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Research Article

# A System Approach to Development Mathematical Models of Ethanol Behavior in Heathy S Fasting Fang Subjects

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## Abstract

Numerous workers described investigations of ethanol pharmacokinetics [1-7]. Therefore, the present study was not aimed at investigating ethanol pharmacokinetics. Instead, the present study was aimed at providing further illustrative examples of a successful use of computational and modeling tools from system engineering in pharmacokinetic investigations. The previous example showing the successful use of modeling tools from system engineering in pharmacokinetic investigations can be find in the full-text articles that are available free of charge on the following website of the author: http://www.uef.sav.sk/durisova.htm

***Keywords:*** *Oral Administration; Dynamic System; Mathematical Model*

## Introduction

Numerous studies published previously described investigations of the pharmacokinetic behavior of ethanol, using traditional pharmacokinetic modeling methods [1-9].

The study by Wilkinson., *et al.* 1977 [1] described an investigation of pharmacokinetics of orally administered ethanol to normal healthy adult fasting subjects. The present study is a free continuation of the study by Wilkinson., *et al*. 1977, published in June 1977 Issue of the Journal Pharmacokinetics and Biopharmaceutics, therefore the data available in the study by Wilkinson., *et al*. 1977 were used. An advanced modeling method implemented in the computer program CTDB [8-25] was employed for modeling purposes. The goal of the present study was to provide further illustrative examples of a successful use of computational and modeling tools from the theory of dynamic systems in pharmacokinetic investigations.

In the preparation of illustrative examples, the data available in the study by Wilkinson., *et al*. 1977 [1], and an advanced modeling method implemented in the computer program named CTDB were employed [8].

In addition, a simplifying assumption was made i.e. an assumption that the pharmacokinetic behavior of ethanol in fasting subjects [1] can be approximately described by linear mathematical models.

An example of a successful use of the computer CTDB [12] can be find in the study by Dedík., *et al.* published in September 2007 Issue of the Journal Diabetes Research and Clinical Practice
http://www.uef.sav.sk/advanced_files/OGTT-2007.pdf

The mathematical models developed in the present study, successfully described mean capillary ethanol concentration-time profiles of the fasting subjects participating in the study by Wilkinson., *et al*. 1977 [1] and in the present study.

## Methods

The data of normal adult male healthy fasting subjects (thereafter only the subjects), taken from the study by Wilkinson., *et al*. 1977 [1] were used.

The advanced mathematical modeling method described in the study by Dedík., *et al*. published in September 2007 Issue of the Journal Diabetes Research and Clinical Practice and implemented in the computer program named CTDB was employed for modeling purposes [8]. In addition, it was assumed that the pharmacokinetic behavior of ethanol in the healthy male subjects was a result of repetitive passages of ethanol around the circulation [9]. The demo version of the computer program CTDB can be find on the following author's web site: http://www.uef.sav.sk/advanced.htmhat

The development of mathematical models of the pharmacokinetic behavior of the orally administered ethanol to the adult male fasting subjects enrolled in the study [1] was performed as described later on:
At the beginning of the model development process, the following simplifying assumption was made: i.e. an assumption that the pharmacokinetic behavior of ethanol in the bodies of the healthy male fasting subjects can be approximately described by linear models [1, 8-27].

The development of mathematical models was performed in the following successive steps:
On the first step of the model development process, an ADME related dynamic system was defined in Laplace domain for the subjects, using the transfer function, denoted by H(s) and described by Equation (1):

$$H(s) = \frac{C(s)}{I(s)}. \quad (1)$$

In Equation (1): S is the Laplace variable, I(S) is the Laplace domain counterpart of the mathematically transformed oral administration of ethanol to the healthy subjects [1] and C(S) is the Laplace domain counterpart of the mathematically transformed capillary ethanol concentration time profile obtained after the oral administration ethanol to healthy male subjects [1,9].

On the second step of the model development process, a mathematical model of the dynamic system was developed; using the advanced modeling method implemented in the computer program CTDB [8].

The general form of the model transfer function $H_M(S)$ used also in the present study, is described by the following equation:

$$H_M(s) = G\frac{a_0 + a_1 s + \ldots + a_n s^n}{1 + b_1 s + \ldots + b_m s^m}. \quad (2)$$

On the right-hand-side of Equation (2) is the Padé approximant to the model transfer function $H_M(s)$ [10,28-30], $G$ is an estimator of the model parameter traditionally called a gain of a dynamic system, $a_1, \cdots a_n, b_1, \cdots b_m$ are additional model parameters, *n* is the highest degree of the numerator polynomial, and *m* is the highest degree of the denominator polynomial, where *n<m* see for example the studies [8] and references therein.

On the third step of the model development process, the model transfer function $H_M(s)$ was converted into the equivalent model frequency response function (denoted by $F_M(i\omega_j)$ ) in the frequency domain; see for example, the studies cited above.

After that, the previously published non-iterative method [31] was employed to determine the model frequency response function $F_M(i\omega_j)$ of the subjects, and to determine point estimates of the parameters of the model frequency response function $F_M(i\omega_j)$ in the frequency domain.

The general form of a model frequency of function $F_M(i\omega_j)$ is described by Equation (3). It was also used in the present study:

$$F_M(i\omega_j) = G\frac{a_0 + a_1 i\omega_j + \ldots + a_n(i\omega)^n}{1 + b_1 i\omega_j + \ldots + b_m(i\omega_j)^m} \quad (3)$$

Besides, the radial frequency and the imaginary unit the meaning of the symbols used in Equation (3) is the same as the meaning of the symbols used in Equation (2).

On the forth step of the model development process, the best model of the frequency response function $F_M(i\omega_j)$ was selected using the Akaike information criterion, modified for the use in the complex domain [9,29] was employed to select the best model of the pharmacokinetic behavior of ethanol in the volunteers [7].

On the fourth step of the model development process, a) the output $C(s)$ of the model developed corresponding to the ethanol input $I(s)$ was determined, using a numerical simulation method in the time domain.

After that, the output $C(s)$ was refined, using the Gauss-Newton and Monte-Carlo method [] in the time domain.

Finally, the outcomes of the models developed and the concentration-time profiles of ethanol were mutually statistically compared, and in such a way, a validation on the models was performed.

## Results

As seen in Figures 1-4, the mathematical models developed successfully described capillary ethanol concentration-time profiles measured after the oral administration ethanol to healthy adult male fasting subjects

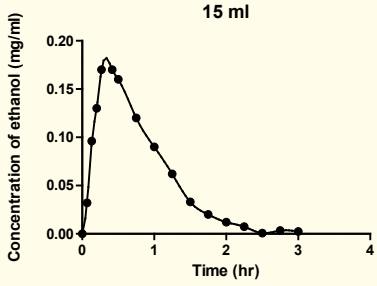


***Figure 1:*** *Capillary ethanol concentrations measured after the oral administration ethanol to adult male heathy subjects [1] and the model developed.*

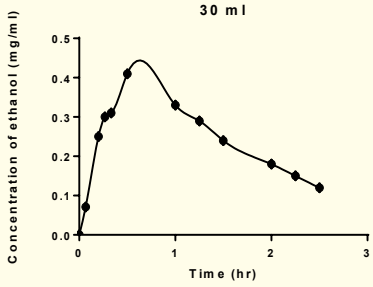


***Figure 2:*** *Capillary ethanol concentrations measured after the oral administration ethanol to adult male healthy subjects [1] and the model developed.*

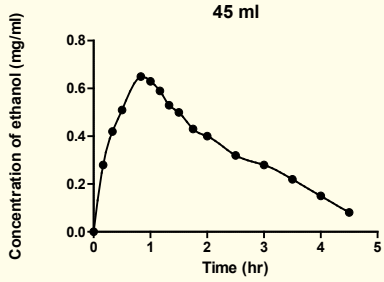


***Figure 3:*** *Capillary ethanol concentrations measured following the oral administration ethanol to adult male healthy subjects [1] and the model developed.*

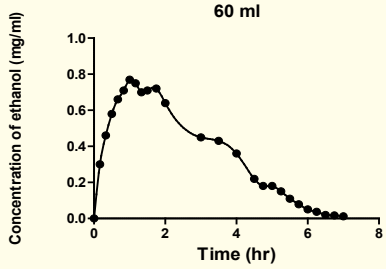


***Figure 4:*** *Capillary ethanol concentrations measured following the oral administration ethanol to adult male healthy subjects [1] and the model developed.*

## Discussion

The modeling method used in the present study utilized computational and modeling tools from system engineering. This method starts with a non-iterative algorithm and thus it does not require initial estimates of model parameters [8,9,31-41]. Both these facts markedly simplify and speed up the modeling procedure. Moreover, and what is even more important, the modeling method utilized enables to use identical model structures for the development of models of various pharmacokinetic processes (e.g. drug dissolution, drug bioavailability, etc.) what is in contrast to mutually different modeling methods, commonly employed in PK, PD, and PK/PD studies [9].

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