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A model for predicting the permeation of dimethyl sulfoxide into articular cartilage, and its application to the liquidus-tracking method ☆

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ABSTRACT

Long-term storage of articular cartilage (AC) has excited great interest due to the practical surgical significance of this tissue. The liquidus-tracking (LT) method developed by Pegg et al. (2006) [29] for vitreous preservation of AC achieved reasonable survival of post-warming chondrocytes *in situ*, but the design of the entire procedure was more dependent on trial and error. Mathematical modeling would help to better understand the LT process, and thereby make possible improvements to attain higher cell survival. Mass transfer plays a dominant role in the LT process. In the present study, a diffusion model based on the free-volume theory and the Flory–Huggins thermodynamics theory was developed to predict the permeation of dimethyl sulfoxide (Me_2SO) into AC. A comparison between the predicted mean concentration of Me_2SO in the AC disc and the experimental data over wide temperature and concentration ranges [−30 to 37 °C, 10 to 64.5% (w/w)] shows that the developed model can accurately describe the permeation of Me_2SO into AC [coefficient of determination (R^2): 0.951–1.000, mean relative error (MRE): 0.8–12.8%]. With this model, the spatial and temporal distribution of Me_2SO in the AC disc during a loading/unloading process can be obtained. Application of the model to Pegg et al.'s LT procedure revealed that the liquidus line is virtually not followed for the center part of the AC disc. The presently developed model will be a useful tool in the analysis and design of the LT method for vitreous preservation of AC.

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Introduction

Articular cartilage (AC) is of great importance for normal joint function. Unlike other tissues, AC lesions generally do not heal, or heal only partially under certain physiological conditions [16]. Osteochondral allografting has been proved to be an effective method to treat osteochondral defects [11,31]. However, difficulties in successful preservation of AC have significantly limited the application of this kind of treatment. Vitrification is considered as the most promising approach for long-term storage of tissues [9,27,36]. Usually, vitrification of AC is accomplished by combination of a high concentration of cryoprotectant (CPA) cocktail and rapid cooling and warming to minimize nucleation and ice-crystal growth [6,13,24,35]. However, to achieve rapid cooling and warming is sometimes technically difficult, especially for bulky samples. Recently, Pegg et al. developed a novel method called "Liquidus-tracking" (LT) to vitrify AC discs using a single CPA – dimethyl sulfoxide (Me_2SO) [29]. In the LT method, the tissue remains above the freezing point of its aqueous phase at all times of addition and removal which assures no ice formation regardless of cooling or warming rate. Meanwhile, low temperature protect cells against the chemical toxicity of Me_2SO at high concentrations.

The LT method was demonstrated to be effective for ovine AC discs. To spread its application to AC discs of other species or other tissues, more work has to be done to better understand the mechanism of the method. The Me_2SO addition and removal steps adopted by Pegg et al. were possibly dependent on rich experience and trial-and-error test, for example, 30 min for each subzero loading and unloading step [29]. Although Pegg et al. measured the concentration of Me_2SO in AC disc at the end of each addition step to ensure that the tissue did not freeze, the judgment was based on the mean concentration of Me_2SO inside the tissue, which assumed default even distribution of Me_2SO. Of course this is not the true case. During a loading step, the concentration of Me_2SO at the surface layer of the AC disc increases quickly, but it takes a longer time for Me_2SO to penetrate into the deeper layers. The larger the tissue size is, the more serious the nonuniformity will be. Besides, such nonuniformity would be exacerbated with decreasing temperature due to reduced diffusivity as well. Experimental measurement of the spatial distribution of Me_2SO inside the tissue is difficult, especially at low temperatures. An accurate physical model is thus necessary to predict not only the overall uptake of Me_2SO by the AC

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disc, but also the spatial distribution of Me_2SO at any time point. The latter will be of critical importance for designing the LT steps to completely avoid local freezing.

Traditionally, permeation of CPA into AC is treated as a Fick diffusion process with a constant diffusion coefficient [18,20,22,23,34]. In order to consider the particularity of AC, a triphasic model from biomechanical discipline was introduced by Zhang and Pegg [43], and improved by Abazari et al. [1,3] recently. The triphasic model takes into account nonideality of CPA solution, tissue shrinkage, transport of water and natural inhomogeneities of AC. Spatial and temporal distribution of Me_2SO in AC sample, predicted by the triphasic model, was confirmed with MRI measurements [2] and modeling of permeation times was utilized to develop a cryopreservation procedure for human AC [17]. The triphasic model was demonstrated be of advantage over the Fick's law model [2], but the diffusion coefficient is still treated as a constant, and fitting to permeation data for determination of its value is required as well. We previously developed a model to describe the permeation of Me_2SO into AC, wherein the diffusion coefficient as a function of temperature and concentration was calculated through existing physical correlations [40]. However, the applicability of that model at low temperatures is uncertain, especially the physical meaning of the model, since the viscosities of pure components, Me_2SO and water, are essential in the model calculation, while the viscosities of Me_2SO and water at temperatures below their own melting point are generally unavailable.

In this study, an attempt was made to develop a model to predict the permeation of Me_2SO into AC over extended temperature ranges. The model was constructed based on the free-volume theory [37,38] and the Flory–Huggins thermodynamics theory [10]. The developed model was validated using the experimental permeation data over wide temperature and concentration regions, and its application to the LT method for vitreous preservation of AC was discussed.

Model development

The basic assumptions incorporated in development of the model are the same as we previously made [40], briefly as follows: (1) no Me_2SO generation or consumption in AC, no Me_2SO transport by convection, and no temperature and pressure gradients; (2) negligible changes of tissue size during permeation; (3) the AC is simplified as a homogeneous isotropic porous media; (4) the composition and temperature dependence and non-ideal behavior of Me_2SO diffusion in AC is assumed similar to those in bulk solution; (5) the uptake of Me_2SO by the chondrocytes is neglected; (6) the interstitial fluid of AC is considered as a binary solution of Me_2SO and water.

With these assumptions, the diffusion of Me_2SO in AC can be described by the equation of continuity below in mass units [4],

$$\frac{\partial w_d}{\partial t} = \nabla \cdot \left(D^{eff}_{d,AC} \nabla w_d \right), \tag{1}$$

where w_d is the mass fraction of Me_2SO in the interstitial fluid, $D^{eff}_{d,AC}$ is the effective diffusion coefficient, and t is the time. $D^{eff}_{d,AC}$ was determined by the equation derived by Maroudas [21] that uses a tortuosity factor, λ, and the diffusion coefficient of a substance (here Me_2SO) in water, D_{dw}:

$$D^{eff}_{d,AC} = D_{dw} \frac{H}{\lambda^2}, \tag{2}$$

where H is the water content of fresh AC by mass. For binary diffusion, the diffusion coefficients of two components in each other are the same. Thus, there exists $D_{dw} = D_{wd}$ for Me_2SO/water system. The equation relating the mutual diffusion coefficient (here D_{dw} or D_{wd}) to the solvent self-diffusion coefficient in a solution was given by Crank [8], i.e.,

$$D_{dw} = D_{wd} = D_w \phi_w \frac{\partial \left[\Delta \mu_w / (RT) \right]_{T,P}}{\partial \phi_w}, \tag{3}$$

where D_w is the self-diffusion coefficient of water in Me_2SO/water solution, μ_w is the chemical potential of water, ϕ_w is the volume fraction of water, R is the universal gas constant, and T is the absolute temperature.

The self-diffusion coefficient of water in Me_2SO/water solution can be calculated through the free volume model [37,38]:

$$D_w = D_{w,0} \exp\left(-\frac{V_w}{\bar{V}_{FH}/\gamma} \right), \tag{4}$$

$$V^*_w = w_w \hat{V}^*_w + \xi w_d \hat{V}^*_d, \tag{5}$$

$$\bar{V}_{FH} = w_w K_{w1} (K_{w2} - T_{gw} + T) + w_d K_{d1} (K_{d2} - T_{gd} + T), \tag{6}$$

where V_w is the critical local hole free volume required for a molecule of species one (water) to jump to a new position, $\bar{V}_{FH}$ is the average hole free volume per molecule in the liquid, γ is an overlap factor accounting for one free volume available to multiple molecules, $D_{w,0}$ is the pre-exponential factor, $\hat{V}^*_w$ and $\hat{V}^*_d$ are the specific volumes of water and Me_2SO at 0 K respectively, ξ is the ratio of the molar volume of a jumping unit of water to that of Me_2SO, T_{gw} and T_{gd} are the glass transition temperatures of water and Me_2SO respectively, K_{w1} and K_{w2} are the free volume parameters for water, K_{d1} and $K_{d2}K_{d2}$ are the free volume parameters for Me_2SO. ξ can be reckoned as follows [37],

$$\xi = \frac{\hat{V}_w M_w}{\hat{V}_d M_d}, \tag{7}$$

where M_w and M_d are the molecule weights of water and Me_2SO, respectively. $D_{w,0}$ is considered as a function of composition, and expressed by the polynomial below,

$$\ln D_{w,0} = A w_d^2 + B w_d + C, \tag{8}$$

where A, B, and C are constants.

According to the Flory–Huggins thermodynamics theory [10], the term $[\Delta \mu_w/(RT)]_{T,P}$ in Eq. (3) can be expressed as follows,

$$\left(\frac{\Delta \mu_w}{RT} \right)_{T,P} = \ln \phi_w + \left(1 - \frac{1}{y} \right)(1 - \phi_w) + \chi (1 - \phi_w)^2, \tag{9}$$

where y is the relative molecule volume, and χ is the Flory–Huggins interaction parameter. y is defined by the equation below [10],

$$y = \frac{M_d \hat{V}_d}{M_w \hat{V}_w}. \tag{10}$$

where $\hat{V}_d$ and $\hat{V}_w$ are the specific volumes of Me_2SO and water, respectively.

Determination of model parameters

There are totally 16 independent parameters (see Table 1) that need to be determined in the model. The specific volumes ($\hat{V}_d$, $\hat{V}_w$), the molecular weights (M_d, M_w), the glass transition temperature of water (T_{gw}), and the two free volume parameters of water (K_{w1}/γ, K_{w2}) are either well-known or already reported in literatures. The specific volumes at 0 K for water and Me_2SO ($\hat{V}^*_w$, $\hat{V}^*_d$) were estimated from Sugden's atomic increment method as detailed in Ref. [14]. The glass transition temperature of Me_2SO, T_{gd}, was determined by fitting the Gordon-Taylor (GT) equation to

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