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A new mathematical approach to predict the actual drug release from hydrogels

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ABSTRACT

In the present study, we have developed a mathematical model of drug release from a film of highly swellable gelatin based hydrogel mixed with graphene. The model considers the hydrogel volume expansion because of the swelling as well as the non-linear concentration dependence of the diffusion coefficients for the solvent and the drug. An additionl term is considered for the drug diffusion coefficient enabling the model to predict the drug maximum release from the hydrogel. The model parameters are estimated by genetic algorithem and the model resutls are validated using data sets obtained from experiments on Zoledronic acid, the model drug, loaded hydrogel samples made from several weigth ratios of gelatin to graphene crosslinked with different amounts of glutaraldehyde. The model is further developed to mathematically predict the drug conrolled release into *in vivo* environment and the impact of several factors influencing the release rate into the surrounding environment is investigated.

1. Introduction

Developing new therapeutic biomolecules have been widely pursued in many research projects within the past few decades (Convertino et al., 2016; Goole and Amighi, 2016; Bahreyni et al., 2017). In spite of the achievements in pharmacology in terms of drug development for various diseases, efficient delivery of the drugs to the targeted organs at their effective concentration is still a challenging topic in pharmaceutical sciences (Singh et al., 2016; Joseph et al., 2017). Targeted delivery and controlled release of various drugs using novel delivery systems are emerging topics in pharmaceutical sciences assisting researchers to maximize the therapeutic efficiency with minimal drug usage (Kamaly et al., 2016; Esmaeili and Singh, 2017; Lei et al., 2016; Park, 2014).

Various drug delivery systems (DDS) have been designed so far among which hydrogel-based DDS has received remarkable attentions in controlled release delivery (Vashist et al., 2014; Peppas and Van Blarcom, 2016; Annabi et al., 2014; Jensen et al., 2016). Hydrogels are three-dimensional (3D) cross-linked networks capable of keeping a large amount of water while staying insoluble in aqueous solution (Deng et al., 2013; Gaharwar et al., 2014). Latest studies on the developments of hydrogel-based DDS have focused on reducing the cytotoxicity, improving the mechanical properties and enhancing the release properties of the hydrogels (Vashist et al., 2014; Munoz et al., 2017). Hydrogel-based DDS can be formed from either cross-linking of co/homopolymers or polymerization of monofunctional molecules and cross-linking with multifunctional monomers simultaneously (Van Kampen, 2016).

Due to the physiological limitations associated with *in vivo* experimentation, precise evaluation of various controlled release DDS is very difficult, if not impossible (Peppas and Narasimhan, 2014). On the other hand, high expenses of in vitro and possible *in vivo* experimentaions limit the number of conducted experiments for DDS investigations (Park, 2014; Peppas and Narasimhan, 2014). An alternative cost effective approch assisting the researchers to minimize the number of required experiments for DDS evaluation is mathematical modeling. It provides predictions of DDS mechanism of action in computer environment without any budgetary limitations.

Many studies have focused on the mathematical modeling of the drug release from hydrogels each of which has a number of assumptions. Juncu et al. (Juncu et al., 2016) proposed a model for controlled release system that ignores the polymer expansion. They considered the dissolution of the polymer and formulated the drug release as the solvent diffuses into the non-swellable polymer. Other researchers such as Peppas et al. (Peppas et al., 1980) and Cohen et al. (Cohen and Erneux, 1988) also suggested a model for swelling-controlled release systems with no inclusion of polymer dissolution. Wu (Wu et al., 2005) suggested a two-dimensional system with one moving interface with no polymer glassy/rubbery interface transition consideration. Lin et al.

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(Lin and Peng, 2005) and Hsieh (Hsieh, 2012) proposed a controlled drug release model for a swellable spherical DDS with polymer glassy/rubbery interface moving boundary.

In this paper, we propose a mathematical model based on Lin et al. and Hsieh model with the difference that a non-linear concentration dependence of the diffusion coefficients for both the drug and the solvent is used. In addition, a new diffusion coefficient form for the drug is proposed. It is assumed that diffusion coefficient of the drug follows an exponential function of the drug concentration in addition to the concentration of the solvent. This provides a mathematical explanation of partial drug release from the carriers and would help in mathematical modeling of the maximum drug release from the DDS. The model parameters are estimated by genetic algorithm optimization method using the data obtained from experiments performed on a drug loaded gelatin-graphene hydrogel. Finally, using the Manga (Manga and Jha, 2017) method, the pharmacokinetic of the released drug from the designed DDS is mathematically modelled and the drug realsese, metabolism and elimination rates in the presumed surrounding plasma and body tissue is predicted.

2. Materials and methods

2.1. Reagents

All chemicals and reagents used for hydrogel samples preparation including graphene nanoplatelets (Grade C, XG Sciences), gelatin (Microbiology, Merck) and glutaraldehyde (Merck) were of analytical grade from mercantile companies without any further purification. Zoledronic acid (Novartis) was used as the drug model. All other chemicals were used as received in their analytical purity.

2.2. Synthesis of gelatin/graphene nanoplatelets (GNPs) hydrogels

To prepare the hydrogel, GNPs were dispersed in distilled water and sonicated for 30 min. Then, gelatin in weight ratios indicated in Table 1 was added to the mixture to prepare 9 solutions. All solutions were stirred for 45 min and sonicated for 15 min to complete homogenization. Diluted glutaraldehyde (GA) solution in different weight ratios was added dropwise into the stirring gelatin-GNPs solutions. The solutions were poured into plastic molds and then, were kept overnight at − 20 °C. After cross-linking, the gelatin-GNPs hydrogels were submerged in distilled water at 25 °C for 48 h to let the unreacted chemicals leach out during which the deionized water was replaced every 16 h. Afterwards, all samples were freeze dried for 48 h at − 70 °C.

To characterize the hydrogel samples, FTIR and SEM analyses were performed and their results for the first three samples are typically shown in the Supplementary data.

2.3. Hydrogel swelling experiment

Hydrogel samples were soaked in phosphate-buffered saline (PBS) and were weighed at predetermined time intervals to measure the amount of absorbed solvent. Triplicate samples were used for each hydrogel indicated in Table 1 and the results were reported as the arithmetic means with standard deviation (SD) as the error bar. Therefore, nine sets of experimental data were obtained from the experiment performed on the hydrogels.

Table 1
GNPs to gelatin weight ratios versus GA amount for samples preparation.

Sample	GNPs/gelatin (w/w, %)	GA (m/v, %)
G1	0.5	0.5
G2	1.0	0.5
G3	2.5	0.5
G4	0.5	1.0
G5	1.0	1.0
G6	2.5	1.0
G7	0.5	5.0
G8	1.0	5.0
G9	2.5	5.0

2.4. In vitro drug release experiment

The release mechanism of zoledronic acid (ZA) from the hydrogel samples were investigated by soaking the samples in the PBS solution at 37 °C. The amount of ZA release from hydrogels was quantified by UV/Visible spectroscopy of the samples taken from the medium at predetermined time intervals. To simulate the perfect sink release conditions, the medium was replaced by fresh PBS after each sampling. The subsequent results were normalized with the primary amount of drug load in hydrogel samples. From this experiment performed on the hydrogels indicated in Table 1, another nine sets of experimental data were also obtained.

2.5. Mathematical modeling

The polymeric hydrogel film made from gelatin/GNPs is in its glassy state after being freeze dried. When the film is placed into an aqueous solution environment, the solution slowly begins to penetrate into the porous matrix. As the solution diffuses into the film, the outer portion of the polymer structure changes from the glassy state into the rubbery state. This transition, which is due to either polymer disentanglement or polymer chain relaxation, expands the volume of polymer rubbery region. Simultaneously, the drug entrapped in the glassy region starts diffusing out following this transition enabling the drug to move out of the whole polymeric film into the surrounding medium. Fig. 1 shows a schematic representation of the hydrogel film expansion due to the solution penetration into its structure. When the hydrogel is in an aqueous environment, it starts swelling and its external interface (S_2) begins to move outwards. On the other hand, diffusing the solution into the glassy polymer and turning it into rubbery state leads to the formation of an interface between the rubbery and glassy regions (S_1) which starts moving inwards.

The mathematical modeling of the drug release from the hydrogel comprises the mass balance equation (i.e. Fick's laws of diffusion) for each component over the rubbery region.

The equation describing diffusion of the solvent into the polymer is:

$$\frac{\partial c_s}{\partial t} = \frac{\partial}{\partial x}\left(D_s(c_s)\frac{\partial c_s}{\partial x}\right) \qquad S_1(t) < x < S_2(t) \tag{4}$$

The boundary conditions of Eq. (4) are:

$$c_s = c_{s.e} > c_s^* \qquad x = S_2(t) \tag{5}$$

$$D_s(c_s)\frac{\partial c_s}{\partial x} = -(c_s + K)\frac{dS_1}{dt} \qquad S_1(t) > 0 \qquad x = S_1(t)$$
$$\frac{\partial c_s}{\partial x} = 0 \qquad S_1(t) = 0 \qquad x = S_1(t) \tag{6}$$

The corresponding differential equation representing the drug diffusion is:

$$\frac{\partial c_A}{\partial t} = \frac{\partial}{\partial x}\left(D_A(c_s, c_A)\frac{\partial c_A}{\partial x}\right) \qquad S_1(t) < x < S_2(t) \tag{7}$$

Two types of boundary conditions can be considered for Eq. (7) at $x = S_2(t)$, the Dirichlet (or first-type) boundary condition and Robin (or third-type) boundary condition as follows:

Model 1 $$c_A = 0 \qquad x = S_2(t) \tag{8}$$

Model 2 $$D_A(c_s)\frac{\partial c_A}{\partial x} + P(c_A - c_p) = 0 \qquad x = S_2(t) \tag{9}$$