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Numerical Modelling of Indomethacin Release from Pnipam- G –Peo Micellar Nanoparticles

KEYWORDS: indomethacin release, micellar nanoparticles, numerical modelling

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ABSTRACT *The object of the present paper is the Indomethacin (IMC) release from poly (N-isopropylacrylamide)-graft-poly (ethylene oxide) PNIPAM-g-PEO micellar nanoparticles (NPs). The release study was conducted in acetate and phosphate buffer solutions, pH 4.5 and pH 7.4, respectively, using the dialysis tube method. The nano-sized polymeric micelles were characterized with respect to morphology, drug loading content and in vitro drug release kinetics by Michailova et al. (2010). In the present paper this study was supported by an appropriate mathematical model and a numerical procedure for evaluation of the model parameters was validated under the obtained experimental data for two initial drugs loading at two different pH. The created numerical algorithm was used for simulation of IMC release within a period of 48 hours NPs, neglecting the presence of a membrane.*

Introduction

During the last decade, numerous polymeric nanocarriers of various compositions and geometries have been developed for the delivery and the release of therapeutic agents. Their ability to control the release of drugs is used to achieve targeted delivery through surface modification, protect the drug from degradation, and reduce systemic toxic effect. The important technological advantages of nanoparticles used as drug carriers are high stability and capacity, feasibility of incorporation of both hydrophilic and hydrophobic substances, and feasibility of variable routes of administration, including oral application and inhalation. Nanoparticles can also be designed to allow sustained drug release from the matrix (Gelprina et al., 2005, Gaucher at al., 2010).

A variety of mathematical models for quantitative prediction of the release of different drugs from micro and nano carriers have been presented by Suvacanta et al. (2010) and Ashlee et al. (2013), taking into account the predominant mechanisms of the release kinetics. A mathematical model of indomethacin (IMC) release from PNIPAM-g-PEO vesicular nanoparticles (NPs) was proposed for description of the drug-polymer interaction by Blagoeva et al. (2012).

Recently thermally responsive poly(N-isopropylacrylamide)-graft-poly(ethylene oxide) (PNIPAM-g-PEO) copolymers containing PEO grafts were synthesized and utilized to prepare IMC loaded micellar nanoparticles using a dialysis at room temperature by Michailova et al. (2010).

The aim of the present paper was to develop an appropriate model of IMC release from PMIPAM-g-PEO micellar NPs. The created model was validated by fitting with the obtained experimental results. It was demonstrated that it can be used as an effective simulation tool in the design of nanoparticles of the considered micellar type. Numerical modeling provides insights concerning diffusion and physicochemical processes involved in NPs formulations as well as the effect of pH and polymer-drug weight ratio.

Numerical modelling

The model is proposed under the following assumptions: (1) Two main coupled physicochemical processes control IMC release. The first one is the release of the bound IMC from the micellar nanoparticles included in the formulation. Diffusion of the free drug from the inner container into the outer aqueous phase realizes at the same time as accepted by Michailova et al. (2013); (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) A perfect sink condition at the boundary from the outer membrane side exists.

The model equation describing the first process was offered by Agraval et al. (2006) for micellar solutions of PLA-PEO-PLA triblock copolymers:

$$M_b(t) = M_b - M_b\left(1-at\right)^3 \quad , (1)$$

where M_b and M_{bo} 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 a rate constant referred to overcoming the interaction between the polymer and the embedded drug in the nanoparticles.

The equation of the diffusion of the free drug mass from the inner container, denoted by M_f, is derived on the basis of the Fick's law and the assumptions (2) and (4) as follows:

$$\frac{dM_f(t)}{dt} = -\frac{K}{H}M_f(t) \quad (2)$$

where $K = \frac{DP}{h}$

is the permeability constant, D is the drug diffusivity and h is the membrane thickness. Hear, P is the distribution coefficient and H is the height of the solution in the inner tube. The total mass of the drug released in the outer tube within a period of t hours is denoted by $\overline{M}(t)$, referred to the initial total drug mass and the main model equation for fractional drug release under zero initial condition is obtained:

$$\frac{d\overline{M}}{dt} = \frac{K}{H}\left(\frac{M_{fo}}{M_o} + \frac{M_b(t)}{M_o} - \overline{M}(t)\right) \quad , (3)$$

$$\frac{M_b}{M_o} = \left(1 - \frac{M_{fo}}{M_o}\right)\left(1-\left(1-at\right)^3\right)$$

where $M_{fo} = M_o - M_b$ is the initial value of the free

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drug mass in the solution.

The following procedure for numerical evaluation of the main model parameters (the drug permeability K and the rate parameter a) was proposed:

1st step. The case of drug pure solution (i.e. $M_{f_0} = M_o$) in the inner container is considered in order to evaluate the permeability K on the basis of the available experimental data;

2nd step. Evaluation of the rate parameter a by fitting the model equation (3) to the experimental data for fractional IMC release from NPs assembly;

To evaluate the goodness of the fit the determination coefficient is calculated at each step, as follows:

$$R^2 = 1 - \frac{\sum_{n=1}^{N}\left(R_{num}^n - R_{\exp}^n\right)^2}{\sum_{n=1}^{N}\left(R_{arithm}^n - R_{\exp}^n\right)^2}, \quad (4)$$

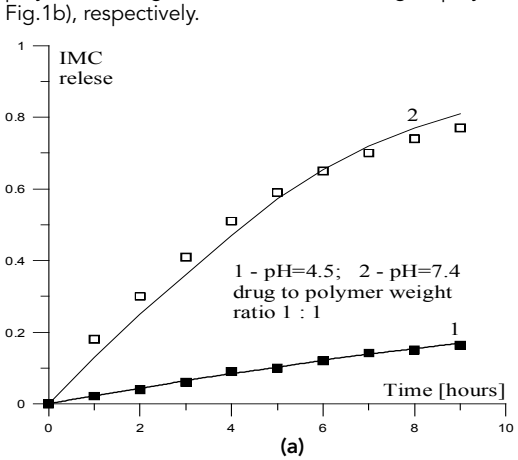
where R_{arithm}^n is the arithmetic mean of the experimental data of the considered drug release;

3rd step. Numerical simulation of IMC release from the considered NPs following (1) (neglecting the presence of membrane) under the obtained value of the rate parameter a.

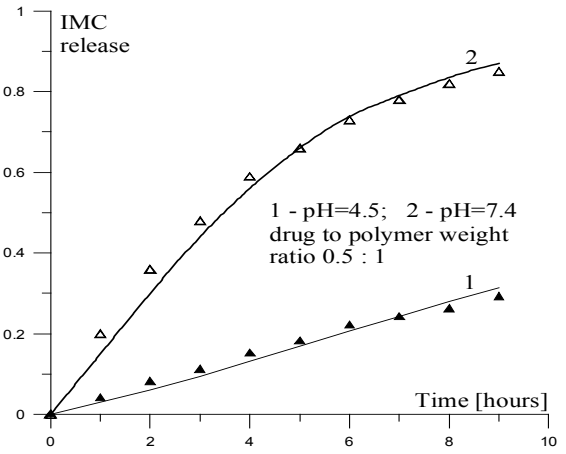
Numerical results

The proposed procedure for numerical evaluation of the model parameters was applied under 37^{0}C for the cases: IMC release in the medium in pH=7.4 and pH=4.5, when drug to polymer weight ratio is 0.5:1 and 1:1, respectively. Fitting the obtained experimental data for IMC release from pure solution we found the following value of the parameter K: $0.175\,\mathrm{cm\,hr^{-1}}$ ($R^2 = 0.99$). Finite difference method was applied when evaluating the fractional drug release $M(t)$. Standard least square method was used when fitting the model equations with experimental data.

Fig.1a represents the model fitting to the available experimental data obtained by Michailova et al. (2010) for IMC release from PNIMPAM-g-PEO NPs assembly under drug-polymer ratio 1:1 in pH=7.4 and pH=4.5. The model parameter a was evaluated to be $0.9\times10^{-1}\,\mathrm{hr^{-1}}$ and $0.56\times10^{-2}\,\mathrm{hr^{-1}}$, respectively ($R^2 = 0.97$ on average). Fig. 1b shows the model fitting for IMC release under drug-polymer ratio 0.5:1 in pH=7.4 and 4.5. The obtained values of a are $0.174\,\mathrm{hr^{-1}}$ and $0.17\times10^{-1}\,\mathrm{hr^{-1}}$, respectively ($R^2 = 0.955$ on average). The model equations were fitted under the initial partial free drug quantity M_{f_0}/M_o equal to: 49%, 10.3% (drug to polymer 1:1, Fig.1a) and 56%, 9.7% (drug to polymer 0.5:1, Fig.1b), respectively.



(a)



(b)

Fig.1 Validation of the model for IMC release in pH=4.5 and 7.4: (a) drug-polymer weight ratio 1:1; (b) drug-polymer weight ratio 0.5:1

A very good correspondence between the numerical results and experimental data for both initial drug loading and the considered values of pH is obtained. A significant effect of pH on the IMC liberation rate is observed. In the period of 9 hours approximately 18% to 30% of the IMC is released in pH = 4.5 while about 80 to 87% of the drug is released in pH = 7.4.

Fig. 2 demonstrates the ability of the model to predict the IMC release profiles within the period of 48 hours neglecting the dialysis as well as the effect of initial drug loading on the release profiles. It is observed that when drug to polymer weight ratio is twice increased the rate of drug liberation is twice decreased.

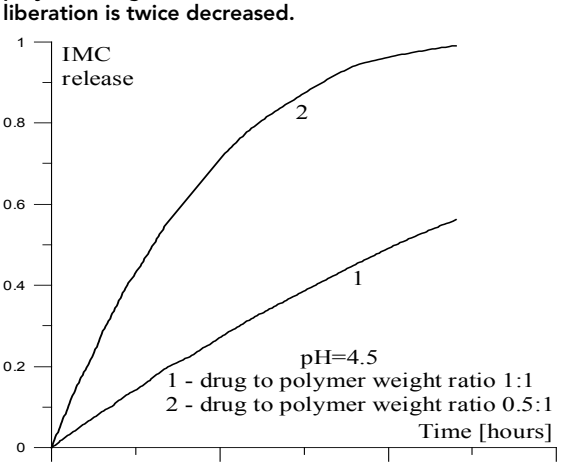


Fig.2 Numerical simulation of IMC release in pH = 4.5 for two drug-polymer weight ratio

Conclusion

The release of the socially important drug indomethacin from a new type of micellar nanoparticles was studied numerically.

An appropriate mathematical model describing IMC release kinetics was proposed assuming that two main physicochemical processes control this kinetics. The idea of a conditional separation of the main processes enables the consecutive evaluation of the drug permeability and the rate constant instead of using more complicated numerical procedures was done by Blagoeva & Nedev (2010).

The model equations were validated for two values of the initial drug loading in two values of pH. It was determined a

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significant pH effect on the rate of drug release from the nanoparticles formulation. Numerical simulation of the fractional IMC release from the considered nano- carrier's solution was performed in pH = 4.5 at both initial drugs loading.

The presented mathematical model and numerical procedure can be used as an effective simulation tool in a future design of nanoparticles of the considered type.

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