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Thesis

A dynamic distributed-parameter modeling approach for performance monitoring of oral drug delivery systems

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All my family,

All my friends.

In memory of my young cousin Julie.

Abstract

Representing more than 50% of a worldwide pharmaceutical market of US$ 400 billions, oral drug delivery systems become naturally the focus of many studies. For almost half a century scientists have attempted to develop a theoretical model capable of predicting oral drug absorption in humans. From steady state or quasi-equilibrium models to complex and computationally intractable dynamic modeling approaches, numerous research efforts tried to address the problem of interest. Surprisingly though, no simple insightful first-principle-based dynamic modeling approaches have been reported in the literature. It is the purpose of the present work to provide a simple dynamic distributed-parameter modeling approach for performance monitoring of oral drug delivery systems.

As a consequence of the complexity of the gastrointestinal tract, drug oral bioavailability is influenced by many different parameters. These parameters range from the compound's physicochemical properties, the physiological factors of the environment to other factors inherent in the drug form itself known as encapsulation factors. Physicochemical properties account for parameters such as drug stability, solubility or diffusivity. Furthermore, the environment, namely the gastrointestinal tract, influences the drug delivery process to the body with its pH, intestinal transit time and the different transport mechanisms that take place.

From a chemical engineering point of view, the human body's anatomy can be analyzed and conceptually realized as a transport-reaction chemical system. Within the proposed modeling framework, the stomach is modeled as a non-ideal continuous-stirred tank reactor (CSTR) and the small intestine is the place where convection-diffusion occurs. The governing transport equations have been solved at steady state conditions in a small intestine represented by the lumen surrounded by its wall. The present work however develops a systematic dynamic first-principle-based distributed-parameter modeling framework where the time-dependent convection-diffusion-reaction model equations are analytically solved, offering the concentration profile in the small intestine lumen and in the wall from the moment the drug is administered until the complete absorption or disintegration of the drug particles.

Once the modeling work is performed, a thorough and insightful sensitivity analysis can be conducted in order to assess the impact of the different process parameters on drug bioavailability.

Keywords

Bioavailability, drug delivery, mass balance approach, dynamic modeling, partial differential equations, sensitivity analysis, dynamic simulations.

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I - Introduction

Major scientific advancements in the medical and biomedical fields have resulted in an increased life expectancy and better public health during the last half of the 20th century. The pharmaceutical world-wide market was estimated to be US$ 200 billions in 1990 and double this size: US$ 400 billions, by 2000. The driving force behind this progress is the considerable investment in research made by the pharmaceutical industry. Moreover, 80% of this market segment accounts for the US and the European top five consumers, headed by Germany and France. Notice, that these countries represent only 15% of the world population. Therefore, this imbalance clearly indicates the great potential for new markets to be realized in emerging/developing countries, where the new generation of products of the pharmaceutical industry is expected to bring hope and social stability.

Within this socioeconomic framework, it is not surprising that pharmaceutical companies are continuously striving for the development of new medically efficient products. In the US, around 18% of the turnover of this industry is invested in R&D efforts. In this fiercely competitive environment drug discovery is pursued on the fast track. Between the moment a new molecule and drug is found and designed, and the moment it will become available in the market seven to twelve years may elapse. The average cost of discovering and developing a new drug is more than US$ 530 millions. This price is justified: innovation is the key for pharmaceutical companies to remain competitive.

Since it can take years of research to discover and produce new molecular design-based drugs, an alternative strategy toward the fulfillment of medical and therapeutic needs would advocate the reconsideration of the ways the drug is delivered. Indeed, instead of finding a new molecule to fit a given problem it can be worthwhile to try to induce a known molecule to act differently inside the body. Therefore, the development of a new drug should often be complemented by a new delivery process and protocol.

The way the drug is delivered critically influences the way it works, not only on the medical but also on the marketing front. Notice that once the drug patent comes to its expiration, a slight modification of the delivery process provides the company with a new protected product. The psychological aspect of taking a drug is of importance as well. A patient might prefer having his prescription to be taken once a day, once a week or only in the morning. The convenience the patient finds in its drug prescription can be a key for the development and market introduction of a competitive product. The medical aspects primarily rely on factors such as drug bioavailability, and the widely accepted thesis that. the answer to different diseases may lie in the same molecule, distributed in diverse ways inside the body.

It is therefore of primary importance to be able to design drug delivery systems in medically efficient and viable protocols, with fewer side effects and enhanced levels of psychological comfort for the patient. As noticed earlier, every new drug delivery system

implies new patents and the control of drug delivery processes is a strategic key comparative advantage in the pharmaceutical business.

There are many ways to administer a drug: oral, inhalation, implant or transdermal. Oral delivery is undoubtedly the most traditional one. It represents more than 50% of the drug market. The reason for this popularity is that this delivery process is recognized to be the most convenient way to absorb a drug. It is also the safest and cheapest. In comparison with other delivery processes, the success in having the patient accepting the medicine is higher for orally delivered drugs.

When a drug is administered, it is of primary importance to know the quantity absorbed by the body as well as the absorption rate. To characterize the therapeutic effects of a drug, tests are realized at the different steps of its development. Every single parameter susceptible of having an influence on the drug efficiency or reliability is subject to study. For that reason, experimental and/or simulation studies should be conducted. However, experiments, even if sometimes unavoidable, can incur dramatic costs in time and in money. The advantage to be in a possession of a process model is the ability to "recreate/re-enact" the experimental conditions, and thus replaces the cost of experiments by the cost of a computer, which is not a major investment these days. Capital expenses can be substantially curtailed in that manner. Also, where experiments can take days to run, including a human error factor that is growing with the amount of within the experiment needs to run, a computer can give a solution in minutes or seconds. An "if-then" approach of the problem can be performed, leading to a faster understanding

of the influence of the parameters under study. Furthermore, being able to generate results in a reproducible way, when experiments can include non controlled parameters influencing the final result and consequently non detectable errors, is precious for the reliability of the results obtained. Therefore, this approach presupposes that the model takes into account all key parameters that experiments include into their respective framework. The incredible advancements in digital computer technology in the 1990's, and at the same time the affordability of their prices opened doors to new discoveries and methodological perspectives.

It is not surprising then that many research attempts have been made to develop models that provide an accurate characterization of the oral drug absorption process. These models are describing the intestinal tract functions under various conditions from steady state to dynamic. If steady state models provide a good understanding of the phenomenon taking place inside the gastrointestinal tract, they do not give access to absorption rates. Although they are usually more complicated, dynamic models present the benefit to offer concentration profiles and therefore absorption rates. Approaches that advocated the development of dynamic process models can be classified into three main categories: mixing tank models, compartmental absorption and transit models, as well as dispersion models [1] . Out of the three existing categories of dynamic models, the dispersion models are based on fundamental physical and chemical laws (first principle-based modeling approach), and in that sense, they represent a more realistic approach. However, they suffer from mathematical complexity and computational intractability that can not be easily overlooked, complicating the implementation stage of the proposed

modeling methods and unnecessarily undermining their practicality from a process performance monitoring point of view. Therefore, there is a true need for the development of a new dynamic modeling framework for oral drug delivery systems that would allow the explicit incorporation of first-principles and fundamental transport-reaction equation, while retaining theoretical simplicity, computational appeal, as well as the capacity to perform insightful investigations into the system's dynamic behavior and reliable process performance monitoring. It should be mentioned, that the proposed modeling framework should recognize the fact that, as a consequence of the complexity of the gastrointestinal tract, the drug oral bioavailability is influenced by many different parameters. These parameters range from the compounds' physicochemical properties, the physiological factors of the environment to the factors inherent to the drug form itself known as encapsulation factors. Physicochemical properties account for parameters such as drug stability, solubility or diffusivity. The environment, namely the gastrointestinal tract, influences the drug delivery to the body with its pH, intestinal transit time and the different transport mechanisms taking place.

Dispersion models are typically realized through fundamental transport equations describing the transport and reaction phenomena that occur in the intestine after the drug injection stage. These equations, which are typically parabolic partial differential equations, take into account the drug degradation kinetics, since the bioavailability of the drug relies on its stability [2] into the intestinal tract environment. The transport equations have already been solved at steady state conditions in a small intestine represented by the lumen surrounded by its wall [3]. The objective of this work is to set up and solve a

simple and analytical dynamic dispersion model for the concentration profile in the small intestine lumen and in the wall from the moment the drug is administered until the complete absorption or disintegration of the drug particles. The gastrointestinal tract is then represented by the succession of three compartments [4], representing the stomach, the small intestine, and the colon. The small intestine is typically composed of three segments: the duodenum, jejunum and ileum, but in the present study they are all lumped into a single element. Exchanges of substances happen between each of these organs and the surrounding fluids. However, drug absorption in the stomach and the colon are relatively slow, and it can be considered that the absorption happens only along the small intestine [5]. On the other hand, a stomach representation is necessary in order to get a boundary condition for the small intestine that is the focus of this study. The present work is thematically partitioned into three parts. First, a model for the stomach chamber is developed based on a non-ideal continuous stirred tank reactor descriptive model. This non-ideal chemical reactor model allows the derivation of an expression for the drug concentration at the lumen entrance, which is going to serve as one of the requisite boundary condition in a well-posed distributed-parameter problem formulated on the basis of the basic transport-reaction equations that govern the drug behavior in the lumen. The concentration profile in the intestine lumen is then calculated using the method of characteristics that finally leads to an expression for the drug concentration into the small intestine wall, which is where the drug becomes available for absorption. From a mathematical point-of-view, the last steps, involve the analytical solution of a system of two coupled time-dependent partial differential equations representing the underlying basic transport-reaction equations. Based on the proposed distributed-parameter dynamic

modeling framework a thorough and insightful sensitivity analysis is made, in order to assess the impact of key process parameters on drug bioavailability.

II - Literature review

Grass et al [6] propose the definition for pharmacokinetics: "the study of the time course of drug and metabolite levels in different fluids, tissues and excreta of the body, and of the mathematical relationships required to describe them". The purpose of this section is consequently to have an idea of what has been done in the study of drug absorption and what are the directions taken by authors.

II.1- In vivo studies

II.1.1 - Animal models:

The use of an animal model is far to be straightforward and many studies are aimed at defining how to fit animal studies to humans. For instance, drug transport in the lymphatic system has been correlated to a number of animal models [7]. The model reliability is therefore linked to the animal chosen and depends on the physiological similarities between the animal and man. Rat is the species that has been the most studied, for example in the case of halofantrine by Porter and Charman [8, 9, 10]. The animal used can be either conscious or unconscious. The authors [9] detail a conscious rat model, and presents the advantages of using conscious rats. These advantages are mainly the inexpensive experiments, the robustness of rats and a success of 70% in describing the lymphatic transport. The model they set up was successfully reused in another study

aimed at the absorption into the blood of a lipophilic drug [11]. Rather than rats, studies can be conducted in animal which can be closer to humans from given points of view, like dogs, pigs or primates. Edwards *et al* [7] studied some larger animal models for the lymphatic drug transport as well, in an attempt to overcome the limitations they met in rat models. The pig, for instance, presents similarities to humans in its gastrointestinal tract. However the absolute mass of drug transported by the lymph cannot be calculated in pigs, since the lymph returns to the systemic circulation. The authors in [7] also developed sheep models, but the huge difference between ruminants and monogastric species like human limit the applications of this model. Their paper puts an emphasis on a dog model. The dog, an adult male greyhound, is conscious and anesthetized, and a cannula is inserted into a jejunal vein to the level of the portal vein and ligatured. All branches going to the thoracic duct are ligatured to assure the return of lymph to the main canal. The model is recognized to be successful in many points. It allows indeed the rapid detection of lipophilic drug candidates; it also permits to administer full size human doses and has been used to establish the role of lymphatic transport in oral bioavailability.

An animal model can be influenced by many parameters. For instance [12] showed that fasting before or after the surgery influences the intestinal lymphatic drug transport. The lymph flow can increase by 75% depending on the solution that is going through the cannula [13]. In [7] is recognized the difficulty to assess the influence of anesthesia on the model. Their results are in conclusion tempered by the fact that a large amount of factors have an impact on the accuracy of the model estimations and that the experimental variables need to be controlled with attention.

II.1.2 - Future developments:

These restraints lead to Danis and Wilding work [14]. It is recognized that getting some information on regional absorption in the jejunum, ileum or in the colon, using animal models is essential in the early steps of a drug development, since it is very hard to abandon a drug candidate once in the full development process. However the bioavailability in animals does not extent well to humans. The same statement is addressed by Grass and Sinko [6]. According to them, the most likely reason for the lack of correlation is differences in physiology, manifested as differences in absorption, metabolism, plasma protein binding, etc. They plotted the absolute bioavailability of various drugs reported in different animals frequently used for animal modeling versus the absolute bioavailability reported in humans. This plot is shown on figure 1 and gives a good picture of the difficulty to relate animal modeling to humans. In their review, [14] explain that some experimental bioavailability studies nowadays can be conducted in man, since some technological advances allowed the development of capsules able to release drugs in desired parts of the intestine. These “intelligent” capsules are then able to deliver a small quantity of drug, a sub-therapeutic dose, to evaluate a regional absorption in the gastro-intestinal tract. The absorption profile of a drug can then be establish in the whole GI tract, saving time in the early developments of the product.

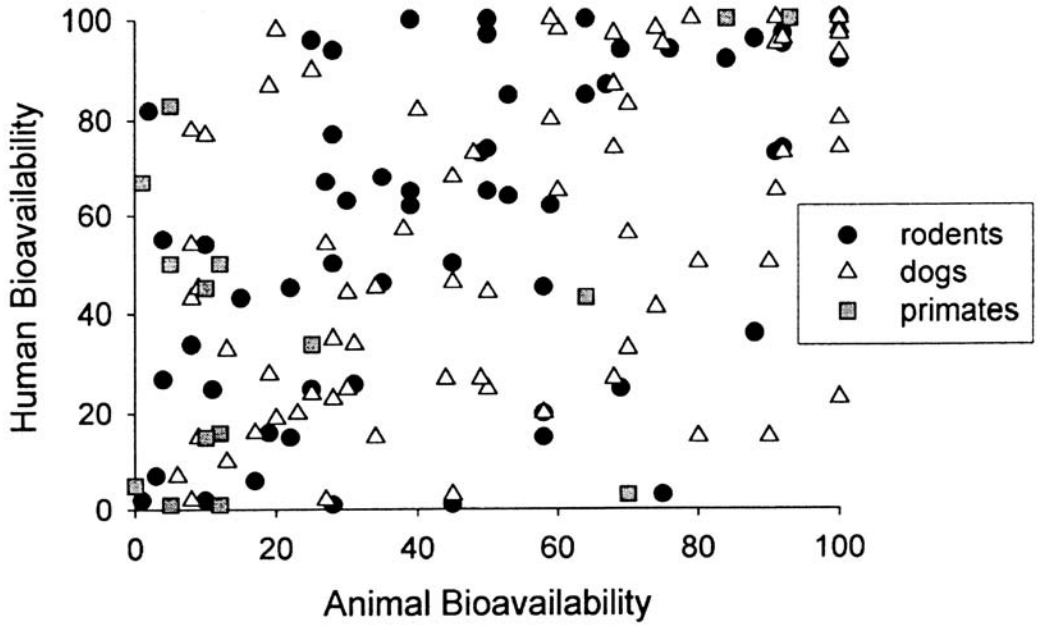

Figure 1 *Comparison between the absolute bioavailability in animals and the absolute bioavailability in humans. There is no apparent link between bioavailability in animals and bioavailability in humans. This illustrates the difficulty to rely on animals to assess the bioavailability of a drug in humans.*

II.2 - Description of the system under study

II.2.1 - The gastrointestinal tract [15]

In her book, Human Anatomy and Physiology, Elaine Marieb divides the digestion process in six common steps. Three of them are used in drug absorption studies:

- Mechanical digestion in the stomach, that breaks ingested particles in even smaller particles.
- Chemical digestion, representing the chemical degradation of the particles or molecules. This phenomenon mainly happens in the stomach.
- Absorption that is the course through the intestine wall of the digestion products from the lumen intestine to the blood.

II.2.2 - The stomach

Once the elements arrive in the stomach, this one contracts in order to break and mix them. The mixing movements are due to peristaltic waves. When these waves arrive at the basis of the stomach, they open the passage from the stomach to the small intestine. This allows the gastric evacuation in the intestine be a non-continuous process [15]. This process occurs as a series of jets with a period of twenty seconds [16]. Firmer and Cutler [18] considered the case of this non-continuous process for stomach emptying, by setting up a computer-based model. As the time dependence in their model was discretized, they explain that obtaining an analytical solution to their model would have been much more

difficult, but the emphasis they put on the process discontinuity enabled them to obtain good results in agreement with experiments ran on rats.

However, stomach models in the literature commonly represent the stomach emptying as a continuous process, which is reasonable when comparing the length of the twenty seconds periods with the digestion time that is of the order of hours. Different mathematical functions have then been used to explain the stomach emptying. Hunt and Stubbs [17], with many others, used a decreasing exponential to describe the phenomenon. Numerous non-exponential functions are reported in [18], such as square root law and other various shapes. However, the decreasing exponential remains the most commonly used function. This leads to the following point in the development of drug absorption models: very often these models are built up in collaboration with chemical engineers, and the stomach is then assimilated to a chemical reactor [19,20] or to a compartment which is subject to physical and mathematical laws. The compartmental approach will be detailed further. For now, the chemical reactor aspect is very interesting because the exponential decrease is typical of the ideal single continuously stirred tank reactor (CSTR) output [21,22]. The fact that both of the decreasing exponential mathematical description and the CSTR modeling support each other explains why both have been using in a more straightforward way rather than slightly different approaches.

II.2.3 - The small intestine

In the small intestine all the absorption processes occurs. Marieb [15] gives a review of the small intestine anatomy. Its length is between 6 and 7 meters in a dead

human body, but only 2 meters in the alive human, because of the muscular tonus. It is composed of three segments, duodenum, jejunum and ileum, of relative lengths of 0.25 meters, 2.5 meters and 3.6 meters. The microscopic anatomy of the small intestine is the key for the absorption. Roughly, the intestine can be described as a lumen surrounded by the intestine wall. The interface between the lumen and the wall is crucial for the absorption. The wall surface is composed of microvillus which increase the interface area, as shown on figure 2, extracted from [23]. The intestinal epithelium is a layer of cells attached between them with tight junctions. Their apexes form the apical surface that faces the intestine lumen.

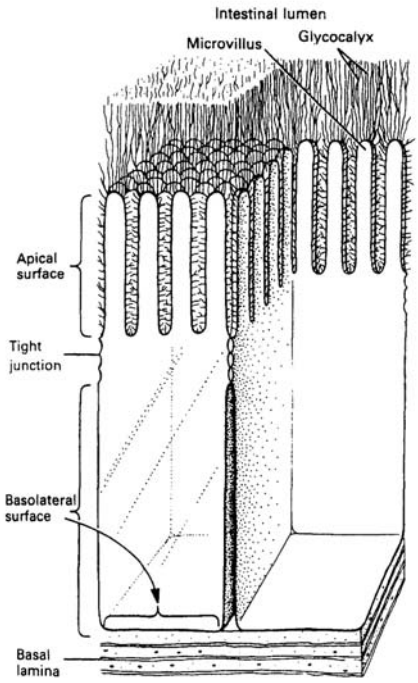

Figure 2 *Schematic representation of intestinal epithelial cells.*

Due to the complexity of the interface between the lumen and the wall, many researchers have been working at the study of the phenomena occurring in this area in

order to characterize their relative influence on the absorption of the molecules from the intestine lumen to the intestine wall.

The mucus is an aqueous mixture covering many epithelial surfaces in the human body. Its presence in the intestine affects the drug absorption. Khanvilkar *et al.* [24] studied the permeability of mucous gels. As they explain, the mucus is produced by the epithelial surface in the eyes, the respiratory tract but also the gastrointestinal tract, where it can have a thickness comprised between 50 and 450 μm [25,26]. In Khanvilkar [24] explicates the function of cytoprotection, lubrication, diffusion barrier. It is then as well a barrier to drug absorption. Moreover it promotes the formation of an unstirred water layer (UWL) [27] where the drug must diffuse before being absorbed across the epithelium. In their work for instance, Porter and Charman [28] put in plain words that the UWL is a major barrier to absorption of poorly water-soluble products. Some drug delivery systems can take advantage of it; these are the so-called muco-adhesive dosage forms [29], but except these latter, for drug absorption in the small intestine the following issues are addressed in [24]:

- How the diffusion is affected by the mucus?
- What factors are responsible for the drug diffusion transport through the mucus?

They used several methods to study the diffusion phenomenon through the mucus. The first one, a classical diffusion cell, is composed of two stirred cells separated by a membrane holder. One of the compartments, the donor, is filled with a drug solution, and the other one, the receiver with a buffer. Mucus is sandwiched between two drug-permeable membranes. Samples are then regularly taken in the two compartments, in order to determine the drug diffusion coefficient in the mucus. A second method

proposed is to use a known volume of mucus with one face exposed to the solution and after a certain time to measure the drug concentration in the mucus at different distances from the source. Some more sophisticated methods derived from UV spectrophotometric techniques [30] can be used. Their review also included a model for the drug diffusion coefficient in the mucus. This model, initially proposed by Peppas *et al.* [31], model the diffusion through the mucus, represented as a network, as a free-volume system, dependent on glycoprotein concentration, molecular size and density of cross links:

$D_n = D_W \, k \, c_m^{-1/3} \, \overline{M}_j \exp\left(- \frac{k' r_i^2}{1/c_m - \bar{v}} \right)$; where D_n is the diffusion coefficient in the mucus, D_W the one in water, c_m the glycoprotein concentration, $\bar{v}$ the specific volume of glycoprotein, $\overline{M}_j$ the average molecular weight, r_i the radius in the network, k and k' are constants. Their conclusions were firstly a good prediction of the models developed, and secondly, and of main importance in our framework, the fact that while mucus appears to represent a significant barrier to the absorption of some compounds, in many cases it adds very little additional resistance to the adsorption process. Small molecules particularly diffuse without any restraint in the mucous gel.

The specific case of highly lipophilic drugs is treated in [28]. This work exposes the challenges for this kind of drugs. The lipid digestion occurs in mainly three steps [32]:

- Dispersion of the fat globules into an emulsion
- Hydrolysis of the fatty acids at the oil/water interface
- Dispersion of the digestion products into an absorbable form

This emulsion then goes into the duodenum. Once in the small intestine a barrier between the bulk and the membrane formed of an UWL is met by the drug molecules. The aqueous nature of this barrier is the reason why highly lipophilic drugs are a specific challenge. However, once in the membrane their lipophilicity is an advantage as it will be exposed further when dealing with the transport processes into the wall.

After a description of the intestinal brush border, [23] studied the role of absorption enhancers in oral drug delivery. The effective delivery of a therapeutic agent via the oral route requires solubility, stability in stomach and the lumen and, as we just reviewed, the ability to pass through the intestine wall. This last parameter depends on the physical and chemical characteristics of the molecules. For instance, if intestinal permeability is good for simple dipeptides, which are actively transported, or small peptides, it becomes problematic for polar drugs and larger peptides and proteins. For these molecules the use of enhancers is suitable. These enhancers are reviewed in [23] with their description and action. Many of them exist, mainly bile salts and surfactants. Their role is to improve the aqueous solubility and the partition coefficient of the drug, when associated to it. Their action sometimes requires an alteration of the tight junctions or of the apical membrane of the intestinal epithelial cell (see figure above). The majority of them act directly on the apical membrane.

The obstacles or helps molecules can meet when penetrating the intestine wall have been reviewed above. Let's now introduce the important notion of partition coefficient. This number is the ratio between the concentrations of a substance in an

aqueous phase and in an oil phase. It gives an idea of the lipophilicity of the molecule it is related to. It is therefore linked to the absorption kinetics from the intestine lumen and the intestine wall, which are respectively of aqueous and lipidic nature. An example of the use of this coefficient in modeling drug absorption in the small intestine can be found in Idkaidek and Abdel-Jabbar work [33]. The concentration at the lumen-wall interface on the wall side is equal to the concentration on the lumen side times the drug partition coefficient. The partition coefficient is then used to obtain a boundary value for diffusion in the wall.

The partition coefficient of a drug can be determined like described in [34]: two solutions of the same volume of oil on the one hand and of buffer on the other hand are mixed with a given amount of drug. When the equilibrium is reached the concentration of drug in both phases is measured, by UV spectroscopy for instance, and the ratio of the two concentrations gives the partition coefficient.

Transport phenomena in the wall have been widely studied. The work proposed by Arturson *et al*. in [35] gives an excellent review of how a drug can be transported through the intestine wall. Four routes exist that a drug molecule can use in the intestine wall. These are exposed on the figure 3 below, extracted from [35]. The four routes are the following:

- The passive transcellular route (1 on the figure)
- The passive paracellular route (2 on the figure)
- The carrier mediated route (3 on the figure)
- The transcytosis route (4 on the figure)

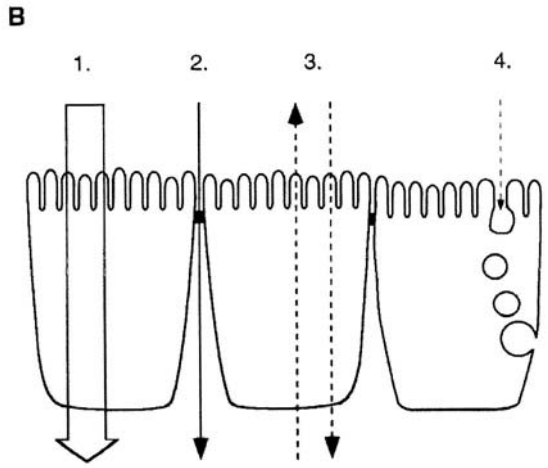

Figure 3 *The different transport routes for a molecule*

The transcytosis route is reserved for very specific molecules and is not considered as a very attractive transport route. As the carrier is saturable, as the drug concentration increase the contribution of the carrier mediated route will decrease relatively to the passive routes. So that, at a certain dose level of drug, the transport through the wall cells is due to passive transport. Therefore, passive transports are commonly accepted by authors as the main transport routes [23,35,36]. Between the two passive transports it would seem logical that a hydrophilic drug would use the paracellular route rather than the transcellular route, because of the lipidic nature of the cells. However, as [35] shows, the surface area of the luminal cell being 1000-fold larger than that of the paracellular space [37] and therefore the larger surface area of the cell membrane will compensate for the difference in the repartition between the cell membrane and the paracellular route.

Passive drug absorption is often studied using Caco-2 (Colon Carcinoma Cell Line) cell monolayers, which are an excellent model for the passive pathways as it is shown in [38,39]. They are aimed at identifying how a drug is transported through the

intestinal epithelium and at identifying the most appropriate enhancer if there is a need for it.

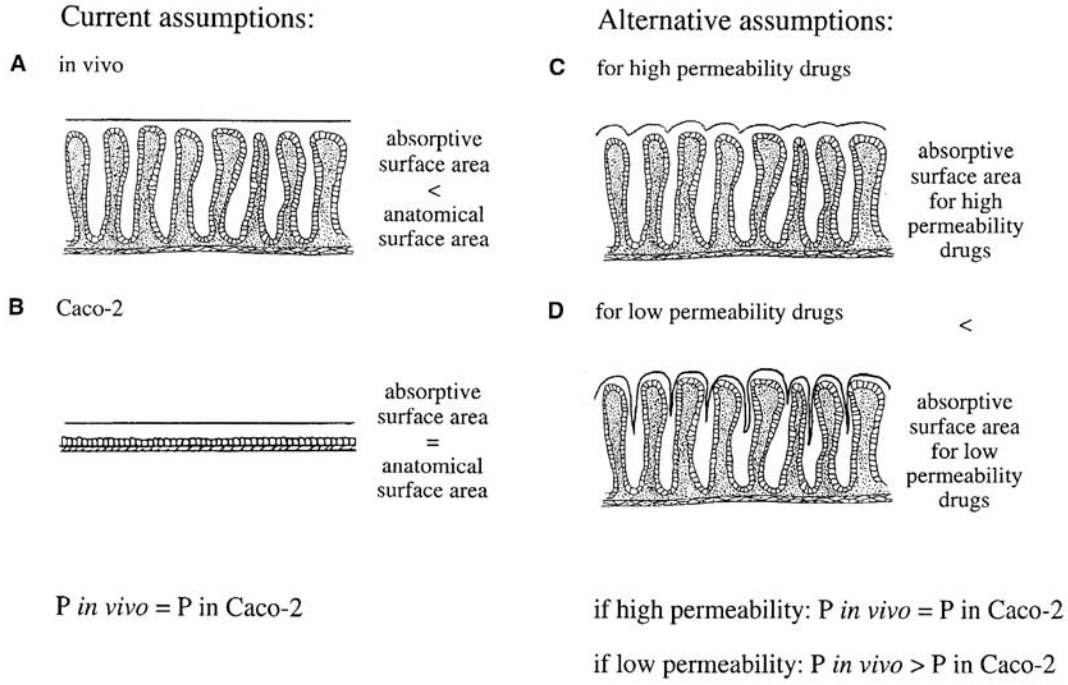

Figure 4 *Comparison of partition coefficients when using a Caco2 cell line. Extracted from [35]*

II.3 - Dynamic models

Now that all the essential concepts of the drug absorption are set up, a review of the dynamic models for oral drug absorption will be presented, based on the notions explained above. Dynamic models present the advantage upon steady state models to provide not only an estimation of the fraction of dose absorbed but also the absorbed drug concentration profiles with time.

As Grass and Sinko clarify in [6], in order to achieve an efficient research and development process for a new drug, there is a real need for competent models. These models must be based on pharmacokinetic properties. They divide them in single-parameter, multi-parameter and combined models.

Single-parameters models are often based on either the partition coefficient or the measurements in Caco-2 cells explained above. The problems met by these models are linked to the data used to run them. Larger sets of data are needed for better predictions. Consequently, a database for absorption parameters has been developed: the iDEA™ database, which has been explained and compared to another used database, Gastroplus™ in [40]. [6] concludes about single-parameter models with their efficiency in identifying significant parameters for drug absorption and their easiness of use, but this has to be balanced with their failure in meeting the test of broader datasets that limits their utility.

Multi-parameters models behave in a closer way to reality, since they include mathematical descriptions of all the significant processes that influence the molecule interactions with its environment. Consequently they are more difficult to develop but also more predictive.

Using a slightly different classification, Yu *et al*. reviewed in [41] the kind of dynamic models in three categories:

- Dispersion models
- Mixing tanks models
- Compartmental absorption and transit models (CAT models)

Mixing tanks models, simpler than dispersion models on a mathematical point of view came out in the 1980's. The principle of mixing tanks is to consider the gastrointestinal tract as a series of perfectly mixed tanks, with linear transfer kinetics. A model based on a single tank would allow a quantity of the drug to reach the colon as soon as it enters the small intestine, leading to an underestimation of the fraction absorbed. Several tanks would oblige the drug to spend some time in the intestine before reaching the colon, but each part of the small intestine would have the same problem, since the mixing tank representing each part would allow some of the drug entering to reach immediately the end of the segment. Based on this statement, the compartmental transit model was developed and replaces now mixing tanks models.

The compartmental absorption and transit (CAT) model was developed by Yu in [41]. In each compartment a set of differential equations describes the drug movement and the drug absorption. Initially, this work is based on a previously published model for the transit only in the small intestine [42]. Then, the CAT model was ameliorated in [41], including drug absorption. The transport problem through the small intestine is divided in several segments. Each segment can have a different volume and flow rate, but they all have the same transit rate constant. The transit rate constant is determined as a ratio between the number of compartments and the total transit time in the intestine. It is then considered that the drug spend a time equal to the transit time constant in each compartment. The absorption is assumed to be minor in the stomach and in the colon, but the drug is directly absorbed from one compartment of the small intestine to the plasma. The CAT approach is illustrated with 7 compartments on figure 5 below.

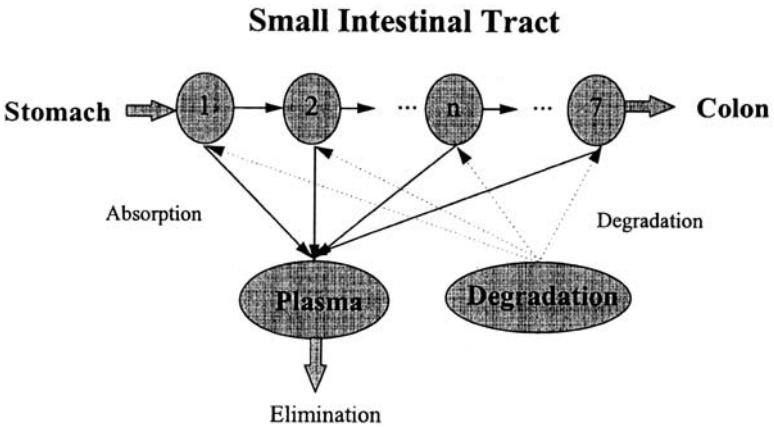

Figure 5 *A schematic diagram of a compartmental absorption and transit (CAT) model. The model considers transit, degradation and absorption of the drug in the small intestine.*

The CAT model has since been improved by its authors in [43] in a saturable absorption model, to take into account both the passive and saturable absorption mechanisms. Many other authors worked on improving CAT models, leading to more and more efficient, but more and more intractable and computationally demanding models. Agoram *et al*. presented in [44] an Advanced CAT model able to simulate non linear response in drug bioavailability and taking into account the influence of inhibitors and inducers of enzymes. A schematic of this Advanced CAT model is given in figure 6. The compartment physiological parameters become compartment dependant, and the colon is included in the model.

Mass balance approaches present the advantage to be based on the physics and chemistry laws describing the phenomenon occurring in the GI tract. These models remain quite simple as long as they are steady state models. Under dynamic conditions, mass balances in the small intestine have already been solved. Firmer [45] published a computer model based on a discretized mass balance to take into account the discontinuity of the stomach emptying. Almost a decade before Ni [46] had developed a

physical model for the

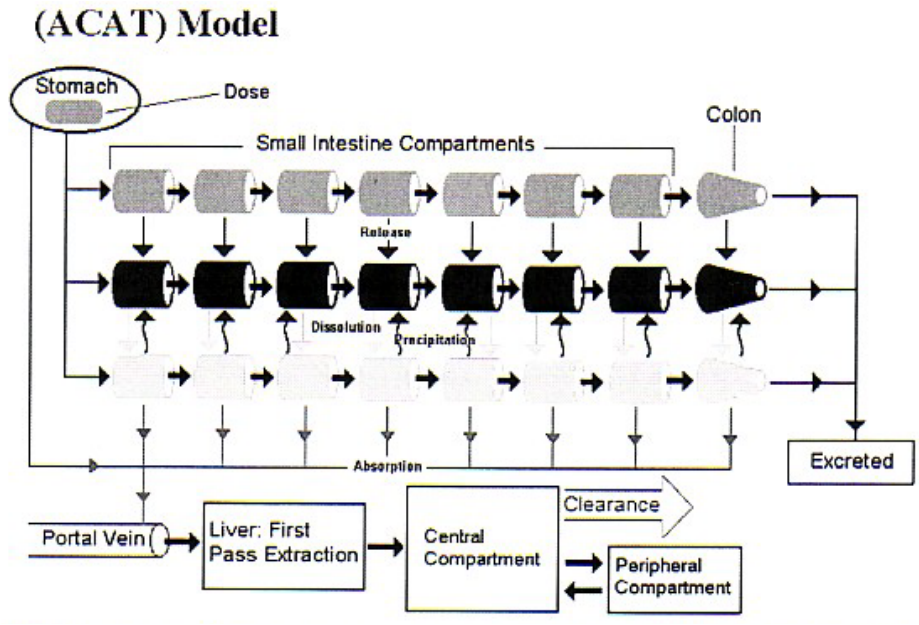

Figure 6 *ACAT model schematic. This model is more complicated than the previously shown CAT model and requires more computational effort.*

longitudinal fluid spreading in the small intestine, associated with the drug absorption. The model is based on a mass balance in a cylindrical geometry representing the small intestine. This mass balance was solved analytically for several input concentration profiles at the beginning of the intestine. They obtained an analytical solution using the Laplace transformation method, and provided a rigorous mathematical solution to their model with the use of the error function. Radial diffusion of the drug molecules in the wall was not included in their model. Their model was applied to the rat small intestine case for different partition coefficients. The concentration profiles they obtained at the small intestine outlet are shown on figure 7.

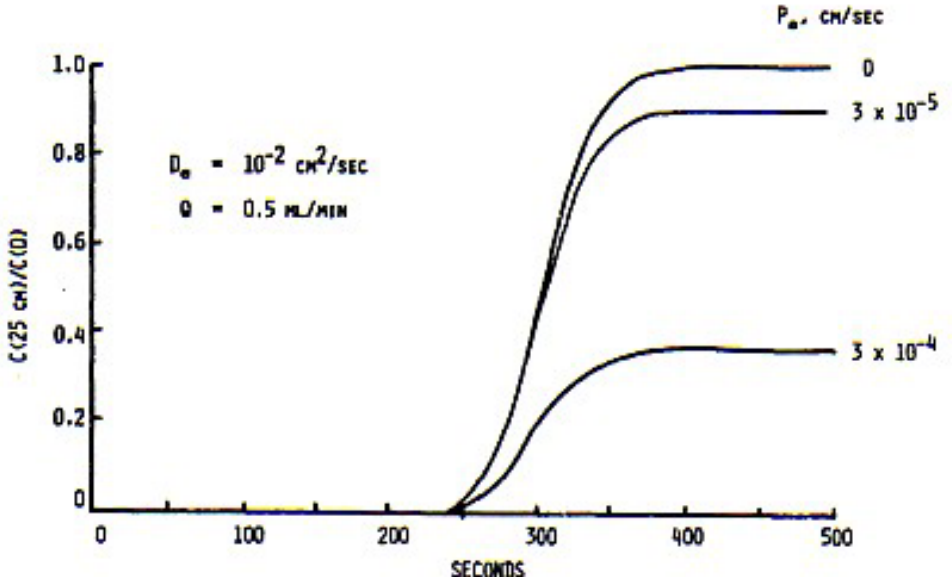

Figure 7 *Concentration profile at the small intestine outlet in a rat, calculated from Ni model.*

II.4 - Conclusion

To conclude this literature review it can be said that there is a need for efficient, reliable models for oral drug absorption. Many approaches exist, but there is a lack of a simple, first principle based model. It is surprising to see that at this time no mass balance has been solved in a dynamic and simple way, taking into account both transport mechanisms through the intestine lumen and through the intestine wall. It is the purpose of this work to provide the solution to such a problem.

III - Modeling approach

The stomach is modeled as a Continuously Stirred Tank Reactor [47] (CSTR). This approach has already been used to model different parts of the gastro-intestinal tract and present the advantage to be very flexible as shown hereafter. Indeed, chemical engineers are dividing chemical reactors in three main categories: batch reactors, plug flow reactors and CSTRs. Batch reactors are a closed process where chemical reactions take place in a closed environment. In plug flow reactors reactions take place along a stream and mixing between species occurs with the turbulence of the flow. In CSTRs the continuous species streams are mixed with a mechanical help (see figure above). In an ideal CSTR the concentration is assumed homogeneous all over the reactor and the residence time attains a mean reference value. However, in a real reactor the fluid particles spend a different time inside the reactor depending on the hydrodynamic profile of the reactor. Therefore, a distribution of the residence times characterizes the reactor. The residence time of a particle depends on the flow path this particle takes between the inlet and the outlet of the CSTR. The two ideal models of continuous reactors are the ideal models of CSTR on one hand and of plug flow reactor (PFR) on the other hand. A non ideal reactor can be assumed to behave in a way in-between these two types of perfect reactors. When the dominant behavior of the real reactor is plug-flow, the deviation of the reactor from ideality is represented by an axial dispersion model [21]. A way to describe the non ideal continuously stirred tank reactor is to replace it by an association of ideal CSTRs in cascade [21]. As the number of reactors in the cascade

increases, the modeled behavior gets closer to a PFR behavior. In this work, as the stomach is assumed to be a CSTR, the non ideality is modeled by the association of only two ideal CSTR in cascade. This choice allows us to observe a behavior closer from the CSTR behavior than from a PFR one.

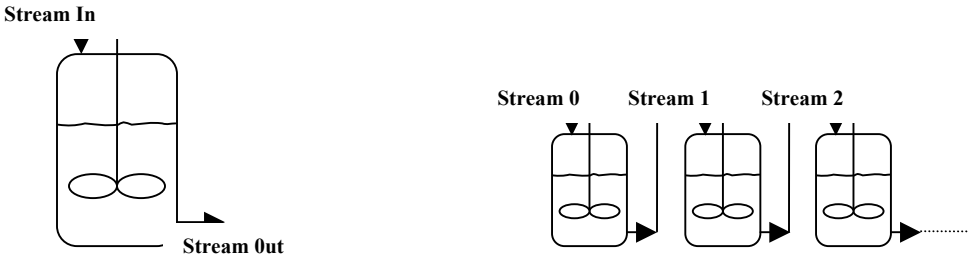

Figure 8 *Stomach modeling, single CSTR and CSTRs in cascade*

The feeding strategy is assumed to be an impulse. It is considered that at a time $t = 0$ a given number of drug molecules are deposited into the stomach, as the patient swallows his dose. Moreover, drug decomposition inside the stomach is taken into account. The drug decomposition kinetics is taken as a first order reaction, with a reaction rate k. Under these conditions the response on the concentration profile at the outlet of the stomach is given by the following expression:

$$c(t) = c_0 \tau \left(\frac{2}{\tau}\right)^2 t \times \exp\left(-\frac{2 \times t}{\tau}\right) \times \exp(-k \times t) \qquad (1)$$

Besides the stomach chamber, the small intestine is the main focus of our study. In the work presented in [2], Idkaidek considers the mass transfer into the small intestine by convection in the lumen and by diffusion into the walls. The small intestine is represented by a cylindrical geometry surrounded with a wall of constant width. This representation regroups duodenum, jejunum and ileum assembled in one single system.

Note that drug decomposition kinetics is assumed to be first order, which is consistent with the assumption of diluted solution in the stomach.

The assumption of a diluted solution in the intestine is in agreement with the continuous water secretion [2] and the kinetics is still first order. The transport processes occur at a constant temperature, the fluid velocity in the lumen is considered to be constant and the diffusion coefficient is held constant as well.

In the lumen intestine the drug is transported by a convection phenomenon. The fluid going through the lumen is carrying the drug in the direction of drug decreasing concentration. Moreover the drug keeps on being degraded in the lumen obeying the same first order kinetics, but with a kinetics rate that can be different according to the different physiological conditions in the lumen in comparison with the stomach.

A standard mass balance equation for the diluted drug in the lumen intestine yields:

$$\frac{\partial c_L(x,t)}{\partial t} = a \times \frac{\partial c_L(x,t)}{\partial x} + b \times c_L(x,t) \qquad (2)$$

where

a = fluid velocity

b = kinetic rate constant

c_L = drug concentration in the lumen

From the concentration calculated in the lumen intestine a boundary condition can be assessed for the wall using the drug partition coefficient P. This coefficient is a measure of how much the drug is lipophilic. As the lumen is mostly an aqueous phase, the cells of the intestine wall are lipoidal in nature, and therefore the drug partition coefficient quantifies the ability of the drug to go from the lumen to the wall across the wall membranes. This is a thermodynamic equilibrium. Two very important aspects of

our modeling approach lie in this drug partition coefficient concept. Firstly, the thermodynamic equilibrium is assumed to be reached at each moment. The time scales dealt with in the study of the fluxes inside the lumen intestine are supposed to be large enough for a thermodynamic equilibrium to be attained. Secondly, it would not be a reasonable assumption to consider only an axial flux in the lumen if the drug under consideration is of highly lipophilic nature. In that case the attraction of the molecule for the lipoidal phase might play a role in the mass balance considered to solve the drug concentration profile in the intestine lumen. When the phenomenon is under study at steady-state, as in [2], it makes sense to study drugs with partition coefficients greater than 1, since equilibrium is supposed to be reached in the mass balance treatment. However, with dynamic conditions if the phenomenon of attraction of the drug molecules by the wall cells is too important, the flux along the lumen intestine cannot be assumed to be only axial anymore. Our model has then to be restrained to drugs with a partition coefficient not higher than one, namely non-lipophilic drugs.

Once in the small intestine wall, no fluid flux occurs and the drug transport is due to the only drug concentration gradient. Fick's second law of diffusion describes this transport mode. The diffusion associated with the degradation kinetics yields to the following mass balance:

$$\frac{\partial c_W(y,t)}{\partial t} = D\frac{\partial^2 c_W(y,t)}{\partial y^2} + b' \times c_W(y,t) \qquad (3)$$

where

D = diffusion coefficient

b' = kinetic rate constant

c_W = drug concentration into the wall

In their paper [2], Idkaek et al. used Cartesian coordinates and not cylindrical coordinates. A justification for this approximation can be the relative thinness of the wall compared to the overall intestine radius. We used Cartesian coordinates as well. The calculation in cylindrical coordinates would have been pretty much the same, and regarding our final results this approximation should not have any important impact on the concentration values observed in the intestine wall.

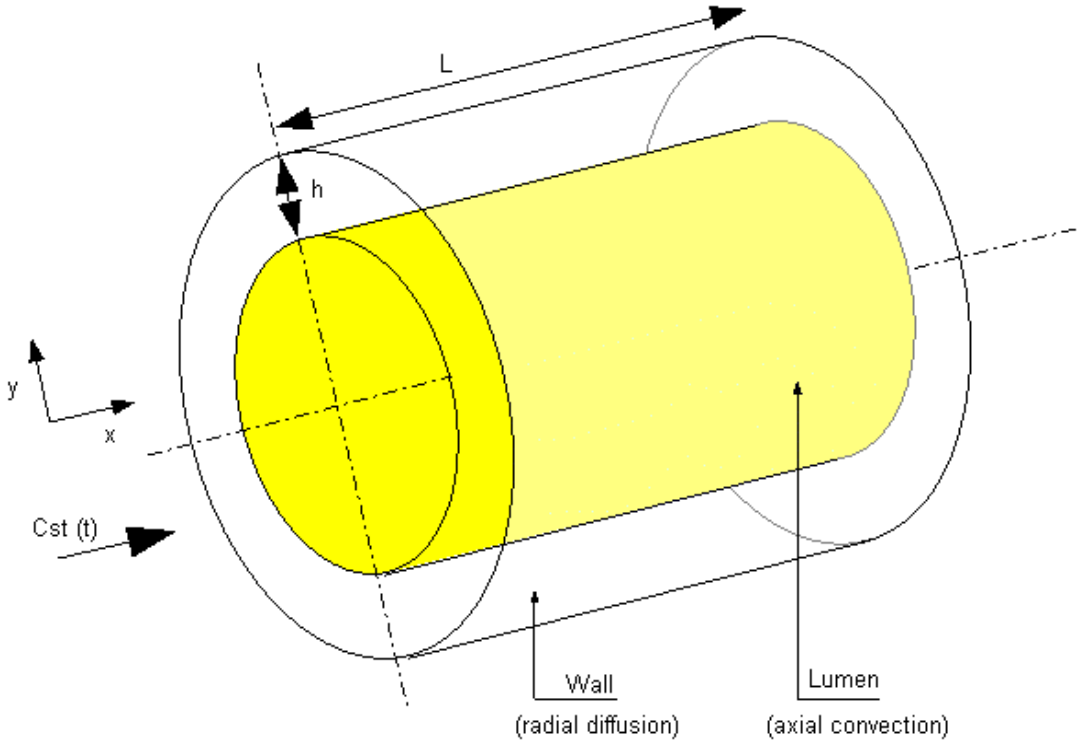

Figure 9 *Small intestine representation. h is the wall thickness, L the small intestine length. Axial convection occurs in the x direction, radial diffusion through the wall occurs in the y direction.*

IV - Model development

At the intestine lumen inlet, the drug concentration profile coincides with the one at the stomach chamber exit. The second boundary condition is the sink assumption in the colon. As well as for the stomach, the drug initial profile in the lumen is taken to be zero.

$$c_L(0,t) = c_{St}(t) \qquad \text{at} \qquad x = 0$$

$$\text{and} \qquad c_L(x,0) = 0 \qquad \text{at} \qquad t = 0 \tag{5}$$

The mass balance can then be solved analytically using the method of characteristics described in appendix B. This leads to the following drug concentration profile:

$$\hat{c}_L(\hat{x},\hat{t}) = \frac{4T}{\tau}(\hat{t}-\hat{x}) \times \exp\left(-\frac{2\times(\hat{t}-\hat{x})\times T}{\tau}\right) \times \exp\left(-k\times(\hat{t}-\hat{x})\times T\right) \times \exp\left(-b\frac{L}{a}\hat{x}\right) \tag{6}$$

where

$\hat{x}$ = dimensionless position along the lumen intestine

$\hat{t}$ = dimensionless time

The axial position in the intestine is related to the total length of the small intestine L and the time constant $T = -\frac{L}{a}$, linking real time to dimensionless time represents the time for a particle from the lumen fluid at a velocity a to reach the end of the lumen intestine.

The boundary conditions for the problem of drug diffusion into the wall are on the lumen border the concentration in the lumen assorted to a partition coefficient and zero at the wall limit for poisoning reasons. Initially there is no drug in the wall.

$$c_W(x,0,t) = P \times c_L(\hat{x},\hat{t})$$
$$c_W(x,h,t) = 0$$

and

$$c_W(x,y,0) = 0 \tag{7}$$

Appendix C contains the solution procedure of equation (3) for under the above set of initial and boundary conditions. The expression derived for the concentration profile in the wall is given in terms of the following the Fourier series:

$$c_W\left(\hat{x},y,\hat{t}\right)=\sum_{n=1}^{\infty}g_n\left(\hat{t}\right)\times\sin\left(\frac{n\pi}{h}y\right)+\frac{h-y}{h}c_{in}\times\hat{c}\left(\hat{x},\hat{t}\right) \tag{8}$$

With:

$$g_n\left(\hat{t}\right)=-\frac{2P}{n\pi}\times\frac{K\left(\hat{x}\right)}{b'-\theta+\Gamma_n}\times\left[\frac{1}{T}\left(1+\frac{\theta}{b'-\theta+\Gamma_n}\right)+\theta\hat{x}-\frac{\theta\left(b'-\theta\right)}{b'-\theta+\Gamma_n}\hat{t}\right]\times\exp\left(\left(b'-\theta\right)T\times\hat{t}\right)$$
$$+C_n\times\exp\left(-\Gamma_nT\times\hat{t}\right)$$

And:

$$C_n=\frac{2P}{n\pi}\times\frac{K\left(\hat{x}\right)}{b'-\theta+\Gamma_n}\times\left\{\left[\frac{1}{T}\left(1+\frac{\theta}{b'-\theta+\Gamma_n}\right)+\theta\left(1-\frac{\left(b'-\theta\right)}{b'-\theta+\Gamma_n}\right)\hat{x}\right]\right\}\times\exp\left(\left(b'-\theta+\Gamma_n\right)T\times\hat{x}\right)$$

where y represents the position through the wall.

The origin for y is at the interface between the lumen intestine and the wall, and its upper limit is h, the wall thickness.

Note that y is not dimensionless.

Numerically, it can be proven that only a few terms in the Fourier series suffice. The series can be truncated pretty fast, since its coefficients are relatively small and decreasing with n. The model can in that case be even more simplified.

The fact that the Fourier coefficients remain small compared to the second part of the expression $\frac{h-y}{h}c_{in}\times\hat{c}\left(\hat{x},\hat{t}\right)$ shows that this linear profile is a good initial guess for the concentration profile, since the Fourier series is not correcting it in a considerable way. An interpretation of this is that the diffusion is quick enough in comparison with the changes in the boundary condition at the wall-lumen interface imposed by convection

phenomenon to reach this linear profile given by the second part of the concentration expression.

V – Main results and discussion

V.1 - Stomach model

The stomach outlet concentration exhibits a zero concentration at the initial time. This makes physical sense since at this time none of the drug particles administered had enough time to reach the stomach outlet. This would not have been the case though in a configuration where the stomach would have been described by one single ideal CSTR. Then the concentration reaches a maximum where the largest amount of drug is available at the stomach outlet and finally decreases since the majority of the drug has either been degraded inside the stomach or has already been driven out in the lumen intestine. The two parameters describing this concentration profile are thus the kinetic rate in the stomach k and the main residence time τ . The choice of these parameters is described in table 1. Note that $\frac{J}{\tau}$ and the rate constant should be of the same order of magnitude to sense their relative influences on the outlet shape. As our main modeling purpose is not the stomach but the drug behavior, more importance is given to the rate constant in comparison with the ratio $\frac{J}{\tau}$.

Curve	A	B	C	D	E
$k\ \left(\min^{-1}\right)$	10^{-2}	10^{-2}	10^{-2}	10^{-2}	10^{-3}
$\tau\ (s)$	1800	3600	5400	7200	1800

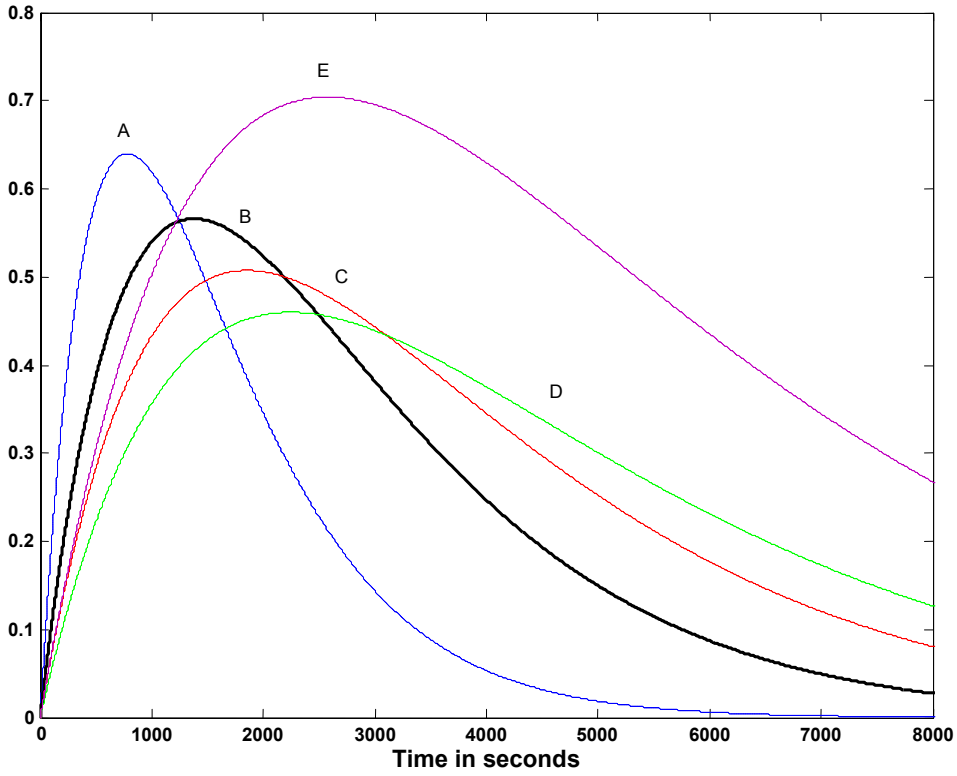

Figure 10 *Stomach outlet concentration profiles.*

The proposed modeling approach allows the simulation of a broad range of dynamic behaviors for the stomach by varying the parameters considered. Moreover, the outlet shape can be modified to approach a less distributed concentration profile by increasing in the model the number of ideal CSTR in the cascade. Using more than two CSTRs in cascade would not complicate the concentration expression in the lumen but will drive to more delicate calculations for the diffusion equation in the wall. However, as it will be shown further, diffusion through the wall is of much smaller impact on the absorbed drug fraction than convection through the lumen. Therefore one could be interested in adapting the stomach model to a specific number of reactors and give less

importance to the wall diffusion phenomena. For instance a number of CSTRs in cascade greater or equal to three will give an initial slope equal to zero, that possibly being one of the features one could desire for its lumen time dependant boundary condition.

In the rest of the simulations, the stomach parameters are set to the ones of curve C, which are $k = 10^{-2}\,\text{min}^{-1}$ and $\tau = 5400\,\text{sec}$, that is one hour and a half. This value corresponds more or less to an average of digestion time for a human.

V.2 – Intestine lumen

The lumen intestine model is depending on the fluid velocity a and the drug disintegration kinetic coefficient b. The fluid velocity is set to its physiological value [2], and is thus not a varying parameter in this work. The stomach parameters used are those of the set B in table 1. The different values given to the lumen parameters are given in table 2 below.

Curve	A	A'	B	C	D
b (min^{-1})	$5\ 10^{-3}$	10^{-4}	$1\ 10^{-3}$	$1\ 10^{-2}$	$1\ 10^{-1}$
a (m/s)	$1.1\ 10^{-5}$	$1.1\ 10^{-5}$	$1.1\ 10^{-5}$	$1.1\ 10^{-5}$	$1.1\ 10^{-5}$

Figures 11, 12, and 13 are representations of the dimensionless concentration along the intestine lumen. The kinetics rate constant was increased from figure 8 to figure 10. On these plots the concentration is red on the z axis. These plots show each concentration at each time and position along the lumen. The two domains explained in appendix B can be observed. For the domain where the dimensionless time $\hat{t}$ is less than $\hat{x}$ the dimensionless position in the intestine, the concentration is zero. This domain matches to

all the coordinates where the drug did not had time enough to reach the corresponding position. It is delimited by the $\hat{t} = \hat{x}$ line. Above this line is the other domain, where $\hat{t}$ is greater than $\hat{x}$. Here the concentration is different from zero until a certain time. Moreover the concentration curve for one fixed $\hat{x}$ has the same overall shape than the concentration profile at the stomach outlet, moderated by the fact that drug degradation occurred within the time the drug took to reach $\hat{x}$.

The influence of the kinetics on the drug distribution along the intestine lumen is of great importance. Whereas on figure 11 almost no drug is degraded through the intestine and a big amount is going in the colon, on figure 13 the strong kinetics make the drug molecules to be degraded far before they reach the end of the small intestine. Thus strong degradation kinetics would reduce the surface for the drug to be absorbed in the wall along the intestine lumen.

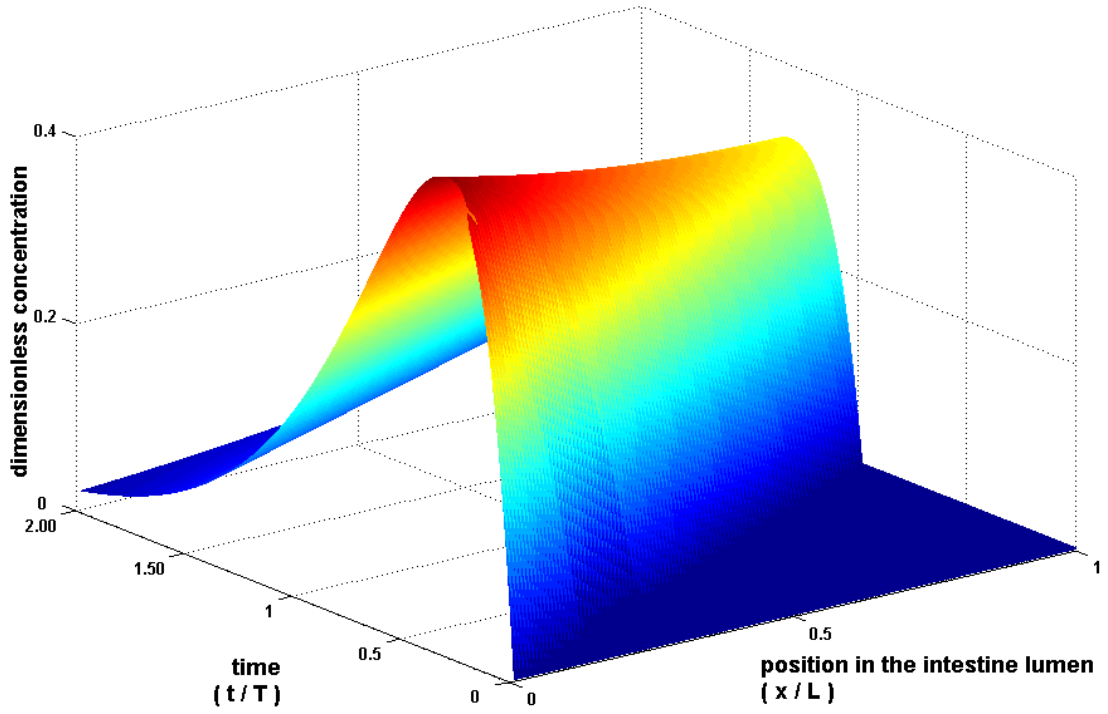

Figure 11 *Drug concentration profile in the lumen intestine, condition set B.*

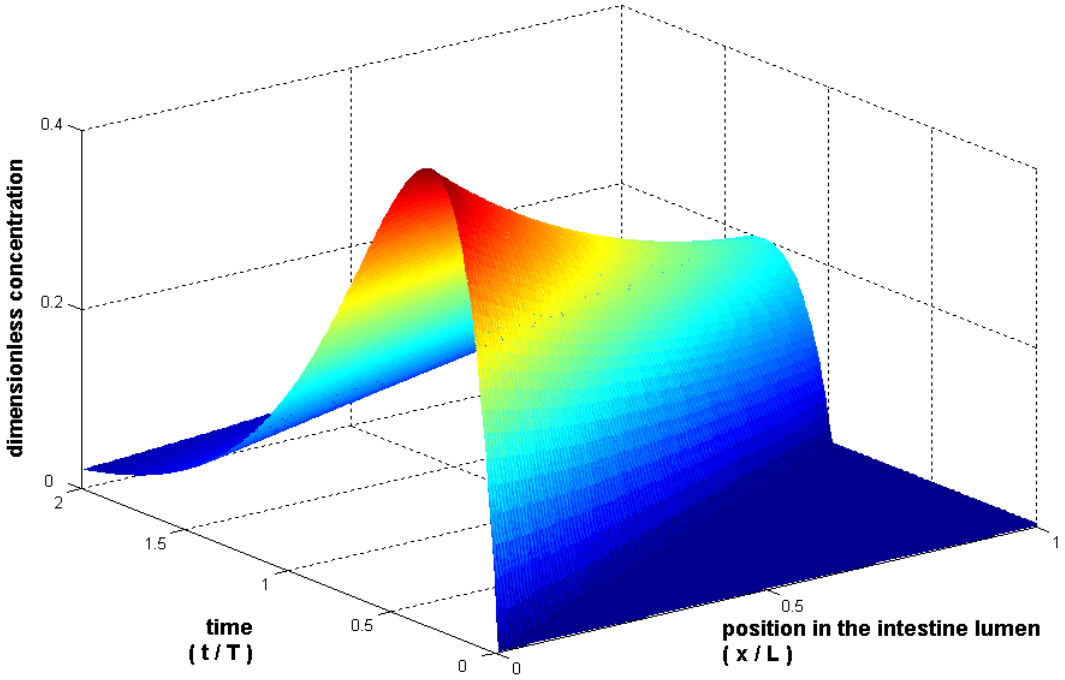

Figure 12 *Drug concentration profile in the lumen intestine, condition set C.*

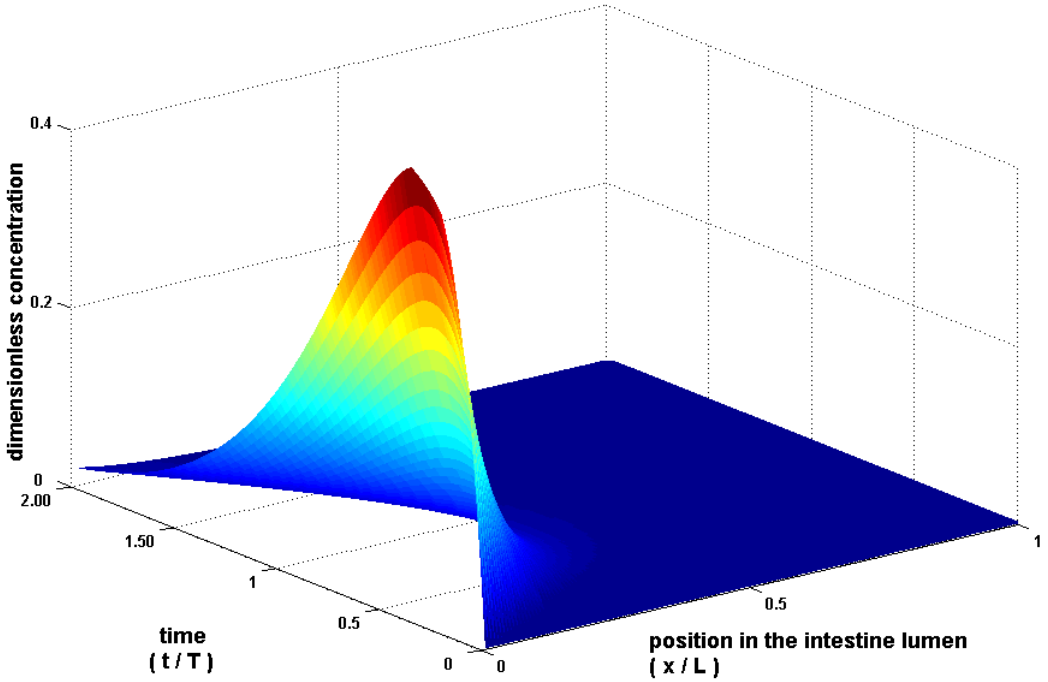

Figure 13 *Drug concentration profile in the lumen intestine, condition set D.*

Figure 14 represents the mean concentrations along the lumen variation with time. Not surprisingly, strong kinetics does not allow the dimensionless concentration to reach very high values. From the intermediate concentration profiles C and B to the concentration profile A the kinetic rate is decreasing and the effect on the increasing values reached by the concentration is understandable. Although the difference between the kinetics rates of the concentration profiles A and A' is of the same order than the one between those of profiles A and B, the difference between profiles A and A' is not of the same magnitude. This illustrates the limit of the drug degradation in comparison with the transport phenomena. The majority of the drug particles reached by convection the end of the small intestine before the drug degradation effect to be of great importance.

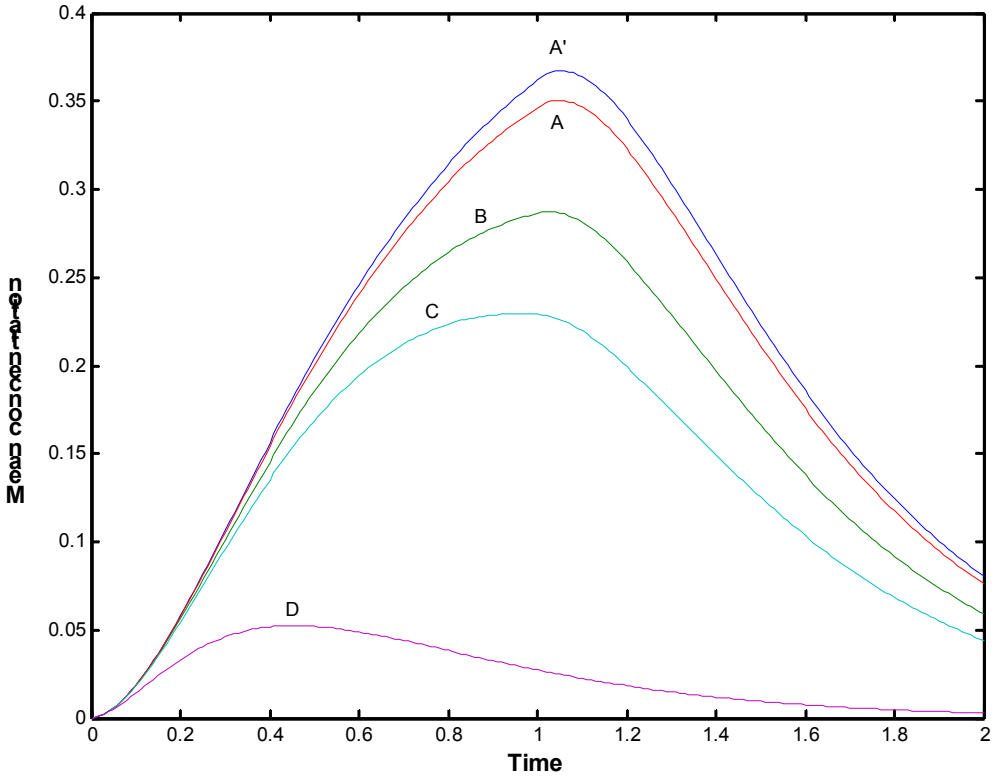

Figure 14. *Mean drug concentration in the lumen versus time.*

V.3 - Intestine wall

The simulations have been run with the following sets of parameters:

Curve	*G*	*H*	*I*	*J*	*K*	*L*	*M*	*N*
D (m^2/s)	$5\ 10^{-8}$	10^{-8}	10^{-7}	10^{-6}	10^{-3}	$5\ 10^{-8}$	$5\ 10^{-8}$	$5\ 10^{-8}$
b' (min^{-1})	10^{-2}	10^{-2}	10^{-2}	10^{-2}	10^{-2}	10^{-3}	10^{-1}	1

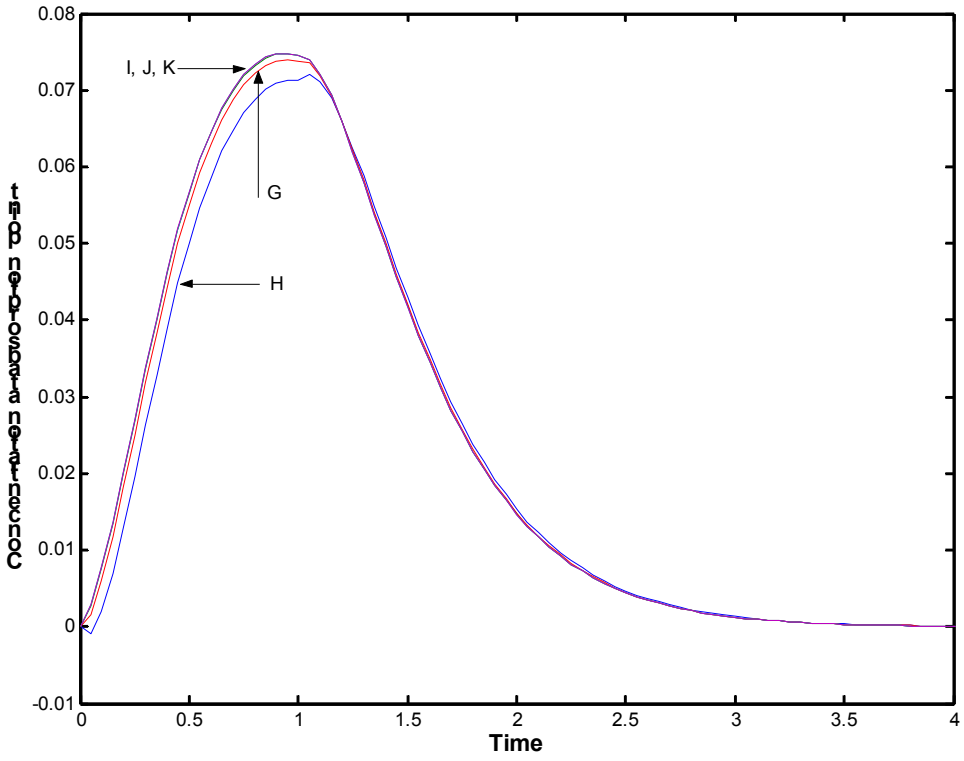

Figure 15 *Outer wall concentration profile. Influence of the drug diffusion coefficient.*

In order to plot the concentration profiles in the wall the values for drug degradation rate in the stomach and in the intestine lumen were set up to stationary values, so that the only influence on each plot is only the one of the parameter under study.

Figure 15 represents the influence of the drug diffusivity into the wall. Idkaidek and Abdel-Jabbar in [2] used a range of values for D of the order of 10^{-4} cm^2/s. For these values of D, as it can been seen on figure 15, the diffusion coefficient does not have much influence on the concentration profile at the absorption point. In a more general manner, there are very low differences observed between the concentration profiles with even differences between diffusion coefficients of several orders of magnitude. The diffusion coefficient does not seem to be a key factor for the transport of the drug through the wall. At steady state already, the dimensionless concentration values in the wall calculated in [2] were not showing a significant dependence on the diffusion coefficient. Moreover the values that were calculated with our model begin at zero, as the drug has not reached the wall yet, then increase until an average value of 0.07, and finally decrease as the finite amount of drug that was given to the patient was either degraded or removed from the small intestine. This value of 0.07 is comparable with the values calculated in [2].

Figure 16 shows that the drug degradation kinetic rate has some influence when it is large enough to affect the drug during its quick diffusion through the wall. The concentration profile N represents the concentration profile for a degradation rate of 1 min^{-1}. This rate is higher of one order of magnitude than the concentration profile M and relatively presents a major difference with the other profiles.

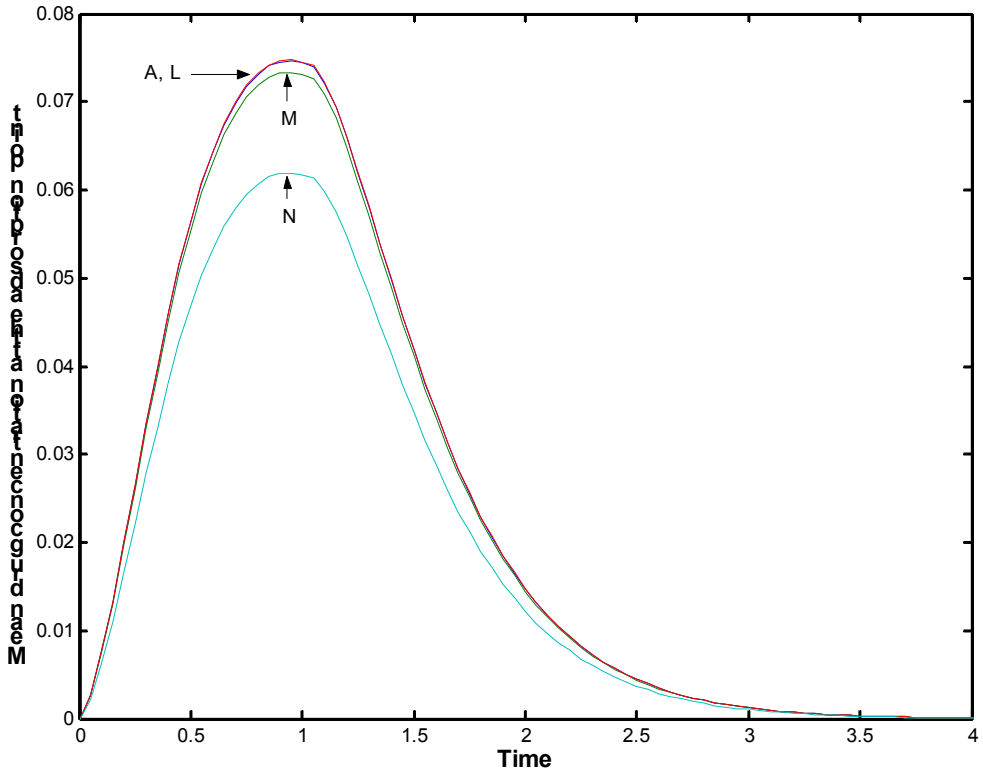

Figure 16. *Outer wall concentration profile. Influence of the drug decomposition kinetic rate.*

V.4 – Small intestine

Interesting information would be to know the ratio of drug molecules initially administrated to the patient that are actually absorbed by the body. As our calculations have been based on the concentration so far, some more parameters are needed. We consider that the human stomach has an average volume V, the small intestine of length L and inner diameter d with the surrounding wall of thickness h.

$$V_{Intestine} = \pi \times (d + h)^2 \times L$$

The drug absorption happens in the external last part of the wall of thickness dy. Therefore the volume where no absorption occurs is the volume V' of the inner cylinder of radius $d + h - dy$.

$$V'_{Intestine} = \pi \times (d + h - dy)^2 \times L$$

Hence the volume where adsorption takes place is, the difference between the two previous volumes, that is, assuming dy small enough to linearize our expression:

$$V_{Ads} = 2\pi \times (d + h) \times dy \times L$$

Therefore the amount of drug moles adsorbed at the time t is

$$n(t) = V_{Ads} \times c_0 \times \int_0^1 \hat{c}_W (\hat{x}, y_{Ads}, \hat{t}) d\hat{x}$$

Originally the amount of drug moles is

$$n_0 = V_{Stomach} \times c_0$$

At the time t the fraction of drug administrated at first is then

$$f(\hat{t}) = \frac{V_{Ads}}{V_{Stomach}} \int_0^1 \hat{c}_W (\hat{x}, y_{Ads}, \hat{t}) d\hat{x}$$

Upon this drug fraction definition the influence of the different model parameters have been studied.

Curve	I	II	III	IV	V	VI	VII
b (min^{-1})	10^{-2}	10^{-1}	10^{-4}	10^{-2}	10^{-2}	10^{-1}	10^{-4}
b' (min^{-1})	10^{-2}	1	10^{-3}	1	$10^{—3}$	10^{-2}	10^{-2}
D (m^2/s)	$5\ 10^{-8}$	$5\ 10^{-8}$	10^{-7}	$5\ 10^{-8}$	10^{-7}	$5\ 10^{-8}$	$5\ 10^{-8}$

Profiles II and III present the two extremes of the fraction of drug profiles. They respectively include the parameters that led to low or high concentration values when studying independently the lumen intestine and the intestine wall. There is an order 10 of

magnitude between the two profiles. A median profile (profile I) was also calculated based on the median parameters found in the lumen and the wall.

Next, in order to study the relative importance on the overall absorption of the transport mechanisms in both the lumen and the wall, the parameters of one were fixed at median values while these of the other were taking extreme values. Therefore, curve V represents the upper extreme of the wall diffusion and curve IV the lower one. On the other hand the curve VI is the lower border of the lumen contribution and curve VII its higher one. Notice that the lumen transport phenomena are of much greater influence than the diffusion through the wall.

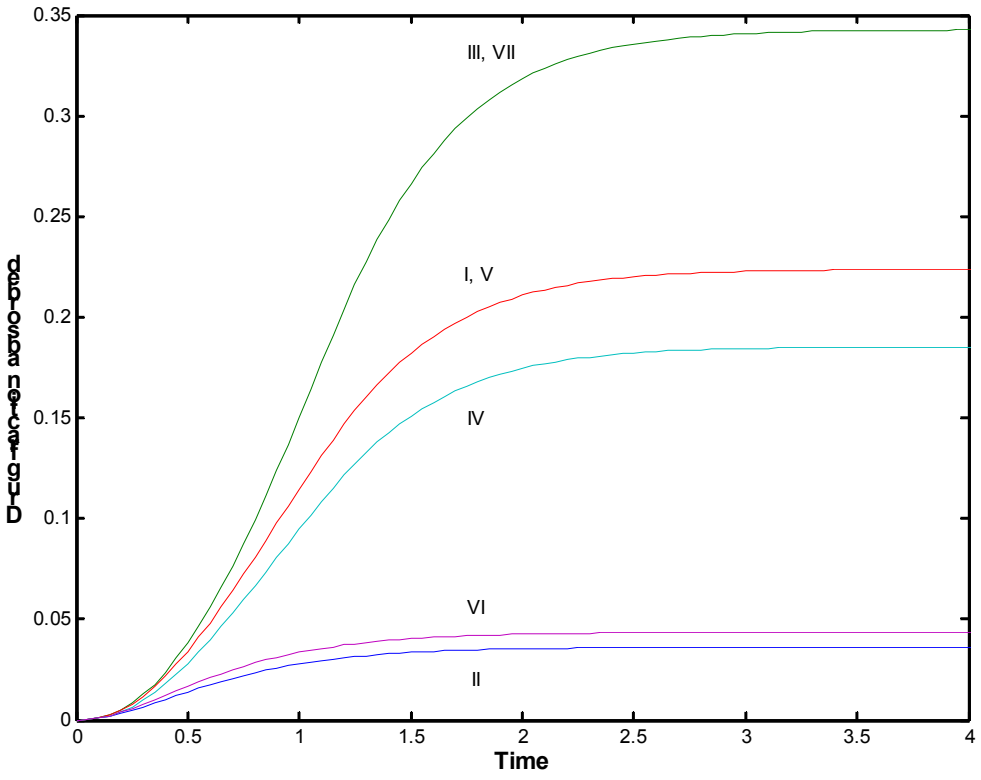

Figure 17 *Cumulative drug concentration available for absorption.*

VI - Conclusions

The model developed presents a simple analytical solution to a mass balance approach to the drug absorption problem in the small intestine. The mass balance approach was based on the succession of the transport by convection associated to drug degradation in the intestine lumen at first and secondly to diffusion in the intestine wall, again associated with drug degradation. The model is then whispered to cover the most general case, and as the equations solved are physically based they gave a rigorous and comprehensive solution. A time dependant boundary condition for the transport through the lumen was imposed by the stomach response to an impulse in the concentration of drug. This input for the stomach model corresponds to the sudden swallowing of the drug solution by the patient.

The relative influences of the two transport processes on the drug absorption profile were discussed. The transport inside the intestine lumen appears to be of greater importance than the diffusion in the wall.

The concentration profiles and the values obtained match with what can be found in the literature. This model is able to provide not only the bioavailability of an oral administered drug but also the drug rate absorption.

Moreover, the model includes a representation for the stomach. This CSTR approach of the stomach is not new, but the originality of the approach used is to assume a non-ideal CSTR. This allows more flexibility in the concentration profile entering the small intestine. The number of reactors in cascade was limited to two, for simplicity reasons in the Fourier series development used for the drug diffusion into the wall. As it

has been said, wall diffusion shows less influence than lumen convection. Therefore, it could be interesting to give more importance to detailing the stomach model with a suitable number of CSTRs in cascade, and to assess a linear profile for the drug diffusion in the wall. The solution would remain simple in that case.

The importance of developing an analytical solution resides in the ability this provides to go further after the system under consideration with a starting point given by the expression found.

Appendix A: Concentration derivation at the stomach outlet.

- The solution to the differential equation A.1:

$$\frac{dx}{dt} = ax + bu \tag{A.1}$$

with the initial condition equal to zero and an impulse input

$$x(t=0) = 0$$
$$u(t) = M\delta(t)$$

is found using the Laplace transform.

In the Laplace domain, equation A.1 becomes, when x is expressed in deviation form:

$$sX(s) = aX(s) + bM \tag{A.2}$$

Where s denotes the Laplace variable

and the solution of this is then given by

$$X(s) = \frac{bM}{s-a}$$

Therefore, going back to the time domain

$$x(t) = bM\ \exp(at)$$

Consequently, the expression of x in a non deviation form is:

$$x = x_{steady\ state} + bM\ \exp(at)$$

If we consider now the following second differential equation (A.3):

$$\frac{dx}{dt} = ax \tag{A.3}$$

But with this time the non zero initial condition

$$x(t=0) = bM$$

The same method of Laplace transform drives us to the solution

$$x = x_{steady\ state} + bM\ \exp(at)$$

which is exactly the same solution than A.1 solution.

- Let's now consider the case of two CSTRs in cascade, of total volume V. The flux going through the two reactors is F. This case is illustrated on figure A.1 next.

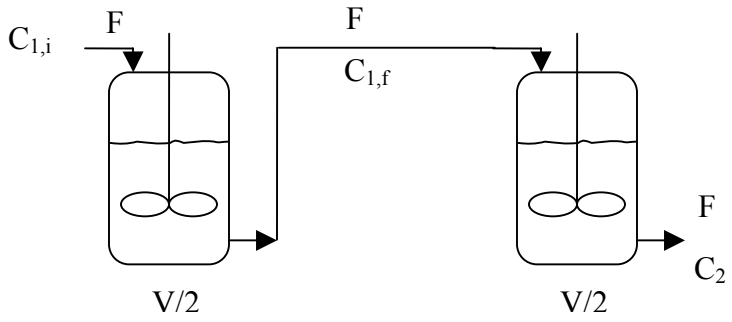

Figure A.1 *Two identical CSTRs in cascade.*

Writing and solving the mass balances in the two CSTRs in cascade system described above is similar to the mathematical approach developed in the first part of this appendix. The first CSTR input is an impulse in concentration of magnitude c_0. The mass balance on this reactor is thus given by equation A.1:

$$\frac{dc_1}{dt} = -\left(\frac{2\,F}{V} + k\right)c_1 + \left(\frac{2\,F}{V} + k\right)c_{input}$$

(A.1)

with the set of conditions:

$$c_1(t=0) = 0$$
$$c_{input}(t) = c_0\delta(t)$$

This leads to the solution for $c_1(t)$:

$$c_1(t) = c_0 \times \exp\left(-\left(k + 1/\tau\right)t\right) \tag{A.3}$$

Where $\tau = \dfrac{V}{2\,F}$

The second CSTR is described by the mass balance:

$$\frac{dc_2}{dt} = -\left(\frac{2\,F}{V} + k\right)c_2 + \left(\frac{2\,F}{V} + k\right)c_1 \tag{A.1}$$

With the initial condition:

$$c_2(t = 0) = 0$$

A.1 can be transformed, using the expression previously found for $c_1(t)$, in:

$$\frac{dc_2}{dt} = -\left(\frac{2\,F}{V} + k\right)c_2 + \left(\frac{2\,F}{V} + k\right) \times \exp\left(-\left(k + 1/\tau\right)t\right) \tag{A.4}$$

According to the solution found for A.2, the solution for A.4 is therefore:

$$c_2(t) = \frac{c_0\ t}{\tau} \times \exp\left(-\left(k + 1/\tau\right)t\right)$$

Note that this expression can easily be generalized to the case of J CSTRs in cascade. In this case, the solution for the concentration at the outlet of the J^{th} reactor would be given by the expression:

$$c_J(t) = \frac{c_0\ t^{J-1}}{(n-1)!\ \tau^{n-1}} \times \exp\left(-\left(k + 1/\tau\right)t\right)$$

Where τ would be in the case of J CSTRs in cascade:

$$\tau = \frac{V}{J\ F}$$

Appendix B: Method of characteristics

The characteristic method is used to solve the non steady state convection equation with a source term due to the first order kinetics of the drug decomposition reaction. This equation is written:

$$\frac{\partial c_L(x,t)}{\partial t} = a \times \frac{\partial c_L(x,t)}{\partial x} + b \times c_L(x,t) \qquad \text{(B1)}$$

where a stands for the fluid velocity and b for the kinetic rate constant. Notice that both a and b are negative values.

(B1) can be rewritten in a dimensionless form:

$$\frac{1}{T}\frac{\partial \hat{c}_L(\hat{x},\hat{t})}{\partial \hat{t}} - \frac{a}{L} \times \frac{\partial \hat{c}_L(\hat{x},\hat{t})}{\partial \hat{x}} = b\frac{L}{T} \times \hat{c}_L(\hat{x},\hat{t}) \qquad \text{(B2)}$$

where L is the length of the lumen intestine, and $T = -\frac{L}{a}$ a time constant.

In this study the initial concentration profile is taken equal to zero, considering that the intestine does not contain any drug:

$$\hat{c}_L(x,0) = \hat{c}_L^0(x) = 0 .$$

The boundary condition is defined previously as the outlet concentration of a semi-batch reactor, thus:

$$\hat{c}_L(0,\hat{t}) = \hat{c}_L^i(\hat{t}) = \tau\left(\frac{J}{\tau}\right)^J \frac{T^{J-1} \times t^{J-1} \times \exp\left(-\frac{J \times \hat{t} \times T}{\tau}\right)}{(J-1)!} \times \exp(-k \times \hat{t} \times T).$$

Equation (B2) is describing a surface $\hat{c}_L = \hat{c}_L(\hat{x},\hat{t})$ that can be written in parametric forms using two different parameters, s and ζ. (figure B1)

The parameter s describes the surface. It is then possible to write:

$$\frac{d\hat{c}}{ds} = \frac{\partial \hat{c}}{\partial x}\frac{dx}{ds} + \frac{\partial \hat{c}}{\partial t}\frac{dt}{ds} \qquad \text{(B3)}$$

Identification between the terms of equation (B2) and those of equation (B3) gives the following system of ordinary differential equations:

$$\frac{d\hat{t}}{ds} = \frac{1}{T}$$

$$\frac{d\hat{x}}{ds} = -\frac{a}{L}$$

$$\frac{d\hat{c}_L}{ds} = b\frac{L}{T} \times \hat{c}_L(\hat{x},\hat{t})$$

The integration of this system leads to:

$$\hat{t} = \frac{1}{T}s + k_1$$

$$\hat{x} = -\frac{a}{L}s + k_2$$

$$\hat{c}_L = k_3 \times \exp\left(b\frac{L}{T}s\right)$$

The next step being to determine the constants k_1, k_2 and k_3.

- First the initial condition branch is used. This curve is described by:

$$\hat{t} = 0$$
$$\hat{x} = \zeta \qquad \text{at s=0}$$
$$\hat{c}_L = \hat{c}_L^0(\zeta)$$

where ζ is taken between 0 and 1, since it describes $\hat{x}$.

Thus, at s=0: $k_1 = 0, k_2 = \zeta$ and $k_3 = 0$. This leads to the expression for the surface according to the initial concentration profile:

$$\hat{t} = \frac{1}{T} s$$
$$\hat{x} = -\frac{a}{L} s + \zeta$$

$$\hat{c}_L(\hat{x}, \hat{t}) = 0$$

As ζ lies from 0 to 1, this impose the relation between $\hat{x}$ and $\hat{t}$:

$$\hat{t} \le \hat{x}$$

- Then the boundary condition branch can be used.

In that case the curve is described by:

$$\hat{t} = \zeta$$
$$\hat{x} = 0$$
$$\hat{c}_L = \hat{c}_L^i(\zeta)$$

Moreover, ζ lies from 0 to infinity.(The time is not bounded as the intestine length is)

This leads to: $k_1 = \zeta, k_2 = 0$

and $k_3 = \hat{c}_L^i(\zeta) = \tau\left(\frac{J}{\tau}\right)^J \frac{T^{J-1} \times \zeta^{J-1} \times \exp\left(-\frac{J \times \zeta \times T}{\tau}\right)}{(J-1)!} \times \exp(-k \times \zeta \times T).$

Thus,

$$\hat{t} = \frac{1}{T}s + \zeta$$

$$\hat{x} = -\frac{a}{L}s$$

Notice that $\zeta = \hat{t} - \hat{x}$ and the expression for $\hat{c}_L(\hat{x},\hat{t})$ becomes:

$$\hat{c}_L(\hat{x},\hat{t}) = \tau\left(\frac{J}{\tau}\right)^J \frac{T^{J-1}(\hat{t}-\hat{x})^{J-1} \times \exp\left(-\frac{J\times(\hat{t}-\hat{x})\times T}{\tau}\right)}{(J-1)!} \times \exp\left(-k\times(\hat{t}-\hat{x})\times T\right)\times \exp\left(-b\frac{L}{a}\hat{x}\right)$$

Moreover, $\zeta = \hat{t} - \hat{x}$ impose the validity domain for this expression of $\hat{c}_L(\hat{x},\hat{t})$ to be:

$\hat{t} \geq \hat{x}$.

For the rest of the calculations J is taken equal to 2.

Thus, the expression for $\hat{c}_L(\hat{x},\hat{t})$ simplifies in

$$\hat{c}_L(\hat{x},\hat{t}) = \frac{4T}{\tau}(\hat{t}-\hat{x})\times \exp\left(-\frac{2\times(\hat{t}-\hat{x})\times T}{\tau}\right)\times \exp\left(-k\times(\hat{t}-\hat{x})\times T\right)\times \exp\left(-b\frac{L}{a}\hat{x}\right)$$

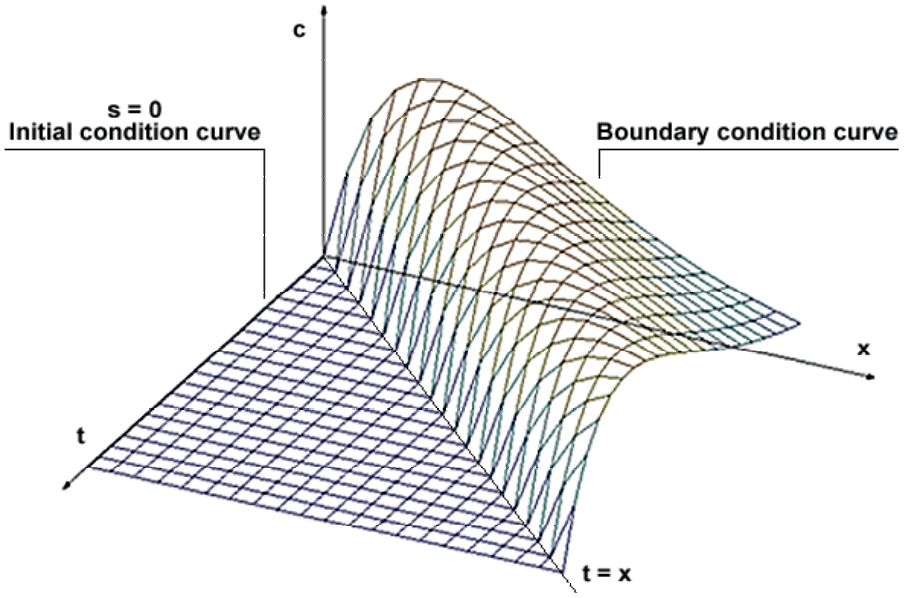

Figure B1. *Concentration surface function of the parameters s and* ζ .

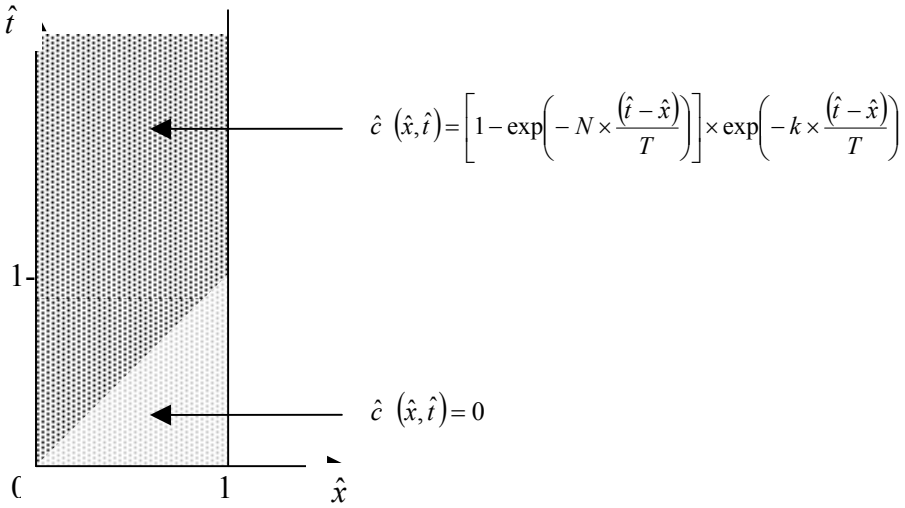

Figure B2. *Validity domains for the expressions of the concentration in the intestine lumen.*

It is important to note that at the border between the two domains found, the two expressions corresponding to each domain match.

Appendix C: Fourier Transform method.

The diffusion through the wall is represented by the Fick's second law associated with a source term, due to the drug decomposition kinetics.

$$\frac{1}{T}\frac{\partial \hat{c}_W(\hat{x},y,\hat{t})}{\partial \hat{t}} = D\frac{\partial^2 \hat{c}_W(\hat{x},y,\hat{t})}{\partial y^2} + b'\hat{c}_W(y,\hat{t}) \qquad \text{(C.1)}$$

The boundary conditions are:

$$\hat{c}_W(\hat{x},0,\hat{t}) = P\times\hat{c}_L(\hat{x},\hat{t})$$
$$\hat{c}_W(\hat{x},h,\hat{t}) = 0$$

and the initial concentration profile in the wall is zero:

$$\hat{c}_W(\hat{x},y,0) = 0$$

The function $u(\hat{x},y,\hat{t}) = \hat{c}_W(\hat{x},y,\hat{t}) - \frac{h-y}{h}P\times\hat{c}_L(\hat{x},\hat{t})$ satisfies the equation:

$$\frac{1}{T}\frac{\partial u(\hat{x},y,\hat{t})}{\partial \hat{t}} - \frac{1}{T}\frac{y-h}{h}P\times\frac{\partial \hat{c}_L(\hat{x},\hat{t})}{\partial \hat{t}} = D\frac{\partial^2 u(\hat{x},y,\hat{t})}{\partial y^2} + b'u(y,\hat{t}) - b'\frac{y-h}{h}P\times\hat{c}_L(\hat{x},\hat{t}) \qquad \text{(C.2)}$$

with the boundary conditions:

$$u(\hat{x},0,\hat{t}) = 0$$
$$u(\hat{x},h,\hat{t}) = 0$$

and the initial concentration profile equal to zero as well:

$$u(\hat{x},y,0) = 0$$

with this new boundary conditions it is possible to define $u(\hat{x},y,\hat{t})$ as a sine Fourier Series.

$$u(\hat{x},y,\hat{t}) = \sum_{n=1}^{\infty} g_n(\hat{t}) \sin\left(\frac{n\pi}{h} y\right)$$

Recalling $\hat{c}_L(\hat{x},\hat{t})$, the expression for $\frac{\partial \hat{c}_L(\hat{x},\hat{t})}{\partial \hat{t}}$ can be derivated:

$$\frac{\partial \hat{c}_L(\hat{x},\hat{t})}{\partial \hat{t}} = K(\hat{x}) \times \left[1 - T\left(\frac{2}{\tau} + k\right)(\hat{t} - \hat{x})\right] \times \exp\left(-T\left(\frac{2}{\tau} + k\right)\hat{t}\right)$$

With:

$$K(\hat{x}) = \frac{4T}{\tau} \times \exp\left(\left(\frac{2T}{\tau} + kT - b\frac{L}{a}\right)\hat{x}\right)$$

and the equation C2 can be rearranged as follow:

$$\frac{1}{T}\frac{\partial u(\hat{x},y,\hat{t})}{\partial \hat{t}} - D\frac{\partial^2 u(\hat{x},y,\hat{t})}{\partial y^2} - b'u(\hat{x},y,\hat{t}) = F(\hat{x},y,\hat{t}) \qquad \text{(C.3)}$$

With:

$$F(\hat{x},y,\hat{t}) = \frac{y-h}{h} P \times \left(\frac{1}{T}\frac{\partial \hat{c}_L(\hat{x},\hat{t})}{\partial \hat{t}} + b' \times \hat{c}_L(\hat{x},\hat{t})\right) \quad \text{for } \hat{t} \geq \hat{x},$$

$F(\hat{x},y,\hat{t}) = 0$ otherwise.

and $F(\hat{x},y,\hat{t})$ is developed in a sine Series:

$$F(\hat{x},y,\hat{t}) = -P \times \left(\frac{1}{T}\frac{\partial \hat{c}_L(\hat{x},\hat{t})}{\partial \hat{t}} + b' \times \hat{c}_L(\hat{x},\hat{t})\right) \times \sum_{n=1}^{\infty} \frac{2}{n\pi} \sin\left(\frac{n\pi}{h} y\right)$$

Equation C3 can thus reduce to:

$$\frac{dg_n(\hat{t})}{d\hat{t}} + \Gamma_n \times g_n(\hat{t}) = -P \times \left(\frac{1}{T}\frac{\partial \hat{c}_L(\hat{x},\hat{t})}{\partial \hat{t}} + b' \times \hat{c}_L(\hat{x},\hat{t})\right) \times \frac{2}{n\pi} \qquad \text{(C.4)}$$

for $\hat{t} \geq \hat{x}$

and:

$$\frac{dg_n(\hat{t})}{d\hat{t}} + \Gamma_n \times g_n(\hat{t}) = 0 \qquad \text{(C.4')}$$

for $\hat{t} \le \hat{x}$

where: $\Gamma_n = D\left(\frac{n\pi}{h}\right)^2 - b'$

The solution of equation C.4' is trivial due to the zero drug concentration into the wall at these moments.

For $\hat{t} \ge \hat{x}$

By posing: $\theta = \frac{2}{\tau} + k - b'$

The solution of equation C.4 is:

$$g_n(\hat{t}) = -\frac{2P}{n\pi} \times \frac{K(\hat{x})}{b' - \theta + \Gamma_n} \times \left[\frac{1}{T}\left(1 + \frac{\theta}{b' - \theta + \Gamma_n}\right) + \theta\hat{x} - \frac{\theta(b' - \theta)}{b' - \theta + \Gamma_n}\hat{t} \right] \times \exp\left((b' - \theta)T \times \hat{t}\right)$$
$$+ C_n \times \exp\left(-\Gamma_n T \times \hat{t}\right)$$

The integration constant is calculated using the initial zero concentration profile on the domain border $\hat{t} = \hat{x}$:

$$C_n = \frac{2P}{n\pi} \times \frac{K(\hat{x})}{b' - \theta + \Gamma_n} \times \left\{ \left[\frac{1}{T}\left(1 + \frac{\theta}{b' - \theta + \Gamma_n}\right) + \theta\left(1 - \frac{(b' - \theta)}{b' - \theta + \Gamma_n}\right)\hat{x} \right] \right\} \times \exp\left((b' - \theta + \Gamma_n)T \times \hat{x}\right)$$

Recall that $u(\hat{x}, y, \hat{t}) = c_W(\hat{x}, y, \hat{t}) - \frac{h - y}{h} P \times \hat{c}(\hat{x}, \hat{t})$ and the concentration of drug into the wall is represented by:

$$c_W(\hat{x}, y, \hat{t}) = \sum_{n=1}^{\infty} g_n(t) \times \sin\left(\frac{n\pi}{h} y\right) + \frac{h - y}{h} c_{in} \times \hat{c}(\hat{x}, \hat{t})$$

Note that, in the formula above, $g_n(\hat{t})$ is a function vanishing quickly with respect to n.

In the calculation of the concentration profile the sum has been stopped at n = 4.

Notation and abbreviation

Nomenclature

a	Fluid velocity in the intestine lumen
b	Drug decomposition kinetic rate in the intestine lumen
b'	Drug decomposition kinetic rate in the intestine wall
c	Concentration
d	Small intestine diameter (2.5 cm)
D	Diffusion constant in the wall
f	Mole fraction absorbed
h	Wall thickness
J	Number of ideal CSTR in cascade for the stomach model
k	Drug decomposition kinetic rate in the stomach
L	Position scale parameter
V	Stomach volume (1L)
V_{Ads}	Adsorption region volume
t	Time
T	Time scale parameter
τ	Mean residence time of the stomach assimilated to a CSTR
x	Axial coordinate in the intestine
y	Position in the intestine wall

Subscripts – superscripts

L	Lumen
St	Stomach outlet
W	Intestine wall
^	Dimensionless expressions
0	Initial conditions

Abbreviations

Caco	Colon Carcinoma Cell
CAT	Compartmental Absorption and Transit
CSTR	Continuously Stirred Tank Reactor
GI	Gastro-Intestinal
PFR	Plug Flow Reactor
UWL	Unstirred Water Layer

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