SEMI-EMPIRICAL VS. MECHANISTICAL KINETIC MODELS USED TO DESIGN DRUG DELIVERY SYSTEMS

Ionela LUȚĂ[1], Gheorghe MARIA[2]

Deşi modelele mecanistice ce descriu cinetica de eliberare a medicamentelor de pe suporți multivalenți sunt dificil de utilizat, necesitând eforturi experimentale şi de calcul considerabile pentru a caracteriza procesul, aceste modele complexe sunt instrumente adecvate în reprezentarea comportamentului sistemelor de eliberare. Alternativ, modelele simplificate/semi-empirice sunt utilizate frecvent pentru estimarea rapidă a cineticii proceselor de eliberare a medicamentelor. Pornind de la curbele cinetice "intrinseci" de eliberare a unei molecule de medicament şi dezvoltând o ipoteză simplificatoare bazată pe invarianții reacției, se poate obține un model cinetic aparent, precum şi unul global ce caracterizează procesul reversibil. Pentru a determina pierderea de informație care se înregistrează atunci când se utilizează modele simple, s-a realizat o comparație a modelelor complexe cu unele modele semi-empirice (Korsmeyer-Peppas, Lin-Ho). Sistemul analizat în aplicația de față se referă la eliberarea succesivă de grupări medicamentoase, legate prin punți de disulfură de un suport dendrimeric tetravalent funcționalizat, în condiții artificiale de laborator care mimează mediul reducător din plasma umană.

Even if derivation of mechanistic kinetic models for drug release from multivalent supports is a difficult task, requiring steady experimental and numerical identification efforts to characterize the process, they are reliable tools in representing the behavior of a delivery system to the target tissue. Alternatively, simplified/semi-empirical models for drug release are often used for quick process kinetics estimation. Starting from "intrinsic" kinetic curves of released biological active molecules and intermediates, and developing a lumping rule based on reaction invariants, an apparent kinetic model, and also an overall kinetics characterizing the reversible process, is obtained from an extended one. Predictions of the three-levels of complexity models are also compared with those of semi-empirical Korsmeyer-Peppas and Lin-Ho models to determine the information loss when simplified models are used for drug design purposes. An example of the release case of hydrophobic biological active molecules in human plasma, following the reaction of disulphide bonds linking the drug ligands to a multivalent dendrimeric support with the reductive agents from liquid environment is presented.

Keywords: drug release; isothermal kinetics; model reduction

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Symbols

c_j	-	concentration of species, mol L^{-1}
K_{eq}	-	equilibrium constant, mol L^{-1}
k	-	constant in the kinetic models
k_{ij} , k_i , k_g , k_{gr}	-	rate constants, with units in s, mol L^{-1}
$M(t)$	-	cumulative mass of drug released at time *t* in liquid
M_∞	-	cumulative mass of drug released at infinite time *t* in liquid
n	-	Korsmeyer-Peppas model exponent
t	-	time, s

Subscipts

0	-	initial
eq	-	equilibrium
exp	-	experimental
red	-	reduced form
ox	-	oxidized form

Abbreviations

A, B, C, D, E	-	lumped species
DTT	-	dithiothreitol
EKM	-	extended (compartmented) kinetic model
KPM	-	Korsmeyer-Peppas model
L	-	ligand
LHM	-	Lin-Ho kinetic model
LSH	-	free drug
OKM	-	overall kinetic model
R	-	dendrimeric core
RKM	-	reduced kinetic model

1. Introduction

Over the past decades, increasingly efforts have been made to develop efficient drug delivery systems, leading to a wide range of applications in medicine (drug release) and industrial area (separation, catalysis, biosynthesis, environmental engineering, etc. [1]). The biologically active compounds can be incorporated in solid supports (functionalised by a certain procedure), in order to obtain a better control of the release. Thus, biological active molecules are "immobilized" on a suitable support (powder, beads, foils, fibres, mesoporous matrices, etc.) made from a large variety of materials (ceramics, clay, gels, polymers, etc.) tailored (by functionalization, cross-linking, co-polymerisation, crystallization) to increase the support availability with less influence on the

biological active molecule activity. Basically, the drug delivery system structure is designed to facilitate the dosage, to control the release duration, and to minimize the harm to the patient by reducing the dosage frequency [2, 3, 4].

According to Chien & Lin (2002), the drug delivery systems of controlled release can be classified in four categories (presented in Figure 1): pre-programmed rate (the release rate is controlled by adjusting the diffusion rate of the polymeric/inorganic matrix through the support membrane), activation-modulated (the release rate is controlled by using physical, chemical or biochemical means – osmotic or hydrodynamic pressure, mechanical, magnetic or sonic forces, redox agents, enzymes), feed-back regulated (the release of the drug is triggered by various agents present in the body fluid), and site-targeting delivery (this type is still in a conceptual stage, as long as only the release rate can be controlled and not the transport path to the target tissue) [3].

The control of a drug release system can be improved by using an adequate kinetic model with significant parameters, by accounting for the processes that take place on the support surface (adsorption or desorption), the diffusional transport in pores, polymeric support, membrane, and interface. A trade-off between model simplicity and its significance is usually realised, by mechanistically describing the release process [5]. The rate at which the active groups are released in the receptor fluid body is very important, being directly dependent on the support, drug, and linking molecules nature, and also on the support characteristics (porous or nonporous), on the environment, release conditions (pH, temperature, mixing), and initial and maximum drug dose on the support [2,6,7,8].

The release models are usually derived from the diffusion (permeation) theory and solved for every studied system. Fick-type equations are integrated for various geometries (thin sheet, rectangular parallelepiped, cylinder of finite or infinite length, sphere), with known initial (uniform or non-uniform field distribution in the solid) and boundary conditions (at the solid-liquid or membrane interface with an external diffusion layer or with bulk liquid) [5,9]. Analytical solutions give the drug distribution over the diffusion direction and time, the release rate and the quantity of the released drug until a certain time $M(t)$ compared to the total amount of drug released at an infinite time M_∞. The estimated model parameters from experimental kinetic curves are then related to the characteristics of the support, drug ligand, and receptor environment thus allowing ranging the release rate by designing a suitable delivery system.

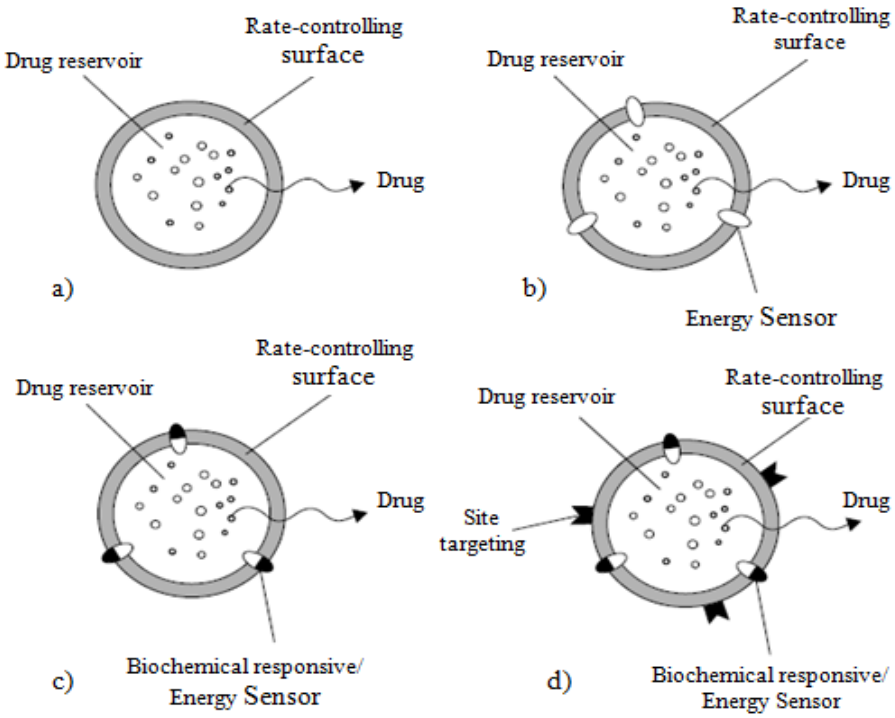

Fig. 1. The four types of controlled-release drug delivery systems: a) pre-programmed rate; b) activation-modulated; c) feedback-regulated; d) site targeting (after [3]).

Even if an adequate kinetic model is a reliable tool in representing the process dynamics, including parameters of physical meaning, this model requires steady experimental and computational efforts to adapt its structure and size according to the available data and utilization scope. Thus, simplified or semi – empirical models are often used for a quick representation of the drug release, being derived from the extended mechanistic models by using simplificatory hypothesis. Among them it is worth to mention power-law models, $M(t)/M_\infty = kt^n$ [2,10] (for the diffusion in support, membrane, or swelling systems), algebraic models describing diffusion in a polymer matrix, membrane, or drug reservoir, models for chemically controlled release of zero-, first-, or second-order. As mentioned in literature, the n-parameter is an indicative of the release mechanism for various forms of the support (slab, cylinder or spherical): in the Fickian diffusion-controlled release, $n = 0.5$, in non-Fickian swelling controlled release, $n = 1$, while for $n \prec\prec 0.5$, the release involves chemical reactions [10,11,12]. A statistical correlation of this simplified model parameters with the structural properties of the drug-support system (porosity, tortuosity, pore

size, drug load, diffusivity and solubility of the drug in the solvent, pH, support dimensions and composition, environment properties, etc. [13]) is required, in order to be useful in designing a suitable support-drug delivery system. Functionalization of the support with suitable crosslinkers changes significantly the properties of the support surface (hydrophilicity, hydrophobicity, resistance to surface attack agents), thus affecting the release rate, and requiring steady experiments to derive the optimal structure and release conditions.

If a detailed mechanistic model is available, it is interesting to study the distortion of the drug release dynamics predictions when various levels of model simplification are used. The aim of this paper is to analyse the detailed release dynamics under various conditions starting from a known "intrinsic" drug release mechanism, in order to determine the information loss when simplified models are used for the same predictive purpose. The study also points out the importance of the model structure for designing a drug release system.

A case study for the release of some hydrophobic biological active molecules (dansyl groups L) in human plasma is approached, involving the chemical reaction of disulphide bonds (linking the biological active molecules to a multivalent dendrimeric support) with the reductive agents from the liquid environment (such as glutathione, cysteine, homocysteine). The experimental data of Zhang et al. [14] have been used, derived in a synthetic release environment that mimics the reductive action of human plasma.

2. The extended reaction pathway of drug release from multivalent dendrimers

In order to exemplify a mechanistical model of a chemically controlled drug release system, a case study was selected from literature. The example refers to the experimental study of Zhang et al. [14] concerning the four biological active molecules successive release from a multivalent dendrimeric support (based on melamine) in a synthetic liquid environment that mimics the reductive action of human plasma.

The drug support is a dendrimer that has a regular and highly branched three dimensional structure [4], being usually used in medical applications for drug delivery, development of vaccines, antivirals, antibacterials, or other industrial applications. Hydrophobic biological active molecules (densyl groups denoted by L) have been attached on their surface by disulphide bonds, which can be exchange by thiol groups upon exposure to the reducing environment of human plasma. The globular and adjustable structure of dendrimers offers the opportunity to adjust the release rate of various biological active molecules.

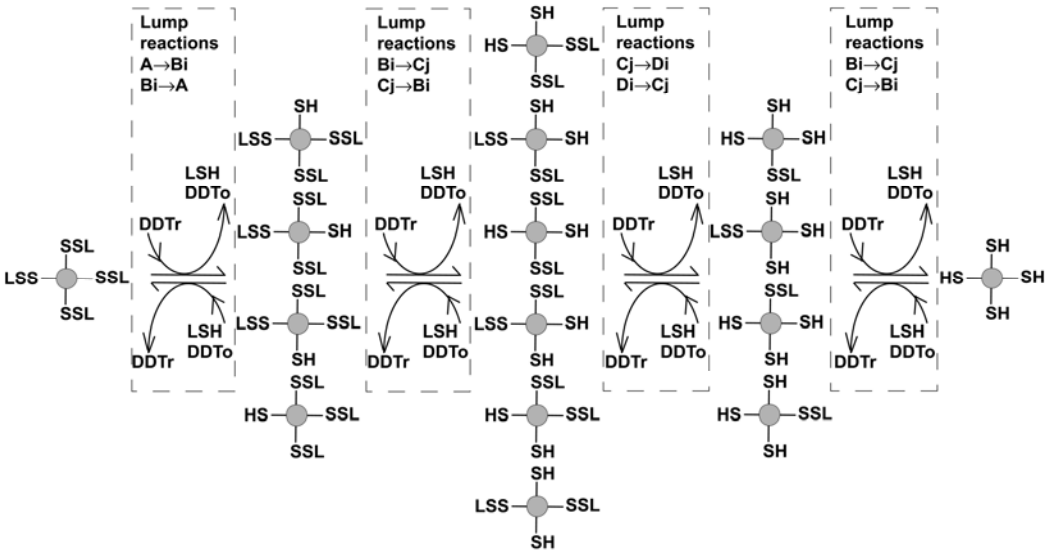

Fig. 2. The successive biological active molecules (L) release from a dendrimeric drug support in human plasma

(a reductive environment) (after [15]). Notations A, $B = \{B_1, B_2, B_3, B_4\}$, $C = \{C_1, C_2, C_3, C_4, C_5, C_6\}$, $D = \{D_1, D_2, D_3, D_4\}$, E denominate the conformational isomers of dendritic structures with various numbers of linked biological active molecules.

The release schema of L-groups attached to support (R-S-S-L) by breaking disulfide bridges with thiol groups formation is presented in figure 2. Reactions occur in the presence of DTT_{red} and leads to a free thiol group on the dendrimer R-S-H, a free L-S-H drug and the oxidized DTT_{ox}. The biological active molecules of a fully covered tetravalent dentritic macromolecule are released successively. Thus, in the first step results four conformational isomers $R(SH)(SSL)_3$ (B_i in Table 1); then, by breaking RS-SL bonds six possible conformational isomers $R(SH)_2(SSL)_2$ are obtained (Fig. 2, C_i in Table 1). In the third release step, it results four isomers $R(SH)_3(SSL)$ (D_i in Table 1), and finally a single macromolecule $R(SH)_4$ denoted by E. The complex release mechanism involves reversible reactions and all possible interactions between isomers, leading to construct an extended model including 64 direct-reverse reactions and 16 species (denoted by EKM, Fig. 2, Table 1 [14]).

Table 1

Extended kinetic model (EKM) for drug (L) release in human plasma from the dendrimeric multivalent support R (units in min. and mM) [14].

Consecutive release reactions	*Rate constants*
$A + DTT_{red} \underset{k_{B_iA}}{\overset{k_{AB_i}}{\rightleftarrows}} B_i + DTT_{ox} + LSH$, $i = 1,...,4$	k_{AB_i} =1.415·10^{-4} k_{B_iA}=3.61·10^{-2}
$B_i + DTT_{red} \underset{k_{C_jB_i}}{\overset{k_{B_iC_j}}{\rightleftarrows}} C_j + DTT_{ox} + LSH$, *j = 1,2,*6 for *i = 1*; *j = 2,3,4* for *i = 2*; *j = 4,5,*6 for *i = 3*; *j = 1,3,5* for *i = 4*	$k_{B_iC_j}$ =1.743·10^{-4} $k_{C_jB_i}$ =2.275·10^{-2}
$C_i + DTT_{red} \underset{k_{D_jC_i}}{\overset{k_{C_iD_j}}{\rightleftarrows}} D_j + DTT_{ox} + LSH$, *j = 1,4* for *i = 1*; *j = 1,2* for *i = 2*; *j = 1,3* for *i = 3*; *j = 2,3* for *i = 4*; *j = 3,4* for *i = 5*; *j = 2,4* for *i = 6*	$k_{C_iD_j}$ =2.755·10^{-4} $k_{D_jC_i}$ =1.83·10^{-2}
$D_i + DTT_{red} \underset{k_{EDi}}{\overset{k_{D_iE}}{\rightleftarrows}} E + DTT_{ox} + LSH$, , *i = 1-4*	k_{D_iE} =4.52·10^{-4} k_{ED_i} =0.3675·10^{-2}

Table 2

Reduced kinetic model (RKM) for drug (L) release in human plasma from the dendrimeric multivalent support R (units in min. and mM) [16].

Consecutive release reactions	*Rate constants*
$A + DTT_{red} \underset{k_{BA}}{\overset{k_{AB}}{\rightleftarrows}} B + DTT_{ox} + LSH$	k_{AB} =5.66·10^{-4} k_{BA} =3.61·10^{-2}
$B + DTT_{red} \underset{k_{CB}}{\overset{k_{BC}}{\rightleftarrows}} C + DTT_{ox} + LSH$	k_{BC} =5.23·10^{-4} k_{CB} =4.55·10^{-2}
$C + DTT_{red} \underset{k_{DC}}{\overset{k_{CD}}{\rightleftarrows}} D + DTT_{ox} + LSH$	k_{CD} =5.51·10^{-4} k_{DC} =5.49·10^{-2}
$D + DTT_{red} \underset{k_{ED}}{\overset{k_{DE}}{\rightleftarrows}} E + DTT_{ox} + LSH$	k_{DE} =4.52·10^{-4} k_{ED} =1.47·10^{-2}

By carrying out lab-scale batch experiments under isothermal and iso-pH conditions, Zhang et al. [14] determined the evolution of A, E, and lumped B, C, D species concentrations over 7200 min, under certain initial conditions. Based on that, the EKM rate constants $k_{i,j}$ have been identified by Maria [16] (Table 1), by using the hypothesis of equal kinetic contributions of every isomer belonging to a certain lump (B, C, D). The EKM predictions, presented in Fig. 3, match very well with the experimental data.

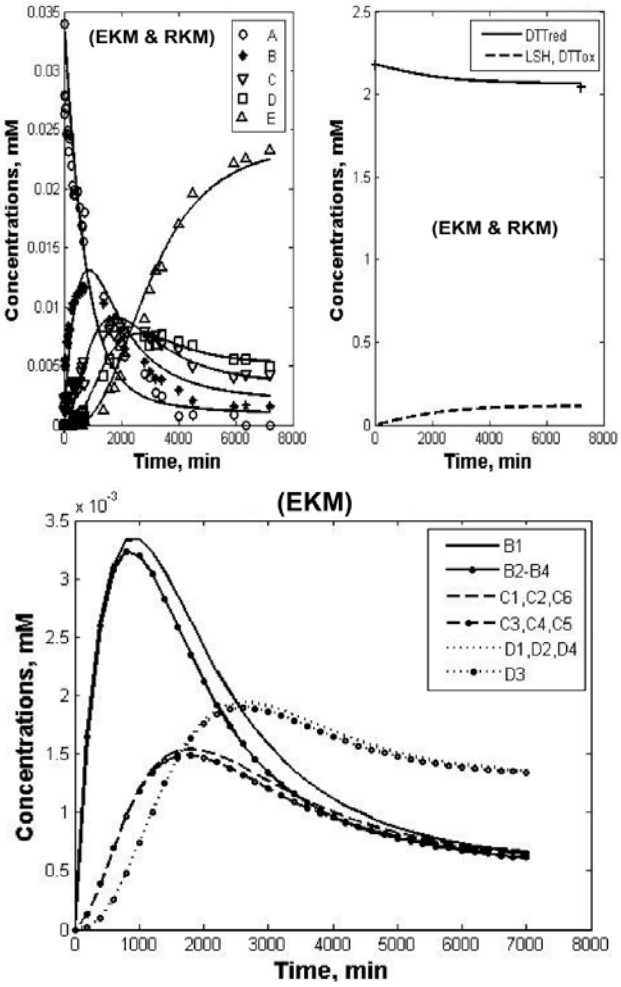

Fig. 3. Experimental points and species concentrations predicted by the EKM (all figures) and RKM (up figures, superposed curves over EKM) (after [14,16]).

3. Lumped and overall kinetic models for drug release in a synthetic medium

The extended kinetic model, with 64 reactions and 16 species involved, has been reduced to a grouped form by using a lumping rule based on the invariants of the chemical system [16]. An apparent kinetic model with four reversible reactions, and involving five lumped species A-E, has been thus obtained (see Table 2). The RKM (reduced kinetic model) rate constants $k_{i,j}$ have been determined by using the following linking relationships [16]:

$$k_{AB} = 4 \cdot k_{AB_i};\ k_{BA} = k_{B_i A},\ i = 1,...,4. \tag{1}$$

$$k_{BC} = 3 \cdot k_{B_i C_j};\ k_{CB} = 2 \cdot k_{C_j B_i},\ i = 1,...,4;\ j = 1,...,6. \tag{2}$$

$$k_{CD} = 2 \cdot k_{C_i D_j};\ k_{DC} = 3 \cdot k_{D_j C_i},\ i = 1,...,6;\ j = 1,...,4. \tag{3}$$

$$k_{DE} = k_{D_i E};\ k_{ED} = 4 \cdot k_{ED_i},\ i = 1,...,4. \tag{4}$$

The RKM predictions, presented in Fig. 2, match very well with the experimental data, being very close to those obtained by using the extended path. This also results in the similarity of the adequacy indices values, the model error standard deviation being 1.6879×10^{-3} mM for the EKM, and 1.6740×10^{-3} mM for the RKM.

By comparing the apparent rate constants with the intrinsic ones, it can be observed that the intrinsic constants are in general smaller for both forward and reverse release reactions (Fig. 4). One can conclude that model reduction by species lumping introduces a bias in the estimated rate constants, which tends to compensate the loss in the system diversity, leading to higher apparent rates of the process steps.

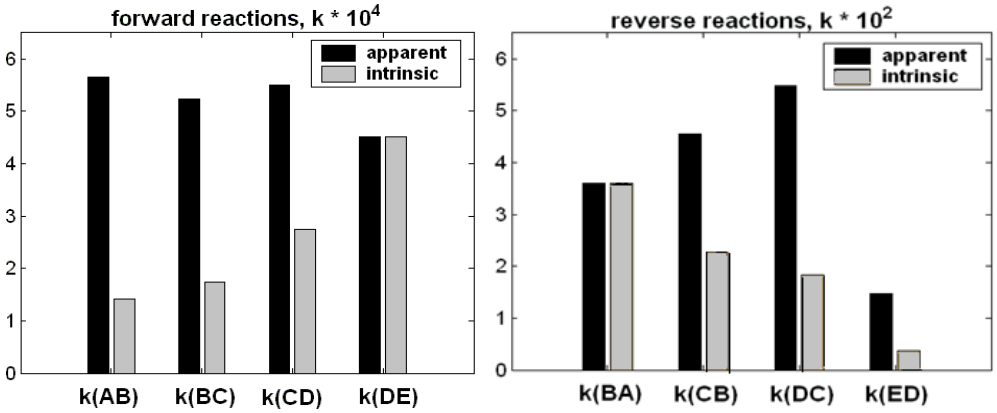

Fig. 4. Intrinsic (EKM) vs. apparent (RKM) rate constants (after [16]).

On the other hand, one can propose an overall reaction model (OKM) of biological active molecules (L) release in human plasma from the dendrimeric support as fallows:

$$A + 4\ DTT_{red} \underset{k_{gr}}{\overset{k_g}{\rightleftharpoons}} E + 4\ DTT_{ox} + 4\ LSH, \tag{5}$$

where k_g and k_{gr} are the rate constants for the overall release reactions. The k_g rate constant was estimated based on experimental kinetic curves [$c_A(t)$, $c_E(t)$] and using the least squares method, leading to k_g=1.6982·10^{-5} (1/min·mM^4). The constant k_{gr} was estimated by using the $K_{eq} = k_g / k_{gr}$ value given by EKM, leading to k_{gr}=3.0661·10^{+2} (1/min·mM^8).

By comparing the predictions of the OKM for A and E species with those obtained using RKM, one can observe that an important bias is introduced in the predictions of the global model. However, the predictions for the DTT_{red}, DTT_{ox} and LSH species are practically unbiased, revealing that an overall reaction approach could be used successfully to predict the release dynamics of some biologically active molecules of interest (Fig. 5). It is also to note that a global kinetic model based on an overall release reaction can be derived, even if the EKM or RKM are not available. The essential advantage of the OKM over the empirical models is the intrinsic consistency, the rate constants not being dependent on the initial load of drug on the support, and presenting physical meaning. Eventually, if experimental information is available, correlations of the OKM parameters with the structural properties of the drug-support system can be realised for drug design purposes.

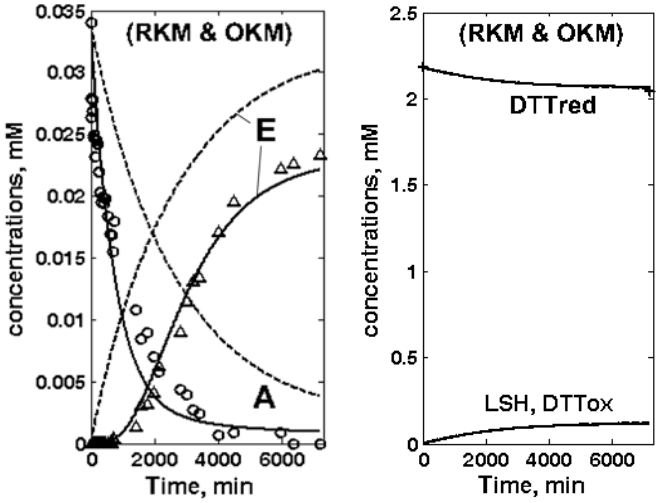

Fig. 5. The predictions for OKM (---) and RKM (——) vs experimental data for drug L release from a dendrimeric support (after [19]).

4. Semi-empirical models (Korsmeyer-Peppas / Lin-Ho) for drug release

Due to the simplicity of semi-empirical models, they are frequently used to characterize the process dynamics of the drug release. Thus, if a mechanistic model is available (such are EKM, RKM, and OKM), it is interesting to analyse the quality of a semi-empirical model vs. EKM, RKM, and OKM. In this respect, semi-empirical models of Lin & Ho (LHM) [17,18] and also of Korsmeyer & Peppas (KPM) were considered. The KPM is usually used to globally characterize the diffusion during the release process, but it could also be used to interpret its parameters when a chemical process is involved.

In both cases, the model parameters have been estimated from "experimental" kinetic curves $M(t) = c_{LSH}(t)$ (generated by means of EKM), by using the linearized form of the model (Eq. 6). The equilibrium $c_{LSH,e}$ values ($M_\infty = c_{LSH,e}$) have been generated with the EKM under various initial $c_{A,0}$ conditions, that is $c_{A,0} \in \{0.01 \quad 0.034 \quad 0.10 \quad 0.20\}$ mM, resulting M_∞ = {0.0397, 0.1161, 0.1788, 0.2144} mM. The LHM equation and the liniarized equation of the semi-empirical Korsmeyer-Peppas model are the followings:

$$\frac{M(t)}{M_\infty} = \frac{M_\infty kt}{1 + M_\infty kt} \tag{6}$$

$$\ln\frac{M(t)}{M_\infty} = \ln(k) + n\ \ln(t) \tag{7}$$

The predictions of the KPM and LHM for various initial conditions are displayed in Fig. 6. Different sets of model parameters are obtained for each initial concentration $c_{A,0}$, that is $n \in \{0.53, 0.44, 0.16, 0.05\}$ for $c_{A,0} \in \{0.01, 0.034, 0.10, 0.20\}$ mM, respectively, indicating different transport mechanisms. Thus, the value of $n \approx 0.5$ (for low levels of $c_{A,0}$) indicates a Fickian mechanism of the release process, while n values smaller then 0.5 (for higher $c_{A,0}$ levels) clearly suggests a chemically controlled release mechanism. These results with the global models indicate a high level of uncertainty because of the low accuracy of the extrapolations, being quite risky when they are used to design a drug delivery system. Consequently, an adjustment of the model parameters with the operating conditions is required every time. Also, to be useful for design purposes, additional correlations must be made to relate the model constants to the structural properties of the drug support system. These extended statistical correlations may lead to very high levels of uncertainty in predictions, regardless of the total lack of physical significance of the ad-hoc algebraic correlations.

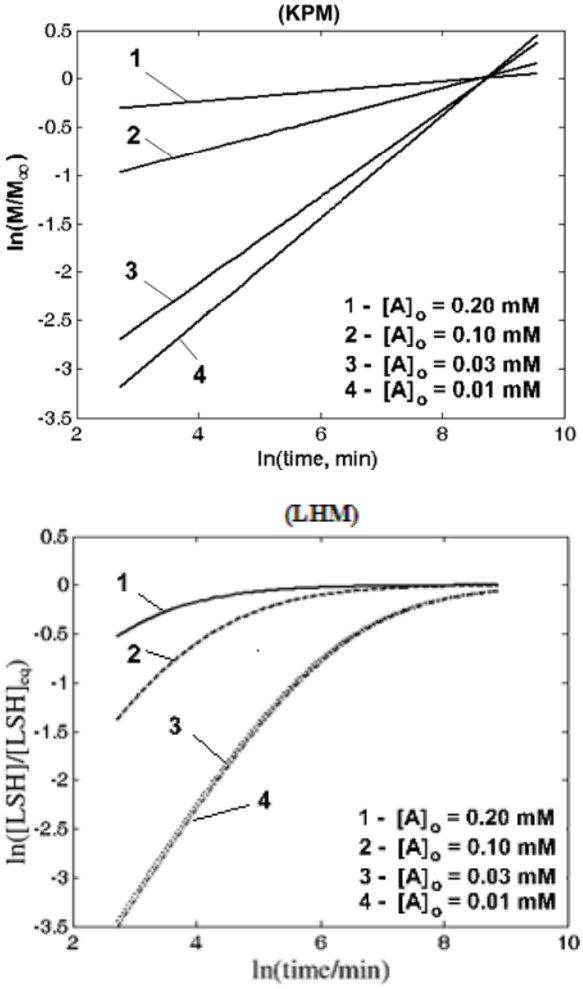

Fig. 6. Predictions of L-groups release from multivalent support given by KMP (up figure) and LHM (down): (1) $[A]_o$= 0.20 mM (n=0.05); (2) $[A]_o$= 0.10 mM (n=0.16); (3) $[A]_o$= 0.03 mM (n=0.44); (4) $[A]_o$= 0.01 mM (n=0.53) (after [19]).

5. Conclusions

The choice of a simple but reliable kinetic model is one of the most important aspects of any engineering problem, including the case of designing drug delivery systems. The use of mechanistic models allows an accurate representation of the process, thus allowing the interpretation of the reaction steps and of the physical meaning of the parameters. The computational effort for

adapting the models structure and size is influenced by the availability of experimental information and also by the modeling scope.

All the semi-empirical global models (LHM or KPM) present several inconveniences. For example, for every initial condition data set, an adjustment of the model parameters is necessary, even if the model adequacy is satisfactory. This means that instead of using one set of parameters, a correlation between the model constants and the operating conditions is required. Also, the structural properties of the drug-support system must to be correlated with the model constants in order to make the model useful for design purposes. Eventually, all these algebraic correlations will lead to a total lack of physical significance of the model parameters and to a very high level of uncertainty in predictions.

This paper points out the importance of keeping the physical significance of the reduced model terms and parameters in studying and designing the drug delivery systems. Such an approach presents the tremendous advantage of using simple linking relationships between the reduced (apparent) and extended ("intrinsic") models (as the case of EKM, RKM, and OKM in the present study), based on the estimated lumped rate constants and lumping rules proposed in the dedicated literature, leading to much higher reliability of model predictions.

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