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Research Paper

Disease specific modeling: Simulation of the pharmacokinetics of meloxicam and ibuprofen in disease state vs. healthy conditions

May Almukainzi, Fakhreddin Jamali, Ali Aghazadeh-Habashi, Raimar Löbenberg *

Faculty of Pharmacy & Pharmaceutical Science, University of Alberta, Edmonton, AB, Canada

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ABSTRACT

Purpose: Studies have shown altered pharmacokinetic patterns (PK) in patient suffering from acute pain. Thus, we aimed to simulate pharmacokinetics of meloxicam and ibuprofen in pain and pain-free states using a physiological based software program to identify the underlining mechanistic changes for the observed differences.

Method: Published *in vivo* data of meloxicam and ibuprofen were used for the simulations. Two drug formulations were studied: a fast dissolving (FD) and regular release (RR) tablet formulation. The oral bioavailability was compared between these formulations in vagally suppressed rats (gastric dysfunction) and a control group. For ibuprofen additional human data of a control and post dental surgery group were used. All simulations were performed using GastroPlus™. The *in vivo* drug release and PK of all formulations were estimated for both drugs using the software's immediate release (IR) or gastric release (GR) models.

Result: For meloxicam, the IR model predicted the *in vivo* absorption in the control group after administration of the FD and RR formulations. When gastric dysfunction was induced, the IR model did not predict absorption while the GR model did for both formulations, FD and RR. For ibuprofen, the predictions were also very close for both formulations, using the IR model for the control group and the GR model for the vagally suppressed condition in rats and humans.

Conclusions: Gastric control of the drug release in pain/disease state was identified as the major factor causing the observed differences in the pharmacokinetics. Computer simulations of disease states can be employed to optimize drug release from dosage forms to overcome the reported shortfalls in the drug absorption.

1. Introduction

Oral formulations are the most commonly administered dosage forms. They need to undergo disintegration and dissolution for the active ingredient to be absorbed. There are several factors that impact drug dissolution such as the physicochemical properties of the drug and the host's physiological environment. For instance, gastrointestinal motility, in general, and gastric emptying, in particular, have a significant role in the rate and onset of drug absorption. These physiological factors could be altered significantly under abnormal (disease) conditions [1,2]. Delayed gastric emptying can be found in patients with post abdominal and dental surgery, which is usually associated with pain [1,3–5]. Studies have suggested that drug absorption patterns of the nonsteroidal anti-inflammatory drugs (NSAIDs) are altered in pain suffering patents [4,6]. It has also been found that the drug absorption is less affected by gastric motility when a drug is administered as fast dissolving formulation [4,6,7].

Despite the complexity of the drug absorption process, computer simulations that incorporate physiologically based factors have proven to be useful in predicting pharmacokinetic (PK) pattern under different physiological conditions, such as fasted and fed state [8–10]. The Compartmental Absorption and Transit (CAT) model is the first physiologically based absorption model used in a commercial software [11]. The basic assumption of the

Abbreviations: ACAT, Advanced Compartmental Absorption and Transit; BCS, biopharmaceutical drug classification system; CAT, Compartmental Absorption and Transit; FD, fast dissolving; GR, gastric release; IR, immediate release; IVIVC, *in vivo/in vitro* correlations; MAE, mean absolute error; NSAID, nonsteroidal anti-inflammatory drug; Obs, observed; PSA, parameter sensitivity analysis; PK, pharmacokinetics; Pre, predicted; RR, regular release; RMSE, root mean squared error; f2, similarity factor.

* Corresponding author. Tel.: +1 780 492 1255; fax: +1 780 492 1217.
E-mail address: raimar.loebenberg@ualberta.ca (R. Löbenberg).

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CAT model is that a drug is passing through the gastrointestinal tract and the dissolved fraction is absorbed in each compartment into the portal vein. This approach takes into account three factors [12]. The first one represents the physicochemical factors such as a drug solubility and p*Ka*. The second is related to physiological factors, for example, the pH in each section of the gut and gastric emptying. The last factor is interrelated to formulation characteristics such as surface area and drug particle size. Therefore, this approach can be considered as a powerful tool to simulate *in vivo* drug absorption. The model has been fine-tuned over the years to accurately account for the observed human small intestinal physiological parameters [12]. The Advanced-CAT (ACAT) model assumes that a drug passes through 18 compartments (stomach, seven compartments for the small intestine, colon and nine enterocyte compartments) see Fig. 1; three different drug states are differentiated (unreleased, undissolved, and dissolved). The amount of drug absorbed is the sum of the amounts being absorbed/exsorpted (secretion from enterocytes to lumen) for each compartment. The ACAT model includes the possibility to define regionally dependent absorption, pH-dependent solubility, precipitation, influx and efflux transporters, and gut metabolism. Compartment properties are set by default to published experimental data, accounting for pH, volume, and permeability characteristics in the corresponding intestinal region [11]. Transit of a drug material between the compartments is modeled as a first order process that accounts for transit time in each compartment based on the physiological value for the corresponding region. The theoretical basis and mathematical description of the ACAT model are described further in detail by Yu and Agoram et al. [11,12].

Different studies provided evidence that computer simulations are powerful tools to estimate drug absorption in healthy humans [8,9]. Other studies have demonstrated the application of computer simulations in establishing *in vivo/in vitro* correlations (IVIVC) [13,14]. Therefore, regulatory agencies such as FDA, and EMA recognized and utilized *in silico* modeling in decision making [15,16]. Recent studies have expanded the use of these simulations to disease states where physiological factors might have changed [17,18]. These attempts in diseases modeling aimed to provide mechanistic insights to understand the physiological changes, and hence, the possible outcomes in different disease conditions. Pain is a very common and happens to almost everyone at least once in his/her life. Ibuprofen and meloxicam are NSAIDs that are widely used to treat pain.

We hypothesized that one can predict the PK pattern of drugs under normal and gastric dysfunctional conditions using a suitable disease model with gastric control of the drug release. We, therefore, used computer simulations to predict the PK of meloxicam in normal and gastric dysfunction conditions and ibuprofen in pain and pain-free states.

2. Methods

For meloxicam, published data using normal and gastric dysfunctional rats were used [6] to simulate the observed data sets. Published ibuprofen pharmacokinetic data under healthy and post dental surgery pain conditions in humans as well as those in normal healthy rats and rats with gastric dysfunction were used to simulate the reported data [3,4]. In both, meloxicam and ibuprofen studies, two formulations had been used: a fast dissolving (FD) and a regular release (RR) formulation. The pharmacokinetics of both drugs was simulated under two conditions stated above. All

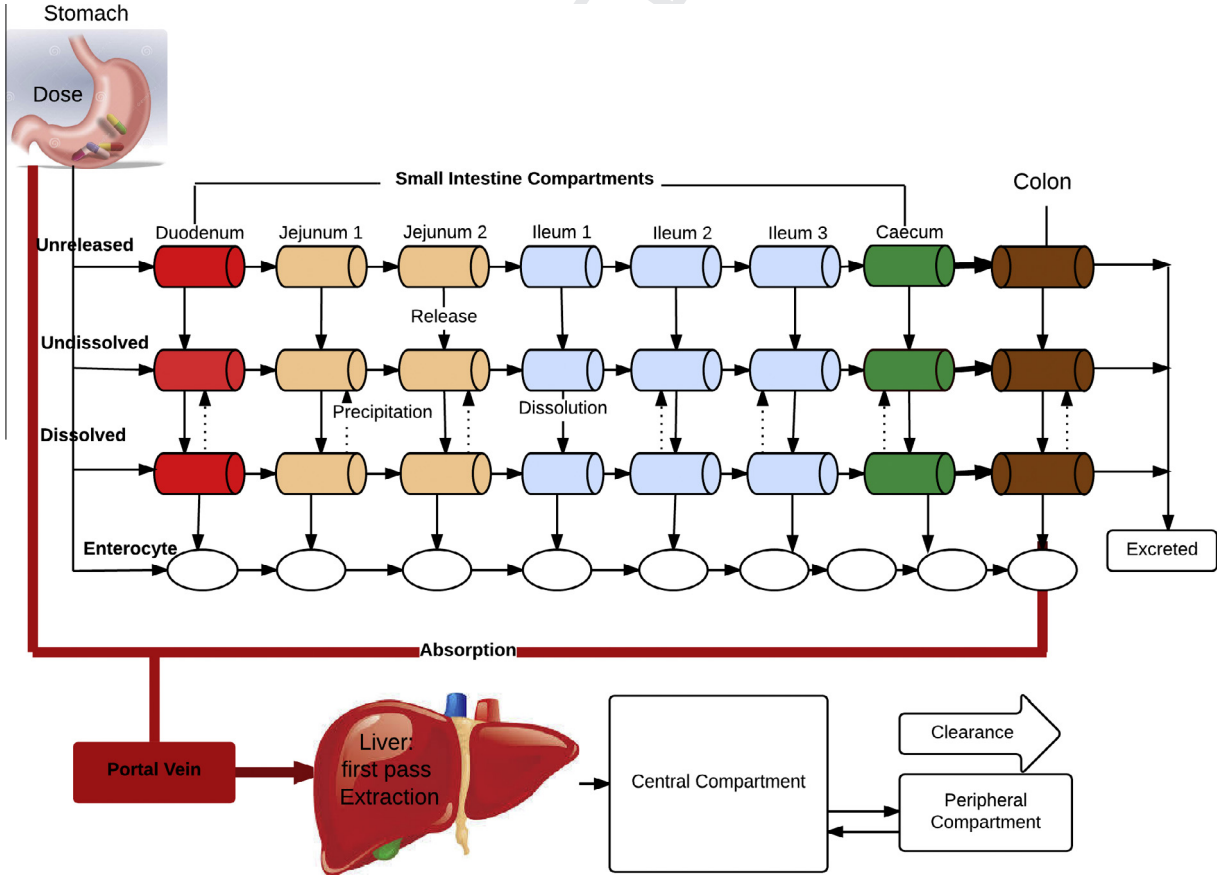

Fig. 1. ACAT model in GastroPlus™.

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