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Modeling the drugs' passive transfer in the body based on their chromatographic behavior

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ABSTRACT

One of the most challenging aims in modern analytical chemistry and pharmaceutical analysis is to create models for drugs' behavior based on simulation experiments. Since drugs' effects are closely related to their molecular properties, numerous characteristics of drugs are used in order to acquire a model of passive absorption and transfer in the human body. Importantly, such direction in innovative bioanalytical methodologies is also of stressful need in the area of personalized medicine to implement nanotechnological and genomics advancements.

Simulation experiments were carried out by examining and interpreting the chromatographic behavior of 113 analytes/drugs (400 observations) in RP-HPLC. The dataset employed for this purpose included 73 descriptors which are referring to the physicochemical properties of the mobile phase mixture in different proportions, the physicochemical properties of the analytes and the structural characteristics of their molecules. A series of different software packages was used to calculate all the descriptors apart from those referring to the structure of analytes.

The correlation of the descriptors with the retention time of the analytes eluted from a C_4 column with an aqueous mobile phase was employed as dataset to introduce the behavior models in the human body. Their evaluation with a Partial Least Squares (PLS) software proved that the chromatographic behavior of a drug on a lipophilic stationary and a polar mobile phase is directly related to its drug-ability. At the same time, the behavior of an unknown drug in the human body can be predicted with reliability via the Artificial Neural Networks (ANNs) software.

1. Introduction

Pharmacokinetics refers to the actions taken by the human body to deal with a medicine. These actions involve drug absorption into the body, distribution of the drug to various tissues, metabolism and excretion (ADME); with absorption being the most significant of the aforesaid processes.

At the same time, drug-likeness can be defined as a complex balance of a variety of molecular properties and structural features which determine whether a particular molecule is similar to known drugs. A traditional method to evaluate a likely orally active drug for human is to check compliance of Lipinski's Rule of five [1]. The rule is based on the observation that most drugs are relatively small and lipophilic molecules and describes molecular properties which are important for drugs' pharmacokinetics. Over the past decade Lipinski's research has led to further investigation by scientists to extend profiling tools to lead-like properties of compounds hoping that a better starting point in early discovery can decrease both experimental time and cost. Some methods allow, by using the Rule of Five and/or other properties, to rapidly identify compounds that could be more suitable for high throughput screening and for parallel synthesis efforts. According to Ghose et al. [2], a drug-like molecule has a logarithm of octanol/water partition coefficient (log P) between −0.4 and 5.6, molecular weight (M.W.) 160–500 g/mol, molar refractivity (MR) of 40–130, number of atoms 20–70 and polar surface area not greater than 140 Å^2. Five properties have also been found to be of importance in oral administration by Lobell et al. [3]. Such boundaries are still

Abbreviations: ADME, Absorption Distribution Metabolism Excretion; ANNs, Artificial Neural Networks; log *D*, octanol/water distribution coefficient; log *P*, octanol/water partition coefficient; PAPMA, Parallel Artificial Membrane Permeability Assay; PCA, Principal Component Analysis; PLS, Partial Least Squares; PRESS, prediction error sum of squares; RMSEE, Root Mean Square Error of Estimation; RMSEP, Root Mean Square Error of Prediction; RP-HPLC, reversed phase high performance liquid chromatography; R^2, correlation coefficient; Q^2, prediction ability.

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presented from time to time by scientists based on empirical rules and experimental data [4].

So far however, when medicinal chemists tried to assess drug-likeness, much molecular information (descriptors) was left out in their research. Given the confidence with which these descriptors are often used as early screening tools [5], a question rises: Which is the proportion of potentially valuable compounds/drugs that are synthesized based on incomplete or faulty information?

A missing dimension when encoding chemical information is certainly the dynamic nature of molecules and their behavior at in vivo or in vitro models. Since it is relatively hard to find a model in which numerous and complex mechanism(s) either participate or/and describe the term drug-likeness such an approach is proven to be rather difficult. Recently, Parallel Artificial Membrane Permeability Assay (PAMPA) is used as an in vitro model of passive, transcellular permeability. Although this technique is an artificial promising method, it is considered as time consuming, relatively expensive as well as difficult to implement [6].

According to the literature a new column technology known as Immobilized Artificial Membrane (IAM) column [7] is considered to be a reliable mimic of membranes. Still, such membranes may have a demerit; they are relatively unstable and in some cases they cannot simulate passive diffusion. For example, a small molecule that contains many carboxylic or hydroxylic groups will be retained on IAM (due to ionic forces) and this drug will apparently be attributed a better drug-ability value compared to a molecule with positive log D [8]. However, the above is in conflict with the rules related to membranes' lipophilicity letting the truth lie somewhere in between.

Nowadays, the drug delivery era witnesses major advancements toward establishing personalized medicine concepts in health and pharmaceutical care [9]. Within the frame of this work and toward creating a solid infrastructure to ensure the practical clinical utility of personalized medicine approach worldwide, the development and application of innovative and more powerful bioanalytical methods to implement the nano-technological and genomics advancements is needed.

To this end, the present work is an effort to correlate the behavior of an analyte/drug in HPLC with the passive transfer of the drug in the human body, facing this phenomenon from a different point of view using a butyl column. Thus, a simulation was based on the fact that the descriptors found to affect the retardation of an analyte on reversed phase HPLC (i.e. physicochemical properties or structural characteristics) are those that are studied and seem to influence its drugability in a similar way. Actually, the mechanisms responsible for the retention of a substance on a lipophilic column against the aqueous mobile phase are those which determine its ability to cross cell membranes as well as its transfer in the blood stream.

Numerous reports that have been published describing the retention behavior of analytes on RP-HPLC columns provided useful information of such a mechanism [10]. Owing to the wide range of stationary phases and the variety of possible chromatographic systems the selection of a suitable starting point for method development is difficult. This effort gets more complicated if we take into account the fact that many physicochemical properties of compounds can potentially influence their retention behavior as well.

Nowadays, chromatography has been combined with different chemometric tools trying to explain molecular interactions between the mobile phase, the analyte and the stationary phase material [11–13]. This relationship between chromatographic parameters and molecular descriptors, characterizing the molecular structure of the analytes, is well known under the acronym QSRR (Quantitative Structure–Retention Relationships). QSRR is employed by analytical chemists to help them identify unknown members of individual classes of analytes with pharmacological, toxicological, environmental or chemical interest [14,15].

Table 1
List of descriptors related to the analytes and the mobile phase.

Descriptors related to the analytes	
Lipophilicity and hydrophilicity	Oil–water partition coefficient (log P), oil–water distribution coefficient (log D), aqueous solubility (solub), hydrophilic factor (H_y), organic carbon–water partition coefficient (KOC), Moriguchi octanol–water coeff. (MLOGP)
Constitutional	Molecular weight (M.W.), structural characteristics (number and type of rings, number of specific atoms, functional groups), aromatic ratio (ARR), unsaturation index (U_i)
Geometrical	Molecular volume (V_p), polar surface area (PSA), molecular surface area (Surf Ar), solvent accessible surface area (SASA)
Topological	Global topological charge index (JGT), harmonic oscillator model of aromaticity (HOMA), free rotatable bonds (FRB)
Electronic	Dipole moment (DM), polarizability (PLZ), hydrogen bonding parameters (HBD and HBA), HOMO and LUMO energies, refractivity (Refra)
Drug-relevant	Drug-likeness, drug-score
Descriptors related to the mobile phase	
Eluting power (SiO_2, Al_2O_3, C_{18}), dipole moment, polarizability, Hildebrand solubility parameter, P' Snyder constant, Solv. log P, Solv. HBD, viscosity	

Hence, our research has focused on two areas. The first was to explain the retention of an analyte on a C_4 column emphasizing on parameters which determine their behavior. The second was to explore how such a behavior model could coincide with drug-likeness. The software employed for modeling in this research was PLS to latent structures and ANNs.

PLS regression analysis is a commonly used statistical technique for performing multivariate calibration with the ability to analyse datasets with a larger number of predictor variables than objects and in situations where there is more than one dependent variable. ANNs have also been used as an alternative mathematical approach to clarify interactions between the probes, the mobile and the stationary phase in HPLC. They are massively parallel systems with a large number of interconnected simple processors [16–18].

The results showed that a C_4 column may function as an indirect tool for predicting the ability of a substance to permeate tissues in the human body. Indeed, the chromatographic behavior of the analytes on a C_4 column is found to be defined directly by a number of parameters (lipophilicity, polar surface area, refractivity, solubility in water, molar volume, ability to donate or accept H atoms) which also determine the drug transfer properties. Thus, we could say that the retention time of a potential drug on a C_4 column can be used to predict the degree of the drug transfer in the human body or its passive absorption.

2. Experimental

2.1. Software and calculations

2.1.1. Dataset build-up

Designing the dataset which contains 400 observations with 73 independent variables (X) and one depended variable (Y) expressed as $\log(t_{ratio})$ ($\log(t_{ratio}) = \log(t_{R(analyte)}/t_{R(benzene)})$) had been a rather difficult and extensive part of the present study. More specifically, the first column of the dataset contains the observations; refers to the analyte in question and the proportion of MeOH in the mobile phase mixture. The next part which is the main body of the dataset contains 73 columns (X variables) and it is further divided in two subparts. The first part includes the physicochemical properties which characterize the mobile phase and the second refers to the analytes including a number of their physicochemical or structural characteristics (Table 1).