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NEW MATHEMATICAL MODEL BASED ON THE KINETIC PROFILE FOR THE PREDICTION OF MULTISTAGE DRUG RELEASE FROM DELIVERY SYSTEMS

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ABSTRACT

Because of a broad number of interdependent effects occurring during the release of drugs from controlled delivery systems, the associated phenomena become complex. Despite the availability of many researches to simulate these pharmacokinetics and dynamic aspects, the applicable models stay limited. In this work, we have developed an innovative mathematical model to predict the multistage-profiles of drug release. Thanks to the succession use of power functions reproducing the kinetic profile, the universal applicability of the proposed modeling becomes possible. This mathematical model makes it possible, in other words, to propose a behaviour law for the family of drug-carriers studied after experimental data adjustment of their release profiles. The physical mechanisms are not directly modelled here, but they are contained in the modelled kinetics. In this way any group of physical mechanisms, coupled or not, are taken into account. To assess the development's accuracy; we compare a published data set to predictions. The chosen examples here exploit distinct results about the effects of the coupled flow rate, drug-concentration, and the radius of the cylinder of the micro-needle patches. Predictions of this model are reachable from accessible design factors; we expect so users will select it to guide the formulations of a broad range of custom drug delivery system.

Keywords: Drug release; Kinetics; Mathematical modeling; Predicting liberation profile

INTRODUCTION

The improvement of mathematical models simulating the spatio-temporal behavior of drug delivery systems will make it possible to reduce their development time [1-5]. The empirical models are developed for a family of drug carriers based on experimental data. To preserve all their interest, they must stay precise in predicting the release profile out of the data set used for the adjustment. Improving the model accuracy needs an appropriate description of the fundamental mechanisms involved behind the physical-

processes [6-13]. However, the complexity of drug delivery systems makes it difficult comprehension their underlying mechanisms, particularly in vivo. The alternative is to adopt fitting approaches to capture experimental data sets. These fitting models typically contain fewer factors than purely mechanistic modeling. The advantage of this type of models concerns the simplicity of usage allowing their dissemination across the scientific community [14]. However, their validity is limited to the space utilized to define its setting data [15-17]. For a family of drug carriers, it is necessary to properly adjust the precision of the model.

1

Controlling the liberation profile involves identifying nature and number of the most influencing factors [18-20].

Referring to earlier studies and researches, drug release profiles can contain various stages. (Figure 1) presents examples of common drug liberation shapes: Burst release, (Figure 1a) normally short-lived, delivers high liberation rates that can be achieved in the initial stages after activation. Lag release, (Figure 1b) represents the delay in the release of the drug. Either this time is anticipated in the design of the drug delivery system, or it is imposed on it while adapting to its environment. It represents the first stage of the release profile. In the fast release, (Figure 1b) consistent amount of drug over a limited period, typically less than 30 minutes for the tablets and capsules releases into the body quickly whereas, in slow- release (Figure 1a) drug release takes place into the body slowly over an extended period. In this way there are so fewer concentration peaks; like that, few side effects are expected. Extended-release, (Figure 1) is another type where the release profile typically tries mimicking zero-order release [21-24].

Drug release models are developed to describe the behavior of a system and gain a better understanding of its properties. When therapy is to provide significant concentration at the start of treatment, the specification will be geared towards rapid release or burst-release. Latency will be favored in the case of oral administration to reduce the risk of toxicity. In the case that the release profile obtained following the desired design did not accommodate the therapeutic need, modifications would then be applied to the initial conception until the system converges [26].

Therefore, a broad range of models is published with diverse levels of complexity and empiricism. In attendance, an innovative predictive mathematical model is proposed. This is applicable to various modes of administration like tablets, patches, drug stents, etc.

MATERIALS AND METHODS

Innovative-model for predicting the multistage profile of drug- release kinetics

The aim of this novel model is to formulate a function for calculating the cumulative drug-release for a group of drug delivery agents with similar properties. This model, should in fine: i.) Take into account the influence of the design settings and the operating conditions on the amount of drug released of drug-carriers. These settings or conditions are, for example, the flow rate of the fluid in circulation; the drug charge ratio; the properties of the materials of the support film, etc. ii.) Allow taking into account changes in the kinetics of drug release as a function of time throughout the period of therapeutic use envisaged for the drug-carrier. Equation 1 shows the equation related to the described model:

$$LogM_{t} = LogK + n_{t}Logt$$
 Eq. 1

K is a constant depending on both concentration and the time, which is different for each stage of the release profile. Therefore, it can be obtained easily by the maximum values of the concentration and time in that stage. It is defined by the unit of (concentration.time⁻ⁿ). Therefore, the model will be presented in the below form:

$$LogM_t = Log\left(\frac{M_i}{t_i^{n_i}}\right) + n_iLogt$$
 Eq. 2

$$\frac{M_t}{M_i} = \left(\frac{t}{t_i}\right)^{n_i}$$
Eq. 3

Where $0 \le M_i \le M_{i+1}$, $M_0=0$, i=0 to K, "i" is the number of steps identified for the release profile. M_t is the drug released at the time "t", M_i and t_i are respectively the maximum amount of the drug release and maximum time of the release at each stage. This equation is applicable to whatever the dimensions of its variables and factors. The power coefficients "n_i" corresponds to the slopes of the straight lines identified in the Log-Log reference system. Their distinction demonstrates the presence of



Figure 1: Common release profiles and steps during the release.

various release kinetics of the drug. The values of these slopes and the other two settings " t_i and M_i " can depend on many aspects. For example the concentration of the active substance in the carriers, the thickness of the matrix layers, the physicochemical properties of the drug, and polymer used. Like the solubility, hydrophilicity, hydrophobicity, particles-size of drug, porosity, and durability of the polymer, etc.

To reproduce effectively any drug-release profile, it is enough to calculate accurately the values of the settings, " n_i , t_i and M_i ". The Douglas-Peucker [27] algorithm is adapted to this need. More explanation is given in the first example of the results section.

Proposal of a generic drug-release profile

Based on the various profiles described above, in (Figure 2) generic case containing the essential types of these profiles is proposed. In this way, present generic profile successively contains the following profiles: lag-time, fast-release, extended-release, and slow-release.

Then the capacity of the main available empirical models to adjust this generic profile is evaluated. The failure of these assessments led to propose the present alternative mathematical model.



All of the experimental data used in this study have been repeated unless three times and are expressed as mean \pm standard deviation. The R-Squared are indicated for each analyzed case.

RESULTS AND DISCUSSION

Fail of accurately adjustment of the generic profile by a selection of existing mathematical models

The kinetics of drug release from the generic-profile was analyzed using the zero-order and first-order, as well as the Korsmeyer-Peppas, Weibul, Higuchi and Hixon-Crowell models. The results showed in (Figure 3) do not agree completely with the data of the generic profile, and that regardless of the model used. Indeed, the calculations are carried out only for one stage while the generic profile is composed of four distinct kinetics. It is, therefore, necessary the mathematical model considers these aspects to respond to the problem correctly.

Application in multistage of the Higuchi model's and comparison with our proposal



Figure 2: Release profile of a certain drug in a certain polymeric matrix.

(Figure 4) represents the results of the Higuchi model applied to the proposed generic profile in a multi-stage manner. These results reveal the following two limitations: First, only three out of four stages are captured. Next, the power



Figure 3: One step fitting of data results with different mathematical models.



Figure 4: (a) Step defining for the release profile of the figure 2 by the aid of the Higuchi model (b) Reconstruction the data points by using Higuchi fit

function is identical over the three stages the coefficient n is invariably equal to 0.5 (Fickian model). These limits lead to significant differences in the comparison. To overcome these disadvantages, the simultaneous use of the power function proposed by Korsmeyer-Peppas and the stage's detection algorithm would represent an alternative. The ability to restore all the stages that describe the kinetics of the drug-release profile and to adapt to the change in kinetics by adequately differentiating the power coefficients of the various stages. Our model enunciates above incorporates these aspects. (Figure 5) exposes the data calculated with the proposed model, in comparison with those of the generic profile. This figure clearly illustrates the relevance of the correlation between the data in the generic profile and values calculated using equation 1.

Assessment of the model on a selection of experimental

data

This section deals with experimental data available by the authors and in the literature. They therefore successively address: A study of the simultaneous effect of the flow rate and drug concentration at mono-stage, drug-concentration at two stages and radius of the cylinder of a micro needlespatch.

Taking into account the simultaneous effect of the flow rate and concentration in the model [28]

In a study by Abbasnezhad et al. they have observed in-vitro the influence of the flow rate on the kinetics of Diclofenac release from polyurethane films. Experimental data of this study are employed here to establish the simultaneous effect of the flow rate and the drug concentration in the proposed model. As a reminder, these data relate to three



Figure 5: (a) Step defining by the aide of Douglas-Peucker algorithm and the constants needs for defining the model (b) Reconstruction the data points by using model.



Figure 6: Cumulative release of Diclofenac form PU matrix in (a) flow less state (b) flow rate of Q=7.5 ml/s and (c) flow rate of Q=23.5 ml/s.



Figure 7: Experimental results obtained from PU+10 Diclofenac at (a) Q = 0 ml/s, (b) Q = 7.5 ml/s, (c) Q = 23.5 ml/s, and traced in the form of $\text{Log} \frac{M_{e}}{M_{e}}$ in accordance to the Log $\frac{1}{M_{e}}$, (K=1).



Figure 8: Correlation between the values of n and reduced Reynolds number.

separate flow rates: 0 ml/s, 7.5 ml/s and 23 ml/s, and three drug concentrations: 10%, 20% and 30%. (Figure 6) illustrates all of these results. (Figure 7) shows in a Log-Log referential the graphs of the cumulative release rate as a function of time. The proposed algorithm provides only one stage for all experiments, suggesting in consequence one kinetic of release. The direct use of these calculated settings will predict the release behavior for any other flow rates and/or percentages of medication. (Figure 8) shows the evolution of the coefficient "n" as a function of the concentration and the flow rate, represented by a reduced Reynolds: $\overline{Re} = Re/Re_{critical}, Re_{critical} = 50000.$

We notice, in this case, a slight effect of the concentration. The (Figure 9a) shows for the three flow rates the evolution of the setting "^ti" as a function of the concentration. In this figure, it should be mentioned the addition of the point (0,100%), corresponds to the theoretical concentration 100% of drug and 0 for the time "ti". Indeed, for this significantly concentration, the release of the entire drug would be practically instantaneous (^ti=0), supposing of course the manufacture of the drug delivery carrier is possible. The (Figure 9b) gives the values of the coefficients A and B, extracted from the regressions proposed in (Figure 9a) as a function of the reduced-Reynolds number. (Figure 10) shows, with example, the prediction of our model for a 7.5 ml/s of flow rate. Various concentrations ranging from 5% to 80% are considered. Ultimately, to assess the validity of these predictions, two results are presented in (Figure 11). Successively: i) Prediction for the 6.5 ml/s of flow rate and two concentrations, 10% and 20%. ii) Prediction for the flow rate of 7.5 ml/s and the concentration of 15%. In both cases, the comparisons with the experimental data are remarkable.

Influence of the drug concentration

As another study in multi-step experimental data dispensable in the study by Li et al. [29] have been selected.



Figure 9: (a) Correlation between the values of the maximum time of the release in accordance to the drug concentration (fitting equation: $y=-coef.A \times Ln(x)+coef.B$) (b) Values of coefficients obtained from Figure 9(a) in accordance to the reduced Reynolds number.



Figure 10: Results for predicting the release behavior of different percentage of Diclofenac in the matrix of the PU at the flow rate of 7.5 ml/s.



Figure 11: Experimental data obtained with (a) PU+10 and 20% drug at the flow rate of 6.5 ml/s, R² are respectively 0.99 and 0.98(b) PU+15% drug at the flow rate of 7.5 ml/s, R²=0.98; at T=37 °C.

 Table 1: The important parameters that have been used in the studies of Li et al. [29] and Mckittrick et al. [4].

| Studies | Li et al. [29] | McKittrick et al. [4] |
|---------------------|----------------------------------|-------------------------------|
| Drug used | Sirolimus | Sirolimus |
| Polymer used | PDLLA | PDLLA |
| Release medium | Buffer solution | Buffer solution |
| Test condition | Glass vial (agitation 75 rpm) | Glass vial (agitation 20 rpm) |
| Drug delivery agent | Single layer | Single layer |
| Test conditions | In vitro | In vitro |
| Temperature | 37°C | 37°C |
| Measuring method | HPLC | UV |

These are separate in-vitro release trials of Sirolimus from stent-shaped PDLLA samples. Three Sirolimus concentrations correspond to these samples: 50%, 33% and 25%. All of this data was employed to evaluate the approach provided above. The proposed algorithm makes it possible to define the number of stages and the values of the settings necessary for the reproduction of these three release profiles of Sirolimos.

These settings make it possible to establish, for this family of drug carriers and for each, a mathematical relationship as a function of the concentration. The number of stages is also collected for this family, two in this case. Experimental data from another article McKittrick et al. [30] are chosen to test the agreement of the results calculated by the



Figure 12: Comparing the data results of Li et al. [29] and reproducing with the model, $R^2=1$ (K=2).



Figure 13: Data results from McKittrick, et al. [4] Sirolimus/ PDLLA with the ratio of 75/25. Comparing the results of model from the constants obtained from the data experiments of Li, et al. [29] $R^2=0.99(K=2)$.



Figure 14: (a) Data experimental of the study Chavoshi, et al. [31] $R^2=1$ for all three curves, (b) Comparison of the data experimental and the predicted curve of the model $R^2=0.99$, (k=3).

model with these data. This study equally concerns the release of Sirolimos from PDLLA, but for an extrapolated concentration of 75%. (Table 1) summarizes the test conditions for these two studies.

(Figure 12) shows the reproduction of experimental data from the study by Li et al. (Figure 13) illustrates the model calculated in comparison with the data from the study by McKittrick et al., the results are in good agreement.

Influence of the equivalent radius of the cylinder of a microneedles-patch

The results from the mathematical model dispensable in the study by Chavoshi et al. [31] have been selected. These are separate calculus of release of the Aspirin from biodegradable polymeric micro needles of four equivalentradiuses of cylinders: $3.3 \mu m$, $0.723 \mu m$, $0.38 \mu m$, $0.33 \mu m$. Data from 3 radii, $3.3 \mu m$, $0.723 \mu m$, and $0.33 \mu m$, are used to calculate the settings for this family of drug-patches of microneedles. This time, the proposed algorithm identifies three stages. The data of the 0.38- μm radius are reserved to assess the validity of the approach as before. (Figure 14) shows the data from the four Aspirin release calculus. The results are in good agreement, not only for the three radii used for the data adjustment, but especially also for the data of the radius 0.38 μ m reserved for the proof of the model prediction.

CONCLUSION

We have developed a new model for predicting the release of multi-stage drugs from drug delivery systems. The shape of the release profile can result in one or more kinetic occurring. By summing a series of power functions, the proposed model adjusts this profile. Each function represents a stage and is defined by three factors (Mi, ti and ni), which may depend on design data for the drug support or on the conditions of its operation. They grant each stage's kinetic properties. We illustrate the power of this approach by presenting several cases of medicine carriers. The materials, drug design factors, operating conditions and technology of the delivery devices selected for this purpose are varied. Although the range of examples selected is relatively limited compared to the extremely many varieties of existing drug-carriers, the approach stays easily applicable to other series of administration systems. It is enough to possess a set of representative experimental data.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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