



Controlled drug release through regulated biodegradation of poly(lactic acid) using inorganic salts



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ABSTRACT

Biodegradation rate of poly(lactic acid) (PLA) has been regulated, both increase and decrease with respect to the biodegradation of pure PLA, by embedding meager amount of inorganic salts in polymer matrix. Biodegradation is performed in enzyme medium on suspension and film and the extent of biodegradation is measured through spectroscopic technique which is also verified by weight loss measurement. Media pH has been controlled using trace amount of inorganic salt which eventually control the biodegradation of PLA. High performance liquid chromatography confirms the hydrolytic degradation of PLA to its monomer/oligomer. Induced pH by metal salts show maximum degradation at alkaline range (with calcium salt) while inhibition is observed in acidic medium (with iron salt). The pH of media changes the conformation of enzyme which in turn regulate the rate of biodegradation. Thermal degradation and increment of modulus indicate improvement in thermo-mechanical properties of PLA in presence of inorganic salts. Functional stability of enzyme with metal salts corresponding to acidic and alkaline pH has been established through a model to explain the conformational changes of the active sites of enzyme at varying pH influencing the rate of hydrolysis leading to regulated biodegradation of PLA. The tuned biodegradation has been applied for the controlled release of drug from the polymer matrix (both sustained and enhanced cumulative release as compared to pure polymer). The cell proliferation and adhesion are influenced by the acidic and basic nature of polymeric material tuned by two different inorganic salts showing better adhesion and proliferation in calcium based composite and, therefore, suggest biological use of these composites in biomedical applications.

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1. Introduction

The degradation of polyesters in non-biological ways such as photo, chemical, thermal, oxidative, mechanical and weathering produce free radical derivatives which deviate normal metabolic pathway of biotic systems. Moreover, social awareness and environmental concern has augmented the demand of renewable and biodegradable polymers. Poly(lactic acid) (PLA) is a biodegradable aliphatic polymer having hydrolysable ester bond which is catalyzed by integrated approach of enzyme and/or microbes. PLA has received special attention owing to its monomeric yield of lactic acid [1], assimilated by the indigenous microbes via acetic acid and propanoic acid intermediate [2]. Although, lactic acid is considered to be nontoxic metabolite converted to pyruvate in higher organ-

ism that considered as energy yielding intermediate. Taking this advantage, PLA has spectrum of applications in field of biomedical, agricultural and food packaging sector to replace synthetic and non-biodegradable polymers. Degradation of PLA using biological agents is a sound and green approach to transform it into eventual end products of carbon dioxide and water [3]. Recently, microbial lipases have been acknowledged for hydrolysis of polyester bonds. For instance, recognition of the ester chain of acyl group [4], pH-dependent hydrolysis of ibuprofen esters [5], degradation of bioplastic [6], regioselective acylation [7] and discrimination of optically pure compound deduce the mechanism of synthetic and hydrolytic reactions [6,8,9]. Hence, lipase-mediated resolutions are being exploited for application of biomedical, biodegradation, pharmaceutical, food, flavor, cosmetics, leather, textile, detergent and paper industries.

Controlled release of drugs or active molecules from polymeric systems is typically carried out by regulating the rates of diffusion, hydrolytic and enzymatic process including polymer

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degradation. The release behavior of polymeric drug delivery systems highly depends on physicochemical parameters and chemical structure of the materials [10]. Andreopoulos, et al. controlled the release properties of drug by using two different molecular weight ($M_w = 2 \times 10^3$ and 2×10^4) of PLA. It was evident that as molecular weight of the matrix decreases, water penetration is facilitated, consequently, drug release is enhanced [11]. PLA is blended with a number of polymers to influence the degradation rate affecting the crystallinity of the initial polymer matrix that regulates the first phase of degradation and drug release profile. For control of anti-inflammatory drug release of dexamethasone (DEX) was investigated in PLLA and PLGA copolymer to tune the drug release profile. The drug release rate in PLLA was about 10% during first 24 h and release only about 16% after 28 days. Burst release of about 40% in 24 h, and 68% of the DEX was released after 28 days from PLGA [12]. Release of drugs (gentamycin and naltrexone) from PLA particles was observed for more than 7 weeks, indicating matrix-controlled diffusion of the drug from the polymer microsphere [13].

Recently, the thrust area of research is to focus on tuning the rate of polymer degradation using nanoparticles as fillers but production costs of nanoparticles restricted their wide range applications. Therefore, the exploration of inorganic filler such as metal salts could have been promising options for preparation of polymer composite. Calcium carbonate (CaCO_3) is one of the most abundant materials on our planet and has been considered better choice as inorganic filler for preparation of polymer composites. Calcium carbonate is a white sparingly soluble inorganic salt of calcium and carbonate. It is naturally occurring inorganic biomaterial found in shells of marine organisms such as snails, pearls, and eggshells along with bones and teeth. Calcium carbonate is versatile and widely used filler incorporated during variety of products formation of paper, plastics, glass fiber, print ink, paint pigment, rubber, cosmetics and pharmaceuticals [14]. The batch fermentation of lactic acid production was controlled by CaCO_3 to maintain the optimum pH of media and enzyme activity [15]. Nano sized CaCO_3 particles (<100 nm) was reported with many unique properties compared to regular particles [14]. Poly(L-lactide)/calcium carbonate composites was prepared by melt-mixing using micrometer-size and nanosize calcium carbonate (CaCO_3) particles before and after modification with calcium stearate. The catalytic effect of alkaline CaCO_3 lowered the activation energy of PLA composite during degradation while it improved the mechanical properties. The tensile strength and modulus values of PLA composite was improved without a significant loss in the elongation at break when the nanosize CaCO_3 was incorporated [16]. Shi et al. compared the precipitated calcium carbonate/poly(lactic acid) and halloysite/poly(lactic acid) nanocomposites [17]. Osteoconductive β -tricalcium phosphate and bioabsorbable poly(L,D-lactide) have been used to improve the biocompatibility and osteoconductivity of bioabsorbable polymers. The acidic degradation products of poly(L,D-lactide) were neutralized by the alkaline degradation products of β -tricalcium phosphate particles [18]. Iron is an important element exists in minerals such as Fe^{2+} (e.g., pyrite) and Fe^{3+} (hematite) or in mixed valence (magnetite). Salts/minerals of iron are an essential oligo-element controlling biomass in surface and ground waters. In acidic aqueous solution, Fe^{3+} ion exists as the complex of hexa-aquo $[\text{Fe}(\text{OH}_2)_6]^{3+}$ with octahedral geometry [19]. Yu et al. [20] have prepared PCL/ Fe_3O_4 composite to investigate the effect of Fe_3O_4 filler on in-vitro degradation and the effect of the degradation on shape memory behavior. The biodegradable nanocomposites containing transition metals such as Fe, Cu, In and Ag exert a stronger toxic action against bacteria [21]. Thus, our objective is to investigate the role of inorganic salts as reinforcing filler to regulate the rate of biodegradation of PLA, because of its low cost and ease of availability and processability and secondly, to regulate the drug release rate

using controlled biodegradation of PLA composites along with the biocompatibility of the developed material for biomedical applications.

2. Materials and methods

2.1. Preparation of film and suspension

The film of pure poly(lactic acid) and its composites were prepared via solution route by dissolving/dispersing polymer and other ingredients for composites in dichloromethane (DCM) solvent followed by evaporation of solvent. For composites, 0.05 and 0.02 wt.% of CaCO_3 and FeCl_3 salts were dispersed, respectively, in polymer matrix to prepare the composites. The solution was sonicated for 30 min to ensure good dispersion and proper mixing of metal salts with polymers. Henceforth, PLA- CaCO_3 and PLA- FeCl_3 composites with the above mentioned compositions will be termed as PLA-Ca and PLA-Fe, respectively. Appropriate amount of solution was poured on glass slide to prepare the thin films of ~0.05 mm by evaporating the solvent followed by drying under reduced pressure at 80 °C. The uniform dispersions of salts in PLA matrix was observed from the bright field TEM images with particle diameter of 150 nm while size of the salt embedded in polymer was measured to be ~300 nm, as evident from dynamic light scattering measurement of their suspension. PLA suspension was prepared in water using dioxane as organic solvent to make homogeneous suspension after sonication for 30 min. Particle size of PLA in the suspension was kept ~275 nm as measured through particle size analyzer at 25 °C using 90° scattering angle.

2.2. Enzymatic biodegradation of suspension and film

The PLA suspensions were used to measure the biodegradation kinetics of polymer. The basic and acidic pH of the suspension was adjusted by using metal salts namely CaCO_3 and FeCl_3 , respectively. The assay mixture contains 2 ml of polymer suspension and 1 ml of lipase (1 mg/ml). The reaction mixture was stirred after the addition of enzyme and the decrease in optical density of polymer suspension was measured spectrophotometrically at 600 nm as a function of time. For the biodegradation of film, initial dimension of the samples was taken as $\sim 10 \times 10 \times 0.05 \text{ mm}^3$ and were placed in a small vial containing 3 ml of enzyme (1 mg/ml) at 37 °C under constant stirring. Enzymatic biodegradation of films was studied in an environmental chamber at constant humidity of 85% at 37 °C. The percentage weight loss of the film was measured with time to calculate the biodegradation rate after enzyme treatment. Initial weight of film has been measured as control was incubated in enzyme solution. The biodegradation was carried out for several hours and the samples were taken out at predetermined time of exposure, washed with water, and dried under reduced pressure at room temperature for constant weight before analyses. The percentage weight loss after enzyme treatment has been considered as the measure of biodegradation during that time period was calculated via simple mathematical formula, implementing difference of initial and final weight is divided by initial weight multiplied by hundred. Similarly, the degradation of PLA and its composites was performed in compost media keeping initial dimensions of the samples of $\sim 10 \times 10 \times 0.1 \text{ mm}^3$. The weight loss percentage was calculated using the formula

$$\% \text{wt. loss} = (w_i - w_f) / w_i \times 100$$

where, w_i is initial weight, w_f is final weight or at predetermined time.

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