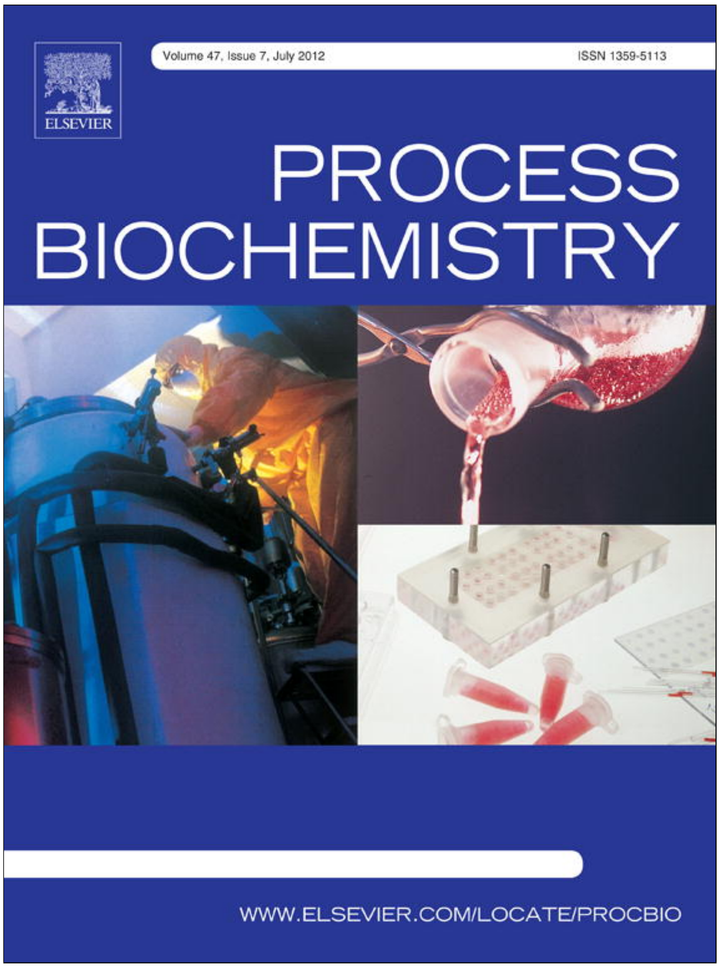

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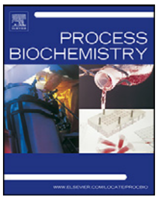

Review

Lipase/esterase-catalyzed synthesis of aliphatic polyesters *via* polycondensation: A review

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ABSTRACT

Over the last decade, there has been an increasing interest in lipase/esterase-catalyzed polycondensation as an alternative to metal-based catalytic process, because the former can proceed under mild reaction conditions and does not cause undesirable side reactions or produce trace metallic residues. In this review, the *in vitro* synthesis of aliphatic polyesters by polycondensation using lipases or esterases is systematically summarized, especially for the synthesis of complex and well-defined polyesters. The polycondensation of diols with diacids or their activated esters, including alkyl, haloalkyl and vinyl esters, through esterification and transesterification polycondensation reactions is discussed. In addition, three or more monomers can also be polymerized simultaneously, which provides a new route for preparing functional polymers. Self-polycondensation with respect to hydroxyl and mercapto acids or their esters is another reaction mode discussed in the review. Finally, concurrent enzymatic ring-opening polymerization and polycondensation has been developed to construct novel polyesters with tailor-made structures and properties. Overall, the review demonstrates that lipase/esterase-catalyzed synthesis of polyesters *via* polycondensation provides an effective platform for conducting "eco-friendly polymer chemistry".

Contents

1. Introduction

Aliphatic polyesters are among the most widely used biodegradable polymers in environmental and biomedical fields. Generally, these polymers are synthesized *via* chemical polycondensation reactions using a wide range of catalysts, such as acetates of manganese, zinc, calcium, cobalt and magnesium, antimony oxide, and titanium oxides [1]. However, these reactions are usually conducted at temperatures of 180–280 °C, and cause undesirable side reactions such as dehydration of diols and β-scission of polyesters to form acid and alkene end groups [1]. Meanwhile, high reaction temperatures are not suitable for thermally or chemically unstable monomers and functional groups, including siloxane, epoxy and vinyl moieties. In addition to temperature concerns, trace residues of metallic catalysts can cause unfavorable effects on environment and toxicity in biomedical applications. Furthermore, traditional chemical catalysts generally lack selectivity and the designed functional polyesters are hard to produce. Thus, the

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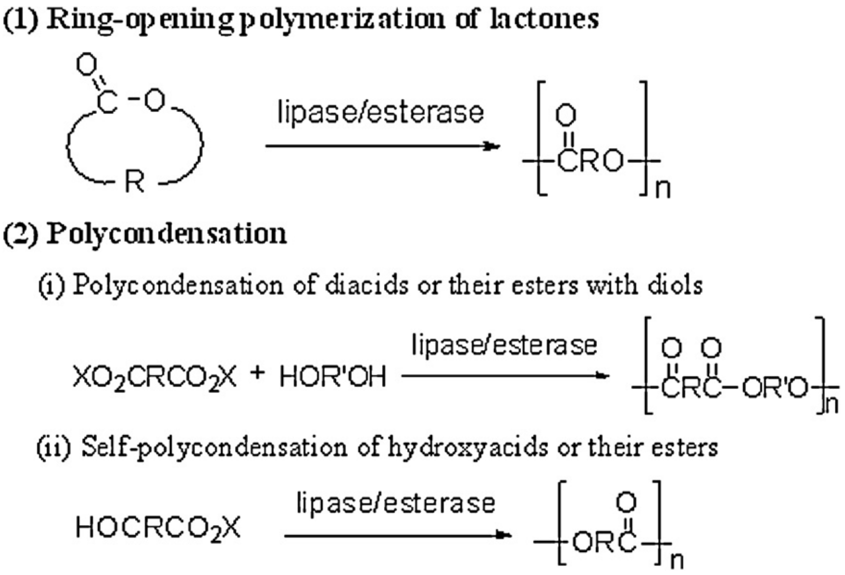

Fig. 1. Two major routes of enzymatic polyester synthesis.

discovery of new and versatile polycondensation catalysts to catalyze reactions under mild conditions with chemo-, regio- and enantioselectivity, is of great significance.

Compared with chemical route, enzymatic polycondensation, especially lipase/esterase-catalyzed polymerization, has many advantages [2], including (1) high catalytic activity, (2) mild reaction conditions, (3) high control of enantio-, chemo- and regioselectivity, and (4) few by-products (a clean process). Thus, enzymatic polycondensation has been regarded as an environment-friendly synthetic process for polymeric materials and a good example of "eco-friendly polymer synthesis" [3–9].

Lipases and esterases are members of the "α/β-hydrolase fold" family and can catalyze the hydrolysis of fatty acid esters in an aqueous environment. Moreover, lipases and esterases are stable in organic solvents and can catalyze the reverse reactions in non-aqueous media, resulting in esterification or transesterification [10]. Therefore, the family of lipases/esterases is a highly versatile class of biocatalysts for synthesizing organic compounds, especially for polyester synthesis. Generally, enzymatic polyester synthesis proceeds *via* two major routes (Fig. 1): (1) ring-opening polymerization of lactones and (2) polycondensation, which is further divided into polycondensation of diacids or their activated esters with diols and self-polycondensation of hydroxyacids or their activated esters. This paper reviews recent developments in the synthesis of aliphatic polyesters using lipase/esterase-catalyzed polycondensation reactions.

2. Polycondensation of dicarboxylic acids or their derivatives with diols

As mentioned above, lipase/esterase-catalyzed esterification and transesterification reactions can be used to produce polyesters in non-aqueous media. Thus, various dicarboxylic acids and their activated or non-activated esters have been polymerized with diols [5,11].

2.1. Esterification polycondensation

As the esterification polycondensation of dicarboxylic acids with diols does not require the activation of a carboxyl group or protection–deprotection, it was widely investigated at the early stage of this field.

In 1984, Okumura et al. [12] studied the *Aspergillus niger* lipase-catalyzed esterification polycondensation of a series of dicarboxylic acids with diols, but only oligomers (three, five or seven units) were produced. The phenomenon was probably caused by the water molecules shifting the equilibrium away from polyester synthesis and so reducing product yield and molecular weight. Thus, to further improve the product yield and molecular weight, some strategies were considered to remove the water molecules, *e.g.*, addition of molecular sieves or reduced pressure. For example, under the addition of 4 Å molecular sieves, the polycondensation of adipic acid and 1,4-butanediol would produce a polyester with a relatively higher degree of polymerization (DP) of 20 [13]. Linko et al. [14,15] systematically investigated the esterification polycondensation of dicarboxylic acids and diols using *Candida antarctica* lipase B (CALB), and some crucial rules were summarized. The solvents with a high boiling point, *e.g.*, diphenyl ether, were favorable for the polyester synthesis, and a polyester with high number-average molecular weight (M_n) of 28,500 g/mol were obtained using adipic acid and 1,8-octanediol as monomers. In a vacuum (0.15 mmHg), enzymatic polymerization of adipic acid and 1,6-hexanediol resulted in a polyester with a high weight-average molecular weight (M_w) and polydispersity index (PDI, the ratio of M_w to M_n) of 77,400 g/mol and 4.4, respectively. More importantly, the reaction involving monomers bearing longer alkylene chain lengths of diacids and diols yielded relatively higher molecular weights than those involving monomers with a shorter chain length. Similar to CALB, a novel cutinase from *Humicola insolens* (HIC) was explored having significant polycondensation activity and higher reactivity toward long chain diacids and diols [16,17]. In conclusion, through the optimization of reaction conditions (biocatalysts, substrates, solvents and removal of water molecules), polyesters with high molecular weight could be produced in a high yield, and these classic rules could be used as guidelines in enzymatic synthesis of polyesters.

In addition to organic solvents, enzymatic esterification polycondensation can also be conducted in solvent-free system, and even in aqueous system, which will make the enzymatic reactions more eco-friendly. Although the enzymes and monomers were in a heterogeneous state in the solvent-free system, CALB could efficiently catalyze the polycondensation of adipic acid and 1,8-ocatanediol to give an M_n value of 15,000 g/mol at 24 h of reaction (similar to that in organic solvents) [18]. According to the

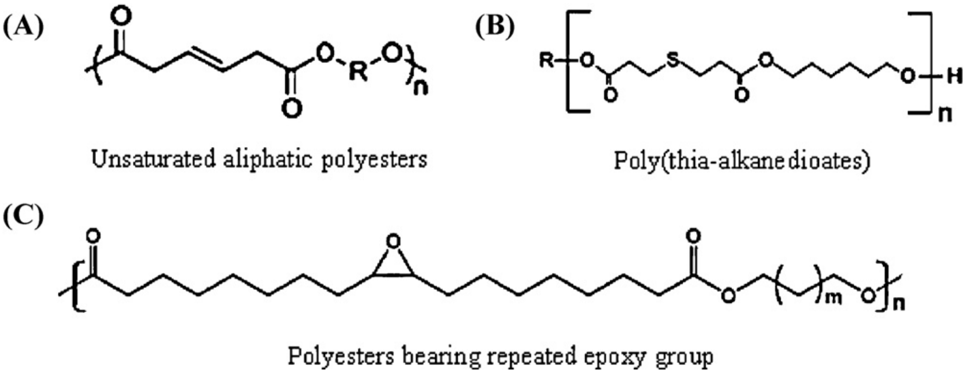

Fig. 2. Structures of polyesters with functional groups synthesized by lipase-catalyzed polycondensation reactions.

mechanism of enzymatic polycondensation, water molecules produced in the esterification polycondensation are unfavorable for the reaction and will limit the product yield and molecular weight. Surprisingly, lipase-catalyzed esterification polycondensations of dicarboxylic acids and diols can occur in water to result in a high product yield and molecular weight [19–22]. These findings are significant for organic synthesis and provide an important basis for realizing the eco-friendly polymer synthesis in water.

Chemical polycondensation reactions are usually conducted at high temperatures (180–280 °C), and the high temperatures are unfavorable for the thermally and chemically unstable monomers. Reversely, enzymatic polycondensation provides an efficient tool for temperature sensitive monomers, especially those unsuitable for high temperatures, like those with functional groups include epoxy, vinyl and siloxane moieties. Besides saturated polyesters, unsaturated polyesters, poly(thia-alkanedioates) and polyesters with epoxidized repeat units have been synthesized using CALB as catalyst [23–25], as shown in Fig. 2. Yang et al. [25] first prepared α,ω-diacids from bio-based ω-carboxy fatty acid monomers *via* the ω-oxidization pathway of *Candida tropicalis*, and then the monomers were polymerized with diols through the CALB-catalyzed polycondensation reaction, resulting in polyesters with M_w values of 25,000–57,000 g/mol. Silicon-containing polyesters have attracted much attention due to their unique properties, *e.g.*, low glass transition temperature, low surface energy, high gas permeability and good biocompatibility [26]. As the traditional chemical route usually requires extreme pH or temperature, mild enzymatic polycondensation thus displays a good potential in preparing these polyesters. Enzymatic polycondensation of 1,3-bis(3-carboxypropyl)tetramethyldisiloxane with different alkanediols (1,4-butanediol, 1,6-hexanediol and 1,8-octanediol) was conducted in a solvent-free system under reduced pressure to yield silicon-containing polyesters with the highest M_w value of 20,000 g/mol [26], as shown in Fig. 3. The polymerization of this monomer with poly(ethylene glycol) would result in an amphiphilic block copolymer [27]. In addition, α,ω-bis(3-hydroxypropyl) polydimethylsiloxane has been enzymatically polymerized with a series of diacids (succinic acid, adipic acid and sebacic acid) to produce polysiloxane-polyester copolymers with high yield (>90%) [28].

In addition to diols, esterification polycondensation has been extended to polyols including sugar components. When glycerol and adipic acid were used as monomers, the product was a hydroxylated polyester due to the stronger reactivity of lipase toward 1- and 3-primary hydroxyl groups than 2-secondary one [29]. Korupp et al. [30] successfully performed the enzymatic poly(glyceryl adipate) synthesis on a 500 g scale with monomer conversion more than 90%, and desired molecular weights of 2000–3000 g/mol were achieved through the optimization of reaction conditions (*e.g.*, temperature, pressure, enzyme concentration, reactants ratio, stirrer type, stirring rate and reaction time). Glycerol could also be polymerized with oleic diacid using CALB as catalyst, yielding polyesters with M_n values of 6000–9100 g/mol during 6–24 h with low branching degrees (13–16%) [31]. Meanwhile, these polyesters were not cross-linked, and a gel fraction was not observed. In contrast to enzymatic synthesis, using dibutyl tin oxide as catalyst, a polyester with M_n of 1700 g/mol was produced and a gel was formed due to the cross-linking. Using 1-thioglycerol as a monomer to be polymerized with 1,12-dodecanedioic acid, thiol-functionalized copolyesters were produced with an M_w of 170,000 g/mol [32]. When the polycondensation between adipic acid and sorbitol was performed using CALB as catalyst, water-soluble poly(sorbityl

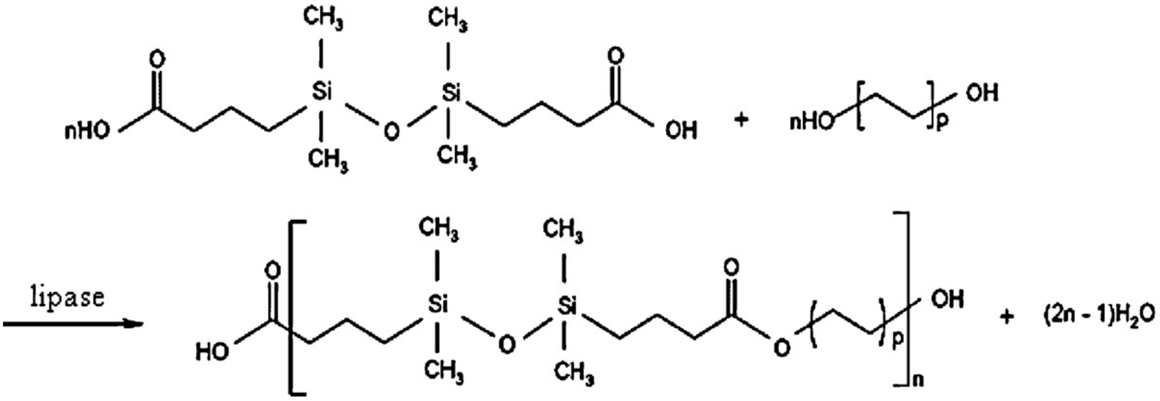

Fig. 3. Lipase-catalyzed polycondensation reaction of different diols (p = 2, 3 and 4) with 1,3-bis(3-carboxypropyl)tetramethyldisiloxane.

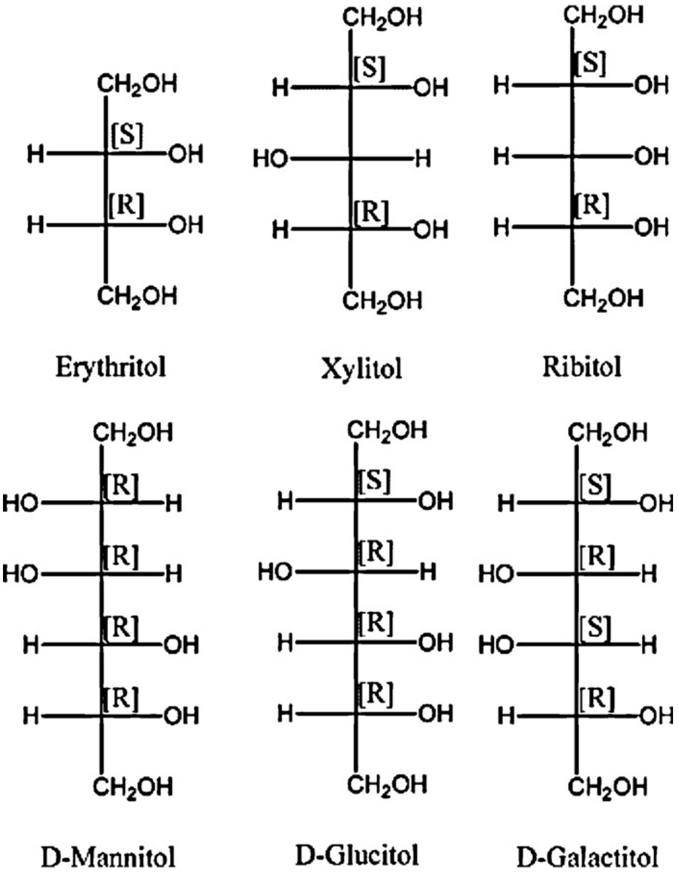

Fig. 4. Structures and stereochemistry of sugars used in enzymatic polycondensation.

adipate) was produced with an M_n of 10,800 g/mol, and sorbitol was mainly esterified at the 1- and 6-primary hydroxyl group with high regioselectivity (85 ± 5%) [33,34]. Other sugars, such as erythritol (C4), xylitol (C5), ribitol (C5), mannitol (C6), glucitol (C6) and galactitol (C6), have also been polymerized with diacids (Fig. 4) [35]. During the reaction, the primary hydroxyl group was of higher reactivity than the secondary hydroxyl group, and thus the stereochemistry of sugar polyols did not change in the enzymatic polycondensation.

2.2. Transesterification polycondensation

It has generally been accepted that the polycondensation reaction can be shifted to polyester synthesis through the activation of dicarboxylic acids, including alkyl, haloalkyl and vinyl esters. Early studies assumed that the activation by electron withdrawing groups was favorable for the enzymatic polycondensation reaction [1,36]. However, it is still unclear whether the activation of dicarboxylic acid is necessary for the improvement in product yield or molecular weight [1,25].

Alkyl esters are the most widely used method of activation as the alcohols of low boiling point can easily be removed from the reaction system by molecular sieves, nitrogen bubbling or reduced pressure to shift the equilibrium toward polyester synthesis [11]. Azim et al. [37] used diethyl succinate and 1,4-butanediol as substrates to form a monophasic reaction system and then optimized the reaction conditions (reaction medium, time and temperature) to yield poly(butylene succinate) with an M_w value of 38,000 g/mol (PDI = 1.39). This strategy successfully solved the problem of the phase separation of reactants when 1,4-butanediol and succinic acid were used as monomers, which would be favorable for the synthesis of poly(butylene succinate). To further increase the molecular weight of poly(butylene succinate), a novel strategy was developed [38]: 1,4-butanediol and dimethyl succinate were first enzymatically polymerized in dilute toluene to form a cyclic oligomer and then the cyclic oligomer was repolymerized *via* ring-opening polymerization to produce high-molecular-weight poly(butylene succinate) in concentrated toluene or in solvent-free system. Compared with the direct polycondensation (M_w = 45,000 g/mol), this method dramatically improved the product molecular weight (M_w = 130,000 g/mol). Similar to poly(butylene succinate) synthesis, 1,4-butanediol and diethyl sebacate could be used as monomers to synthesize poly(butylene sebacate), and the reactions could be conducted in a solvent-free system or ionic liquids to produce polyesters with an M_w value up to 15,800 g/mol [39–42]. Notably, a mixture of linear polyesters and macrocyclic oligomers was observed in these reactions [43]. When dimethyl 3,3′-thiodipropionate or dimethyl 2-mercaptosuccinate were subjected to polymerization with 1,6-hexanediol, linear polyesters containing the thioether function or free pendant mercapto group were obtained, respectively [24,44]. In addition, aliphatic dithiol–diacid type polythioester with an M_w value of 10,200 g/mol in 90% yield could also be synthesized by the CALB-catalyzed transesterification polycondensation of hexane-1,6-dithiol and diethyl sebacate [45]. A two-step strategy combining cyclization with subsequent ring-opening polymerization (mentioned above) has been hypothesized to obtain a polythioester with high molecular weight.

In addition to aliphatic polyesters, the activation through alkyl esters could be employed to prepare other polyesters or polycarbonates with novel structures and properties. Polyesters bearing tertiary amino substituents are particularly promising due to their biodegradability, low toxicity and outstanding gene transfection efficiency [46]. However, there were few synthetic methods to prepare amino-containing polyesters due to the deactivation of metal catalysts caused by amino groups. Recently, CALB has been reported to efficiently catalyze the poly(amine-*co*-ester)s synthesis *via* polycondensation of diesters with amino-substituted diols (Fig. 5), and these materials are very efficient nonviral vectors for safe and efficient DNA delivery in gene therapy [47,48]. Compared with polyesters (ester linkage), aliphatic polycarbonates are more enzymatically hydrolyzable and hydrolytically stable; as such, aliphatic polycarbonates are attractive options in biomedical and related fields. To date, several researchers have employed polytransesterification to synthesize aliphatic polycarbonates, *e.g.*, polycondensation of diethyl carbonate with 1,3-propanediol [49], 1,4-butanediol [50] and 1,6-hexanediol [51]. Through these reactions, the products with high molecular weight (up to 40,000 g/mol) were prepared, especially by combining the first oligomerization in low vacuum and the second repolymerization in high vacuum.

To shift the equilibrium toward the polymer synthesis more effectively, activation of esters using halogenated alcohols like 2-chloroethanol, 2,2,2-trifluroethanol and 2,2,2-trichloroethanol, was conducted [4,5]. The use of these halogenated alcohols could increase the electrophilicity of the acyl carbonyl and avoid significant alcoholysis of the products by decreasing the nucleophilicity of the leaving alkoxy group. In 1989, Wallace et al. [52] first used the halogenated alcohol to activate the diacids; and the subsequent polymerization of bis(2,2,2-trichloroethyl) glutarate and 1,4-butanediol resulted in a polyester with an M_w value of 7900 g/mol. Remove of the produced 2,2,2-trifluroethanol could dramatically improve the product molecular weight to 40,000 g/mol [53]. In addition, polytransesterification of bis(2,2,2-trichloroethyl) adipate with 1,4-butanediol was conducted in supercritical fluids, to produce polyesters with M_n values lower than 4000 g/mol [54]. Given that the halogenated alcohols

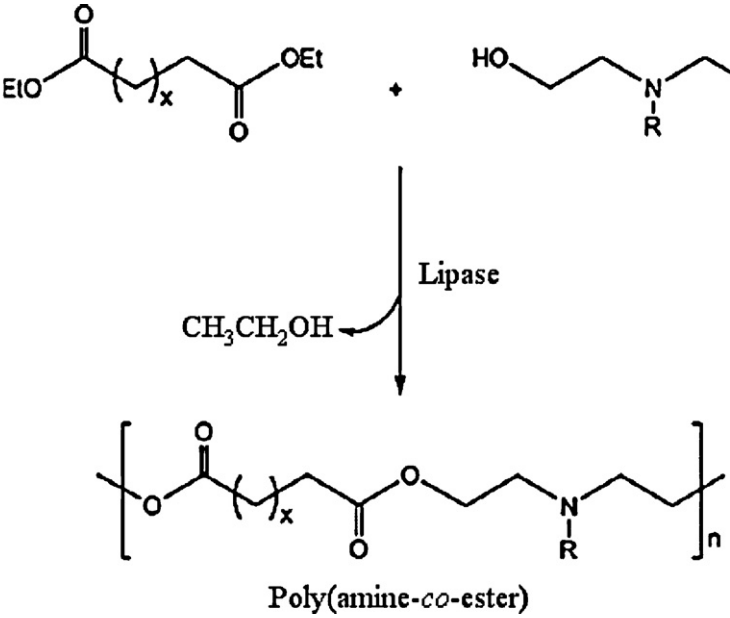

Fig. 5. Enzymatic synthesis of poly(amine-*co*-ester) *via* polycondensation.

produced in the reactions are detrimental for the activity and stability of biocatalysts, this activation strategy was not effective for the improvement of product yield and molecular weight, as mainly investigated in the early studies.

The use of vinyl ester in lipase-catalyzed acylation is another efficient method to perform the irreversible process, as the product (vinyl alcohol) can easily tautomerize to acetaldehyde [4,5]. Thus, polytransesterification involving divinyl esters proceeds much faster than those involving an alkyl ester or a haloalkyl ester. The polycondensation of divinyl adipate and divinyl sebacate with a series of diols has been systematically investigated using several lipases of different origins (CALB, *Mucor miehei* lipase, *Pseudomonas sp.* lipase and *Pseudomonas fluorescens* lipase); the product molecular weight was *ca.* 21,000 g/mol [55–57]. The polymerization of divinyl adipate and 1,4-butanediol were most widely investigated with *ca.* 30,000 g/mol as the highest molecular weight [58,59]. When divinyl sebacate and triols were polymerized using a lipase catalyst, the reactions displayed high regioselectivity toward the 1- and 3-hydroxyl groups [60,61], and thus this method can be employed to construct linear polyesters bearing pendant hydroxyl groups [62] or epoxide-containing polyesters [63]. Metral et al. [64] used a hydrazide-containing monomer, 1,2-bisglycoylhydrazine, for polymerization with vinyl-activated adipic, suberic or sebacic acid (Fig. 6). The synthesized poly(ester hydrazide)s are highly crystalline, which was the first report in a study on the synthesis of biodegradable poly(hydrazide)s. Recently, an aliphatic polyester bearing a pendant azide group was successfully synthesized *via* the lipase-catalyzed polycondensation of divinyl adipate and 2-(azidomethyl)-2-methylpropane-1,3-diol, and then the “click” reaction (copper-catalyzed azide–alkyne cycloaddition) was performed with mono alkyne-functional poly(ethylene oxide) [65], as shown in Fig. 7. The research was the first synthesis to combine enzymatic polycondensation with the “click” reaction in a one-pot reaction; thus, the unique chemoenzymatic route was of great significance in the synthesis of novel functional polymers.

2.3. Copolymerization of three or more monomers

In addition to the copolymerization of two monomers, three or more monomers have also been copolymerized to construct novel functional polymers. For example, through the copolymerization of adipic acid, 1,8-octanediol and bis(hydroxymethyl)butyric acid, a linear aliphatic polyester with a pendant carboxylic acid group has been successfully prepared (Fig. 8), with M_w values of 2300–21,900 g/mol [66]. Li et al. [67] constructed a polyester containing pendant hydroxyl group through the copolymerization of adipic acid, L-malic acid and 1,8-octanediol, with M_w values of 4700–9500 g/mol. Through the optimization of reaction conditions, polyesters with the highest M_w of 16,600 g/mol were obtained [68]. Dai et al. [69] prepared a type of block copolyesters *via* the enzymatic polycondensation of divinyl adipate with poly[(R)-3-hydroxybutyrate]-diol and poly[(R)-3-hydroxyoctanoate]-diol through both one- and two-step method, and the polyesters obtained are potential to be widely used as thermoplastic biodegradable and biocompatible materials.

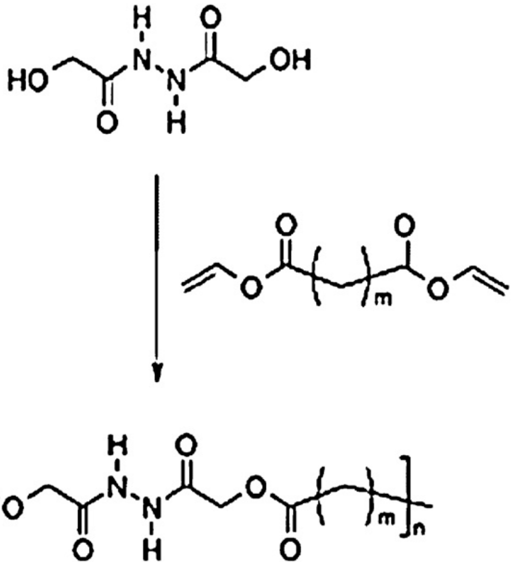

Fig. 6. Enzymatic synthesis of poly(ester hydrazide)s *via* polycondensation.

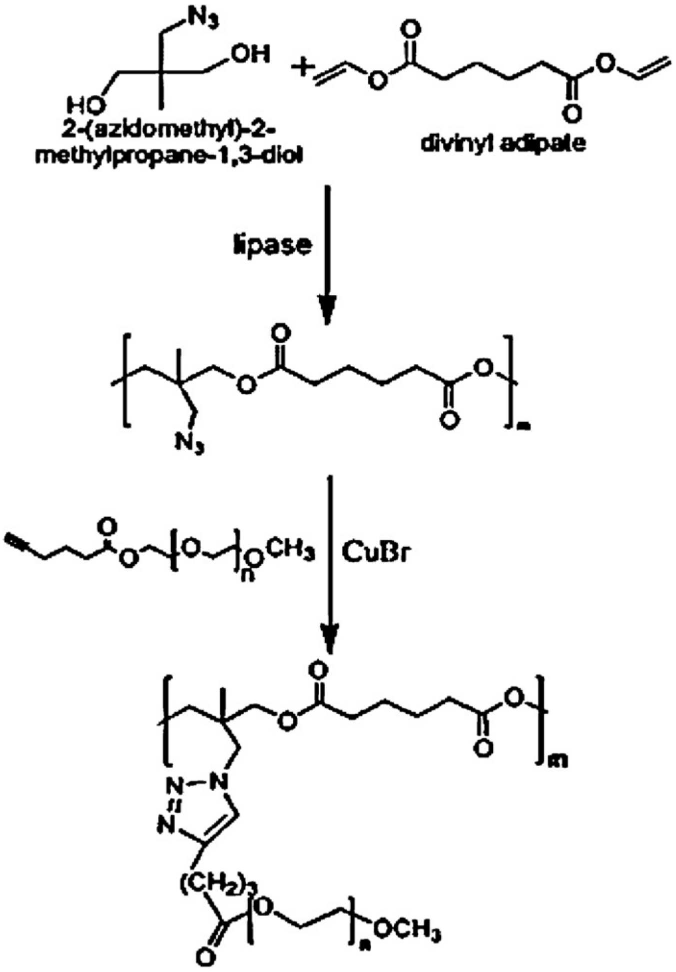

Fig. 7. Synthesis of graft copolymers combining enzymatic polycondensation and “click” reaction [65].

The incorporation of carbohydrates into non-polysaccharide structures is an important strategy to attain (i) highly functional polymers, (ii) specific biological functions, and (iii) complex systems that act as “smart” materials [33]. The synthesis of polyol polyesters has been widely investigated *via* the enzymatic copolymerization of adipic acid, 1,8-octanediol and sorbitol/glycerol/trimethylolpropane [70–73]. Among these polyols, trimethylolpropane was once used to construct branched copolyesters with branching degree of 20–74% [73]. These materials possessed high biocompatibility and might be widely used in the field of tissue engineering. Similar to polyesters, other types of polymers, *e.g.*, polyester carbonate copolymers [74,75], aliphatic polycarbonate polyols [76] and aliphatic polyesteramides [77,78], have also been synthesized *via* the lipase-catalyzed copolymerization of three monomers. Previous research has indicated that copolymerization of three or more monomers could be used to prepare a variety of functional polymers, as well as providing a promising tool to alter the properties of traditional polymers.

3. Polycondensation of hydroxyacids and mercaptoacids or their esters

3.1. Polycondensation of hydroxyacids and their esters

Similar to polycondensation of dicarboxylic acids or their derivatives with diols, self-polycondensation of hydroxyacids and their esters can also be performed by esterification (dehydration) and transesterification polycondensation. In 1985, Ajima et al. [79] first reported the polymerization of 10-hydroxydecanoic acid and glycolic acid using PEG-modified lipase and esterase, respectively; the resultant products were oligomers with DP values greater than 5. Previous reports have shown that several lipases, *e.g.*, CALB and porcine pancreatic lipase (PPL), induced the polymerization of lactic acid but that the obtained polylactides were of low molecular weight [80,81]. Using PPL as a catalyst, 3-hydroxybutyric acid and 12-hydroxyldodecanoic acid were successfully polymerized, with M_n values of 290–2900 g/mol, depending on the monomers and reaction conditions [82]. Through the polycondensation of ω-hydroxyacids of variable chain lengths, the reactivity was determined as follows: 16-hydroxyhexadecanoic acid ≈ 12-hydroxydodecanoic acid ≈ 10-hydroxydecanoic acid > 6-hydroxyhexanoic acid [83]. For HIC-catalyzed polycondensation of ω-hydroxyacids, similar chain selectivity was observed, but 10-hydroxydecanoic acid and 6-hydroxyhexanoic acid could not be polymerized [17]. Thus, lipases exhibited higher reactivity toward long chain monomers in the polycondensation of hydroxyacids, which could be attributed to the fact that lipases were more easily activated upon binding to a higher hydrophobic substrate due to the peculiar interfacial activation of lipases. In addition to homopolymerization, lipase-catalyzed copolymerization of two or more hydroxyacids is an effective tool for the modification of polymers' properties, *e.g.*, copolymerization of lactic and glycolic acid to synthesize a common drug delivery carrier poly(lactic-*co*-glycolic acid) [84].

The preparation of polymers from renewable resources to reduce the dependency on fossil fuels has been of immense interest as an alternative to traditional petroleum feedstocks [85,86]. The principal monomer in the outer bark of birch is *cis*-9,10-epoxy-18-hydroxyoctadecanoic acid (100 g/kg dry outer bark in *Betula verrucosa*), and lipase could efficiently catalyze the polymerization

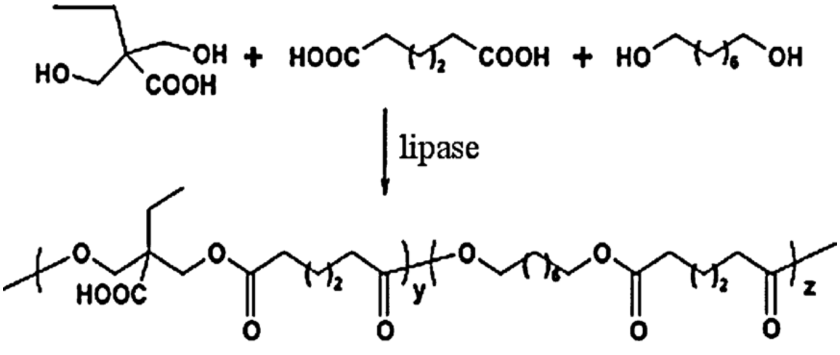

Fig. 8. Lipase-catalyzed synthesis of aliphatic polyesters containing pendant carboxylic acid groups.

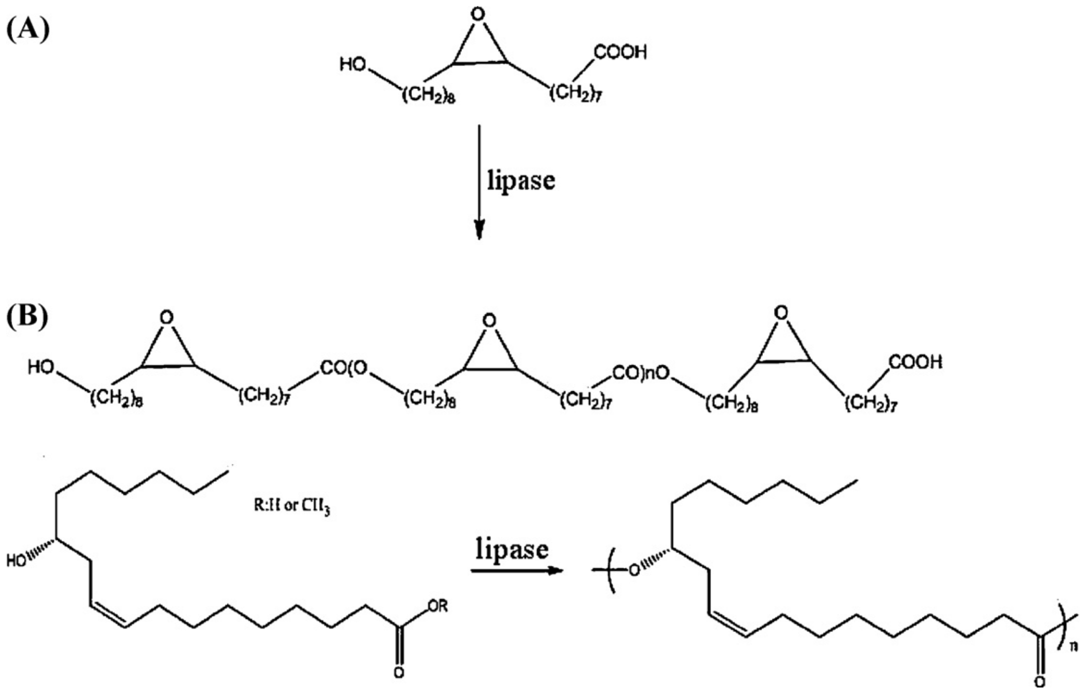

Fig. 9. Lipase-catalyzed polycondensation of *cis*-9,10-epoxy-18-hydroxyoctadecanoic acid (A) and ricinoleic acid (B).

of this monomer with 100% monomer conversion to yield epoxy-functionalized polyesters with the highest M_w of 20,000 g/mol (Fig. 9A) [87]. Ricinoleic acid, a main component derived from castor oil, has been polymerized by lipase catalysis (Fig. 9B), and the polyricinoleate obtained was of high molecular weight (M_w = 100,600 g/mol) [88,89]. The product could be cross-linked to a chloroform insoluble polymer using dicumyl peroxide as a catalyst [90]. In addition, it also could be converted to methyl 12-hydroxystearate *via* hydrogenation and then copolymerized with 12-hydroxydodecanoic acid to construct novel green and sustainable elastomers [91].

Various hydroxyesters, including the ethyl esters of 3-hydrobutyric acid, 4-hydroxybutyric acid, 5-hydroxyhexanoic acid, 6-hydroxyhexanoic acid, 5-hydroxydodecanoic acid and 15-hydroxypentadecanoic acid, have been enzymatically polymerized to produce the corresponding polyesters with M_n values of 3400–5400 g/mol [92]. Ohara et al. [93] studied the lipase-catalyzed oligomerization of alkyl D- and L-lactates monomers and found that oligomerization occurred enantioselectively only for D-lactates in a good yield; however, no reactions were observed for all the L-lactates. This finding was direct evidence that the enantioselectivity in lipase catalysis is governed by the deacylation step.

3.2. *Polycondensation of mercaptoacids*

Direct polycondensation of mercaptoalkanoic acids could be employed to prepare aliphatic polythioesters. In the CALB-catalyzed polymerization of 11-mercaptoundecanoic acid, a high yield of poly(11-mercaptoundecanoate) with an M_w of 34,000 g/mol was obtained [94]. The product exhibited a relatively higher melting point than the corresponding poly(11-hydroxyundecanoate). Meanwhile, polythioesters could be easily transformed into cyclic oligomers *via* lipase catalysis, and could subsequently be polymerized through the ring-opening polymerization to promote sustainable chemical recycling. To further improve the product molecular weight, 6-mercaptohexanoic acid could be transformed into cyclic oligomers *via* lipase catalysis in dilute toluene solution, and these cyclic oligomers were then repolymerized, or copolymerized with other lactones, *e.g.*, ε-caprolactone [95].

4. Combination of ring-opening polymerization and polycondensation

A typical example of the versatility of lipase-catalyzed polymerization reactions is the ability to concurrently catalyze the ring-opening polymerization and polycondensation to synthesize novel polyesters with tailor-made structural and physical properties [1]. For example, Namekawa et al. [96] systematically investigated the combination of ring-opening polymerization of 11-undecanolide, 12-dodecanolide or ω-pentadecalactone with the polycondensation of divinyl adipate, divinyl sebacate or α,ω-glycols simultaneously, using CALB and *P. cepacia* lipase as catalysts. The reactions resulted in relatively high molecular weight products (M_n = 5300–12,000 g/mol) and moderate yields (27–80%). Similarly, CALB could catalyze the polymerization of 3-hydrobutyric acid and D-glucono-δ-lactone to yield a mixture of linear and cyclic polyesters with moderate molecular weight [97]. Due to the relatively high amount of 3-hydrobutyric acid in the reaction system and its strong reactivity, the 3-hydrobutyric acid homopolymer was also produced in the reaction [97].

ω-Pentadecalactone was the most widely used monomer to be combined with the polycondensation reactions, due to its high reactivity in lipase-catalyzed ring-opening polymerization [98]. For example, ω-pentadecalactone was copolymerized with glycidol and adipic acid to form epoxide-terminated polymers [99]; using CALB as catalyst, ω-pentadecalactone was copolymerized with ethyl glycolate to obtain a product with a high degree of crystallinity [100]. When ω-pentadecalactone, 1,4-butanediol and dialkyl succinate or carbonate were copolymerized *via* a two-stage process (oligomerization under low vacuum followed by polymerization under high vacuum), all the random copolyesters obtained were of high thermostablity and high degree of crystallinity, and could be used as promising drug delivery systems [101–104]. Using the oil-in-water single emulsion technique to prepare 100–300 nm nanoparticles for camptothecin (CPT) delivery, the CPT-loaded nanoparticles showed a significant enhancement of cellular uptake, higher cytotoxicity against several cancer cell lines *in vitro*, a longer circulation time, and substantially better anti-tumor efficacy *in vivo* than free CPT. These results demonstrated that these copolyesters may be used as long-term stable and effective drug delivery systems in cancer therapy. Similarly, the combination of ring-opening polymerization of 12-dodecanolide or 16-hexadecanolide with 12-hydroxystearate was performed to prepare novel biodegradable and bio-based thermoplastic elastomers with high M_w values of 140,000–290,000 g/mol [105].

5. Conclusions

In this review, lipase/esterase-catalyzed polycondensation reaction has shown to be a powerful tool for synthesizing aliphatic polyesters. Compared with conventional chemical route, this technique exhibits many advantages, such as no need of protection–deprotection, high enantio-, chemo- or regioselectivity, and synthesizing metal-free polymers under mild reaction conditions. More importantly, it can be applicable with many thermally or chemically unstable monomers, including siloxane, epoxy and vinyl moieties, which provides an important option for the polymer chemist. To date, the strategy is still applied at the laboratory scale, mainly due to the limitation in cost and catalytic activity of enzymes. Exploring novel biocatalysts from natural sources, especially thermophiles, is an efficient tool for the industrial application of enzymatic polycondensation. Other routes to achieve this goal are protein engineering and immobilization strategies that allow constructing tailor-made highly active, stable, and enantio- and regioselective enzyme catalysts. The many advantages that enzyme catalysis provides to polycondensation will facilitate the future development of scientific and technological tools for the commercially viable production of biomaterials.

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