GASTRO-INTESTINAL MODELLING FOR DRUGS BIOAVAILABILITY

[1]POMPAMARCELLO, [2]MAURO CAPOCELLI, [3]VINCENZO PIEMONTE

[1]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
[2]Unit of Process Engineering, Department of Engineering, University Campus Bio-Medico di Roma, via Álvaro del Portillo 21, 00128 Rome, Italy
[3]Head of 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
E-mail: [1]marci93.gp@libero.it, [2]m.capocelli@unicampus.it, [3]v.piemonte@unicampus.it

Abstract - This work focuses on a mathematical model able to describe the gastro-intestinal physiology and providing a rational tool for the design of an artificial gastro-intestinal system. This latter is mainly devoted to analyse the absorption and bioavailability of drugs and nutrients through in vitro tests in order to overcome (or, at least, to partially replace) in vivo trials. The provided model realizes a conjunction ring (with extended prediction capability) between in vivo tests and mechanical-laboratory models emulating the human body. On this basis, no empirical equations controlling the gastric emptying are implemented in this model as frequent in the cited literature and all the sub-unit, and the related system of equations are physiologically based. More in detail, the model structure consists of six compartments (stomach, duodenum, jejunum, ileum, colon and blood) interconnected through pipes and valves. Paracetamol, Ketoprofen, Irbesartan, and Ketoconazole are considered and analysed in this work as reference drugs. The mathematical model has been validated against in vivo literature data. The results obtained show a very good model reliability and highlight the possibility to realize tailored simulations for different couples patient-drug, including food adsorption dynamics.

Keywords - Gastro-intestinal model, drugs bioavailability, Drug Absorption, Membrane bioreactors.

I. INTRODUCTION

The gastro intestinal system (GI) is the responsible for digestion and absorption of the nutrients orally administrated in the organism [1,2]. It is composed by mouth, the stomach and the intestine, (duodenum, jejunum, ileum and colon). Enzymatic digestion reactions take place both in the stomach and the duodenum: in the first case enzymes and gastric juices are produced in the stomach epithelium, in the second case the synergic interaction between liver and pancreas produces enzymes that can digest the chyme in output from the stomach [3].
Drugs absorption is a complex phenomenon that starts from jejunum and ends in the colon, through the passage (in counter current flux) of the blood [4,5,6]. This behaviour is the most interesting during drugs design and development phases. The absorption of a drug is given by the synergic interaction between the active transport and the diffusion through the intestinal wall, but the emptying of the stomach determines sensitively the absorption time and the final bioavailability [8].

The emptying time of the stomach is controlled by the stomach state: in the digestion phase, the emptying is controlled by duodenum, having the function to empty the stomach only at the end of the digestion cycle: the duodenum is filled by chyme until it reaches its maximum volume, duodenum stops the emptying of stomach, it starts the digestion of nutrients, and in the end, it empties itself to jejunum while stomach fills it again [7-11]. The intestinal tract motility is influenced by its state: in the fasted phase, the motility is different from the digestion phase [12].
Drug absorption depends on its chemical-physical proprieties: the drugs in capsule, for example, need to be disintegrated before to enter in solution [9]. The intestinal membrane can transport drug for passive diffusion, facilitated diffusion, pinocytosis or active transport [5,11-14].
The passive diffusion starts with a difference in concentration between blood and intestine. The key variables are the liposolubility of the drug and its molecular dimension. Fat-soluble drugs, with small molecular dimension, spread very fast through the membrane [1,5,15].
Facilitated diffusion is similar to passive diffusion, but it is faster. The transporting molecule of the membrane is linked reversibly with the substrate external at the membrane. So, this process creates a carrier-substrate structure that allows to spread the substrate inside the membrane very quickly [2,15].
The active transport, indeed, is selective, using energy and allowing the transport against concentration gradient. The drug to use this kind of absorption needs to have an anionic structure or to be similar to vitamins structure. This kind of absorption, furthermore, exists only in a few parts of the small intestine. The pinocytosis allows the cell to incorporate liquids or solid particles: the membrane cell forms a vesicle that detaching it moves inside the cell itself. This phenomenon uses energy too. The organism uses the pinocytosis for that drug with structure similar to a protein. As consequence, the absorption of a drug is a complex phenomenon to be

studied. The fundamental parameters used in pharmacokinetic are: absorption time, maximum drug concentration in the blood and elimination time [2,15].
The term bioavailability is used both for the amount of drug administered in the body, and for the amount of drug available after administration (the drug available for absorption). The bioavailability is the measure of the therapeutic activity [2,15]. A drug needs to be inside a therapeutic range to work properly; this therapeutic range refersto the drug concentration in bloodrequired to achieve the therapeutic effect with minimal toxicity. The oral administration does not give the possibility to stay in the therapeutic range a lot of time, for this reason, we try to make a new gastro intestinal model that helps to improve the oral administration of an existing drug or to provide an useful tool to rationale design new ones [2,8,15,16].
In summary, the bioavailability of a drug taken by oral administration in fasted phase depends on:

- Kind of formulation;
- Kind of molecule;
- Subject health.

If the drug is oral administrated in digestive phase (with food), the main variables are:

- pH of the compartment (stomach, duodenum, etc.);
- Motility;
- Chemical reactions between two or more drugs;
- Biochemical reaction of drug during its transport in the apparatus;
- Bacteria flora;

In this work we try to reproduce the entire drug absorption process through mathematical models mainly based on the use of membrane reactors. All the mathematical models, available in literature, refer to correlations adapted by experimental tests.
Single compartment model describes the organism with a single compartment: the absorption, metabolization and elimination of the drug are represented by material flux in input and output from well mixed compartment. Diffusion through the membrane and the drug distribution in the tissues are not considered. The model although reductive is used in clinical practice. Two-compartment model divides the organism in two parts: in this way, it considers the emptying speed and the drug distribution [2,15].
To the best of our knowledge, there are no models fully based on the unitary operations principles (typical of chemical engineering knowledge), able to simulate the gastro-intestinal tract by a physiologically based approach.

II. MATHEMATICAL MODELING

In order to write a physiological model of the gastro intestinal system, we have considered six compartments: stomach, duodenum, jejunum, ileum, colon, blood.
All the compartments are linked to each other with valves that control the flux in input and output from the compartments. The output flow from a compartment represents the input flow to the next ($\mathrm{Q_i^{out}} = \mathrm{Q_{i+1}^{in}}$).
The emptying of the stomach is controlled by enzymatic reactions in the duodenum: if the reactions are fast, then the emptying stomach will be quick. This system allows to control the emptying of the stomach without any external function or parameter, but only using physiological processes.
The system equations reported below is derived from material balance applied to each compartment.
In order to easier understand the equations, V represents the volume of the compartment and C the concentration. For the stomach

$$\mathrm{V_1}\frac{\mathrm{dC_{1,s}}}{\mathrm{dt}} + \mathrm{C_{1,s}}\frac{\mathrm{dV_1}}{\mathrm{dt}} = \mathrm{Q_1^{in}}\left(\mathrm{C_1^{in}}\right) - (-\mathrm{r_1})\mathrm{V_1} - \mathrm{Q_1^{out}}\left(\mathrm{C_{1,s}}\right) - \left(-\mathrm{r_{s,d}}\right)\mathrm{V_1} \quad (1)$$

$$V_1\frac{dC_{1,p}}{dt} + C_{1,p}\frac{dV_1}{dt} = -Q_1^{out}\left(C_{1,p}\right) + (-r_1)V_1 - \left(-r_{p,d}\right)V_1 \quad (2)$$

$$V_1 = V_{1,0} + Q_1^{in} * t - Q_1^{out} * t \quad (3)$$

The concentration variable (C) must be interpreted as a vector of four substrate (s):

- Lipids;
- Starch;
- Proteins;
- Drug.

The enzymatic reactions and the possibly reactions between
nutrients and drug are:

$$(-r_1) = \frac{v_{max,1} * C_{1,s}}{K_{m,1} + C_{1,s}} \quad (4)$$

$$\left(-r_{s,d}\right) = k_r * C_{1,s} \quad (5)$$

$$\left(-r_{p,d}\right) = k_{r2} * C_{1,p} \quad (6)$$

The duodenum controls the emptying of the stomach, digests the chyme, and empties itself into the jejunum compartment. In this compartment too, we consider the possibility that the nutrients could react with the drug (Eqs. (10)-12)).

$$V_2\frac{dC_{2,s}}{dt}+C_{2,s}\frac{dV_2}{dt}=Q_2^{in}\left(C_{1,s}\right)-(-r_2)V_2-\left(-r_{s,d}\right)V_2 \quad (7)$$

$$V_2\frac{dC_{2,p}}{dt}+C_{2,p}\frac{dV_2}{dt}=-Q_2^{out}\left(C_{2,p}\right)+(-r_2)V_2+Q_2^{in}C_{1,p}-\left(-r_{p,d}\right)V_2 \quad (8)$$

$$V_2=V_{2,0}+Q_2^{in}\cdot t-Q_2^{out}\cdot t+Q_{2,ext}\cdot t \quad (9)$$

$$(-r_2)=\frac{v_{max,2}\cdot C_{2,s}}{K_{m,2}+C_{2,s}} \quad (10)$$

$$\left(-r_{s,d}\right)=k_r\cdot C_{2,s} \quad (11)$$

$$\left(-r_{p,d}\right)=k_{r2}\cdot C_{2,p} \quad (12)$$

The third compartment (jejunum) is composed by a bioreactor for the stock of the chyme (Eqs. (13)-(14)) and by a hollow tubular membranebioreactor for the drug absorption (Eq. (15)-(16)).We consider both active and passive transports (diffusive). The initial conditions are written for $0<z<L$ with $C_p(z)=C_b(z)=0$, while the boundary conditions are $C_p(0)=C_3$ and $C_b(0)=C_4$ (where C_4 is the drug concentration in blood).

$$V_3\frac{dC_{3,p}}{dt}+C_{3,p}\frac{dV_3}{dt}=Q_3^{in}\left(C_{2,p}\right)-Q_3^{out}\left(C_{3,p}\right) \quad (13)$$

$$V_3=V_{3,0}+Q_3^{in}\cdot t-Q_3^{out}\cdot t+Q_{3,ext}\cdot t \quad (14)$$

$$\frac{dC_p}{dt}=-v_p\frac{\delta C_p(z)}{\delta z}-\frac{2k_{0ll}}{R_1}\left(\mathrm{C_p}-\mathrm{C_b}\right)-\left(-\mathrm{r_{abs_active}}\right) \quad (15)$$

$$\frac{\mathrm{dC_b}}{\mathrm{dt}}=-\mathrm{v_b}\frac{\delta \mathrm{C_{b(z)}}}{\delta \mathrm{z}}+\frac{2\mathrm{k_{0ll}R_1}}{(\mathrm{R_2^2}-\mathrm{R_1^2})}\left(\mathrm{C_p}-\mathrm{C_b}\right)+\left(-\mathrm{r_{abs_active}}\right) \quad (16)$$

being:

- k_{0ll} the drug permeability;
- r_a the active transport coefficient.

$$(-\mathrm{r_a})=\mathrm{k_{abs}}\cdot\mathrm{C_p} \quad (17)$$

In the blood compartment (Eqs. (18)-(19)), we study the drug concentration over time. The boundary condition is $C_b^{in}=C_b(L)$, with $C_b(L)$ the drug concentration in the tubular reactor in $z=L$.

$$\frac{\mathrm{dC_4}}{\mathrm{dt}}=\frac{\mathrm{Q_4}}{\mathrm{V_4}}\mathrm{C_b^{in}}-(-\mathrm{r_{el}})-\frac{\mathrm{Q_4}}{\mathrm{V_4}}\mathrm{C_4} \quad (18)$$

$$(-\mathrm{r_{el}})=\mathrm{K_{el}}\cdot\mathrm{C_4} \quad (19)$$

Finally, ileum and colon compartments are modelled as the jejunum compartment.

III. RESULTS

The drugs analysed in this work are ketoprofen and paracetamol, ibersartan and ketoconazole. Ketoprofen is a fan used for the pain treatment and inflammatory state. If the treatment lasts for a long time, the gastric mucosa could be damaged [14]. Paracetamol is used for its antipyretic and analgesic propriety. An improper treatment could lead to a serious damaged of liver [13].Irbesartan is used for cardiac problem [16], while ketoconazole is an antifungal medication and it is used to treat fungal infections [17].

Model parameter estimations have been obtained through the fitting of in vivo results, available in literature [13,14,16,17]. Fitted parameters are reported in Table 1, whileemptying times for each compartment arereported in Table 2.

Figs. from 1 to 4 show the comparison between the drug concentration in the bloodcalculated by our model (blue lines) and the in vivo data (orange point) collected from literature. As one can see from the figures, model simulations follow very well the in vivo data, with a maximum drug concentration very close to the experimentaldata. It is interesting to highlight the good performance of the model achieved with a low number of adjustable parameters, which have a well-defined physiological meaning. All the others model parameters can be obtained from the physio-anatomic knowledge of human gastro-intestinal apparatus. Furthermore, it is possible to simulate intestine reduction due to surgical operations or several diseases of the same gastro-intestinal system by varying geometrical and operating model parameters such as tubular membrane reactors length, chyme velocity, directly related to intestine motility, blood velocity, etc.

Table 1. Model parameters obtained from fitting of in-vivo tests

	Jejunum		Ileum		Colon		Blood
	K_{tr}	K_{0ll}	K_{tr}	K_{0ll}	K_{tr}	K_{0ll}	K_e
Paracetamol	10^{-8}	$6*10^{-4}$	$5*10^{-8}$	$6*10^{-4}$	$5*10^{-6}$	$5*10^{-6}$	$2*10^{-6}$
Ketoprofen	$4*10^{-8}$	$8*10^{-8}$	$4*10^{-8}$	$8*10^{-2}$	$5*10^{-6}$	$5*10^{-6}$	$4*10^{-6}$
Irbesartan	10^{-7}	$3*10^{-8}$	$5*10^{-10}$	10^{-8}	$5*10^{-10}$	10^{-8}	10^{-4}
Ketoconazole	10^{-9}	$5*10^{-4}$	$2*10^{-6}$	$5*10^{-6}$	$9*10^{-6}$	$3*10^{-6}$	$2*10^{-4}$

Table 2. Emptying times for each model compartment.

	Stomach	Duodenum	Jejunum	Ileum	Colon
Emptying time (min)	15	15	100	80	1000

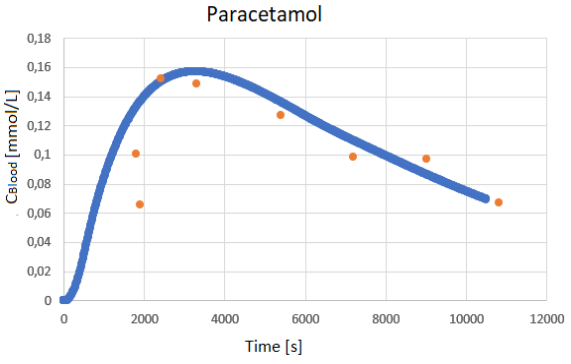


Fig. 1Paracetamol concentration in Blood compartment during the time

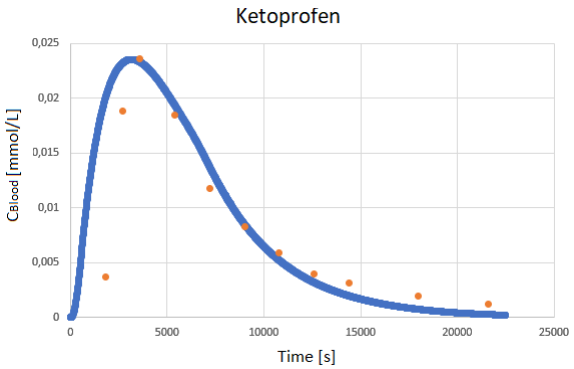


Fig. 2Ketoprofen concentration in Blood compartment during the time

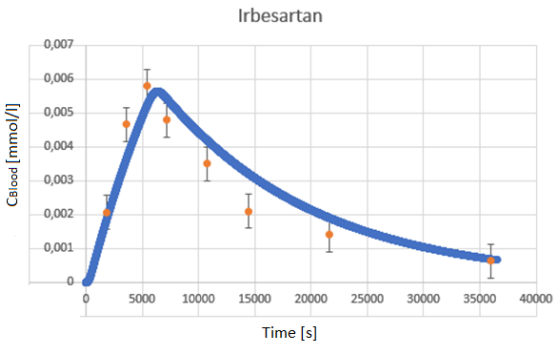


Fig. 3 Irbesartan concentration in Blood compartment during the time

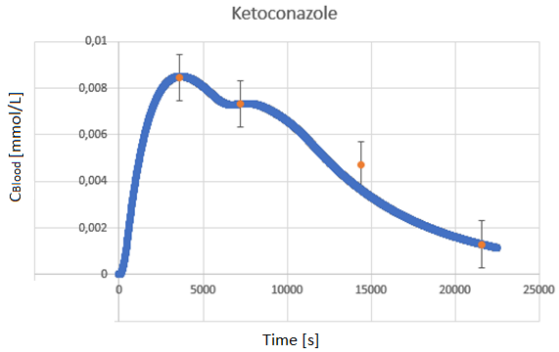


Fig. 4 Ketoconazole concentration in Blood compartment during the time

CONCLUSIONS

In conclusion, the bioavailability and the absorption of a drug are two important factors, that need to be deep analysed by rigorous mathematical models. The main innovations of the proposed approach are the novel 6-compartments structure and the introduction of membrane reactors able provide a qualitative analysis of drug absorption in the blood and its bioavailability. A model, able to use few parameters and variables to describe the complexity of human physiology, could permit to create new personalization system of drug administration: keeping in mind the health state of a subject, a physiological model could be used to study a therapy for that subject in particular. Furthermore, a predictive model could be used to revolutionize the production of a drug, permitting the knowledge of an important data before the in vivo test.

NOMENCLATURE

- $C_{i,j}$ concentration vector (lipid, protein, starch, drug);
- C_p hollow fiber concentration, body side;
- C_b hollow fiber concentration, shell side;
- outoutput from compartment;
- k_{abs} active absorption coefficient;
- k_{el} drug elimination coefficient;
- $k_r$first-order kinetic constant for bolus-drug interaction;
- k_{r2} reaction coefficient for chyme-drug interaction;
- $K_{m,i}$ Michaelis Menten parameter;
- k_{0ll}cell permeability to the drug;
- Q_i flow rate;
- $Q_{i,ext}$ external flux flow rate;
- r_a active transport;
- r_i enzymatic reaction;
- $r_{j,d}$reaction between j and drug (d);
- r_{el}drug elimination reaction;
- v_p product velocity, body side;
- v_b blood velocity, shell side;
- $v_{max,i}$ Michaelis Menten parameter;
- V_i volume;
- t time;
- z linear space;

Subscript/superscript

- in input to the compartment;
- irelated to the i^{th}compartment;
- srelated to the substrate j;
- p related to the product;
- out output from compartment;

REFERENCES

[1] J. Hirtz (1985), "The gastrointestinal absorptionofdrugsin man: a review ofcurrent concepts and methods of investigation", Br. J. clin. Pharmac. 19, 77S-83S

[2] S. Lakshmana Prabu, T.N.K. Suriyaprakash, K. Ruckmani, R.Thirumurugan (2015), "Biopharmaceutics and Pharmacokinetics", Inthech, Cap. 5

[3] MansMinekusChapter 5 The TNO Gastro-Intestinal Model (TIM) The Impact of Food Bioactives on Health. In Vitro and Ex Vivo Models. Springer Cham Heidelberg New York Dordrecht London 2015

[4] Y. Wang, J.G.Brasseur, G.G.Banco, A.G.Webb, A.C.Ailiani, T.Neuberger (2010): A multi-scale lattice Boltzmann model of macro- to micro-scale transport with applications to gut function. Philosophical Transactions of The Royal Society A, 368: 2863-288

[5] Masayuki TAKAHASHI, Takuo WASHIO, Norio SUZUKI, Katsuhiro IGETA, and Shinji YAMASHITA (2010), "Investigation of the Intestinal Permeability and First-Pass Metabolism of Gruds in Cynomolgus Monkeys Using Single-Pass Intestinal Perfusion", Pharmaceutical Society of Japan

[6] Arthur C. Guytin, M.D., John E. Hall, PhD (2006), "Medical Physiology", eleventh edition, Unit XII, Elsevier Saunders

[7] Chapter 7 Human Gastric Simulator (Riddet Model) Maria J.Ferrua and R. Paul Singh. The Impact of Food Bioactives on Health. In Vitro and Ex Vivo Models. Springer Cham Heidelberg New York Dordrecht London 2015

[8] Linnea Sjödin, Sandra Visser, Ahmad Al-Saffar Using pharmacokinetic modeling to determine the effect of drug and food on gastrointestinal transit in dogs. Journal of Pharmacological and Toxicological Methods 64 (2011) 42–52

[9] Deanna M. Mudie, Gordon L. Amidon, and Gregory E. Amidon Physiological Parameters for Oral Delivery and In vitro Testing. Mol Pharm. 2010 October 4; 7(5): 1388–1405. doi:10.1021/mp100149j

[10] Pal, K. Indireshkumar, W. Schwizer, B. Abrahamsson, M. Fried, J.G. Bracceur (2004): Gastric flow and mixing studied using computer simulation. Proceedings of the Royal Society B, 271: 2587-2594

[11] M.J. Ferrua, R.P.Singh (2010): Modeling the fluid dynamics in a human stomach to gain insight of food digestion. Journal of Food Science, 75 (7): R151-R162

[12] Chapter 6Dynamic Gastric Model (DGM) Eva C.Thuenemann , Giuseppina Mandalari,Gillian T. Rich, and Richard M. Faulks. In Vitro and Ex Vivo Models. Springer Cham Heidelberg New York Dordrecht London 2015

[13] J. A. Clements, Ph.D., R. C. Heading, W. S. Nimmo, and L. F. Prescott, M.D. (1978), "Kinetics of Acetaminophen absorption and gastric emptying in man", The C. V. Mosby Co.

[14] Gilles Caillè, B. Pharm, M. Sc., Ph. D., Patrick' Du Souich, M. D., Ph.D., Jean Guy Besnerm, Sc., Ph.D., Pierre Gervais, B. Sc. Pharm., M. Sc., Manon Vezina, MSc., Ph. D. (1989), "Effetcs of Food and Sucralfate on the Pharmacokinetics of Naproxen and Ketoprofen n Humans", The Aemrican Journal of Medicine Volume 85 (suppl 6A)

[15] Adam M. Persky, PhD (2013), "Foundations in Pharmacokinetics"

[16] Nimish N., Vachharajani,WenChyiShyu,Robert A. Smith& Douglas S. Greene1, "The effects of age and gender on the pharmacokinetics of irbesartan", Br J ClinPharmacol 1998; 46: 611–613;

[17] Tawfique K. Daneshmend and David W. Warnock, "Clinical Pharmacokinetics of Ketoconazole", Clinical Pharmacokinetics 14: 13-34 (1988).

★★★