PREDICTION OF HUMAN INTESTINAL PERMEABILITY SINGLE-PASS INTESTINAL PERFUSION IN RAT: A QSAR/QSPR APPROACH

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Abstract

The aim of the study was the prediction of human intestinal permeability and fraction absorbed of oral dose using QSAR/QSPR methods. To explore physicochemical and topological properties of 15 compounds responsible for their Human intestinal permeability, a quantitative structure activity relationship, Hansch approach was applied on sixteen compounds. Various physicochemical and topological descriptors and reported Human intestinal permeability values of different 15 compounds were used as independent variables and dependent variable respectively. The best models for 15 different compounds were first validated by Regression analysis. It was revealed that physicochemical parameter Density, polarizability, Molecular Volume, Parachore and topological parameter J play a very significant role to predict the human intestinal permeability and these studies provide an insight to design new molecules.

Key words: QSAR, Hansch approach

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Introduction:

Drugs are most commonly administered via oral route. In fact the vast majority of pharmaceutical dosage forms are designed for oral administration. However not all of the compounds have compatible properties for the development of oral dosage forms. Often poor bioavailability results in the termination of development of new drugs. Therefore, optimized bioavailability of drugs is one of the most important goals for the pharmaceutical industry. The two principal routes of absorption across small intestinal epithelium are paracellular and transcellular. Typically, lipophilic drugs are absorbed by the transcellular route, whereas hydrophilic drugs are slowly absorbed via the transcellular pathway or in some cases via the paracellular route. Both passive and active (carrier mediated) processes may contribute to the permeability to drugs transported by the transcellular pathway (1). For instance several amino acid analogues such as α-methyldopa (2), Ldopa (3) and baclofen (4) are transported by large neutral amino acid transporter and orally absorbed cephalosporins are substrates for the H+/oligopeptide transporter (5). The efficiency of drug absorption is also influenced by efflux proteins lining the small intestine. For example Pglycoprotein (P-gp) is a phosphorylated and glycosylated efflux protein belonging to a family of plasma membrane proteins encoded by the multidrug resistance gene(s) (1). It functions as a membrane-localized drug transport mechanism that has the ability to actively pump its substrates out of the cell. This could reduce the efficiency of absorption of common, orally absorbed drugs like digoxin, carbamazepine and propranolol. Recognition of the much broader specificity of P-gp and its functional effects on intestinal drug transport could lead to strategies for improving absorption, either by incorporating structural features in drug design that reduce interaction with P-gp or by the use of specific P-gp inhibitors (1).the name of different compounds with there calculated value of different physiochemical and topological parameters are given below in table 1.

Table - 1: Human Intestinal Permeability values (Human Fa) and Calculated Topological and physicochemical parameter used in present study

comp no	Compound name	Human Fa	Pol	Pc	Den	MV	J
1	Naproxen	1	26.37	504.6	1.197	192.2	2.839
2	Ketoprofen	1	28.46	563.7	1.198	212.2	2.374
3	Furosemide	0.61	30.03	606.2	1.606	205.8	2.432
4	Antipyrine	1	21.62	416.1	1.156	162.7	3.097
5	Hydrochlorothiazide	0.54	24.86	493.3	1.693	175.8	2.341
6	Propranolol	0.9	31.31	606.1	1.093	237.1	3.022
7	Piroxicam	0.99	32.97	638.5	1.549	213.8	2.178
8	Atenolol	0.5	24.23	502.3	1.03	203	3.429
9	Cimetidine	0.79	26.2	487.4	1.31	182.1	3.531
10	Ranitidine	0.5	33.95	687.5	1.184	265.4	3.956
11	Carbamazepine	0.97	27.62	513.4	1.266	186.5	2.228
12	Phenol red	1	36.62	691.7	1.477	239.7	2.285
13	Cephalexin	0.98	35.64	704.4	1.45	239.5	2.202
14	Ibuprofen	1	24.09	497.6	1.029	200.3	4.652
15	α-Methyl dops	0.1	21.36	439.3	1.403	150.4	3.652

Moreover the rat in situ intestinal permeability values for tested compounds are presented which some of them have not yet been reported. Human intestinal permeabilities have been obtained from published data in which the regional perfusion approach in human jejunum was used. The goal was to obtain a more reliable correlation to predict human intestinal permeability and fraction of dose absorbed using rat intestinal permeability. The obtained values were compared with previously published data in the rat as well. The human intestinal permeability is used for this QSAR study is taken from literature[6].

Results and Discussion:

Quantitative structure activity relationships (QSAR) studies are tools of predicting endpoints of interest in organic molecules acting as drugs[7]. Many physiological activities of molecules can be related to their composition and structures. Molecular descriptors, which are the numerical representation of the molecular structures, are used to perform QSAR analysis [8].Quantitative structure activity relationships (QSAR) have been shown to be powerful research tool and two basic kinds of molecular descriptions used in QSAR, One of them involves parameters that bear relation to free energy and usually represent some of the important physicochemical properties of the molecules (Hansch approach)[8,9] Another category of molecular descriptor is the topological index which is produced directly from molecular structure[10,11] (topological approach), Among many topological indices that have been proposed since the wiener in 1945, the Randic connectivity index[12], Hosoya index,[13] Balaban index [14,15], Szeged index [12] etc. are well known. In recent years, topological indices[16] have gained attention in explaining biological activities and physical and chemical properties of organic compounds.

Table- 2: Obtained QSAR models for the molecules studied against Fa.

S./No.	Equation	Statistical Characteristics
1.	Fa = 3.1563 - 0.8791 Den + 0.4283 J,	**N=15, R^2 = 0.6446, R^2A = 0.5800, F-ratio = 9.977**
2.	Fa= 2.6851-0.0132 Pol+ 0.8902 DEN + 0.3898J	**N=15, R^2= 0.6898, R^2A = 0.5967, F-ratio = 7.412**
3	Fa = 2.2266 – 0.1435 Pol +0.0067DEN + 0.7405J + 0.2909 PC	**N=15, R^2= 0.8510, R^2A = 0.7848, F-ratio = 12.854**
4.	Fa = 2.1159 – 0.1446 Pol +0.0073 DEN + 0.6592J+ 0.0016 PC + 0.2959MV	**N=15, R^2= 0.8522, R^2A = 0.75899, F-ratio =9.228**
5.	Fa = 1.5026 – 0.1626 Pol –0.0078 DEN+0.5060J+0.0021PC – 0.2735MV	**N=14, R^2= 0.9274, R^2A = 0.8669, F-ratio = 15.324** (Comp.4 is outlier)

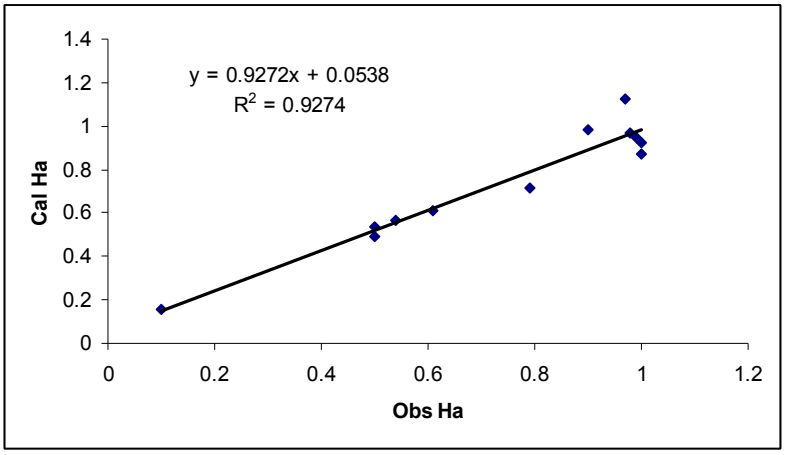
In the above model change in statistics is observed. The variance of 93% suggests that as compared to the four parametric models the present model is much better. These model shows that topological parameter such as Balaban index while physicochemical parameter such as Pol., Parachor , MV and Density are responsible for the modeling of these compounds, both type of parameter play important role for the modeling of different

compounds which have high human intestinal permeability value .the observed and calculated values are given below in table 3.

Table- 3: The observed and calculated values of human permeability value Fa

Compound No.	Observed	Fa	
		Predicted	Residual
1	1	0.873	0.127
2	1	0.92	0.08
3	0.61	0.608	0.002
4	0.54	0.566	-0.026
5	0.9	0.981	-0.081
6	0.99	0.949	0.041
7	0.5	0.489	0.011
8	0.79	0.712	0.078
9	0.5	0.533	-0.033
10	0.97	1.128	-0.158
11		1.189	
12	0.98	0.966	0.014
13		0.164	
14	0.1	0.154	-0.054

Fig. 1: Graph between observed and calculated human intestinal permeability Fa.



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