Medical Engineering and Physics 74 (2019) 106–114

Contents lists available at ScienceDirect

Medical Engineering and Physics

journal homepage: www.elsevier.com/locate/medengphy

A new gastro-intestinal mathematical model to study drug bioavailability

Marcello Pompa [a], Mauro Capocelli [b,*], Vincenzo Piemonte [a]

[a] Unit of Chemical-physics Fundamentals in Chemical Engineering, Department of Engineering, University Campus Bio-Medico di Roma, via Álvaro del Portillo 21, 00128 Rome, Italy
[b] Unit of Process Engineering, Department of Engineering, University Campus Bio-Medico di Roma, via Álvaro del Portillo 21, 00128 Rome, Italy

ARTICLE INFO

Article history:
Received 10 April 2018
Revised 27 August 2019
Accepted 13 September 2019

Keywords:
Reaction-diffusion
Transport phenomena
Pharmacokinetic
Paracetamol
Ketoprofen

ABSTRACT

This work focuses on a new mathematical model which describes the gastro-intestinal absorption of drugs and the effect of food interactions on drugs bioavailability. The model structure consists of five compartments (stomach, duodenum, jejunum feeding, intestine and blood) simulated though different *in-series* reactors. All the enzymatic reactions taking place in the gastro-intestinal system are described through the Michaelis–Menten kinetic equations. The model has been tested for drug administration (paracetamol and ketoprofen) with and without the meal digestion. The model has been validated through pharmacokinetics curves obtained from *in vivo* tests (reported in the literature) and used to simulate the drug absorption dynamics in different conditions. The maximum blood concentration were 0.153 mmol L^{-1} and 0.0243 mmol L^{-1}, respectively for paracetamol and ketoprofen. The time to reach the maximum concentration for the paracetamol and ketoprofen was around 55 min. In case of contemporary meal digestion, the maximum concentration of paracetamol in the blood was 0.100 mmol L^{-1} and 0.0135 mmol L^{-1} for ketoprofen; the time to reach the maximum concentration was 3 h and 45 min for paracetamol and 3 h and 35 min for ketoprofen. The drugs showed different pharmacokinetics, in agreement with the literature, during the digestion of food. To show the predictive capacity of the model, the simulations were also compared against additional experimental data (obtained from *in vivo* tests available in the literature) relative to ketoprofen administration with food.

1. Introduction

The absorption of drugs by oral administration is a combination of several processes occurring in the gastro-intestinal system and generating significant losses and delays until the drug dose reaches the systemic circulation. Indeed, the actual drug concentration in the blood depends on the complex mechanisms of reaction and transport phenomena that influence the bioavailability and the related real drug utilization [1–3]. Optimizing the dosage during the disease treatment and predicting the meal influence on the overall drug availability is fundamental to keep the drug concentration within the therapeutic range as well as to avoid under- and over-dosage or to prevent gastric toxicity [3].

After the oral administration, the drug starts to dissolve into the digestive fluids held in the stomach. Here, the drug is progressively delivered to the intestine where it is absorbed. This delivery mechanism is controlled by the gastric emptying (GE), a critical factor in drug absorption. GE is clearly influenced by the presence of food that often leads to observe slower dynamics of the same drug absorption. Inside the intestine, the drug absorption is controlled by the mechanisms of diffusion and active transport. The diffusion depends on the drug permeability through the cells while the active transport is function of several biological mechanisms, well described in the cited literature [1–4].

The recent research contributes on the Gastro Intestinal (GI) activity cover both the experimental observations and the modelling approaches: from the optical mapping and bioelectrical recording to the mathematical and computational modelling of the intestine tissue, with particular reference to the Multiphysics and the constitutive formulations [3–7].

Using the knowledge derived from the aforementioned research sectors, a complementary field, related to the ideation and optimization of GI in-silico models to simulate drug absorption, has been developed. In-silico models are able to simplify the complexity of the gastro intestinal tract with the final aim of predicting the drug distribution in blood, tissues, and organs [8]. Moreover, in-silico models have the potential to provide non-invasive preclinical

* Corresponding author.
E-mail address: m.capocelli@unicampus.it (M. Capocelli).

https://doi.org/10.1016/j.medengphy.2019.09.015
1350-4533/

Nomenclature

C_x,j	concentration of substrates and products in the xth compartment
C_x,i	concentration of products i the xth compartment
C_f	hollow fiber concentration, body (fiber) side
C_b	hollow fiber concentration, shell (blood) side
k_{abs}	active absorption coefficient
k_{el}	drug elimination coefficient
k_{bd}	first-order kinetic constant for bolus-drug interaction
k_{cd}	reaction coefficient for chime-drug interaction
$K_{m,i}$	Michaelis Menten parameter
k_{0v}	cell permeability to the drug
Q_i	flow rate
Q'_i	external flux flow rate
r_i	enzymatic reaction
R_1	internal radius of the hollow fiber membrane
R_2	external radius of the hollow fiber membrane
Rs	internal radius of the shell in the hollow fiber membrane
t	time
v_p	product velocity, body side
v_b	blood velocity, shell side
$v_{max,i}$	Michaelis–Menten parameter
V_i	volume
V_{Hb}	intestinal hold-up of blood
z	space variable

experimentation methods [9] as well as to improve the effectiveness of *in vivo* and *in vitro* tests [10].

According to Lamberti et al. [8], the edge of the research achievements is given today by the reliability and the meaningfulness of the pharmacokinetics parameters. In the GI tract simulation, for drug absorption and pharmacokinetics, several state-of-the-art models are based on very few compartments [9]. Furthermore, pharmacokinetic models rarely include any physiological insight inspired by other fields of research (e.g. Transport Phenomena, Computational Fluid Dynamics, Chemical Engineering Reactors, etc.). As an example, the approaches based on the Computational Fluid Dynamics (CFD) study the contraction of stomach and characterise the fluid dynamics of gastric contents, the nutrient absorption as well as the duodenum dynamics [11–16]. This kind of knowledge could represent the data input to more complex in-silico models.

Conventionally, in single-compartmental models, the input and output streams are described by a first order kinetic (without any physiological nature) reproducing the distribution of a drug in a confined volume [9]. To obtain a more reliable time distribution of the drug concentration, the two-compartmental models, divide the human body into a gastro-intestinal (GI) tract and a peripheral body to reproduce the interaction between the body and the surrounding tissues. This latter also includes the drug elimination by the organism.

Globally speaking, most compartment-models are able to offer a statistical interpretation of the drug availability through simplified kinetics and black-box approaches and often implement "apparent" volumes (with no necessary physiological meaning) with input and output stream described by a first order kinetic [17].

In this framework, a series of works, coming from the process engineering applied to the biomedical sector, have implemented different compartments simulated through (more or less rigorous) physiological models. The fundamentals of process simulation, transport phenomena and reactor engineering could represent the glue that holds together the different research areas in this sector (from the GI tract simulation to the engineering of artificial organ). The work that most inspires this sector is that of Sorensen [18] that presented the system and process analysis of "a big portion of the human body" in order to analyse the glucose metabolism and its use to improve insulin therapies for diabetes. With a similar approach, this research group has been focused on several organs and functions by focusing on unit operations, transport phenomena and bio-chemical reactions [19,20]. Recently, Piemonte and co-authors discussed a three compartmental model for simulating the insulin-glucose interaction in the sector of artificial pancreas development [19]. Other examples of the mentioned approach are given in the cited literature [20,21].

A branch of complementary research includes *in vitro* models and lab-scale devices, fundamental to integrate multi-scale and multi-disciplinary information. Some of them have the goal to develop experimental *in vitro* or *ex vivo* models of human intestine to investigate the pathophysiology (with and without a living microbiome). These systems range from the small scale reactors to more complex prototypes able to integrate the digestion dynamics, the microorganisms survivor as well as the nutrient absorption [22].

The TNO Gastro-Intestinal Model (TIM) is a lab-scale prototype (defined as a multi-compartmental "mechanical" model) designed to simulate the conditions in the lumen of the gastro-intestinal tract. It has been successfully tested with a wide variety of food and pharmaceuticals under different conditions (flow rates and composition of digestive fluids, pH values, etc.) to understand the absorption through the gut wall (bio-accessibility) [22]. With a similar purpose, the Food Research of Norwich has developed the Dynamic Gastric Model (DGM) (*in vitro* model) where gastric acids and enzyme secretions are introduced within the food bolus and the masticated material is subjected to physiological shear and grinding forces in functionally-distinct zones before the ejection (duodenal processing) [23]. The fluid mechanical conditions driving the disintegration and mixing are also reproduced in the Human Gastric Simulator (HGS), mainly used for food digestion diagnosis [24]. In this framework, mimicking the functionality of organs on the micro-scale represents a key challenge to develop artificial organs [25–27].

Organs-on-chips are microfluidic cell culture systems that embody the structure, function, physiology, and pathology of living human organs *in vitro* [25–29]. The microfluidic devices have enabled the multi-scale R&D in this field through the culture of living cells in microchannels [29].

In this variegated and multi-scale panorama of experimental and theoretical research, we propose a novel mathematical model (5-compartments *in-silico* model) to describe the physiological behaviour of the GI system and to study drug bioavailability and drug-food interactions. Our *in-silico* model takes inspiration from the TIM to better describe the GI-tract behaviour through the approach of unit operations from the chemical engineering know-how. This model also realizes a conjunction ring between *in vivo* tests and "mechanical laboratory models" to obtain an extended prediction capability by simulating the real physiology of the human body. For example, our model considers the enzymatic reactions occurring in the stomach and does not implement any empirical equation to control the gastric emptying. Few model parameters related to drug absorption and consumption have been obtained from the model-fitting of experimental data. In such a way, it is possible to produce tailored simulations for different "patient-drug" couples (also including food absorption dynamics) with a system of equations that is globally based on the physiology.

The potentiality of this model is represented in Fig. 1. According to this view and the cited R&D fields, our model can involve several results, from experimental data of bio-availability to the CFD simulations (as model input). Once trained with experimen-

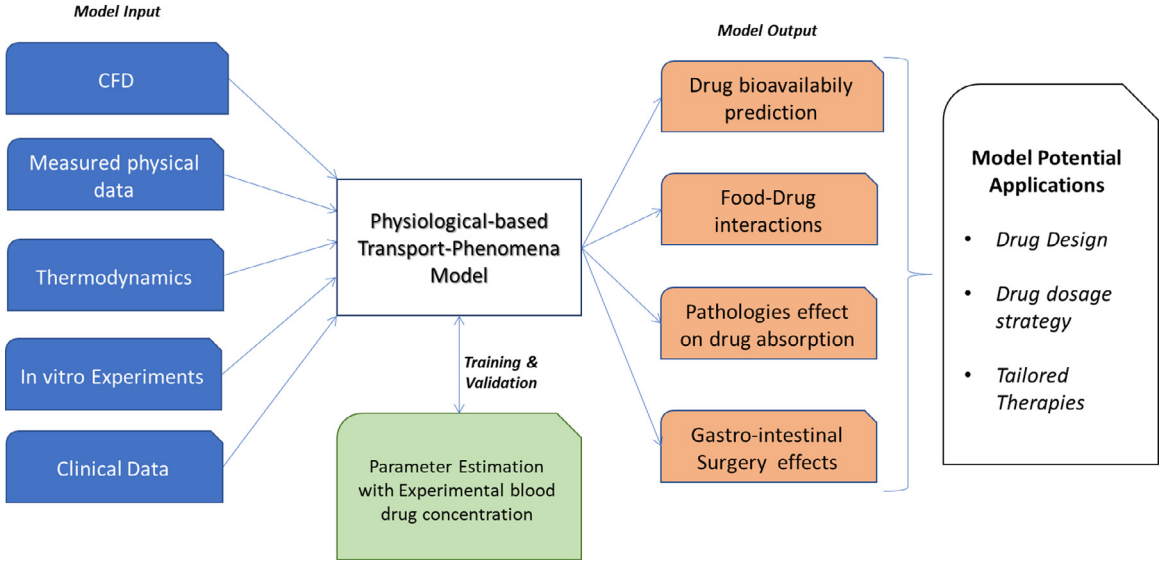


Fig. 1. Application context of the proposed model.

tal data, the model outputs cover different purposes and working conditions (once translated into boundary and initial conditions of the mathematical model). Some examples of the potential applications are: (i) drug dosage strategy; (ii) food-drug interaction, (iii) pathological interferences on drug absorption, (iv) design and optimization of experimental "mechanical" apparatus.

In the following, our original model is described, trained and tested for different protocols (of paracetamol and ketoprofen) to reproduce the experimental data from the literature [30–32]. The model utilizes adjustable physiological parameters that can be estimated from experimental and theoretical works available in the literature [33–37].

2. Mathematical modelling

2.1. Model description

In order to reproduce the physiology of the gastro-intestinal tract (in relation to the drugs bioavailability), the model includes five compartments (described in the following) as depicted in the process flow diagram of Fig. 2. These compartments are: (1) stomach; (2) duodenum; (3) jejunum feeding; (4) intestine; (5) blood. All compartments are virtually linked through valves controlling the input and output flows.

The enzymatic reactions (lipase, protease and amylase) are implemented in the stomach and duodenum compartments. The intestine compartment, modelled through a hollow fibre reactor, is linked to the blood. The counter-current hollow fibre reactor is designed to reproduce the drug absorption by taking into account for both diffusion and active transport of nutrients and drugs. The flowrate exiting from a compartment is fed to the adjacent one. The inlet stream to compartment 1 contains both the bolus and the drug. The emptying of the stomach compartment is controlled by enzymatic reactions in the duodenum: the valve located at the compartment output is normally closed until all bolus constituents (lipid, protein and starch) are converted into products. Therefore, the enzymatic reaction rate controls the gastric emptying (GE) and, consequently, the absorption of the drug. The system of equations describing the whole process are derived through mass balances for each compartment.

The stomach compartment (1) simulates the storage and the partial digestion and is fundamental for the timing of the subsequent unit operations (in all the downstream compartments). It is described by Eqs. (1)–(3) where the subscript j is related to the four substrates (lipid, protein, starch and drug) and the subscript i to the products.

$$V_1\frac{dC_{1,\mathrm{j}}}{dt}+C_{1,\mathrm{j}}\frac{dV_1}{dt}=Q_1^{in}\cdot C_j^{in}-r_{1,j}\cdot V_1-Q_1^{out}\cdot C_{1,\mathrm{j}}-k_{bd}\cdot C_{1,\mathrm{j}}\cdot V_1 \tag{1}$$

$$V_1\frac{dC_{1,\mathrm{i}}}{dt}+C_{1,\mathrm{i}}\frac{dV_1}{dt}=-Q_1^{out}\cdot C_i^{in}+r_{1,j}\cdot V_1-k_{\mathrm{cd}}\cdot C_{1,\mathrm{i}}\cdot V_1 \tag{2}$$

$$\frac{\partial \mathrm{V}_1}{\partial \mathrm{t}}=+\mathrm{Q}_1^{in}-\mathrm{Q}_1^{out}+\mathrm{Q}_1' \tag{3}$$

$$r_{1,j}=\frac{v_{max1,j}\cdot C_{1,j}}{K_{m,j}+C_{1,\mathrm{j}}} \tag{4}$$

where C is the concentration of substrates and products, V is the reactor volume, Q is the main stream flow rate and Q' represents the external flowrate (e.g. gastric fluids for the stomach). The possible first-order reaction between bolus and drug and between chyme and drug are respectively controlled by the reaction constants k_{bd} and k_{cd}. The stomach enzymatic reaction rate ($r_{1,j}$ for each jth substrate) is reported in Eq. (4). In the case of drug, the $r_{1,j}$ is zero since it is not degraded by enzymatic reactions.

The second compartment consists of the duodenum which represents the unit operation of "enzymatic reaction" to complete the digestion process. It is described by the system of Eqs. (5)–(7) with the enzymatic reactions in the duodenum ($r_{2,j}$) described by Eq. (8).

$$V_2\frac{dC_{2,\mathrm{j}}}{dt}+C_{2,\mathrm{j}}\frac{dV_2}{dt}=Q_2^{in}\cdot C_{1,j}-r_{2,j}\cdot V_2-k_{bd}\cdot C_{2,\mathrm{j}}\cdot V_2 \tag{5}$$

$$V_2\frac{dC_{2,\mathrm{i}}}{dt}+C_{2,\mathrm{i}}\frac{dV_2}{dt}=-Q_2^{out}\cdot C_{2,\mathrm{i}}+r_{2,j}\cdot V_2+Q_2^{in}C_{1,\mathrm{i}}-k_{\mathrm{cd}}\cdot C_{2,\mathrm{i}}\cdot V_2 \tag{6}$$

$$\frac{\partial \mathrm{V}_2}{\partial \mathrm{t}}=+\mathrm{Q}_2^{in}-\mathrm{Q}_2^{out}+\mathrm{Q}_2' \tag{7}$$

$$r_{2,j}=\frac{v_{max,2,j}\cdot C_{2,\mathrm{j}}}{K_{m,j}+C_{2,\mathrm{j}}} \tag{8}$$

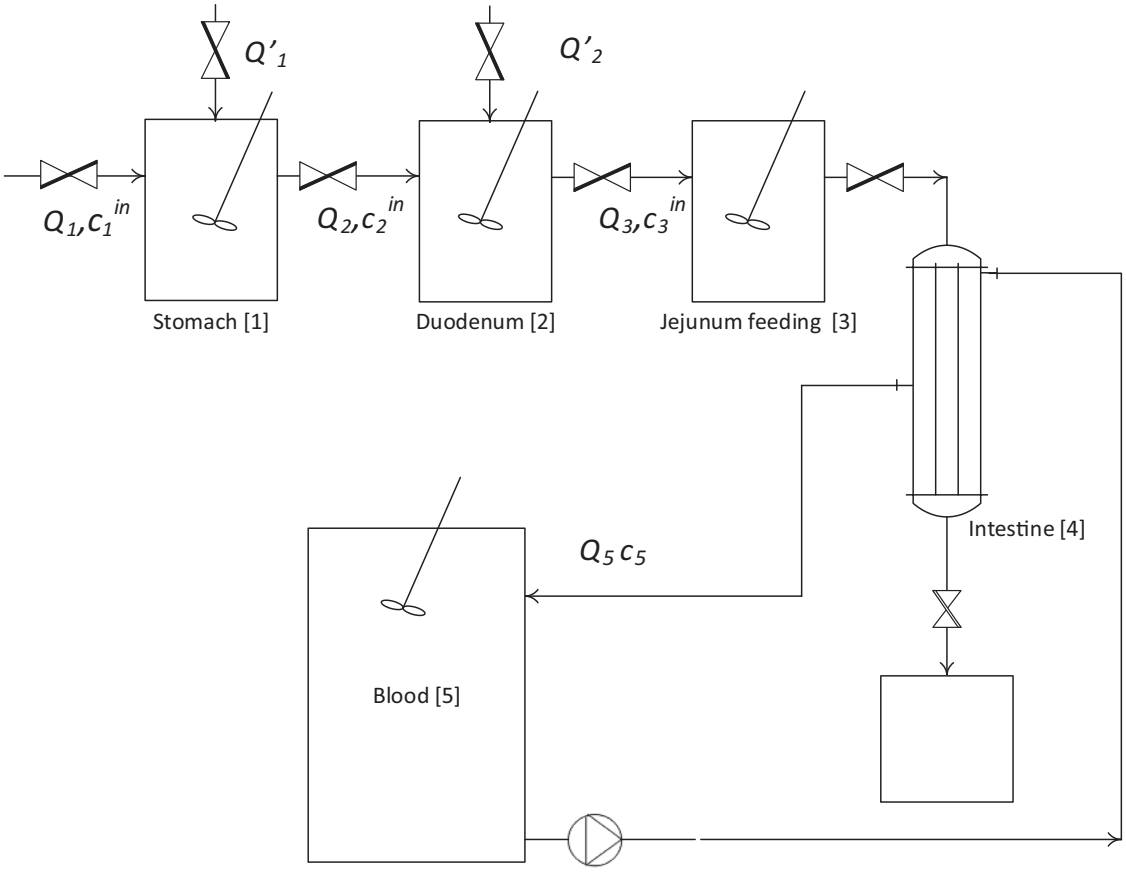
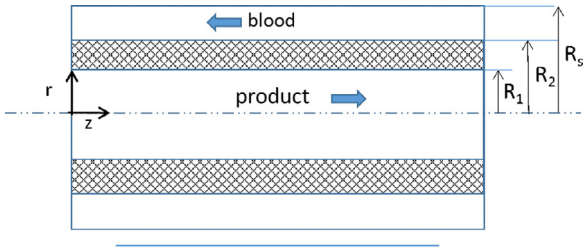


Fig. 2. Schematic of the Gastro-Intestinal model for drugs absorption.



L [m]	R_1 [m]	R_2 [m]	R_s [m]
6	0.0125	0.0175	0.0318

Fig. 3. Hollow fiber reactor geometry and parameters.

Here, the external flowrate Q_2' consists of biliary juices.

The third and fourth compartments consisting of "jejunum-feeding" and intestine are implemented to simulate the supplying of both the chyme and drug. Eqs. (9) and (10) are related to the jejunum-feeding compartment, while the Eqs. (11) and (12) are related to the intestine compartment, simulated as a hollow fiber reactor of 6 m (see Fig. 3 for further details).

$$V_3 \frac{dC_{3,i}}{dt} + C_{3,i} \frac{dV_3}{dt} = Q_3^{in} \cdot C_{2,i} - Q_3^{out} \cdot C_{3,i} \tag{9}$$

$$\frac{\partial V_3}{\partial t} = +Q_3^{in} - Q_3^{out} \tag{10}$$

$$\frac{dC_{4f}}{dt} = -v_f \frac{dC_{4f}(z)}{dz} - \frac{2k_{Ov}}{R_1}\left(C_{4f} - C_{4s}\right) - k_{abs} \cdot C_{4f} \tag{11}$$

$$\frac{dC_{4s}}{dt} = -v_s \frac{dC_{4s}(z)}{dz} + \frac{2k_{Ov}R_2}{\left(R_s^2 - R_2^2\right)}\left(C_{4f} - C_{4s}\right) + k_{abs} \cdot C_{4f} \tag{12}$$

$$\frac{dC_5}{dt} = \frac{Q_5}{V_5}\left(C_5^{in} - C_5\right) - k_{el} \cdot C_5 \tag{13}$$

Eq. (11) is relative to the mass balance in the hollow fiber including the active transport of drugs while Eq. (12) is related to mass balance in the reactor shell. The initial conditions for $0 < z < L$ are $C_{4f}(z) = C_{4s}(z) = 0$ (initially empty). The boundary conditions are $C_{4s}(0) = C_3$ and $C_{4s}(L) = C_5$. Here the subscripts f and s stand for fibre and shell side, respectively; while C_5 refers to the blood compartment. It is worth noting that, downstream of the duodenum, all the substrates, except for drugs, are converted into products. Furthermore, as simplified model hypothesis, downstream of this compartment, only the drug transport is considered (no drug-product interactions have been considered). The fifth compartment (blood) allows to estimate the final drug bioavailability and is described by Eq. (13) with the boundary condition $C_5^{in} = C_{4s}(0)$. The coefficient k_{Ov} is the overall mass transport coefficient (of the drug) that accounts for permeability through the cell membrane (passive transport). The coefficient k_{abs} regulates the active transport rate and k_{el} is the elimination rate in the human blood (drug utilization from the body).

The whole system including all the interconnected unit operations and described by Eqs. (1)–(13) has been solved numerically by the gPROMS package (Process System Enterprises, London, UK) using a first order backward finite difference method. The same software has been used to perform data fitting in order to estimate the adjustable parameters, following a least squares criterion.

Table 1
Michaelis-Menten reaction parameters [35–38].

	Stomach		Duodenum		Reference
	K_m[mmol L^{-1}]	V_{max}[mmols$^{-1}L^{-1}$]	K_m[mmol L^{-1}]	V_{max}[mmols$^{-1}L^{-1}$]	
Lipase	0.24	$5.5 \cdot 10^{-6}$	0.22	0.0036	[35]
Protease	0	0	0.000135	0.00046	[36]
Amylase	$5.7 \cdot 10^{-4}$	$3.31 \cdot 10^{-8}$	0.0096	0.000552	[37,38]

Table 2
Parameters used for model compartments [22,34].

	Stomach	Duodenum	jejunum feeding (in)	jejunum feeding (out)	intestine (hollow fiber side)	Blood
Initial volume [L]	0.1	0.02	0.13		Empty	5
Flowrate [L s^{-1}]	1	0.05	0.02	0.00125	0.00125	$3.3 \cdot 10^{-2}$
External flowrate [Ls^{-1}]	$2.\cdot 10^{-7}$	$2.\cdot 10^{-7}$	0	0		0
Operation type	Semi-bacth (pulsed mode)	Semi-bacth (pulsed mode)	Fed-bacth	Continuous	Continuous	Continuous
Operation time [s]	1	1	2.5	NA	NA	NA

In the following, the first simulation results from this novel model are presented. Firstly, the values of some parameters (that minimize the error between modelling and simulation results) have been found (training mode). Successively, the model has been implemented to predict some literature results by fixing all the independent variable (predictive mode).

2.2. Parameters and conditions

As above-mentioned, the enzymatic reactions in the duodenum control the emptying of the stomach compartment. The set of reactions is described by the Michaelis–Menten kinetic equation, where the parameters have been estimated for a meal consisting of bread and butter (Table 1). The slower reaction in the duodenum limits the stomach emptying. The protease reaction is described by the average values of kinetic parameters related to chymotrypsin, pepsin and trypsin, therefore linking the mathematical model with a more reliable physiological approach [35–38].

Each compartment is characterized by a variable volume due to the variability of the inlet and outlet flowrate. Both the stomach and duodenum work as semi-batch reactors, while jejunum feeding and intestine work in a continuous mode, mimicking the actual human physiology. In detail, once the stomach is full, it starts the emptying in a discontinuous way by sending a first bolus which is about twenty time smaller than the whole volume contained in the stomach. The duodenum at this point starts the enzymatic reactions to degrade the substrates: when the substrates contained in the bolus are completely degraded, the duodenum starts the emptying phase. When the duodenum is empty, a second bolus (fed to the stomach) is admitted, thus generating a pulsed fluid dynamics until the stomach is completely emptied. Meanwhile, the intestine feeding is filled and emptied with different flowrates (in particular the output flow is smaller than the incoming flowrate). This means that the intestine feeding compartment works as a fed-batch for the loading operation and as a continuous reactor for the emptying phase in order to assure a continuous inlet flowrate to the intestine. Table 2 reports the initial volumes, the values of the inlet and outlet flowrates, as well as the operating regimes for each compartment.

Hollow-fiber parameters, taken from literature [10], are reported in Fig. 2. The product velocity in the fiber-side is $v_f = 0.0013$ m s^{-1} and the blood velocity in the shell side is $v_s = 0.21$ m s^{-1}. The radius value of the veins in the intestinal tract has been deducted by an equivalence assuming an intestinal hold up of about 1 L in Eq. (14).

$$V_{Hb} = \pi L\left(R_s^2 - R_2^2\right) \tag{14}$$

where R_s is the equivalent radius of the veins (shell side) in the intestinal tract and V_{Hb} is the intestinal hold-up of blood.

3. Parameters estimation

The model has been implemented to analyse the pharmacokinetic of two drugs: paracetamol and ketoprofen. Paracetamol is a drug used for its analgesic and antipyretic properties. Prolonged use, diverging from the therapeutic range could damage the liver. Ketoprofen is a non-steroidal anti-inflammatory drug with analgesic and antipyretic effects, commonly used to treat pain. Ketoprofen could damage the gastric mucosa if not administrated in a controlled therapeutic range. The key model parameters for the two drugs have been obtained by fitting experimental values from *in vivo* tests, reported in the literature [30–32]. This procedure is reported in the Sections 3.1 for paracetamol and 3.2 for ketoprofen.

3.1. Paracetamol parameters estimation

The protocol used for model training required an administration of 1 g of paracetamol after 4 h of fasting. Paracetamol administration was performed with a glass of 400 ml of orange juice [30]. The protocol included a further injection of meperidine that delays the data by 30 min. These data has been implemented to perform the first training test. Fig. 4 reports the good agreement between *in vivo* data and model simulation. The maximum drug concentration $C_{5,max}$ in the blood compartment (mmol L^{-1}) is 0.153 for the *in vivo* test and 0.154 for the simulation. The time to reach $C_{5,max}$ is 40 min and 55 min, respectively for the tests and for the simulation. Time to fall outside the therapeutic range is about 3 h and 30 min, differing of about 10 min between the tests and the simulations.

3.2. Ketoprofen parameters estimation

In vivo test protocols prescribed an administration of 50 mg of Ketoprofen with empty stomach; experimental data were obtained in presence and absence of sucralfate [31]. These latter has been used for the estimation procedure. Fig. 5 shows the good agreement between literature data and model simulation. The maximum concentration error is not more than 0.0007 mmol L^{-1}. The temporal value observed to reach the maximum concentration is around

Table 3
Estimated Parameters for Paracetamol and Ketoprofen [30,31].

Drugs	K_{Ov}[m s^{-1}]	K_{ass} [s^{-1}]	K_{el} [s^{-1}]	Therapeutic range [mmol L^{-1}]
Paracetamol	$1.57*10^{-6}$	$0.16*10^{-3}$	$0.10*10^{-3}$	0.066 – 0.16
Ketoprofen	$8.4*10^{-6}$	$0.14*10^{-2}$	$0.165*10^{-3}$	0.00157 – 0.024

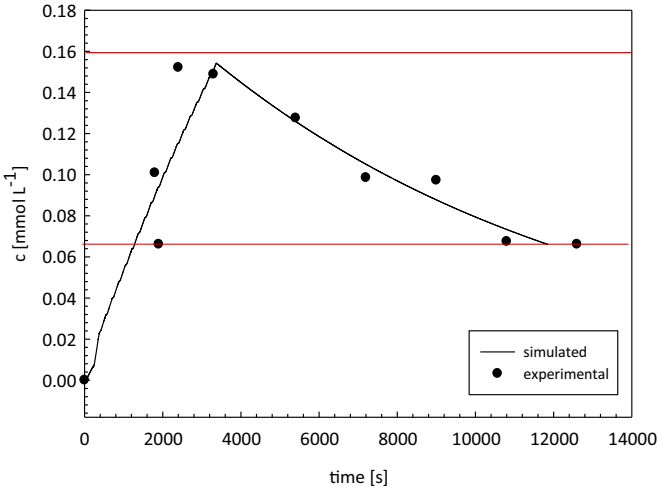


Fig. 4. Paracetamol concentration in the blood. Orange points are the experimental data [31]; horizontal lines limit the therapeutic range.

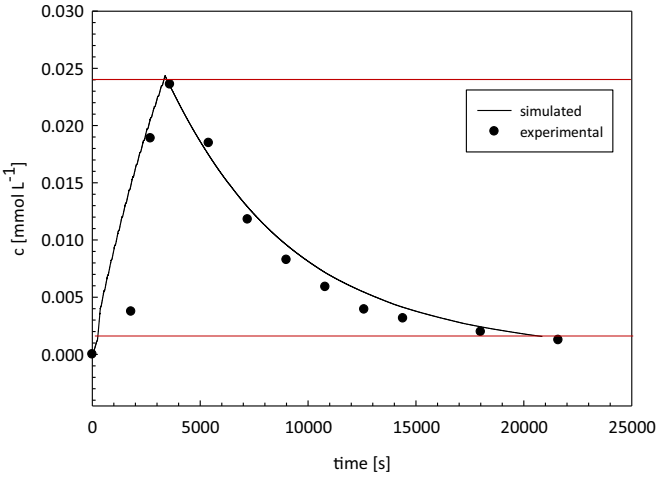


Fig. 5. Ketoprofenconcentration in the blood compartment. Full circles represent experimental data [31]; horizontal lines limit the therapeutic range.

1 h for the test and 55 min for the simulation and the time to observe values outside the therapeutic range is 5 h and 40 min for the test and 5 h and 47 min for the simulations.

The estimated parameters after the training procedures are reported in Table 3 for both paracetamol and ketoprofen.

4. Simulations

The model, once trained as described, has been used to predict the drug concentration in the blood compartment. The first focus of these predictive simulations has been the individuation of the optimal conditions for the drug administration in terms of timing and dosage to obtain a blood concentration confined within the therapeutic range. Moreover, the simulations have been performed separately, by following different protocols (with and without food administration) to study the influence of the meal on the absorption process and, consequently, on the drug bioavailability. In order to highlights the effect on the GE (strongly influenced by the lipid initial content), the input (in trials with food) included a bolus containing the meal used for the training phase [30,31], composed by lipids (2 mmol L^{-1}), proteins ($4.375 \cdot 10^{-4}$ mmol L^{-1}) and starches ($75 \cdot 10^{-3}$ mmol L^{-1}), equivalent to the nutrient input of 150 g of bread and 20 g of butter.

Fig. 6 reports the results of the simulation of the emptying dynamics. The proteins concentration is not reported because of its lower order of magnitude. At each cycle, the lipid concentration is slightly smaller than 2 mmol L^{-1} because of the dilution in the compartment. Fig. 6 highlights the pulsed operational mode of both stomach and duodenum. The digestion process takes about 3 h and 45 min. In this time, the drug is absorbed in a discontinuous way (unlike the standard protocol without meal). The enzymatic reactions in the stomach compartment are slower with respect to the duodenum ones. The emptying pattern is given by the maximum and minimum concentration of the nutrients: when there is a minimum, the GE starts; when there is a maximum, the GE stops. The simulation continues after the digestion since the absorption prosecutes in the adjacent compartments. The substantial difference between the two protocols is the time necessary to reach the minimum and maximum concentration, with the first protocol (no food) faster than the second one (with food).

Fig. 7 shows the simulation results (without food) as final blood concentration for two different successive administration of paracetamol. The initial concentration of paracetamol in the first compartment is 6.6 mmol L^{-1}, based on the administered dose of 1000 mg for an adult of 65 kg, a common dosage as reported on a commercial package leaflet. The absence of food allows the drug to be quickly absorbed, hence the drug concentration rapidly reaches a maximum in the blood compartment, as depicted in Fig. 7. At the same time, the drug consumption is very slow compared to the duration of the absorption phase. The maximum concentration is 0.154 (mmol L^{-1}) and it is reached in approximately 1 h The time necessary to exceed the therapeutic range is 11,900 s (around 3 h and 20 min). In this way, by knowing pharmacokinetic of paracetamol, it is possible to optimize its administration procedure. The second administration occurs when the blood drug concentration falls below the lower therapeutic limit and consists of a half dosage. The results are (qualitatively) in good agreement with the prescription of the information booklet. In the second protocol (dotted blue line), the meal is represented by the contribution of lipids, proteins and starch, as described above (equivalent to bread and butter), for which the model has been previously tested. In this case, it is possible to better modulate the therapy and to let the drug concentration stay longer in therapeutic range (2 h and 48 min *vs*5 h and 30 min).

Similar results are reported for ketoprofen in Fig. 8. By assuming an administration of 50 mg of ketoprofen, the initial concentration in the first compartment is equal to 0.196 mmol L^{-1}. The therapeutic range of ketoprofen is greater than the paracetamol one. The drug consumption phase is really slow compared to the absorption phase. The maximum concentration is 0.0243 mmol L^{-1} and it is reached in approximately 1 h. The time to overcome the therapeutic limit is 20,500 s (around 5 h and 40 min). The second administration of the same dose (50 mg) occurs when the concentration goes below the therapeutic limit. With this protocol, the blood concentration is not confined in the therapeutic range: to

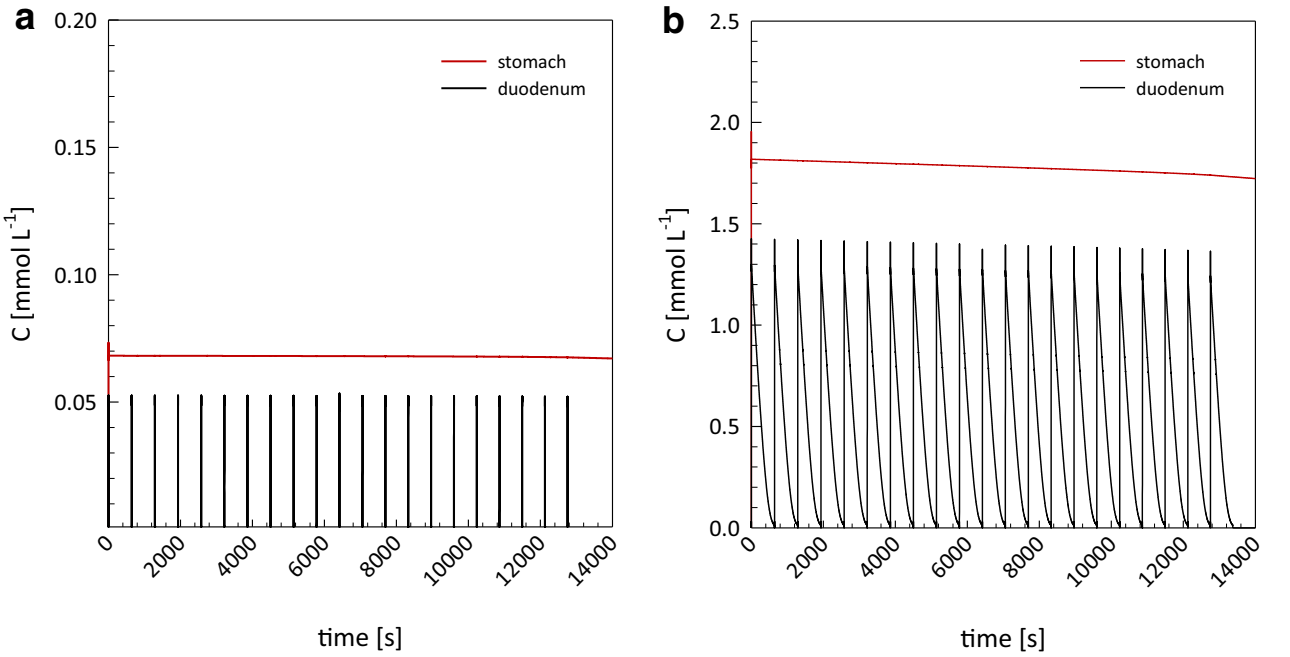


Fig. 6. Enzymatic reaction in stomach and duodenum and compartment emptying: dynamics of starch (a) and lipid (b) digestion.

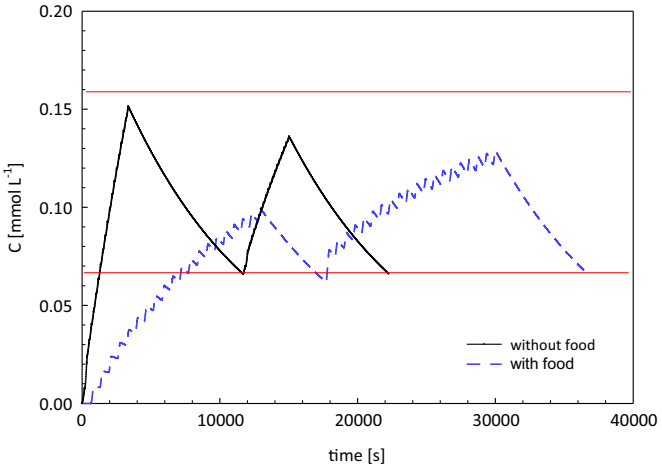


Fig. 7. Variation of the Paracetamol concentration in the blood compartment in absence of food with single and double administration (full line) and with food (dashed line). 1st administration = 1000 mg; 2nd administration = 500 mg.

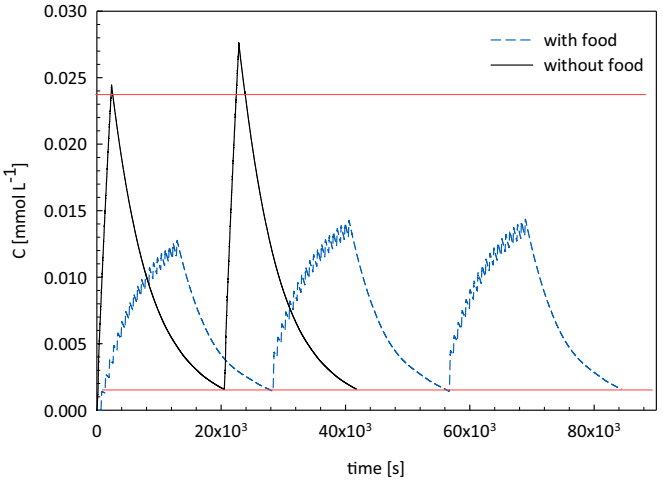


Fig. 8. Ketoprofen concentration in the blood compartment after single administration (full line) and double administration (full line) and with meal (dashed line). 1st administration = 50 mg; 2nd administration = 50 mg.

stay in the therapeutic range, the second administration has to be lower than the first one. As for paracetamol, the absorption dynamics of ketoprofen between the first and the second protocol is quite different. The dotted line describes the simulation results for more than one administration as suggested by the leaflet: one administration every six hours with meal. Again, this last finding confirms the good reliability of the model and the importance to study food-drug interaction: by comparing the different protocols it is possible to observe that drug concentration in the second administration remains within the therapeutic range during the whole period. The second administration with food allows the drug concentration to be confined longer within the therapeutic range (2 h and 48 min *vs*5 h and 30 min).

The comparison between the two protocols is reported in Table 4. The results reported so far allowed a first qualitative comparison between the simulations and the therapeutic prescriptions reported in the booklets by demonstrating that: (1) an administration following the procedure suggested in the booklet is confined in the therapeutic range; (2) small deviations from the indicated drug dosage can generate fluctuations outside the therapeutic range.

A quantitative comparison between simulations and experiments has been realized by implementing some additional tests reported in the literature. Caillé et al. measured the ketoprofen concentration in blood samples (10 ml) by high-pressure liquid chromatography from 12 male volunteers which had a breakfast containing 240 ml of milk, 150 ml of orange juice, two eggs, two slices of bread, and 10 g of butter. This meal is equivalent to 16% of protein, 55% of lipid and 29% of carbohydrate for a total of 784 kcal [31]. Fig. 9 shows the simulation (continuous line) of this experimental procedure with the square representing the measured values.

Table 4
Comparison data from tests.

Protocol	Maximum concentration C_{max} (mmol L^{-1})	Time to reach C_{max}	Time in therapeutic range	Time to go out from therapeutic range	Time to reach minimum concentration
Paracetamol trial 1	0.153	55 min	~ 3 h	3h 20 min	20 min
Paracetamol trial 2	0.100	3*h* 45 min	~ 3h	4 h 48 min	1*h* 48 min
Ketoprofen trial 1	0.0243	55 min	5*h* 33 min	5h 40 min	6 min
Ketoprofen trial 2	0.0135	3*h* 35 min	7*h* 30 min	7h 40 min	10 min

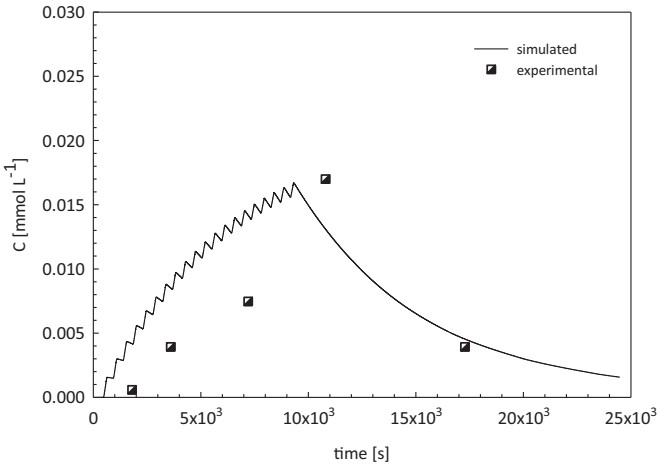


Fig. 9. Ketoprofen concentration in the blood compartment after single administration from the model simulation (full line) and from *in vivo* experimental analysis (square symbol) [31].

Despite some errors in the identification of the initial conditions from the reference, the model, that here has been used as a rigorous predictive tool (already trained with previous data in absence of food), is able to reproduce the experimental behaviour in presence of food (M.S.E. = $3 \cdot 10^{-5}$). The rigorous simulation of a real GE behaviour, carried out by introducing enzymatic reactions, allowed to globally predict the trends, especially from the point of view of the peak identification. The initial data are not very well reproduced because it is difficult to establish the initial time of the experimentation from the given description and because the original data are quite scattered at the beginning [31].

5. Conclusion

Gastric emptying is a critical factor in drug absorption and it is slower in the presence of food. Therefore, the food-drug interaction results into a slower dynamic of drug absorption. At the moment, there are no physiologically-based models able to introduce these complex dynamics in the drug absorption behaviour.

This paper presented the application of a chemical engineering analysis to Gastro-Intestinal system, in order to provide a reliable tool for the assessment of the drug bioavailability. The presented model has been firstly validated against literature data and therefore used as predictive tool to analyse paracetamol and ketoprofen bioavailability. In both cases it has shown a good reliability confirming the good potential of the novel physical-mathematical approach.

In particular, the maximum blood concentration was 0.153 mmol L^{-1} and 0.0243 mmol L^{-1}, respectively for paracetamol and ketoprofen. The time to reach the maximum concentration for the paracetamol and ketoprofen is around 55 min. During the meal digestion, the drugs show a different pharmacokinetics, found qualitatively and quantitatively in agreement with the literature data. The maximum concentration of paracetamol in the blood is 0.100 mmol L^{-1}, while it is 0.0135 mmol L^{-1} for ketoprofen. The time to reach the maximum concentration is 3 h and 45 min for paracetamol and 3 h and 35 min for ketoprofen.

Although the model has been trained in the case of no-meal, it was also able to predict experimental points (obtained *in vivo*) of blood concentration relative to ketoprofen administration with food since it well predicts how the food assumption affects the gastric emptying.

The model does not take into account the complex relationships between contractions of the intestinal wall and effective pulsed motility of the chyme, in addition to the micellar effect of biliary juices on the effective absorption of the drug. Moreover, all the interactions between the microbiota and the drug as well as the relative changes of motility deriving from an alteration of the microbiota have been neglected.

A new version of the model is under development with the aim to reduce the current simplifications described above. The proposed model, after further improvements, could be used: (i) to simulate the physiological processes of the GI tract; (ii) to predict the influence of the GI tract diseases on the digestion and consequently on the absorption of drugs; (iii) to predict the interaction between different foods and drugs and to analyse the bioavailability of drugs and nutrients; (iv) to support and to optimize *in vitro* tests; (v) to provide a rational tool for the design of an artificial gastro-intestinal system and/or a lab-scale devices able to mimic the physiology of gastro intestinal tract; (vi) to develop in-silico clinical trials giving guidelines for drug design.

Declaration of Competing Interest

None.

Funding

None

Ethical approval

Not required

References

[1] Hirtz J. The gastrointestinal absorptionofdrugsin man: a review ofcurrent concepts and methods of investigation. Br J Clin Pharmac 1985;19:77S–83S.
[2] Prabu SL, Suriyaprakash TNK, Ruckmani K., Thirumurugan R. Biopharmaceutics and pharmacokinetics 2015; IntechOpen, doi:10.5772/61160. Available from: https://www.intechopen.com/books/basic-pharmacokinetic-concepts-and-some-clinical-applications/biopharmaceutics-and-pharmacokinetics.
[3] Pullan A, Cheng L, Yassi R, Buist M. Modelling gastrointestinal bioelectric activity. Prog Biophys Mol Biol 2004;85(2–3):523–50.
[4] O'Grady G, Du P, Cheng LK, Egbuji JU, Lammers WJ, Windsor JA, Pullan AJ. Origin and propagation of human gastric slow-wave activity defined by high-resolution mapping. Am J Phys Gastrointest Liver Physiol 2010;299:G585–92.
[5] O'Grady G, Egbuji JU, Du P, Cheng LK, Pullan AJ, Windsor JA. High-frequency gastric electrical stimulation for the treatment of gastroparesis: a meta-analysis. World J Surg 2009;33(8):1693–701.
[6] Gizzi A, Cherubini C, Migliori S, Alloni R, Portuesi R, Filippi S. On the electrical intestine turbulence induced by temperature changes. Phys Biol 2010;7(1):16011.

[7] O'Grady G, Angeli TR, Du P, et al. Abnormal initiation and conduction of slow-wave activity in gastroparesis, defined by high-resolution electrical mapping. Gastroenterology 2012;143(3):589–98.
[8] Lamberti G, Cascone S, Marra F, Titomanlio G, d'Amore M, Barba AA. Gastrointestinal behavior and ADME phenomena: II. Insilicosimulation. J Drug Deliv Sci Technol 2016;35:165e171.
[9] Sjödin L, Visser S, Al-Saffar A. Using pharmacokinetic modeling to determine the effect of drug and food on gastrointestinal transit in dogs. J Pharmacol Toxicol Methods 2011;64(1):42–52.
[10] Mudie DM, Amidon GL, Amidon GE. Physiological parameters for oral delivery and *in vitro* testing. Mol Pharm 2010;7(5):1388–405.
[11] Pal A, Indireshkumar K, Schwizer W, Abrahamsson B, Fried M, Bracceur JG. Gastric flow and mixing studied using computer simulation. Proc R Soc B 2004;271(1557):2587–94.
[12] Ferrua MJ, Singh RP. Modeling the fluid dynamics in a human stomach to gain insight of food digestion. J. Food Sci. 2010;75(7):R151–62.
[13] Wang Y, Brasseur JG, Banco GG, Webb AG, Ailiani AC, Neuberger T. A multi-scale lattice Boltzmann model of macro- to micro-scale transport with applications to gut function. Philos Trans R Soc A 2010;368:2863 288.
[14] Altomare A, Gizzi A, Guarino MP, Loppini A, Cocca S, Dipaola M, Alloni R, Cicala M, Filippi S. Experimental evidence and mathematical modeling of thermal effects on human colonic smooth muscle contractility. Am J Physiol Gastrointest Liver Physiol 2014;307(1):G77–88.
[15] Gizzi A, Pandolfi A, Vasta M. Viscoelectromechanicsmodeling of intestine wall hyperelasticity. Int J Comput Methods Eng Sci Mech 2016;17(3):143–55. doi:10.1080/15502287.2015.1082678.
[16] Bianchi D, Monaldo E, Gizzi A, Marino M, Filippi S, Vairo G. A FSI computational framework for vascular physiopathology: a novel flow-tissue multiscale strategy. Med Eng Phys 2017;47:25–37.
[17] Persky AM. Pharmacokinetics of the dietary supplement creatine Ph.D. Thesis. Gainesville, FL: University of Florida; 2013.
[18] Sorensen JT. A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes. Ph.D. Thesis submitted to the Massachusetts Institute of Technology in 1985.
[19] Piemonte V, Capocelli M, De Santis L, Maurizi A, Pozzilli P. A novel three-compartmental model for artificial pancreas: development and validation. Artif Organs 2017;41(12):E326–36.
[20] Annesini MC, Piemonte V, Turchetti L. Artificial liver devices: a chemical engineering analysis. Asia Pac J Chem Eng 2011;6(4):639–48. doi:10.1002/apj.464.
[21] Annesini MC, Marrelli L, Piemonte V, Turchetti L. Artificial organ engineering. Springer; 2017. ISBN 978-1-4471-6442-5, ISBN 978-1-4471-6443-2 (ebook).
[22] Minekus M. The TNO gastro-intestinal model (TIM) the impact of food bioactives on health. Vitro and *ex vivo* models. Heidelberg New York Dordrecht London: Springer Cham; 2015.
[23] Thuenemann EC, Mandalari G, Rich GT, Faulks RM. Dynamic gastric model (DGM) *in vitro* and *ex vivo* models. Heidelberg New York: Springer Cham; 2015.
[24] Ferrua MJ, Singh RP. Human gastric simulator (Riddet model) the impact of food bioactives on health. Vitro and *ex vivo* models. Heidelberg New York: Springer Cham; 2015.
[25] Kim HJ, Huh D, Hamilton G, Ingber DE. Human gut-on- a-chip inhabited by microbial flora that experiences intestinal peristalsis-like motions and flow. Lab Chip 2012;12(12):2165–74.
[26] Huh D, Kim HJ, Fraser JP, Shea DE, Khan M, Bahinski A, Hamilton GA, Ingber DE. Author information Microfabrication of human organs-on-chips. Nat Protoc 2013;8:2135–57.
[27] Piemonte V, Cerbelli S, Capocelli M, Di Paola L, Prisciandaro M, Basile A. Design of microfluidic bioreactors: transport regimes. Asia Pac J Chem Eng 2018;13(5):e2238.
[28] Gizzi A, Giannitelli SM, Trombetta M, Cherubini C, Filippi S, De Ninno A, Businaro L, Gerardino A, Rainer A. Computationally informed design of a multi-axial actuated microfluidic chip device. Sci Rep 2017;7(1):5489.
[29] Bein A, Shin W, Jalili-Firoozinezhad S, Park MH, Sontheimer-Phelps A, Tovaglieri A, Chalkiadaki A, Kim HJ, Ingber DE. Microfluidic organ-on-a-chip models of human intestine. Cell Mol Gastroenterol Hepatol 2018;5(4):659–68.
[30] Clements JA, Heading RC, Nimmo WS, Prescott LF. Kinetics of acetaminophen absorption and gastric emptying in man. Clin Pharmacol Ther 1978;24(4):420–31.
[31] Caillè G, Du Souich P, Besnerm JG, Gervais P, Vezina P. Effetcs of food and sucralfate on the pharmacokinetics of naproxen and ketoprofen in humans. Am J Med 1989;86(6A):38–44 9.
[32] Takahashi M, Washio T, Suzuki N, Igeta K, Yamashita S. Investigation of the intestinal permeability and first-pass metabolism of gruds in cynomolgus monkeys using single-pass intestinal perfusion. Biol Pharm Bull 2010;33(1):111–16.
[33] Elashoff JD, Reedy TJ, Meyer JH. Analysis of gastric emptying data. Gastroenterology 1982;83:1306–12.
[34] Guytin AC, Hall JE. Medical physiology. 11th ed. Elsevier Saunders; 2006. Unit XII.
[35] Borcstrom B, Erlanson C. Pancreatic lipase and co-lipase, interactions and effects of bile salts and other detergents. Eur J Biochem 1973;37(1):60–8 1.
[36] Sakač N, Sak-Bosnar M. Potentiometric study of Alfa-Amylase kinetics using a platinum redox sensor. Int J Electrochem Sci 2012;7:3008–17.
[37] Inagami T. The mechanism of the specificity of trypsin catalysis. J Biol Chem 1963;239:3.
[38] Heu MS, Kim HR, Pyeun JH. Comparison of trypsin and chymotrypsin from the viscera of anchovy, Engraulis japonica.com. Biochem Physionl 1995;112B(3):557–67.