Chapter 13
Human Oral Bioavailability Prediction of Four Kinds of Drugs

Aixia Yan
Beijing University of Chemical Technology, China

Zhi Wang
Beijing University of Chemical Technology, China

Jiaxuan Li
Beijing University of Chemical Technology, China

Meng Meng
Beijing University of Chemical Technology, China

ABSTRACT

In the development of drugs intended for oral use, good drug absorption and appropriate drug delivery are very important. Now the predictions for drug absorption and oral bioavailability follow similar approach: calculate molecular descriptors for molecules and build the prediction models. This approach works well for the prediction of compounds which cross a cell membrane from a region of high concentration to one of low concentration, but it does not work very well for the prediction of oral bioavailability, which represents the percentage of an oral dose which is able to produce a pharmacological activity. The models for bioavailability had limited predictability because there are a variety of pharmacokinetic factors influencing human oral bioavailability. Recent study has shown that good quantitative relationship could be obtained for subsets of drugs, such as those that have similar structure or the same pharmacological activity, or those that exhibit similar absorption and metabolism mechanisms. In this work, using MLR (Multiple Linear Regression) and SVM (Support Vector Machine), quantitative bioavail-

DOI: 10.4018/978-1-60960-064-8.ch013

ability prediction models were built for four kinds of drugs,which are Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Antagonists, Calcium Channel Blockers, Sodium and Potassium Channels Blockers and Quinolone Antimicrobial Agents. Explorations into subsets of compounds were performed and reliable prediction models were built for these four kinds of drugs. This work represents an exploration in predicting human oral bioavailability and could be used in other dataset of compounds with the same pharmacological activity.

INTRODUCTION

In drug development, a large amount of possible drug candidate molecules, called "lead compounds", may be predicted through drug design and computational modeling. However, about 95% of lead compounds have failed in the development stages, and 50% of these failures were shown to be due to unfavorable absorption, distribution, metabolism, and excretion (ADME) properties (Beresford et al., 2002). In the development of drugs intended for oral use, good drug absorption and appropriate drug delivery are very important (Hou & Xu, 2004).

Inadequate bioavailability is one of the main reasons that cause many promising drug candidates failed in clinical trials. Bioavailability represents the percentage of an oral dose which is able to produce a pharmacological activity, in other words, the fraction of the oral dose that reaches the arterial blood in an active form. Oral bioavailability is related to several factors, such as gastrointestinal transition and absorption, intestinal membrane permeation, and intestinal/hepatic first-pass metabolism. Moreover, during absorption, many researchers have suggested that gut wall Cytochrome P_{450} 3A4 and P-glycoprotein, the multidrug transporter, act in a concerted manner to control the absorption of their substrates (Van Asperen et al., 1998; Lampen et al., 1998; Hall et al., 1999). One possible method to maximize oral absorption would be to design a molecule that acts as a substrate of P-glycoprotein and CYP3A4 (Van de Waterbeemd, 2001).

Some researchers have summarized general molecular properties of drug molecules that may lead to good drug absorbency. Veber et al. (2002) reported studies on rat bioavailability data for 1100 drug candidates. It was found that drug molecules having fewer than 10 rotatable bonds and less than 140 $Å^2$ PSA (Polar Surface Area) (or a hydrogen bond count less than 12) usually showed more than 20% rat oral bioavailability. Lu et al. (2004) investigated the relationship between number of rotatable bonds and PSA for rat oral bioavailability of 434 molecules. Compared to Veber's work (Veber et al., 2002), Lu et al. reported that the prediction results were dependent on the calculation methods.

There are also quantitative studies in order to predict bioavailability. Hirono et al. (1994) reported a quantitative structure-bioavailability model for 188 noncongeneric organic drugs; the drugs were separated into three groups: nonaromatics, aromatics, and heteroaromatics. Based on each group's chemical and physical properties, a quantitative model was developed. Andrews et al. (2000) reported a QSAR (Quantitative Structure and Activity Relationship) model based on 591 compounds and 85 descriptors. The model achieved a good correlation (r^2=0.71), but overfitting problem may exist from the cross-validation result (q^2=0.58).

Yoshida et al. (2000) published a classification model for human oral bioavailability. This model can get a correct rate of 60% for the test group. Turner et al. (2003) reported a QSAR model for a dataset of 169 compounds using stepwise regression method. The regression model were built based on a training set including 159 compounds and validated by a test set including 10 compounds. Although the correlation coefficient of 0.72 was