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Molecular Design and Evaluation of Biodegradable Polymers Using a Statistical Approach

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Abstract

The challenging paradigm of bioresorbable polymers, whether in drug delivery or tissue engineering, states that a fine-tuning of the interplay between polymer properties (e.g., thermal, degradation), and the degree of cell/tissue replacement and remodeling is required. In this paper we describe how changes in the molecular architecture of a series of terpolymers allow for the design of polymers with varying glass transition temperatures and degradation rates. The effect of each component in the terpolymers is quantified via design of experiment (DoE) analysis. A linear relationship between terpolymer components and resulting T_g (ranging from 34 to 86 °C) was demonstrated. These findings were further supported with mass-per-flexible-bond (MPFB) analysis. The effect of terpolymer composition on the *in vitro* degradation of these polymers revealed molecular weight loss ranging from 20 to 60% within the first 24 hours. DoE modeling further illustrated the linear (but reciprocal) relationship between structure elements and degradation for these polymers. Thus, we describe a simple technique to provide insight into the structure property relationship of degradable polymers, specifically applied using a new family of tyrosine-derived polycarbonates, allowing for optimal design of materials for specific applications.

Keywords

Glass transition; polymer degradation; Design of Experiments; modeling; polycarbonates

Introduction

Degradable polymeric biomaterials have been studied and applied in numerous areas varying from tissue engineering to drug delivery systems. The regulation of the interplay between material properties and its intended application is a complex and challenging task [1, 2]. Degradation and resorption rates and mechanism, mechanical and thermal properties, and drug release rates are only some of the properties needed to be in tune with tissue reaction, growth, and remodeling [3–5]. Due to the diversity of polymeric materials, and the complexity of structure-property relationships, substantial effort has been placed on applying computational, combinatorial, and high-throughput techniques allowing polymers to be synthesized and screened in an accelerated manner [6, 7]. Such methods have been specifically applied towards biomaterial discovery, where polymer properties and cell-

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polymer interactions have been characterized through high-throughput synthesis and characterization methods [8–11]. With regards to polymer degradation, most models rely on either discrete or continuous mathematical models performed in retrospect [12–14]. Numerous examples depend on specifically applying design of experiments (DoE) methodology for the development of polymeric materials, their synthesis, and characterization [15, 16, 6]. DoE utilizes statistics and probability to define the minimal number experimental runs required to determine the effects of selected independent variables on the properties of products [17–19].

In this paper, we attempt to provide a statistical insight to the structure-property relationships for a small library of structurally-related biodegradable polymers. The effect of polymer architecture was modeled through a design of experiment approach for both glass transition temperatures and degradation rates. We applied DoE on a small library of tyrosine-derived polycarbonate (TyPC) terpolymers. Additionally, we compared the DoE-derived model for glass transition to those values obtained from the “mass-per-flexible-bond” (M/f) parameter. The (M/f) correlates the ratio of mass and the number of flexible bonds of the repeating units in polymers to their T_g as a simple representation of the polymer’s conformational entropy and has been evaluated by Schut *et al.*, for homo-, co-, and terpolymers.[20] We chose polycarbonates since they allow the study of different polymers with a diverse chemical architecture and physical properties while maintaining their inherent biocompatibility[21–24, 20, 25]. TyPCs have been under development for the last two decades as homo-[26] and co-polymers[27]. Recently TyPC terpolymers have emerged based on the polymerization of desaminotyrosyltyrosine ethyl ester (DTE), desaminotyrosyl-tyrosine (DT), and low molecular weight blocks of poly(ethylene glycol) (PEG). These terpolymers have shown to hold the potential to provide tailor-made properties for specific applications. The inclusion of both DT and PEG onto the polymer backbone provides the unique ability to manipulate the thermal properties and degradation and resorption rates. Such changes in degradation and resorption rates have been exploited towards a wide variety of biomedical applications, including bone tissue engineering [28], neural tissue engineering[29], vascular stents[30], and drug delivery applications [31]. The diversity of this polymer system could benefit from a simple correlation model between structure and property. Such model could allow prediction of specific polymer properties, resulting in reduced development efforts. A series of nine polycarbonates were designed using DoE and synthesized using an automated parallel synthesizer in an attempt to identify a correlation between the terpolymer architecture and both the T_g and the degradation (where the term ‘degradation’ refers to the loss of molecular weight caused by the hydrolysis of the carbonate bonds) [32].

Materials and Methods

Polymer synthesis

Desaminotyrosyl-tyrosine alkyl esters (DTR), desaminotyrosyl-tyrosine free acid (DT), and low molecular weight blocks of poly(ethylene glycol) (PEG) based terpolymers were synthesized by condensation reaction of triphosgene and tyrosine-derived diphenol. An automated parallel synthesis protocol was performed on a Chemspeed Accelerator SLT100 as previously described [24]. Molecular weights (number average, M_n) and polydispersity index (PDI) were determined using GPC relative to polystyrene standards.

The representation ‘EXXY(MW)’ is used to name poly(DTE-*co*-XX%-DT-*co*-YY%-PEGMW carbonate) where E refers to the ethyl pendent chain, while XX and YY refer to the mol percent of DT and PEG respectively. MW is the weight average molecular weight of the PEG block. As an example, poly(DTE-*co*-15%-DT-*co*-02%-PEG2K carbonate) will be noted as E1502(2K).

DOE

Nine different terpolymers formulations were prepared according to a two factor, three level full factorial DoE [18]. DT low level, middle level, and high level were 15, 25, and 35 % - mol respectively. The PEG2K low level, middle level, and high level were 2, 4, and 6 % - mol respectively. A three-level, full-factorial DOE allows for the evaluation of the first and second order effects of each component of the formulation (%DTE, %PEG, and %DT) on the product properties and also to detect any interactions, if present, between the components [17–19].

Mass-per-flexible-bond ratio of polymers

The assignment of the (M/f) ratio of polymers, including the assignment of bond flexibility and calculations from mol percent, was done following a previously published method [20]. More information about the calculations for this specific set of polymers can be found in the supplementary material.

Glass transition temperature analysis

The glass transition temperature was analyzed using a Perkin Elmer DSC 7 differential scanning calorimeter operated under nitrogen. The scanning curves were collected at a heating rate of 10°C/min. Dry T_g was determined from re-heat scans.

Polymer degradation studies

First solvent cast films were prepared. Polymer powder was dissolved at 10% w/v in tetrahydrofuran and cast into polytetrafluoroethylene dishes; the solvent was evaporated overnight under nitrogen in a chemical hood, followed by 7 days of vacuum drying at 40 °C. Discs punched from cast films were placed in scintillation vials containing phosphate-buffered saline, pH = 7.4, and incubated at 37 °C for the duration of the study. For analysis, samples were washed with distilled water and subsequently frozen and lyophilized to remove all water, then dissolved in dimethylformamide containing 0.1% trifluoroacetic acid in preparation for molecular weight determinations using GPC [29].

Results and discussion

The structure of poly(DTR-*co*-XX%-DT-*co*-YY%-PEGMW carbonate) terpolymers is illustrated in Figure 1. In our study, the R pendant chain is ethyl, and the designation of these polymers is EXXYY(2K)

The effect of molecular composition on the glass transition temperature (T_g) and molecular weight (MW) retention of a series of poly(DTE-*co*-DT-*co*-PEG2K carbonate)s was studied using a series of terpolymers with varying DT (15, 25, and 35%) and PEG2K (2, 4, and 6%) content. This range, provided throughout this paper in % mol, allows for comparison of the effect of DT and PEG since when translated to weight percent, PEG and DT content are similar (e.g. E1502(2k) contains 13 wt % DT and 10 wt % PEG, while E3506(2k) contains 26 wt % DT and 25 wt % PEG). All polymers were synthesized to high molecular weights (values of over 100 kD relative to polystyrene standards). The corresponding molecular weights are listed in Table 1, illustrating no specific correlation between composition and initial MW.

Table 2 lists the results of the full factorial DoE approach and analysis including the measured and modeled T_g values, with the corresponding residual values. The averaged residual is taken as the error. The low average residual value is an indication for good-quality DoE [18]. The model-function resulting from the DoE analysis is shown as Eq. 1. First order (linear) effects are significantly higher than second order (parabolic) effects, and

the interaction between both factors (%PEG2K and %DT) is negligible compared to the error (average residual).

$$T_g = 57.8 - 20.8(\%PEG) + 1.7(\%PEG)^2 + 5.3(\%DT) - 0.1(\%DT)^2 - 0.8(\%PEG)(\%DT) \pm 1.3 \quad \text{Eq. 1}$$

Figure 2 illustrates the changes in glass transition temperatures as a function of %DT and %PEG2K for the actual and modeled DoE values. While DT increases the glass transition temperature at a given PEG content, PEG decreases the glass transition temperature at a given DT content. With regards to the individual effects of the PEG and DT components, the T_g reduction when DTR polymers are copolymerized with increasing mol fraction of PEG blocks has been previously observed [27]. Similarly in DTR copolymers with DT (namely poly(DTR-*co*-DT carbonate)s), a T_g increase was observed with increasing mol fraction of DT [21]. In this current study, we observed that this trend is maintained when terpolymers are synthesized. An increase in the mol fraction of PEG2K resulted in a decrease in the T_g due to the added chain flexibility to the overall molecular structure, in contrast with the effect of the DT constituent, *i.e.*, the free acid pendent chain, which increases the T_g of tyrosine polymers through increased hydrogen bonding [20].

Moreover, the results from the DoE model can be related to the overall polymer flexibility through the comparison of the values to those obtained from the MPFB analysis. We recognize that DoE does not provide a full picture regarding the observed T_g and the polymer structure; however, by using a complementary analysis such as the MPFB, we can support our findings regarding chemical structure and chain flexibility. These findings are further illustrated by observing the response surface plot (Figure 3) where the DoE correlation between PEG2K percentile, DT percentile and T_g is illustrated. Furthermore, DoE analysis reveals that the factor '%PEG2K' has a greater effect in the alteration of the glass transition temperature (reduction of T_g) compared to the effect of the factor '%DT' (slight increase of T_g). This phenomenon has been previously implied by Magno et al., [23], but the correlation between the factors is first reported here. Thus, a prediction of the glass transition temperature of polymers within the realm of the surface provided in Figure 3 is possible. Since the polymers within this “design space” are structurally-related to each other, a researcher can use this as a tool for the rational design of a polymer within a specific family of polymers [7].

The effect of the molecular architecture on the degradation of the polymers can be observed through analysis of the molecular weight retention as a function of time (up to four weeks) as shown in figure 4. The effect of increasing the %PEG2K at a given DT content is seen in Figure 4A, while the effect of the increase of %DT at a given PEG2K content is seen in Figure 4B. It is evident from figure 4 that both DT and PEG2K contribute to increased degradation rates (lesser MW retention). It has been reported that accelerated degradation of DTE based polymers can be achieved via the individual copolymerization with either PEG [27] or DT [21] due to increased water uptake resulting in an increased hydrolysis rate.

Figure 4 illustrates that the loss of molecular weight is at its greatest during the initial stages of degradation, regardless of the composition. This phenomenon has been previously described by Tangpasuthadol et al. [32], who additionally, illustrated that the rate of degradation remains constant throughout the incubation period. For these reasons, to evaluate the accuracy of the DoE model, we used the molecular weight loss of the first 24 h of each polymer as the data set. The resulting DoE analysis is shown in table 3. Even within 24 h, a wide range of hydrolysis is observed, ranging from 20% loss of MW (E1502(2k)) to 59% loss of initial MW (E3506(2k)).

The retained MW model-function resulting from the DoE analysis is shown as Eq. 2. First order (linear) effects are significantly higher than second order (parabolic) effects, and the interaction between both factors (%PEG2K and %DT) is negligible compared to the error (average residual).

$$MW_{retained} = 0.575 - 0.061(\%PEG) + 0.011(\%PEG)^2 - 0.122(\%DT) + 0.005(\%DT)^2 + 0.015(\%PEG)(\%DT) \pm 0.022 \quad \text{Eq. 2}$$

Unlike with glass transition temperature, the addition of both DT and PEG resulted in greater loss of molecular weight. Moreover this change was more greatly affected by the changes in DT content compared to the effect of changes in PEG2K content. These findings are exemplified through the response surface plot (figure 5) where the DoE correlation between PEG2K percentile, DT percentile and retained MW is illustrated.

The modeling of polymer degradation is regarded as a non-trivial task affected by various factors such as monomer solubility in aqueous environment and water uptake kinetics [13]. Though the possibility to modify (and accelerate) degradation properties using both molecular constituents has been extensively reported for various applications [21, 29, 23, 31], the methodical analysis and quantification of the effect of each component has yet to be performed.

In biomedical applications, achieving accelerated degradation using PEG has been reported in various polymer systems [33, 34], but such use could prove cumbersome. PEG has shown to alter cell-biomaterial interaction through reduction of protein adsorption [35], reduction of cell attachment and proliferation [27], alteration of cell fate [25], and reduction of material strength [27]. Conversely, the addition of DT not only increases degradation rate, but allows for increased protein adsorption, cell attachment, and proliferation [36, 35]. The tailoring of material properties, specifically polymer-protein-cell interactions via the combination of DT and PEG has shown great potential in biomaterial developments. Nevertheless, the analysis of the effect of each component has yet to be performed. We have shown that by using DoE, the modeling of relatively simple material properties (T_g), and more complex ones (degradation) is possible. Moreover, we have shown that each molecular component affects these properties individually. Thus, it is conceivable that such technique could be applied towards complex biological interactions, possibly elucidating whether the effects of DT and PEG are independent or not.

Conclusions

A simple and straightforward technique for the evaluation of structure-property relationships in tyrosine-derived terpolymers using DoE approach has been described. Additionally, the relative effect of each component of the polymer composition has been identified. While DT increases T_g , PEG reduces it to greater effect. In contrast, both compositional constituents increase degradation rates during the initial 24 h, but DT has a greater impact. This methodology could be applied to a larger library of polymers, allowing for more rational materials selection based on property prediction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Structure of tyrosine-derived terpolymers. In our study, the R pendant chain is ethyl.

Fig. 2. Measured and modeled glass transition temperature of a series of poly(DTE-*co*-XX%-DT-*co*-YY%-PEG2K carbonate) terpolymers with varying amounts of DT and PEG2K monomers.

Fig. 3.
DoE response surface plot illustrating the correlation between %PEG2K, %DT and T_g.

Fig. 4. Molecular weight loss as a function of time for various poly(DTE-*co*-XX%-DT-*co*-YY%-PEG2K carbonate) terpolymers illustrating the effect of addition of PEG2K (a) and the effect of addition of DT(b). Large images, first 36 hours; inserts, 4 weeks.

Fig. 5. DoE response surface plot illustrating the correlation between %PEG2K, %DT and degradation during the first 24 h (molecular weight retention).

Table 1

Initial molecular weights of synthesized polymers

Polymer	E1502	E1504	E1506	E2502	E2504	E2506	E3502	E3504	E3506
M _w (kD)	160.5	235.1	278.2	203.2	246.6	246.3	210.6	145.4	233.9

Table 2Full factorial DoE and MPFB of experiment for T_g .

DOE Sample	%PEG (A)	%DT (B)	Interaction (AB)	(M/dp	T_g (°C) Result	T_g (°C) DoE Model	T_g (°C) MPFB Model	Residual (Result-DoE)	Residual (Result-MPFB)
1	2 (-1)	15 (-1)	(1)	30.7	74.0	74.1	74.9	0.1	0.9
2	6 (1)	15 (-1)	(-1)	28.0	34.0	34.0	33.4	0.0	0.6
3	2 (-1)	35 (1)	(-1)	31.3	86.0	86.3	84.1	0.3	1.9
4	6 (1)	35 (1)	(1)	28.5	43.0	43.1	40.9	0.1	2.1
5	4 (0)	25 (0)		29.5	54.0	57.8	56.7	3.8	2.7
6	6 (1)	25 (0)		28.2	39.0	38.7	37.1	0.3	1.9
7	2 (-1)	25 (0)		31.0	81.0	80.3	79.5	0.7	1.5
8	4 (0)	35 (1)		29.8	60.0	63.0	60.9	3.0	0.9
9	4 (0)	15 (-1)		29.3	49.0	52.3	52.6	3.3	3.6
							Average	1.3	1.8

Table 3

Full factorial DoE of experiment for fractional MW retention.

DOE Sample	%PEG (A)	%DT (B)	Interact (AB)	Mw Result	Mw Model	Residual
1	2 (-1)	15 (-1)	(1)	0.801	0.789	0.012
2	6 (1)	15 (-1)	(-1)	0.618	0.637	0.019
3	2 (-1)	35 (1)	(-1)	0.538	0.515	0.023
4	6 (1)	35 (1)	(1)	0.415	0.422	0.007
5	4 (0)	25 (0)		0.553	0.575	0.022
6	6 (1)	25 (0)		0.540	0.524	0.015
7	2 (-1)	25 (0)		0.602	0.647	0.045
8	4 (0)	35 (1)		0.421	0.458	0.037
9	4 (0)	15 (-1)		0.688	0.703	0.014
					Average	0.022