APPLICATIONS OF MECHANISTIC MODELING AND SIMULATIONS IN COMPOUND AND DOSAGE FORMS SELECTIONS

by

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ABSTRACT

Physiologically based pharmacokinetic (PBPK) modeling and simulation techniques have been adopted in the pharmaceutical industry to aid in compound selection and dosage form development in recent years. This is a result of easier access to computers and advanced knowledge of species physiology. The mechanistic modeling approach utilizes the compound's physiochemical properties, formulation related factors, route of administration and species physiology in order to predict the concentration-time profile in plasma and tissues. In this dissertation, different predictive and mechanistic models (ADMET®, ACAT®, OCCAT® and metabolite tracking approaches in Gastroplus®) were applied to simulate the concentration time profiles of various compounds.

We applied mechanistic modeling techniques to predict the concentration-time profiles of curcumin and its analogs in order to identify potential drug candidates for future preclinical and clinical studies. An in silico based absorption, distribution, metabolism, excretion and toxicity (ADMET) prediction tool in Gastroplus® (version 8.5, Simulations Plus, Inc., Lancaster, CA, USA) was utilized. For this purpose, we performed model qualifications by comparing the simulated pharmacokinetics data of pure curcumin and compared to the observed data from literature. Curcumin analogues and other compounds that showed higher potential for oral absorption were selected for further study. In our second project, we evaluated the predictability of the new oral

cavity compartmental absorption and transit (OCCAT®) model by utilizing commercial buccal and sublingual (fentanyl, buprenorphine, nicotine, miconazole, rizaptriptan and testosterone) formulations. The new OCCAT™ model was able to simulate the PK parameters/profiles of published multiple doses of buccal and sublingual drugs administered to healthy and patient population. Varying degrees of bias was observed for all the simulated PK parameter values as compared to the published parameter values for the compounds tested based on the computed % predictability error.

Although, the new OCCAT model can be used to support the formulation development and regulatory decisions, its applicability and the predictability for specific drug needs to be adequately qualified. In another project, we conducted mechanistic analysis to track the metabolites of tenofovir disoproxil fumarate (TDF) using PBPK modeling. The main goal of the project was to track the pharmacokinetics of a prodrug, tenofovir disoproxil fumarate (TDF) and its parent drug, tenofovir. Finally, the mechanistic modeling approach was utilized to simulate the disposition, including potential metabolic pathways of 4-benzylpiperidine based on its predicted physiochemical properties.

CHAPTER 1

INTRODUCTION

The high cost of drug discovery process and the low success in drug approval rate defined as a "growing crises" by the FDA have increased over the years (Zhang et al 2006). These crises have demanded for new approaches to improve efficiency in developing safe and efficacious drugs. Model-based drug development (MBDD) has been considered as a great tool to attenuate these difficulties. MBDD is a quantitative technique which comprises utilizing exposure-response models, pharmacometric models and disease models to support drug discovery process. The main focus of MBDD is to construct mathematical models in order to define the input-output relationship within disease and drug models for knowledge assessments and to support decision making process. One example of MBDD approaches is the utilization of physiologically based pharmacokinetic (PBPK).

The United States Food and Drug Administration (USFDA) and other regulatory agencies have encouraged the utility of physiologically based pharmacokinetic (PBPK) modeling and simulation methodologies in compound and dosage form selection and development (Zhao, Zhang et al. 2011; Wagner, Zhao et al. 2015). PBPK modeling and simulation is a mechanistic approach which can aid in simulating the pharmacokinetics

(PK) of drugs in different species (human and animals), including the effect of intrinsic and extrinsic properties relating to drug's absorption, distribution, metabolism, and excretion (ADME) (Zhang et al. 2011). The PBPK modeling and simulation technique is mainly based on the physiochemical properties of the drug, the formulation, species physiology and route of administration. Similar to empirical compartmental models, PBPK models are characterized by differential equations with specific species physiology for parameterization based on mechanistic structure in order to simulate the PK of a drug. PBPK models depend on drug model and system components. The drug dependent components include the physicochemical properties such as the solubility, permeability, log P and pKa. The system components include organ weight and blood flows to different tissues.

In building the PBPK models, intrinsic (such as age, race, disease state, gender, genetics and pregnancy/lactation) and extrinsic factors (such as drug-drug interactions, medical practices, diet, smoking and alcohol) are considered. The components are separated where mechanistic models are built to investigate the impact of intrinsic and extrinsic factors on the system. Recently, due to the simulation power of this mechanistic modeling methodology, many pharmaceutical companies have adopted the PBPK approach to assist with formulations and dosage form selections in recent years (Peters, Ungell et al. 2009). In this dissertation, we utilized mechanistic modeling methods to understand physicochemical properties, oral absorption potential, parent-metabolite tracking of a prodrug, prediction of buccal and sublingual absorption of drugs and prediction of metabolic liability for various drug compounds. We applied the advanced compartmental absorption and transit (ACAT) module to predict the PK profile of

curcumin and its analogs. Different curcumin analogs were designed by Dr. Bowen's group at the Center for Drug Design, Mercer University College of Pharmacy. The main objective was to identify the curcumin analogs which may be potential oncology drug candidates for future preclinical and clinical studies based on absorption, distribution, metabolism, excretion and toxicity (ADMET) predictions using Gastroplus®. The physicochemical properties such as pKa, log D, solubility and permeability were computed by ADMET predictor® module for the analogs of curcumin. The intrinsic clearance for the curcumin analogs were unknown and bioavailability could not be determined after oral administration. However, the fraction absorbed (Fa %) for each analogs of curcumin was estimated.

This activity was qualified by comparing simulated PK profile of curcumin to published data. We utilized metabolite tracking approach to predict tenofovir prodrug concentrations in plasma. TDF was an ester prodrug of tenofovir and get cleaved to tenofovir in plasma. The half-life of this conversion was very rapid (<5 min) as reported in the FDA (www.accessdata.fda.gov) drug label and no prodrug concentrations had been reported in plasma to the best of our knowledge. Therefore, we utilized ACAT model in Gastroplus to predict the oral absorption of TDF into plasma and using metabolite tracking methods, conversion to tenofovir and pharmacokinetic profiles of both TDF and TFV were simulated using Gastroplus®.

We tested the predictability of the new oral cavity compartmental absorption and transit (OCCAT) model to predict PK profiles of various drug molecules that are commercially available as buccal/sublingual formulations and compare to the published data. Pharmacokinetic data from commercial buccal/sublingual formulations of fentanyl,

buprenorphine, nicotine, nitroglycerine, testosterone and rizatriptan were applied for this evaluation.

Furthermore, we applied bottom-up modeling approach to predict the concentration-time profiles of 4-benzylpiperidine. This medication is currently under pre-clinical study as potential medication intervention for the treatment of cocaine addiction. In a previous study, trained rhesus monkeys discriminated between 0.4 mg/kg cocaine and saline when administered intramuscularly with monoamine releasers producing a dose- and time-dependent substitution for cocaine (Negus, Baumann et al. 2009). The study showed that 4-benzylpiperidine had the most rapid onset compared to other tested drugs such as phenmetrazine and benzylpiperazine. (Negus et al 2009). While 4-benzylpiperidine showed promise, there are currently no publications addressing the absorption, distribution, metabolism and excretion (ADME).

The specific aims of this dissertation were:

1. To predict the oral absorption of curcumin and its analogs using Gastroplus®
2. To track kinetics of tenofovir and its prodrug using metabolite module in Gastroplus®
3. To test the predictability of the new oral cavity compartmental absorption and transit (OCCAT®) model using commercial buccal/sublingual formulations.
4. To apply physiologically based pharmacokinetic (PBPK) modeling approach to simulate the pharmacokinetic and profile of 4-benzylpiperidine using both the oral and transdermal

CHAPTER 2

LITERATURE REVIEW

The attrition rate during drug development processes still remains a challenge in the pharmaceutical industries over a many years (Zhang et.al 2008). It is mostly crucial to understand the desirable and undesirable effects of a drug as related to its concentration at various sites of action, usually related to the blood or tissue concentration of the drug (Peters 2012). The desired dose that produces blood and tissue concentrations is determined by the absorption, distribution, metabolism, and excretion (ADME) properties of the drug. Modeling and simulation have been adopted as a useful tool to support drug discovery and formulation developments. The approach of model-based drug development (MBDD) is an outcome of "learn-confirm paradigm" concept postulated by Lewis Sheiner in 1997 (Sheiner et al 1997).

There are several mathematical and statistical models utilized based on the nature of drug development question. The models utilized in this project include quantitative structure-activity relationships (QSAR) models, pharmacokinetics and pharmacodynamics (PK/PD) models, various physiologically-based pharmacokinetic (PBPK) models such as advanced compartmental absorption and transit (ACAT) model and oral cavity compartmental absorption and transit (OCCAT) model. Quantitative structure-activity relationships (QSAR)

QSAR models have been utilized as an advance computational predictive tools for simulating the physicochemical and metabolic properties of compounds based on their chemical structures in drug discovery for many years (Cherkasov, Muratov et al. 2014). The QSAR model utilizes chemometric techniques in order to determine statistical correlation for compounds based on their structure design and functional units (Peters 2012; Cherkasov, Muratov et al. 2014). Their predictive capabilities are dependent on specific training set of the chemical space of physicochemical properties and biological activities based on chemical structures of the compounds incorporated. Since the nineteenth century, many QSAR techniques have been reported in literature. For example, Crum-Brown and Fraser et al 1868 applied the QSAR methodology to determine if there is a correlation between chemical composition and physiological characteristics of chemical substance.

The main emphasis of their work was on the physiological effects of salts derived from ammonium bases such as Strychnia, Brucia, Thebaia, Codeia, Morphia, and Nicotia. Similarly, Mills et al 1884 simulated the boiling and melting points for compounds in the same series with a developed QSAR model. The results were accurate with a degree (C or F) margin. Furthermore, Heritage and Lowis et al. 1997 utilized QSAR approach along with new technique called Hologram built in specialized fragment fingerprint for simulating biological properties of compounds. The new Hologram utilized bin occupancies as atomic descriptors for predicting the best architectures for compoundincorporated. The methodology have been applied for simulating the nonproprietary data of compounds such as $\log P_{ow}$, in both explanatory and predictive modes.

This approach has been utilized in other research projects for demonstrating its utility to a wide range of data from biological systems. Currently, QSAR techniques are mostly applicable in the pharmaceutical industries for predicting biological properties of untested and optimize lead compounds.

Pharmacokinetics and Pharmacodynamics (PK/PD) models

PK/PD models are applied in all stages of drug discovery (Zhao, Zhang et al. 2011). PK models are mainly applied to predict the compound's absorption, distribution, metabolism and excretion in the body. PK models utilize set of parameters (CL, Vd, Ka and K) to characterize drug disposition in the body (Peters, Ungell et al. 2009). The complex drug disposition in body is generalized into one, two and three compartments models regarding the plasma as the central compartment. The PK model structures as well as the estimated parameter are derived by data driven approach. PK models are linked with the PD models to describe exposure dose-response relationship (Duwal, Schütte et al. 2012).

It is mostly applied in conjunction with allometric scaling and physiological models in order to extrapolate the results from animal studies to man (Negus, Baumann et al. 2009). Simulated dose proportionality studies can also be performed using the PK/PD models. Pharmacokinetic parameters (CL, Vd, Ka and K) are generally estimated by nonlinear regression programs by fitting different compartment models to the observed data. The best fit and final models are selected based on defined statistical criterion (Xia, Yang et al. 2015).

Physiologically-based pharmacokinetic (PBPK) models

PBPK models are mechanistic approach to predict the concentration-time profiles both in plasma and in tissues. The model applies differential equations with specific species physiological parameters as well as physicochemical parameters to evaluate the PK of a drug when administered through specific route. The models trace the schematic complexity of drug transport into realistic physiological compartments such as the tissues, organs and organ systems (Jones and Rowland-Yeo 2013). In other words, PBPK models deal with the specific anatomy and physiology of species involved not depending on the drug information or data. Although, PBPK model concepts have been known earlier but they have not been applied due lack of unavailability in computing resources and the existence physiological data (Peters 2012; Jones and Rowland-Yeo 2013). PBPK models depend on drug model and system components. The drug depended components include the physicochemical properties such as the solubility, permeability, log P and pKa. The system components include organ weight and blood flows into different tissues.

Earlier in 1937 and 1971, Teorell and Bischoff first applied the techniques to characterize the multi-compartmental PK model describe the PK of a drug by incorporating physiological parameters analysis using physiological parameters (Teorell 1937; Bischoff, Dedrick et al. 1971; Peters 2012; Jones and Rowland-Yeo 2013). Professor Teorell derived differential equations in order to characterize drug's pharmacokinetic properties in plasma and tissues. His work had been considered as rudimentary one but the ability to derive formulas to describe the concentration- time profiles in blood and tissues cement the fundamentals of PBPK models. Previously,