Research Paper

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Modelling of 3-N Butylphthalide Release Frompeg – Lipidnanoparticles Used for Brain Ischameia Therapy

Pharmaceutical science

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ABSTRACT

Numerical modeling of 3-NButylphthalide release from polymersome lipid nanoparticles at pH 7.4 phosphate-buffered saline (as dissolution media) is performed. The experimental data obtained in vitro for the drug release measured by anultraviolet spectrophotometer (Ying-mei Lu et al., 2014) is used for validating the presented model. A very good correspondence between the available experimental data and the numerical results is evaluated for the considered two types of drug loaded polyethylene glycol (PEG) lipid nanoparticles. A numerical simulation of drugsrelease is studied within a period of 24 hours. It is established that the prediction of 3-NButylphthalide release can be successfully realized using the data within the first 6 hours.

Introduction

The search for the neuroprotective agents for acute ischemic stroke has been frustrating and not yet yielded promising results for the last two decades (Patel R. et al., 2013).

A strategy is needed to overcome the conventional blood-brain barrier by developing a highly efficient delivery system specifically targeting the brain (Neuwelt. E. et al., 2008).

A promising delivery system for brain disease could be a suitable nanoparticles solution. Recently Ying-mei Lu et al. (2014) realized their hypothesis that PEG-lipid nanoparticles (PLNs) containing the 3-n Butylphthalide (dl-NBP) can be successfully used for treating brain ischemia *in vivo*. They reported that Fas ligand antibody conjugated PEG-lipid nanoparticles can be a key component of an immunoreactive response loop by recruiting microglia to an injured region for compensatory repair or tissue remodeling (Ying-mei Lu et al., 2012).

In vitro drug release at pH 7.4 phosphate-buffered saline (PBS) has been used as dissolution media. The dl-NBP lipid loaded nanoparticles solution (6 ml) hasbeen put into a plastic tube containing 30 ml PBS solution. The drug release in the solution has been determined by an ultraviolet spectrophotometer incomparison to the standard comparisoncurve (Ying-mei Lu et al., 2014).

Recently two mathematical models of indomethacin release from polymersome nanoparticles (micellar and vesicular) nanoparticles were proposed taking into account the predominant mechanisms of drug liberation.They were validated on the basis of available experimental data and were used for analyzing the effect of temperature, pH and ethanol content (Michailova V. et al., 2010; Blagoeva R. et al., 2012; Blagoeva, R. et al., 2014).

The aim of the present paper is to offer an appropriate approach to numerical modeling of the release of dl-NBP from lipid loaded nanoparticles solution on the basis of an *in vitro* experiment.

Model of drug release

The model of drug release was proposed under the assumptions (Blagoeva et al., 2012):

(1) The main physicochemical process controllingdl-NBP release isovercoming the polymer-drug interaction in the micellar PLNs;
(2) The diffusion of the free drug in the dissolution mediumis neglected;
(3) The concentrations of the free drug and the bound one are uniformly distributed in the plastic container;

The model equation of the considered physicochemical process was offered as follows (Blagoeva et al., 2014):

$$(1)\ M_b(t) = M_{b0}\left(1 - \frac{1}{(1+at)^{3/2}}\right),$$

where M_b and M_{b0} are the current value of the decreasing mass of the bound drug within the container and its initial value. The model parameter *a* isthe rate constant referred to overcoming the interaction between the polymer and the embedded drug in the nanoparticles.

The modelrate parameter*a* can be numerically evaluated fitting the equations(1) to the experimental data for fractional drug release from NPs assembly. In order to evaluate the goodness of fit the determination coefficient is calculated as follows:

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

where R^n_{arithm} is the arithmetic mean of the experimental data of the considered fractional drug release.

Model validation and numerical simulation

An *in vitro* test for dl-NBP release at pH 7.4 phosphate-buffered saline as dissolution media is performed. Two types of drug loaded PEG-lipid nanoparticles are used. The current dl-NBP concentration is determined by an ultraviolet spectrophotometer in comparison to the standard curve (Ying-mei Lu et al., 2014).

The model equation of drug release has been validated for two cases: dl-NBP loaded nanoparticles and antibody modified dl-NBP loaded nanoparticles.

Figs. 1-2 represent model fitting to the experimental data obtained for each of the both types of PLNs.

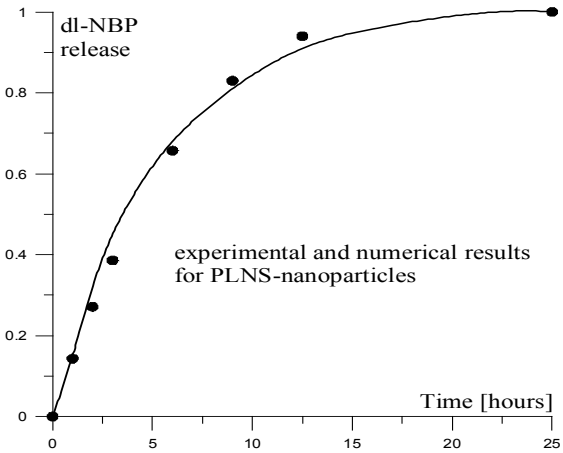

Fig.1 Fitting the model curve to the experimental data for PLNs

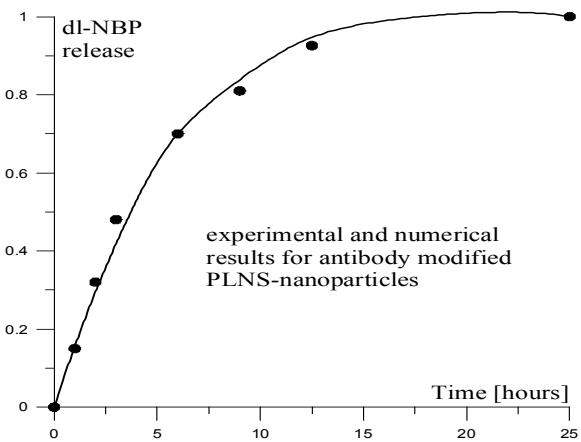

Fig.2 Fitting the model curve to the experimental data for modified PLNs

The following values of the rate parameter *a*are obtained: $a = 0.05\ s^{-1}$, $a = 0.055 s^{-1}$ at , respectively. The drug release profiles show a bilinear behavior in the period of 24 hours (a rapid increase up to 9 hours, followed by retarded liberation). Significant differences in the release rate are not observed for both cases.

It would be useful and less expensive to evaluate the rate parameter on the basis of the data within the first 6 hours in order to extrapolate the drug release under the obtained value of *a* within a longer period of time.

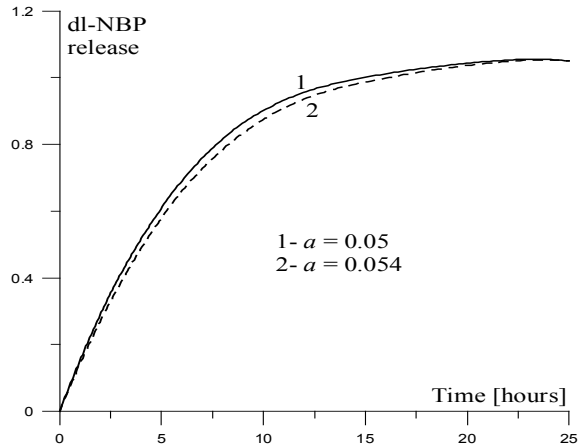

Fig.3 Numericalsimulation of drug releasefor two data sets

Fig.3 presents the comparison of the numerical curves obtained for dl-NBP loaded nanoparticles at two different data sets (6 hours, $a = 0.054 s^{-1}$ and 24 hours, $a = 0.05\ s^{-1}$, respectively).

A similar numerical calculation performed in the case of antibody modified dl-NBP loaded nanoparticles demonstrates an almost full coincidence.

Conclusion

The release of 3-n Butylphthalide from PEG-lipid micellar nanoparticles and Fas ligand antibody conjugated ones, used for therapy of brain ischemia, has been numerically studied.

An appropriate mathematical model describing the drug release kinetics has been offered. The main physicochemical process, controllingdl-NBP release,isovercoming the polymer-drug interaction in the micellar PLNs.

The model is validated on the basis of drug release test for pH 7.4 phosphate-buffered The presented approach to mathematical modeling can be used as a cheap simulation tool in a future design of different nanoparticles solutions.

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