Research Article

PREDICTION OF DRUG-IN-RAT PERMEABILITY AS A FUNCTION OF SELECTED DRUG MOLECULAR PROPERTIES

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ABSTRACT

The drug-in-rat permeability rate coefficient for thirteen types was examined. As drug or drug-like molecules are, in general, complex structures of amphiphilic nature, (i.e., having both hydrophobic and hydrophilic moieties), the permeation rate was expressed as a function of some selected molecular descriptors; namely, the Ghose-Crippen octanol-water partition coefficient, ALOGP; the hydrophilicity, Hy; the mean topological charge index of order 1, JGI1; the mean topological charge index of order 2, JGI2; the mean atomic polarizability (scaled on carbon atom), Mp; the mean electro-topological state, Ms; the mean atomic van der Waals volume (scaled on carbon atom), Mv; the number of rotatable bonds, RBN; the number of acceptor atoms for H-bonds (N,O,F), nHAcc; the number of donor atoms for H-bonds (N and O), nHDon; and finally the Kier flexibility index, PHI. Using the non-linear regression approach, it was found that the drug-in-rat permeability rate data can be adequately and satisfactorily described by the two molecular descriptors nHAcc and ALOGP, with JGI1 being the weight factor. To have a drug with high rat permeability rate coefficient, it is proposed that it has to have a low value of nHAcc, accompanied by high values of both ALOGP and JGI1. In other words, the molecule has to be of lipophilic nature and with an extended form.

Keywords: Drug Permeability, Molecular Descriptor, Oral Bioavailability, Molecular Branching, Chemometrics, DRAGON Software, Topological Charge Index.

INTRODUCTION

By definition, a system is complex when its behavior as a whole is not calculable from the properties of its constituents. Drug or drug-like molecular properties do not depend only on the properties of the constituting atoms but also on their mutual connections; it is in principle a holistic system; i.e. its emerging properties cannot be expressed as the sum of the properties of its constituents, but they are also dependent upon the whole molecule's architecture and stability.

To explain the complex relationships between molecules and observed quantities, two main tracks were developed: The first attempts to decipher relationships between molecular structures and physico-chemical properties; Quantitative Structure-Property Relationships (QSPR); and the second between molecular structures and biological activities; Quantitative Structure-Activity Relationships (QSAR). Molecular descriptors are thus the information encoded in the molecular structure, being expressed into one or more numbers, used to establish quantitative relationships between structures on one side and properties, or biological activities, on the other side.

For a drug, properties like chemical stability, oral availability, good pharmacokinetic properties, lack of toxicity, minimum addictive potential, crystallinity, ease of formulation, and practical availability by synthesis or isolation are of utmost importance. Properties such as oral bioavailability or membrane permeability have often been correlated to molecular descriptors, like: log P, molecular weight (MW), and number of hydrogen bond acceptors and donors in a molecule. The Lipinski drug-like index (or rule-of-five, RO5) is the first drug-like filter proposed to predict oral bioavailability of compounds that have achieved phase II clinical status[1,2]. This filter predicts that poor absorption or permeation is more likely when more than one violation is registered for the four following rules: more than 5 H-bond donors, MWT over 500, log P over 5, and/or more than 10 H-bond acceptors. The rules were derived from the analysis of 2245 drugs from the World Drug Index (WDI) database. However there are plenty of examples available for RO5 violation amongst the existing drugs. Majority of violations come from antibiotics, antifungals, vitamins, and cardiac glycosides. Still these classes of compound are orally bioavailable because they possess groups which act as substrates for transporters[3].

Further modification to predict oral bioavailability in terms of molecular descriptor was proposed by Veber et al.[4] via substituting the four Lipinski rules with the following two rules: (a) number of rotatable bonds≤10, and (b) polar surface area (PSA)≤140 Å2 or the sum of H-bond acceptors and H-bond donors≤12. Although Navia and Chaturvedi[5] proposed that molecular flexibility allowed changes in surface properties from aqueous-compatible to lipid-compatible are important for a good permeation rate, Veber et al.'s examined data did not support this reasonable hypothesis, which may be valid in the specific classes of compounds to which Navia and Chaturvedi refer. Instead, Veber et al. found a negative correlation between the average membrane permeation rate and average rotational bond count (which is clearly molecular weight independent in the permeation rate ranges below 300 nm/s). The latter finding may reflect a

possible entropic cost of changes in conformation required to present an appropriate exterior to the hydrocarbon interior of the membrane.

Intestinal drug absorption is a key factor for oral bioavailability. Both permeability of the intestinal mucosa for orally administered drugs, as well as drug solubility in the intestinal fluids at the site(s) of drug absorption are important parameters determining the extent (and rate) of oral drug absorption. For scarcely water soluble drugs, drug solubility in the gastro-intestinal environment may limit the local intraluminal drug concentrations that drive intestinal absorption[6].

In the present article, the permeation rate of some drug molecules will be examined as a function of some selected molecular descriptors; namely, the Ghose-Crippen octanol-water partition coefficient, **ALOGP**; the hydrophilicity, **Hy**; the mean topological charge index of order 1, **JGI1**; the mean topological charge index of order 2, **JGI2**; the mean atomic polarizability (scaled on carbon atom), **Mp**; the mean electro-topological state, **Ms**; the mean atomic vander Waals volume (scaled on carbon atom), **Mv**; the number of rotatable bonds, **RBN**; the number of acceptor atoms for H-bonds (N,O,F), **nHAcc**; the number of donor atoms for H-bonds (N and O), **nHDon**; and finally the Kier flexibility index, **PHI**. It is to be mentioned here that this study is not a typical QSAR study; where QSAR needs a large, broad, diversified and well distributed set of compounds, which is then randomly divided into a training set and a smaller test set. This is a typical curve-fitting study; where the dependent variable is expressed here as a function of, at most, two independent variables, chosen at a time, out of the list of pertinent variables.

MATERIALS AND METHODS

As drug or drug-like molecules are, in general, complex structures of amphiphilic nature, (i.e., having both hydrophobic and hydrophilic moieties), then it will be inappropriate to shorten the list of pertinent variables as was previously done with simple inorganic[7] and simple organic[8] molecules. Consequently, a few, out of a huge number of, molecular descriptors which are thought to have an influence on the permeation rate will be considered. Such a list of selected molecular descriptors will be analyzed in light of the goodness of a model to predict the variability of the permeation rate coefficient as function of the selected variables under study.

There are different packages, available on world-wide web, for calculation of molecular descriptors. DRAGON® (http://www.talete.mi.it/dragon.htm), MarvinSketch® (http://www.chemaxon.com/products/marvin/), and VolSurf® (http://www.moldiscovery.com/) are just examples of such packages. DRAGON® was used to evaluate the molecular descriptors for a given drug. The definition of each molecular descriptor is shown below. Further details can be found in [9]. The nomenclature of DRAGON® software was used.

ALOGP: The Ghose-Crippen octanol water coefficient (ALOGP) is a group contribution model for the octanol-water partition coefficient. ALOGP is defined as follows:

$$\boldsymbol{ALOGP} = \sum_k a_k N_k \qquad (1)$$

where a_k is the group contribution coefficient for the k[th] fragment type and N_k is the number of occurrences for the k[th] fragment type.

Hy: The hydrophilicity or hydrophilic index. It is defined by:

$$H_y = \frac{(1+N_{Hy})\times log_2(1+N_{Hy}) + N_C \times \left(\frac{1}{A} log_2 \frac{1}{A}\right) + \sqrt{\frac{N_{Hy}}{A^2}}}{log_2(1+A)} \qquad (2)$$

where N_{Hy} is the number of hydrophilic groups (–OH,–SH,–NH), N_C the number of carbon atoms, and A the number of atoms (hydrogen excluded). For example, water has Hy=3.00; for methane Hy=0.0; and the lowest value is -1 for alkane with N_C=1000.

JGIk: The mean topological charge index of order k. For each path of length k, it is defined by:

$$JGIk = \frac{G_k}{A-1} = \frac{\frac{1}{2}\times \sum_{i=1}^{A} \sum_{j=1}^{A} |CT_{ij}| \times \delta(d_{ij};k)}{A-1} \qquad (3)$$

where d_{ij} is the topological distance between i[th] and j[th] atoms; $\delta(d_{ij};k)$ is a Kronecker delta function equal to 1 if $d_{ij} = k$, zero otherwise; CT_{ij} the charge term corresponding to a pair of vertices with topological distance $d_{ij} = k$; and the denominator *A-1* is the number of edges in an acyclic molecule. Hence, the more extended the molecule, the higher **JGI1** will be and the more compact the molecule the lower **JGI1** will be.

It is worth-mentioning here that **JGI1** can be correlated to the molecular branching or compactness[9]. Molecular branching is a molecular property comprising several structural variables such as number of branching, valence, distances apart, distances from the graph center, and length of branches. Given this multifaceted definition of branching, its quantification is not an easy task. However, operational definitions of branching can be given by selected molecular indices, called branching indices, which, to some extent, reflect the branching of molecules as intended in an intuitive way. For example, the Wiener index increases with the number of atoms (i.e., the molecular size) and, for a constant number of atoms, reaches a maximum for linear structure and a minimum for the most branched and cyclic structures. Another example is the Harary index which increases with both molecular size and molecular branching; it is therefore a measure of molecular compactness like the Wiener index. However, the Harary index seems to be a more discriminating index than the Wiener index.

The polarization effect at atomic level, where dipoles $\mu_{IND,i}$ are induced on each atom as:

$$\mu_{IND,i} = \alpha_i \times E_i \qquad (4a)$$

where E_i is the electric field at the i[th] atom and α_i the corresponding polarizability, assumed to be isotropic. α_i can be further expressed as:

$$\alpha_i = \alpha_i^o - a_i q_i \quad (4b)$$

where α_i^o is the effective atomic polarizability of a neutral atom and a_i the charge coefficient.

M_P: The mean polarizability of a molecule is calculated by summing the atomic contributions:

$$M_P = \frac{\sum_{i=1}^{nAT} \alpha_i}{nAT} \quad (5)$$

where *nAT* represents the total number of atoms.

The electro-topological state S_i of the i[th] atom in the molecule, called E-state index (or electro-topological state index) gives information related to the electronic and topological state of the atom in the molecule and is defined as:

$$S_i = I_i + \Delta I_i = I_i + \sum_{j=1}^{A} \frac{I_i - I_j}{(d_{ij}+1)^k} \quad (6)$$

where I_i is the intrinsic state of the i[th] atom and ΔI_i is the field effect on the i[th] atom calculated as the perturbation of the intrinsic state of i[th] atom by all other atoms in the molecule, d_{ij} is the topological distance between the i[th] atom and the j[th] atoms, and A is the number of atoms. The exponent k is a parameter to modify the influence of distant or nearby atoms for particular studies. Usually it is taken as *k=2*.

M_S: The mean electro-topological state is defined as:

$$M_S = \frac{S_S}{nSK} = \frac{\sum_{i=1}^{nSK} S_i}{nSK} = \frac{\sum_{i=1}^{nSK} I_i + \Delta I_i = I_i + \sum_{j=1}^{A} \frac{I_i - I_j}{(d_{ij}+1)^k}}{nSK} \quad (7)$$

where *nSK* represents the number of non-hydrogen atoms.

The vander Waals volume, also called intrinsic molecular volume VI, is the volume of the space within the vander Waals molecular surface. The vander Waals radius is the distance at which the attractive and repulsive forces between two non-bonded atoms are balanced, thus the vander Waals volume may be regarded as an impenetrable volume for other molecules.

The sum of the vander Waals volumes (scale on carbon atom) is given by:

$$S_V = \sum_{i=1}^{A} \frac{V_i^{vdw}}{V_C^{vdw}} \quad (8)$$

where V_i^{vdw} is the vander Waal's volume of the i[th] atom divided by that of carbon atom, V_C^{vdw}.

M_V: The mean atomic vander Waals volume (scaled on carbon atom) is calculated by dividing the sum of the van der Waals volumes by the number of atoms:

$$M_V = \frac{S_V}{nAT} \quad (9)$$

RBN: Molecular flexibility depends on the number of rotatable bonds in the molecule structure. It is obtained simply by counting the non-terminal, non-cyclic, single bonds except C-N amide bond.

nHAcc: The number of acceptor atoms for H-bonds (N,O,F).

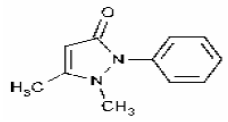
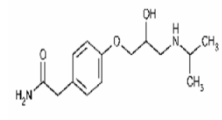
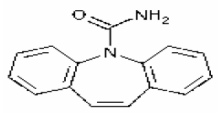
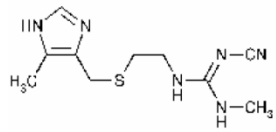
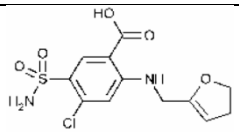
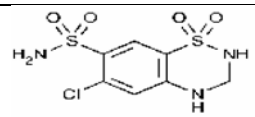
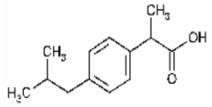
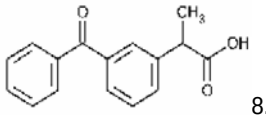
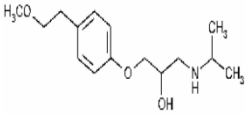
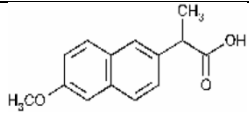
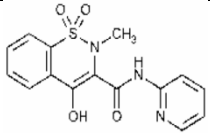
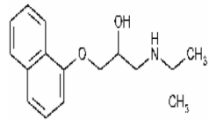
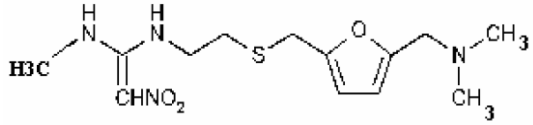
nHDon: The number of donor atoms for H-bonds (N and O).

PHI (Φ): The Kier flexibility index. This is a measure of molecular flexibility derived from the Kier alpha-modified shape descriptors κ_α^1 and κ_α^2 and is given by:

$$\Phi = \frac{\kappa_\alpha^1 \times \kappa_\alpha^2}{A} \quad (10)$$

where *A* is the total number of atoms in a molecule. The Kier shape indices calculated from the H-depleted molecular graph depend on the heteroatoms by the parameter α; κ_α^1 encodes information about the count of atoms and relative cyclicity of molecules, whereas κ_α^2 encodes information about branching or relative spatial density of molecules. The atom count A allows comparisons among isomers. Table 1 lists in alphabetical order the drugs to be examined.

Table 1: Chemical structure of drugs under study

 1. Antipyrine	 2. Atenolol
 3. Carbamazepine	 4. Cimetidine
 5. Furosemide	 6. Hydrochlorothiazide
 7. Ibuprofen	 8. Ketoprofen
 9. Metoprolol	 10. Naproxen
 11. Piroxicam	 12. Propranolol
 13. Ranitidine	

RESULTS AND DISCUSSION

DRAGON® software was used to estimate the molecular descriptors. It requires, however, inputting the chemical formula as Simplified Molecular Input Line Entry Specification (SMILES) format. Further information about the rules on how to construct a SMILES notation for a given molecule can be found at: http://www.daylight.com/dayhtml_tutorials/languages/smiles/index.html.

Table 2 shows the calculated values of selected molecular descriptors using DRAGON®. The last column shows their rat intestinal permeability data which were taken from[10]. The process of scaling (values will then be between 0 & 1 as a fraction, or 0 and 100 as per cent) was done for the sake of making variables of equal weight (contribution) from regression standpoint. The scaled value for each molecular descriptor (i.e., each column in Table 2) is calculated as follows:

$$Scaled\ Value = \frac{(Calculated\ value - Min.value\ in\ a\ coulmn)}{(Max.value\ in\ a\ column - Min.value\ in\ a\ column)} \quad (11)$$

The MATLAB® surface fitting tool was used to fit a multi-dimensional, non-linear regression problem as is the case here. The general formula for curve-fitting is:

$$Z = (X, Y)$$

where Z is the dependent variable and X & Y are the independent variables.

As the number of permeability data is only 13, only two independent variables at a time can be chosen to make the regression process reliable. The permeability rate coefficient (PERM) was fitted as a function of only two variables (*X*) and (*Y*) out of the list given in Table 2. The following model was used as a tool to conduct a comparison among different pairwise combinations of molecular descriptors to see which will be able to better predict the variability in rat permeability rate data:

$$PERM = a + b * X + c * X^2 + d * Y + e * Y^2 \quad (12)$$

Table 2: Values of molecular descriptors using DRAGON(R) and rat permeability data[10]. Scaled values are shown bottom.

Species	Mv	Mp	Ms	RBN	JGI1	JGI2	nHDon	nHAcc	Hy	ALOGP	PHI	PERM× 10^{-5}cm/s
Antipyrine	0.63	0.66	2.29	1	0.167	0.085	0	3	-0.766	1.62	2.196	5.9
Atenolol	0.57	0.61	2.48	8	0.237	0.074	4	5	1.986	0.669	6.668	1.6
Carbamazepine	0.68	0.71	2.3	0	0.125	0.071	2	3	0.32	2.679	2.558	6.2
Cimetidine	0.61	0.65	2.31	7	0.147	0.078	3	5	1.366	0.61	6.524	4.8
Furosemide	0.63	0.68	2.82	5	0.205	0.089	4	7	2.939	0.641	5.604	3.3
H-chlor-thiazide	0.67	0.73	3.09	4	0.235	0.106	4	6	3.347	-1.397	4.752	2
Ibuprofin	0.59	0.63	2.41	4	0.267	0.089	1	2	-0.33	3.582	4.043	20
Ketoprofen	0.66	0.69	2.61	4	0.175	0.091	1	3	-0.353	3.336	3.885	9.6
Metoprolol	0.56	0.6	2.18	9	0.211	0.068	2	4	0.341	1.757	7.675	3.3
Naproxen	0.64	0.67	2.48	3	0.222	0.089	1	3	-0.314	2.824	3.227	11
Piroxicam	0.67	0.7	2.77	5	0.167	0.083	2	7	0.407	0.987	5.243	7.9
Propranolol	0.6	0.64	2.14	6	0.175	0.077	2	3	0.29	2.54	4.912	5.6
Ranitidine	0.58	0.63	2.44	10	0.238	0.043	2	6	0.472	1.466	8.451	2.2
Species	**Mv**	**Mp**	**Ms**	**RBN**	**JGI1**	**JGI2**	**nHDon**	**nHAcc**	**Hy**	**ALOGP**	**PHI**	**PERM**
Antipyrine	0.58333	0.46154	0.15789	0.10000	0.29577	0.66667	0.00000	0.20000	0.00000	0.60594	0.00000	0.23370
Atenolol	0.08333	0.07692	0.35789	0.80000	0.78873	0.49206	1.00000	0.60000	0.66910	0.41494	0.71495	0.00000
Carbamazepine	1.00000	0.84615	0.16842	0.00000	0.00000	0.44444	0.50000	0.20000	0.26404	0.81864	0.05787	0.25000
Cimetidine	0.41667	0.38462	0.17895	0.70000	0.15493	0.55556	0.75000	0.60000	0.51836	0.40309	0.69193	0.17391
Furosemide	0.58333	0.61538	0.71579	0.50000	0.56338	0.73016	1.00000	1.00000	0.90080	0.40932	0.54484	0.09239
H-chlor-thiazide	0.91667	1.00000	1.00000	0.40000	0.77465	1.00000	1.00000	0.80000	1.00000	0.00000	0.40863	0.02174
Ibuprofin	0.25000	0.23077	0.28421	0.40000	1.00000	0.73016	0.25000	0.00000	0.10601	1.00000	0.29528	1.00000
Ketoprofen	0.83333	0.69231	0.49474	0.40000	0.35211	0.76190	0.25000	0.20000	0.10041	0.95059	0.27002	0.43478
Metoprolol	0.00000	0.00000	0.04211	0.90000	0.60563	0.39683	0.50000	0.40000	0.26915	0.63346	0.87594	0.09239
Naproxen	0.66667	0.53846	0.35789	0.30000	0.68310	0.73016	0.25000	0.20000	0.10990	0.84776	0.16483	0.51087
Piroxicam	0.91667	0.76923	0.66316	0.50000	0.29577	0.63492	0.50000	1.00000	0.28519	0.47881	0.48713	0.34239
Propranolol	0.33333	0.30769	0.00000	0.60000	0.35211	0.53968	0.50000	0.20000	0.25675	0.79072	0.43421	0.21739
Ranitidine	0.16667	0.23077	0.31579	1.00000	0.79577	0.00000	0.50000	0.80000	0.30100	0.57502	1.00000	0.03261

It should be pointed out here that the model form (i.e., polynomial of degree 2) is identical for both X and Y. This makes the order of variables immaterial. All possible pairwise permutations (55 non-repeated pairs) were tested. Table 3 shows the five top cases with the highest correlation coefficient, R^2. It is worth-mentioning that the scaled data were used for telling which of the molecular descriptors better describe the variability of permeability, without having any bias by the physical magnitudes of the molecular descriptors.

Table 3: List of the best five cases, out of all possible pair wise permutations (55 non-repeated cases), with the highest correlation coefficient, R^2.

#	Correlation coefficient, R^2	The pair of independent variables X & Y for $PERM: Z = f(X, Y)$
1	0.8232	**(ALOGP, nHAcc)**
2	0.8232	**(JGI1, nHAcc)**
3	0.8378	**(Ms, nHAcc)**
4	0.8367	**(RBN, nHAcc)**
5	0.8260	**(PHI, nHAcc)**

From Table 3, it can be seen that almost any of the five cases may be used to predict (or, describe) the variability of drug-in-rat permeability rate coefficients. One more thing to notice is that **nHAcc** is present in all five cases. Further zooming or reduction of the five possible cases can be done by incorporating the weight function in the non-linear regression process.

If a weighted non-linear regression is carried out, further improvement can be achieved. This was done when considering curve-fitting

$$PERM = f(Molecular\ descriptor\ from\ Table\ 3, nHAcc)$$

while the weight function is permutated over all other variables in Tables 3 except the variables under concern. Table 4 shows the results of the weighted curve-fitting using the scaled values.

Table 4: The weighted non-linear regression of the best five cases present in Table 3 using the scaled values.

#	Independent variables	The weight function	R^2
1	**(ALOGP, nHAcc)**	**JGI1**	0.940
2	**(JGI1, nHAcc)**	**RBN**	0.911
3	**(Ms, nHAcc)**	**JGI1**	0.943
4	**(RBN, nHAcc)**	**JGI1**	0.928
5	**(PHI, nHAcc)**	**JGI1**	0.927

From Table 4 one can see that the best cases will be case 1 and 3 as both are characterized by the highest R^2 value.

Figure 1 shows the permeability rate coefficient as a function of **ALOGP** and **nHAcc** molecular descriptors, which represents case 1 in Table 4. The red zone means maximum rat permeability and the dark blue means minimum. The maximum rat permeability rate coefficient is found at very low **nHAcc** and very high **ALOGP** values. R^2, with **JGI1** as a weight factor, is 0.94. One may notice that the topology of **PERM** indicates that it is very sensitive to the variation in **nHAcc** while almost insensitive to that of **ALOGP,** except at very low **nHAcc**.

Figure 2 shows the permeability rate coefficient as a function of **Ms** and **nHAcc** molecular descriptors, which represents case 3 in Table 4. The red zone means maximum rat permeability and the dark blue means minimum. The maximum rat permeability rate coefficient is found at very low **nHAcc** and almost independent of **Ms**. R^2, with **JGI1** as a weight factor, is 0.94. Again, one may notice that the topology of **PERM** indicates that it is very sensitive to the variation in **nHAcc** while almost insensitive to that of **Ms**.

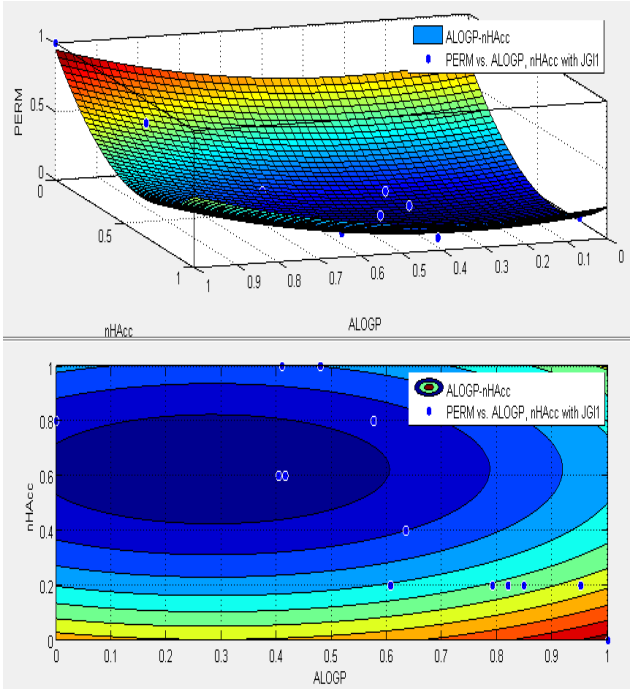


Figure 1: The drug-in-rat permeability rate coefficient as a function of **ALOGP** and **nHAcc** for the examined drugs.

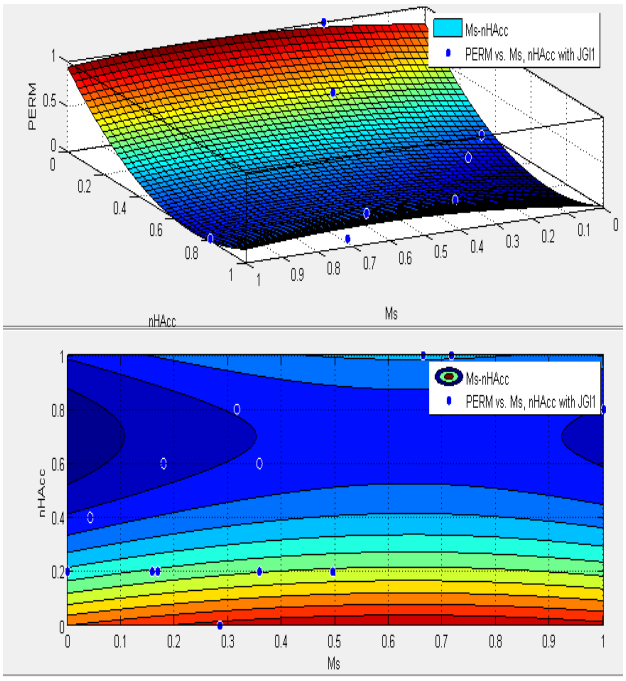


Figure 2: The drug-in-rat permeability rate coefficient as a function of **Ms** and **nHAcc** for the examined drugs.

The following proposition is presented here in light of traits shown in figures 1 and 2:

To have a drug with high rat permeability, it is proposed here that it has to have a low value of **nHAcc,**

accompanied by high values of both **ALOGP** and **JGI1**. Examples of drugs meeting the afore-mentioned criterion are: Ibuprofen, Ketoprofen, and Naproxen. Notice that Ibuprofen has the highest rat permeability rate coefficient (**PERM**=100%) given that it has the lowest **nHAcc** (0%); highest **JGI1** (100%); and highest **ALOGP** (100%). Other drugs more or less violate the afore-mentioned criterion in one aspect or another.

It is worth mentioning here that if someone looks at the experimentally-measured rat permeability data, one may think for a moment that Piroxicam although it does not have a low **nHAcc** value (in fact, it has the highest **nHAcc** value), nevertheless, it has a relatively high value of rat permeability. Well, if the comparison is made based on the scaled values (between 0 and 100%) then one will realize that Piroxicam has a permeability value equivalent to 34.2% which is considered to be low not high.

The proposition that a drug has to have high values of **ALOGP**, **JGI1**, and **nHAcc** is discernable in terms of permeation through a bilayer lipid membrane (i.e., the intestine). High **ALOGP** and low **NHAcc** means practically that the molecule is of lipophilic nature or coated by an oil layer or shell. On the other hand, high **JGI1** means that the molecule is more extended than it is branched or compacted (see the definition of **JGIk** in Theory section) which means that the extended form of a molecule experiences less resistance (less steric effects) to penetration than the branched form, given all other things are equal (i.e., total number of non-hydrogen atoms, or molecular weight is the same). For example, in this regard Ibuprofen has the highest **JGI1** (100%) index; i.e., the most extended form; whereas Carbamazepine has the lowest **JGI1** (0%) index; i.e., the most branched form (see Table 1 for comparing the chemical structure of Ibuprofen with that of Carbamazepine).

CONCLUSION

1. In general, the drug-in-rat permeability rate data can be adequately and satisfactorily described by the two molecular descriptors **nHAcc** and **ALOGP**, with **JGI1** as the weight factor.
2. To have a drug with high rat permeability rate coefficient, it appears that it has to have a low value of **nHAcc**, accompanied by high values of both **ALOGP** and **JGI1**. In other words, the molecule has to be of lipophilic nature and with an extended form.

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