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Modeling of small-molecule release from crosslinked hydrogel microspheres: Effect of crosslinking and enzymatic degradation of hydrogel matrix

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ABSTRACT

A diffusion-based model describing the drug release from a charged hydrogel (gelatin) microsphere undergoing enzymatic degradation is presented. The model elucidates the effect of glutaraldehyde, a crosslinking agent, on the release profile in terms of the initial drug distribution, diffusivity of the drug, degradation rate of gelatin and its ability to form polyionic complex with the drug. The model was validated by comparing with *in vitro* release of trypan blue, an acidic model drug, from basic gelatin microspheres. While drug release was not a simple function of glutaraldehyde concentration, the effective diffusivity was found to be inversely proportional to glutaraldehyde concentration in the form of a power function when the initial drug distribution was taken into consideration. For these reasons, the present model can accurately predict drug release with no adjustable parameters, given the collagenase concentration. The present model may help design certain release scenarios from biodegradable charged hydrogels for the oppositely charged drugs and biomolecules.

1. Introduction

Charged hydrogel microspheres possess great potential for the delivery of oppositely charged biomolecules. Among all, gelatin has attracted much attention in many biomedical applications because of its excellent biocompatibility and its degradability to non-toxic products (Iwanaga et al., 2003; Mitsunaga et al., 2005). The isoelectric point of gelatin derived from collagen can be modified during fabrication (Tabata and Ikada, 1998). This unique aspect allows one to design and form a polyionic complex between gelatin and oppositely charged biomolecules. For these reasons, gelatin is frequently utilized in tissue engineering and gene therapy in various forms, such as disks, sponges and microparticles (Yamamoto et al., 2001; Okamoto et al., 2004; Kasper et al., 2005; Patel et al., 2008; Zarana et al., 2008). For example, the release profiles of ^{125}I-labeled basic fibroblast growth factor (bFGF), transforming growth factor-β1 (TGF-β1), bone morphogenetic protein-2 (BMP-2) and vascular endothelial growth factor (VEGF) from acidic or basic gelatin disks or microparticles have been studied (Yamamoto et al., 2001; Zarana et al., 2008). Gelatin microparticles were also employed to increase transfection probability at the delivery site by the controlled release of plasmid DNA *in vivo* (Kasper et al., 2005). In spite of this, little comprehensive quantitative analysis has been available to date that may help design the release profiles of gelatin as a drug carrier.

Mladenovska et al. assumed a biexponential function for the release from hydrogel devices based on the frequently observed biphasic release pattern for hydrogel (Mladenovska et al., 2001). Although the presumed biexponential function does simplify the mathematic formulation, the fundamental mechanisms responsible for the biphasic release pattern have not been elucidated. It is also known that not all the release profiles follow the biphasic pattern (Holland et al., 2004; Young et al., 2005).

Mathematical modeling is important to systematically explore and design potentially new devices for controlled release. In general, release of a water soluble active agent from degradable matrix devices is determined by a interrelated action of the following processes (Tzafriri, 2000): (a) diffusion of the external aqueous medium and degradation catalyst, i.e., enzyme into the device, (b) relaxation of the polymer matrix, including swelling, (c) liberation of the immobilized active agent due to hydrolytic or enzymatic degradation of the matrix, (d) diffusion of the mobile active agent from the bulk of the matrix to its surface, and (e) diffusion across the boundary layer. These processes are reciprocal, which makes general mathematical modeling a formidable task. As a result, phenomenological models which account for only the release-limiting factors have been used.

Swelling or hydration was often considered to predict the release from hydrogel devices to account for hydrolysis. In this case the resulting models would depend on the swelling inter-

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face number (Kim et al., 1992), S_w, which was empirically adjusted for the release process (Jeong et al., 2000; Siepmann and Peppas, 2001). Attempts were also made to take into account viscoelastic response and diffusion during polymer swelling (Brazel and Peppas, 2000). Although some of these models produced results in agreement with experimental data, they required many adjustable parameters (Hopfenberg and Frisch, 1969). Recently, some unified mathematical models were proposed to predict drug release from biodegradable (Lemaire et al., 2003) or eroding polymer matrices with all parameters obtained prior to the controlled release experiments (Rothstein et al., 2009). These models, however, were not applicable to charged hydrogel due to the specific assumption of the polymer degradation kinetics, exclusion of the enzymatic effect or attraction between drug and polymer matrix in the model. Tzafriri (2000) reported a drug release model from polymer matrices entirely or partially due to the enzymatic polymer degradation but no effects of enzyme and crosslinking agent concentrations were included in the model. Therefore, to the best of our knowledge, no mathematical model proposed to date is suitable to predict drug release from gelatin microspheres while accounting for the processing parameters.

Herein, we propose a mathematical model to account for the release of a water-soluble charged agent from crosslinked hydrogel microspheres, incorporating polymer degradation and specific drug distribution as a function of the crosslinking agent concentration. Specifically, the current model combines a diffusion–reaction equation, which accounts for polyionic complex formation between drug and crosslinked hydrogel matrix, with polymer degradation and drug distribution dictated by the crosslinking agent concentration. Uniform basic gelatin microspheres (GMS) of 100-μm diameter (wet) were used for the study. The effective diffusivities were determined by fitting Fick's diffusion model to *in vitro* release of trypan blue, an acidic model drug, from GMS in the absence of collagenase. The relationship between the enzymatic degradation rate of GMS and the concentration of glutaraldehyde (GA), a crosslinking agent, was obtained by fitting the proposed model to the *in vitro* release data from GMS crosslinked with the GA concentrations of 0.125%, 0.375% and 0.875% (v/v) in phosphate buffered saline solution (PBS) in the presence of collagenase 1A. Thus-obtained degradation parameter was then used for the present model to predict the release of trypan blue from GMS crosslinked with GA concentrations of 0.25% and 0.625% (v/v).

2. Materials and methods

2.1. Materials

Gelatin (IEP = 9.0, MW = 100 kDa) was provided by Nitta Gelatin Co., Osaka, Japan. Span 85 (Sigma–Aldrich), hexane (Fluka), acetone (Sigma–Aldrich), canola oil (Schnucks), 25% glutaraldehyde (GTA) (Sigma–Aldrich), trypan blue (Sigma–Aldrich) and phosphate buffered saline (PBS) (Sigma–Aldrich) and collagenase 1A (Sigma–Aldrich) were purchased from Sigma–Aldrich, USA. Alexa fluor 430 was purchased from Invitrogen. All materials were used as obtained.

2.2. Microsphere fabrication

Uniform GMS were prepared by the method developed by us and reported elsewhere (Choy et al., 2007). The GMS were crosslinked in a 0.125% (v/v) GA solution at 4 °C for 24 h, and transferred to a glycine solution at room temperature to deactivate the remaining glutaraldehyde (Tabata et al., 1999). The resulting spheres were then washed with DI water and lyophilized. This was repeated for the 0.25, 0.375, 0.625 and 0.875% (v/v) GA solutions.

2.3. In vitro drug release

GMS were impregnated with a drug, trypan blue or Alexa fluor 430, by adding a 0.1% (w/v) aqueous solution in a ratio of 5 μl/mg and cured for 2 h at room temperature. The drug-loaded GMS were incubated in two release media (1.5 ml for each sample), prepared using phosphate buffered saline (PBS) with and without an enzyme (collagenase 1A, 373 ng/ml), at 37 °C for 18 days with continuous agitation using a Thermo Scientific tube shaker/rotator at a rotation speed of 8 rpm. The supernatant was sampled at scheduled times and its optical absorption (620 nm) was measured spectrophotometrically using a Gilford Response Spectrometer.

2.4. Intraparticle drug distribution

The distribution of Alexa Fluor 430 within the GMS was obtained by measuring the fluorescence intensity distribution (Excitation at 430 nm and Emission at 540 nm) at the equatorial cross-section using a confocal laser scanning microscope (CLSM, Olympus Fluoview FV 300 Laser Scanning Biologic Microscope). The CLSM images were taken immediately after drug loading and after 15 days to remove all the mobile drug in PBS without collagenase, to account for the distributions of the total drug and the ionically attached drug, respectively (Choy et al., 2008). The images obtained were converted into intensity plots and radial distributions by averaging the intensity at a given radial distance from the GMS center. The resulting intensity plots were normalized so that the amount of the drug inside the microsphere corresponded to that observed in the release experiment. The mobile drug was assessed by subtracting the distribution of the immobilized drug from the initial drug distribution.

3. Theory and mathematical model

3.1. Release paradigm and case definition

During the process of loading a finite amount of drug via hydration of the polymer matrix, drug molecules move inwards by diffusion and capillary forces, forming a polyionic complex with gelatin or remaining free inside the microsphere (Young et al., 2005). If the drug loading amount is in excess of the amount that gelatin can bind, this loading process results in two pools of drug within the microspheres: one pool is mobile drug which is free to diffuse and the other pool is immobilized drug which is immobilized by the gelatin matrix and is released only upon matrix degradation. The initial distribution of mobile and immobilized drug is affected by many factors including crosslinking agent concentration, microsphere size, and isoelectric point of gelatin. In the present model, we incorporate the initial distribution of mobile or immobilized drug obtained by converting the fluorescence intensity distribution of drug at the equatorial cross-section of the GMS to drug distribution. By doing so, we introduce in the model the heterogeneous binding strength of crosslinked GMS.

When dispersing GMS in a buffer solution, water or buffer begins to hydrate the matrix and mobile drug starts to diffuse while immobilized drug remains stationary within the microsphere. Hydration in GMS is much faster than the release and therefore not a rate-limiting process. Due to the fast hydration, we assume the matrix geometry to remain unchanged during the release process. This assumption of invariant geometry is likely to hold since gelatin degradation is a bulk degradation process (Gabriel et al., 2003). In addition, it can be assumed that the surface of the microspheres is most resistant to erosion and that the sphere remains the same

size until most of the drug has been released, which is valid for most crosslinked gelatin where the crosslinking agent is introduced from outside via absorption (Choy et al., 2008).

With the gelatin degradation catalyzed by collagenase, both mobile and immobilized drug are released. The degradation depends on both the crosslinking density of gelatin and the enzyme activity. A single diffusion coefficient is used in the model with which we implicitly assume that the degradation-liberated drug behaves similarly to the mobile drug and that the heterogeneous crosslinking density within the GMS introduces negligible changes in diffusivity throughout the microsphere. This is justified by the fact that the diffusivity increased only 1.5 times in our experiment when the crosslinking agent concentration increased sevenfold. The diffusion coefficient is also hypothesized to be time-invariant during the particle degradation. This assumption is valid if most of the drug is released prior to disintegration of GMS or significant matrix degradation, leading to nearly invariant polymer density.

3.2. Model development

Drug release is governed by a diffusion–reaction equation with a source term arising from the liberation of immobilized drug, which is originally stationary due to the polyionic attraction between the drug and the polymer. Therefore,

$$\frac{\partial C}{\partial t} = \frac{1}{r^2}\left\{\frac{\partial}{\partial r}\left(D\cdot r^2\frac{\partial C}{\partial r}\right)\right\} + \frac{\partial C_s}{\partial t} \tag{1}$$

where C is the time-dependent concentration of mobile drug which is free to diffuse, C_s is the time-dependent concentration of immobilized drug, and D is the diffusion coefficient of the drug through the polymer matrix. The equation is solved using the following boundary conditions:

$$\left.\frac{\partial C}{\partial r}\right|_{r=0} = 0 \tag{2}$$

$$C|_{r=R} = 0 \tag{3}$$

where R is the radius of the GMS. The boundary condition Eq. (3) corresponds to the assumption of an infinite sink: that is, the rate at which the drug diffuses out to the surface of the microsphere is equal to the rate at which the drug leaves the microsphere. Hence there is no accumulation of the drug on the surface (Kanjickal and Lopina, 2004). This boundary condition might be used to describe *in vivo* drug release when GMS are administered into a well-mixed bulk solution, as in the case of intravenous injection. The boundary condition might require an adjustment according to the specific application which might lead to a numerical, rather than analytical, solution. In this case, the complexity will increase but the model might still predict the release profiles with an adjustment of the boundary condition according to the actual *in vivo* situation. The initial condition is:

$$C(r)|_{t=0} = C_{m0}(r) \tag{4}$$

where $[C_{m0}(r)]$ is the distribution of the drug which initially does not form ionic-complex with the gelatin matrix. This drug distribution within gelatin microspheres was obtained as described in Section 2.4.

The diffusion constants could be obtained by modeling the first three-day drug release from gelatin microspheres in PBS solution in the absence of enzymatic degradation of polymer matrix. In this case, the second term on the right-hand side of Eq. (1) becomes zero.

In drug release accompanying polymer degradation, the liberation rate of the immobilized drug participating in the diffusion process is dictated by the mechanism of enzymatic polymer degradation. In general, enzymatically catalyzed polymer degradation reaction is described by the Michaelis–Menten equation (Lenz, 1993; Tzafriri, 2000; Berg et al., 2006) as shown in Eqs. (5)–(7) where K_M, represents the Michaelis–Menten constant, k kinetic parameter, E for enzyme, S for polymer and P for final product. Usually V_{max} and K_M are constants for a given enzyme–substrate pair.

$$\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k_2} \mathrm{E} + \mathrm{P} \tag{5}$$

$$\frac{\partial[\mathrm{S}]}{\partial t} = -k_2[\mathrm{E}]_0\frac{[\mathrm{S}]}{K_M + [\mathrm{S}]} = -\frac{V_{max}[\mathrm{S}]}{K_M + [\mathrm{S}]} \tag{6}$$

$$K_M = \frac{k_{-1} + k_2}{k_1} \tag{7}$$

It has been known that collagenase is efficient in catalyzing hydrolysis of collagen with k_2/K_M up to $10^6\,M^{-1}\,S^{-1}$ (Welgus et al., 1981), when the most efficient enzyme reaches a range of 10^8–$10^{10}\,M^{-1}\,S^{-1}$ (perfect enzyme) (Stroppolo et al., 2001). Since gelatin is more susceptible to degradation than collagen, we assume that collagenase catalyzes a reaction each time the enzyme molecule encounters gelatin molecule and that an upper theoretical limit has thus reached for the efficiency, which suggests the limit $[\mathrm{S}] \ll K_M$ and very little ES complex is formed, i.e. $[\mathrm{E}]_0 \approx [\mathrm{E}]$. By applying the limit to Eq. (6), it reduces to

$$\frac{\partial[\mathrm{S}]}{\partial t} = -\mu[\mathrm{S}], \quad \mu = \frac{V_{max}}{K_M} \tag{8}$$

Eq. (8) suggests that decomposition rate of the polymer matrix is a function of polymer concentration characterized by parameter μ which should be a function of glutaraldehyde concentration and enzyme concentration and but independent of time if the total enzyme concentration does not change over time. In the *in vitro* experiment performed in the present work, the collagenase concentration was fixed to 373 ng/ml which mimics the synovial fluid of a patient with osteoarthritis.

Seeing that immobilization of drug molecules in GMS is ascribable to the polyionic attraction between each other, the liberation rate of immobilized drug is assumed to be proportional to the polymer degradation rate and that the immobilizing capacity of polymer substrate σ may be treated as a constant, $C_i = \sigma S$, where C_i denotes the concentration of immobilized drug; thus, the liberation rate of immobilized drug can be derived from Eq. (8)

$$C_i(t) = C_{i0}e^{-\mu t} \tag{9}$$

where C_{i0} is the initial distribution of immobilized drug concentration.

Note that the relationship between C_i and the concentration of liberated drug C_s is $C_s = C_{i0} - C_i$ and, therefore, we can also obtain

$$\frac{\partial C_s}{\partial t} = \mu\cdot C_{i0}e^{-\mu t} \tag{10}$$

Substituting Eq. (10) into Eq. (1), the diffusion equation for small molecule release from a gelatin microsphere degraded by enzyme becomes

$$\frac{\partial C}{\partial t} = \frac{1}{r^2}\left\{\frac{\partial}{\partial r}\left(D\cdot r^2\frac{\partial C}{\partial r}\right)\right\} + \mu\cdot C_{i0}e^{-\mu t} \tag{11}$$

This model accounts for the drug release mediated by both the initially mobile drug and the immobile drug liberated during the polymer-degradation process. The nonuniform distributions of initially mobile and immobile drugs are also included in this model via the initial conditions, Eqs. (4) and (10).

The relationship between the degradation-related release constant μ and the glutaraldehyde concentration is now required for the release to be determined by Eq. (11) with no adjustable parameters. To achieve this, the parameter μ was first chosen to minimize

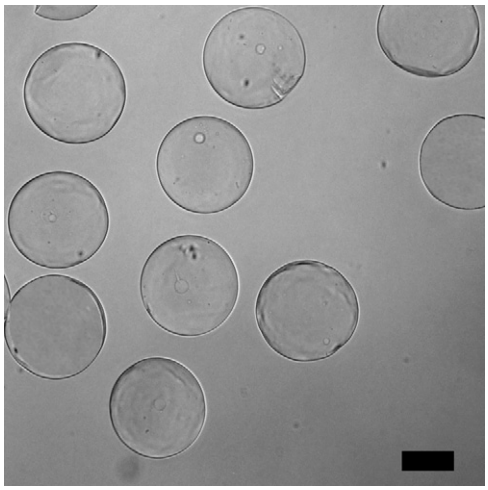

Fig. 1. Optical micrograph of crosslinked GMS in wet state. The scale bar is 50 μm.

the sum of squares of the differences between the experimental release data and the solution of Eq. (11) for three GA concentrations: 0.125%, 0.375% and 0.875% (v/v). Subsequently, a numerical equation relating μ and the glutaraldehyde concentration could be established.

4. Results and discussion

4.1. Microsphere fabrication

Fig. 1 shows an optical micrograph of the crosslinked GMS used in this study, showing the size uniformity and sphericity of wet GMS of 100-μm diameter. Considering that the actual drug release takes place in aqueous media, it is important to retain the uniformity of the GMS when swollen so that the uncertainties in the GMS size may be eliminated.

4.2. Intraparticle drug distribution

We reported previously that the GA concentration affected the initial distributions of both mobile and immobilized drug in GMS (Choy et al., 2008). The present model explicitly includes initially nonuniform distributions of such mobile and immobilized drugs within GMS as the initial conditions for the mathematical model (Eqs. (4) and (10)).

Fig. 2(A) shows the total drug distribution in the GMS, both mobile and immobilized drug, indicating that the total drug concentration was higher at the center for the sample with 0.125% GA but slightly lower for the ones with 0.375 and 0.875% GA. This could be attributed to the suppressed drug diffusion resulting from the smaller pores and/or fewer number of pores of the highly crosslinked GMS (Choy et al., 2008).

Fig. 2(B) shows the distributions of the immobilized drug which were normalized to its % amount obtained from the release profiles, exhibiting a higher concentration at the center of GMS in all cases. This may be explained by the inhomogeneous crosslinking density of gelatin, which is higher at the surface and lower near the center. Different affinities of crosslinked gelatin to drug are suggested by the decrease of zeta potential of basic gelatin as the GA concentration increases (Choy et al., 2008), giving rise to weaker interaction with acidic agent. The extent of inhomogeneous crosslinking would become more significant at a higher GA concentration due to the fact that crosslinking starts from the surface, impeding the inward diffusion of GA.

The initial mobile drug distribution was obtained by subtracting the immobilized drug distribution from the total drug distribution. The mobile drug distribution was determined by drug diffusion and polyionic attraction between drug and gelatin during the drug loading. The mobile drug was released from GMS by simple diffusion most likely contributing to the initial burst in the release profile. Therefore, one might reduce the initial burst by lowering the amount of drug diffusively loaded into GMS, which can be achieved by decreasing either the concentration or the volume of the drug solution with all other parameters fixed.

4.3. Model results

4.3.1. Diffusion constants

The diffusion constants were obtained by solving the diffusion equation Eq. (1) with the initial mobile drug distributions in a manner to accurately model the first three-day drug releases by pure diffusion, as described in the foregoing. The diffusion constants were chosen to minimize the *R*-squared value. The resulting drug release profiles predicted by the model are compared with the experimental data in Fig. 3(A) in overall good agreement. The semi-empirically determined diffusion constants and the fitting curve using a power function with an *R*-squared value of 0.99 are plotted in Fig. 3(B), which are seen to generally decrease with increasing concentration of GA. This may be an indication of higher GMS crosslinking giving rise to higher diffusion barrier because crosslinking agent shortens the polymer chains between the crosslinking sites leading to reduced free volume accessible by

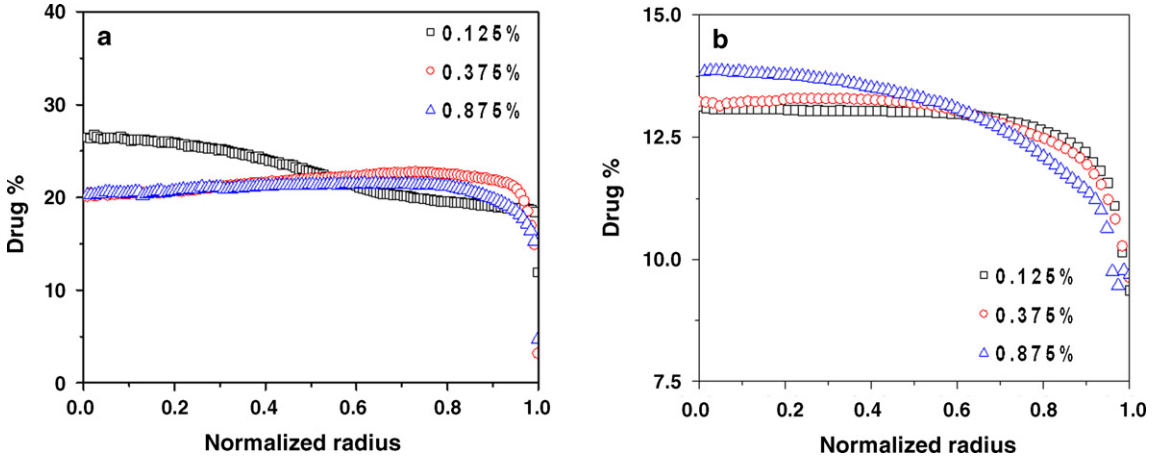

Fig. 2. Initial distributions of total drug (A) and immobilized drug (B) within GMS treated with GA of different concentrations obtained from analysis of CLSM images.

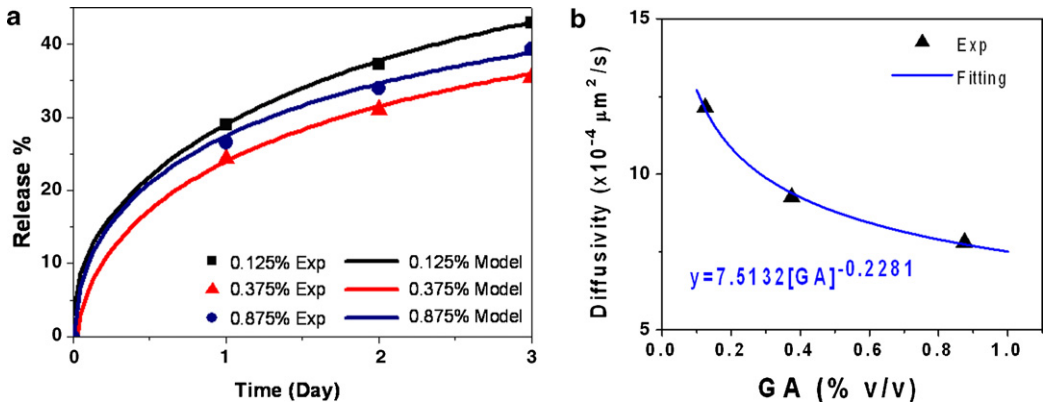

Fig. 3. (A) *In vitro* trypan blue releases from GMS with no enzymatic degradation treated with GA concentration of 0.125%, 0.375%, and 0.875% (v/v) (labeled as E) and their respective model results (labeled M) with corresponding diffusivities. (B) Diffusion constants in the model as a function of GA concentration and its fitting curve with a *R*-squared value of 0.89.

the penetrating medium. It has been seen in Fig. 3(A), however, that the drug release rates from GMS first fall in the absence of matrix degradation, then rebound when crosslinking agent concentration exceeds 0.375% (v/v). Although constants for the fitting curve might vary as different drugs are employed because of drug mobility, the trend is likely to remain the same producing a good estimation in the case of different drugs.

Fig. 3(A) shows that in the absence of matrix degradation, the drug release rates, as GA concentration increases, first fall then rebound when the concentration exceeds 0.375% (v/v). These results, in turn, may imply that, without taking into consideration of other effects, the effective diffusion constants will not be a monotonous function of GA concentration. This observation was considered as evidence that a simple diffusion model was not suitable for the release phenomenon in previous work by others (Ruiz et al., 2000). However, here we show that by incorporating accurate drug distribution, diffusivity of a diffusion model inversely depends on GA concentration suggesting the importance of the present work incorporating the drug distribution inside GMS to correctly account for the drug release behavior.

4.3.2. *Drug release from gelatin microspheres undergoing degradation*

The degradation-related release constant μ as a function of GA concentration, that was needed to close the mathematical model, was derived by first using it as a fitting parameter in Eq. (11) to calculate the drug release from GMS, crosslinked at GA concentrations of 0.125%, 0.375% and 0.875% (v/v). The fitting consisted of minimizing the sum of squares of deviations of the theoretical release profiles from the experimental data. The diffusivities used were obtained as previously mentioned. Fig. 4 shows the predictions of the model and the experimental results in excellent agreement. To include the effect of crosslinking agent concentration in the model, an empirical exponential decay function fit was used to relate the degradation constant μ to GA concentration:

$$\mu = 0.36(1 + 0.1 \cdot \exp^{(-14.29 \times C_{GA})}) \quad (12)$$

where C_{GA} is the volume percent concentration of GA used to crosslink GMS. This dependence was specifically chosen as it gave the best fit to the data ($R^2 > 0.99$). That μ decreases slowly as GA concentration rises suggests a saturation effect of GA concentration in impeding the release. This phenomenon may be elucidated by the crosslinking process facilitated by diffusion and the stronger diffusion barrier resulting from higher GA concentration, as described in Section 4.2. According to Michaelis–Menten equation (Eqs. (5)–(7)), the degradation constant μ is proportional to the enzyme concentration or its square due to anomalous diffusive motion of the enzyme when the gelatin matrix is large (Fadda et al., 2003). Therefore, Eq. (12) could be modified to make it applicable to other enzyme concentration.

With the degradation-related release constant μ predicted by Eq. (12), the diffusion–reaction equation Eq. (11) was solved to predict the release from GMS treated with 0.25% and 0.625% (v/v) GA. The comparison between model predictions and experimental data is shown in Fig. 5. A good agreement is seen between the model and the experiment, which may be attributed to the fact that the model accounts for the nonuniform drug distribution, the drug-binding ability of the polymer matrix and the polymer degradation rate which are all influenced by the crosslinking agent concentration. Since the *in vitro* drug release experiment was carried out in a small vile (1.5 ml) with a low rotation speed, it is likely that the effect of the complex boundary condition for *in vivo* application might not be significant. Therefore, our model could be used to correctly predict drug release with or even without modification of the boundary conditions. The reasons for the discrepancy between the model prediction and experimental data may be as follows. First, some level of dissolution of GA-crosslinked GMS might take place in 37 °C aqueous solution further affecting the diffusion-mediated release behavior. Second, while the diffusivities used in the model were assumed to be constant within the microsphere throughout the release process, it is reasonable to anticipate some variation in the diffusion coefficient within the microsphere and during the drug release process as the polymer matrix degradation

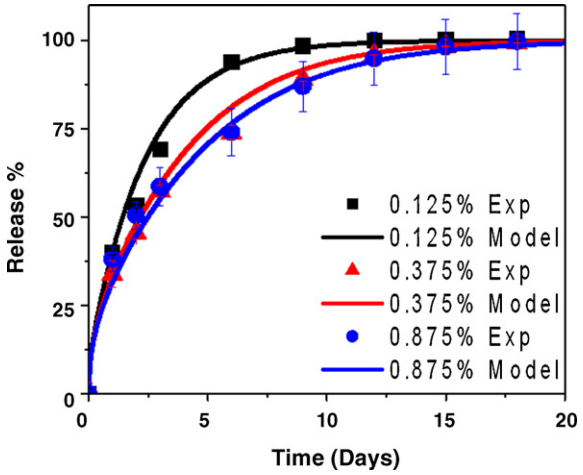

Fig. 4. Comparison between the model and *in vitro* trypan blue release from enzymatically degrading GMS crosslinked with GA of concentration of 0.125%, 0.375% and 0.875% with degradation parameter 1, 0.38 and 0.36 respectively.

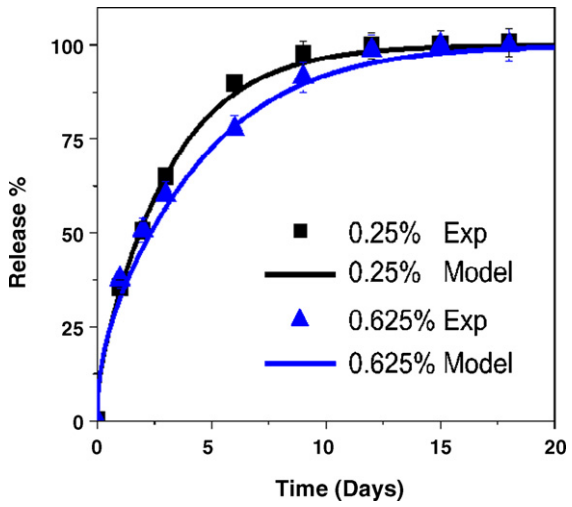

Fig. 5. Comparison between model predictions and *in vitro* drug release from enzymatically degrading GMS crosslinked with GA concentration of 0.25% and 0.625%.

progresses. Also, the degradation-related constant μ was assumed to be independent of the locations inside the gelatin microspheres whereas the crosslinking density is a function of radius. In this model, the effect of heterogeneous crosslinking density was considered to affect only the ability of the gelatin matrix to bind with the drug and, therefore, the resulting drug distribution within the microsphere. However, since the predictions of the present model are in reasonable agreement with the experimental data, it may be concluded that the dissolution of GMS in 37 °C solution and radial variation and time-dependence of the diffusion coefficient resulting from heterogeneous crosslinking and degradation rate do not contribute significantly.

5. Conclusions

A mathematical model has been proposed to describe the release of an acidic drug from crosslinked basic gelatin microspheres, which is based on diffusion of the drug and enzymatic degradation (Michaelis–Menten kinetics) of the polymer matrix as a function of the crosslinker (GA) concentration. The model took into consideration the initial intraparticle distributions of the mobile and immobilized drug affected by the changes in GA concentration. Semi-empirically determined diffusion constants were employed in the model and were shown to be inversely proportional to GA concentration in the form of a power function in spite of the fact that the release rates were not a monotonously decreasing function of GA concentration. A relationship, Eq. (12), between the degradation-related release constant and the GA concentration was established which, when incorporated into the model, gave rise to predicted drug release in good agreement with the experimental data with no adjustable parameters. It may, therefore, be concluded that the present model can serve as a useful tool in predicting drug release from uniform gelatin microspheres and provide guidance in the design of certain drug release scenarios of practical importance.

Acknowledgments

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