DOI: 10.25205/978-5-4437-1843-9-290

MODELING OF THE SPATIOTEMPORAL DISTRIBUTION OF MEDICINES

F. M. Etezova[1], Y. R. Nartsissov[1,2], E. V. Mashkovtseva[1,3]

[1] *Institute of Cytochemistry and Molecular Pharmacology, Moscow*
[2] *Biomedical Research Group, BiDiPharma GmbH, Siek, Germany*
[3] *Pirogov Russian National Research Medical University, Moscow*

✉ etezova@icmph.org

Abstract

The assessment and prediction of conjugated and toxic metabolite concentrations within biological systems represents a critical component of pharmacokinetic investigations. This task is crucial, as many pharmacological agents can be transformed into toxic metabolites. Our goal was to develop a comprehensive, multicompartmental model that provides accurate quantitative description of metabolite disposition, taking into account the detailed inter-compartmental transfer of substances throughout the physiological system.

The developed model represents a multi-compartmental system consisting of seven interconnected compartments forming a closed system of vessels and organs. In this study, the intestines and liver are considered as discrete compartments, as they are the most critical for describing the process of drug dissolution and metabolism when administered orally. The portal vein and artery, as well as the hepatic vein, are assumed as separate compartments to ensure precise simulation of hepatic hemodynamics.

This model describes how a test substance is distributed throughout the body after oral administration, taking into account the first-pass metabolic effects. Inter-compartmental transport kinetics is determined by hemodynamic processes, diffusion, and convection [1, 2]. We considered paracetamol as a test substance due to its well-characterized hepatotoxic properties.

The developed model is consistent with the known anatomical and physiological parameters and has been validated in terms of hemodynamic characteristics such as blood flow velocity in individual compartments of the model and complete circulatory transit time. It reproduces the pharmacokinetic characteristics of a test substance. The profile of paracetamol concentrations and its metabolites across various dosage regimens demonstrates the possibility of estimating the dose of acetaminophen based circulating metabolite levels over extended time periods, as well as predicting the concentration of toxic metabolites at various doses. However, the model is versatile, as it can account for the consumption and elimination of any substance by the model's compartments, and also allows for the inclusion of any number of enzymes. This enables the description of biochemical processes of any complexity that follow enzymatic kinetics.

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