Industrial Engineering & Translational Medicine: The Role of Modeling

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A novel approach is becoming the mainstream in medicine, bringing the engineering approach in the early stages of investigations in pharmacology and biomedical science: the so-called "translational medicine". It has been defined as the process of turning appropriate biological discoveries into drugs and medical devices that can be used in the treatment of patients. The translational medicine is based on the cooperative efforts of different disciplines, all aimed at the same objective: to follow the full path of a novel therapeutic tool "from the bench to bedside". During the first phase of a translational research, the aim is the translation of non-human research findings, from the laboratory and from animal studies, into therapies for patients. In this field, the industrial engineers (particularly, chemical engineers and biomedical engineers) usually play a main role.

One of the most relevant tool commonly used by engineers, and usually not available to medical and pharmaceutical researchers is the mathematical modeling, i.e. the use of properly written equations to describe the physical reality. In the following, some of the most relevant achievement of my research group was briefly summarized, in order to emphasize the relevance of mathematical modeling in translational medicine studies.

The Modeling in Drug Release Studies

The controlled release of drugs is a key topic in modern pharmacology. Pharmaceutical systems able to produce the drug release with a tailored kinetics are of great industrial interest. Matrices made of hydrogels are able to give tailored drug release profiles [1,2]. The process of formulation and testing of novel matrices systems is usually based on a large set of experiments, with the single guide of the formulator experience. By changing each preparative parameters, it is easy to reach a very high number of experimental tests. This is a cumbersome issue, and any shortcut could give great advantages to the process. The design of these systems requires a deep knowledge of the phenomena involved during matrix hydration/dissolution in the stomach and in the gastro-intestinal tract. The phenomena can be described in term of mathematical equations (modeling) which can be solved by properly designed software (numerical code). The mathematical modeling of the phenomena, once the code was fully predictive, could be a tremendous aid in the formulation, since it could save resources substituting experiments with calculations. Indeed, the availability of a reliable mathematical model, able to predict the release kinetic from drug delivery systems, could actually replace the resource-consuming trial-and-error procedures usually followed in the manufacture of these latter [3].

The recently proposed model was based on the transient balance equations for drug and water, and the related constitutive equations for diffusivity and material density. The numerical solution of the model equations allowed to describe all the observed phenomena: the water diffusion into the matrix, the polymer swelling and erosion phenomena which cause a non-affine volume increase (i.e. a deformation in matrix's shape), the drug diffusion and release. The model was applied firstly to matrices made of HPMC (hydroxyl-propyl-methyl-cellulose) and theophylline, and it was tuned by comparison with experimental data gathered working with these systems (Figure 1) [3]. Once proved the

model to be descriptive of all the observed phenomena, the model was applied to a different system (HPMC-diclofenac matrices), and it was found able to predict the experimental behavior without any further optimization stage [4].

The Modeling in Pharmacokinetics Studies

Motivated by the guiding principles stated by FDA: "The basic principle in an in vivo bioavailability study is that no unnecessary human research should be done", the research in this field is focused on the development of in-silico tools for the investigation of the pharmacokinetics of drugs. The studies in this field were developed with the aim of limiting the use of unnecessary animal and human tests, replacing them with computer-assisted calculations [5].

To predict the drug concentration within the human body, during and after the drug administration, is one of the main goals in pharmacology. The branch of pharmacology devoted to the study of the processes that affect drug distribution and the evolution of drug concentration within various regions of the body is the pharmacokinetics: "the study of the time course of drug and metabolite levels in different fluids, tissues and excreta of the body, and the mathematical relationship required to describe them"[6].

The approaches which can be used in the description of the fate of a drug within the body are two: compartmental and non-compartmental. The non-compartmental approach consists in finding the fitting mathematical law for the available experimental data, therefore it doesn't propose a physical interpretation of the events that happen in
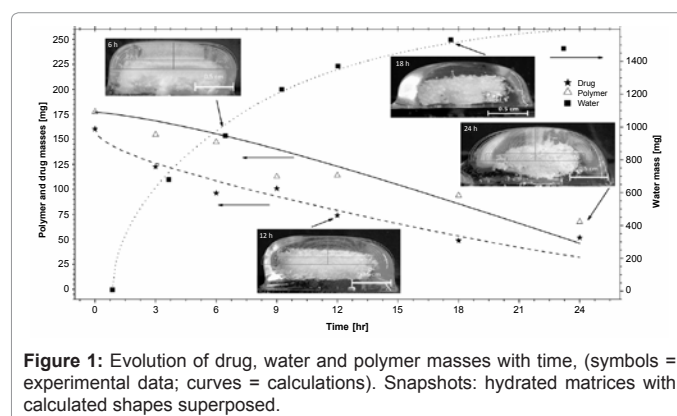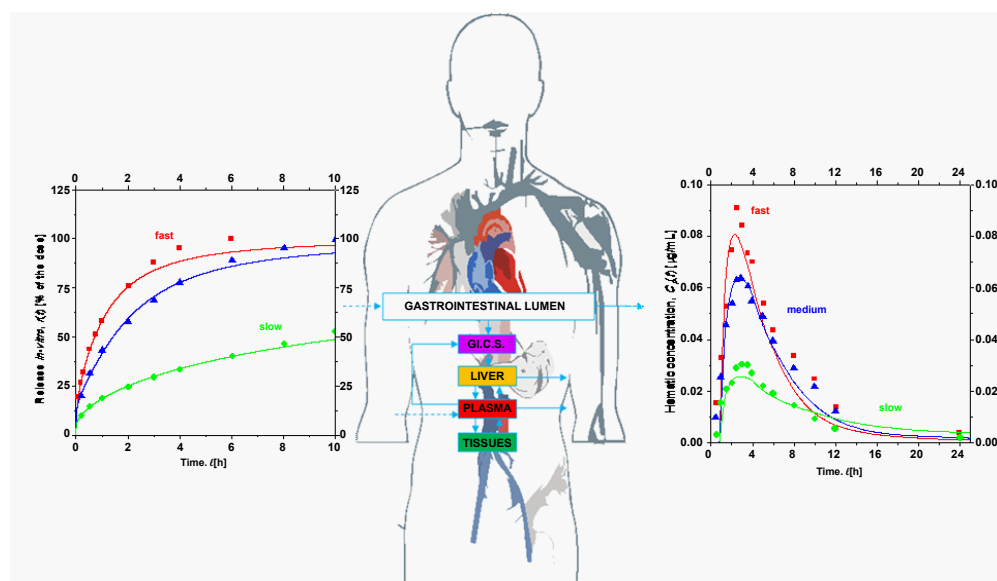

Figure 1: Evolution of drug, water and polymer masses with time, (symbols = experimental data; curves = calculations). Snapshots: hydrated matrices with calculated shapes superposed.

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Figure 2: On the left, release rate with time (in-vitro tests); on the right, hematic concentrations with time (in-vivo tests). Symbols = experimental data; curves = calculations. In the middle: schematic of the pharmacokinetic model.

the body. The compartmental approach is based on the schematization of the body by a system of interconnected volumes, the compartments, which can be easily identified by a chemical engineer as chemical reactors (usually continuous stirred) or as physical contacting units. Two major groups of compartmental models can be used in pharmacokinetic modeling: the mechanistic and the physiologically-based ones. The first category includes models in which the compartments don't represent necessarily anatomical units. The last one includes the models in which each compartment is representative of a tissue or an organ of the body and in which the interconnections between the compartments reproduce the effective ones between tissues or organs (physiologically based pharmacokinetics models, PBPK) [7].

Usually, pharmacokinetic modeling is aimed to establish correlations between the in-vitro release data with in-vivo hematic drug concentration (or different measurements of the drug in the bodies of living beings), a case history is reported in Figure 2 [7]. Our PBPK model was able, once tuned by comparison with one set of in-vitro/in-vivo data (in the case of Figure 2, the medium-rate release tablet data have been used), to predict what happens after the administration of pharmaceuticals with a different release rate. Indeed, the fast- and the slow-rate in-vivo data have been predicted with the model without any further optimization. The potential savings in term of resource and development time are thus evident.

Conclusions

The use of mathematical modeling, a tool usually adopted by engineers in their work, has been proved to be of great aid in translational medicine studies. In particular:

1. The complex process of controlled release of drug from matrices has been modeled. All the observed phenomena have been quantified and described by suitable equations. The proposed model has been proved able to reproduce all the phenomena which take place during the process. Therefore, the model constitutes a tool which could allow a great time saving in the development of novel solid oral dosage pharmaceuticals.

2. What happens to a drug once administered to a living being could be described mathematically, and a recently proposed physiologically based pharmacokinetic model (PBPK model) has been proved able to describe the hematic levels of drug after its administration for various physiologies (rat, human) and for different administration routes (intravenous injection, oral administration), for several drugs. The availability of such a tool, once more, could allow to avoid the excessive use of human or animal tests (which are both resource consuming and ethically problematic).

References

1. Barba AA, Damore M, Chirico S, Lamberti G, Titomanlio G (2009) A general code to predict the drug release kinetics from different shaped matrices. Eur J Pharm Sci 36: 359-368.

2. Siepmann J, Siepmann F (2008) Mathematical modeling of drug delivery. Int J Pharm 364: 328-343.

3. Lamberti G, Galdi I, Barba AA (2011) Controlled release from hydrogel-based solid matrices. A model accounting for water up-take, swelling and erosion. Int J Pharm 407: 78-86.

4. Lamberti G (2012) Parametric simulation of drug release from hydrogel-based matrices. J Pharm Pharmacol 64: 48-51.

5. Thomas S (2009) Physiologically-based simulation modelling for the reduction of animal use in the discovery of novel pharmaceuticals. Altern Lab Ani 37: 497-511.

6. Di Muria M, Lamberti G, Titomanlio G (2009) Modeling the pharmacokinetics of extended release pharmaceutical systems. Heat Mass Transfer 45: 579-589.

7. Di Muria M, Lamberti G, Titomanlio G (2010) Physiologically Based Pharmacokinetics: A Simple, All Purpose Model. Ind Eng Chem Res 49: 2969-2978.