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Tailoring elastic properties of PLGA/TiO₂ biomaterials

T. Fiedler^{1,*}, I.V. Belova¹, G.E. Murch¹, J. A. Roether², A.R. Boccaccini³

¹University Centre for Mass and Thermal Transport in Engineering Materials, School of Engineering, University of Newcastle, Australia

²Institute of Polymer Materials, Department of Materials Science and Engineering, University of Erlangen-Nuremberg, 91058 Erlangen, Germany

³Institute of Biomaterials, Department of Materials Science and Engineering, University of Erlangen-Nuremberg, 91058 Erlangen, Germany

* Thomas.Fiedler@newcastle.edu.au, Tel. +61 2492 16188, Fax +61 2492 16946

Abstract This paper addresses the mechanical properties of titania reinforced poly(lactic-co-glycolic acid) (PLGA), a composite material being considered for applications in bone tissue engineering. Titania nano-particles are added to the PLGA matrix for the improvement of mechanical properties. By changing the fraction of reinforcement, mechanical properties can be adjusted to match values of the surrounding tissue for mechanical compatibility. Numerical finite element and theoretical analyses were conducted to obtain simple design guidelines for tailoring the mechanical properties of these promising composites.

Keywords Biomaterial; particle reinforced composite; elastic properties; finite element analysis; analytical analysis.

Introduction

As put forward by Hench and Polak [1], third generation biomaterials are simultaneously resorbable and bioactive. These materials are being considered for applications in regenerative medicine and tissue engineering as, properly engineered, they can support the body's self-healing mechanisms [1, 2]. These biomaterials are required to tackle the increasing healthcare problems posed by a rapidly aging population, particularly in the industrialised world. Third generation biomaterials will allow a significantly decrease in the amount of revision surgery, or even completely avoiding it, thus saving clinical and financial resources. More importantly, the avoidance of painful and often risky revision surgery procedures will increase the quality of life of millions of patients.

As a result of intensive research, promising prototypes of 3rd generation biomaterials are being developed. A convenient combination of materials in this context involves biodegradable polymers and inorganic fillers forming composites [3-5]. Titania (TiO_2) foams with PDLA-Bioglass® coatings [6] and titania reinforced biopolymers, e.g. PLGA [7,8], PLA [9] and PCL [5] exhibit great potential for bone tissue engineering scaffolds. However, the two major challenges, achievement of biological and mechanical compatibility, remain to be mastered in these composites. In current developments, attempts are being made to position signalling molecules on the surfaces of biomaterials in order to control protein interaction and so to improve biocompatibility [10]. The second major challenge and the focus of this research is mechanical compatibility between the biomaterial and the surrounding tissue. This requires the careful tailoring of (time-dependant) mechanical properties. Due to the complexity of the task, this can best be achieved using computational modelling. The material considered here is poly(lactic-co-glycolic acid) (PLGA) co-polymer. According to the manufacturer, this polymer is completely amorphous and exhibits a relatively low Young's modulus ($E_{\text{PLGA}} = 1.37 \text{ GPa}$ [7]). In order to increase the stiffness, the material is reinforced by adding TiO_2 nanoparticles ($E_{\text{TiO}_2} = 283 \text{ GPa}$ [11]). These composites are prepared by the solvent casting technique in which the polymer is dissolved in a suitable solvent, e.g. dimethyl carbonate (DMC), and TiO_2 nanoparticles are added in the adequate proportion. Subsequently, the mixtures are sonicated for a short period of time to improve the dispersion of titanium dioxide and to desegregate possible agglomerations [7]. Within the compass of this research, special focus is given to the scalability of the composite's Young's modulus and Poisson's ratio by varying the volume fraction of titania nanoparticles in the PLGA matrix. Results are compared with typical values of bone tissue. In parallel, a theoretical analysis is conducted that provides lower and upper bounds of the material properties.

Numerical analysis

A finite element analysis was conducted. To this end, model structures (see Fig. 1a,b) are generated using a random growth algorithm. The PLGA matrix (dark grey) is reinforced by titania particles (light grey) until the required titania volume fraction is reached. Spherical particles are generated sequentially at random coordinates. Before successfully adding a new particle, intersection with existing particles is checked. If intersection occurs, a new set of random coordinates is chosen and so on. The maximum achievable particle volume fraction of this algorithm is $\Phi \approx 0.52$ for random sphere distributions. Higher volume fractions (up to the maximum packing density $\pi/\sqrt{18}$ of equally sized spheres) are achieved by considering body-centred cubic and face-centred cubic sphere arrangements. It should be mentioned here that at present very limited information is available on the PLGA – titania interface. The current model assumes perfect contact between the two phases. However, the focus of the current research is elastic properties of the reinforced biomaterial where the interface behaviour is of minor importance.

Fig. 1 Model structures: a) $\Phi = 0.09$, b) $\Phi = 0.5$, c) boundary conditions

A finite element analysis of uni-axial compressive testing was performed (see Fig. 1c). With this aim, normal displacement is constrained ($u = 0$) at the lower surface of the cubic sample. At the opposing surface a time (t) dependent displacement boundary condition $u = a \cdot t$ is prescribed to introduce compressive loading. All finite element simulations are quasi-static ($a \rightarrow 0$) and no dynamic effects are considered. The evaluation is done using a subroutine that calculates technical strains ε and stresses σ . The effective Young's modulus is the gradient of the resulting stress strain curve, i.e. $E = \sigma / \varepsilon$ and Poisson's ratio is the ratio of strains ε perpendicular (subscript $\perp$) and parallel to the loading direction, i.e. $\nu = -\varepsilon_{\perp} / \varepsilon$. Material anisotropy can be investigated in three perpendicular directions by rotating the cubical model about a principal axis by $\pi/2$. Within the compass of the finite element analysis, all constituents are modelled as isotropic ideal elastic materials, i.e. $E_{\text{TiO}_2} = 283 \text{ GPa}$, $\nu_{\text{TiO}_2} = 0.28$, $E_{\text{PLGA}} = 1.37 \text{ GPa}$ and $\nu_{\text{PLGA}} = 0.44$. Prior to the systematic study of elastic properties, mesh refinement analyses are performed to ensure numerical convergence. A minimum of $3.2 \cdot 10^6$ nodes was found to be sufficient, i.e. there is no significant change in the calculated Young's modulus using higher numbers of nodes. All finite element analyses were carried out using MSC.Marc.

Analytical Approach

According to the analytical treatment presented in ref. [12], the following derivation of the effective elastic properties of the composite can be considered. The average stresses $\bar{\sigma}$ and strains $\bar{\varepsilon}$ of the composite material can be approximated as:

$$\bar{\sigma} = (1 - \Phi)\bar{\sigma}_{\text{PLGA}} + \Phi\bar{\sigma}_{\text{TiO}_2} \quad \text{and} \quad \bar{\varepsilon} = (1 - \Phi)\bar{\varepsilon}_{\text{PLGA}} + \Phi\bar{\varepsilon}_{\text{TiO}_2} \quad (1)$$

where stresses in the matrix and the inclusions are given by the following relations $\bar{\sigma}_{\text{PLGA}} = \mathbf{C}_{\text{PLGA}}\bar{\varepsilon}_{\text{PLGA}}$ and $\bar{\sigma}_{\text{TiO}_2} = \mathbf{C}_{\text{TiO}_2}\bar{\varepsilon}_{\text{TiO}_2}$ ($\mathbf{C}_{\text{PLGA}}$ and $\mathbf{C}_{\text{TiO}_2}$ are the elastic tensors of matrix (PLGA) and inclusions (titania particles), respectively). The effective elastic tensor $\bar{\mathbf{C}}$ of the composite material can be then defined using similar relation between the total stresses $\bar{\sigma}$ and total strains $\bar{\varepsilon}$: $\bar{\sigma} = \bar{\mathbf{C}}\bar{\varepsilon}$. According to Eshelby [13], the following relation can be derived (we write it in the present notation):

$$\bar{\varepsilon}_{TiO_2} = \mathbf{A} \bar{\varepsilon}_{PLGA}, \quad (2)$$

where $\mathbf{A}$ is the strain-concentration factor and can be calculated using the following expression:

$$\mathbf{A} = [\mathbf{S} \mathbf{C}_{PLGA}^{-1} (\mathbf{C}_{TiO_2} - \mathbf{C}_{PLGA}) + \mathbf{I}]^{-1} \quad (3)$$

where tensor $\mathbf{S}$ is the Eshelby tensor. The tensor $\mathbf{S}$ depends on the geometric shape of the inclusions and the elastic properties of the matrix material. The Eshelby tensor must possess symmetry conditions $S_{ijkl} = S_{jikl} = S_{ijlk}$. For the spherical inclusions the elements of tensor $\mathbf{S}$ are [14]:

$$S_{ijkl} = \frac{5\nu - 1}{15(1 - \nu)} \delta_{ij} \delta_{kl} + \frac{4 - 5\nu}{15(1 - \nu)} (\delta_{ik} \delta_{jl} + \delta_{il} \delta_{jk}) \quad (4)$$

where ν is the Poisson's ratio of the matrix phase, here it is PLGA, and therefore

$$S_{1111} = S_{2222} = S_{3333} = 0.57143; S_{2211} = S_{1122} = S_{1133} = S_{3311} = S_{2233} = S_{3322} = 0.14286; \\ S_{2323} = S_{1313} = S_{1212} = 0.21429.$$

Upon substituting all of these relations into Eq (1) we arrive at the following expression for the effective elastic tensor of composite $\bar{\mathbf{C}}$:

$$\bar{\mathbf{C}} = ((1 - \Phi) \mathbf{C}_{PLGA} + \Phi \mathbf{C}_{TiO_2} \mathbf{A}) [(1 - \Phi) \mathbf{I} + \Phi \mathbf{A}]^{-1} \quad (5)$$

Then the effective Young's modulus E_1 and the Poisson's ratio ν_1 as (using usual matrix subscripts) are:

$$E_1 = \frac{(\bar{C}_{11} - \bar{C}_{12})(\bar{C}_{11} + 2\bar{C}_{12})}{\bar{C}_{11} + \bar{C}_{12}}; \quad \nu_1 = \frac{\bar{C}_{12}}{\bar{C}_{11} + \bar{C}_{12}} \quad (6)$$

For the (theoretical) upper limit when Φ_{TiO_2} is close to unity we can use the 'inverse' version of Eq (5) where the matrix became the TiO_2 phase and the inclusions (approximated by spheres) became the PLGA phase:

$$\bar{\mathbf{C}}_i = (\Phi \mathbf{C}_{TiO_2} + (1 - \Phi) \mathbf{C}_{PLGA} \mathbf{A}_i) [\Phi \mathbf{I} + (1 - \Phi) \mathbf{A}_i]^{-1} \quad (7)$$

where $\mathbf{A}_i$ is given by:

$$\mathbf{A}_i = [\mathbf{S}_i \mathbf{C}_{TiO_2}^{-1} (\mathbf{C}_{PLGA} - \mathbf{C}_{TiO_2}) + \mathbf{I}]^{-1} \quad (8)$$

and components of the Eshelby tensor $\mathbf{S}_i$ are:

$$S_{i1111} = S_{i2222} = S_{i3333} = 0.51852; S_{i2211} = S_{i1122} = S_{i1133} = S_{i3311} = S_{i12233} = S_{i3322} = 0.03704; \\ S_{i2323} = S_{i1313} = S_{i1212} = 0.24074.$$

The corresponding upper limits for the effective Young's modulus E_2 and the Poisson's ratio ν_2 are given by:

$$E_2 = \frac{(\bar{C}_{i11} - \bar{C}_{i12})(\bar{C}_{i11} + 2\bar{C}_{i12})}{\bar{C}_{i11} + \bar{C}_{i12}}; \quad \nu_2 = \frac{\bar{C}_{i12}}{\bar{C}_{i11} + \bar{C}_{i12}} \quad (9)$$

Results

Figure 2 shows the effective Young's modulus E plotted versus the titania volume fraction Φ_{TiO_2} . Results of the Finite Element analysis are indicated by cross markers. In addition, analytical solutions are drawn for the upper limit (Eq. (9)) and the lower limit (Eq. (6)). Good agreement between analytical limits and numerical results can be observed. Finite element analysis of Young's modulus reveals isotropic behaviour. At volume fractions $\Phi_{\text{TiO}_2} < 0.4$ only a small increase of the elastic material property is found and results are close to the lower analytical limit. The explanation is that deformation predominantly occurs within the soft PLGA matrix and reinforcements merely cause localised strain concentrations. However, adding further reinforcements causes a distinct increase in the effective Young's modulus: titania particles start to form long range networks, i.e. they show percolation behaviour. As a result, deformation is no longer restricted to the PLGA matrix and the titania particles ($E_{\text{TiO}_2} \approx 200 \cdot E_{\text{PLGA}}$) must deform themselves to allow macroscopic deformation. At the global scale, the effective Young's modulus can be described using the expression $E(\Phi) = E_{\text{PLGA}} \cdot e^{c \cdot \Phi}$ (full line in Fig. 2) with the coefficient $c = 6$.

Fig. 2 Young's modulus plotted vs volume fraction of spherical TiO_2 inclusions

It is of particular interest to compare effective Young's modulus with characteristic values of human bone. Three different types of bone, namely mandibular bone $E = 3$ GPa [15], cortical bone $E = 18.6\text{--}20.7$ GPa [16] and trabecular bone $E = 10.4\text{--}14.8$ GPa [16, 17] are considered. Figure 3 demonstrates how the effective Young's modulus of these different bone tissues can

be matched by changing the titania volume fraction in the composite. It should be mentioned here that applications in tissue engineering require scaffolds that exhibit interconnected porosity in order to promote the formation of new bone tissue [18]. It is well known that porosity will decrease the stiffness of the construct. A detailed study of this effect will be addressed in our future research.

Fig. 3 Young's modulus of PLGA/TiO₂ composites compared to typical material properties of bone tissue

Results for Poisson's ratio ν are shown in Fig. 4. Finite Element results are plotted as cross markers and analytical upper and lower bounds are drawn as dashed and dotted lines, respectively. Analogous to Young's modulus, Finite Element analysis indicates isotropic properties, i.e. transversal contraction is similar in all perpendicular directions and does not depend on the loading direction. The highest Poisson's ratio is observed for pure PLGA. Addition of titania reinforcements continuously decreases the effective Poisson's ratio up to a volume fraction $\Phi_{TiO_2} \approx 0.5$. It is interesting to note that Poisson's ratio of the composite is below the corresponding values of both constituents. This is in good agreement with observations reported in [19]. A possible explanation is in the high stiffness of the spherical titania reinforcements that suppresses transversal contraction, in particular after percolation of spheres occurs. Above this volume fraction, a slight increase of Poisson's ratio can be observed following the trend of the analytical relation (9) that predicts convergence towards ν_{TiO_2} .

Fig. 4 Poisson's ratio plotted vs TiO_2 volume fraction

Conclusions

The present work addressed the elastic properties of PLGA/titania composites. Finite element and analytical analyses were conducted for the characterisation of the effective Young's modulus and effective Poisson's ratio. Analytical relations have proven adequate upper and lower bounds for the effective Young's modulus. Finite element analysis indicates isotropic elastic properties. Based on the finite element results, a power law relation for effective Young's modulus was determined as a function of the titania volume fraction. The material property was found to be governed by the percolation behaviour of titania inclusions: at low TiO_2 volume fractions deformation is limited to the soft PLGA matrix and relatively low effective Young's moduli are obtained. A distinct increase in the composite stiffness is found for $\Phi_{\text{TiO}_2} > 0.4$ where significant numbers of TiO_2 nanoparticles start to exhibit percolation behaviour. The scalability of Young's modulus was demonstrated by the comparison with characteristic values of bone tissue. In addition, Poisson's ratio was investigated for its dependence on the titania volume fraction. Analytical relations provide lower and upper bounds for this material parameter. The approaches presented here are of broad applicability, e.g. they can be adapted to predict the elastic constants of the great variety of biocompatible polymer/inorganic inclusion composites being currently developed for bone tissue engineering.

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