Numerical Analysis of Indomethacin Release from Polymersome Nanoparticles. Effect of Ethanol Content

KEYWORDS
- Indomethacin release
- Polymersome nanoparticles
- Mathematical model
- Numerical simulation

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### ABSTRACT
Numerical analysis of indomethacin release from polymersome nanoparticles was performed. In vitro release study was conducted in distilled water containing different ethanol content using dialysis tube method. The recently proposed by the author's mathematical model of drug release was validated under the obtained experimental results. It was used for establishing the effect of ethanol content in the nanoparticles solution upon drug release. Numerical simulation of indomethacin release was realized within a period of 36 hours in the case of membrane presence, as well as when neglecting it.

### Introduction
Polymersomes are lamellar, enclosed nanostructures of amphiphilic block copolymers that currently have attracted great interest because of their structural analogies with living organelles (LoPresti, 2009) and potential applications as nanosized reactors (Qi, Small, 2009) or drug delivery systems (Christian, & Discher, 2009). Over the last decade, various polymersomes have been designed to meet the specific demands of drug delivery, such as biodegradability, targetability and responsiveness to biologically relevant stimuli (pH, temperature, reductive environment) (Meng et al., 2009). Temperature-responsiveness issues have been commonly addressed by introducing a thermo-responsive polymeric block in either the polymersome core or corona (Rijcken et al., 2007; Meng et al., 2009).

Temperature responsive polymers like poly(N-isopropylacrylamide) (PNIPAM) homopolymer and its copolymers have been widely applied for the formation of thermo-sensitive drug delivery systems as they exhibit reversible phase transition in water around body temperature, the lower critical solution temperature (LCST) (Liu, 2009; Wei, 2009). Additives such as salts, hydrophobic drugs or some polar organic solvents affect significantly their critical temperature by changing the hydrophilic/hydrophobic balance within the polymer molecule via different mechanisms of hydration/dehydration (Eckman et al., 2001; Costa and Freitas, 2002; Wang, Craig, Langmuir, 2012; Coughlan and Corrigan, 2006). For example, lower alcohols like ethanol depress the LCST of PNIPAM in mixed solutions of water and alcohol as a result of competitive hydrogen bonding of the two solvents onto the amide groups and the hydrophobic effect of the isopropyl groups and the C-H backbone (Tanaka, 2011). These solvation effects are so strong at certain mixed solvent compositions that they could be utilized to induce micellization of PNIPAM-containing di-block copolymers (Rao & Langmuir, 2007). Based on this special property of PNIPAM, we recently proposed a procedure with ethanol for the formation of PNIPAM-g-PEO core-shell nanoparticles (NPs), including micelles (Michailova et al., 2010) and polymersomes (Michaelova et al., 2013), for prolonged release of a hydrophobic anti-inflammatory drug, Indomethacin (IMC). It was found that the developed self-assemblies used the hydrophilic PEO grafts as a corona and PNIPAM as a hydrophobic core block for directly integrating hydrophobic molecules. Both micelles and polymersomes were able to release IMC in a controlled manner, in which significantly slower drug release was observed at a higher drug loading content and in the presence of ethanol. In these cases, it was likely that intensive polymer-polymer and polymer-drug hydrophobic interactions slowed down the release rate. Since homopolymers of PNIPAM exhibit sharp transition from hydrated to dehydrated state upon addition of ethanol, variation of mixed solvents composition is expected to have strong influence on the drug entrapment and release rate.

The aim of the present work is to examine numerically the effect of ethanol content on IMC release from PNIPAM-g-PEO polymersomes. The mathematical model recently proposed by Blagoeva et al. (2012) is used to study precisely the expected effect on IMC release rate. The model equations are validated for three different values of ethanol content: 5, 10 and 20% (v/v). Numerical simulation of IMC release from the solution of polymersomes is performed for 5 and 20% ethanol content within a period of 36 hours under the presence of membrane as well as when neglecting it.

### Model
The model, describing the experimentally observed drug release, was developed under the assumptions (Blagoeva et al., 2012): (1) Two main coupled physicochemical processes control IMC release - the release of the bound IMC from the vesicular nanoparticles included in the formulation and diffusion of the free drug from the inner container into the outer aqueous phase realizes at the same time; (2) The concentrations of the free drug and the bound one are uniformly distributed in the inner container; (3) The predominant mechanism of the drug release kinetics from the nanoparticles is overcoming the polymer-drug interaction; (4) Perfect sink condition at the boundary from the outer membrane side exists.

The model equation of the first process was offered by Agraval et al. (2006):

$$M_s(t) = M_s \left( \frac{1}{1 + at} \right)^{2/3}$$

(1)

where $M_s$ and $M_d$ are the current value of the decreasing mass of the bound drug within the inner container and its initial value. The model parameter $a$ is the rate constant referred to overcoming the interaction between the polymer and the embedded drug in the nanoparticles.

The diffusion equations of the free drug mass from the inner container, corresponding to the Fick's laws, and the assumptions (2) and (4) are proposed by Blagoeva et al. (2012):
where $\mathcal{D}$ is the permeability constant, $D$ is the drug diffusivity and $h$ is the membrane thickness, $P$ is the distribution coefficient and $H$ is the height of the solution in the inner tube, $\mu_f$ is the free drug mass, $\gamma_f$ is the free drug concentration, $S$ is the membrane surface area and $J$ is the flux passing through it.

The total mass of the drug released in the outer tube within a period of $t$ hours is denoted by $m(t)$, referred to the initial total drug mass. The following model equations for fractional drug release under zero initial condition are obtained:

$$\frac{dM_{f}(t)}{dt} - SJ = -KVc_{i}(t) \tag{2}$$

where $M_{f}(t) - M_{f,0}$ is the initial value of the free drug mass in the solution given from the experiment.

The model parameters (the drug permeability $K$ and the rate parameter $a$) can be numerically evaluated according to the proposed procedure:

- The case of drug pure solution (i.e. $M_{f} = M_{f,0}$) in the inner container is considered in order to evaluate the permeability $K$ of IMC by fitting the model equations (2) to the obtained experimental data;
- The rate parameter $a$ is evaluated under the determined permeability $K$ fitting the equations (3) to the experimental data for fractional IMC release from NPs assembly.

In order to evaluate the goodness of fit the determination coefficient is calculated at each of the above steps, as follows:

$$R^2 = 1 - \frac{\sum_{i=1}^{N}(R_{exp}^i - R_{num}^i)^2}{\sum_{i=1}^{N}(R_{exp}^i - R_{arithm}^i)^2} \tag{4}$$

where $R_{arithm}^i$ is the arithmetic mean of the experimental data of the considered fractional drug release.

**Numerical analysis of drug release**

The proposed procedure for numerical evaluation of the model parameters was applied under 37°C for three cases: IMC release in the medium for 5%, 10% and 20% ethanol of the obtained solution, prepared by slow injection. The model was fitted to the experimental data (Michailova et al., 2013) for IMC release from pure solution first and second, from nanoparticles one. The parameters $K$ and $a$ were found and presented in Table 1. These results show a tendency of decreasing the rate of the main processes with increase of the ethanol content.

| Ethanol content | Permeability K (cm hr⁻¹) | Rate constant a (hr⁻¹) |
|-----------------|--------------------------|------------------------|
| 5% ethanol      | 0.145                    | 0.37                   |
| 10% ethanol     | 0.12                     | 0.13                   |
| 20% ethanol     | 0.10                     | 0.115                  |

The model fitting to the experimental data for IMC release from NPs assembly at 5% ethanol is presented in Fig.1 and Fig.2 in comparison with this one for 10% and 20% ethanol, respectively ($R^2 = 0.9752$ on average). The model parameter $a$ was evaluated under the experimentally measured initial partial free drug quantity $\mu_f$ equal to 19.79%, 13.54% and 25.57%, respectively. A significant effect of increasing the ethanol content from 5% to 10% in contrast within the range 10% - 20% is observed.
Conclusion
A study of the release of the socially important drug IMC from lab-scale experimentally obtained core-shell polymersomes was performed.

The mathematical model recently proposed by Blagoeva et al. (2012) was used to analyze the effect of ethanol content on drug release kinetics from NPs. The model equations were validated for three different values of ethanol content. An obvious tendency of decrease of IMC release rate with increase of ethanol content was observed. Significant differences of IMC release rate were established for 5% and 10% ethanol content as well as for 5% and 20% one.

Numerical simulation of IMC release from the considered polymersomes solution was performed for 5% and 20% ethanol content within a period of 36 hours under the presence of membrane and when neglecting it.

The offered numerical algorithm can be used as an effective simulation tool in a future analysis of drug release from different types of NPs solutions.