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Review

Recent developments in lipase-catalyzed synthesis of polymeric materials

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ABSTRACT

In the past three years, enzymatic polymerization has dramatically developed and provided many successful examples in the construction of functional polymeric materials. In this review, the lipase-catalyzed synthesis of polymeric materials is systematically summarized, focusing on the synthesis of complex and well-defined polyesters. Exploration of novel biocatalysts and reaction media is described, with particular emphasis on the enzymes obtained *via* immobilization or protein engineering strategies, green solvents and reactors. Enzymatic polyester synthesis is then discussed with regard to the different reaction types, including ring-opening polymerization, polycondensation, combination of ring-opening polymerization with polycondensation, and chemoenzymatic polymerization. Using enzymatic polymerization, many polymeric materials with tailor-made structures and properties have been successfully designed and synthesized. Finally, recent developments in catalytic kinetics and mechanistic studies through the use of spectroscopy, mathematics and computer techniques are introduced. Overall, the review demonstrates that lipase-catalyzed synthesis of polymeric materials could be a promising platform for green polymer chemistry, and will be potential to produce biodegradable and biocompatible polymers.

Contents

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1. Introduction

Over the last two decades, enzymatic polymerization, especially the lipase-catalyzed synthesis of aliphatic polyesters, has rapidly developed and become an important synthetic technique for polymeric materials [1–4]. Compared with chemical routes, enzymatic polymerization has many advantages [5], including (1) mild reaction conditions, (2) high control of enantio-, chemo-, and regio-selectivity, (3) few by-products, and (4) high catalytic activity toward macrocyclic lactones that are hard to polymerize *via* chemical catalysis. Moreover, enzymatic polymerization could help to avoid problems associated with trace residues of metallic catalysts, in particular their unfavorable effects on the environment and toxicity in biomedical applications. Thus, enzymatic polymerization has been regarded as a potential alternative to traditional chemical polymerization, providing a good platform for green polymer synthesis.

There are two major modes for lipase-catalyzed synthesis of aliphatic polyesters (Fig. 1): (1) ring-opening polymerization of lactones, and (2) polycondensation, including polycondensation of diacids or their activated esters with diols and polycondensation of hydroxyl acids or their activated esters. In our previous research, thermophilic lipases and esterases have been successfully employed to catalyze the synthesis of aliphatic polyesters, and monomers could be completely converted, producing polymers with low number-average molecular weight (M_n < 3000 g/mol) and narrow distribution [6–12]. In addition, the history and development of these two reactions have been systematically reviewed [13,14]. In the past three years, enzymatic polymerization has dramatically developed and provided many successful examples in the construction of functional polymeric materials. However, some significant issues still need to be addressed to further facilitate theory and technique development in enzymatic polymerization.

In this article, recent developments in lipase-catalyzed polyester synthesis are systematically reviewed, including the exploration of biocatalysts, reaction media and monomers, catalytic kinetics and mechanistic studies. In addition, the review provides a deep insight into the perspectives and future trends of enzymatic polymerization.

2. Exploration of novel biocatalysts and reaction media

2.1. Exploration of novel biocatalysts

Enzymatic polymerization is usually conducted in organic solvents, and thus the enzyme characteristics in such solvents need to be optimized for it to fulfill its biological function *via* immobilization or protein engineering. Among the lipases used in enzymatic polymerization, Novozym 435 (an immobilized *Candida antarctica* lipase B) is the most widely used enzyme for polyester synthesis [15,16]. To broaden the scope of biocatalysts, Zhang et al. constructed a covalently immobilized porcine pancreas lipase using porous silica particles as a support and successfully applied it in the ring-opening polymerization of ε-caprolactone and 5,5-dimethyl-1,3-dioxan-2-one [17]. Compared with the free enzyme, the immobilized enzyme exhibited higher catalytic activity and thermal stability, and polymers with weight-average molecular weight (M_w) of 13,400–25,100 g/mol were obtained. Through physical adsorption onto macroporous acrylic resin, immobilized *C. antarctica* lipase B has been shown to catalyze the synthesis of poly(ε-caprolactone) for up to 10 cycles, affording a polymer with M_w of *ca.* 50,000 g/mol [18]. Besides traditionally immobilized enzymes, ionic liquid coated lipase has also been used in polyester synthesis [19,20]. In these reactions, the use of ionic liquid coated lipase was found to be much superior to the case where the ionic liquid was used just as a reaction medium, allowing poly(ε-caprolactone) and poly(1,4-dioxan-2-one) to be prepared with maximum M_w of 182,000 g/mol. In our laboratory, recombinant *Escherichia coli* whole-cell biocatalyst and cell-debris self-immobilized enzyme have been developed as the thermophilic lipase cloned from *Fervidobacterium nodosum* was bound to or associated with the *E. coli* cell membrane or wall due to its high hydrophobicity, and then successfully applied in the ring-opening polymerization of ε-caprolactone, with comparable monomer conversion (>90%) and M_n values (950–1240 g/mol) over the course of 10 batch reactions [8,12]. Though more and more free or immobilized enzymes have been explored using modern biotechnological techniques, they exhibited no superior characteristics to Novozym 435, and thus constructing cost-effective biocatalysts from natural sources or immobilization is still an urgent work for future industrial enzymatic polymerization.

Protein engineering is an efficient technique for improving the catalytic activity, stability and selectivity of enzymes, which can also alter the substrate specificity. To overcome low activity toward the monomer D,D-lactide, rational design of *C. antarctica* lipase B has been carried out, and the mutant Q157A was shown to exhibit an almost 90-fold improvement of activity in the ring-opening polymerization of D,D-lactide [21]. In spite of these impressive results, M_n value was only improved from 280 to 780 g/mol, and therefore further molecular design of enzymes is still needed to improve the yield and product molecular weight.

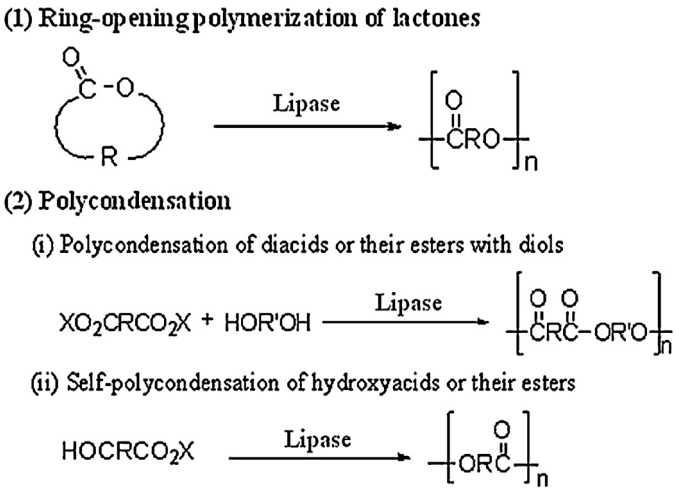

Fig. 1. Two major modes of lipase-catalyzed polyester synthesis.

2.2. Exploration of reaction media

Except for organic solvents and solvent-free systems, an increasing number of reaction media, *e.g.*, ionic liquids, supercritical carbon dioxide ($scCO_2$) and hydrofluorocarbon solvents (HFCs), have been employed in enzymatic polyester synthesis. Using *C. antarctica* lipase B as catalyst, poly(ε-caprolactone) and hyperbranched poly-L-lactide have been successfully prepared in ionic liquids [22,23]. Notably, the monocationic ionic liquid [C_nMIm][PF_6] and dicationic ionic liquid [$C_4(C_6Im)_2$][PF_6]$_2$ were shown to efficiently promote the enzymatic polymerization of ε-caprolactone, with highest M_n and yield of 26,200 g/mol and 62%, respectively. Deep eutectic solvent is a new family of ionic liquid composed of two or three cheap and safe components which are capable of associating with each other through hydrogen bond interactions [24], and enzymatic ring-opening polymerization of ε-caprolactone has been successfully conducted in these reaction systems [25]. The medium $scCO_2$ is a green solvent with many advantages, *e.g.*, low toxicity, no ozone-depletion potential and relative hydrophobicity. To realize the enzymatic