International Journal of Pharmaceutics 418 (2011) 130–141

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Mathematical modeling of simultaneous drug release and *in vivo* absorption

Mario Grassi[a,*], Gaetano Lamberti[b], Sara Cascone[b], Gabriele Grassi[c,d]

[a] Department of Materials and Natural Resources (DMNR), University of Trieste, Via Alfonso Valerio 6/A, I 34127 Trieste, Italy
[b] Department of Chemical and Food Engineering, University of Salerno, Via Ponte don Melillo, I 84084 Fisciano (SA), Italy
[c] Department of Life Sciences, University of Trieste, Via Giorgieri, 1, I-34127 Trieste, Italy
[d] Department of Medical, Technological and Translational Sciences, University Hospital of Cattinara, Trieste, Italy

ARTICLE INFO

Article history:
Received 4 November 2010
Received in revised form
22 December 2010
Accepted 27 December 2010
Available online 13 January 2011

Keywords:
Mathematical model
Oral administration
Transdermal administration
Local administration

ABSTRACT

The attention of this review is focussed on the mathematical modeling of the simultaneous processes of drug release and absorption/distribution/metabolism/elimination (ADME processes) following different administration routes. Among all of them, for their clinical importance, the oral, transdermal and local delivery are considered. The bases of the presented mathematical models are shown after the discussion of the most relevant phenomena characterising the particular administration route considered. Then, model performances are compared to experimental evidences in order to evaluate their reliability and soundness.

The most important conclusion of this review is that despite the complexity of the problem involved in the description of the fate of the drugs after their administration, the scientific community is close to the solution as witnessed by the various interesting and promising approaches here presented about the oral, transdermal and local administration routes.

1. Introduction

The clinical relevance of a proper drug administration promoted the development of more and more refined delivery systems. Accordingly, these systems evolved from those passively preprogrammed to those actively pre- and self-programmed (Lee and Robinson, 1987; Kost and Langer, 2001). This evolution was possible also for the employment of mathematical models that allowed to theoretically study the drug release processes extrapolating the data from the great variety of existing delivery systems (Siepmann and Peppas, 2001a; Langer, 1999). Indeed, a reliable mathematical model can be built only on the basis of a clear knowledge of the phenomena ruling the release kinetics (Grassi and Grassi, 2005; Grassi et al., 2007). Thus, for example, the release kinetics from osmotic systems (Marucci et al., 2008, 2010), erodible systems (Narasimhan, 2001; Siepmann and Göpferich, 2001), hydrophilic (Siepmann and Peppas, 2001b) and hydrophobic matrices (Grassi et al., 2003), complex shaped matrices (Wu and Zhou, 1998) and ensemble of spherical particles (Grassi et al., 2000; Zhou et al., 2004) was mathematically modeled. Contemporarily, the attention of researchers was also focussed on modeling the fate of the drug once released *in vivo* (Amidon et al., 1995; Lennernäs et al., 1994; Peppas and Langer, 2004; Mudie et al., 2010). The complexity of the problem (Macheras and Iliadis, 2006) induced the researchers to emphasize the aspects connected to drug absorption by leaving tissues, distribution among blood/tissues/organs, metabolism and elimination (the so called ADME processes). Accordingly, the release step was either assumed to be very fast (as in the case of drug solutions, where the release step does not exist) with respect to ADME processes or it was assumed to be equal to that observed *in vitro*. In this second case, it was implicitly assumed that ADME processes can not affect the release kinetics even if it is not always the case. A typical example is represented by delivery systems containing amorphous drugs that undergo re-crystallisation which reflects in drug solubility reduction (Nogami et al., 1969; Grassi et al., 2007).

The demand for more and more refined mathematical models able to describe very complex situations obliged and will oblige modellers to increase model versatility. Accordingly, we agree with the convincement that the new challenge in the drug delivery field, for what concerns mathematical modeling, is the combination of mechanistic theories able to realistically describe the simultaneous processes of drug release and the subsequent ADME processes within the human body (Siepmann and Siepmann, 2008). A further, subsequent, challenge relies on pharmacodynamics, i.e. the effect of a drug released from a specific delivery system (Evans, 2010). In so doing, we are proceeding towards the Leonardo da Vinci concept of true science: "*niuna umana investigazione si può dimandare vera scienzia, s'essa non passa per le matematiche dimostrazioni*" (no human investigation can be defined true science if it can not be mathematically demonstrated) (da Vinci, 1651). Thus, every mathematical model able to fit and to predict experimental evidences is not only a powerful tool for the drug delivery system optimisation

* Corresponding author. Tel.: +39 040 5583435; fax: +39 040 569823.
E-mail address: mariog@dicamp.univ.trieste.it (M. Grassi).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2010.12.044

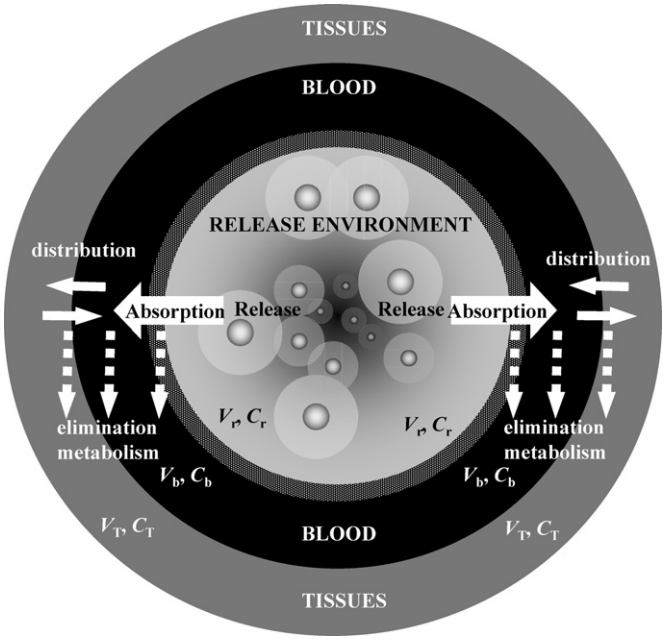

Fig. 1. Drug release and ADME processes. Theoretical scheme depicting the simultaneous drug release, absorption, distribution, metabolism, and elimination processes regardless of the administration route. While the drug is being released from the delivery system (spheres), it is absorbed by blood and, then, it spreads into tissues and organs. V_r, V_b, V_T and C_r, C_b, C_T indicate, respectively, release environment, blood and tissues volume and drug concentration.

but it is also the theoretical legitimacy of the experimental findings. Consequently, the target of this review is to present and to discuss the mathematical models matching the first challenge cited, i.e. the description of the simultaneous drug release and ADME processes. Regardless of the administration route, these models rely on the general theoretical scheme depicted in Fig. 1. While the drug is being released, it is absorbed into blood and, then, it spreads into tissues and organs. In both the absorption and spreading phase, it can undergo metabolism and/or elimination. Although the picture can be much more complex than that described, the important aspect is that the focus of the mathematical model is the ensemble of all the phases involved as a whole (release, absorption, spreading and metabolism/elimination). In other words, the model no longer considers as separate the different phases that can, thus, mutually affect each other. Mathematically speaking, this means that the model implies the simultaneous solution of all the equations necessary for the description of each phase. The more precise and particularised the model is, the more adherent to reality it will be and the more complex its solution will be. As a complete analysis of all the models dealing with the above-mentioned aspect is practically, impossible, we would like to focus the attention on some particularly interesting cases. More in detail, some examples regarding the oral, transdermal and local administration routes will be considered.

2. Oral administration

2.1. The oral route and the release tests

The oral route is the most important drug administration route. Usually, the key phenomena involved in the administration of a solid dosage form are the dissolution and the absorption of the drug. Dissolution is defined as the process by which a solid substance enters in the solvent to yield a solution. Other factors influencing the drug release rate are represented by the solid dosage form physical characteristics, wettability, dissolution medium uptake rate, the (possible) swelling and/or erosion phenomena, the disintegration and the de-aggregation of the dosage form (Banakar, 1992). The rate of drug dissolution can become the rate-limiting dissolution step before the drug appears in blood. As a result, release tests could provide the information necessary to develop more effective dosage forms. Therefore, composition and preparation of dosage form, rate of dissolution and rate of appearance in circulatory system are strongly correlated.

The Biopharmaceutical Classification System (BCS) identifies the solubility and the permeability as the key parameters to describe the drug fate once ingested. According to BCS, drug substances are classified as: class 1 drugs (high solubility and high permeability), class 2 drugs (low solubility and high permeability), class 3 drugs (high solubility and low permeability), and class 4 drugs (low solubility and low permeability) (Amidon et al., 1995). According to these criteria, drugs are considered highly soluble when the highest dose strength of the drug substance is soluble in less than 250 mL of water over a pH range of 1–6.8; drugs are considered highly permeable when the extent of absorption in humans is determined to be greater than 90% of the administered dose. It has long been recognized that solid drugs orally administrated are not immediately available to the biological system since they are absorbed only from a solution. During the development of the dosage form, the *in-vitro* release test serves as a guide in estimating the amount of drug released per unit time in a given dissolution medium. *In-vitro* release tests seem to be the most sensitive and reliable predictors of *in vivo* performances and they offer a meaningful indication of physiological availability.

Therefore, the knowledge of the phenomena which happen to an oral dosage form after swallowing is a pre-requisite to correctly model the full process (drug administration followed by the adsorption/distribution/metabolism/excretion – ADME – phenomena). Usually, release kinetics was investigated by suitable *in vitro* tests, which have to be designed to be as repeatable as possible and to realize conditions as close as possible to the conditions experienced by the pharmaceuticals in the human body. Prior of the description of the modeling approaches, the devices commonly used to test the *in vitro* release kinetics should be known.

Many devices have been reported for determination of the release rate, some of them accepted and classified by the Pharmacopeia(s). The apparatuses used for release testing are the USP (United States Pharmacopeia) apparatuses 1, 2, 3, 4, 5, 6, and 7 (USP-XXIII, 1995). The USP apparatus 1 (basket apparatus) consists of a wire-mesh basket that is attached to a rotation shaft, which is then immersed into a release vessel for the duration of the test. Another official method is the USP apparatus 2, the paddle method. Despite of the simplicity of use and the high degree of standardization, this apparatus is characterized by difficulty to realize pH changes and the fluid dynamics is very far from the real physiology. The USP apparatus 3, the reciprocating cylinder, was based on the recognition of the need to establish *in vitro - in vivo* correlation (IVIVC), since the release results obtained with USP apparatuses 1 and 2 may be affected by mechanical factors, such as shaft wobble, location, centering, deformation of the basket and paddles, and presence of bubble in the dissolution medium. The USP apparatus 4, also known as the flow – through cell, is composed by a small-volume cell containing the sample solution which is subjected to a continuous stream of release medium. The release medium flows through the cell from bottom to top of the cell. Transdermal or patching testing is carried out using USP method 5 (paddle over disc) or USP method 6 (rotating cylinder). Originally introduced in the USP as small-volume option for small transdermal patches, the USP apparatus 7 (reciprocating disk apparatus) was later renamed the reciprocating holder apparatus with the adoption of four additional holders for transdermal system, osmotic pumps and other low dose delivery systems. Therefore, there are a multitude of devices used in

release testing. Many of these suffer from deficiencies, such as too poor agitation, absence of sink condition and inability to program progressive changes in the dissolution environment.

Different apparatuses (not USP approved) were built to overcome these difficulties. The Sartorius Absorption Model was introduced in 1973 (Stricker, 1973). It simulates concomitant release from the dosage form in the gastrointestinal tract and drug absorption through the lipid barrier. The most important features of this model are the two reservoirs for holding different media at 37 °C, a diffusion cell with an artificial lipid barrier of known surface area, and a connecting peristaltic pump which aids the transport of the solution or the media from the reservoir to the compartment of the diffusion cell. Savalle et al. (1989) proposed an *in vitro* method to simulate the gastric emptying of digestive product in 1989. In order to overcome the accumulation of digestion product and the inhibition of proteolysis, a method based on the enzymatic hydrolysis of proteins with simultaneous dialysis of digested products was developed. The gastric digestion unit was composed of a thermostated fermenter regulated at 37 °C. Acidification of the medium and enzyme supply were ensured through two peristaltic pumps with variable flow rates and the pH of the incubation medium was measured, but not controlled, during digestion. Minekus and Havenaar (1996) developed a completed and detailed *in vitro* model which simulates the dynamic physiological processes which occur in the lumen of stomach and in the small intestine of man. The model consists of four successive chambers simulating the stomach, duodenum, jejunum, and ileum. Each compartment is formed by two connected units consisting of a glass jacket with a flexible wall inside. Water is pumped from a bath into the glass jacket around the flexible walls to control the temperature inside. The model mimics gastrointestinal peristalsis, which results in physiological mixing. The pH and the enzymes and bile salts concentrations simulate the dynamic physiological patterns found *in vivo*. Despite of the accurate reproduction of the biochemistry of the gastrointestinal tract, the fluid dynamics, particularly in the stomach compartment, is still far from the real one. Wickham and Faulks proposed an *in vitro* model which may include different stages (Wickham and Richard, 2007). Food materials were first cut and then exposed to low levels of α-amylase at 37 °C (model saliva). First stage simulates the main body of the stomach (the *fundus*), a region with inhomogeneous mixing behavior, distinct acid and enzyme additions. This apparatus comprises an outer vessel into which fluids can be introduced and removed and an inner digestion chamber comprising a rigid portion through which the foodstuff can be introduced and a flexible portion. Second stage of the model provides a simulation of the region of high shear (the *antrum*), mimicking both the rate and strength of contractions evaluated *in vivo*. When sufficiently broken down to mimic physiologic processes and foodstuff size, valve (the *pylorus*) is opened and plunger is pushed upward and the processed food can go out. The real fluid dynamics in this model is well approximated but the simulation is limited to the stomach region, which is not too much relevant in drug delivery, since most of the absorption takes place in the intestine. Garbacz et al. (2008) proposed a new apparatus mimicking hydrodynamic and mechanical condition in gastrointestinal tract to improve the predictability of dissolution testing. This included the simulation of pressure forces due to gut motility, shear forces generated during the propagation, and loss of water contact when the dosage form is located in an intestinal air pocket. The dissolution test device exposes the dosage form to an arbitrary sequence of movements, pressure waves and phase of rest as occur under *in vivo* condition. In this apparatus, the simulation of pressure waves and alternate exposition to solvent/air are introduced and the mechanical behavior is very simple to control but pH changes are difficult to be realized and the fluid dynamics is far to the real one. Each of the presented apparatuses has its characteristic features and its critical points, in particular all of them present a fluid dynamics different from the real one.

2.2. Modeling the in vitro release kinetics

The mathematical modeling of the *in vitro* drug release kinetics was the subject of recent reviews (Grassi and Grassi, 2005; Grassi et al., 2007; Siepmann and Siepmann, 2008). Among the oral forms, the most important ones are the dissolving ones (as powder, suspensions or aggregated in tablets) and the matrices systems, mainly based on hydrogels. The dissolution of the powders is described by the Noyes–Withney equation (Noyes and Whitney, 1897) and it's modifications and improvements. A detailed review on the "history" of the dissolution was recently given by (Dokoumetzidis and Macheras, 2006). The drug release from hydrogels based matrices is a much more complicated issue. A detailed overview of the modeling approaches proposed in literature to describe it was given by Siepmann and Peppas (2001). In their analysis, the starting point was the Higuchi treatment (Higuchi, 1961), which was developed to describe the drug release from an ointment containing a suspended drug and in contact with a perfect sink. The Higuchi equation is not directly applicable to complex systems such as matrices made of polymers and drugs, which could be subjected to swelling and erosion, showing a diffusivity sensible to the solvent concentration. The solution of a pure diffusive problem in a slab gives a release kinetics proportional to the square root of time. Since the experimental behavior observed shows a drug release proportional to different power of time, Peppas (1985) proposed a semi-empirical model in which the drug release is proportional to the sum of two different powers of time. The two terms account for the pure diffusivity contribution (the so-called Fickian transport) and for another contribution to the release, due to the relaxation of the polymer molecules and thus called non-Fickian or case-II "relaxational" contribution. In their following studies, Peppas and co-workers developed a comprehensive mathematical theory able to describe the full set of observed experimental phenomena, during the drug release from tablets made of swellable hydrogels (Siepmann et al., 1999a,b, 2000; Siepmann and Peppas, 2000). The full model was named "sequential layer" since it describes all the phenomena (water diffusion, swelling, drug diffusion, polymer erosion) layer-by-layer from the external towards the interior of the tablet. Their model was able to describe "affine" deformations, i.e. the swelling of cylindrical matrices causes the matrices to increase their size keeping their shape, and the erosion causes the matrices to decrease their size, still remaining cylinders. A model able to describe all phenomena involved for different shaped matrices was pointed out working with pure HPMC first (Chirico et al., 2007), then dealing with matrices made of polymers and drug (Barba et al., 2009). The problem of the drug diffusion in more complex geometries was solved analytically (Fu et al., 1976); in this work the diffusion problem in a finite cylinder in absence of swelling and erosion was solved under the hypothesis of constant diffusivities. More recently, the finite element methods were applied to solve the diffusion problem in tablets of various, even not simple, geometries (convex tablets, hollow cylinders, doughnuts, inwards hemispheres) (Wu and Zhou, 1998), also in presence of moving boundaries (Wu and Zhou, 1999), or in presence of slowly dissolving drugs (Frenning et al., 2005). This approach was never applied in description of swelling and eroding tablets, which is closer to the real situations. Grassi and Grassi (2005) proposed several approaches, with increasing complexity, to model the drug release from solid pharmaceutical forms. A simple model based on the drug balance in the dissolution medium was developed taking into account the resistance to the release due a layer of enteric coating (Grassi et al., 2004b). A much more complex model was developed to describe the release from tablets made of swellable hydrogels, with spher-

ical drug particles, poly-dispersed in size and in different physical states (amorphous, crystalline). The fluxes of water and drug due to the diffusion and to the viscoelastic effects joint to the swelling phenomenon were described and the volume increase due to the swelling was accounted for layer by layer (i.e. dividing the spheres in shells). Of course, the model was completed by the drug balance in the dissolution medium (Grassi et al., 2000). Even in these cases, despite completeness of the analysis proposed, the models were not able to describe non-affine deformations, i.e. the change in shape of the matrices which was observed experimentally as consequence of the hydration in non-spherical matrices.

2.3. Modeling the in vivo pharmacokinetics

The prediction of the drug concentration in the blood, tissue, and organs is the goal of the in-silico pharmacokinetic modeling. The approaches to the modeling of the physiological phenomena can be different on the basis of the details used. The description of the phenomena taking place in the body is much closer to the real physiology if more details are considered.

Three different approaches can be followed to build an *in-silico* model to predict the fate of administered drug: the pure compartment modeling, the physiologically based modeling (PBPK), and the purely mathematical modeling. The compartment approach is based on the schematization of the body by a system of interconnected volumes, the compartments, which can be easily described as chemical reactors or as physical contacting units. In the pure compartmental models, the compartments do not necessarily represent anatomical units. In the physiologically based models, the compartments are representative of a tissue, an organ or a group of organs, each with a specific function, and the interconnection between the compartments reproduces the effective one between tissue and organs. The pure mathematical models are able to correlate the results of an *in vitro* dissolution tests to the *in vivo* drug concentration in the blood. Such correlations are commonly noted as IVIVC: *in vitro*/*in vivo* correlations.

The IVIVC are classified in four levels: level *A*, level *B*, level *C*, and multiple level *C* correlations (FDA, 1997). A level *A* correlation is a point to point relationship between the *in vitro* dissolution profile and the *in vivo* plasma evolution of a drug. A level *B* correlation is a relationship between the mean *in vitro* dissolution time and the mean *in vivo* residence time, obtained by considering the full profile of *in vitro* dissolution and the full *in vivo* plasma evolution. A level *C* correlation is a single point relationship between a dissolution parameter and a PK parameter. A multiple level *C* correlation is a relationship between several points of the dissolution profiles with several PK parameters. Regulatory boards (FDA, USP) accept only Level A IVIVC for scale-up and post-approval changes (SUPAC) which can be justified without the need for additional human studies. A PK model able to correlate the *in vitro* dissolution profile and the *in vivo* plasma evolution, will play the same role of a Level A IVIVC, but it is of great interest since it is physically based.

There are several examples of physiologically based pharmacokinetic compartmental models, the most important is the first whole body physiologically based pharmacokinetic model proposed by Jain et al. (1981). It is based on the schematization of the rat body into 21 compartments, each representative of an anatomical part. The mathematical structure of the model is made up by a system of 38 coupled ordinary differential equations, solved with the initial condition that all the concentrations, but the plasma one, are zero. The simultaneous resolution of the equations requires the knowledge of 98 different model parameters. An application of the model was carried out by the authors in a case of intravenous injections of zinc sulfate in rats and a good agreement between the prediction of the model and the experimental data was found. In spite of the fact that the model gives a complete description of the physiology and it is very accurate, it is too difficult to be adopted for predictive purposes because of the high number of parameters which have to be fitted. Furthermore, the model concerns only the case of intravenous injection in rats and, then, it can not be used for the simulation of oral administration or for human physiology. To overcome the complexity of the Jain model, an algorithm to identify the best lumped model was proposed (Gueorguieva et al., 2006). The procedure provides (i) the grouping of tissue and organs, on the basis of their time constants, obtaining some competing lumped model; (ii) a global sensitivity analysis to find the parameters with the most important effects on the pharmacokinetic profiles; (iii) the selection of the model with the same mean and variance of the arterial concentration time profile obtained by the complete model. A lumped model composed of six compartments was proposed and applied in the case of intravenous injections of barbiturates in rats but it did not show a good agreement with the experimental data (Nestorov et al., 1997).

The complete model developed by Yu et al. (Yu and Amidon, 1999; Yu et al., 1996) is defined as the "Compartment Absorption and Transit" (CAT) model. The schematization of the gastrointestinal tract is made up by 10 compartments. The mathematical structure is made up by 10 ordinary differential equations which have to be solved with the initial conditions (on the fraction of the dose in the gastrointestinal tract and on the plasma concentration) to characterize the time profiles of the drug levels in each compartment. The knowledge of 18 parameters, of the absorption rates, of the degradation rate constants, of the elimination constant and of the distribution volume is required to solve the equation. The CAT model was applied to simulate cases of oral drug administration (both in immediate and in controlled release formulations) and it showed a satisfying agreement between the model prediction and the experimental data. The main drawback of this model is that it can be applied only for oral administration. The CAT model constituted the starting point for the development of the "Advanced Compartmental Absorption and Transit" (ACAT) model (Agoram et al., 2001). This model was implemented into a simulation software, GastroPlus. GastroPlus was tested as an *in-silico* tool for the prediction of the effects of the physiological conditions on physicochemical parameters of some therapeutic substances. Satisfying prediction of the absorption, distribution, metabolism, and excretion (ADME) phenomena were obtained but this model can be used only after several and careful *in vitro* and *in vivo* measurements.

Di Muria et al. (2010) proposed a PKPB model based on a simple representation of the body. It comprises seven compartments, each of them representing an organ, a tissue, a fluid of the body or a group of organs. This model consists of the mass balance equations on the compartments (seven, one for each compartment) and their initial conditions. 22 physiological parameters are used in the model but a very limited number of them (up to five) have to be optimized. The model is able to predict the drug hematic levels for several administration routes. The capabilities of the model were confirmed by the comparison between the model predictions and the experimental data from literature for some case histories.

2.4. Overall models

Summarizing, the administration of an oral dosage form will be followed by two major groups of phenomena:

1. The phenomena which occur to the system after swallowing (the release and/or the solvent uptake, the matrix swelling, the matrix erosion, the drug diffusion and its dissolution),
2. The phenomena which occur to the drug after it is released in the body (the absorption, the distribution, the metabolism, the excretion).

Section 2.1 of this work dealt with the tests required to assess the release kinetics *in vitro* and to their correlations with the real history of pharmaceuticals after their oral administration, emphasizing the needs for test methods which reproduce the real behavior as close as possible; Section 2.2 reviewed the modeling of the phenomena experienced by a solid dosage form after swallowing; Section 2.3 summarized the current approaches followed to model the fate of a drug within a living body, i.e. *in vivo*, after administration. The full modeling of both the aspects of the process is a very difficult task, since it has to describe both the phenomena occurring within the dosage form and the phenomena occurring within the body, outside of the dosage form (Siepmann and Siepmann, 2008).

2.4.1. Purely mathematical approach(es)

The most common approach consists in describing both the processes (the drug release from the dosage form and the drug fate in the body) by means of statistical tools or fitting equations, and to correlate the fitting parameters each other. A lot of example can be found in literature. A nice, simple and efficient example of this approach was given by (Korhonen et al., 2004). In this work, the *in vitro* controlled release of diltiazem (a benzothiazepine used in the treatment of hypertension) from tablets based on starch acetate was assayed and fitted by the power-law equation, $\%R = kt^n$ (in which n is a dimensionless exponent and k is the drug release rate constant, expressed in [time units^{-n}]); meanwhile, the *in vivo* plasma concentration was measured in healthy human volunteers and the recorded histories in term of AUC (Area Under Curve, ng/mL h) were fitted by Hill equation, $AUC = at^b/(c^b + t^b)$. They found that, under the test conditions, $c = 5.6$ [h], $b = 2.0$ [dimensionless], $n = 0.42$ [dimensionless] and a linear relationship exists between the *in vivo* parameter '*a*' and the *in vitro* parameter '*k*', $a = (10.4)k + (45.6)$, in which k is [h^{-n}] and a is [ng/ml h]. Therefore, a Level A IVIVC was found by authors. A modification in the formulation which changes the release kinetics will cause a different value of '*k*', easy to measure by a simple *in vitro* test, but the availability of the IVIVC allows predicting the plasma evolution via the calculation of the new value for the parameter '*a*', without the needs for a cumbersome *in vivo* trial. Similar work was carried out for different systems. Dutta et al. (2005) obtained a Level A IVIVC dealing with divalproex sodium (an anticonvulsant) as released by tablets, which because of different amount of HPMC K15M (an hydrogel used as a controlling release agent) exhibits very different release rates. Thakkar et al. (2009) found a simple correlation between the parameters of the power-law equation, used to fit the *in vitro* release kinetics from floating tablets releasing levofloxacin hemihydrate (an antibiotic), and the observed plasma AUC.

A variation of this approach consists in obtaining the *FRD* (FRaction of drug Dissolved) by fitting the *in vitro* results by simple models (Higuchi's square root (Higuchi, 1963), Korsmeyer–Peppas equation (Korsmeyer et al., 1983), Hixson–Crowells equation (Hixson and Crowell, 1931) or something similar), then to obtain the FRA (FRaction of drug Absorbed) usually by the Wagner–Nelson method (Wagner, 1971) for which $FRA = (C_t + k_{el}AUC_t)/k_{el}AUC_\infty$, where C_t is the plasma drug concentration at time t, k_{el} is the first order elimination constant, AUC_t and AUC_∞ are, respectively, the Area Under Curve for the plasma concentration vs. time at time t and extrapolated to infinity. The last step consists in looking for a (linear) correlation between FRA and FRD, which plays the role of a Level A IVIVC. Several examples of this approach can be found, a couple of them are: the release of metoprolol (a selective β_1 receptor blocker used in treatment of several diseases of the cardiovascular system) from HPMC based tablets (Sirisuth and Eddington, 2002), the release of glipizide (an insulin secretagogue) from xantam/HPMC matrices (Sankalia et al., 2008). An attempt to give some theoretical basis to the purely statistical/mathematical approach was performed by Amidon which, at the same, time gave the foundation to the already mentioned (see Section 2.1) BCS system (Amidon et al., 1995) and proposed a generalized equation to establish the relationship between *in vitro* dissolution data and *in vivo* absorption data (Polli et al., 1996). In this equation, the key role was played by the parameter α, defined as the ratio of the first order permeation rate constant (a pharmacokinetic parameter, to be evaluated *in vivo*) to the first order dissolution rate constant (a release kinetic parameter, to be evaluated *in vitro*). Once more, with their work, authors emphasized the role of dissolution and permeation in the IVIVC definition.

2.4.2. Drug release by pure dissolution

The simplest case which could be described by a full modeling consists in the pure dissolution of the solid dosage form. In this case, the dissolution is usually described by the Noyes–Withney equation (Noyes and Whitney, 1897), which makes the rate of dissolution proportional to the difference between saturation and actual concentration of dissolving drug. The proportionality constant accounts for the particle size and diffusion coefficient of the drug in the solvent. The dissolution profile, which can be obtained *in vitro* and which can be described by the Noyes–Withney equation, is then used as the forcing function for a pharmacokinetic model.

Recently, the aprepitant (an antiemetic antagonist of NK1 receptor) release from micro-sized and nano-sized powders and its pharmacokinetics in fasted and fed humans were described (Shono et al., 2010) by means of Noyes–Withney equation coupled to STELLA® 9.0 software (Cognitus Ltd., North Yorkshire, UK), a commercial pharmacokinetic simulation code. The change in powder size modifies the dissolution rates, and consequently the rate of appearance in plasma. The model was found able to correctly reproduce the observed experimental behavior, both *in vitro* as well as *in vivo*. Willmann and co-workers proposed a physiology-based model to describe the gastrointestinal transit and absorption, in which the GI tract was modeled as a continuous tube with spatially varying properties. The model was implemented in PK Sim software (Bayer Technology Service GmbH, Leverkusen, Germany). They applied the model to rats (Willmann et al., 2003), to humans (Willmann et al., 2004), and to monkeys (Willmann et al., 2007). In these works, the *in vivo* pharmacokinetics was described in detail but the *in vitro* release kinetics was neglected (by considering the drug in liquid form or assuming its immediate release). Recently, the same group dealt with the administration of cilostazol (a vasodilator used in the alleviation of the symptom of intermittent claudication in individuals with peripheral vascular disease) to fasted or fed dogs, by powders of different sizes, hammer-milled, jet-milled (micro-sized), and nano-crystal (nano-sized) (Willmann et al., 2010). In this case, the dissolution and the precipitation kinetics have to be described, and the authors used the NW equation. The full model (dissolution plus pharmacokinetics) was found able to correctly predict the *in vitro* as well as the *in vivo* data.

A similar approach was followed by Carrier and co-workers (Gamsiz et al., 2010a,b), describing the drug dissolution and absorption, alone as well as in presence of cyclo-dextrins (CDs), which are known as dissolution-enhancers and as transporters across membranes. In this case, the pharmacokinetic part of the model is a very simple one-compartment model, accounting for the drug clearance from the plasma (excretion). The full model, named "neutral compound physical mixture (NCPM)", was found able to reproduce the *in vitro* kinetics of Naproxen (a nonsteroidal anti-inflammatory drug, NSAID) and Nifedipine (a dihydropyridine calcium channel blocker, used mainly as an anti-angina), alone or physically mixed with β-CD. The model was successfully compared with *in vivo* data (from literature) of Glibenclamide (anti-diabetic drug) dosed in dogs and Carbamazepine (an anticonvulsant) dosed in rats.

2.4.3. Drug release by more complex processes

The description of drug release kinetics from a solid dosage form, to be administered orally, could be a really hard task (Siepmann and Siepmann, 2008). A number of complex phenomena could be involved, the penetration of the solvent into the matrix, the swelling of the matrix, the erosion of the polymer, the dissolution of the drug, the diffusion of the drug towards the release medium, the change in diffusivity due to the swelling. Due to these difficulties, a full model for the drug release kinetics prediction is still lacking in literature. Then, the integration of the drug release models (for dosage forms which does not simply dissolve) with the pharmacokinetic models is a problem rarely faced off by researchers.

The drug release and the ADME phenomena following the administration of co-extrudate obtained by hot-melt extrusion containing theophylline (TP, a methylxanthine drug used in therapy for respiratory diseases) was described by (Quintavalle et al., 2008). In this work, coaxial cylinders obtained by extrusion, the inner one hydrophilic (polyethylene glycol) and the outer one lipophilic (microcrystalline wax), were dissolved (*in vitro* tests) and they were administered to volunteers, assaying the plasma concentration evolution (*in vivo* tests). The drug release was modeled accounting for TP dissolution and diffusion inside the cylinders (which did not swell and/or erode, keeping the initial size and shape) and assuming that the gastro-intestinal tract is a well stirred homogeneous environment where TP is uniformly distributed. The pharmacokinetic of TP was modeled accounting for the absorption (through intestinal walls) and its elimination, due to metabolism. The novelty of this model relies on the simultaneous solution of the equations ruling TP release (partial differential equation) and TP ADME processes (ordinary differential equations). This was possible due to the introduction of an overall mass balance accounting for the fact that, at anytime, the sum of the drug amount present in the blood, in tissues, metabolised and still present in the cylinders (release system) must be equal to drug dose. The model was found able to satisfactory predict *in vivo* data after a proper parameter fitting session on both *in vitro* and *in vivo* data.

Recently, the drug release and the ADME phenomena due to the administration of vinpocetine (a semisynthetic derivative of vincamine, which is extracted from periwinkle plant; it increases cerebral blood flow and improves memory) to volunteers were investigated (Grassi et al., 2010). The administration form was obtained by co-grinding of vinpocetine with micronized crospovidone (PVP). The produced particles, which exhibit a distribution of sizes, undergo swelling when immersed in a solvent, while the drug dissolves and diffuses inside the polymeric particles. The drug release kinetics was modeled accounting for dissolution, diffusion and swelling (in each class into which the particle size distribution can be subdivided), also accounting for the coexistence of amorphous, nano-crystalline and macro-crystalline phases (this implying the possibility of drug re-crystallisation and, thus drug solubility reduction, during the release process). In addition it was assumed that the gastro-intestinal tract is a well stirred homogeneous environment where vinpocetine is uniformly distributed. The pharmacokinetics was modeled accounting for drug distribution in blood and in other tissues (two physiological compartments). The adsorption, the excretion, the exchange between compartments were accounted for. Once more, model solution implied the simultaneous solution of the equations ruling drug release (partial differential equations) and drug ADME processes (ordinary differential equations). The model was found able to properly fit *in vivo* data on the basis of a previous fitting led on *in vitro* data necessary for the determination of the model parameters ruling drug release. The simultaneous solution of all model equations made possible accounting for the mutual influence of the release and ADME processes, an aspect that is usually neglected

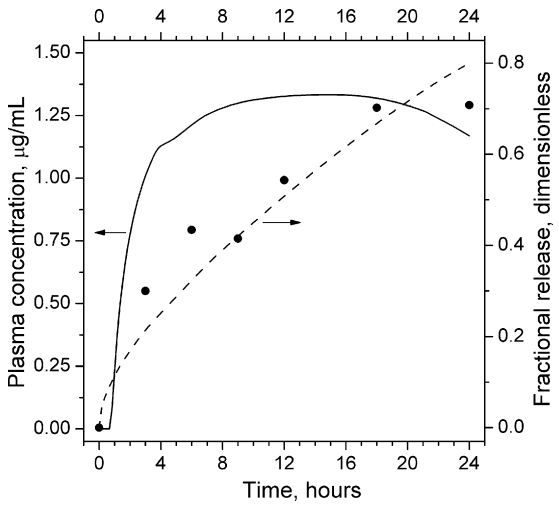

Fig. 2. *In-vitro* and *in vivo* prediction of the Di Muria model (Di Muria et al., 2010). While symbols represent the experimental *in vitro* data, the dashed line indicates model *in vitro* prediction. Solid line is the *in vivo* model prediction.

but can be important especially when dealing with amorphous drug that can undergo re-crystallisation (solubility reduction) during the release process.

Matrices based on hydrogels undergo to complex phenomena, the way summarized at the beginning of this sub-section. The most complete model to describe the release kinetics was proposed some years ago (Siepmann et al., 1999a) and it was called the "sequential layer" model. Even if it takes into account all the relevant phenomena, its major drawbacks is that the matrices were treated as subject to affine deformations, i.e. they increase in size due to the swelling, but they keep the initial shape. The experimental evidence is against this assumption, therefore a detailed model was recently proposed (Lamberti et al., in press), and it was found able to correctly reproduce all the phenomena observed during *in vitro* tests such as the change in shape due to swelling and erosion. The model, which is based on the diffusion of water into a HPMC-based matrix, initially cylindrical in shape and loaded by theophylline, consists in a set of two partial differential equations that can be easily coupled with the physiologically based pharmacokinetic model proposed by Di Muria et al. (2010), composed of seven ordinary differential equations. The coupling of both models gave the results shown in Fig. 2. The release kinetics have been experimentally validated (symbols are the experimental data). The pharmacokinetics predictions were not compared with experimental data. To further validate the full model, two steps have to be performed:

1. Some *in vivo* data should be obtained (the same matrix investigated in the *in vitro* tests should be administered to volunteers and the plasma concentration evolution should be assayed).
2. An *in vitro* test able to reproduce the real physiology should be designed and realized in order to better simulate what happens to the matrix once swallowed.

3. Transdermal administration

In the case of transdermal administration, Fig. 1 assumes the form of Fig. 3. The delivery system is now represented by a patch that can be constituted by different components: reservoir (containing a drug solution or a gel system loaded by a drug), impermeable backing, (polymeric) membrane and adhesive liner. When the reservoir is absent, the patch is called monolithic and the drug is hosted inside the polymeric matrix (Venkatraman et al., 2000). Whereas in homogeneous membranes diffusion controls

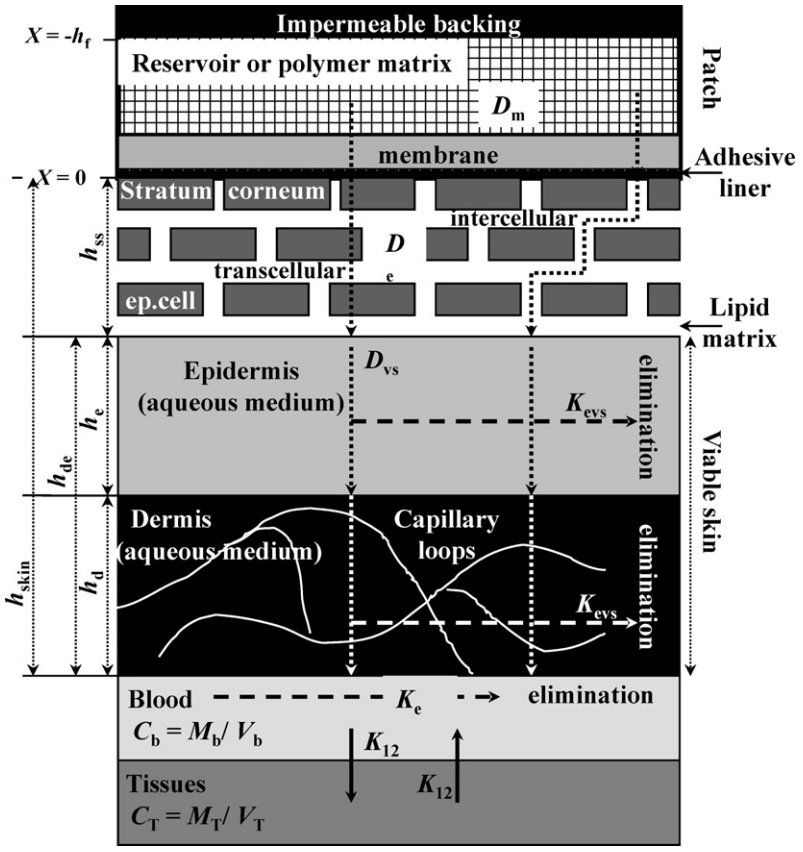

Fig. 3. Schematic representation of the skin and transdermal patch cross section. Once released from the patch, the drug, trancellularly o intercellularly, cross the *stratum corneum* to get the viable skin (epidermis + dermis) where its elimination can occur. Then, it goes in the blood where a further elimination can take place jointly with a distribution towards tissues. D_e is the drug effective diffusion coefficient in the *stratum corneum*, D_{vs} is the drug diffusion coefficient in the viable skin, K_{evs} and K_e are, respectively, the elimination constants in viable skin and blood, while K_{12} and K_{21}, are, respectively, the kinetics constants ruling the exchange among blood and tissues. Finally, C_b and C_T indicate, respectively, drug concentration in blood and tissues.

drug release, in the case of porous membranes convection is the leading drug transport mechanism. Once released from the patch, the drug comes in contact with the skin that can be seen as a particular tri-layers membrane composed by the stratum corneoum (10–20 μm thick), the epidermis (50–100 μm thick) and the dermis (1–2 mm thick) (see Fig. 3). Stratum corneoum is composed by a lipid-rich matrix where flattened, interdigitated, partially desiccated, keratinised dead epidermal cells are organised into a layered, close-packed array (Michaels et al., 1975). It is by far the most important barrier to drug permeation through the skin. Epidermis, a viable tissue devoid of blood vessels, is just below the stratum corneum. The inner-most skin layer is represented by the dermis that contains capillary loops able to take up administered drugs for systemic distribution (Prausnitz et al., 2004). Skin structure is completed by the presence of sweat ducts and hair follicles, vertical holes, characterized by an external orifice of 50–100 μm diameter, crossing the three mentioned layers (Meidan et al., 2005). In principle, these structures favour drug permeation as they represent channels connecting the external environment with the dermis capillary bed. Traditionally, both sweat glands and follicular drug transport in humans have been neglected due to the low skin surface competing to the outer part of these structures (1%) (Michaels et al., 1975). Nowadays, on the contrary, the importance of follicular transport has been reconsidered also in the light of the fact that the potential area available for penetration also includes the internal follicular surface (Meidan et al., 2005).

Drug transport through the skin is a complex phenomenon comprehending physical, chemical and biological interactions. In particular, it implies (a) drug release from the formulation, (b) drug partitioning into the stratum corneum (SC), (c) diffusion through the SC, (d) partitioning from the SC into the aqueous viable epidermis, (e) diffusion through the viable epidermis and into the upper dermis, and (f) uptake into the local capillary network to get the systemic circulation and tissues where drug therapeutic action is performed (Kalia and Guy, 2001). This frame is made more complicated by the skin metabolic activity towards entering drug (Yamashita and Hashida, 2003). It is worth mentioning that although drug diffusion across SC can be transcellular and/or intercellular (see Fig. 3), intercellular lipidic pathway represents the most important route for drug permeation (Yamashita and Hashida, 2003; Kalia and Guy, 2001). Once the physical frame and the most important phenomena have been delineated, it is possible translating them into mathematical terms giving origin to a mathematical model, a mathematical methapor of some aspects of reality (Israel, 1998). Of course, this translation is not unique as it depends on what phenomena are retained as most significant. For example, Oureimchi (Oureimchi and Vergnaoud, 2000) assumed that the skin is composed of two layers. The first one is a homogeneous layer made up by the SC and the epidermis, while the second is represented by the dermis. Additionally, it was supposed that drug concentration in the dermis is always uniform (this environment behaves as a well stirred tank reactor) whereas drug transport in the first layer (denominated skin) and in the patch (delivery system) are ruled by Fick's second law considering one-dimension:

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial X}\left(D\frac{\partial C}{\partial X}\right) \quad (1)$$

where C is drug concentration, t is time, X is the one-dimension coordinate and D is the drug diffusion coefficient. Eq. (1) is solved with the following initial and boundary conditions:

Initial

$$C(X = -h_m) = k_{ps}C_0 \; C(-h_m < X \le 0) = 0 \quad \text{reservoir} \tag{2}$$

$$C(-h_m \le X \le 0) = C_0 \quad \text{monolithic} \tag{3}$$

$$C(0 \le X \le h_{skin}) = 0 \quad \text{skin} \tag{4}$$

Boundary

$$C(X = -h_f) = k_{ps}C_0 \quad \text{reservoir} \tag{5}$$

$$\left.\frac{\partial C}{\partial X}\right|_{X=-h_f} = 0 \quad \text{monolithic} \tag{6}$$

$$D_m \left.\frac{\partial C}{\partial X}\right|_{X=0}^{membrane} = D_s \left.\frac{\partial C}{\partial X}\right|_{X=0}^{skin} \quad C_{skin}(X=0) = k_{pm}C_m(X=0) \tag{7}$$

$$C(X = h_{ss}) = 0 \tag{8}$$

Eq. (2) states that, in the reservoir configuration, membrane is initially drug free while at the membrane/reservoir interface ($X = -h_m$), drug concentration is ruled by the partition coefficient k_{ps} being C_0 the drug concentration in the reservoir environment. On the contrary, in the monolithic situation (Eq. (3)), drug concentration (C_0) is uniform throughout the membrane. Obviously, skin and dermis are assumed drug free (Eq. (4)). Eq. (5) imposes that C_0 is constant over time in the reservoir while an impermeable wall (no flux in the X direction) is assumed in the monolithic configuration (Eq. (6)). Finally, Eq. (7) ensures that no drug accumulation occurs at the membrane/skin interface where the usual partitioning condition (k_{pm}) holds for what concerns drug concentration on the skin and membrane side. D_s and D_m, represent, respectively, drug diffusion coefficient in the skin and in the membrane. Again, for the sake of simplicity, sink conditions were assumed at the skin/dermis interface (Eq. (8)). This assumption, absolutely reasonable, has the great advantage of decoupling the mass transport equation holding in the membrane and in the skin (Eq. (1)) from the equations ruling drug amount in the dermis and in the blood environments:

$$\frac{dM_d}{dt} = -SD_s \left.\frac{\partial C}{\partial X}\right|_{X=h_{ss}+h_e} - K_a M_d \quad \text{dermis} \tag{9}$$

$$\frac{dM_b}{dt} = K_a M_d - K_e M_b \quad \text{blood} \tag{10}$$

Eq. (9) imposes that drug amount in the dermis (M_d) increases due to the drug exiting from the skin and decreases due to blood absorption (K_a is the absorption constant and S is the area of the patch). At the same time, the drug amount in the blood (M_b) depends on the drug absorbed from the dermis and the contribute of first order metabolism (K_e is the elimination constant) (Eq. (10)). After patch removal ($t \ge t_r$) it was assumed that part of the drug leaves the skin according to:

$$D \left.\frac{\partial C}{\partial X}\right|_{X=0} = k_h C_e \tag{11}$$

where k_h is a coefficient of convective transfer of the drug out of the skin while C_e is the drug concentration on the external surface of the skin. The author tested this model on metoprolol release from Scotch Pack 1006 (3M Company, USA) as metoprolol is subject to extensive first pass metabolism following oral administration. The comparison with experimental data (rats) revealed satisfactory model predictions.

Young et al. (1994), developing the original approach of Berner (1985), assumed that skin consists of only the stratum corneoum while the dermis and epidermis belong to the body compartment comprising blood and tissues. Drug amount in the body (M_{bo}) is evaluated according to an equation that is the sum of Eqs. (9–10):

$$\frac{dM_{bo}}{dt} = -SD_m \left.\frac{\partial C}{\partial X}\right|_{X=h_{ss}} - K_e C_{bo} \tag{12}$$

The initial drug amount in the body is set equal to M_{bo}^0. Again, Eq. (1) rules drug transport in the skin (stratum corneoum). Additionally, it was assumed that drug concentration at the skin/patch interface is always constant and equal to C_0, sink conditions hold at the skin/body interface and the skin is drug free at the beginning. Thus, also in this model, the mass transport equation in the skin and the equation ruling drug concentration in the body are decoupled. After patch removal, it was assumed that $C(X=0) = 0$, which corresponds to an infinite values for k_h in Eq. (11). The Young approach, although less refined than that of Oureimchi, has the considerable advantage of yielding to an analytical solution:

Before patch removal

$$C_{bo}(t) = \frac{SDC_0}{V_{bo}h_{ss}}\left(\frac{1-e^{-K_e t}}{k} + 2\sum_{i=1}^{\infty}\frac{(-1)^i}{K_e - k}\left(e^{-kt} - e^{-K_e t}\right)\right) + \frac{M_{bo}^0}{V_{bo}}e^{-K_e t} \tag{13}$$

After patch removal

$$C_{bo}(t) = C_{bo}(t_r)\left(\frac{SD}{V_{bo}h_{ss}}\sum_{i=1}^{\infty}\frac{e^{-kt}}{K_e - k} + \left(1 - \sum_{i=1}^{\infty}\frac{1}{K_e - k}\right)e^{-K_e t}\right)$$

$$k = \frac{i^2\pi^2 D}{(h_{ss})^2} \tag{14}$$

The comparison between model prediction and experimental data (humans) referring to nicotine release is satisfactory.

A possible way to improve the mathematical modeling of drug absorption following transdermal delivery is to generalise the mass transport equation in the patch and in the skin and to couple them with the equations describing the fate of the drug in the blood and in the tissues (see Fig. 3). The first aspect to be considered is that, due to the inhomogeneity of SC, Fick's second law of diffusion should be solved in three dimensions (Michaels et al., 1975). Indeed, drug transport across SC substantially occurs through the intercellular lipidic pathway (Yamashita and Hashida, 2003; Kalia and Guy, 2001). Alternatively, Kushner et al. (2007) suggested to account for SC porosity (ε) and tortuosity (τ) introducing the effective drug diffusion coefficient D_e (Peppas, 1984) into Eq. (1):

$$\frac{\partial C}{\partial t} = D_e \frac{\partial^2 C}{\partial X^2} \quad D_e = \frac{\varepsilon}{\tau}D_{lc} \tag{15}$$

where D_{lc} is the drug diffusion coefficient in the lipidic channels. Then, it should be noted that while drug metabolism does not occur in the SC, it can take place in the viable skin (epidermis + dermis) (Tojo, 2005). Accordingly, Eq. (15) must be coupled with a drug transport equation in the viable skin (VS) accounting for drug elimination assuming, for example, a first order elimination law Eq. (16) (Al-Qallaf et al., 2009):

$$\frac{\partial C}{\partial t} = D_{vs}\frac{\partial^2 C}{\partial X^2} - K_{evs}C \tag{16}$$

where K_{evs} and D_{vs} are, respectively, the drug elimination constant and diffusion coefficient in VS, assumed to be a homogeneous medium. The evaluation of the amount of drug eliminated in VS up

to time t ($M_{evs}(t)$) can be done by means of the following equation:

$$M_{evs}(t) = \int_{V_{vs}} dV \int_0^t K_{evs} C(X,t)\, dt \tag{17}$$

where V_{vs} is the volume of the viable skin where $C > 0$. Finally, in the case of iontophoresis assisted transdermal administration, drug transport in SC and VS must account for the effect of the applied electrical field E (Tojo, 2005, 1989):

$$\frac{\partial C}{\partial t} = D_e \frac{\partial^2 C}{\partial X^2} - \gamma \frac{\partial C}{\partial X} \qquad \text{SC} \tag{18}$$

$$\frac{\partial C}{\partial t} = D_{vs} \frac{\partial^2 C}{\partial X^2} - K_{evs} C - \nu \frac{\partial C}{\partial X} \qquad \text{VS} \tag{19}$$

where:

$$\gamma = \frac{zFE}{RT} \frac{D_e}{h_{ss}} + \nu, \qquad \nu = \alpha \Gamma \tag{20}$$

being z the drug charge number, F the Faraday constant, E the electric field, R the universal gas constant, T the temperature, α a constant parameter and Γ the current density. These equations need to be solved with the above discussed boundary and initial conditions (Eqs. (2–6)) except for Eqs. (7) and (8) that must substituted by:

$$\left(-D_e \frac{\partial C}{\partial X} + \nu C \right)\Big|_{sc} = \left(-D_{vs} \frac{\partial C}{\partial X} + \nu C \right)\Big|_{vs} \tag{21}$$

$$D_s \frac{\partial C}{\partial X}\Big|_{X=h_{skin}} = -k_s \left(C(X = h_{skin}) - C_b \right)$$

$$k_{pskin} = \frac{C(X = h_{skin})}{C_b} \tag{21'}$$

Eq. (21) imposes the absence of drug accumulation at the SC–VS interface, while Eq. (21′) states that the drug flux exiting from the skin depends on the mass transfer coefficient k_s and the difference between the drug concentration in the skin at the skin/blood interface and the drug concentration in the blood C_b. In addition, the partition coefficient k_{pskin} rules the ratio between drug concentration on the skin and blood side at the skin/blood interface. C_b, C_T (drug concentration in the tissues) and M_{eb} (amount of metabolised drug in the blood) can be evaluated, for instance, according to a two compartments pharmacokinetics model with first order elimination (Tojo, 2005):

$$V_b \frac{dC_b}{dt} = -SD_s \frac{\partial C}{\partial X}\Big|_{X=h_{skin}} - K_e C_b V_b - K_{12} C_b V_b + K_{21} C_T V_T \tag{22}$$

$$V_T \frac{dC_T}{dt} = K_{12} C_b V_b - K_{21} C_T V_T \tag{23}$$

$$\frac{dM_{eb}}{dt} = K_e M_b \tag{24}$$

where V_b and V_T are, respectively, blood and tissues volume, while K_{12} and K_{21} represent, respectively, the direct and reverse kinetics constants ruling drug exchange between blood and tissues. In order to close the balance between unknowns and equations, an overall drug mass balance (made up on the patch, skin, blood and tissues) needs to be considered at anytime:

$$M_0 = C_b(t)V_b + C_T(t)V_T + S\left(\int_{patch} C(X,t)\, dX + \int_{skin} C(X,t)\, dX \right) + M_{eb}(t) + M_{evs}(t) \tag{25}$$

where M_0 is the drug dose.

After patch removal ($t > t_r$), Eq. (11) becomes the new boundary condition on skin surface ($X = 0$) while Eq. (25) becomes:

$$M_0 - S\int_{patch} C(X,t_r)\, dX = C_b(t)V_b + C_T(t)V_T + S\int_{skin} C(X,t)\, dX + M_{eb}(t) + M_{evs}(t) \tag{26}$$

Indeed, we must account for the fact that the drug amount still present in the patch at removal time (t_r) is no longer available.

4. Local administration

A huge mathematical modeling activity was performed on local drug delivery systems. For example, it can be mentioned drug delivery to the brain (Reisfeld et al., 1995; Siepmann et al., 2006), the intratumoral delivery (Qian et al., 2002; Feng and Chien, 2003; Weinberg et al., 2008), the cell delivery (Gamsiz et al., 2008), the root canal delivery (Huang et al., 2000), the corneal delivery (Zhang et al., 2004; Li and Chauhan, 2006) and the nasal delivery (Gonda, 1998). Due to the wideness of this field, we decide to focus the attention only on a particularly interesting application regarding in-stent restenosis, a common atherosclerosis complication following percutaneous transluminal coronary angioplasty (PTCA) (Gruntzig et al., 1979). Atherosclerosis can be considered a form of chronic inflammation of the artery wall leading to the development of complex lesions, defined as plaques that narrow the arterial lumen (Ross, 1999). Plaque rupture and thrombosis result in acute clinical complications such as myocardial infarction and stroke, when the event occurs in coronary or cerebral arteries, respectively (Owens et al., 2004). In order to re-vascularize stenotic coronary arteries, since 1979 it has been introduced the so called PTCA, a procedure leading to the enlargement of the stenotic portion of the coronary by means of an expanding balloon. Since 1987 (Sigwart et al., 1987) PTCA has been associated with the deployment of a stent, an expandable metal – or polymeric – tubular mesh that has significantly reduced the rates of early elastic recoil and late constructive remodelling of the vessel, reducing restenosis rate down to 20–30% (Serruys et al., 1994). Unfortunately, however, stents did not definitively solve the restenosis problem as they can induce neointima hyperplasia (in-stent restenosis – ISR) due to the iperproliferation of vascular smooth muscle cells (VSMCs) (Moreno et al., 2004). At this purpose, drug eluting stents (DES) substantially reduced the VSMCs iperproliferation thank to the action of the antiproliferative drugs they can release (Stone et al., 2004). As the success or the failure of a DES largely depends on the anti-proliferative agent released, several drugs were tested. Among them, nucleic acid based drugs (NABD) have been proved to hinder VSMCs exuberant proliferation without inducing cell death (Dapas et al., 2009; Grassi et al., 2004a; Khachigian et al., 2002). This feature may confer to NABD an advantage over the commonly used drugs which display a potent apoptotic effect leading, in the long term, to an excessive cell death. This might contribute to explaining their reduced efficacy in high risk patients and the recently reported problems of late stent thrombosis, a draw back related to the reduction of the re endotelisation of the stented zone (Iakovou et al., 2005; Shuchman, 2006). However, due to their fragile nature, NABD can not be incorporated in the stent for a later release and a proper delivery system is needed. At this purpose, the endoluminal gel paving technique (EGP) (Slepian and Hubbell, 1997), together with the implantation of a bare metal stent after PTCA, seems to be an effective and promising approach. EGP consists of the catheter application of a biocompatible polymer aqueous solution (containing the NABD) on the endoluminal vessel surface followed by *in situ* crosslinking to

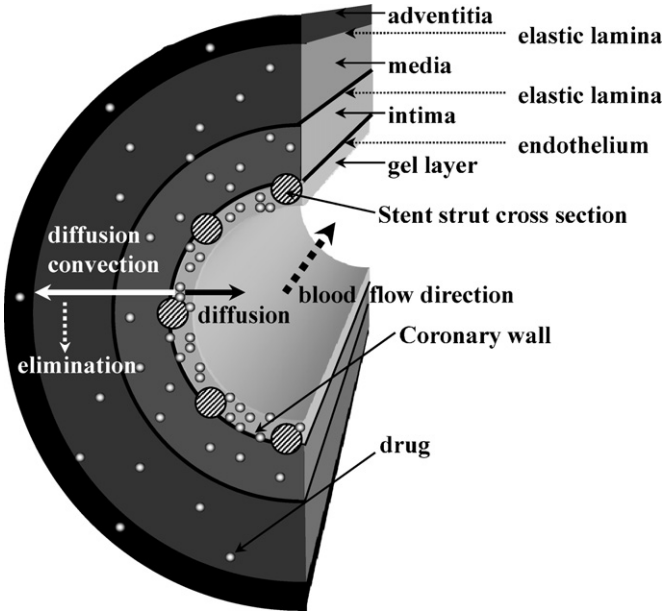

Fig. 4. Cross section of a stented coronary with a gel layer. The drug (spheres), once released from the gel layer (or from the stent, in the drug eluting stents case, DES), can go inside the coronary wall or it can proceed towards the blood stream. The correct designing of the gel/DES properties minimises drug lacking in the blood.

have a gel embedding the stent and adhering to the coronary wall (see Fig. 4).

Regardless of the delivery system considered (DES or EGP), the anti-proliferative drug undergoes the same fate. Indeed, it can be released in the blood stream (failing its therapeutic task) or it can penetrate in the coronary wall. In this second case it partitions in the *intima*, the inner-most layer constituting the coronary wall (see Fig. 4). Here, drug dynamics is essentially due to diffusion, induced by the concentration gradient, and convection (if the gel layer is absent – DES case), due to a radial hydrostatic pressure gradient between lumen and coronary wall (Yang and Burt, 2006). In order to reach the *media* (the middle arterial wall layer), the drug must partition from the *intima* to the internal elastic *lamina* and then to the *media*. Again, diffusion and convection (DES case) govern its motion even though drug binding to proteins and metabolism can affect it. While drug binding to proteins is reversible, metabolism (here meant as cellular internalisation) is irreversible and leads to drug disappearing. In this context, arterial wall can be schematised as an inter-channelled structure (porous medium) where free drug molecules, moving in the fluid filling the channels, progressively bind to proteins and are metabolised (Creel et al., 2000). Again, drug molecule transport to *adventitia* (the outermost arterial wall layer) requires two further steps: *media* – external elastic *lamina* and external elastic *lamina* – *adventitia*. Once in the *adventitia* the molecule is swept out by *vasa vasorum*, lymphatic drainage and lost into connective tissues.

In the EGP case, drug transport in the gel phase can be described according to Fick second with constant diffusion coefficient (D) (Davia et al., 2009; Grassi et al., 2009):

$$\frac{\partial C}{\partial t} = D\nabla^2 C \tag{27}$$

The subsequent drug transport in the artery wall has been approached accounting for both a diffusive and convective transport associated to drug disappearing due to metabolism and/or cellular internalisation (Lovich and Edelman, 1996; Hwang et al., 2003; Prabhu, 2004; Vairo et al., 2010):

$$\frac{\partial C}{\partial t} = D_e\nabla^2 C - v\cdot\nabla C - K_{eaw}C \tag{28}$$

where D_e is the effective drug coefficient in the artery wall (Peppas, 1984), v is the velocity vector and K_{eaw} is the elimination constant in the artery wall. The necessity of introducing an effective diffusion coefficient arises from the inhomogeneity of artery wall due to both the presence of different layers in it (*intima*, *media*, *adventia*, and *laminae*; see Fig. 4), and due to the above discussed artery wall porous nature. Although, in principle, the convective field, generated by the radial hydrostatic pressure gradient existing between lumen and coronary wall, should be time and position dependent, it is usually assumed constant (Hwang et al., 2003). In addition, obviously, in the case of EGP, the convective field disappears where the artery wall is coated by the gel layer. Finally, drug elimination, represented by the action of metabolism and/or cellular internalisation, is assumed to be irreversible even if, in principle, it could be reversible as it happens when the drug interacts with binding sites (Lovich and Edelman, 1996). Eqs. (27) and (28) needs to be solved with the proper initial and boundary conditions. Typically, it is assumed that the drug is present only in the gel layer (EGP) or in the stent (DES), all other zones (artery wall, blood and tissues) being drug free. In addition, the condition of no mass accumulation is assumed at all interfaces:

$$D_{ei}\nabla C_i = D_{ej}\nabla C_j \tag{29}$$

where subscripts "i" and "j" identify two different phases. Of course, in the case of an impermeable phase, the corresponding effective diffusion coefficient is set to zero. Usually, on the external *adventia* side the drug concentration is set to zero as well as at big distance from the stended zone. In order to account for drug passage to blood and tissues (other than the arterial wall), it is possible to use equations such as Eqs. (22–24) where the evaluation of the mass flux going into the blood (first right hand side term in Eq. (22)) needs to be modified in order to account for the different situation (presence or absence of the gel layer, stent geometry and so on). Also in this case an overall mass balance accounting for the eliminated drug, for the drug present in the gel (EGP) or in the stent (DES), in the artery wall surrounding the stented zone, in blood and in tissues, can close the balance between equations and unknowns.

If in the case of oral and transdermal administration the developed mathematical model can be used to fit and to predict experimental data, in this particular application the model is usually demanded to predict the *in vivo* experimental behavior. This is mainly due to the fact that it is very difficult to experimentally detect the distribution of drug in the artery wall and in the blood and tissues at different times (task that is much simpler in the oral and transdermal cases in virtue also of higher doses involved). Accordingly, mathematical models serve to optimize the characteristics of the chosen delivery system in order to theoretically ensure, for example, that a negligible part of the administered dose fails its target spreading in the blood stream. Or, alternatively, it could be interesting to see whether the drug spreads in the artery wall rather than staying just below the *intima* where its anti-proliferative action is mostly requested. This is the typical case where a direct comparison between model predictions and experimental evidence could be performed only on the pharmacodynamics level, i.e. on the effect of the administered drug.

5. Conclusion

Even if the full simulation of the fate of the administered drug is a really hard task, we believe that nowadays the solution to this complex problem is close. Indeed, the examples reported in this review, dealing with the oral, transdermal and local administration,

are both encouraging and promising and they should constitute the core for further and important refinements that should lead, in the future, to the prediction also of pharmacodynamics.

Acknowledgments

This work has been supported by the Italian Ministry of Education (PRIN 2008 (2008HCAJ9T)) and by the "Fondazione Benefica Kathleen Foreman Casali" of Trieste.

References

Al-Qallaf, B., Mori, D., Olatunji, L., Das, D.B., Cui, Z., 2009. Transdermal drug delivery by microneedles: does skin metabolism matter. Int. J. Chem. React. Eng. 7 (A69), 1–23.
Agoram, B., Woltosz, W., Bolger, M., 2001. Predicting the impact of physiological and biochemical processes on oral drug bioavailability. Adv. Drug Deliv. Rev. 50, S41–S67.
Amidon, G.L., Lennernäs, H., Shah, V.P., Crison, J.R., 1995. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res. 12, 413–420.
Banakar, U., 1992. Pharmaceutical Dissolution Testing. Marcell Dekker, New York.
Barba, A.A., d'Amore, 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.
Berner, B., 1985. Pharmacokinetics of transdermal drug delivery. J. Pharm. Sci. 74, 718–721.
Chirico, S., Dalmoro, A., Lamberti, G., Russo, G., Titomanlio, G., 2007. Analysis and modeling of swelling and erosion behavior for pure HPMC tablet. J. Control Release 122, 181–188.
Creel, C., Lovich, M., Edelman, E., 2000. Arterial paclitaxel distribution and deposition. Circ. Res. 86, 879–884.
Dapas, B., Farra, R., Grassi, M., Giansante, C., Fiotti, N., Uxa, L., Rainaldi, G., Mercatanti, A., Colombatti, A., Spessotto, P., Lacovich, V., Guarnirei, G., Grassi, G., 2009. Role of E2F1-cyclinE1-cyclinE2 circuit in human coronary smooth muscle cell proliferation and therapeutic potential of its down regulation by siRNAs. Mol. Med. 15, 296–306.
Davia, L., Grassi, G., Pontrelli, G., Lapasin, R., Perin, D., Grassi, M., 2009. Mathematical modelling of NABD release from endoluminal gel paved stent. Computat. Biol. Chem. 33, 33–40.
da Vinci, L., 1651. Trattato della Pittura.
Di Muria, M., Lamberti, G., Titomanlio, G., 2010. Physiologically based pharmacokinetics: a simple all purpose model. IEC Res. 49, 2969–2978.
Dokoumetzidis, A., Macheras, P., 2006. A century of dissolution research: from Noyes and Whitney to the biopharmaceutics classification system. Int. J. Pharm. 321, 1–11.
Dutta, S., Qiu, Y., Samara, E., Cao, G., Granneman, G., 2005. Once a day extended release dosage form of divalproex sodium III: development and validation of a Level A in vitro–in vivo correlation (IVIVC). J. Pharm. Sci. 94, 1949–1956.
Evans, D., 2010. Iterative method for constructing dosing regimes for controlling HIV dynamics. Sci. Pharm. 78, 588.
FDA, 1997. Guidance for industry. Extended release oral dosage forms: development, evaluation, and application of in vitro/in vivo correlations. Center for Drug Evaluation and Research (CDER).
Feng, S., Chien, S., 2003. Chemotherapeutic engineering: application and further development of chemical engineering principles for chemotherapy of cancer and other diseases. Chem. Eng. Sci. 58, 4087–4114.
Frenning, G., Brohede, U., Stromme, M., 2005. Finite element analysis of the release of slowly dissolving drugs from cylindrical matrix systems. J. Control Release 107, 320–329.
Fu, J.C., Hagemeir, C., Moyer, D.L., 1976. A unified mathematical model for diffusion from drug-polymer composite tablets. J. Biomed. Mater. Res. 10, 743–758.
Gamsiz, D.E., Shah, L.K., Devalapally, H., Mansoor, M., Amiji, M., Carrier, R.L., 2008. A model predicting delivery of saquinavir in nanoparticles to human monocyte/macrophage (Mo/Mac) cells. Biotech. Bioeng. 101, 1072–1082.
Gamsiz, E., Miller, L., Thombre, A., Ahmed, I., Carrier, R., 2010a. Modeling the influence of cyclodextrins on oral absorption of low solubility drugs: I. Model development. Biotech. Bioeng. 105, 409–420.
Gamsiz, E., Miller, L., Thombre, A., Ahmed, I., Carrier, R., 2010b. Modeling the influence of cyclodextrins on oral absorption of low solubility drugs: II. Experimental validation. Biotech. Bioeng. 105, 421–430.
Garbacz, G., Wedemeyer, R., Nagel, S., Giessmann, T., Mönnikes, H., Wilson, C., Siegmund, W., Weitschies, W., 2008. Irregular absorption profiles observed from diclofenac extended release tablets can be predicted using a dissolution test apparatus that mimics in vivo physical stresses. Eur. J. Pharm. Biopharm. 70, 421–428.
Gonda, I., 1998. Mathematical modelling of deposition and disposition of drugs administered via the nose. Adv. Drug Deliv. Rev. 29, 179–184.
Grassi, M., Colombo, I., Lapasin, R., 2000. Drug release from an ensemble of swellable crosslinked polymer particles. J. Control Release 68, 97–113.
Grassi, G., Voinovich, D., Moneghini, M., Franceschinis, B., Perissutti, B., Filipovic-Grcic, J., 2003. Theoretical and experimental study on theophylline release from stearic acid cylindrical delivery systems. J. Control Release 92, 275–289.
Grassi, G., Dawson, P., Guarnieri, G., Kandolf, R., Grassi, M., 2004a. Therapeutic potential of hammerhead ribozymes in the treatment of hyper-proliferative diseases. Curr. Pharm. Biotech. 5, 369–386.
Grassi, M., Zema, L., Sangalli, M.E., Maroni, A., Giordano, F., Gazzaniga, A., 2004b. Modeling of drug release from partially coated matrices made of a high viscosity HPMC. Int. J. Pharm. 276, 107–114.
Grassi, M., Grassi, G., 2005. Mathematical modelling and controlled drug delivery: matrix systems. Curr. Drug Deliv. 2, 97–116.
Grassi, M., Grassi, G., Lapasin, R., Colombo, I., 2007. Understanding Drug Release and Absorption Mechanisms: A Physical and Mathematical Approach. CRC Press, Boca Raton (FL, USA).
Grassi, M., Pontrelli, G., Teresi, L., Grassi, G., Comel, L., Ferluga, A., Galasso, L., 2009. Novel design of drug delivery in stented arteries: a numerical comparative study. Math. Biosci. Eng. 6, 493–508.
Grassi, G., Hasa, D., Voinovich, D., Perissutti, B., Dapas, B., Farra, R., Franceschinis, E., Grassi, M., 2010. Simultaneous release and ADME processes of poorly water-soluble drugs: mathematical modeling. Mol. Pharm. 7, 1488–1497.
Gruntzig, A.R., Senning, A., Siegenthaler, W.E., 1979. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. N. Engl. J. Med. 301, 61–68.
Gueorguieva, I., Nestorov, I., Rowland, M., 2006. Reducing whole body physiologically based pharmacokinetic models using global sensitivity analysis: diazepam case study. J. Pharmacokinet. Pharmacodyn. 33, 1–27.
Higuchi, T., 1961. Rate of release of medicaments from ointment bases containing drugs in suspension. J. Pharm. Sci. 50, 874–875.
Higuchi, T., 1963. Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 52, 1145–1149.
Hixson, A., Crowell, J., 1931. Dependence of reaction velocity upon surface and agitation. Ind. Eng. Chem. 23, 923–931.
Huang, J., Wong, H.L., Zhou, Y., Wu, X.Y., Grad, H., Komorowski, R., Friedman, S., 2000. In vitro studies and modeling of a controlled-release device for root canal therapy. J. Control Release 67, 293–307.
Hwang, C.W., Wu, D., Edelman, E.R., 2003. Impact of transport and drug properties on the local pharmacology of drug-eluting stents. Int. J. Cardiovasc. Interv. 5, 7–12.
Iakovou, I., Schmidt, T., Bonizzoni, E., Ge, L., Sangiorgi, G.M., Stankovic, G., Airoldi, F., Chieffo, A., Montorfano, M., Carlino, M., Michev, I., Corvaja, N., Briguori, C., Gerckens, U., Grube, E., Colombo, A., 2005. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 293, 2126–2130.
Israel, G., 1998. Balthazar van der pol e il primo modello matematico del battito cardiaco. In: Freguglia, P. (Ed.), Modelli Matematici nelle Scienze Biologiche. QuattroVenti, Urbino (Italy), pp. 133–162.
Jain, R., Gerlowski, L., Weissbrod, J., Wang, J., Pierson, R., 1981. Kinetics of uptake, distribution, and excretion of zinc in rats. Annals Biomed. Eng. 9, 347–361.
Kalia, Y.N., Guy, R.H., 2001. Modeling transdermal drug release. Adv. Drug Deliv. Rev. 48, 159–172.
Khachigian, L.M., Fahmy, R.G., Zhang, G., Bobryshev, Y.V., Kaniaros, A., 2002. c-Jun regulates vascular smooth muscle cell growth and neointima formation after arterial injury. Inhibition by a novel DNA enzyme targeting c-Jun. J. Biol. Chem. 277, 22985–22991.
Korhonen, O., Kanerva, H., Vidgren, M., Urtti, A., Ketolainen, J., 2004. Evaluation of novel starch acetate-diltiazem controlled release tablets in healthy human volunteers. J. Control Release 95, 515–520.
Korsmeyer, R., Gurny, R., Doelker, E., Buri, P., Peppas, N., 1983. Mechanisms of solute release from porous hydrophilic polymers. Int. J. Pharm. 15, 25–35.
Kost, J., Langer, R., 2001. Responsive polymeric delivery systems. Adv. Drug Deliv. Rev. 46, 125–148.
Kushner, J., Deen, W., Blankschtein, D., Langer, R., 2007. First principles, structures-based transdermal transport model to evaluate lipid partition and diffusion coefficients of hydrophobic permeants solely from stratum corneum permeation experiments. J. Pharm. Sci. 96, 3236–3251.
Lamberti, G., Galdi, I., Barba, A.A. Controlled release from hydrogel-based solid matrices. A model accounting for water up-take, swelling and erosion. Pharm. Res., in press.
Langer, R.S., 1999. An interview with a distinguished pharmaceutical scientist. Pharm. Res. 16, 475–477.
Lee, V.H.L., Robinson, J.R. (Eds.), 1987. Controlled Drug Delivery: Fundamental and Applications. Marcel Dekker, New York.
Lennernäs, H., Ahrensted, O., Ungell, A.-L., 1994. Intestinal drug absorption during induced net water absorption in man: a mechanistic study using antpyrine, atenolol and enalaprilat. Br. J. Clin. Pharmacol. 37, 589–596.
Li, C., Chauhan, A., 2006. Modeling ophthalmic drug delivery by soaked contact lenses. Ind. Eng. Chem. Res. 45, 3718–3734.
Lovich, M.A., Edelman, E.R., 1996. Computational simulations of local vascular heparin deposition and distribution. Am. J. Physiol. 271, H2014–H2024.
Macheras, P., Iliadis, A., 2006. Modeling in Biopharmaceutics, Pharmacokinetics and Pharmacodynamics. Springer, New York.
Marucci, M., Ragnarsson, G., Nyman, U., Axelsson, A., 2008. Mechanistic model for drug release during the lag phase from pellets coated with a semi-permeable membrane. J Control Release 127, 31–40.

Marucci, M., Ragnarsson, G., Nilsson, B., Anders Axelsson, A., 2010. Osmotic pumping release from ethyl–hydroxypropyl–cellulose-coated pellets: a new mechanistic model. J. Control Release 142, 53–60.
Meidan, V.M., Bonner, M.C., Michniak, B.B., 2005. Transfollicular drug delivery – is it a reality? Int. J. Pharm. 306, 1–14.
Michaels, A.S., Chandrasekaran, S.K., Shaw, J.E., 1975. Drug permeation through human skin, theory and in vitro experimental measurement. AIChE J. 21, 985–996.
Minekus, M., Havenaar, R., 1996. In vitro model of an in vivo digestive tract. US Patent 5,525,305.
Moreno, R., Fernandez, C., Alfonso, F., Hernandez, R., Perez-Vizcayno, M.J., Escaned, J., Sabate, M., Banuelos, C., Angiolillo, D.J., Azcona, L., Macaya, C., 2004. Coronary stenting versus balloon angioplasty in small vessels: a meta-analysis from 11 randomized studies. J. Am. Coll. Cardiol. 43, 1964–1972.
Mudie, M.M., Amidon, G.L., Amidon, G.E., 2010. Physiological parameters for oral delivery and in vitro testing. Mol. Pharm. 7, 1388–1405.
Narasimhan, B., 2001. Mathematical models describing polymer dissolution: consequences for drug delivery. Adv. Drug Deliv. Rev. 48, 195–210.
Nestorov, I., Aarons, L., Rowland, M., 1997. Physiologically based pharmacokinetic modeling of a homologous series of barbiturates in the rat: a sensitivity analysis. J. Pharmacokinet. Pharmacodyn. 25, 413–447.
Nogami, H., Nagai, T., Youtsuyanagi, T., 1969. Dissolution phenomena of organic medicinals involving simultaneous phase changes. Chem. Pharm. Bull. 17, 499–509.
Noyes, A., Whitney, W., 1897. The rate of solution of solid substances in their own solutions. J. Am. Chem. Soc. 19, 930–934.
Oureimchi, E.M., Vergnaoud, J.M., 2000. Processes of drug transfer with three different polymeric systems with transdermal drug delivery. Comput. Theor. Polym. Sci. 10, 391–401.
Owens, G.K., Kumar, M.S., Wamhoff, B.R., 2004. Molecular regulation of vascular smooth muscle cell differentiation in development and disease. Physiol. Rev. 84, 767–801.
Peppas, N.A., 1984. Mathematical models for controlled release kinetics. In: Langer, R., Wise, L.D. (Eds.), Medical Applications of Controlled Release Technology, Vol. 2. CRC Press, Boca Raton, pp. 169–187.
Peppas, N.A., 1985. Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta Helv. 60, 110–111.
Peppas, N.A., Langer, R., 2004. Origins and development of biomedical engineering within chemical engineering. AIChE J. 50, 536–546.
Polli, J., Crison, J., Amidon, G., 1996. Novel approach to the analysis of in vitro–in vivo relationships. J. Pharm. Sci. 85, 753–760.
Prabhu, S., 2004. Computational modelling in stent-based drug deliver. Bus. Brief. Med. Device Manufact. Technol. 1, 1–4.
Prausnitz, M.R., Mitragotri, S., Langer, R., 2004. Current status and future potential of transdermal drug delivery. Nat. Rev. Drug Discov. 3, 115–124.
Qian, F., Saidel, G.M., Sutton, D.M., Exner, A., Gao, J., 2002. Combined modeling and experimental approach for the development of dual-release polymer millirods. J. Control Release 83, 427–435.
Quintavalle, U., Voinovich, D., Perissutti, B., Serdoz, F., Grassi, G., Dal Col, A., Grassi, M., 2008. Preparation of sustained release co-extrudates by hot-melt extrusion and mathematical modelling of in vitro/in vivo drug release profiles. Eur. J. Pharm. Sci. 33, 282–293.
Reisfeld, B., Kalyanasundaram, S., Leong, K., 1995. A mathematical model of polymeric controlled drug release and transport in the brain. J. Control Release 36, 199–207.
Ross, R., 1999. Atherosclerosis: an inflammatory disease. N. Engl. J. Med. 340, 115–126.
Sankalia, J., Sankalia, M., Mashru, R., 2008. Drug release and swelling kinetics of directly compressed glipizide sustained-release matrices: establishment of level A IVIVC. J. Control Release 129, 49–58.
Savalle, B., Miranda, G., Pelissier, J., 1989. In vitro simulation of gastric digestion of milk proteins. J. Agricul. Food Chem. 37, 1336–1340.
Serruys, P.W., de Jaegere, P., Kiemeneij, F., Macaya, C., Rutsch, W., Heyndrickx, G., Emanuelsson, H., Marco, J., Legrand, V., Materne, P., 1994. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N. Engl. J. Med. 331, 489–495.
Shono, Y., Jantratid, E., Kesisoglou, F., Reppas, C., Dressman, J., 2010. Forecasting in vivo oral absorption and food effect of micronized and nanosized aprepitant formulations in humans. Eur. J. Pharm. Biopharm. 76, 95–104.
Shuchman, M., 2006. Trading restenosis for thrombosis? New questions about drug-eluting stents. N. Engl. J. Med. 355, 1949–1952.
Siepmann, J., Kranz, H., Bodmeier, R., Peppas, N.A., 1999a. HPMC-matrices for controlled drug delivery: a new model combining diffusion, swelling, and dissolution mechanisms and predicting the release kinetics. Pharm. Res. 16, 1748–1756.
Siepmann, J., Podual, K., Sriwongjanya, M., Peppas, N.A., Bodmeier, R., 1999b. A new model describing the swelling and drug release kinetics from hydroxypropyl methylcellulose tablets. J. Pharm. Sci. 88, 65–72.
Siepmann, J., Kranz, H., Peppas, N.A., Bodmeier, R., 2000. Calculation of the required size and shape of hydroxypropyl methylcellulose matrices to achieve desired drug release profiles. Int. J. Pharm. 201, 151–164.
Siepmann, J., Peppas, N.A., 2000. Hydrophilic matrices for controlled drug delivery: an improved mathematical model to predict the resulting drug release kinetics (the "sequential layer" model). Pharm. Res. 17, 1290–1298.
Siepmann, J., Peppas, N.A., 2001. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv. Drug Deliv. Rev. 48, 139–157.
Siepmann, J., Göpferich, A., 2001. Mathematical modeling of bioerodible, polymeric drug delivery systems. Adv. Drug Deliv. Rev. 48, 229–247.
Siepmann, J., Peppas, N., 2001a. Mathematical modeling of controlled drug delivery. Adv. Drug Deliv. Rev. 48, 137–138.
Siepmann, J., Peppas, N.A., 2001b. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv. Drug Deliv. Rev. 48, 139–157.
Siepmann, J., Siepmann, F., 2008. Mathematical modeling of drug delivery. Int. J. Pharm. 314, 101–119.
Siepmann, J., Siepmann, F., Florence, A.T., 2006. Local controlled drug delivery to the brain: Mathematical modelling of the underlying mass transport mechanisms. Int. J. Pharm. 364, 328–343.
Sigwart, U., Puel, J., Mirkovitch, V., Joffre, F., Kappenberger, L., 1987. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N. Engl. J. Med. 316, 701–706.
Sirisuth, N., Eddington, N., 2002. The influence of first pass metabolism on the development and validation of an IVIVC for metoprolol extended release tablets. Eur. J. Pharm. Biopharm. 53, 301–309.
Slepian, M.J., Hubbell, J.A., 1997. Polymeric endoluminal gel paving: hydrogel sytems for local barrier creation and site-specific drug delivery. Adv. Drug Deliv. Rev. 24, 11–30.
Stone, G.W., Ellis, S.G., Cox, D.A., Hermiller, J., O'Shaughnessy, C., Mann, J.T., Turco, M., Caputo, R., Bergin, P., Greenberg, J., Popma, J.J., Russell, M.E., 2004. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N. Engl. J. Med. 350, 221–231.
Stricker, H., 1973. Pharmaceutical resorption in the gastrointestinal tract II. Pharm. Ind. 35, 13–17.
Thakkar, V., Shah, P., Soni, T., Parmar, M., Gohel, M., Gandhi, T., 2009. Fabrication and evaluation of levofloxacin hemihydrate floating tablet. Res. Pharm. Sci. 3, 1–8.
Tojo, K., 1989. Mathematical model of iontophoretic transdermal drug delivery. J. Chem. Eng. Jpn. 22, 512–518.
Tojo, K., 2005. Mathematical Models of Transdermal and Topical Drug Delivery, 2nd ed. Biocom Systems Inc., Japan.
USP-XXIII, 1995. The United States Pharmacopeia.
Vairo, G., Ciuffi, M., Cottone, R., Dubini, G., Migliavacca, F., 2010. Drug release from coronary elutingstents: a multidomain approach. J. Biomech. 43, 1580–1589.
Venkatraman, S., Davar, N., Chester, A., Kleiner, L., 2000. An overview of controlled release systems. In: Wise, D.L. (Ed.), Handbook of Pharmaceutical Controlled Release Technology. Marcel Dekker, New York, Basel, pp. 431–463.
Wagner, J., 1971. Biopharmaceutics and Relevant Pharmacokinetics. Drug Intelligence Publications, Hamilton.
Weinberg, B.D., Blanco, E., Gao, J., 2008. Polymer implants for intratumoral drug delivery and cancer therapy. J. Pharm. Sci. 97, 1681–1702.
Wickham, M.a.F., Richard, F., 2007. International Publication Number WO 2007/010238.
Willmann, S., Schmitt, W., Keldenich, J., Dressman, J., 2003. A physiologic model for simulating gastrointestinal flow and drug absorption in rats. Pharm. Res. 20, 1766–1771.
Willmann, S., Schmitt, W., Keldenich, J., Lippert, J., Dressman, J., 2004. A physiological model for the estimation of the fraction dose absorbed in humans. J. Med. Chem. 47, 4022–4031.
Willmann, S., Edginton, A., Dressman, J., 2007. Development and validation of a physiology-based model for the prediction of oral absorption in monkeys. Pharm. Res. 24, 1275–1282.
Willmann, S., Thelen, K., Becker, C., Dressman, J., Lippert, J., 2010. Mechanism-based prediction of particle-size dependent dissolution and absorption Cilostazol Pharmacokinetics in dogs. Eur. J. Pharm. Biopharm. 76, 83–94.
Wu, X.Y., Zhou, Y., 1998. Finite element analysis of diffusional drug release from complex matrix systems: II. Factors influencing release kinetics. J. Control Release 51, 57–71.
Wu, X.Y., Zhou, Y., 1999. Studies of diffusional release of a dispersed solute from polymeric matrixes by finite element method. J. Pharm. Sci. 88, 1050–1057.
Yamashita, F., Hashida, M., 2003. Mechanistic and empirical modeling of skin permeation of drugs. Adv. Drug Deliv. Rev. 55, 1185–1199.
Yang, C., Burt, H.M., 2006. Drug-eluting stents: factors governing local pharmacokinetics. Adv. Drug Deliv. Rev. 58, 402–411.
Young, M., Chang, Y., Cheng, D., 1994. Mathematical modelling of matrix for transdermal therapeutic system. Proc. Int. Symp. Cont. Rel. Bioact. Mater. 21, 443–444.
Yu, L., Amidon, G., 1999. A compartmental absorption and transit model for estimating oral drug absorption. Int. J. Pharm. 186, 119–125.
Yu, L., Lipka, E., Crison, J., Amidon, G., 1996. Transport approaches to the biopharmaceutical design of oral drug delivery systems: prediction of intestinal absorption. Adv. Drug Deliv. Rev. 19, 359–376.
Zhang, W., Prausnitz, M.R., Edwards, A., 2004. Model of transient drug diffusion across cornea. J. Control Release 99, 241–258.
Zhou, Y., Chu, J.S., Wu, X.Y., 2004. Theoretical analysis of drug release into a finite medium from sphere ensembles with various size and concentration distributions. Eur. J. Pharm. Sci. 22, 251–259.