/2}$	=	- 0.132*Zefirov Charges' Quadrupole Moment Eigenvalue, Smallest + 11.143*ZX Shadow / ZX Rectangle - 11.951*YZ Shadow / YZ Rectangle + 0.681	3	44	0.5014	0.3342	13.4071	0.3397
4.	$t_{1/2}$	=	-10.417*YZ Shadow / YZ Rectangle + 0.43*Number of H-N Bonds + 10.136*ZX Shadow / ZX Rectangle-0.155*Zefirov Charges' Quadrupole Moment Eigenvalue, Smallest-0.783	4	44	0.5825	0.3876	13.6059	0.3619
5.	$t_{1/2}$	=	- 17.233*YZ Shadow / YZ Rectangle + 10.806*XY Shadow / XY Rectangle + 0.811*Number of H-N Bonds + 422.811*Minimum Bond Length for a N Atom - 0.193*Zefirov Charges' Quadrupole Moment Eigenvalue, Smallest - 428.339	5	44	0.6555	0.4730	14.4595	0.5068
6.	$t_{1/2}$	=	- 14.79*YZ Shadow / YZ Rectangle + 10.622*XY Shadow / XY Rectangle + 0.805*Number of H-N Bonds + 530.895*Minimum Bond Length for a N Atom + 0.318*Zefirov Charges' Quadrupole Moment Eigenvalue, Middle + 2.683*Summed Zefirov Positive Charge - 541.522	6	44	0.6915	0.4932	13.8228	0.4913
7.	$t_{1/2}$	=	0.382*Zefirov Charges' Quadrupole Moment Eigenvalue, Middle + 0.781*WPSASA-3, Zefirov - 0.651*Randic Index (Order 3) + 0.503*Number of S Bonds + 146.225*Average Zefirov Charge for a O Atom + 13.628*ZX Shadow / ZX Rectangle7.963	7	44	0.7334	0.5254	14.1486	0.4099

M = Number of molecular descriptors, N = Number of cephalosporins

Goodness of correlations and types of descriptors involved

Constitutional, electrostatic, topological and absorption descriptors resulted in statistically significant correlations of $t_{1/2}$ in selected series of 44 cephalosporins. The R^2 values of equations 1-2 were below 0.5. Although reasonably high values of R^2 were obtained for equations 3-7, Q^2 values were not sufficiently high till five descriptor level. High R^2 value (0.7334) and Q^2 value close to 0.5 was obtained using seven descriptors. Thus Equation 7, as mentioned below, may be considered for the prediction purpose.

As it would be too voluminous to give details of each of the equations obtained, details of only the best correlation in a series is given. The correlation matrix of descriptors used in Equation 7 is given in the Table 3.

The correlation matrix indicates that none of the descriptors used in the correlation are orthogonal with the other descriptors.

The MLR regression coefficients for individual descriptors used in Equation 7 are given in Table 4.

Table 3. Correlation matrix for selected descriptors in Equation 7 of Table 2

	Zefirov Charges' Quadrupole Moment Eigenvalue, Middle	WPSASA-3, Zefirov	Randic Index (Order 3)	Number of S Bonds	Average Zefirov Charge for a O Atom	ZX Shadow / ZX Rectangle	Zefirov Charges' Dipole Moment Magnitude
Zefirov Charges' Quadrupole Moment Eigenvalue, Middle	1.0000						
WPSASA-3, Zefirov	0.2221	1.0000					
Randic Index (Order 3)	0.4607	0.7602	1.0000				
Number of S Bonds	0.3069	0.3400	0.6275	1.0000			
Average Zefirov Charge for a O Atom	0.3663	0.0253	0.5471	0.3524	1.0000		
ZX Shadow / ZX Rectangle	-0.0244	-0.2830	-0.2548	-0.2289	-0.1073	1.0000	
Zefirov Charges' Dipole Moment Magnitude	0.0319	-0.0690	0.1795	0.2925	0.1447	-0.4363	1.0000

Table 4. MLR regression coefficients and t-values for $t_{1/2}$ in cephalosporins

Desc. Name	Coeff.	t	p(t)	SE
Intercept	7.9635	1.9715	0.056387	4.0392
Zefirov Charges' Quadrupole Moment Eigenvalue, Middle	0.3820	4.7599	3.12E-05	0.0802
WPSASA-3, Zefirov	0.7815	7.3730	1.07E-08	0.1060
Randic Index (Order 3)	-0.6508	-6.0836	5.37E-07	0.1070
Number of S Bonds	0.5033	4.7720	3.01E-05	0.1055
Average Zefirov Charge for a O Atom	146.2246	4.5908	5.21E-05	31.8517
ZX Shadow / ZX Rectangle	13.6275	4.6144	4.85E-05	2.9533
Zefirov Charges' Dipole Moment Magnitude	2.4085	2.8825	0.006615	0.8356

The plots of observed versus predicted elimination half-life values is given in Figure 2.

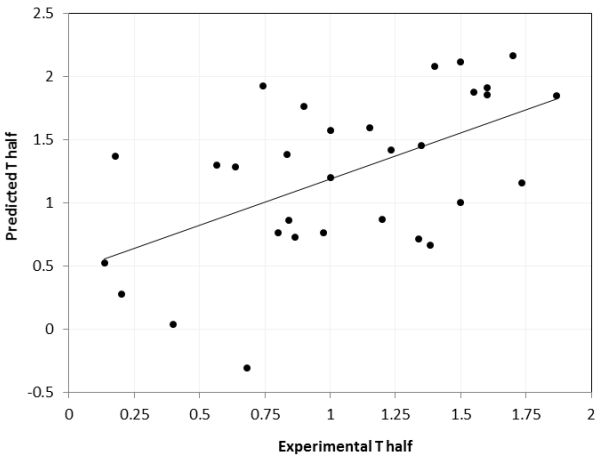


Figure 2. Plot of experimental vs predicted $T_{1/2}$

Conclusion

Structure-pharmacokinetic relationships were established for the pharmacokinetic property – elimination half-life in the drug series, i.e. cephalosporins. Constitutional, electrostatic, topological and absorption descriptors resulted in statistically significant correlations of $t_{1/2}$ in this series. Equation with high R^2 value (0.7334) and Q^2 value close to 0.5 was obtained using seven descriptors. The same may be used for prediction purpose.

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References

1. Kennedy T. Managing the Drug Discovery/Development Interface. Drug Discov Today 1997; 2: 436-444.
2. Kerns, E.H., Di, L., Kerns, E.H., and Di, L. Chapter 2 - Advantages of Good Drug-like Properties., Academic Press: San Diego. 2008; 6.
3. Yee, L.C. and Wei, Y.C., Current Modeling Methods Used in QSAR/QSPR, in Statistical Modelling of Molecular Descriptors in QSAR/QSPR. Wiley-VCH Verlag GmbH & Co. KGaA. 2012; 1-31.
4. Kuchar, M. QSAR in Design of Bioactive Compounds: Proceedings of the 2nd Telesymposium on Medicinal Chemistry, Telesymposia proceedings. J.R. Prous Science January 1992.
5. Ivanciuc, O. 3D QSAR Models in QSPR/QSAR Studies by Molecular Descriptors, M.V. Diudea Nova Science: Huntington, NY. 2001; 233-280.
6. Reich, S.H., Fuhry, M.A., Nguyen, D., Pino, M.J., Welsh, K.M., Webber, S., Janson, C.A., Jordan, S.R., Matthews, D.A., Smith, W.W., and et al. Design and synthesis of novel 6,7-imidazotetrahydroquinoline inhibitors of thymidylate synthase using iterative protein crystal structure analysis. J Med Chem 1992; 35(5):847-58.
7. Kuntz, I.D., Meng, E.C., and Shoichet, B.K. Structure-Based Molecular Design. Accounts of Chemical Research 1994; 27(5):117.
8. Ariens, E.J., Drug Design., NY: Academic Press, A subsidiary of harcourt Brace Jovanovich. 1971.
9. Brown, A., Crum, F., and Thomas, R. On the Connection between Chemical Constitution and Physiological Action. Part. I. On the Physiological Action of the Salts of the Ammonium Bases, derived from Strychnia, Brucia, Thebaia, Codeia, Morphia, and Nicotia 1868; 25(01):151.
10. Richet, M.C., Note on the Relationship between toxicity and Physical properties. Compt Rend Soc Biol (Paris) 1893; 45:775-776.
11. Meyer, H. Theory of alcohol anesthesia. First Communication what quality of the Anasthetics determine their narcotic effect. Arch Exp Path Pharm 1899; 42:109-118.
12. Overton, C.E. Studies of the anesthetic, contributing to the overall Pharmacology at the same time. 1901
13. Hammett, L.P. Some Relations between Reaction Rates and Equilibrium Constants. Chemical Reviews 1935; 17(1):125-136.
14. Taft, R.W. Separation of polar, steric and resonance effects in reactivity, in Steric effects in organic chemistry M.S. Newman. John Wiley and Sons Inc: New York. 1956; 556-675.
15. Marrone TJ, Briggs JM, McCammon JA. Structure-Based Drug Design: Computational Advances. Annu Rev Pharmacol Toxicol 1997; 37:71-90.
16. Kuntz ID, Meng EC, Shoichet BK. Receptor-Based Molecular Design. Acc Chem. Res 1994; 27:117-123.
17. Klebe G. Recent Developments in Structure-Based Drug Design. J Mol Med 2000; 78: 269- 281.
18. Cronin and Mark, T.D. Quantitative Structure–Activity Relationships (QSARs) – Applications and Methodology, in Recent Advances in QSAR Studies, T. Puzyn, J. Leszczynski, and M.T. Cronin, Editors., Springer Netherlands. 2010; 3-11.
19. Bergan, T. Pharmacokinetic properties of cephalosporins. Drugs 1987; 34 (Suppl. 2):89-104.

20. Vozeh, S., Schmidlin, O., and Taeschner, W. Pharmacokinetic drug data. Clin Pharmacokin 1988; 15:254-282.

21. Noble, J.T. and Barza, M. Pharmacokinetic properties of the newer cephalosporins: A valid basis for drug selection? Drugs 1985; 30:175-181.