An Approach to Modeling Drug Release from Polymersome Nanoparticles Based on PNIPAM-g-PEO Graft Copolymer

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Abstract: The recently proposed by the authors numerical approach to modelling of drug release from polymersome nanoparticles based on PNIPAM-g-PEO graft copolymer is generalized on the basis of different model dependent methods. It takes into account the specific features of the experimental procedure and equipment used during the experimental study of the drug release kinetics. The rate parameters are numerically evaluated when fitting each model curve to the available experimental data for indomethacin. Numerical simulation of drug release for 5% and 20% ethanol content is performed and the reliability of the used approach is discussed. It is established that the drug release rate is strongly influenced by the ethanol content. The considered numerical approach enables modeling of different drugs release under the same experimental equipment as well as inclusion of some new model functions describing other mechanisms controlling the release kinetics.

Keywords: PNIPAM-g-PEO polymersome nanoparticles, Drug release, Model dependent methods, Numerical simulation.

Introduction
Polymersomes are enclosed membrane nanostructures of amphiphilic block copolymers [11] that currently have attracted great interest because of their structural analogies with living organelles [17] and potential applications as nanosized reactors [23] or drug delivery systems [9, 16]. Over the last decade, various polymersomes have been designed to meet the specific demands of drug delivery, such as biodegradability, targetability and responsiveness to physiologically relevant stimuli (pH, temperature, reductive environment) [18]. Temperature-responsiveness issues have been commonly addressed by introducing a thermo-responsive polymeric block in either the polymersome core or corona [18, 26]. The conversion of the thermally sensitive component from hydrophobic to a more hydrophilic state or vice versa in response to small changes in temperature permits temporal and spatial delivery control of the incorporated drug [26].

Temperature responsive homopolymers poly(N-isopropylacrylamide) (PNIPAM) and their hydrophilic block copolymers PNIPAM-poly (ethylene oxide) (PNIPAM-PEO) have attracted special attention because they exhibit reversible phase transition in water around body temperature, the lower critical solution temperature (LCST) [34]. Below the LCST, these copolymers readily dissolve in water; at temperatures above the critical point, they self-
assemble into single chain or inter-chain nanostructures consisting of a hydrophilic PEO shell and a hydrophobic PNIPAM core, which can integrate hydrophobic guest molecules [7, 8, 24, 38]. A major concern in the design of drug-loaded PNIPAM-PEO block copolymer nanoparticles (NPs) consists in establishing a reliable and convenient method to achieve high loading contents in their micellar cores while controlling their geometry. In this aim, we recently proposed a low-temperature method in hydro-ethanolic solutions to form PNIPAM-g-PEO nanoparticles loaded with a remarkably high content of Indomethacin (IMC) (~90-140% w/w), a hydrophobic water-insoluble drug [19, 21]. In this procedure, the polymer was forced down a specific self-assembly pathway through a combination of solvent mixing [25] lowering the LCST below the preparation temperature (20 °C) [15, 19, 35] and association of IMC with PNIPAM [10, 36]. We found out that the graft copolymers could be tuned to self-assemble into multi-chain micelles and polymersomes by controlling the quantity of added ethanol to the solvent mixture. The resultant self-assemblies were kinetically trapped but stable due to strong H-bonding and hydrophobic interactions among the molecules of IMC and PNIPAM. Both micelles and polymersomes released the drug in a controlled manner, in which significantly slower drug release was observed at higher loading content [19] and in the presence of ethanol [4, 20].

During the last two decades the mathematical modelling of controlled drug release was proved as a very useful and effective tool for prediction of the release kinetics before the release systems are realized [2, 3, 12, 13, 22, 29-33]. A growing interest in the field of study of drug release from micro and nano-carriers has been observed for the last ten years [5, 6, 28, 37].

An approach to modelling of indomethacin (IMC) release from polymersome NPs based on PNIPAM-g-PEO graft copolymer was developed taking into account the specific features of the experimental procedure and equipment. It was successfully validated for NPs at different temperature, ethanol content and rate of ethanol injection [16, 20, 23].

The aim of the present paper is to continue the study of the proposed numerical approach to modeling the drug release from the polymersome NPs based on poly(N-isopropylacrylamide)-g-poly (ethylene oxide) (PNIPAM-g-PEO) graft copolymer validating some popular model dependent methods of drug dissolution and surface erosion.

**Generalized numerical approach**

The following assumptions for modeling the experimentally measured drug release are considered [1, 5, 32]: (1) Two main coupled physicochemical processes control IMC release. The first one is the release of the bounded IMC from the polymersome NPs included in the physicochemical formulation. The second process is the dialysis of the free drug from the inner container into the outer aqueous phase; (2) The drug (the free part as well as the bounded one) is uniformly distributed in the inner container; (3) The predominant mechanism of the drug liberation from the polymersome NPs is overcoming the polymer-drug interaction; (4) Overcoming the polymer-drug interaction is much slower process as compared to diffusion of drug through the polymer.

The methods of approach to investigate the drug release kinetics can be classified into three categories: statistical methods; model dependent methods; model independent methods. Model dependent methods of drug release are based on different mathematical functions which describe the dissolution or erosion profile [32]. The considered general form of the mathematical expression of fractional drug liberation from NPs is the following:
\[ M_b(t) = F(t), \]  \hspace{1cm} (1)

where \( M_b, M_{b0}, t \) are the current value of the decreasing mass of the bounded drug, its initial value and the time; \( F(t) \) is the introduced generalized function.

Taking into account the coupled physicochemical processes realizing during the experiment (release of the bounded drug in the inner solution and diffusion of the free drug from the inner container into the outer aqueous phase) the following model equation of fractional drug release is derived [5]:

\[
\frac{d\bar{M}(t)}{dt} = K \left( \frac{M_{f0}}{M_0} + \frac{M_b(t)}{M_0} - \bar{M}(t) \right), \quad \frac{M_b(t)}{M_0} = \left( 1 - \frac{M_{f0}}{M_0} \right) F(t), \quad (2)
\]

where \( \bar{M}(t) \) is the total mass of the drug released in the outer tube within a period of \( t \) hours; \( K = \frac{DP}{h} \) is the permeability constant, \( D \) is the drug diffusivity, \( h \) is the membrane thickness, \( P \) is the distribution coefficient and \( H \) is the height of the solution in the inner tube; \( M_{f0} = M_0 - M_{b0} \) is the initial value of the free drug mass in the solution given from the experiment.

The following popular functions for the fractional drug release profile are considered:

- Zero order model function, corresponding to the so called Peppas equation \( \left( M/M_0 = k_0 t^n \right) \), when \( n > 0.85, [22, 27] \):

\[
F(t) = k_0 t, \quad (3)
\]

where \( k_0 \) is the zero order release constant.

- First order model function, derived from the equation for the first order kinetics [32]:

\[
F(t) = \exp(-k_1 t), \quad (4)
\]

where \( k_1 \) is the first order rate constant.

- Surface erosion model function (Hopfenberg [14]):

\[
F(t) = 1 - (1 - k_{H} t)^3 \quad (5)
\]

- Model function of Agrawal [1], derived in case of breaking of the polymer-drug linkage:

\[
F(t) = 1 - \frac{1}{(1 + at)^{3/2}}, \quad (6)
\]

where \( k_H \) and \( a \) are rate parameters connected with surface erosion and overcoming the polymer-drug interaction.
The presented approach to modeling drug release from NPs is validated on the basis of experimental data for IMC release at different ethanol content according to the following numerical procedure for each of the functions (3)-(6):

- **1st step.** The permeability $K$ is evaluated on the basis of data from an experiment performed in the case of pure drug solution ($M_{f0} = M_0$);
- **2nd step.** The rate constant is evaluated under the determined parameter $K$ fitting the model Eq. (2) to the obtained data from the considered experiment.

The determination coefficient is calculated at each step according to the formula:

$$ R^2 = 1 - \frac{\sum_{n=1}^{N} \left( R_{\text{num}}^n - R_{\exp}^n \right)^2}{\sum_{n=1}^{N} \left( R_{\text{arithm}}^n - R_{\exp}^n \right)^2}, $$

where $R_{\text{arithm}}^n$ is the arithmetic mean of the experimental data of the considered drug release, $R_{\text{num}}^n$ and $R_{\exp}^n$ are the numerical results and the experimental data, respectively.

- **3rd step.** Numerical simulation of drug release from the considered NPs following (1) under the obtained value of the rate parameter.

**Numerical results**

The comparison between experimental data (dots) [20] and numerical results (curves) for functions (3)-(6) in the case of 5% ethanol content and 37 °C is shown in Fig. 1.

![Fig. 1 Validation of the model equation (2) at 5% ethanol and 37 °C: 1 – model function (6); 2 – model function (5); 3 – zero order function; large dash curve – first order function (1).](image)

A very good agreement is obtained for model functions (5) and (6) when the determination coefficient ($R^2$) is 0.92 and 0.985, respectively. The corresponding model parameters are
evaluated as follows: $K = 0.145 \text{ cm hr}^{-1}$, $k_H = 0.095 \text{ hr}^{-1}$, $a = 0.37 \text{ hr}^{-1}$. It is obvious that zero and first order models do not satisfactorily describe the considered release profile.

The requirement not to present the numerical results with determination coefficient less than 0.90 (as these once corresponding to 1st order function in Fig. 1) is accepted for our future considerations.

Figs. 2a and 2b represent fitting of the model equation (2) to the experimental results in the case of 10% and 20% ethanol content at 37 °C.

![Graph](image1)

![Graph](image2)

Fig. 2 Validation of the model for IMC release at 37 °C for: (a) for 10% ethanol content; (b) for 20% ethanol content; 1 – function (6), 2 – function (5), 3 – zero order function (1).

Satisfactory numerical results for describing the release profile when increasing the ethanol content are obtained in the cases of functions (6), (5) and (3). The rate parameters are evaluated for $K = 0.12 \text{ cm hr}^{-1}$ and $K = 0.1 \text{ cm hr}^{-1}$ as follows:
respectively. We can conclude that the surface erosion function and zero order function are more appropriate for slower drug release kinetics which is observed when the ethanol content is high (10% and 20%).

Numerical simulation of drug liberation from the considered nanocarriers into the solution is performed using each of the evaluated rate parameters for two main cases: 5% and 20% ethanol content. Fig. 3 shows that the drug release at 5% ethanol is approximately twice faster than this one at 20% ethanol.

Fig. 3 Numerical simulation of IMC release from NPs into the solution at 37 °C for:
(a) 5% ethanol content within the period of 8 hours;
(b) 20% ethanol content within the period of 16 hours.

The curves 1 corresponding to the Agrawal function (6) describe an initial burst release (up to the first three and six hours, respectively), followed by a sustained liberation, better than the
other curves. The zero order model function (straight line 3) does not give realistic results after an initial time period (6 and 13 hours for 5% and 20% ethanol, respectively). It can be recommended when describing a slow increase within the first 8 hours (see Fig. 3b). Modeling by the Hopfenberg function (curves 2) has the restriction to be used for a long time period (the fractional release exceeds the unit). This period is about 10 hours for the release in Fig. 3a and about 30 hours for this one in Fig. 3b. There is no such restriction for the application of the Agrawal model function.

**Conclusion**

A numerical approach to modeling of drug release from polymersome NPs was developed and validated using the available experimental data for the socially important drug indomethacin. In the present paper the proposed approach was generalized on the basis of model dependent methods of drug dissolution and surface erosion. The idea of a conditional separation of the main processes enables the consecutive evaluation of the drug permeability and the rate constant for each model function instead of using more complicated numerical procedures.

Numerical simulation of drug release for 5% and 20% ethanol content at 37 °C is performed and the reliability of the used approach is evaluated. We can conclude that the most appropriate model function is the Agrawal one, corresponding to overcoming the polymer drug linkage.

The considered numerical approach enables modeling of drugs release under the same experimental equipment as well as inclusion of new model functions for other mechanisms controlling the release kinetics. It will be used in our future studies of modeling the drug delivery in vivo.

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**References**

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