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In silico model of drug permeability across sublingual mucosa

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ABSTRACT

The objective of this work was to develop an *in silico* model to predict the sublingual permeability of a drug based on physicochemical descriptors of a molecule. Fourteen model drugs with diverse physicochemical properties were selected for this study. Molecular volume, molecular weight, log *P*, log *D* (pH 6.8), pK_a, total polar surface area, hydrogen bond acceptors and donors (HBD), number of rotatable bonds, solubility (pH 6.8), and melting point were used as molecular descriptors. Apparent permeability coefficients (P_e) of drugs across porcine sublingual mucosa were determined experimentally. Multiple linear regression (MLR) was used to develop the model with permeability as the response variable and various descriptors as the predictive variables. Q^2, the cross-validated correlation coefficient, was used to assess the prediction ability of the model. MLR analysis showed that HBD and log *D* were the significant descriptors ($P < 0.05$, $Q^2 = 0.88$) in the sublingual permeability model. The resulting model is expressed as the following equation:

$$\log P_e = -5.08 - 0.24 \cdot \mathrm{HBD} + 0.53 \cdot \log D$$

An excellent fit with R^2 of 0.93 was obtained between experimental and predicted permeabilities. The analysis of contributions of molecular descriptors to sublingual permeability revealed the molecular structure basis of permeation across sublingual mucosa. In conclusion, an *in silico* model was developed to predict sublingual permeability of drugs using known descriptors for evaluating the feasibility of sublingual drug delivery.

1. Introduction

Sublingual delivery refers to a mode of drug delivery in which delivery systems are placed under the tongue and drugs are absorbed via the blood vessels in that region. As one of the oldest alternative routes of drug administration, sublingual route has several advantages, including bypassing the gastrointestinal and first pass hepatic elimination, easy to administer, and fast onset of action. This route of administration has been recognized for drug delivery over a century ago, but only a few drugs have been successfully delivered via this mode. The high cost of the *in vivo* studies is one of the reasons that limited the extensive investigation of the potential candidates to be delivered via the sublingual route. Therefore, *in vitro* studies can be a very useful tool to study the feasibility of delivering a compound across the sublingual mucosa. Indeed, *in vitro* permeation studies across the porcine sublingual mucosa are commonly used to study the permeability of different permeants across the sublingual mucosa.[1,2] The limitations associated with the *in vitro* permeation studies are the availability of fresh tissues and requirement of lengthy experimental time. These limitations prevent a formulation scientist from evaluating large number of drug candidates in

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high throughput screening or performing a quick estimation for the permeability of a potential candidate for sublingual delivery. An *in silico* model could circumvent these disadvantages of *in vitro* permeation studies and serve as a fast and cost effective approach in assessing the potential of sublingual delivery for a given compound or large number of compounds.

Over the last two decades, much attention has been paid to the development of *in silico* models based on known parameters to predict the physicochemical properties of drug like molecules, such as solubility, partition and permeability coefficients.

These *in silico* models are being used in the early stage of drug development to increase the efficiency of drug discovery and product development. Permeability of the drug is one of the most important properties that govern the absorption of drugs across different biological barriers. Because of the importance of permeability and quick return of estimated results by computational approaches, various *in silico* models are being explored for predicting drug permeation across the intestine, skin, buccal mucosa, and the blood brain barrier.[3–8]

Various physicochemical and molecular descriptors are linked to the permeability of a molecule across biological barriers. These descriptors include molecular volume (MV), molecular weight (MW), log *P* (octanol–water partition coefficient), log *D* (distribution coefficient at pH 6.8), pK_a, total polar surface area (TPSA), hydrogen bond acceptors (HBAs) and donors (HBDs), number of rotatable bonds (nRotBs), solubility (pH 6.8), and melting point (mp). Quantitative structure–permeability relationship (QSPR) method has been used to statistically relate different molecular descriptors to the permeability of drugs across biological barriers.[9] The relationship between a response variable and the multiple predictor variables can be determined by multiple linear regression (MLR), which has been used to establish the quantitative relationship between molecular descriptors and permeability of a drug or drug-like molecule. *In silico* prediction of permeation based on QSPR and using a multiple linear regression for biological barriers has been previously explored. For example, predictive models for transbuccal[6] and transdermal permeability can be found in the literature.[10] The physiological and biochemical composition varies between the different biological membranes resulting in different permeation barrier properties. The sublingual mucosa has its own characteristics and differs from skin and buccal mucosa in terms of the thickness of the epithelial layer, composition of lipids, and the level of keratinization.[11] Though both the sublingual and buccal mucosa are nonkeratinized oral mucosae, the sublingual mucosa is thinner and has lower total lipid content.[2] Hence, a separate model must be developed to describe the relationship between the drug permeability across the sublingual mucosa and physicochemical descriptors. Porcine sublingual mucosa was selected as the *in vitro* model for this study as it closely resembles the human sublingual mucosa in terms of histological characteristics, biochemical compositions, and permeability.[2] The aim of this study is to develop an *in silico* model that is capable of predicting the permeability of a drug across the porcine sublingual mucosa based on known chemical, structural, and physicochemical descriptors.

2. Materials and methods

2.1. Materials

The model drugs (caffeine, furosemide, naproxen, antipyrine, warfarin, propranolol hydrochloride, atenolol, pindolol, lidocaine, amitriptyline, bupivacaine hydrochloride, diltiazem and verapamil) were purchased from Sigma Chemicals (St. Louis, MO). Nimesulide was purchased from Alexis Biochemicals (Lausen, Switzerland). HPLC grade solvents were purchased from Fisher Scientific (Bridgewater, NJ). All other reagents were of analytical grade and used as received.

2.2. Selection of drugs and descriptors

The model drugs selected were structurally diverse, covering a wide range of physicochemical properties, and stable under the experimental pH conditions (Table 1). The model drugs used in this study included 4 acidic (furosemide, naproxen, warfarin and nimesulide), 8 basic (lidocaine, propranolol, atenolol, bupivacaine, verapamil, diltiazem, amitriptyline and pindolol), and 2 neutral (caffeine and antipyrine) molecules. The descriptors selected for this study were MV, MW, log *P*, log *D*, pK_a, TPSA, HBA, HBD, nRotB, solubility (at pH 6.8), and mp. Solubility of these compounds was determined experimentally using the shake-flask method as described in the following section. The values of log *P*, log *D*, pK_a and mp were obtained from the literature. The remaining descriptors were calculated using Molinspiration.[12]

2.3. Determination of solubility

Excess amount of drug was added to the screw cap glass vials containing 1 mL of isotonic phosphate buffer solution (pH 6.8). The contents were then gently shaken in a 37 °C walk-in incubator for approximately 24 h or until the concentration reached equilibrium. The pH in the vial was adjusted to pH 6.8 using 0.1 N HCl or NaOH before and after reaching equilibrium. After filtration through a 0.2 μm filter (Fisherbrand®, Fisher Scientific, Pittsburgh, PA) and dilution at 37 °C, the samples were quantified by using HPLC. All experiments were conducted in triplicate.

2.4. Tissue preparation

Porcine sublingual mucosa from the floor of mouth region was obtained immediately after pigs were slaughtered from Long Ranch (Manteca, CA) and stored in phosphate buffered saline (pH 7.4) until further use. The underlying tissue was removed using surgical scissors to obtain a constant tissue thickness around 500 ± 50 μm. The tissues were used for permeation studies within 2 h after slaughtering of the animals.

2.5. Permeation study

Permeation studies were conducted using porcine sublingual mucosa at 37 °C with side-by-side diffusion cells (PermeGear Inc., Riegelsville, PA). The side-by-side diffusion cells had a cross sectional area of 0.68 cm^2 and a volume of 3.5 mL for