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A new method for evaluating sirolimus actual release kinetics of degradable polymer matrix via numerical convolution

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ABSTRACT

Currently, the stent implant is the main treatment strategy for severe coronary artery stenosis. Sirolimus, an anti-proliferative drug coated on stents, is the key drug commonly used to inhibit restenosis. To meet the safety and achieve the desired therapeutic effect, the release rate of sirolimus from drug-loaded coatings must be controlled. High-performance liquid chromatography (HPLC) is a common method for *in vitro* release testing of drug-loaded coatings, which uses phosphate buffered solution (PBS) to simulate blood for release testing. However, this method only measures the amount of drug at different times through discrete sampling. Sirolimus particles are unstable and decay in an aqueous solution, and the decay rate is not a simple linear relationship. So the actual release of sirolimus cannot be obtained easily. In this paper, we refined a new method to derive the actual drug release of sirolimus. This method involves drug decay, numerical convolution, and pharmacokinetic classical (Weibull and Korsmeyer–Peppas) functions. In addition, the release experiments of two kinds of polymer drug-loaded matrix were carried out to provide model validation data. The results demonstrated that the new method is applicable and accurate for obtaining the actual release before hydrolysis. Moreover, the numerical convolution method is model-independent and versatile. It can be generalized to other micro/nano particle drugs with hydrolysis phenomena and can provide a reference for the analysis of the drug-loaded matrix.

1. Introduction

Currently, degradable polymer drug-loaded coatings are widely used in various implanted medical devices, such as heart stents, oral implants, or bone joints [1–3]. Drug-loaded coatings, the surface layer of the device matrix, are composed mainly of degradable polymers and drugs. Through the degradation of polymers, it locally releases drugs to achieve anti-thrombotic, anti-proliferative, antibacterial and other functions, and different release rates seriously affect clinical results [4–6].

In the device development stage, due to the extremely high cost of conducting *in vivo* experiments and animal experiments, it is necessary to use *in vitro* release experiments for drug evaluation. *In vitro* sustained release experiments generally use the flow-through cell Setup (USP 4), the reciprocating holder apparatus (USP 7) or Incubation setups [7–11]. The release medium mostly uses phosphate buffered solution Phosphate buffered saline (PBS, pH = 7.4) to simulate the stable blood environment *in vivo*. Then the drug content in the release medium is tested using high-performance liquid chromatography (HPLC) to evaluate the release rate of the drug in the drug-loaded matrix [12–17]. The schematic diagram of the specific experimental steps is shown in Fig. 1, where Fig. 1a represents the normal test method: detect the drug in the release medium, and Fig. 1b represents the reverse test method [18,19]: do not focus on the release or do not detect the drug concentration in the medium, but to detect the remaining unreleased drugs in the polymer-matrix.

Because functional drugs used in stents or other devices are generally hydrophobic drugs, they are not stable and easily hydrolyzed in aqueous solutions [20,21]. For example, the sirolimus drug used in the stent has a complex molecular structure, with 31 macrolide rings and 15 stereoisomeric centers. After hydrolysis, it appears ring-opening and generates different degradation products [22] and the hydrolyzed drug cannot be detected by HPLC. However, most scientific studies automatically ignore this problem. Wei Xu et al. compared the 14-day release properties of sirolimus in different polymer (PDLLA, PCL, PLCL) coatings on

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magnesium alloy stents [14]. Zhao jian et al. sprayed PDLLA coatings with different sirolimus ratios on 3D printed PLLA scaffolds to their release performance [23]. When processing the data, researchers default to the amount of drug measured in the medium as the matrix release for subsequent analysis [14,23–26]. Although the implantation environment of medical devices is the human body, the preliminary research work certainly need to be carried out *in vitro*. Reducing the error of experimental data *in vitro* can obtain more accurate drug release curves and provide better support for release simulation and *in vivo* prediction [27,28]. At present, classical models (Higuchi model, KP model or Weibull model, etc.) [29–31]are often used to analyze the release mechanism of the drug-loaded matrix to obtain fitting parameters and to infer the release mechanism. Therefore, a more accurate *in vitro* release curve is conducive to the evaluation of the mechanism.

In vitro release studies, in addition to sample preparation and test methods, there are also the effects of coating solvents [32] and release media additives [33] on the *in vitro* release curve. Therefore, to obtain the actual release curve, it is necessary to propose a new method to analyze the matrix drug release rate problem under different influencing factors. In this paper, the study proposes a novel method that does not require additional experiments and only combines numerical convolution to achieve the correction of the release. The method analyzes the release of the drug carrier as a whole system and takes the drug hydrolysis process into account in the system. The system analysis model is shown in Fig. 2. The specific modeling process is described in the theoretical analysis of Section 2. In this paper, the accuracy of the new method is verified by the combination of experiment and theory. The third section is the experimental part, which provides data support for model verification. The fourth section verifies and discusses the theoretical formula based on the experimental data. The results of data analysis show that the release curve modified by this method has high accuracy. It can also provide more realistic data support for the subsequent evaluation, simulation or mechanism study of the controlled release of coating.

In conclusion, the numerical convolution method in this paper can be easily applied to the *in vitro* release data analysis of various drug-loaded substrates, with good repeatability and accuracy (considering drug instability), saving samples.

2. Theoretical analysis

Numerical convolution is an operation in analytical mathematics, which has been widely used in medical research and industry. The mathematical form is shown in *Equation* (1).

$$(f*g)(n)=\int_{-\infty}^{+\infty} f(\tau)g(n-\tau)d\tau \ \text{ OR } \ (f*g)(n)=\sum_{\tau=0}^{n} f(\tau)g(n-\tau) \qquad (1)$$

The formula uses the notation τ instead of x or t to show that convolution can be applied to physical problems in space or time. In this paper, the cumulative release of drugs involves time, so t is chosen instead of τ. In an engineering sense, numerical convolution is an operation that describes the aggregate result of exerting some kind of influence on the persistence of a system. The colloquial expression is output = input * system. The schematic diagram of the data optimization and analysis process of the drug release system is shown in Fig. 2.

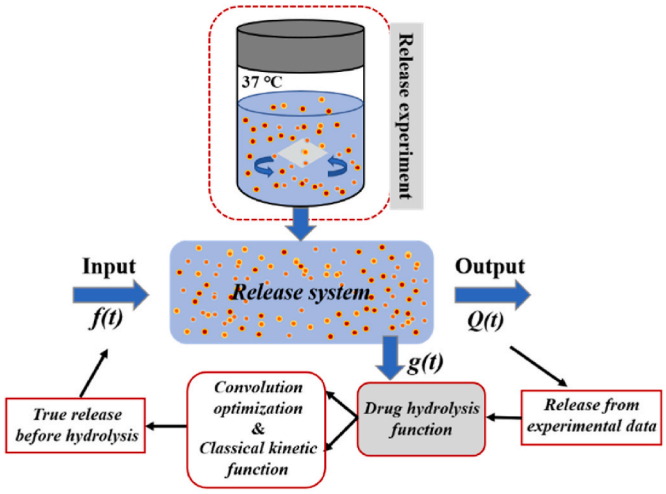

Fig. 2. Schematic diagram of data optimization and analysis process of the drug release system.

In the figure, the input function *f*(t) represents the actual release rate of the drug-loaded matrix before drug hydrolysis in the release medium. The function *g* (t) represents the recovery rate of the drug in the release medium, and the response output function *Q*(t) represents the drug release amount measured by HPLC. Corresponding to the discrete sampling experiment, the detected release *Q*(T) expression is shown in *Equation* (2):

$$Q(T)=(f*g)(T)=\int_0^T f(t)g(T-t)dt \qquad (2)$$

According to the experimental data (See Section 3), the drug hydrolysis function *g*(t) and the detected release function *Q*(t) in the formula are known conditions. The actual drug release rate *f*(t) needs to be calculated and the solution process is called deconvolution. After obtaining *f*(t), the actual drug release *M*(T) before hydrolysis can be obtained by integrating it, as shown in *Equation* (3):

$$M(T)=\int_0^T f(t)dt \qquad (3)$$

Due to the discrete sampling in the *in vitro* drug release experiment, the drug release is accumulated, and the sampling intervals of the drug-loaded matrix are different. If deconvolution calculation is used, the *f* (t) obtained in different intervals may have large errors. In order to avoid problems caused by deconvolution, *Equation* (2) is transformed into

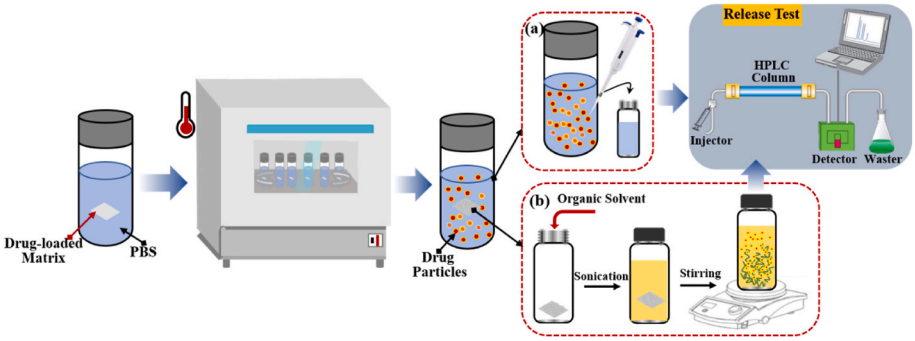

Fig. 1. Schematic diagram of *in vitro* drug release testing (a) normal method, (b) reverse method.

Equation (4):

$$F(T) = \left(q * \frac{1}{g}\right)(T) = \int_0^T q(t)\frac{1}{g(T-t)}dt \tag{4}$$

For *Equation* (4), we can plug in the known q(t) and g(t) functions and integrate them. The theoretical release F(t) within each sampling interval was obtained, and the total actual drug release is shown in *Equation* (5):

$$M(t) = \sum_{k=0}^{n}\int_{t_k}^{t_{k+1}} q(t)\frac{1}{g(T-t)}dt \tag{5}$$

Different functions will be selected to fit and analyze the drug release curve. Generally, Weibull and KP functions have a high degree of fitting [34]. In the paper, these two functions are also combined in the theoretical and experimental analysis part, so the form of q(t) is shown in *Equation* (6) as follows

$$q(t) = \frac{dQ_{Wb}}{dt} = \frac{d\left(1 - e^{-\frac{t^b}{a}}\right)}{dt} \text{ or } q(t) = \frac{dQ_{KP}}{dt} = \frac{d(k_1 t^n)}{dt} \tag{6}$$

The following abbreviated notations were used in the figures, text and equation in the drug delivery system:

Wb Weibull function;
KP Korsmeyer–Peppas;
Q the amount of drug released from drug-loaded matrix by HPLC test in release medium;
Q_i i = *Wb/KP,* drug release amount fitting under two functions;
q rate of drug release based on fitting function;
g drug hydrolysis rate function;
F the actual amount of drug released from the drug-loaded matrix in the interval;
f rate of drug released in the interval;
M the actual cumulative drug release before drug hydrolysis.

3. Experimental details

In this paper, the shaker method was used to study the controlled release of degradable polymer drug-loaded matrix films, and the *in vitro* drug release was detected by HPLC.

3.1. Materials

The main experimental materials mainly included organic solvents, degradable polymers and drugs. The organic solvent was methylene chloride (DCM). The drug-loaded polymers were racemic polylactic acid (PDLLA, IV = 0.25 dL/g ~ 0.35 dL/g, R203S) and polycaprolactone (PLCL, IV = 0.8 dL/g). The anti-proliferative drug rapamycin (sirolimus) was chosen as the release drug. The release medium was composed of PBS and the surfactant polyoxyethylene ether (Brij58, Mn, 1124).

3.2. Preparation and characterization of sirolimus-loaded coatings/films

The experimental samples in this paper were the degradable blend polymer drug-loaded film, and the preparation formula is shown in Table 1 below.

The samples were prepared by ultrasonic atomization spraying and the preparation details have been shown in previous articles [35].

Table 1
Formula of drug-loaded film sample.

Sample	Polymers (PDLLA: PLCL)	Polymer: Sirolimus	DCM
Film-6040d	60:40	2:1	4%
Film-5050d	50:50	2:1	4%

3.3. In-vitro sirolimus release

3.3.1. Release conditions

The release medium was PBS solution (PH = 7.4). Because Sirolimus has very low solubility in aqueous solutions, the non-ionic active agent Brij58 was introduced at a concentration of 0.1%. The determination of this release medium can be viewed from previous studies [36]. The drug-loaded film was placed into a clean brown bottle with 10 mL release medium and placed into a shaker (Shanghai ZhiCheng Co., Ltd. China) with a constant temperature of 37 °C and a constant speed of 100 rpm. The discrete sampling points were set as 1 day, 3 days, 7 days and 14 days.

HPLC parameters: 1 mL of release medium was taken out and drug concentration was measured by HPLC (Agilent 1200, C18 column) with acetonitrile: water (65:35) as the mobile phase with a flow rate of 1 mL/min and a UV–Vis detector set at 278 nm. All the release experiments were repeated 3 times and the mean ±standard deviations were reported.

3.3.2. Release methods: normal and reverse sampling tests

Normal sampling tests (Fig. 1a): Remove the sample at the sampling point and place it in the fresh medium. The amount of drug in the old release medium solution was tested to obtain the amount of drug released from the drug-loaded matrix in the interval. Then the cumulative drug release curve is obtained.

Reverse sampling test (Fig. 1b): Samples were taken and washed with deionized water to remove surface drugs. After that, it was dissolved by DCM ultrasonic shock, then the filtered solution was tested to obtain the remaining drug content of the matrix. Finally, drug release was calculated based on the total drug load. The advantage of the test method is that it does not need to pay attention to the drug hydrolysis in the medium. However, this method requires a large number of samples and can be used as a supplementary method or as a comparison of the degree of drug hydrolysis.

3.3.3. Drug hydrolysis attenuation test

1 mg of rapamycin powder was dissolved in a brown bottle containing 5 mL DCM. The drug changes from the crystalline state to an amorphous form, making it consistent with the crystal structure in the drug-loaded matrix. The brown bottle was left open at room temperature to allow the organic solvent to volatilize, then transferred to the 25 mL release medium (0.1% Brij58/PBS) into the bottle. The attenuation experiment was carried out for 7 days, and the intermediate sampling points were set as 1, 2, 3, 4 and 7 days.

4. Result and discussion

4.1. Comparison results of normal and reverse sampling tests

In vitro release experiments were carried out on drug-loaded matrix film by two methods: normal and reverse sampling tests and the results were shown in Fig. 3 below.

It can be seen from the results that the release data of the two methods are different, and the longer the sampling interval, the more serious the hydrolysis loss. On the 14th day, the difference between the normal and reverse sampling is more than 20%. In order to quantitatively and intuitively explain the difference, we used the similarity factor to quantitatively evaluate the experimental data. The similarity factor is calculated by Equation (7) as follows:

$$f_2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum[R_t - T_t]^2\right]^{-0.5} \times 100\right\} \tag{7}$$

Where n is the number of sampling time points, R_t is the reference release (normal sampling test) at time t, T_t is the test release (reverse sampling test) at t time.

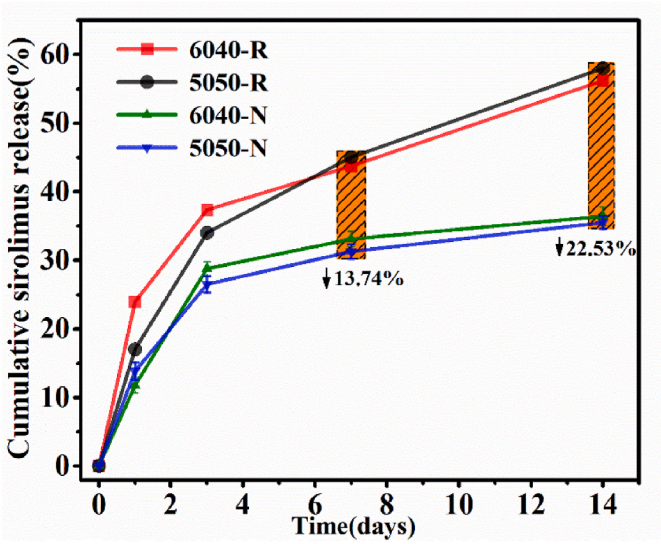

Fig. 3. Cumulative sirolimus release curves for normal and reverse sampling test methods.

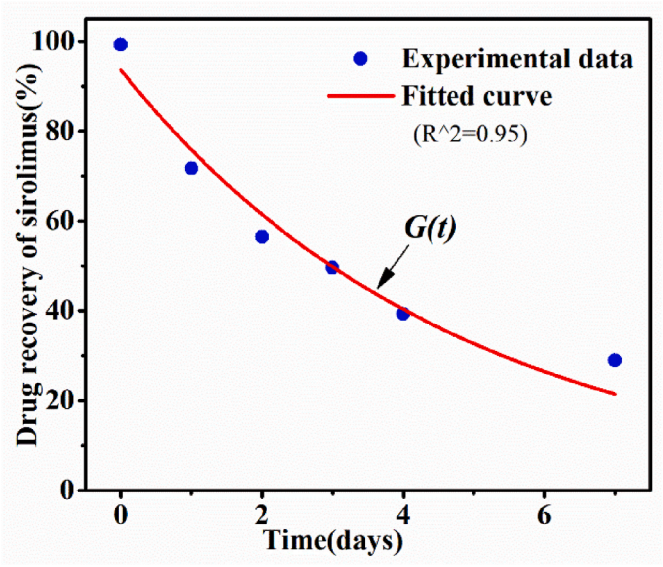

Fig. 4. Recovery of amorphous sirolimus in PBS release medium.

The calculated similarity factor value was 44.5, less than 50, indicating that the drug release curves obtained by the normal and reverse methods were significantly different. This further indicates that the effect of hydrolysis loss occurring in the release medium cannot be ignored. Therefore, it is necessary to modify the experimental data of drug release in post-processing.

4.2. Attenuation function analysis of drug hydrolysis

According to experiment 3.3.3, the drug concentration should be 40 μg/mL theoretically, and the concentration of the solution was tested to be 39.70 μg/mL by HPLC instrument and calibrated curve, that is, the drug concentration at time 0 was obtained. Then samples were then taken at the corresponding sampling points. The test concentrations were 28.49, 22.44, 19.71, 15.61 and 11.51 μg/mL, respectively. According to the research conclusions of relevant scholars [37,38], the decay curve of rapamycin in aqueous solution follows the first-order kinetic equation ($\ln\frac{C_t}{C_0} = -k_1 t$). *Equation* 8 is obtained by exponential deformation as follows:

$$C_t/C_0 = e^{-k_1 t} \text{ or } C_t = C_0 \times e^{-k_1 t} \tag{8}$$

Where, C_0 is the drug concentration before decay; C_t is the drug concentration at decay time t; k_1 is the decay rate constant.

Combined with the existing experimental data, the drug attenuation was corrected and fitted using the origin. The fitting results are shown in Fig. 4 below. Meanwhile, the sirolimus recovery function is $G(t) = C_t/C_0 = 0.9375 \times e^{-0.2106t} \times 100\%$.

4.3. Numerical convolution analysis process

According to the theory in section 2, numerical convolution was performed on the release data of the drug-loaded matrix to obtain the actual drug release before hydrolysis. The analysis processes are as follows:

(1) Firstly, the experimental data of the drug-loaded matrix were fitted by empirical model, and the experimental release $Q(t)$ was obtained. The fitting result of the Weibull model for the 6040d drug-loaded matrix was $Q(t) = 100 \times (1 - e^{-0.18t^{0.38}})$.

(2) After that, the release rate q(t) was obtained by differentiating the release quantity function $Q(t)$: $q(t) = Q(t)' = 100 \times (0.18 \times 0.38t^{-0.62}e^{-0.18t^{0.38}})$.

(3) Then, the obtained functions $q(t)$ and $g(t)$ are put into the numerical convolution formula, and the calculation form of $M(t)$ in each sampling interval period is shown in *Equation* 9.

$$M(t) = 100 \times \left(\sum_{k=0}^{n} \int_{t_k}^{t_{k+1}} \frac{b}{aA} t^{b-1} e^{k_2(t_{k+1}-t)} e^{-\frac{t^b}{a}} dt \right) = \sum_{k=0}^{n} \times \int_{t_k}^{t_{k+1}} 7.29t^{-0.62} e^{0.21(t_{k+1}-t)} e^{-0.18t^{0.38}} dt \tag{9}$$

(4) Combined with Matlab software, the function was integrated, and the cumulative release $M(t)$ of each interval was obtained. Finally, the actual drug release function $M(t)$ before hydrolysis was obtained by fitting these data. And the fitting result of 6040d drug-loaded matrix was $M(t) = 100 \times (1 - e^{-0.2t^{0.58}})$.

When the KP model was used for analysis, the experimental data were fitted by this model, and the fitting release quantity function $Q(t)$ and release rate $q(t)$ under this model were obtained. As in the above steps (3) and (4), the numerical convolution was used for integration and fitting to obtain the actual release function $M(t)$ under the KP model. The fitting results of the KP model for the 6040d drug-loaded matrix were shown in *Equation* 10.

$$\begin{cases} Q(t) = 16.8t^{0.32} \\ M(t) = 17.86t^{0.45} \end{cases} \tag{10}$$

Similarly, the convolution integral process of 5050d drug-loaded matrix was consistent with the above process, and the fitting function result is shown in the red box in Fig. 5b below.

4.4. Verification, validation and reliability application to the sirolimus-loaded polymer matrix

Combined with drug recovery function and drug release data of 6040d and 5050d drug-loaded matrix, the numerical convolution method was analyzed to verify the applicability and accuracy of the theoretical model. The drug release data were analyzed and modified by the model combined with Weibull and KP functions, and the results are shown in Fig. 5.

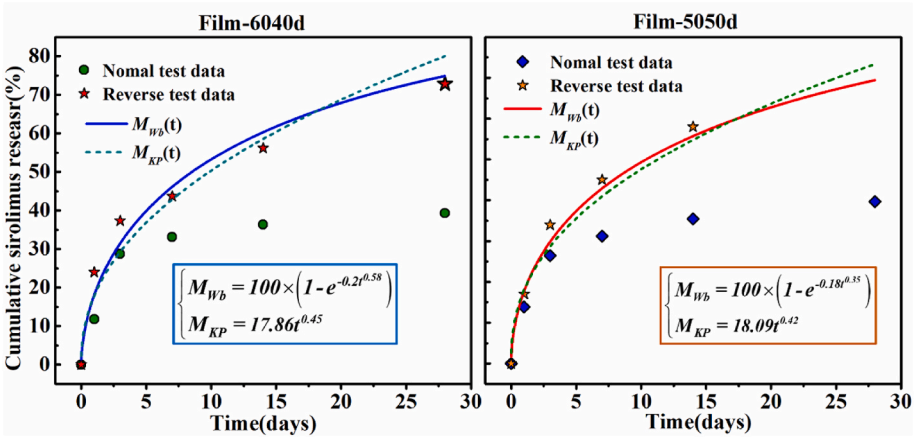

Fig. 5. Verification: the actual drug release curves of the two drug-loaded films (6040d, 5050d)under the Weibull and KP models based on theoretical formulas.

It can be seen that the release curve is in good agreement with the experimental data. The drug release curve before hydrolysis can be obtained by using the method, and the model realizes the correction and optimization of *in vitro* release data. It can be seen that the release curve is in good agreement with the experimental data. The theoretical model can obtain the actual release before hydrolysis, and realize the correction and optimization of *in vitro* experimental data.

Comparing the release curves fitted by Weibull and KP equations, it is found that they are very close, but there are differences in the prediction of later data and M_{Wb} curve is more convergent. We used the M(t) fitting equation to predict the 28-day release data of the 6040d drug-loaded matrix, which were 74.9% and 80%, respectively. The experimental data from the reverse sampling test was 72.8%. Therefore, the predicted values using the Weibull function may be closer to the experimental values. The comparative study also provides a reference for subsequent researchers.

5. Conclusion

In this paper, an effective numerical convolution calculation method is proposed to analyze the release kinetics of sirolimus in the drug-loaded polymer matrix, and the new method continues to use the existing HPLC to test the drug release and only needs to add a set of sirolimus decay curves in the same release medium to obtain the actual release curve. And the accuracy of this method is verified by experimental data. This work has demonstrated that the numerical convolution method is model-independent and can be generalized to other micro/nano particle drugs. The new method can also be used in conjunction with existing shaker incubation setups *in vitro* release tests and to develop the drug-loaded matrix with different release rates.

CRediT author statement

Fengqin Li: Methodology, Investigation, Writing - original draft. **Gutian Zhao:** Investigation, Data Curation, Visualization. **Guizhong Tian:** Conceptualization, Review, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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