Quantitative Structure Protein Binding Relationships for some Non-Steroidal Antiinflammatory Drugs

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Quantitative structure-protein binding relationships (QSPBR) have been derived for six non-steroidal antiinflammatory drugs (NSAIDs). Ninety eight topological indices (TIs) for six NSAIDs used in this study were calculated using software Polly 2.3. Variables having statistically significant correlations with association constants were considered to be predictors of the model. Linear relationships between association constants and relevant variables derived using multiple linear regression analysis, were useful in predicting drug binding affinity. The association constants were found to be functions of the degree of complexity (I^D), path connectivity indices ($^1\chi$ and $^3\chi$) and the number of paths, P_9. Thus, size and shape of the drug molecule plays an important role in the binding of NSAIDs to serum albumin.

Quantitative structure-activity relationships (QSARs) are mathematical models which aim at predicting properties of molecules from their structure. Topological parameters have been extensively utilized in the prediction of biological activity as well as physico-chemical, biomedical and toxicological properties of molecules[1-3]. Quantitative analysis of structure-activity relationships play an important role in drug development[4-6]. Numerous studies on various aspects of QSAR-guided drug design are being published[7-9]. However, most of the receptors for drugs are proteinacious in nature. For example the administered drugs are extensively and reversibly bond to serum albumin and drug is transported mainly as a complex with protein. The nature and magnitude of drug-protein interaction significantly influences the biological activity of a drug[10-12]. Since binding depends on the structure of the drug molecule, quantitative structure-protein binding relationships (QSPBR) can provide a useful method of predicting drug binding affinities and understanding the nature of drug-protein interaction from structural parameters of the drug. This aspect of the problem has not received adequate attention so far. Present paper reports quantitative relationships between various topological indices and association constants for the binding of six non-steroidal anti-inflammatory drugs (NSAIDs) to serum albumin.

Association constants K_1 and K_2 for the binding of six NSAIDs to serum albumin were taken from Borga and Borga[13]. The data is given in Table 1. The ninety eight topological indices (Tis) for six NSAIDs used in this study were calculated using Polly 2.3 which uses SMILES notation input of chemical structures[14]. The TIs calculated by POLLY 2.3 include the Weiner index, Connectivity indices and information theoretic indices defined on distance matrices of graphs as well as a set of parameters derived on the neighborhood complexity of vertices in hydrogen-filled molecular graphs. The methods used for the calculation of TIs are described[15].

Initially all the TI's were transformed by the natural logarithm of the index plus one. This is routinely done to scale the indices since there may be a difference of several orders of magnitude between indices and some may equal zero. From the original set of 98 indices, it was necessary to remove some indices. Twelve indices were completely redundant because they had values of zero for all compounds.

On the remaining indices common data reduction techniques such as Variable clustering and Principal component analysis could not be used since the sample size is very small. That is, the number of descriptors is much larger than the number of samples and thus the

TABLE 1 : COMPARISON OF EXPERIMENTALLY DETERMINED ASSOCIATION CONSTANTS AND THOSE PREDICTED

Drug	Association Constant				
	log K_1			log K_2	
	Experimental value*	Calculated from Eq. 1**	Calculated from Eq. 2**	Experimental value*	Calculated from Eq. 3**
Diclofenac	5.5901	5.5879	5.6660	3.9666	4.0107
Fenoprofen	5.7545	5.9557	5.8582	4.0376	4.1998
Flurbiprofen	7.1818	6.2893	-	5.2581	-
Ketoprofen	5.2815	5.6615	5.5402	3.3054	3.5346
Naproxen	6.6925	7.0580	6.7115	4.2541	4.0721
Tolmetin	5.8894	5.8380	5.6460	3.9431	3.6722

*Values taken from Borga and Borga[13].
**Association, constants predicted from the topological indices using equations 1,2 and 3

probability of chance correlations in very high[16]. Bivariate correlation matrix between association constants (log K_1 and log K_2) and topological indices was obtained using statistical software SPSS. Only those variables having statistically significant correlations were retained. Multiple linear regression analysis was performed on the retained variables. Quadratic equations were also fitted to the data.

Bivariate correlation matrix between association constant (log K_1) and topological indices showed that only two topological indices, degree of complexity (I^D) and path connectivity index ($^1\chi$), with correlation coefficients 0.746 and 0.737 were significant up to 0.1 level. They were considered to be predictors of the model. Multiple linear regression analysis was performed on these variables (Eq. 1). Correlation between log K_2 and topological indices showed that no variable had correlation coefficient significant even up to the 0.1 level.

$$\log K_1 = -374.89\ I^D + 92.03\ ^1\chi + 18041 \qquad (1)$$
r=0.756, SE=61.04

Table 1 shows that the association constant reported by Borga and Borga[13] for flurbiprofen has abnormally high value. It may be mentioned that the values reported in the literature[17,18] for flurbiprofen are lower by a factor of 2 to 9. It is seen that the correlation coefficients improve considerably when this sample is removed from analysis. Bivariate correlation matrix between log K_1 and topo-

logical indices now showed thirteen variables with correlation coefficients significant up to 0.1 level and three variables I^D, $^1\chi$ and the number of paths P_9 with correlation coefficients -0.927, -0.915 and 0.889 significant up to 0.05 level. Correlation of topological indices with log K_2 showed only one variable $^3\chi$ with correlation coefficient 0.793 significant up to 0.11 level. Linear equations (Eqs. 2&3) were derived for the relationship between log K_1 and log K_2 and the relevant significant variables. Quadratic equations fitted to the above retained variables did not give better fit of the data.

$$\log K_1 = 56.13\ I^D - 33.04\ ^1\chi + 3.87\ P_9 - 739.97 \qquad (2)$$
r = 0.951, SE = 32.57
$$\log K_2 = -16.59\ ^3\chi + 1823 \qquad (3)$$
r = 0.793, SE = 24.98

No significant correlation was observed between molecular weight (log MW) and partition coefficient (log P) and the association constants (log K_1 and log K_2) in a linear or quadratic fit. Experimentally determined association constants and those predicted from theoretical molecular descriptors (Eqs. 1,2 and 3) are shown in Table 1. The agreement is fairly good.

Thus association constants were found to be functions of the degree of complexity (I^D), path connectivity indices ($^1\chi$ and $^3\chi$) and the number of paths, P_9. The size and shape of the drug molecule, therefore, plays an important role in the binding of NSAIDs to serum albumin.

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Effect of Sodium Lauryl Sulfate on the Release of Rifampicin from Guar Gum Matrix

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The release of rifampicin from a matrix compressed from a physical mixture of rifampicin, guar gum and sodium lauryl sulfate was investigated. When sodium lauryl sulfate was incorporated in the matrix, the release of rifampicin was found to be linearly related to the square root of time, however, the release depended on the concentration of the sodium lauryl sulfate. As the concentration of sodium lauryl sulfate increased upto 15%, the release progressively slowed to a minimum, which could be due to the formation of a poorly soluble complex. As the concentration increased further, the release increased as the complex was micellarly solubilized.

One of the simplest method to obtain a controlled release product is to embed or disperse the active ingredient in a heterogeneous matrix by compressing a physical mixture of the compound with a polymeric material. Various studies of the release from matrices in which a surfactant had been incorporated showed a faster release with the addition of the surfactant[1-5]. Choulis and Papadopoulos[6] found that the release of quinine sulfate from a nylon matrix containing sodium lauryl sulfate (SLS)

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