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A physiologically-based diffusion-compartment model for transdermal administration – The melatonin case study

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ABSTRACT

There is a significant hype in the medical sector for the transdermal administration of drugs as it allows achieving a combination of multiple advantages: non-invasive procedure, pain avoidance, no first-pass hepatic metabolism, and induction of sustained plasma levels. This paper proposes a model for the study and prediction of drug transport through skin and the following distribution to human body. This is achieved by an innovative combination of the physiologically-based compartmental approach with Fick's laws of diffusion. The skin model features three strata: stratum corneum, viable epidermis, and dermis, which have a major impact on the absorption, distribution, and metabolism of transdermal drugs. The combined model accounts for skin transport via diffusion equations, and absorption and distribution in the rest of the body (*i.e.* organs/tissues) via material balances on homogeneous compartments. Experimental data of transdermal melatonin allow validation. Main applications are optimization of the dosage and study of skin transport.

1. Introduction

Recent years have seen a rising interest in transdermal (TD) delivery as an efficient route for drug administration. Fig. 1 shows the number of transdermal drugs approved by Food and Drug Administration (FDA, USA) since 1996 (FDA Orange Book, 2017).

This interest arises from some advantages that transdermal delivery exhibits if compared to other routes of administration (*e.g.*, enteral and parenteral). From a practical point of view, the most evident appeal of percutaneous (*i.e.* TD) delivery consists of combining a positive patient compliance with ease of administration. In fact, TD delivery does not necessarily require specialized medical staff and is non-invasive. From the pharmacokinetic point of view, the main advantage is that the drug is directly administered to the systemic circulation. This means avoiding the first-pass hepatic metabolism, which is the main cause for the characteristic low bioavailability resulting from oral route, although some minor metabolism or binding to cellular components may occur in the skin (Prausnitz and Langer, 2008). Therefore, skin permeation is an attractive alternative whenever factors such as gastrointestinal pH, drug interaction with food, and liver diseases prevent oral administration (Mali, 2015). Furthermore, TD delivery ensures no risks of sudden fluctuations or peaks of the drug concentration in plasma, which translates into sustained levels and reduced side effects.

On the other hand, TD application comes with high inter-patient variability related to age, gender, physical characteristics, genetic factors, and living habits (Sandby-Moller et al., 2003), and is not suitable for all drugs. In fact, some physicochemical characteristics such as molecular weight and solubility may have a significant impact on the pharmacokinetics, and therefore must be taken into account when selecting the route of administration. In addition, slow absorption is another undesired pharmacokinetic trait that is intrinsic to TD administration.

In order to simulate the transdermal administration route of drugs and their distribution, metabolism, and excretion (*i.e.* ADME processes) within the human body, we developed a physiologically-based diffusion-compartment pharmacokinetic (PB-DCPK) model. This dynamic model can be useful for the assessment of the optimal dosage, and in general for the development of drugs/substances for TD delivery, evaluation of toxicity/positive effects, and analysis of skin transport mechanisms.

Some authors describe skin transport by assuming stationary conditions, as their only goal is to either analyze or explain specific experimental data (Anissimov et al., 2013). Higaki et al. (2002), and Singh and Roberts (1994) developed compartment models that allow describing drugs pharmacokinetics in the skin layers, in the

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List of acronyms and abbreviations

ADME	Absorption, Distribution, Metabolism, and Elimination
DCPK	Diffusion-Compartment PharmacoKinetics
DE	DErmis
FDA	Food and Drug Administration
ICU	Intensive Care Unit
ODE	Ordinary Differential Equations
PB	Physiologically-Based
PBDCPK	Physiologically-Based Diffusion-Compartment PharmacoKinetics
PDE	Partial Differential Equations
SC	Stratum Corneum
TD	TransDermal
TDD	TransDermal Device
VE	Viable Epidermis

systemic circulation, and in some tissues of the body, *e.g.*, muscles, adipose tissue. However, they only focused on some specific tissues and did not consider the parameters governing skin transport as depending on skin depth. In fact, skin was described as a bi-layer homogenous concentration compartment. Furthermore, they did not consider the possibility of any occurring metabolism or binding.

The idea of describing skin transport as a function of both time and space is not new. In fact, Marquez-Lago et al. (2010) proposed a noteworthy 3D porous media model of the stratum corneum (*i.e.* the most superficial layer of the skin epidermis) but did not investigate the distribution in the whole human body. Kretsos et al. (2004) employed diffusion equations focused exclusively on skin penetration. This manuscript attempts to combine two aspects investigated in the literature: (i) the physiologically oriented approach towards skin transport and (ii) the attention to ADME processes within the rest of the body.

The proposed model is applied to the simulation and prediction of TD melatonin pharmacokinetics. Melatonin is a biogenic amine that is commonly found in animals, plants, and microbes. In mammals, melatonin is the main substance produced by the pineal gland (Brzezinski, 1997). In humans the endogenous production follows the day-night cycle (*aka* "circadian rhythm"), with a baseline level of about 10 pg/mL during the day. Melatonin concentration starts increasing with the onset of darkness and peaks (60 – 100 pg/mL) at 2–4 AM. Afterwards, the concentration gradually decreases and stabilizes on the daily baseline value. Several researchers are nowadays interested in melatonin numerous benefits on the human body. In humans, melatonin is regularly employed as a treatment for sleep disturbances (*e.g.*, jet lag, night-shift workers, people suffering from insomnia) (Brzezinski, 1997). Melatonin proved to benefit patients suffering from mood disorders (*e.g.*, depression, seasonal affective disorder), and neurological pathologies (*e.g.*, Alzheimer's disease) (Hickie and Rogers, 2011; Srinivasan et al., 2006). There is some evidence of antiproliferative effects in cancer and anti-aging effects through anti-oxidant and free-radical scavenging mechanisms (Karbownik et al., 2001; Kleszczynski and Fischer, 2012; Mehta and Kaur, 2014; Srinivasan et al., 2008). A disruption of the circadian rhythm of melatonin can be observed in intensive care unit (ICU) patients (Mistraletti et al., 2010). ICU stay is thought to have a series of negative effects on patients' sleep and, in general, on their health status. As ICU patients' conditions can be improved by the melatonin anti-oxidant, immunoregulatory, and sleep regulatory properties, it is possible to administer exogenous melatonin in order to restore the endogenous production rhythm. Indeed, it is desirable that the pharmacokinetics of exogenous melatonin mimics the sustained endogenous profile. Therefore, for this specific case, the previously reported advantages of the transdermal administration are convenient, and the slow absorption becomes actually a useful characteristic, despite being a drawback for most drugs. Furthermore, melatonin physicochemical characteristics (*i.e.* low molecular weight and lipophilicity) increase the probability of crossing the skin barrier.

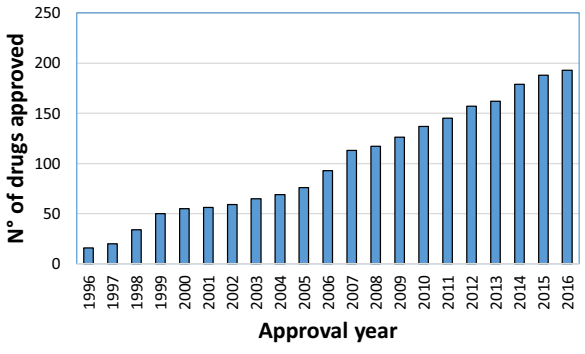

Fig. 1. Cumulative amount of transdermal drugs approved by Food and Drug Administration (FDA) since 1996 (FDA Orange Book, 2017).

2. Methods

2.1. Skin histology and transdermal devices

An in-depth understanding of human anatomy and physiology allows driving the engineers' modeling activity of the transdermal administration route and correlated PBDCPK. Skin is the means for transdermal release of drugs and deserves a comprehensive insight to recognize the main mass transfer phenomena that rule their percutaneous delivery to the systemic blood flow. Human skin is the largest organ of the body and consists of three main layers: epidermis, dermis, and hypodermis (*i.e.* subcutaneous tissue). Epidermis is the thinnest and most superficial layer, and the most important for its protective function. Dermis (thickness 1.5 – 4 mm, Anissimov et al. (2013)) is thicker and consists of connective tissue. It contains nerves, sweat glands, hair follicles, and blood and lymphatic vessels. Hypodermis mainly consists of adipose tissue and sweat glands. Its main function is to support epidermis and dermis.

From the modeling point of view and according to the skin physiology, it is more consistent to separately consider two sublayers of the epidermis: stratum corneum (*SC*) (average thickness of fore-arms, face, abdomen 10 – 30 μm, (Anissimov et al., 2013) and viable epidermis (*VE*) (average thickness of fore-arms, face, and abdomen 50 – 100 μm, (Anissimov et al., 2013). In fact, *SC* is the outermost stratum and consists of a keratinized tissue, which comprises low hydrated and highly dense cell layers. For this reason, it is the most difficult to penetrate. *VE* is a more aqueous phase, and can be site of metabolism, binding, and active transport. In some models, it is merged with dermis, which is an aqueous medium as well (Jepps et al., 2013).

Differently from topical delivery, the goal of transdermal (or percutaneous) delivery is to pass the skin barrier and enter systemic circulation. In this case, drugs are directly applied on the skin in gel or transdermal devices (TDDs), *i.e.* patches. Hence, the amount of drug and the surface of the skin area on which the drug is applied are key parameters. Patches contain therapeutic amounts of drugs, and mainly consist of a backing for protection from the external environment and a polymeric matrix that controls the drug release. Patches often contain some penetration enhancement agents (*e.g.*, alcohols) to improve skin penetration of the drug, and